National Institute for Health and Care Excellence

Final

Urinary tract infection in under 16s: diagnosis and management

[B] Evidence review for symptoms and signs

NICE guideline NG224

Evidence review underpinning recommendations 1.1.1 and 1.1.2, 1.1.4 to 1.1.9 and 1.1.11 and research recommendations in the NICE guideline

July 2022

Final

This evidence review was developed by Guideline Development Team

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1 Diagnosis: symptoms and signs

1.1 Review question

What symptoms and signs are suggestive of urinary tract infection in under 16s?

1.1.1 Introduction

The levels of UTI in the UK are unclear, as many published studies have focused on UTI in paediatric emergency departments and are US based. However, the EURICA study (O'Brien et al 2013), conducted in UK general practice, found that 5.9% of babies and children <5 years who presented with an acute illness had a UTI. It is important to promptly identify babies, children and young people who might have a UTI to alleviate short term distress from the infection and to prevent longer-term problems from renal complications. In addition, it is uncertain if some urinary tract infections in babies, children and young people might be self-limiting or even if the symptoms have resolved in untreated infection whether longer-term complications might still occur.

When an acutely unwell baby, child or young person is assessed for the presence of a UTI the process usually involves several steps beginning with assessment of individual factors such as gender, previous medical history, previous urinary tract infection, clinical symptoms and signs. This is followed by urinalysis (for example dipstick testing) with laboratory analysis of urine samples (microscopy, culture, and sensitivity) providing the final diagnosis.

There has been considerable uncertainty about the diagnostic value of individual symptoms and signs and any proposed combinations of symptoms and signs in babies, children and young people. This was highlighted in the NICE 2007 guideline which made a research recommendation for a large study to be carried out in primary and secondary care to evaluate the association between symptoms and signs and UTI. This guideline update was prompted by several new primary studies looking at symptoms and signs for the initial diagnosis of UTIs and in particular, the DUTY study (Hay et al 2016) which was designed to answer the 2007 research recommendation. This review aims to determine which symptoms and signs (or combination of these) are useful in the diagnosis of urinary tract infection in babies, children and young people, or in whom further tests should be conducted, and which are not to improve the accuracy of the initial stage of the UTI diagnostic pathway.

1.1.2 Summary of the protocol

Population	Babies, children, or young people from birth to under 16 years old.
Test	Symptoms and signs including but not limited to: • abdominal pain/crying • dysuria (pain or crying when voiding) • headache • jaundice • haematuria (blood in the urine) • high fever over 38 or 39 degrees • shivering • rigors • vomiting • lethargy/malaise • irritability • poor feeding

	• failure to thrive • offensive or smelly urine • loin tenderness • frequency (increased passing of urine) or holding urine in • dysfunctional voiding • diarrhoea • changes in continence • cloudy urine • cough or ear symptoms • sore throat • skin mottling • skin rash • redness in perineal area • parental suspicion of a UTI • previous UTI Or a combination of symptoms and signs (for example as an algorithm).
Reference standard	Microbiologically confirmed urinary tract infection (microscopy, culture, and sensitivity).
Outcomes	Diagnostic association measures: • Odds ratio Diagnostic accuracy metrics: • Positive and negative likelihood ratio (LRs) • Sensitivity and specificity • AUC (for diagnostic prediction models only)

1.1.3 Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual. Methods specific to this review question are described in the review protocol in appendix A and appendix L.

Declarations of interest were recorded according to NICE's conflicts of interest policy.

The following additional methods apply to this review:

1. The reference list from the DUTY study (Hay et al 2016) that triggered this update was used to identify additional potentially relevant studies for inclusion in this review.
2. Although priority screening was used to try to organise the references in the search the full database was screened. The diverse nature of the symptoms, signs and study designs that could contain them meant that it was not possible to be terminate the sift early based on our criteria (see the review protocol for more details).
3. This review included babies, children, or young people from birth to under 16 years old who present as acutely unwell to a healthcare setting and who could potentially have UTI (i.e., not presenting with a clear alternative diagnosis like trauma). This included babies, children, or young people from birth to under 16 years old who have a recurrent UTI (with the exception of sexually active girls with recurrent UTIs or recurrent UTIs due to a diagnosed urinary tract malformation as these are out of scope of the guideline).
4. Babies, children, or young people from birth to under 16 years old who are being treated with prophylactic antibiotics for UTIs were also included. The antibiotics used prophylactically to prevent recurrence in babies, children, or young people under 16 years are the same antibiotics but given at a typically lower dose and with lower frequency (see NICE NG112) compared to when used for treatment of an UTI (see NICE NG109). Although prophylaxis reduces the risk of recurrence of UTI this

reduction is not absolute, and recurrence or reinfection can occur in a child taking antimicrobial prophylaxis. This requires prompt diagnosis and treatment with a different antibiotic, to help prevent/overcome antimicrobial resistance. Diagnostically these babies, children, or young people will have symptoms, signs and likely microbiological growth and this group are included in the review.

5. Babies, children, or young people treated with antibiotics within the last 48 hours are unlikely to have significant growth or even if they do the reference test results are likely to be confounded by the previous treatment which will remain in the system for up to 48 hours. This group is therefore not included in the review.
6. Studies with babies, children or young people under 16 years old who have been treated with an antimicrobial between the index and reference test sample collection may be excluded if, in the committee's judgment, the antimicrobial could have affected the reference test result.
7. Studies that recruited people in the excluded categories as well as those of interest and do not report data separately were downgraded for indirectness or excluded based on committee input.
8. In this review a symptom is defined as something that is expressed by the person with the condition or by their surrogate (parent or carer). A sign is something that is observed or elicited by another person, such as the healthcare professional. There is often overlap between the 2 criteria.
9. Although some studies reported data for a clinician's opinion on the likelihood of a urinary tract infection before dipstick and culture is not included because this would be based on a combination of symptoms and signs and would be subjective and dependent on clinician experience.
10. This review included all studies that meet inclusion criteria of a microbiologically confirmed urinary tract infection (microscopy, culture, and sensitivity) with the option of analysing the results by definition as a subgroup analysis.
11. We planned to carry out a number of subgroup analyses (see review protocol in appendix A) however, data was only available to allow us to carry out the age subgroup analysis.
12. For the age subgroup, studies were grouped using mean age or percentage of participants under a specific age reported by the studies included in the Boon et al 2021 systematic review, plus Ibeneme et al 2014, Struthers et al 2003, or Williams-Smith et al 2020. Four subgroups were used: <2 years; 2 to <5 years, <5 years, and <16 years and the choice of using <2 years and 2 to <5 years or < 5 years was made based on the studies included in each individual meta-analysis. The <16 category does not include studies that specifically recruited babies and children under 5 years old but rather includes studies who recruited babies, children and young people up to this age. Where mean or median ages were available this was taken into account when assigning the study to an age subgroup.
13. The collection method was not used as a subgroup because this matched the age subgroups when studies reported participants <2 years old (for example urine sample collected with a clean towel put into the child's nappy after cleaning their bottom referred as 'nappy pad' [DUTY study] Hay et al 2016) and participants 2 to <5 years (for example urine sample collected straight from the child into a urine container referred as 'clean catch' [DUTY study] Hay et al 2016). Other studies used mixed methods for collecting urine samples without reporting data by type of collection method.
14. Test and treat RCTs were not included in the study types of interest because the committee were not aware of any test and treat RCTs that addressed this specific question and for reasons of efficiency during the searches.

15. Studies that use urine samples that have been collected from cotton wool balls, gauze and sanitary towels were excluded because the NICE UTI in under 16s guideline (CG54) says that 'cotton wool balls, gauze and sanitary towels should not be used to collect urine in babies and children'.
16. GRADE was assessed at the level of likelihood ratios (LRs). 2 clinical decision thresholds were determined (2.0 for likelihood ratios over 1 and 0.5 for likelihood ratios under 1. These decision thresholds were used with the line of no effect (1.0) to determine whether imprecision was not serious, serious (confidence interval crossing one threshold) or very serious (confidence interval crossing 1.0 and either 0.5 or 2).
17. When interpreting the LRs for the summary GRADE table the terminology used was taken from the Table 14 in appendix M, with the exception of point estimate values that fall between 2 and 0.5 or if the 95% CI crosses 1.0. These were described as not meaningfully altering the probability of having a UTI.
18. The Boon et al 2021 systematic review (SR) was assessed using the ROBIS tool and judged to be of high quality and directly applicable to this review (see appendix M for methods). We have therefore used it as the basis for this review. Relevant LR data was extracted from the Boon et al 2021 SR and back calculated to give 2x2 data using the Cochrane RevMan calculator to allow meta- analysis to be carried out with the addition of new studies and removal of those that did not meet our inclusion criteria.
19. Where data for additional outcomes not reported by the Boon et al 2021 SR was extracted from the primary studies included in the Boon et al 2021 SR this is noted in the Boon et al 2021 evidence table.
20. The authors of the Boon et al 2021 SR assessed the risk of bias and applicability of their included studies using the QUADAS-2 tool, presenting these at the domain level rather than per study overall. We made a judgement of overall risk of bias using this domain information based on the following criteria: if 1 risk of bias domain was red (high), or there were 3 yellow (unclear) domains then we judged the study to be at high risk of bias. If there were 2 yellow (unclear) domains, then we judged the study to be at moderate risk of bias and if there was 1 yellow (unclear) domain or all domains were green (low risk) then we judged the study to be at low risk of bias.
21. Since diagnostic test accuracy data in the form of LRs (and not association data) was available in the Boon et al 2021 SR and could be calculated from the additional studies identified in the search no association data was extracted from individual studies for this review.
22. Some of the data included in the Boon et al 2021 SR was previously unpublished and obtained directly from the authors of a small number of studies.
23. Only external validation studies for diagnostic models of symptoms and signs of the study designs listed in the protocol were included in this review.

Protocol deviation

A sensitivity analysis was carried out after discussing studies with the committee in the meeting. It was agreed that Pylkkanen et al 1979 should be removed in sensitivity analyses due to a number of factors, first the study only reports results for less than half of the children it recruited (200 of 377) and lacks explanation as to why this is the case, secondly the prevalence of UTI is much higher (≈61%) than in other studies (median prevalence was 10% in the Boon et al 2021 SR) although this may be appropriate given the method of urine sample collection and population, additionally, the study recruited babies, children and young people under the age of 18 years (although 64.5% were aged ≤2 years) the study has limited applicability to the guideline population. Additionally, the committee thought it very likely that there have been changes in practice since the date of this study. The analyses with this

study were used to make recommendations and draft the table of symptoms and signs but this table was updated to reflect the analyses without Pylkkanen et al 1979. The changes resulting from this reanalysis had a minor impact on the committee's decision making (see Table 6 cells with changes are highlighted in yellow).

1.1.4 Diagnostic evidence

1.1.4.1 Included studies

A literature search was conducted which identified 5414 articles. Of these, 133 potentially relevant quantitative papers were identified after screening the titles and abstracts against the review protocol. This review included 31 papers of which 30 were primary papers and 1 was a SR (Boon et al 2021).

Of the 31 included papers:

- There were 29 studies because the DUTY study (Hay et al 2016) comprised of 3 included papers.
- The Boon et al 2021 SR contained 35 studies, of which 24 met the inclusion criteria for this review and are counted within the 31 papers mentioned above.
- Twenty-four studies addressed symptoms and signs, including 3 not included in the Boon et al 2021 SR (Ibeneme et al 2014; Struthers et al 2003 and Williams-Smith et al 2020).
- Three studies looked at diagnostic model validation (De et al 2013; Diaz et al 2015 and Boon et al 2022)
- One study (Zorc et al 2005) provided data on separate symptoms and signs as well as being a diagnostic model validation study.

The Boon et al 2021 SR was judged to be of high quality and directly applicable to this review (see the methods in appendix L for an explanation of what this means and how it was assessed). We have therefore used it as the basis for this review and extracted data directly from it.

For the characteristics of the included studies see section 1.1.5 Summary of studies included in the diagnostic evidence, appendix C for the full evidence tables and section 1.1.12 References – included studies.

1.1.4.2 Excluded studies

The studies that were excluded at full text are listed in appendix J with reasons for their exclusion.

1.1.5 Summary of studies included in the diagnostic evidence

Systematic review

Study	Number of included studies	Inclusion criteria	Exclusion criteria	Signs and symptoms explored	Reference standard
Boon 2021	35 [Our review included 24 of the studies. The included and excluded studies are listed in the detailed evidence table for this review in appendix D.]	• ≤18 years of age • Prospective cross-sectional diagnostic accuracy studies, diagnostic nested case-control studies, and retrospective cohort studies. • Took place in ambulatory care setting	• case-control studies with differential sampling scheme for case and control • reviews • letters • comments and conference abstracts • sample sizes of <50 children • high-risk participants such as children who are premature or malnourished	• vomiting • bed wetting • urgency • nausea • pale colour • capillary refill time • elevated heart rate • tachycardia • cyanosis • altered consciousness • purpura • grunting • sleepiness • symptom duration • muscle aches/pains • social interaction • failure to thrive • diarrhoea • poor feeding • fever characteristics • abdominal pain • previous UTI • irritability	Diagnosis of UTI confirmed by urine culture (see Table 1 for thresholds used)

				• general appearance • chills • dehydration • bulging fontanelle • absence of specific non-UTI symptoms (e.g. cough, respiratory symptoms) • shivering • jaundice • haematuria • suprapubic tenderness • renal angle tenderness • cloudy urine • darker urine • smelly urine • flank pain • back pain • frequency • decreased feeding • poor weight gain • loin tenderness • dysuria • constipation • no nappy rash	

Primary studies looking at symptoms and signs

Table 1 Characteristics of the primary studies looking at symptoms and signs

These study characteristics were taken from the Boon et al 2021 systematic review with the exception of Ibeneme et al 2014, Struthers et al 2003 and Williams-Smith et al 2020, which have been added by the NICE Guideline Development Team.

The abbreviations are as follows: UTI= urinary tract infection; USA= United States; UK= United Kingdom; ED= Emergency departments; FP= family practices; OD= outpatient department of a hospital; HC= health centres; PO= paediatricians' offices; Pros= Prospective design; retro= Retrospective design; cx= cross-sectional design; cons= consecutive enrolment; conv= convenience sampling; y= years; d= days; m= months; °C= degrees Celsius; FWS = fever without a source for infection; WBC= white blood cell (in urine); UC= urethral catheterization; SPA=suprapubic aspiration; MS=midstream sample; CC= clean catch sample (first stream); BS=bag specimen; NP= nappy pad sample; NR= not reported; cfu= colony forming unit; ml=millilitre. UTI prevalence= No. of children with UTI/sample size.

Study	Country	Design	Setting	Age range (median/mean)	% female	UTI prevalence %	Inclusion criteria	Urine culture reference standard threshold
Bonadio 1991	USA	Retro, cons	ED	1-2m (NR)	NR	16/683 (2.3%)	Fever (>38◦C)	single pathogen ≥ 10^5cfu/ml
Craig 2010	Australia	Pros, cons, cx	ED	<5y (NR)	56%	543/15781 (3.4%)	Fever (≥38◦C) or 'felt hot'	SPA: any cfu/ml MS: ≥ 10^5cfu/ml UC: ≥10^4cfu/ml
Dobbs 1987	UK	Pros, cx	HC	0-14y (NR)	nr	16/75 (21.3%)	Symptoms of UTI	≥ 10^5cfu/ml, ≥10^4 to 10^5cfu/ml and ≥ 10^2 wbc/mm^3 (MS)
Duong 2016	Belgium	Pros. cons, cx	ED	≤16y (44m)	59%	221/1247 (17.7%)	Specimen available	single pathogen SPA: any cfu/ml CC/UC: ≥ 10^5cfu/ml
Festo 2011	Tanzania	Pros, cons, cx	HC	2m-5y (18m)	48%	147/370 (39.7%)	Fever	SPA: any cfu/ml MS: ≥ 10^5cfu/ml

Study	Country	Design	Setting	Age range (median/mean)	% female	UTI prevalence %	Inclusion criteria	Urine culture reference standard threshold
Gauthier 2012	Canada	Pros, cons, cx	ED	1m-3y (12m)	57%	51/331 (15.4%)	Symptoms of UTI: Fever without source (>38.5◦C), Irritability or vomiting	SPA: any cfu/ml of gram-negative species SPA: ≥ 10^4cfu/ml gram positive species UC: ≥ 10^5cfu/ml UC: ≥ 10^4cfu/ml pseudomonas species CC/MS: ≥ 10^5cfu/ml
Gorelick 2000	USA	Pros, cons, cx	ED	<2y (11m)	100%	63/1469 (4.3%)	Fever without source (≥38.3◦C)	single pathogen ≥ 10^4cfu/ml (UC)
Hay 2016 (Includes Hay 2016a, Hay 2016b and Butler 2016)	UK	Pros, cons, cx	FP, ED, WC	<5y (CC: 94%>2y) (NP: 82%<2y)	CC: 54% NP: 48%	CC: 60/2740 (2.2%) NP: 30/2277 (1.3%)	≥1 symptoms of UTI (NICE-2)	single pathogen ≥ 10^5cfu/ml (NP, CC, BS)
Hoberman 1993	USA	Pros, cons, cx	ED	≤1y (68%>2m)	44%	50/945 (5.3%)	Fever (≥38.3◦C)	≥ 10^4cfu/ml (UC)
Ibeneme 2014	Nigeria	Pros, cons, cx	PO	1-59m (31.1m)	44%	22/200 (11%)	Fever (≥37.6◦C)	single pathogen ≥ 10^5cfu/ml
Kanegaye 2014	USA	Pros, conv, cx	ED	≤4y (8.1m)	59%	42/342 (12.3%)	Fever (≥38◦C) and test results available	≥ 5x10^4cfu/ml (UC)
Kartika 2006	Indonesia	Pros, cx	ED, OD	2m-14y (5.6y)	58%	82/205 (40%)	Suspicion of UTI	single pathogen (CC, MS)
Lizama 2005	Chile	Retro, cons	ED	11d,14y (2.3y)	65%	246/1140 (21.6%)	Specimen available	SPA: any cfu/ml UC: ≥ 10^4cfu/ml MS: ≥ 10^5cfu/ml
Mitiku 2018	Ethiopia	Pros, cons, cx	OD	<15y (20.5%<1y) (60%<5y)	38%	74/269 (27.5%)	At least 1 symptom of UTI: ≥37.5◦C, vomiting, dysuria, frequency,	≥ 10^5cfu/ml (MS)

Study	Country	Design	Setting	Age range (median/mean)	% female	UTI prevalence %	Inclusion criteria	Urine culture reference standard threshold
							urgency, loin pain, darker change	
Msaki 2012	Tanzania	Pros, cons, cx	HC	2m-5y (15m)	55%	47/231 (20.3%)	Fever (≥37.5◦C)	≥ 10^5cfu/ml (MS)
Musa-Aisien 2003	Nigeria	Pros, cons, cx	ED	1m-5y (18m)	41%	26/300 (8.7%)	Fever (≥38◦C)	≥ 10^5cfu/ml (SPA, CC or MS)
Newman 2002	USA	Pros, cx	PO	≤3m (32%<1m) (75%<2m)	48%	161/1666 (9.7%)	Fever (≥38◦C)	single pathogen: SPA: ≥ 10^2cfu/ml UC: ≥ 2x10^4cfu/ml BS/CC: ≥10^5cfu/ml
O'Brien 2013	UK	Pros, cons, cx	FP	≤5y (2.3y)	48%	35/597 (5.9%)	Illness episode <28d	≥ 10^5cfu/ml (NP, CC)
Pylkkanen 1979	Finland	Pros, cx	OD	<18y (64.5%≤2y)	NR	127/200 (63.5%)	Suspicion of UTI	any cfu/ml (uricult and blood agar plate; SPA)
Shaw 1998	USA	Pros, cons, cx	ED	Boys <1y (41.5%<6m); Girls <2y (55.3%<12m)	61%	80/2411 (3.3%)	Fever (≥38.5◦C) and symptoms of UTI	≥ 10^4cfu/ml (UC)
Struthers 2003	UK	Pros, cons, cx	PO	<6y (NR)	NR	7/110 (6.4%)	Unwell/febrile	Single pathogen ≥ 10^5cfu/ml
Velasco 2015	Spain	Pros, cons, cx	ED	<90d (46d)	40%	547/3401 (16.1%)	Fever (≥38◦C) and test results available	single pathogen ≥ 5x10^4cfu/ml (SPA, UC)
Verbakel 2015	Belgium	Pros, cons, cx	FP, ED, OD	1/-16y (2.0y)	48%	87/756 (11.5%)	Illness episode ≤5d	≥ 10^5cfu/ml (NR)
Williams-Smith 2020	Switzerland	Pros, cons, cohort	ED	≤36m (4.4m)	46%	47/173 (27%)	Fever without source (≥38◦C), <10d in duration	single pathogen ≥ 10^4cfu/ml (UC)
Zorc (2005)	USA	Pros, cx	ED	≤60d	44%	91/1005 (9.1%)	Fever (≥38◦C)	SPA: ≥ 10^3cfu/ml

Study	Country	Design	Setting	Age range (median/mean)	% female	UTI prevalence %	Inclusion criteria	Urine culture reference standard threshold
				(35.5d)				UC: ≥ $5x10^4$cfu/ml UC: ≥ 10^4cfu/ml + positive urinalysis

Primary studies assessing diagnostic models

Table 2 Characteristics of primary studies looking at diagnostic models

Study	Country	Design	Prediction model	Factors	UTI prevalence %	Inclusion criteria	Urine culture reference standard threshold
De 2013	Australia	Post-hoc analysis of data collected for the Febrile Evaluation of Children in the Emergency Room (FEVER) study.	NICE traffic light	Colour, activity, respiratory, circulation and hydration, other (list of symptoms under heading of 'other' in algorithm).	362/365 (9.9%)	<5 years old with a febrile illness	Suprapubic aspiration: any cfu/ml Clean catch sample (first stream)/ midstream: ≥ 10^5cfu/ml Urethral catheterization: ≥10^4cfu/ml
Diaz 2015	Spain	Retrospective cohort study	Yale Observation scale	Quality of cry, reaction to parents, arousability, skin colour, hydration, social response	76/314 (24.2%)	< 3 months Fever (≥38◦C) and tests available	≥ $5x10^4$cfu/ml (Suprapubic aspiration, urethral catheterization)
Zorc 2005	USA	Prospective, cross-sectional study	Yale Observation scale	Quality of cry, reaction to parents, arousability, skin	91/1005 (9.1%)	Fever (≥38◦C)	Suprapubic aspiration: ≥ 10^3cfu/ml Urethral catheterization: ≥ $5x10^4$cfu/ml Urethral catheterization: ≥ 10^4cfu/ml + positive urinalysis

				colour, hydration, social response			
Boon 2022	Belgium	Post-hoc analysis of cross-sectional study	DUTY (signs and symptoms model)	High risk if 5+ points): Dysuria (2), malodorous urine (2), history of UTI (1), absence of severe cough (2), severity of illness (2, when >6 on a scale of 0-10).	26/297 (8.8%)	<5 years old	Single pathogen ≥ 10^5cfu/ml
			UTIcalc	High risk if 2% risk or greater on online calculator: Age < 12months, Fever ≥39°C, non-African American ethnicity, female gender, uncircumcised male, fever without source.	4/96 (4.2%)	(≥38◦C), <2 years old with urinary tract abnormalities	Single pathogen ≥ 5x10^4cfu/ml
			Gorelick	High risk if 2+ criteria are present: Age <12 months, Caucasian, Fever ≥39°C, fever 2 or more days, fever without source	23/100 (23%)	Fever (≥38◦C), <2 years old	Single pathogen ≥ 5x10^4cfu/ml with pyuria

See appendix D for full evidence tables.

1.1.6 Summary of the diagnostic evidence

Summary GRADE table for symptoms and signs individually

When interpreting the LRs for the summary GRADE table the terminology used was taken from Table 14 in appendix M, with the exception of point estimate values that fall between 0.5 and 2 or if the 95% CI crosses 1.0. These were described as not meaningfully altering the probability of having a UTI.

Table 3 Summary GRADE table for symptoms and signs individually

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
Urinary symptoms (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	0.08 (0.06, 0.1)	0.98 (0.98, 0.98)	LR+ 4.38 (3.21, 5.97)	The presence of urinary symptoms leads to a **moderate increase** in the probability of having a UTI, (95% CI ranges from moderate to large increase).	Low
					LR- 0.94 (0.92, 0.96)	The absence of urinary symptoms **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
Dysuria (pooled < 14 years)							
9 [a]	Prospective - cross sectional Retrospective - cohort	5813	0.32 (0.14, 0.58)	0.89 (0.79, 0.94)	LR+ 2.87 (1.75, 4.32)	The presence of dysuria leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase).	Very low
					LR- 0.76 (0.52, 0.93)	The absence of dysuria **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Very low
Dysuria (pooled < 2 years)							
7 [b]	Prospective - cross sectional Retrospective - cohort	3000	0.24 (0.08, 0.53)	0.91 (0.80, 0.96)	LR+ 2.62 (1.36, 4.44)	The presence of dysuria leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase).	Very low
					LR- 0.82 (0.57, 0.97)	The absence of dysuria **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Very low
Dysuria (2 to < 5 years)							

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
1 (Hay 2016)	Prospective - cross sectional	2740	0.55 (0.41, 0.67)	0.88 (0.86, 0.89)	LR+ 4.42 (3.41, 5.75)	The presence of dysuria leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from moderate to large increase).	High
					LR- 0.52 (0.39, 0.69)	The absence of dysuria **does not meaningfully alter** the probability of having a UTI (95% CI ranges from slight to moderate decrease).	Moderate
Dysuria (< 14 years)							
1 (Dobbs and Fleming 1987)	Prospective - cross sectional	75	0.75 (0.49, 0.9)	0.71 (0.58, 0.81)	LR+ 2.6 (1.59, 4.25)	The presence of dysuria leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase).	Very low
					LR- 0.35 (0.15, 0.83)	The absence of dysuria leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from slight to large decrease).	Very low
Frequency (pooled < 14 years)							
6 [c]	Prospective - cross sectional Retrospective - cohort	6068	0.26 (0.13, 0.46)	0.87 (0.74, 0.94)	LR+ 2.02 (1.42, 2.81)	The presence of frequency leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase).	Very low
					LR- 0.84 (0.70, 0.94)	The absence of frequency **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Very low
Frequency (pooled < 2 years)							
4 (O'Brien 2013, Lizama 2005, Pylkkanen 1979, Ibeneme 2014)	Prospective - cross sectional Retrospective - cohort	2139	0.22 (0.16, 0.31)	0.90 (0.82, 0.95)	LR+ 1.77 (1.02, 3.05)	The presence of frequency **does not meaningfully alter** the probability of having a UTI (95% CI ranges from slight to moderate increase).	Very low
					LR- 0.93 (0.84, 1.02)	The absence of frequency **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Frequency (< 5 years)							

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
1 (Hay 20160	Prospective - cross sectional	3856	0.44 (0.34, 0.55)	0.78 (0.76, 0.79)	LR+ 1.99 (1.53, 2.57)	The presence of frequency **does not meaningfully alter** the probability of having a UTI (95% CI ranges from slight to moderate increase).	Moderate
					LR- 0.72 (0.59, 0.88)	The absence of frequency **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
Frequency (< 14 years)							
1 (Dobbs and Fleming 1987)	Prospective - cross sectional	75	0.63 (0.38, 0.82)	0.71 (0.58, 0.81)	LR+ 2.17 (1.25, 3.77)	The presence of frequency leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase).	Very low
					LR- 0.53 (0.27, 1.01)	The absence of frequency **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Bed wetting (pooled < 14 years)							
4 (Hay 2016, O'Brien 2013, Dobbs and Fleming 1987 and Pylkkanen 1979)	Prospective - cross sectional	5636	0.15 (0.09, 0.25)	0.93 (0.88, 0.97)	LR+ 2.86 (1.81, 4.53)	The presence of bed wetting leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase).	Moderate
					LR- 0.92 (0.88, 0.96)	The absence of bed wetting **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Very low
Bed wetting (pooled < 2 years)							
2 (O'Brien 2013 and Pylkkanen 1979)	Prospective - cross sectional	797	0.10 (0.05, 0.16)	0.95 (0.92, 0.96)	LR+ 2.53 (1.18, 5.39)	The presence of bed wetting leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to large increase).	Moderate
					LR- 0.94 (0.89, 1.00)	The absence of bed wetting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Bed wetting (< 5 years)							

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
1 (Hay 2016)	Prospective - cross sectional	4764	0.17 (0.11, 0.26)	0.96 (0.95, 0.96)	LR+ 4.03 (2.53, 6.44)	The presence of bed wetting leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from moderate to large increase).	High
					LR- 0.87 (0.79, 0.95)	The absence of bed wetting **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
Bed wetting (< 14 years)							
1 (Dobbs and Fleming 1987)	Prospective - cross sectional	75	0.31 (0.14, 0.57)	0.8 (0.68, 0.88)	LR+ 1.54 (0.63, 3.72)	The presence of bed wetting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.86 (0.61, 1.23)	The absence of bed wetting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0range).	Very low
Urgency (pooled < 14 years)							
2 (Dobbs and Fleming 1987 and Ibeneme 2014)	Prospective - cross sectional	275	0.10 (0.01, 0.52)	0.97 (0.48, 1.00)	LR+ 1.40 (0.50, 3.96)	The presence of urgency **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.98 (0.93, 1.05)	The absence of urgency **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Urgency (< 5 years)							
1 (Ibenem e 2014)	Prospective - cross sectional	200	0.02 (0, 0.27)	0.99 (0.96, 1.0)	LR+ 2.59 (0.11, 61.82)	The presence of urgency **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Low
					LR- 0.99 (0.93, 1.05)	The absence of urgency **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Urgency (< 14 years)							
1 (Dobbs and Fleming 1987)	Prospective - cross sectional	75	0.19 (0.06, 0.45)	0.85 (0.73, 0.92)	LR+ 1.23 (0.38, 4.02)	The presence of urgency **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.96 (0.74, 1.24)	The absence of urgency **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Oliguria (≤ 3 months)							

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
1 (Newman 2002)	Prospective - cross sectional	1666	0.18 (0.13, 0.25)	0.85 (0.83, 0.87)	LR+ 1.23 (0.85, 1.77)	The presence of oliguria **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 0.96 (0.90, 1.04)	The absence of oliguria **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Haematuria (pooled < 14 years) Note: *unclear if blood was visible or on dipstick in all studies*							
4 (Hay 2016, Dobbs and Fleming 1987, Lizama 2005 and Pylkkanen 1979)	Prospective - cross sectional Retrospective - cohort	5815	0.05 (0.03, 0.07)	0.99 (0.96, 1.00)	LR+ 3.02 (1.68, 5.43)	The presence of haematuria leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to large increase).	Very low
					LR- 0.97 (0.95, 0.99)	The absence of haematuria **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
Haematuria (pooled < 2 years) Note: *unclear if blood was visible or on dipstick in all studies*							
2 (Lizama 2005 and Pylkkanen 1979)	Prospective - cross sectional Retrospective - cohort	1340	0.05 (0.03, 0.08)	0.98 (0.97, 0.99)	LR+ 2.57 (1.33, 4.99)	The presence of haematuria leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase).	Very low
					LR- 0.97 (0.94, 0.99)	The absence of haematuria **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
Haematuria (< 5 years) Note: *unclear if blood was visible or on dipstick in all studies*							
1 (Hay 2016)	Prospective - cross sectional	4400	0.02 (0.01, 0.09)	1.0 (0.99, 1.0)	LR+ 6.13 (1.43, 26.24)	The presence of haematuria leads to a **large increase** in the probability of having a UTI (95% CI ranges from slight to very large increase).	Moderate
					LR- 0.98 (0.95, 1.01)	The absence of haematuria **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Haematuria (< 14 years) Note: *unclear if blood was visible or on dipstick in all studies*							
1 (Dobbs	Prospective - cross sectional	75	0.06 (0.01, 0.34)	0.98 (0.89, 1.0)	LR+ 3.69 (0.24, 55.76)	The presence of haematuria **does not meaningfully alter** l the probability of having a UTI (95% CI crosses 1.0).	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
and Fleming 1987)					LR- 0.95 (0.84, 1.09)	The absence of haematuria **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Cloudy urine (pooled < 5 years)							
2 (Hay 2016, Kartika 2006)	Prospective - cross sectional	2717	0.39 (0.02, 0.95)	0.91 (0.75, 0.97)	LR+ 3.51 (1.50, 8.25)	The presence of cloudy urine leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from a slight to large increase).	Very low
					LR- 0.50 (0.14, 1.79)	The absence of cloudy urine **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Cloudy urine (2 to < 5 years)							
1 (Hay 2016)	Prospective - cross sectional	2512	0.10 (0.04, 0.22)	0.95 (0.94, 0.96)	LR+ 2.09 (0.89, 4.88)	The presence of cloudy urine **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Low
					LR- 0.95 (0.86, 1.04)	The absence of cloudy urine **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Cloudy urine (< 5 years)							
1 (Kartika 2006)	Prospective - cross sectional	205	0.78 (0.68, 0.86)	0.85 (0.77, 0.9)	LR+ 5.05 (3.29, 7.76)	The presence of cloudy urine leads to a **large increase** in the probability of having a UTI (95% CI ranges from a moderate to large increase).	Low
					LR- 0.26 (0.17, 0.39)	The absence of cloudy urine leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from large to moderate decrease).	Low
Darker urine (< 2 years)							
1 (Hay 2016)	Prospective - cross sectional	2277	0.22 (0.09, 0.43)	0.95 (0.94, 0.95)	LR+ 3.81 (1.82, 7.96)	The presence of darker urine leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to large increase).	Moderate
					LR- 0.84 (0.71, 1.01)	The absence of darker urine **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Malodorous urine (pooled < 14 years)							
5 [d]	Prospective - cross sectional	5735	0.33 (0.13, 0.63)	0.86 (0.57, 0.96)	LR+ 2.55 (1.14, 5.45)	The presence of malodorous urine leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to large increase).	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
					LR- 0.78 (0.55, 0.95)	The absence of malodorous urine **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Very low
Malodorous urine (pooled < 2 years)							
3 (Gauthier 2012, Pylkkanen 1979, Struthers 2003)	Prospective - cross sectional	643	0.28 (0.04, 0.77)	0.70 (0.45, 0.86)	LR+ 1.49 (0.72, 3.08)	The presence of malodorous urine **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.86 (0.65, 1.15)	The absence of malodorous urine **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Malodorous urine (< 5 years)							
1 (Hay 2016)	Prospective - cross sectional	5017	0.54 (0.44, 0.63)	0.85 (0.84, 0.86)	LR+ 3.71 (3.06, 4.50)	The presence of malodorous urine leads to a **moderate increase** in the probability of having a UTI (95% CI within this range).	High
					LR- 0.54 (0.44, 0.67)	The absence of malodorous urine **does not meaningfully alter** the probability of having a UTI (95% CI ranges from moderate to slight decrease).	Moderate
Malodorous urine (< 14 years)							
1 (Dobbs and Fleming 1987)	Prospective - cross sectional	75	0.13 (0.03, 0.39)	0.92 (0.81, 0.96)	LR+ 1.48 (0.31, 6.91)	The presence of malodorous urine **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.96 (0.78, 1.17)	The absence of malodorous urine **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
No diaper rash (< 2 years)							
1 (Hay 2016)	Prospective - cross sectional	2277	0.96 (0.75, 0.99)	0.25 (0.23, 0.27)	LR+ 1.29 (1.20, 1.38)	The presence of diaper **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
					LR- 0.13 (0.02, 0.92)	The absence of diaper rash leads to a **large decrease** in the probability of having a UTI (95% CI ranges very large to slight decrease).	Moderate
Suprapubic tenderness (< 5 years)							

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
1 (Hay 2016)	Prospective - cross sectional	4199	0.06 (0.02, 0.14)	0.99 (0.99, 1.00)	LR+ 7.94 (3.18, 19.86)	The presence of suprapubic tenderness leads to a **large increase** in the probability of having a UTI (95% CI ranges from a moderate to very large increase).	High
					LR- 0.95 (0.89, 1.00)	The absence of suprapubic tenderness **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Loin tenderness (2 to < 5 years)							
1 (Hay 2016)	Prospective - cross sectional	2300	0.02 (0, 0.14)	1.00 (1.00, 1.00)	LR+ 16.63 (3.30, 83.86)	The presence of loin tenderness leads to a **very large increase** in the probability of having a UTI (95% CI ranges from a moderate to very large increase).	High
					LR- 0.97 (0.92, 1.02)	The absence of loin tenderness **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Renal angle tenderness (< 5 years)							
1 (Ibenem e 2014)	Prospective - cross sectional	200	0.07 (0.01, 0.27)	1.00 (0.96, 1.00)	LR+ 23.35 (0.98, 556.42)	The presence of renal angle tenderness **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Low
					LR- 0.94 (0.84, 1.05)	The absence of renal angle tenderness **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Flank pain (< 2 years)							
1 (Festo 2011)	Prospective - cross sectional	373	0.14 (0.09, 0.21)	0.79 (0.74, 0.84)	LR+ 0.69 (0.43, 1.12)	The presence of flank pain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 1.08 (0.98, 1.18)	The absence of flank pain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Back pain (< 2 years)							
1 (Pylkkan en 1979)	Prospective - cross sectional	200	0.02 (0.01, 0.07)	0.99 (0.91, 1)	LR+ 1.72 (0.18, 16.28)	The presence of back pain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.99 (0.95, 1.03)	The absence of back pain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Vomiting (pooled < 5 years)							

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
9 [e]	Prospective - cross sectional Retrospective - cohort	9635	0.24 (0.15, 0.36)	0.72 (0.63, 0.79)	LR+ 0.85 (0.68, 1.03)	The presence of vomiting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 1.06 (0.99, 1.11)	The absence of vomiting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Vomiting (pooled < 2 years)							
8 [f]	Prospective - cross sectional Retrospective - cohort	4623	0.23 (0.14, 0.37)	0.72 (0.62, 0.81)	LR+ 0.84 (0.65, 1.04)	The presence of vomiting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 1.06 (0.98, 1.12)	The absence of vomiting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Vomiting (< 5 years)							
1 (Hay 2016)	Prospective - cross sectional	5012	0.32 (0.24, 0.42)	0.67 (0.65, 0.68)	LR+ 0.96 (0.72, 1.28)	The presence of vomiting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 1.02 (0.89, 1.17)	The absence of vomiting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Nausea (< 14 years)							
1 (Dobbs and Fleming 1987)	Prospective - cross sectional	75	0.06 (0.01, 0.34)	0.8 (0.68, 0.88)	LR+ 0.31 (0.04, 2.19)	The presence of nausea **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 1.18 (0.98. 1.41)	The absence of nausea **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Diarrhoea (pooled < 5 years)							
8 [g]	Prospective - cross sectional Retrospective - cohort	18753	0.19 (0.11, 0.31)	0.80 (0.71, 0.86)	LR+ 0.95 (0.67, 1.28)	The presence of diarrhoea **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 1.01 (0.92, 1.09)	The absence of diarrhoea **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Diarrhoea (pooled < 2 years)							
7 [h]	Prospective - cross sectional Retrospective - cohort	2952	0.18 (0.10, 0.30)	0.81 (0.73, 0.87)	LR+ 0.96 (0.68, 1.29)	The presence of diarrhoea **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 1.01 (0.92, 1.08)	The absence of diarrhoea **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
Diarrhoea (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	0.22 (0.18, 0.26)	0.74 (0.73, 0.75)	LR+ 0.83 (0.70, 0.99)	The presence of diarrhoea **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 1.06 (1.01, 1.11)	The absence of diarrhoea **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
Constipation (pooled < 5 years)							
2 (Hay 2016, Pylkkanen 1979)	Prospective - cross sectional	5212	0.05 (0.00, 0.80)	0.95 (0.41, 1.00)	LR+ 1.52 (1.10, 2.11)	The presence of constipation **does not meaningfully alter** the probability of having a UTI (95% CI ranges from slight to moderate increase).	Moderate
					LR- 0.96 (0.85, 1.08)	The absence of constipation **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Constipation (< 2 years)							
1 (Pylkkanen 1979)	Prospective - cross sectional	200	0 (0, 0.06)	0.99 (0.9, 1.0)	LR+ 0.57 (0.01, 28.22)	The presence of constipation **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 1.0 (0.98, 1.03)	The absence of constipation **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Constipation (< 5 years)							
1 (Hay 2016)	Prospective - cross sectional	5012	0.27 (0.19, 0.37)	0.82 (0.81, 0.83)	LR+ 1.52 (1.10, 2.11)	The presence of constipation **does not meaningfully alter** the probability of having a UTI (95% CI ranges from slight to moderate increase).	Moderate
					LR- 0.89 (0.79, 1.0)	The absence of constipation **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Abdominal pain (pooled < 5 years)							
8 [i]	Prospective - cross sectional Retrospective - cohort	5797	0.27 (0.14, 0.45)	0.83 (0.66, 0.93)	LR+ 1.70 (0.83, 3.22)	The presence of abdominal pain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.88 (0.70, 1.06)	The absence of abdominal pain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Abdominal pain (pooled < 2 years)							
7 [j]	Prospective - cross sectional	3056	0.29 (0.15, 0.50)	0.78 (0.62, 0.88)	LR+ 1.39 (0.70, 2.47)	The presence of abdominal pain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
	Retrospective - cohort				LR- 0.91 (0.68, 1.12)	The absence of abdominal pain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Abdominal pain (2 to < 5 years)							
1 (Hay 2016)	Prospective - cross sectional	2740	0.13 (0.06, 0.24)	0.98 (0.97, 0.98)	LR+ 6.45 (3.07, 13.54)	The presence of abdominal pain leads to a **large increase** in the probability of having a UTI (95% CI ranges from moderate to very large increase).	High
					LR- 0.89 (0.80, 0.98)	The absence of abdominal pain **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
Poor feeding (pooled < 5 years)							
3 (Hay 2016, Hoberman 1993 and O'Brien 2013)	Prospective - cross sectional	6025	0.69 (0.61, 0.76)	0.34 (0.22, 0.50)	LR+ 1.04 (0.85, 1.28)	The presence of poor feeding **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Low
					LR- 0.98 (0.68, 1.42)	The absence of poor feeding **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Low
Poor feeding (pooled < 2 years)							
2 (Hoberman 1993, O'Brien 2013)	Prospective - cross sectional	1013	0.67 (0.54, 0.78)	0.40 (0.31, 0.51)	LR+ 1.16 (0.93, 1.44)	The presence of poor feeding **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 0.80 (0.54, 1.17)	The absence of poor feeding **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Poor feeding (< 5 years)							
1 (Hay 2016)	Prospective - cross sectional	5012	0.7 (0.6, 0.78)	0.24 (0.23, 0.25)	LR+ 0.92 (0.81, 1.05)	The presence of poor feeding **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 1.24 (0.91, 1.68)	The absence of poor feeding **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Decreased feeding (≤ 3 months)							

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
1 (Newman 2002)	Prospective - cross sectional	1666	0.37 (0.30, 0.44)	0.63 (0.60, 0.65)	LR+ 0.98 (0.79, 1.21)	The presence of decreased feeding **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 1.01 (0.89, 1.15)	The absence of decreased feeding **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Poor weight gain (< 5 years)							
1(Hay 2016)	Prospective - cross sectional	3607	0.13 (0.07, 0.22)	0.85 (0.83, 0.86)	LR+ 0.81 (0.44, 1.5)	The presence of poor weight gain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 1.03 (0.95, 1.13)	The absence of poor weight gain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
No source of fever (pooled < 5 years)							
4 (Craig 2010, Hoberman 1993, Shaw 1998, Pylkkanen 1979)	Prospective - cross sectional	19476	0.67 (0.24, 0.93)	0.57 (0.12, 0.93)	LR+ 1.53 (0.63, 3.73)	The absence of a source of fever **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.55 (0.24, 1.24)	The presence of a source of fever **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
No source of fever (pooled < 2 years)							
3 (Hoberman 1993, Shaw 1998, Pylkkanen 1979)	Prospective - cross sectional	3675	0.50 (0.09, 0.91)	0.76 (0.53, 0.90)	LR+ 1.79 (0.72, 4.42)	The absence of a source of fever **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.52 (0.18, 1.51)	The presence of a source of fever **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
No source of fever (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	0.95 (0.92, 0.96)	0.08 (0.08, 0.09)	LR+ 1.03 (1.01, 1.05)	The absence of a source of fever **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
					LR- 0.66 (0.45, 0.96)	The presence of a source of fever **does not meaningfully alter** the probability of having a UTI (95% CI ranges from moderate to slight decrease).	Very low
No convulsions (pooled data only reported < 2 years)							
2 (Musa Aisien 2003, Pylkkanen 1979)	Prospective - cross sectional	500	0.96 (0.92, 0.98)	0.09 (0.05, 0.16)	LR+ 1.04 (0.98, 1.11)	The absence of convulsions **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.56 (0.19, 1.65)	The presence of convulsions **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
No bulging fontanelle (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	9339	1 (0.98, 1)	0 (0, 0)	LR+ 1.0 (1.0, 1.0)	The absence of bulging fontanelle **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 23.91 (0.48, 1203.31)	The presence of a bulging fontanelle **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
No respiratory symptoms (pooled < 5 years)							
2 (Craig 2010, Lizama 2005)	Prospective - cross sectional Retrospective - cohort	16941	0.64 (0.37, 0.84)	0.55 (0.20, 0.85)	LR+ 1.47 (0.94, 2.30)	The absence of respiratory symptoms **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.68 (0.62, 0.74)	The presence of respiratory symptoms **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
No respiratory symptoms (< 2 years)							
1 (Lizama 2005)	Retrospective - cohort	1140	0.76 (0.70, 0.81)	0.35 (0.32, 0.39)	LR+ 1.17 (1.08, 1.28)	The absence of respiratory symptoms **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.69 (0.54, 0.87)	The presence of respiratory symptoms **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
No respiratory symptoms (< 5 years)							

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
1 (Craig 2010)	Prospective - cross sectional	15801	0.51 (0.46, 0.55)	0.73 (0.72, 0.73)	LR+ 1.85 (1.69, 2.03)	The absence of respiratory symptoms **does not meaningfully alter** the probability of having a UTI (95% CI ranges from slight to moderate increase).	Very low
					LR- 0.68 (0.62, 0.74)	The presence of respiratory symptoms **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
No cough (pooled < 5 years)							
4 (Hay 2016, Craig 2010, Newman 2002, Verbakel 2016)	Prospective - cross sectional	20946	0.69 (0.48, 0.85)	0.33 (0.19, 0.51)	LR+ 1.22 (0.92, 1.62)	The absence of cough **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.75 (0.54, 1.03)	The presence of cough **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
No cough (pooled < 2 years)							
2 (Newman 2002, Verbakel 2015)	Prospective - cross sectional	2405	0.93 (0.08, 1.00)	0.11 (0.00, 0.88)	LR+ 1.01 (1.00, 1.02)	The absence of cough **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 0.93 (0.74, 1.18)	The presence of cough **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
No cough (2 to < 5 years)							
1 (Hay 2016)	Prospective - cross sectional	2740	0.40 (0.28, 0.53)	0.72 (0.70, 0.73)	LR+ 1.41 (1.02, 1.96)	The absence of cough **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
					LR- 0.84 (0.67, 1.04)	The presence of cough **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
No cough (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	0.69 (0.64, 0.73)	0.55 (0.54, 0.56)	LR+ 1.52 (1.43, 1.62)	The absence of cough **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.57 (0.50, 0.65)	The presence of cough **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
No breathing difficulty (pooled < 5 years)							
2 (Craig 2010, Newman 2002)	Prospective - cross sectional	17467	0.94 (0.91, 0.95)	0.13 (0.13, 0.14)	LR+ 1.08 (1.06, 1.11)	The absence of breathing difficulties **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.47 (0.35, 0.64)	The presence of breathing difficulties leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from moderate to slight decrease).	Very low
No breathing difficulty (≤ 3 months)							
1 (Newman 2002)	Prospective - cross sectional	1666	0.93 (0.88, 0.96)	0.14 (0.12, 0.16)	LR+ 1.09 (1.04, 1.14)	The absence of breathing difficulties **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
					LR- 0.47 (0.26, 0.84)	The presence of breathing difficulties leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from moderate to slight decrease).	Moderate
No breathing difficulty (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	0.94 (0.91, 0.96)	0.13 (0.13, 0.14)	LR+ 1.08 (1.05, 1.11)	The absence of breathing difficulties **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.47 (0.33, 0.67)	The presence of breathing difficulties leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from moderate to slight decrease).	Very low
No chest crackles (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	0.96 (0.94, 0.98)	0.08 (0.08, 0.09)	LR+ 1.05 (1.03, 1.07)	The absence of chest crackles **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.45 (0.28, 0.71)	The presence of chest crackles leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from moderate to slight decrease).	Very low
No abnormal chest sounds (< 5 years)							

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
2 (Craig 2010, Newman 2002)	Prospective - cross sectional	17467	0.96 (0.86, 0.99)	0.09 (0.02, 0.28)	LR+ 1.07 (0.99, 1.15)	The absence of abnormal chest sounds **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.43 (0.31, 0.59)	The presence of abnormal chest sounds leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from moderate to slight decrease).	Very low
No abnormal chest sounds (≤ 3 months)							
1 (Newman 2002)	Prospective - cross sectional	1666	0.98 (0.95, 0.99)	0.05 (0.04, 0.06)	LR+ 1.03 (1.01, 1.05)	The absence of abnormal chest sounds **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
					LR- 0.40 (0.13, 1.24)	The presence of abnormal chest sounds **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Low
No abnormal chest sounds (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	0.93 (0.9, 0.95)	0.16 (0.16, 0.17)	LR+ 1.11 (1.08, 1.14)	The absence of abnormal chest sounds **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.43 (0.31, 0.60)	The presence of abnormal chest sounds leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from moderate to slight decrease).	Very low
No stridor (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	1 (0.99, 1)	0.01 (0.01, 0.01)	LR+ 1.01 (1.01, 1.01)	The absence of stridor **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.17 (0.02, 1.22)	The presence of stridor **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
No wheezing (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	0.99 (0.97, 0.99)	0.06 (0.06, 0.07)	LR+ 1.05 (1.04, 1.06)	The absence of wheezing **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.24 (0.11, 0.49)	The presence of wheezing leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from large to moderate decrease).	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
Normal ENT (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	0.63 (0.59, 0.68)	0.55 (0.54, 0.56)	LR+ 1.4 (1.3, 1.5)	Normal ENT **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.67 (0.59, 0.75)	Abnormal ENT **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
Normal ear examination (2 to <5 years)							
1 (Hay 2016)	Prospective - cross sectional	2740	0.93 (0.82, 0.97)	0.23 (0.22, 0.25)	LR+ 1.21 (1.12, 1.31)	Normal ear exam **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
					LR- 0.31 (0.12, 0.8)	Abnormal ear exam leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from large to slight decrease).	Moderate
Normal tympanic membranes (≤ 3 months)							
1 (Newman 2002)	Prospective - cross sectional	1666	0.96 (0.92, 0.98)	0.01 (0, 0.01)	LR+ 0.97 (0.94, 1.0)	Normal tympanic membranes **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 4.93 (1.85, 13.15)	Abnormal tympanic membranes leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to very large increase).	Moderate
No runny nose (≤ 3 months)							
1 (Newman 2002)	Prospective - cross sectional	1666	0.95 (0.91, 0.98)	0.10 (0.09, 0.12)	LR+ 1.06 (1.02, 1.1)	The absence of a runny nose **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
					LR- 0.47 (0.23, 0.93)	The presence of a runny nose leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from moderate to slight decrease).	Moderate
Previous UTI (pooled < 15 years)							
6 [k]	Prospective - cross sectional	5860	0.18 (0.11, 0.29)	0.92 (0.85, 0.96)	LR+ 2.40 (1.63, 3.46)	Prior UTI leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase).	Very low
					LR- 0.88 (0.81, 0.94)	The absence of prior UTI **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
Previous UTI (pooled < 2 years)							

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
3 (Shaw 1998, Kanegaye 2014, Gauthier 2012)	Prospective - cross sectional	4462	0.13 (0.06, 0.27)	0.95 (0.86, 0.98)	LR+ 2.45 (1.60, 3.77)	Prior UTI leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase).	Very low
					LR- 0.95 (0.93, 0.98)	The absence of prior UTI **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
Previous UTI (2 to < 5 years)							
1 (Hay 2016)	Prospective - cross sectional	2740	0.2 (0.11, 0.33)	0.94 (0.93, 0.95)	LR+ 3.2 (1.85, 5.53)	Prior UTI leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to large increase).	Moderate
					LR- 0.85 (0.75, 0.97)	The absence of prior UTI **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
Previous UTI (pooled < 15 years)							
2 (Dobbs and Fleming 1987, Mitiku 2018)	Prospective - cross sectional	344	0.22 (0.04, 0.67)	0.88 (0.65, 0.96)	LR+ 1.72 (0.98, 3.02)	Prior UTI **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.91 (0.72, 1.16)	The absence of prior UTI **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Low
Abnormal general appearance (pooled < 5 years)							
3 (Hay 2016, Craig 2010, Shaw 1998)	Prospective - cross sectional	23124	0.48 (0.27, 0.70)	0.62 (0.39, 0.81)	LR+ 1.26 (0.96, 1.64)	Abnormal general appearance **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.85 (0.72, 1.00)	Normal general appearance **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Abnormal general appearance (< 2 years)							
1 (Shaw 1998)	Prospective - cross sectional	2331	0.49 (0.37, 0.6)	0.72 (0.7, 0.73)	LR+ 1.71 (1.33, 2.19)	Abnormal general appearance **does not meaningfully alter** the probability of having a UTI (95% CI ranges from slight to moderate increase).	Moderate

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
					LR- 0.72 (0.57, 0.9)	Normal general appearance **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
Abnormal general appearance (pooled < 5 years)							
2 (Hay 2016, Craig 2010)	Prospective - cross sectional	20793	0.48 (0.17, 0.80)	0.57 (0.28, 0.82)	LR+ 1.13 (1.06, 1.20)	Abnormal general appearance **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.90 (0.75, 1.07)	Normal general appearance **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Initial appearance (moderately or very ill) (≤ 3 months)							
1 (Newman 2002)	Prospective - cross sectional	1666	0.39 (0.31, 0.46)	0.64 (0.62, 0.67)	LR+ 1.08 (0.88, 1.33)	Initial appearance being moderate or very ill **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 0.95 (0.84, 1.09)	Initial appearance not being moderate or very ill **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Irritability (pooled data only reported < 2 years)							
5 [l]	Prospective - cross sectional	2411	0.28 (0.05, 0.77)	0.75 (0.36, 0.94)	LR+ 1.11 (0.72, 1.44)	The presence of irritability **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 0.92 (0.63, 1.04)	The absence of irritability **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Shivering/chills (pooled < 5 years)							
1 (Hay 2016, Williams-Smith 2020)	Prospective – cross sectional	5186	0.24 (0.14, 0.39)	0.87 (0.49, 0.98)	LR+ 1.78 (0.57, 5.63)	The presence of shivering/chills **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0)	Very low
					LR- 0.92 (0.83, 1.02)	The absence of shivering/chills **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0)	Very low
Shivering or chills (< 5 years)							
1 (Hay 2016)	Prospective - cross sectional	5012	0.3 (0.22, 0.39)	0.73 (0.71, 0.74)	LR+ 1.09 (0.8, 1.47)	The presence of shivering **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 0.97 (0.85, 1.1)	The absence of shivering **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
Chills (< 2 years) (grouped with shivering above in pooled analysis)							
1 (Williams-Smith 2020)	Prospective - cross sectional	173	0.17 (0.09, 0.31)	0.95 (0.9, 0.98)	LR+ 3.57 (1.31, 9.76)	The presence of chills leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to large increase).	Very low
					LR- 0.87 (0.76, 1.00)	The absence of chills **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Dehydrated (≤ 3 months)							
1 (Newman 2002)	Prospective - cross sectional	1666	0.05 (0.03, 0.1)	0.92 (0.91, 0.93)	LR+ 0.68 (0.35, 1.32)	The presence of dehydration **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 1.03 (0.99, 1.07)	The absence of dehydration **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Not alert (≤ 3 months)							
1 (Newman 2002)	Prospective - cross sectional	1666	0.19 (0.13, 0.25)	0.76 (0.74, 0.78)	LR+ 0.77 (0.56, 1.08)	Being not alert **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 1.07 (0.99, 1.16)	Being alert **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Pale colour (≤ 3 months)							
1 (Newman 2002)	Prospective - cross sectional	1666	0.1 (0.06, 0.16)	0.91 (0.89, 0.92)	LR+ 1.12 (0.7, 1.81)	The presence of pale colour **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 0.99 (0.94, 1.04)	The absence of pale colour **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Capillary refill time > 3 seconds (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	0.01 (0.01, 0.03)	1 (1, 1)	LR+ 4.85 (2.07, 11.38)	Capillary refill time >3 seconds leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from moderate to very large increase).	Low
					LR- 0.99 (0.98, 1.00)	Capillary refill time ≤3 seconds **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Capillary refill time ≥ 2 seconds (< 2 years)							
1 (William	Prospective - cross sectional	173	0.34 (0.22, 0.49)	0.79 (0.71, 0.86)	LR+ 1.65 (0.98, 2.79)	Capillary refill time ≥2 seconds **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
s-Smith 2020)					LR- 0.83 (0.66, 1.04)	Capillary refill time <2 seconds **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Elevated heart rate (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	0.51 (0.47, 0.56)	0.58 (0.57, 0.59)	LR+ 1.22 (1.12, 1.33)	The presence of an elevated heart rate **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.84 (0.77, 0.92)	The absence of an elevated heart rate **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
Jaundice (< 5 years)							
1 (Musa Aisien 2003)	Prospective - cross sectional	300	0.04 (0.01, 0.22)	0.98 (0.96, 0.99)	LR+ 2.02 (0.25, 16.68)	The presence of jaundice **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.98 (0.91, 1.06)	The absence of jaundice **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
No fluid intake (< 5 years)							
1 (Craig 2010)	Prospective - cross sectional	15801	0.01 (0.01, 0.03)	1 (1, 1)	LR+ 4.31 (1.85, 10.06)	The absence of fluid intake leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to very large increase).	Very low
					LR- 0.99 (0.98, 1.00)	The presence of fluid intake **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Fever duration > 24 hours (≤ 3 months)							
1 (Newman 2002)	Prospective - cross sectional	1666	0.19 (0.14, 0.26)	0.9 (0.88, 0.91)	LR+ 1.88 (1.33, 2.65)	The presence of fever duration >24 hours **does not meaningfully alter** the probability of having a UTI (95% CI ranges from slight to moderate increase).	Moderate
					LR- 0.9 (0.83, 0.97)	The absence of fever duration >24 hours **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
Fever duration > 48 hours (< 2 years)							
1 (William	Prospective - cross sectional	173	0.23 (0.13, 0.38)	0.90 (0.84, 0.95)	LR+ 2.46 (1.16, 5.18)	The presence of fever duration >48 hours leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to large increase).	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
s-Smith 2020)					LR- 0.85 (0.72, 1.00)	The absence of fever duration >48 hours **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Fever duration > 72 hours (< 2 years)							
1 (Gauthier 2012)	Prospective - cross sectional	330	0.48 (0.35, 0.62)	0.64 (0.58, 0.69)	LR+ 1.34 (0.96, 1.85)	The presence of fever duration >72 hours **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.81 (0.61, 1.07)	The absence of fever duration >72 hours **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Fever duration > 5 days (< 5 years)							
1 (Festo 2011)	Prospective - cross sectional	370	0.43 (0.35, 0.51)	0.68 (0.62, 0.74)	LR+ 1.33 (1.02, 1.74)	The presence of fever duration >5 days **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
					LR- 0.84 (0.72, 1.00)	The absence of fever duration >5 days **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Fever duration > 1 week (pooled < 5 years)							
2 (Musa Aisien 2003, Ibeneme 2014)	Prospective - cross sectional	500	0.51 (0.12, 0.88)	0.80 (0.76, 0.83)	LR+ 2.33 (0.87, 6.29)	The presence of fever duration >1 week **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.57 (0.21, 1.57)	The absence of fever duration >1 week **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Degree of fever (≥ 39°C) (pooled < 5 years)							
8 [m]	Prospective – cross sectional Retrospective - cohort	7726	0.55 (0.38, 0.72)	0.64 (0.48, 0.77)	LR+ 1.54 (1.07, 2.18)	The presence of fever ≥39°C **does not meaningfully alter** the probability of having a UTI (95% CI ranges from slight to moderate increase).	Very low
					LR- 0.71 (0.49, 0.95)	The absence of fever ≥39°C **does not meaningfully alter** the probability of having a UTI (95% CI ranges from moderate to slight decrease).	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
Degree of fever (≥39°C) (pooled < 2 years)							
7 [n]	Prospective – cross sectional Retrospective - cohort	6478	0.57 (0.37, 0.75)	0.62 (0.45, 0.77)	LR+ 1.53 (1.00, 2.28)	The presence of fever ≥39°C **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.70 (0.44, 1.00)	The absence of fever ≥39°**C does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Degree of fever (≥39°C) (< 5 years)							
1 (Duong 2016)	Prospective – cross sectional	1247	0.45 (0.38, 0.51)	0.73 (0.70, 0.76)	LR+ 1.67 (1.4, 2.00)	The presence of fever **does not meaningfully alter** the probability of having a UTI (95% CI ranges from slight to moderate increase).	Moderate
					LR- 0.75 (0.67, 0.85)	The absence of fever ≥39°**C does not meaningfully alter** the probability of having a UTI (95% CI within this range).	High
Tachypnoea (< 2 years)							
1 (Williams-Smith 2020)	Prospective – cross sectional	173	0.3 (0.19, 0.44)	0.82 (0.74, 0.88)	LR+ 1.63 (0.92, 2.9)	The presence of tachypnoea **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.86 (0.7, 1.05)	The absence of tachypnoea **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Tachycardia (< 2 years)							
1 (Williams-Smith 2020)	Prospective – cross sectional	173	0.32 (0.2, 0.46)	0.75 (0.67, 0.82)	LR+ 1.3 (0.77, 2.18)	The presence of tachycardia **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.9 (0.72, 1.12)	The absence of tachycardia **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Cyanosis (< 2 years)							
1 (Williams-Smith 2020)	Prospective – cross sectional	173	0.01 (0, 0.15)	0.99 (0.94, 1)	LR+ 0.88 (0.04, 21.28)	The presence of cyanosis **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 1 (0.97, 1.04)	The absence of cyanosis **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Altered consciousness (< 2 years)							
1 (William	Prospective – cross sectional	173	0.01 (0, 0.15)	0.98 (0.93, 0.99)	LR+ 0.53 (0.03, 10.82)	The presence of altered consciousness **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
s-Smith 2020)					LR- 1.01 (0.97, 1.05)	The absence of altered consciousness **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Purpura (< 2 years)							
1 (William s-Smith 2020)	Prospective – cross sectional	173	0.01 (0, 0.15)	1 (0.94, 1)	LR+ 2.65 (0.05, 131.48)	The presence of purpura **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.99 (0.96, 1.02)	The absence of purpura **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Grunting (< 2 years)							
1 (William s-Smith 2020)	Prospective – cross sectional	173	0.06 (0.02, 0.18)	0.96 (0.91, 0.98)	LR+ 1.61 (0.4, 6.47)	The presence of grunting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 0.97 (0.9, 1.06)	The absence of grunting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Failure to thrive (< 5 years)							
1 (Festo 2011)	Prospective - cross sectional	370	0.01 (0, 0.05)	0.99 (0.96, 1)	LR+ 1.5 (0.21, 10.53)	The presence of failure to thrive **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Low
					LR- 1 (0.97, 1.02)	The absence of failure to thrive **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Increased sleepiness (≤ 3 months)							
1 (Newma n 2002)	Prospective - cross sectional	1666	0.34 (0.27, 0.41)	0.7 (0.68, 0.72)	LR+ 1.12 (0.89, 1.41)	The presence of increased sleepiness **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 0.95 (0.85, 1.06)	The absence of increased sleepiness **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Decreased social interaction (≤ 3 months)							
1 (Newma n 2002)	Prospective - cross sectional	1666	0.23 (0.17, 0.3)	0.74 (0.71, 0.76)	LR+ 0.87 (0.65, 1.17)	The presence of decreased social interaction **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
					LR- 1.05 (0.96, 1.14)	The absence of decreased social interaction **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Decreased activity (≤ 3 months)							
1 (Newman 2002)	Prospective - cross sectional	1666	0.17 (0.12, 0.24)	0.82 (0.8, 0.83)	LR+ 0.94 (0.66, 1.34)	The presence of decreased activity **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
					LR- 1.01 (0.94, 1.09)	The absence of decreased activity **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Moderate
Symptoms for 9 days or less (< 14 years)							
1 (Dobbs and Fleming 1987)	Prospective - cross sectional	75	0.94 (0.66, 0.99)	0.34 (0.23, 0.47)	LR+ 1.42 (1.14, 1.77)	The presence of symptoms for 9 days or less **does not meaningfully alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.18 (0.03, 1.27)	The absence of symptoms for 9 days or less **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Fever alone (< 2 years)							
1 (Pylkkanen 1979)	Prospective - cross sectional	200	0.1 (0.06, 0.17)	0.88 (0.78, 0.93)	LR+ 0.83 (0.37, 1.85)	The presence of fever alone **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
					LR- 1.02 (0.92, 1.14)	The absence of fever alone **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Very low
Muscle aches or pains (< 5 years)							
1 (O'Brien 2013)	Prospective - cross sectional	597	0.01 (0, 0.19)	0.9 (0.87, 0.92)	LR+ 0.14 (0.01, 2.23)	The presence of muscle aches/pains **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0).	Low
					LR- 1.09 (1.04, 1.15)	The absence of muscle aches/pains **does not alter** the probability of having a UTI (95% CI within this range).	High

References

a. Hay 2016, O'Brien 2013, Gauthier 2012, Msaki 2012, Dobbs and Fleming 1987, Lizama 2005, Festo 2011, Pylkkanen 1979 and Ibeneme 2014
b. O'Brien 2013, Gauthier 2012, Msaki 2012, Lizama 2005, Festo 2011, Pylkkanen 1979, Ibeneme 2014
c. Hay 2016, O'Brien 2013, Dobbs and Fleming 1987, Lizama 2005, Pylkkanen 1979 and Ibeneme 2014
d. Hay 2016, Gauthier 2012, Dobbs and Fleming 1987, Pylkkanen 1979, Struthers 2003

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
e. Hay 2016, Musa Aisien 2003, Newman 2002, Gauthier 2012, Lizama 2005, Festo 2011, Pylkkanen 1979, Ibeneme 2014 and Hoberman 1993							
f. Musa Aisien 2003, Newman 2002, Gauthier 2012, Lizama 2005, Festo 2011, Pylkkanen 1979, Ibeneme 2014, Hoberman 1993							
g. Craig 2010, Musa Aisien 2003, Gauthier 2012, Lizama 2005, Festo 2011, Pylkkanen 1979, Ibeneme 2014 and Hoberman 1993							
h. Musa Aisien 2003, Gauthier 2012, Lizama 2005, Festo 2011, Pylkkanen 1979, Ibeneme 2014 and Hoberman 1993							
i. Hay 2016, Musa Aisien 2003, Verbakel 2015, Gauthier 2012, Msaki 2012, Lizama 2005, Pylkkanen 1979, Ibeneme 2014							
j. Musa Aisien 2003, Verbakel 2015, Gauthier 2012, Msaki 2012, Lizama 2005, Pylkkanen 1979, Ibeneme 2014							
k. Hay 2016, Shaw 1998, Kanegaye 2014, Gauthier 2012, Dobbs and Fleming 1987, Mitiku 2018							
l. O'Brien 2013, Musa Aisien 2003, Verbakel 2016, Festo 2011 and Hoberman 1993							
m. Williams-Smith 2020, Festo 2011, Newman 2002, Bonadio 1991, Duong 2016, Hoberman 1993, Msaki 2012 and Shaw 1998							
n. Williams-Smith 2020, Festo 2011, Newman 2002, Bonadio 1991, Hoberman 1993, Msaki 2012, Shaw 1998							

Table 4 Summary of the symptoms and signs likely to increase or decrease the likelihood of UTI in children based on evidence from the sensitivity analyses (i.e., without the Pylkkanen 1979).

The committee used this table in their discussions to help them compile the table of symptoms and signs which form part of the recommendations. The grey cells are symptoms and signs the committee decided not to include in their recommendations. See section 1.1.10.3 Benefits and harms for more information about the committee discussions and reasons for including or not including these factors in their recommendations. See summary GRADE Table 3 (main analyses) and Table 6 (sensitivity analyses) for more information about the results.

	Large increase in probability of UTI if present	Quality	Moderate increase in probability of UTI if present	Quality	Large decrease in probability of UTI if present	Quality	Moderate decrease in probability of UTI if present	Quality
<3 months			Abnormal tympanic membranes	Moderate			Runny nose present	Moderate
							Breathing difficulty present	Moderate
<2 years			Dysuria	Very low	Diaper rash	Moderate	Fever with source	Low
			Bed wetting	Moderate				
			Darker urine	Moderate				
			Previous UTI	Very low				
			Frequency	Very low				
			Haematuria	Very low				
<3 years			Chills	Very low				
			Fever duration >48 hours	Very low				
2 to <5 years	Loin tenderness	High	Dysuria	High			Abnormal ear examination	Moderate
			Abdominal pain	High				
			Previous UTI	Moderate				
<5 years	Haematuria	Moderate	Urinary symptoms	Low			Breathing difficulty present	Very low
	Suprapubic tenderness	High	Bed wetting	High			Abnormal chest sounds present	Very low
	Cloudy urine	Low	Malodorous urine	High			Wheezing present	Low
			Capillary refill >3 seconds	Low			Chest crackles present	Very low
			No fluid intake	Very low			Cloudy urine not present	Low
<14 years			Dysuria	Very low			Dysuria absent	Very low
			Frequency	Very low				
Pooled data								
			Dysuria (0-14 yrs)	Very low			Breathing difficulty present (0-5 yrs)	Very low
			Frequency (0-14 yrs)	Very low			Abnormal chest sounds present (0-5 yrs)	Very low
			Bed wetting (0-14 yrs)	Low			Fever with source (0-5 yrs)	Low
			Previous UTI (0-15 yrs)	Very low				
			Haematuria (0-14 yrs)	Very low				
			Cloudy urine (0-14 yrs)	Very low				

Table 5 Symptoms and signs with both positive and negative likelihood ratios that do not meaningfully alter the probability of UTI in children <16.

Results are taken from the sensitivity analysis removing Pylkkanen 1979. Where the point estimate value falls between 0.5 and 2 or if the 95% CI crosses 1.0 these factors were described as not meaningfully altering the probability of having a UTI. See summary GRADE Table 6 and Table 7 for more information about the results.

Symptom or sign (age group)	Quality for +/− LR	Symptom or sign	Quality for +/− LR
Oliguria (≤3 months)	Moderate/ moderate	Tachycardia (<2 years)	Very low/ very low
Fever duration >24 hours (≤3 months)	Moderate/ high	Elevated heart rate (<5 years)	Low/ low
Fever duration >72 hours (<2 years)	Very low/ very low	Altered consciousness (<2 years)	Very low/ very low
Fever duration >5 days (<5 years)	High/ moderate	Cyanosis (<2 years)	Very low/ very low
Fever duration >7 days (<5 years)	Very low/ very low	Capillary refill time ≥2 seconds (<2 years)	Very low/ very low
Normal ENT (<5 years)	Low/ low	Decreased activity (≤3 months)	Moderate/ moderate
Tachypnoea (<2 years)	Very low/ very low	Fever alone (<2 years)	Very low/ very low
Initial appearance (moderately or very ill) (≤3 months)	Moderate/ moderate	Grunting (<2 years)	Very low/ very low
Shivering/chills (< 5 years)	Very low/ very low	Urgency (<14 years, <5 years and <14 years)	Very low/ moderate
Shivering (< 5 years)	Moderate/ moderate	Irritability (<2 years)	Moderate/ very low
Dehydrated (≤3 months)	Moderate/ moderate	Fever ≥39°C (<5 years, <2 years)	Very low/ very low
Pale colour (≤3 months)	Moderate/ moderate	Fever ≥39°C (<5 years)	Moderate/ high
Not alert (≤3 months)	Moderate/ moderate	Abnormal general appearance (<5 years)	Very low/ very low
Flank pain (<2 years)	Moderate/ moderate	Abnormal general appearance (<2 years)	Moderate/ high
Back pain (<2 years)	Very low/ very low	Poor feeding (<5 years)	Low/ low
Decreased feeding (≤3 months)	Moderate/ moderate	Poor feeding (<2 years and <5 years)	Moderate/ moderate
Muscle aches or pains (<5 years)	Low/ high	No cough (<5 years)	Very low/ very low
Nausea (<14 years)	Very low/ very low	No cough (<2 years)	Moderate/ very low
Poor weight gain (<5 years)	Moderate/ moderate	No cough (2 to <5 years)	High/ moderate
Symptoms for 9 days or less (<14 years)	Low/ very low	No respiratory symptoms (<5 years)	Very low/ low
Decreased social interaction (≤3 months)	Moderate/ moderate	No respiratory symptoms (<2 years)	Low/ low

Failure to thrive (<5 years)	Low/ moderate	Vomiting (<5 years)	Very low/ very low
Increased sleepiness (≤3 months)	Moderate/ moderate	Vomiting (<2 years)	Moderate/ moderate
Diarrhoea (all ages, <2 years)	Very low/ very low	No convulsions (<2 years)	Very low/ very low
Diarrhoea (<5 years)	Low/ low	Constipation (<2 years)	Very low/ very low
Constipation (all ages)	Moderate/ very low	Constipation (<5 years)	Moderate/ moderate

Sensitivity analysis for symptoms and signs individually- summary GRADE table

When interpreting the LRs for the summary GRADE table the terminology used was taken from Table 14 in appendix M, with the exception of point estimate values that fall between 0.5 and 2 or if the 95% CI crosses 1.0. These were described as not meaningfully altering the probability of having a UTI. For context we have added information about whether the result or quality has changed from the main analysis. Interpretations or quality ratings that are highlighted yellow are where the analysis has moved from effect to no effect or from no effect to an effect, or where the quality of the evidence has changed.

Table 6 Summary GRADE table for symptoms and signs individually (sensitivity analysis removing Pylkkanen 1979 at committee request)

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation [compared to initial analysis]	Quality [compared to initial analysis]
Dysuria (pooled < 14 years)							
8 [a]	Prospective - cross sectional Retrospective - cohort	5615	0.31 (0.11, 0.61)	0.90 (0.81, 0.95)	LR+ 3.13 (1.87, 4.62)	The presence of dysuria leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase). [same interpretation]	Very low [same quality]
					LR- 0.75 (0.47, 0.94)	The absence of dysuria **does not meaningfully alter** the probability of having a UTI (95% CI ranges from moderate to slight decrease). [same interpretation]	Very low [same quality]
Dysuria (pooled < 2 years)							
6 [b]	Prospective - cross sectional Retrospective - cohort	2800	0.21 (0.06, 0.56)	0.92 (0.83, 0.97)	LR+ 2.86 (1.33, 4.94)	The presence of dysuria leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase). [same interpretation]	Very low [same quality]
					LR- 0.83 (0.52, 0.98)	The absence of dysuria **does not meaningfully alter** the probability of having a UTI (95% CI within this range). [same interpretation]	Very low [same quality]
Frequency (pooled < 14 years)							
5 [c]	Prospective - cross sectional	5870	0.27 (0.11, 0.53)	0.88 (0.73, 0.96)	LR+ 2.31 (1.82, 2.90)	The presence of frequency leads to a **moderate increase** in the probability of having a UTI (95% CI	Very low [same quality]

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation [compared to initial analysis]	Quality [compared to initial analysis]
	Retrospective - cohort					ranges from slight to moderate increase). [same interpretation]	
					LR- 0.82 (0.64, 0.94)	The absence of frequency **does not meaningfully alter** the probability of having a UTI (95% CI within this range). [same interpretation]	Very low [same quality]
Frequency (pooled < 2 years)							
3 (O'Brien 2013, Lizama 2005, Ibeneme 2014)	Prospective - cross sectional Retrospective - cohort	1939	0.20 (0.11, 0.36)	0.93 (0.86, 0.96)	LR+ 2.41 (1.81, 3.21)	The presence of frequency leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase). [is **did not meaningfully alter** in main analysis]	Very low [same quality]
					LR- 0.91 (0.81, 1.02)	The absence of frequency **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
Bed wetting (pooled < 14 years)							
3 (Hay 2016, O'Brien 2013, Dobbs and Fleming 1987)	Prospective - cross sectional	5436	0.18 (0.12, 0.27)	0.92 (0.85, 0.96)	LR+ 2.73 (1.52, 4.90)	The presence of bed wetting leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to moderate increase). [same interpretation]	Low [is moderate in main analysis]
					LR- 0.88 (0.82, 0.95)	The absence of bed wetting **does not meaningfully alter** the probability of having a UTI (95% CI within this range). [same interpretation]	High [is very low in main analysis]
Bed wetting (< 2 years)							
1 (O'Brien 2013)	Prospective - cross sectional	597	0.14 (0.06, 0.29)	0.94 (0.92, 0.96)	LR+ 2.43 (1.01, 5.87)	The presence of bed wetting leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to large increase). [same interpretation]	Moderate [same quality]
					LR- 0.91 (0.8, 1.04)	The absence of bed wetting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Moderate [is very low in main analysis]
Haematuria (pooled < 14 years) Note: *unclear if blood was visible or on dipstick in all studies*							

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation [compared to initial analysis]	Quality [compared to initial analysis]
3 (Hay 2016, Dobbs and Fleming 1987, Lizama 2005)	Prospective - cross sectional Retrospective - cohort	5615	0.04 (0.03, 0.07)	0.99 (0.97, 1.00)	LR+ 3.18 (1.68, 6.01)	The presence of haematuria leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to large increase). [same interpretation]	Very low [same quality]
					LR- 0.97 (0.95, 1.00)	The absence of haematuria **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [is low in main analysis]
Haematuria (< 2 years) Note: *unclear if blood was visible or on dipstick in all studies*							
1 (Lizama 2005)	Retrospective - cohort	1140	0.05 (0.03, 0.08)	0.98 (0.97, 0.99)	LR+ 2.66 (1.27, 5.54)	The presence of haematuria leads to a **moderate increase** in the probability of having a UTI (95% CI ranges from slight to large increase). [same interpretation]	Very low [same quality]
					LR- 0.97 (0.94, 1.00)	The absence of haematuria **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [is low in main analysis]
Malodorous urine (pooled < 14 years)							
4 (Hay 2016, Gauthier 2012, Dobbs and Fleming 1987, Struthers 2003)	Prospective - cross sectional	5533	0.46 (0.31, 0.62)	0.76 (0.56, 0.89)	LR+ 1.89 (0.98, 3.62)	The presence of malodorous urine **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [is **moderate increase** in main analysis]	Very low [same quality]
					LR- 0.75 (0.53, 1.07)	The absence of malodorous urine **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
Malodorous urine (pooled < 2 years)							
2 (Gauthier 2012,	Prospective - cross sectional	441	0.54 (0.41, 0.67)	0.59 (0.38, 0.77)	LR+ 1.35 (0.65, 2.77)	The presence of malodorous urine **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation [compared to initial analysis]	Quality [compared to initial analysis]
Struthers 2003)					LR- 0.82 (0.45, 1.48)	The absence of malodorous urine **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
Vomiting (pooled < 5 years)							
8 [d]	Prospective - cross sectional Retrospective - cohort	9435	0.24 (0.14, 0.39)	0.72 (0.61, 0.80)	LR+ 0.86 (0.67, 1.05)	The presence of vomiting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Low [is very low in main analysis]
					LR- 1.05 (0.97, 1.11)	The absence of vomiting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
Vomiting (pooled < 2 years)							
7 [e]	Prospective - cross sectional Retrospective - cohort	4423	0.23 (0.12, 0.40)	0.72 (0.60, 0.82)	LR+ 0.85 (0.63, 1.08)	The presence of vomiting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
					LR- 1.05 (0.96, 1.13)	The absence of vomiting **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
Diarrhoea (pooled < 5 years)							
7 [f]	Prospective - cross sectional Retrospective - cohort	18553	0.20 (0.11, 0.34)	0.79 (0.69, 0.86)	LR+ 0.94 (0.64, 1.30)	The presence of diarrhoea **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
					LR- 1.01 (0.91, 1.10)	The absence of diarrhoea **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
Diarrhoea (pooled < 2 years)							
6 [g]	Prospective - cross sectional	2752	0.20 (0.10, 0.37)	0.79 (0.68, 0.87)	LR+ 0.98 (0.61, 1.45)	The presence of diarrhoea **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation [compared to initial analysis]	Quality [compared to initial analysis]
	Retrospective - cohort				LR- 1.00 (0.87, 1.10)	The absence of diarrhoea **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
Constipation (< 5 years)							
1 (Hay 2016)	Prospective - cross sectional	5012	0.27 (0.19, 0.37)	0.82 (0.81, 0.83)	LR+ 1.52 (1.10, 2.11)	The presence of constipation **does not meaningfully alter** the probability of having a UTI (95% CI ranges from slight to moderate increase). [same interpretation]	Moderate [same quality]
					LR- 0.89 (0.79, 1.0)	The absence of constipation **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Moderate [is very low in main analysis]
Abdominal pain (pooled < 5 years)							
7 [h]	Prospective - cross sectional Retrospective - cohort	5597	0.26 (0.12, 0.47)	0.85 (0.67, 0.94)	LR+ 1.87 (0.80, 3.84)	The presence of abdominal pain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
					LR- 0.87 (0.67, 1.06)	The absence of abdominal pain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
Abdominal pain (pooled < 2 years)							
6 [i]	Prospective - cross sectional Retrospective - cohort	2856	0.29 (0.12, 0.54)	0.80 (0.62, 0.90)	LR+ 1.50 (0.64, 2.91)	The presence of abdominal pain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
					LR- 0.89 (0.62, 1.14)	The absence of abdominal pain **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
No source of fever (pooled < 5 years)							
3 (Craig 2010,	Prospective - cross sectional	19276	0.85 (0.66, 0.94)	0.43 (0.05, 0.91)	LR+ 1.84 (0.67, 5.05)	The absence of a source of fever **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation [compared to initial analysis]	Quality [compared to initial analysis]
Hoberman 1993, Shaw 1998)					LR- 0.44 (0.20, 0.95)	The presence of a source of fever leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from moderate to slight decrease). [is **does not meaningfully alter** in main analysis]	Low [is very low quality in main analysis]
No source of fever (pooled < 2 years)							
2 (Hoberman 1993, Shaw 1998)	Prospective - cross sectional	3475	0.77 (0.61, 0.88)	0.68 (0.38, 0.88)	LR+ 2.46 (0.88, 6.89)	The absence of a source of fever **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
					LR- 0.36 (0.13, 0.96)	The presence of a source of fever leads to a **moderate decrease** in the probability of having a UTI (95% CI ranges from large to slight decrease). [is **does not meaningfully alter** in main analysis]	Low [is very low quality in main analysis]
No convulsions (data only reported < 2 years)							
1 (Musa Aisien 2003)	Prospective - cross sectional	300	0.96 (0.78, 0.99)	0.11 (0.08, 0.15)	LR+ 1.08 (0.99, 1.18)	The absence of convulsions **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]
					LR- 0.34 (0.05, 2.38)	The presence of convulsions **does not meaningfully alter** the probability of having a UTI (95% CI crosses 1.0). [same interpretation]	Very low [same quality]

References

a. Hay 2016, O'Brien 2013, Gauthier 2012, Msaki 2012, Dobbs and Fleming 1987, Lizama 2005, Festo 2011, Ibeneme 2014
b. O'Brien 2013, Gauthier 2012, Msaki 2012, Lizama 2005, Festo 2011, Ibeneme 2014
c. Hay 2016, O'Brien 2013, Dobbs and Fleming 1987, Lizama 2005, Ibeneme 2014
d. Hay 2016, Musa Aisien 2003, Newman 2002, Gauthier 2012, Lizama 2005, Festo 2011, Ibeneme 2014, Hoberman 1993
e. Musa Aisien 2003, Newman 2002, Gauthier 2012, Lizama 2005, Festo 2011, Ibeneme 2014, Hoberman 1993
f. Craig 2010, Musa Aisien 2003, Gauthier 2012, Lizama 2005, Festo 2011, Ibeneme 2014, Hoberman 1993
g. Musa Aisien 2003, Gauthier 2012, Lizama 2005, Festo 2011, Ibeneme 2014, Hoberman 1993
h. Hay 2016, Musa Aisien 2003, Verbakel 2015, Gauthier 2012, Msaki 2012, Lizama 2005, Ibeneme 2014
i. Musa Aisien 2003, Verbakel 2015, Gauthier 2012, Msaki 2012, Lizama 2005, Ibeneme 2014

Summary GRADE table for diagnostic models combining symptoms and signs

When interpreting the LRs for the summary GRADE table the terminology used was taken from Table 14 in appendix M, with the exception of values that fall between 0.5 and 2 and 0.5. These were described as not altering the probability of having a UTI.

Table 7 Summary GRADE table for diagnostic models combining symptoms and signs

Tool	Study	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
UTIcalc	Boon 2022	96	0.75 (0.19, 0.99)	0.16 (0.09, 0.25)	LR+ 0.90 (0.51, 1.59)	A UTIcalc score ≥2% **does not alter** the probability of having a UTI (95% CI within this range).	Moderate
					LR- 1.53 (0.26, 8.91)	A UTIcalc score <2% **does not alter** the probability of having a UTI (95% CI ranges from moderate decrease to large increase).	Low
Gorelick	Boon 2022	100	0.91 (0.72, 0.99)	0.08 (0.03, 0.16)	LR+ 0.99 (0.86, 1.14)	A high-risk Gorelick score **does not alter** the probability of having a UTI (95% CI within this range).	Moderate
					LR- 1.12 (0.24, 5.16)	A non-high-risk Gorelick score **does not alter** the probability of having a UTI (95% CI ranges from moderate decrease to large increase).	Low
DUTY	Boon 2022	297	0.08 (0.01, 0.25)	0.99 (0.96, 1.00)	LR+ 6.95 (1.22, 39.72)	A high-risk DUTY score leads to a **large increase** in the probability of having a UTI (95% CI ranges from a slight to a very large increase).	Moderate
					LR- 0.93 (0.84, 1.04)	A non-high-risk DUTY score **does not alter** the probability of having a UTI (95% CI within this range).	Moderate
Yale	Zorc 2005	995	0.04 (0.02, 0.11)	0.93 (0.91, 0.95)	LR+ 0.59 (0.22, 1.59)	A high-risk Yale observation score **does not alter** the probability of having a UTI (95% CI ranges from a slight decrease to a slight increase).	Very low
					LR- 1.03 (0.98, 1.08)	A non-high-risk Yale observation score **does not alter** the probability of having a UTI (95% CI within this range).	Low

Tool	Study	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Interpretation	Quality
Yale	Diaz 2016	314	0.13 (0.07, 0.23)	0.86 (0.81, 0.90)	LR+ 0.92 (0.48, 1.18)	A high-risk Yale observation score **does not alter** the probability of having a UTI (95% CI ranges from a moderate decrease to a slight increase).	Very low
					LR- 1.01 (0.92, 1.12)	A non-high-risk Yale observation score **does not alter** the probability of having a UTI (95% CI within this range).	Low
NICE traffic light system	De 2013	3653	0.79 (0.74to 0.82)	0.25 (0.23 to 0.26)	LR+ 1.04 (0.98, 1.10)	An amber or red NICE traffic light rating **does not alter** the probability of having a UTI (95% CI within this range).	Low
					LR- 0.88 (0.72, 1.08)	A green NICE traffic light rating **does not alter** the probability of having a UTI (95% CI within this range).	Low

Summary GRADE table for c-statistics for diagnostic models combining symptoms and signs

Table 8 Summary GRADE table for c-statistics for diagnostic models combining symptoms and signs

No. of studies	Study design	Sample size	Effect size (95% CI)	Interpretation	Quality
DUTY	Boon 2022	297	AUC 0.55 (0.43-0.68)	The DUTY score has **poor** classification accuracy for detecting UTI (95% CI ranges from poor to adequate accuracy)	Low

See Appendix F for full GRADE tables.

1.1.7 Economic evidence

1.1.7.1 Included studies

A single search was performed to identify published economic evaluations of relevance to the review question in this guideline update (see Appendix B). This search retrieved 1,172 studies. Based on title and abstract screening, 1,168 of the studies could confidently be excluded for this question. 3 studies were excluded following the full-text review. Thus, the review for this question includes 1 study from the existing literature.

1.1.7.2 Excluded studies

See Appendix J for excluded studies and reasons for exclusion.

1.1.8 Summary of included economic evidence

Table 9 provides summary details of the included study. See Appendix H for a full evidence table and assessment of applicability and limitations.

Table 9: Summary of economic evidence

Methods, applicability, and limitations	Base-case results						Uncertainty
	Intervention	Absolute		Incremental			
		Cost (£)	Effects[1]	Cost (£)	Effects[1]	INMB	
Hay et al. (2016) Multiple models using both decision trees and Markov models to compare both the short-term as well as the medium- and long-term benefits, harms and costs of different urine sampling strategies for acutely unwell children <5 years old presenting to primary care. **Effectiveness:** Risk stratification for the different sampling strategies were obtained from the results from the DUTY study. **Costs:** Short-term resource use from DUTY RCT, expert opinion, UK reference costs, published sources and a prescription cost analysis. Medium- and long-term resource use from DUTY RCT, a UK study on nephrology management and UK reference costs. **Utilities:** Elicited from caregivers of children with rotavirus infection <3 years old	**Short-term costs and benefits**						**Deterministic:** For clean catch samples, the sample none and DUTY 5% strategies were not sensitive to any 1 parameter: that is to say more conservative approaches to urine sampling strategies represented an effective use of NHS resources. Although not presented, authors report similar results were found for deterministic analysis using nappy pad samples. **Probabilistic:** For both clean-catch and nappy pad samples, the sample none strategy had the greatest probability (99.9% and 100% respectively) of being an effective use of NHS resources.
	Clean catch						
	Clinical judgement	£45.02	20.709	-	-	-	
	Sample none	£43.64	20.708	-£1.38	-0.001	1.34 (1.32 to 1.36)	
	DUTY 5%	£44.28	20.709	-£0.74	0	0.74 (0.72 to 0.76)	
	DUTY 10%	£45.01	20.709	-£0.01	0	0.02 (0.01 to 0.04)	
	DUTY 20%	£46.59	20.709	£1.57	0	-1.54 (-1.56 to -1.51)	
	Sample all	£60.23	20.710	£15.21	0.001	-15.14 (-15.25 to -15.03)	
	DUTY points ≥ 6	NR	20.708	NR	-0.001	0.79 (0.77 to 0.81)	
	DUTY points ≥ 5	NR	20.709	NR	0	0.42 (0.40 to 0.44)	
	DUTY points ≥ 4	NR	20.709	NR	0	-1.76 (-1.79 to -1.74)	
	DUTY points ≥ 3	NR	20.709	NR	0	-2.40 (-2.42 to -2.37)	
	Nappy pad						
	Clinical judgement	£44.10	20.708	-	-	-	
	Sample none	£43.64	20.708	-£0.46	0	0.44 (0.42 to 0.47)	
	DUTY 5%	£44.54	20.709	£0.44	0.001	-0.42 (-0.44 to -0.39)	
	DUTY 10%	£45.38	20.709	£1.28	0.001	-1.25 (-1.27 to -1.23)	
	DUTY 20%	£46.99	20.709	£2.89	0.001	-2.84 (-2.87 to -2.82)	
	Sample all	£62.10	20.710	£18.00	0.002	-17.91 (-18.05 to -17.78)	

Methods, applicability, and limitations	Base-case results					Uncertainty
	Intervention	Absolute		Incremental		
		Cost (£)	Effects[1]	Cost (£)	Effects[1]	INMB
in Canada using HUI2 questionnaire. **Directly applicable with minor limitations (Table 12)**	**Medium- and long-term costs and benefits – clean catch**					
	Clean catch					**Deterministic:** No deterministic sensitivity analysis presented. **Probabilistic:** For both clean-catch and nappy pad samples, the sample none strategy had the greatest probability (100% for both) of being an effective use of NHS resources, assuming QALYs are valued at £20,000 each.
	Clinical judgement	£200.16	25.722	-	-	-
	Sample none	£196.13	25.722	-£4.03	0	3.94 (3.90 to 3.96)
	DUTY 5%	£197.92	25.722	-£2.24	0	2.24 (2.22 to 2.26)
	DUTY 10%	£200.10	25.722	-£0.06	0	0.09 (0.08 to 0.11)
	DUTY 20%	£204.85	25.722	£4.69	0	-4.63 (-4.67 to -4.59)
	Sample all	£245.99	25.722	£45.83	0	-45.73 (-45.99 to -45.41)
	DUTY points ≥ 6	£197.77	25.722	-£2.39	0	2.35 (2.33 to 2.37)
	DUTY points ≥ 5	£198.94	25.722	-£1.22	0	1.22 (1.20 to 1.24)
	DUTY points ≥ 4	£205.54	25.722	£5.38	0	-5.34 (-5.38 to -5.29)
	DUTY points ≥ 3	£207.43	25.722	£7.27	0	-7.23 (-7.29 to -7.17)
	Nappy pad					
	Clinical judgement	£197.47	25.722	-	-	-
	Sample none	£196.13	25.722	-£1.34	0	1.31 (1.29 to 1.32)
	DUTY 5%	£198.75	25.722	£1.28	0	-1.24 (-1.26 to -1.22)
	DUTY 10%	£201.31	25.722	£3.84	0	-3.78 (-3.81 to -3.74)
	DUTY 20%	£206.23	25.722	£8.76	0	-8.68 (-8.74 to -8.62)
	Sample all	£252.44	25.722	£54.97	0	-54.81 (-55.17 to -54.44)

Methods, applicability, and limitations	Base-case results						Uncertainty
	Intervention	Absolute		Incremental			
		Cost (£)	Effects[1]	Cost (£)	Effects[1]	INMB	

1 – Effects are measured in the form of quality-adjusted life days (QALDs) for short term outcomes, and in the form of quality-adjusted life years (QALYs) for medium- long-term outcomes.
Abbreviations: HUI2 = Health Utilities Index; NR = Not reported

1.1.9 Economic model

No economic modelling was undertaken for this review because the scoping team agreed that the economic evidence included was of sufficient quality to make recommendations.

1.1.10 Economic evidence statements

- One cost-utility analysis found that in children less than 5 years old, when a clean catch sample is obtained, strategies where fewer samples were sent for diagnostic testing had a positive incremental net monetary benefit compared with clinical judgement, representing an effective use of NHS resources. However, strategies that in more samples being sent for diagnostic testing, had a negative incremental net monetary benefit, representing an ineffective use of NHS resources. These results were seen in both the short-term analysis as well as the medium- and long-term analysis. When a nappy pad sample is obtained, all sampling strategies excluding 'sample none' had a negative incremental net monetary benefit, indicating sending nappy pad samples for diagnostic testing is not an effective use of NHS resources. This analysis was assessed as directly applicable with minor limitations.

1.1.11 The committee's discussion and interpretation of the evidence

1.1.11.1. The outcomes measures that matter most

The committee discussed the consequences of late, missed or misdiagnosis of urinary tract infection (UTI) in babies, children, and young people. The committee recognised that there are 4 possible scenarios related to the use of symptoms and signs before proceeding to further testing and treatment:

- The first occurs when a symptom or sign (or a combination of them) accurately identifies a person as having a UTI (true positive result). In this scenario the person is (assuming further tests are accurate) promptly treated with antibiotics.
- The second is that a symptom or sign (or a combination of them) accurately rules out the presence of UTI (true negative result). In this scenario no further tests or treatment for UTI are required or given and other diagnoses for the person's illness can be explored.
- The third is where a symptom or sign (or a combination of them) suggest the presence of a UTI when in the baby, child or young person does not have one (false positive result). In this scenario they are likely to undergo unnecessary additional testing and treatment with antibiotics, which can have side effects (for example antibiotic associated diarrhoea) and lead to a greater risk of antimicrobial resistance with its associated individual and wider societal consequences. Also treating people who do not have UTI delays the investigation and diagnosis of their actual illness.
- The final scenario is when a symptom or sign (or a combination of them) suggest that no UTI is present when in fact the person has a UTI (false negative result). In this case the diagnosis of UTI may be missed or treatment delayed. The impact of this varies from person to person and is dependent upon several factors including their age and the site of infection (upper or lower UTI). It ranges from additional suffering caused by untreated infection and missed schooling (which can be a particular issue for babies, children and young people suffering recurrent infections) to problems with kidney function (renal scarring).

The committee agreed that ideally there needs to be a balance between the sensitivity and specificity of a test to best reduce the numbers of babies, children and young people who fall into the last 2 scenarios (false positives and false negatives). If a symptom, sign or diagnostic test is very sensitive but not sufficiently specific then too many babies, children

and young people may fall into the false positives group and will be treated unnecessarily. However, if the test is very specific and not very sensitive then too many babies and children with UTI will be missed (false negatives).

The committee agreed with the use of likelihood ratios as primary outcome measures because the interpretation of these measures was easy to understand in relation to signs and symptoms. The presence of a particular sign or symptom could increase the likelihood of UTI, while the absence could decrease it. Ideally both of these situations would have been met by the signs and symptoms included in this review, but in practice most of the cases where the LR+ was associated with a meaningful increase in the probability of having a UTI in the presence of a symptom or sign, the absence was not associated with a decrease in probability. The committee agreed that in this review the LR+ (which is most affected by specificity) was the most important outcome measure and could be used to help identify a baby, child or young person with a UTI (help rule in). However, a LR- (which are most affected by sensitivity) associated with a meaningful decrease could also provide useful information to help with the decisions to rule out a UTI. The committee were also interested in the evidence on symptoms and signs whose presence or absence were found to neither increase nor decrease the probability of UTI in babies, children and young people as they could then suggest that those features were not diagnostically useful.

The committee discussed whether positive and negative predictive value (PPV and NPV) would be more clinically useful than LRs. However, they recognised as PPV varies with prevalence and due to the large variability in prevalence of UTI between studies, including between the UK studies, that it would be problematic to use these measures and hard to interpret. Although the committee did note that a minority of studies (n=6) included in the review included more than one study site which might provide more robust prevalence estimates. However, of these multicentre studies 2 were conducted in the UK and the prevalence varied from 1.3% to 6%, and in the non-UK studies from 6.4% to 11.5%.

1.1.11.2 The quality of the evidence

The committee noted that 22 of the studies in the Boon et al 2021 systematic review met the criteria for inclusion in our review protocol (see Appendix A for more details) and looked at symptoms and signs. (Two further studies from the Boon et al 2021 were included in the section on diagnostic models). Of these 14 studies were considered to be at high risk of bias while the remaining studies were low risk of bias. High risk of bias was due mainly to issue with patient selection such as only including a narrow range of participants, using retrospective or convenience/ non- consecutive sampling; or only collecting urine samples from a proportion of the included children. The committee noted that many of the studies included in the Boon et al 2021 review were not designed as diagnostic test accuracy studies, that there was poor and inconsistent reporting of how symptoms and signs were assessed or defined. In addition, in many cases, it was unclear whether the study inclusion and exclusion criteria met those set by the committee (for example, concerning recent antibiotic treatment). Of the 3 additional studies that were identified that looked at symptoms and signs of UTI, Ibeneme et al 2014 and Struthers et al 2003 were both at low risk of bias while Williams-Smith et al 2020 was judged to be at high risk of bias (see Appendix D for full details of assessment of study quality). The studies were judged to be directly applicable in all cases except for Pylkkanen et al 1979, which included babies, children and young people under 18 years old, although 65% were ≤2 years old).

The committee noted that the individual symptoms and signs ranged in quality from high to very low using a modified form of GRADE, with lower quality ratings being more common than higher ones. Common reasons for downgrading were due to the high risk of bias of the included studies and heterogeneity between the results of studies included in the meta-analyses.

The committee discussed the limitations of microscopy, culture, and sensitivity (M, C & S) as a reference standard because, while for the purpose of analyses it is assumed to be 100% sensitive and specific, in practice it is far less so. The committee recognised that the lack of a more accurate reference standard was a limitation of all the studies and this review because this affects the classification of index test results as true positives/ negatives and false positives/ negatives, and therefore their diagnostic test accuracy. The current search did not exclude newer novel diagnostic methods, but no relevant studies were identified that used these methods as a reference test. Therefore, despite the limitations of M, C&S as a reference standard, the committee agreed to use the available evidence as basis for their decision making.

The committee discussed the impact of a missed UTI diagnosis following urine culture. They noted that in the 2007 version of the guideline recommendation 1.1.5.1 addresses this issue. It notes that because there will be a number of false negative results for all diagnostic tests, clinicians should use clinical criteria for their decisions in cases where urine testing does not support the findings. The committee agreed that this is an important recommendation to try to ensure that people who have a UTI that has been missed by the urine testing are treated appropriately.

The committee discussed the settings for the included studies and whether they could limit the generalisability of the findings. Of the 25 studies included in this review, 13 were conducted in emergency department settings (with 1 additional study in emergency and outpatient departments), with a further 2 in outpatient departments, 3 were conducted in health centres, 3 in family practices (2 studies also used emergency, walk-in centres or outpatient departments), and 3 in paediatrician's offices. The committee noted that this is not consistent with clinical practice in the UK, where most cases of UTI in babies, children, and young people are seen in general practice. The committee were concerned that the secondary care (emergency department, outpatient or hospital based) setting of some of these studies may have included babies, children, and young people who were more unwell than are typically seen in general practice and therefore the symptoms and signs may not be representative of most babies, children, and young people. However, they also noted that in the UK certain groups of people, such as those from lower socioeconomic backgrounds or disadvantaged groups like Gypsies, Roma and Travellers, may find it hard to register with or attend general practices or other dedicated primary care settings and therefore use emergency departments for their first line of care. Taking these considerations into account, the committee decided not to make separate recommendations for babies, children, and young people presenting in primary and secondary care settings because they were constrained by the available evidence and were not convinced that it would be useful in practice to analyse it separately by setting.

The committee also discussed the inclusion criteria for the trials and in particular that in over 50% entry was based on having fever (14 of the 25 studies in this review had fever as an entry criteria and in at least 2 other studies unwell or fever was an entry criteria). From their experience, the committee noted that fever, while not uncommon in UTI (particularly upper urinary tract infections such pyelonephritis), is less common in lower UTI (cystitis) which forms the majority of UTI seen in babies, children and young people in primary care practice. Therefore, the committee noted that for many of these studies the individual reported symptoms and signs were in fact symptoms or signs in the presence of fever. The committee noted that the included studies did not report if the final diagnosis of UTI was upper UTI (for example pyelonephritis) or lower (for example cystitis) UTI and no separate evidence was reported for symptoms and signs of commonly associated with these diagnoses separately. The committee decided that although this was a limitation of the evidence base it was still appropriate to make a single set of recommendations for the symptoms and signs of UTI at this time due to absence of specific evidence for the symptoms and signs of lower UTI. However, in their research recommendations on the symptoms and signs of UTI for underrepresented age groups (see below and Appendix K for more details) they requested

that diagnosis of lower UTI be reported separately from upper UTI to try to provide information that could be used in future updates of this guidance

The committee also discussed the ages of the populations in the included studies as 18 of the 25 studies included in this review reported data for babies and children under 5 years of age. Only 2 studies reported data for babies aged less than 3 months old (n=2,349). The remaining studies reported data ranging from under 6 years olds to under 18-year-olds, but in all cases where it was reported the mean/median age of the participants was much lower (under 5 years). The committee were interested in subgrouping the evidence by age group, however, in practice this was limited to the age cohorts reported in the included studies as only the DUTY study (Hay et al 2016) provided separate data for younger (nappy pad collection) and older children (aged < 5 years) within their study. The committee noted that the lack of information about the symptoms and signs in babies and older children and young people was a limitation of the data available. Although the majority of studies included babies and very young children, they did not report the data separately by age group (apart from the DUTY study (Hay et al 2016), but they used <2 and 2-<5 groups). The committee discussed whether the symptoms and signs from babies and children under 5 could be generalised to babies, older children and young people. They agreed that they lacked the information to make separate recommendations by age group and wrote research recommendations for studies to look at the symptoms and signs of UTI in babies under 3 months and children from 5 years to under 16 years to try to address this gap in the literature (see Appendix K for more details). The committee agreed that many symptoms and signs would be generalisable but that some would be more relevant for younger or older age groups. They therefore considered on an individual basis whether each symptom or sign could be extrapolated to a wider population where the evidence was limited to a particular age group.

The committee also discussed whether studies with dissimilar health care systems and populations to the UK should be excluded (for example the Ibeneme et al 2014 and Kartika et al 2006 studies) but as these studies met the inclusion criteria for this review and there was no biological reason to suspect symptoms and signs of UTI would be different in their included study population, these studies were retained in the review.

The committee had identified in the review protocol (see Appendix A) several subgroups of interest. This included possible subgroup analysis by reference test standard (for example 10^4 and 10^5 colony forming units per mL), the method of collection of reference standard (clean-catch, nappy pad collection, bag collection etc.), symptoms and signs of UTI in those with first UTI versus those with previous UTI, and a subgroup of no versus recent antimicrobial treatment. These subgroup analyses were not feasible due to lack of available data. Reference standards varied between and within studies, which often using different thresholds dependent upon methods of obtaining the reference sample but only 1 study (DUTY, Hay et al 2016) reported these data separately. Only the planned age subgroup was possible (see above).

1.1.11.3 Benefits and harms

The committee explored how clinically useful findings were by applying minimal important clinical differences (MID) to the likelihood ratios, for a positive likelihood ratio the MID was 2.0 and for negative likelihood ratio 0.5 with both using 1 (which is a null value for ratios) as the second value. Results which fell within these MIDs were described as not meaningfully altering the likelihood of UTI as they gave a slight increase or decrease in the likelihood of having a UTI and were thought to be non-clinically significant by the committee. Symptoms or signs where the 95% confidence interval crossed 1 were also described as not meaningfully altering the likelihood of UTI (see the section on Methods and process for more details).

The committee decided to subgroup symptoms and signs into 2 groups based on the likelihood ratios: symptoms and signs that meaningfully increased the likelihood of UTI and

those that meaningfully decreased the likelihood of UTI. They discussed the evidence from the meta-analyses (pooled study data) and evidence obtained from single studies, which were summarised in a table (Table 4) to aid their discussions. They used this table to help compile the table of symptoms and signs in the recommendations in the guideline. The factors included in the guideline table were updated to reflect the results of the sensitivity analyses (which excluded the Pylkkanen 1979 study see the Protocol deviation section above) by the addition of fever with source. The committee also examined the symptoms and signs which did not meaningfully alter the likelihood of UTI (Table 5).

The committee discussed the usefulness of each symptom and sign in identifying a UTI for each age group but also whether the findings were likely to be generalisable to all ages covered by the guideline. The committee also discussed the utility of symptoms and signs in different age groups and whether they can be reasonably assessed by healthcare professionals or parents and caregivers (see above and below for more details).

Symptoms and sign that increase the likelihood of UTI

The committee identified that several urinary symptoms (for example dysuria, frequency, bed-wetting, malodorous urine) were useful as their presence moderately increased the likelihood of UTI. Similarly, there were several non-localising symptoms and signs (such as no fluid intake, fever and chills) which if present also increased the likelihood of urinary tract infection. The committee noted that in nearly all cases the associated LR- fell into the does not meaningfully alter category of interpretation, due to the low level of sensitivity of the symptoms and signs as index tests. Therefore, the committee agreed that the absence of these symptoms or signs should not be used to rule out a UTI, but the presence of them could suggest a urinary tract infection is more likely. The exception to this was the absence of dysuria which was associated with a decreased likelihood of a UTI (LR- moderate decrease as well as a LR+ moderate increase) as it had sensitivities and specificities of 75% and 71% respectively. The committee summarised the symptoms and signs suggestive of urinary tract infection in a table in the guideline. They recommended that babies, children and young people with these symptoms and signs should have a urine sample taken for further investigation.

The committee noted the following in relation to specific symptoms and signs:

- Dysuria (pain or discomfort while urinating) is likely to be a useful symptom suggesting the presence of a UTI in most age groups. However, it may be less useful in babies and younger children, for example under the age of 2 years, because they might not be able to speak yet or lack the words to describe the symptom of dysuria.
- Urinary frequency (passing urine more often than normal) is likely to be a useful symptom suggesting the presence of a UTI in most age groups. However, the committee discussed that for babies and younger children who are not, yet toilet trained and still wearing nappies it may be difficult to assess how often they are passing urine. The committee agreed that the presence of urinary frequency in those who are toilet trained or those who can verbalise their symptoms may be useful.
- Although poorly defined in the studies, based on the experience of the committee bed-wetting could be a useful symptom suggesting the presence of a UTI in children and young people who are already usually dry overnight but is of less use in those who are not usually dry overnight. The committee also noted there was no evidence relating to daytime incontinence which from their experience may also be a useful indicator in younger toilet trained children.
- The committee noted that evidence from a single study in babies and children aged <5 years found that the presence of ‘urinary symptoms’ led to a moderate increase in the likelihood of UTI. The committee questioned the definition of ‘urinary symptoms’ but this was not defined in the study. The committee therefore agreed this symptom was of limited usefulness and did not include it in the table.

- Evidence from a single study found that a capillary refill time of >3 seconds in children aged <5 years led to a moderate increase in the likelihood of a UTI. The committee included this sign in the recommendation table but noted that if this sign if present with other signs of sepsis, clinicians should refer to the NICE guideline on sepsis: recognition, diagnosis and early management. They included a cross reference to this guideline in the recommendations.
- Although the presence of normal tympanic membranes in babies <3 months old led to a moderate increase in the likelihood of UTI, the committee were unconvinced by this finding as they agreed that it is very difficult to accurately visualise and assess tympanic membranes in babies of this age. They did not include this in the table for this reason.

Malodourous or smelly urine was associated with an increased likelihood of UTI in babies and children aged <5 years from the evidence. The committee discussed whether smelly urine could be a misleading symptom as strong-smelling urine could be a sign of dehydration, which would not be an uncommon finding in an unwell child. In addition, stale smelling urine, particularly in children wearing nappies could be a normal finding. However, the committee agreed that in their experience there was difference between strong-smelling urine and offensive or foul-smelling (malodourous) urine, so they included it in the table of symptoms and signs but used this terminology to try to make the difference clearer. Although the evidence was only available for children < 2 or <5 years old the committee agreed that this symptom was likely to be relevant for all ages.

The committee noted that darker urine was associated with an increased likelihood of UTI in babies and children aged <2 years but can also be caused by dehydration and that poor fluid intake is not uncommon in unwell children. They noted that this was assessed in a single large study (the DUTY study, Hay et al 2016a) predominantly using nappy pad samples but agreed to include it in the table of symptoms and signs despite these issues. Similarly, evidence from a single study found that the presence of no fluid intake in babies and children aged <5 years led to a moderate increase in the likelihood of UTI. The committee noted that despite being nonspecific, no fluid intake might be a useful symptom of a UTI but agreed that as 'no' fluid intake was likely an unusual finding and agreed to reword this for the table in the guideline as reduced fluid intake.

Based on evidence from a single study in children aged 2 to <5 years, the presence of abdominal pain led to a large increase in the likelihood of UTI. However, for <2 years abdominal pain did not meaningfully alter the likelihood of UTI. In babies and children aged <5 years the presence of suprapubic tenderness led to a large increase in the likelihood of UTI as did the presence of loin tenderness in children aged 2 to <5 years. The committee discussed that although seemingly contradictory these findings were likely to be correct as older children (aged 2 to <5 years) may be better able to discriminate the location of pain while children younger than 2 years may not be adequately able to verbalise or describe these symptoms but may respond to palpation of the bladder or loin area.

The committee discussed the fever related symptoms and signs and how they might be useful in suggesting the presence or absence of a UTI. They noted that most of the studies recruited babies and children with fever as a key inclusion criterion (see above for more discussion about this point). They therefore did not look for the association of the presence of fever with UTI but focused on fever duration and whether there was an identified source of fever. Although fever duration of >48 hours in children aged <3 years led to a moderate increase in the likelihood of UTI based on a single study with very low-quality evidence, other durations of fever in other age groups and fever ≥39°C did not meaningfully alter the probability of having a UTI. Taking the variability of the results into account the committee decided against including fever duration of >48 hours in the table of symptoms and signs in the recommendations, but they did include the presence of fever based on the inclusion criteria of the majority of studies in the analysis. Although fever without source was not associated with an increase in the likelihood of having a UTI in 0-5 year olds, the committee

noted that the presence of a fever with a source was associated with a reduced likelihood of having a UTI (see section below) and this was included in the table of symptoms and signs.

The committee noted that the presence of chills in babies and children aged <2 years led to a moderate increase in the likelihood of UTI based on a single study, but not when pooled with other data (chills and shivers) in a broader age group (<5 years). The committee were unsure what was meant by 'chills' as this was not defined in the paper and thought it could have been shaking associated with a temperature (rigors) as the study inclusion criteria was fever without source (≥38°C), <10d in duration. However, to ensure that the terminology was more easily understandable to babies, children, young people and their families they used the term shivering in the recommendation table.

Although previous UTI is not a symptom or sign, the committee noted that it can be elicited or obtained from clinical records before obtaining a urine sample. In the pooled analyses for all babies, children, and young people aged <15 years a previous urinary tract infection moderately increases the probability of UTI. The committee noted that findings were similar for subgroups aged <2 years and 2 to <5 years, but for those aged <15 years it did not meaningfully alter the likelihood of UTI. The committee questioned how the previous UTI was diagnosed in the studies (self-report or parental or caregiver report versus clinician or laboratory defined UTI) as this may heavily influence the results of the analyses. In the included studies for the outcome, it was generally not, or poorly, defined. The committee agreed that this should also be included in the table but the term 'confirmed previous UTI' should be used to make it clear that a self-report or parental or caregiver report would not be sufficient.

A further two signs (haematuria and cloudy urine) were discussed by the committee. The committee noted that the finding of haematuria (blood in the urine) would always be a reason for further follow-up and investigation. In the included studies it was unclear whether the blood was visible (macroscopic) and only detected through a test (dipstick). Visible blood in UTI was, in the experience of the committee, an uncommon finding and the presence of blood is likely to be due to other diagnoses. If blood is present in urine detected through dipstick testing then this is not a symptom or sign, but a further test which is out-of-scope for this section of the guideline. Microscopic haematuria also shares a common feature with assessment of urine clarity (cloudy urine) as a urine sample may have been taken to assess it. In both the Hay et al 2016 (DUTY) and Kartika et al 2006 studies cloudy urine was laboratory assessed. This places assessment of these outcomes further along the diagnostic pathway, and this review is designed to inform clinicians which babies, children, and young people should have urine samples taken. However, the committee noted that if cloudy urine or visible blood in the urine were reported by the child, their parent or a caregiver then this would be of interest to the clinician and could help them in their decision about whether a urine sample should be obtained.

Symptoms and signs that decrease the likelihood of UTI

The committee also included some symptoms and signs that suggest a urinary tract infection is less likely in the table in the guideline. They noted that a smaller number of symptoms and signs which when present were found to decrease the likelihood of UTI being present (such nappy rash, breathing difficulties, wheezing, chest crackles, abnormal chest sounds or ear examination, runny nose and fever with a source). They noted that the studies did not define the term breathing difficulty, but the result was consistent in the context of other similar respiratory system symptoms and signs. They also discussed that although the extent or definition of nappy rash was not well defined in the study that it may be useful sign that reduces the likelihood of a UTI. The committee noted that many of these symptoms were suggestive of another cause for a baby or child or young person's symptoms or illness. The committee therefore included them in the table in the table of symptoms and signs guideline as suggesting a urinary tract infection is less likely. Where these symptoms or signs are present it may be helpful to consider an alternative diagnosis. They agreed that abnormal

chest sounds, wheezing and crackles were similar enough to be grouped together under the former term for simplicity. Although a runny nose was associated with a decrease in the probability of a UTI the committee decided that it was not a useful factor to use to help exclude UTI in babies as, depending on the season, runny nose may be a very frequent finding in this age group and its presence may mask co-existing UTI and so did not include it in their table for this reason. The committee also noted that the absence of dysuria was associated with a decrease in the likelihood of having a UTI, while the presence was associated with an increase.

Symptoms and signs that do not meaningfully alter likelihood of UTIs

The committee noted that there were many symptoms and signs covered in the evidence review which neither increased or decreased the likelihood of UTI (see Table 5 for details) or were not examined in the evidence base included in this update. These included symptoms and signs reported in the previous version (2007) of the guideline such as sleepiness or lethargy, irritability, poor feeding, vomiting, failure to thrive and jaundice. For some of these symptoms and signs the presence or absence of them did not increase or decrease the likelihood of UTI because the 95% CI crossed the null value (1.0). However, in many cases the finding was less than the committees agreed minimal important clinical difference (0.5 for negative likelihood ratios and 2.0 for positive likelihood ratios, see the Methods and process section for details) and so although the result may have been statistically significant it was not clinically significant. The committee noted however, that in some cases the evidence was low or very low quality and further research may have an effect on the estimate of the effect and lead to some symptoms or signs being added to the table in the guideline and others being removed. They therefore cautioned that the symptoms and signs table contains the minimum list agreed by the committee and is not exhaustive. It should be used alongside clinical judgement when assessing a child as a wider set of symptoms and signs may be justified, if not currently supported by the evidence.

Formulating the recommendations

The committee agreed that the table in the guideline outlining symptoms and signs that increase or decrease the probability of a urinary tract infection could be used to help a clinician make a decision about whether to collect a urine sample for testing. However, since many of the studies that provided the evidence for the analyses were poorly reported or not designed to answer this question, the quality of the evidence supporting the inclusion of many of the symptoms and signs was judged to be low or very low. Therefore, the committee agreed that the table should be used as a guide alongside clinical judgement. They noted that the presence of any single symptom or sign in the left-hand column would increase the likelihood of the baby, child or young person having a UTI but because some of the factors listed, like fever, are non-specific and having a single symptom or sign would not necessarily be sufficient to indicate a UTI. Instead, the committee thought that the presence of a combination of the symptoms and signs listed may provide increased confidence in the likelihood of a UTI being present, but due to a lack of evidence it was not possible to recommend any particular combination of symptoms/signs that together significantly increased the likelihood of a UTI being confirmed on urine testing.

The committee did not list symptoms and signs by age group because the included trials were mainly carried out in babies and children under 5 years old and in most cases the results were not reported separately by age group. The committee agreed that the symptoms and signs could be generalised across the age groups with some caveats. The committee noted that a child's age and/or ability to communicate symptoms (or in whom they cannot be accurately assessed) will affect the usefulness of a particular symptom or sign. For example, while more frequent urination was found to increase the likelihood of a UTI in all ages (under 2 to under 14 years) in the analysis, in those who are not yet toilet trained and who wear a nappy it may be more difficult to assess. They therefore agreed that clinician judgement is

needed when deciding which symptoms and signs are relevant for an individual baby, child or young person.

The committee noted that an existing recommendation in the guideline covers referral of babies under 3 months with suspected UTI to paediatric specialist care and sending a urine sample for urgent microscopy and culture. They noted that babies under 3 months are particularly vulnerable because of their age and that there is a risk of co-infection with urinary tract and other infections such as bacteraemia or meningitis. The committee agreed that it made more clinical sense for this recommendation to sit the section on symptoms and signs and were given permission to move it. The committee agreed that this improved the logical order of the recommendations.

The committee were aware that the list of symptoms and signs in the table in the guideline was not exhaustive and that because of this some babies, children and young people who are unwell due to a UTI risk not being tested further because they lack these symptoms or signs. They agreed that where there is clinical suspicion of UTI in these cases it may be useful to test their urine.

Based on their clinical expertise, the committee noted that routine urine testing should not be undertaken in babies, children and young people over 3 months with symptoms and signs that suggest an alternative site of infection because it is likely to be clinically unnecessary, would waste resources and could increase the stress experienced by the baby or child and their family. However, they noted that the list of symptoms and signs is not exhaustive and agreed that if the baby, child or young people remains unwell and there is diagnostic uncertainty then urine testing should be considered because they could have a UTI instead of, or in addition to, their initial diagnosis.

The committee were aware that the NICE guideline on fever in under 5s: assessment and initial management provides guidance on the differential diagnosis of the causes of fever with no obvious cause. They agreed that clinicians would refer to the UTI guideline if they had a suspicion of UTI, but if, after following the first few recommendations in the symptoms and signs section, a UTI is no longer suspected then the fever in under 5 guideline could help them to identify an alternative diagnosis. This guideline also has recommendations aimed at the paediatric specialist, which cover a range of diagnostic tests to be carried out on babies and children in their care, including when to test urine for a UTI. The committee therefore included these cross references in the recommendations.

The committee recognised that in practice there might be delays in obtaining a urine sample for testing if one cannot be obtained at the time of consultation. For example, babies and younger children may not be able to produce a sample on demand and this will need to be collected later on and returned to the general practice or clinic. They agreed that where possible delays in sample collection should be avoided to ensure rapid and accurate diagnosis and reduce the risk of renal scarring. They noted that once received the samples should be tested as soon as practical. The committee agreed that when a sample cannot be obtained at the consultation parents or carers (as appropriate) should be advised to collect the urine sample and return it for testing as soon as possible, ideally within 24hrs. The committee also included cross references to the sections on urine collection, preservation and testing to direct readers to the next stages in the diagnosis pathway.

The committee noted that it is important to obtain a sample of urine before antibiotics are taken because of the effect on microscopy, culture, and sensitivity test results. This is covered in recommendations in the NICE guideline on urinary tract infection (lower): antimicrobial prescribing and NICE guideline on pyelonephritis (acute): antimicrobial prescribing. The committee agreed to add a cross reference to these recommendations to the relevant section of the guideline (on urine testing) to make this clear. They were given permission to include a paraphrased version of the recommendations as well to reduce the need to move between related UTI guidelines to find the specific information. The committee also highlighted that although it is good practice to obtain a sample of urine before antibiotics

are taken, in cases where babies and children are identified as having a high risk of serious illness, they should not have treatment delayed if a sample cannot be obtained. This agrees with an existing recommendation in the urine collection section.

Diagnostic models combining symptoms and signs

The committee also examined the evidence for several diagnostic algorithms (combinations of symptoms and signs) which have been developed for use in clinical practice to help with the initial diagnosis of a UTI (such as the DUTY score, UTI calc and the NICE traffic light score, see section 1.1.6 for details). However, none of these scoring algorithms were found to be particularly accurate at identifying babies or children with UTIs and the committee therefore did not make any recommendation for their use in practice.

1.1.11.4 Cost effectiveness and resource use

The committee reviewed economic evidence on the cost-effectiveness of various diagnostic strategies to identify children with elevated risk of UTI in whom a urine sample should be collected. The evidence from the literature from 1 UK cost-effectiveness analysis that had minor limitations. One of the primary limitations being the study used caregiver-reported Health Utilities Index 2 derived utility scores for children with rotavirus. This was done because the authors found no studies reporting estimates of quality of life for infants with UTI, and rotavirus was determined to be a suitable proxy given its symptoms closely matched UTI. Despite this limitation, the committee considered this analysis to be highly applicable, both because it was done from the perspective of the UK National Health Service and also because it was a robust study that considered short, medium and long-term impacts of UTI. The cost-effectiveness results were presented in terms of incremental net monetary benefit between clinical judgement and alternative strategies; a positive incremental net monetary benefit indicates that a strategy is cost-effective compared with clinical judgement.

The committee discussed the economic evidence from the UK cost-effectiveness analysis. Although this study looked at children less than 5 years old, the committee felt that the economic evidence was generalisable to older children aged from 5 to 16 years old. This is because the defining feature differentiating younger children compared with older children is how a sample is collected, with it being increasingly likely that a clean catch sample can be obtained the older the child. Thus, while children older than 5 to age 16 were not explicitly considered in the model, the committee felt it was acceptable to generalize this older population to the 'clean catch' sample group that was modelled. In the model's base case, for both the short-term results as well as the medium- and long-term results, the sample none strategy with clean catch samples had the largest positive incremental net monetary benefit. Four other strategies (sample based on a high specificity cut-off of the DUTY risk score – DUTY5%, sample based on an intermediate specificity and sensitivity cut-off of the DUTY risk score – DUTY10%, DUTY points ≥ 6 and DUTY points ≥ 5) retained a positive, albeit to a lesser extent, incremental net monetary benefit, again, for both the short-term results as well as the medium- and long-term results. Four strategies (sample based on a high sensitivity cut-off of the DUTY risk score – DUTY20%, sample all, DUTY points ≥ 4 and DUTY points ≥ 3) resulted in a negative incremental net monetary benefit, again, for both the short-term results as well as the medium- and long-term results.

The analysis also presented results for nappy-pad samples. In the model's base case, for both the short-term results as well as the medium- and long-term results, the sample none strategy with nappy pad samples had a positive incremental net monetary benefit. All of the other strategies (DUTY5%, DUTY10%, DUTY20% and sample all) had a negative incremental net monetary benefit.

The committee understood based on these that more conservative approaches were likely to be cost-effective due to the cost savings associated with reduced testing, whereas strategies

that resulted in an increased number of children being tested for UTI were not cost-effective due to the increased costs associated with testing. However, in light of a validation study that showed the DUTY ≥ 5 points had poor diagnostic accuracy, the committee felt that further discussion of the cost-effectiveness of the DUTY strategies was unnecessary.

However, the committee was reassured by the findings of the cost-effectiveness analysis presented. Namely that the authors found the differences in health and costs between different approaches to be minimal. Thus, while the committee was aware their recommendations on what signs and symptoms clinicians should use to determine who should receive testing for UTI, they were confident based on the results of the cost-effectiveness results they say the ICERs would be below the range NICE normally considers an acceptable use of NHS resources, that is if we value a quality-adjusted life year (QALY) at £20,000 to £30,000.

The committee considered the potential resource impact of its recommendation. Given clinicians already use their clinical judgement and existing NICE guidance on signs and symptoms to determine testing for UTI, the committee did not believe its recommendations would have an impact on overall resource-use because they believed these recommendations were likely reflective of what is already being done in clinical practice.

1.1.11.5 Other factors the committee took into account

The committee also noted that many of the symptoms reported in the studies rely on either parental, caregiver or self-report. Self-report (and to a lesser extent parental and caregiver report) relies on being adequately able to describe the symptom to a healthcare professional. In people who have any form of communication difficulty such as problems with speech or hearing, learning disability or language barrier this may reduce the reliability of the reporting of such symptoms. Additionally, the committee discussed that following surgical intervention on the genitourinary tract, UTI in their experience is more likely and discussed whether female children who have had genital mutilation (FGM) would have the same symptoms and signs of UTI as demonstrated in the studies. As no evidence was found for these subgroups the committee have recommended these as important subgroups for inclusion in the research recommendation for symptoms and signs of UTI in 5 to under 16 year olds (see appendix K for more details). The committee also discussed whether babies, children and young people aged under 16 years with recurrent UTI had the same symptoms and signs as those with acute UTI. No evidence was identified for recurrent UTI, so the committee made another research recommendation (see appendix K for more details). Finally, they made a research recommendation to investigate the experience of children with symptoms and signs of long-term (i.e., chronic or UTI refractory to treatment) UTI as this was also not covered by the evidence.

The committee discussed that many of the symptoms and signs reported in the studies were poorly defined or not quantified. For example, for pain outcomes, the use of validated pain scores was not reported by any study, similarly for diarrhoea outcomes no reference was made to assessment measures such as stool charts. The committee agreed that in future diagnostic studies should make index tests more objective, measurable or as a minimum at least well defined.

The committee noted that the scope of the guideline excludes sexually active girls with recurrent urinary tract infections. However, they were aware that sexual activity may increase the possibility of a urinary tract infection and that symptoms of a sexually transmitted infection (STI) can mimic those of a UTI. The committee discussed that it is important to consider the possibility of STI if the young person is sexually active. They also noted that not all sexual activity is consensual. The committee discussed the implications of this for safeguarding in babies, children and young people under 16 years and whether they should make an additional recommendation highlighting this issue. However, they agreed that clinicians are already aware of safeguarding requirements and noted that the reasons to

consider safeguarding actions would be wider than a single or recurrent urinary tract infection and that to make a specific recommendation here might lead to unnecessary referrals and trauma for these children or young people and their families. The committee were also aware that NICE has several specific guidelines on this topic and agreed that clinicians who have concerns should refer to the NICE guideline on child maltreatment: when to suspect maltreatment in under 18s and the NICE guideline on child abuse and neglect in particular. They also noted that there is statutory guidance about the safeguarding of children and young people provided by the Department for Education.

The committee acknowledged that there are a few relevant NICE guidelines that overlap in care of an unwell child and so the committee added recommendations linking to these documents for safeguarding purposes. The most important issue for the committee was that healthcare professionals should not miss those with sepsis and in any case where sepsis might be a possible consideration the committee agreed that they should see the NICE guideline on sepsis: recognition, diagnosis and early management. The committee also noted that for babies of up to and including 28 days corrected gestational age with a suspected or confirmed bacterial infection healthcare professionals should consult the NICE guideline on neonatal infection: antibiotics for prevention and treatment.

1.1.12 Recommendations supported by this evidence review

This evidence review supports recommendations 1.1.1 to 1.1.2, 1.1.4 to 1.1.9 and 1.1.11 and the research recommendations on symptoms and signs of UTI.

1.1.13 References – included studies

1.1.13.1 Effectiveness

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1.1.13.2 Economic

Hay AD, Birnie K, Busby J, Delaney B, Downing H, Dudley J, Durbaba S, Fletcher M, Harman K, Hollingworth W, Hood K. The Diagnosis of Urinary Tract infection in Young children (DUTY): a diagnostic prospective observational study to derive and validate a clinical algorithm for the diagnosis of urinary tract infection in children presenting to primary care with an acute illness. Health technology assessment. 2016 Jul 31;20(51).

1.1.13.3 Other

O'Brien K, Edwards A, Hood K, Butler CC. Prevalence of urinary tract infection in acutely unwell children in general practice: a prospective study with systematic urine sampling. Br J Gen Pract 2013;63:91–2. http://dx.doi.org/10.3399/bjgp13X663127

Appendices

Appendix A – Review protocols

Review protocol for symptoms and signs for the first stage of UTI diagnosis in under 16s

ID	Field	Content
0.	PROSPERO registration number	CRD42022308609
1.	Review title	Symptoms and signs suggesting the presence of urinary tract infection in under 16s.
2.	Review question	What symptoms and signs are suggestive of urinary tract infection in under 16s?
3.	Objective	To assess the utility of symptoms and signs in identifying whether a baby, child or young person under 16 should undergo further diagnostic tests for the presence of urinary tract infection.
4.	Searches	The following databases will be searched: • EMCare • Cochrane Central Register of Controlled Trials (CENTRAL) • Cochrane Database of Systematic Reviews (CDSR) • Embase • MEDLINE • MEDLINE in Process

		• MEDLINE epub ahead of print • DARE (legacy records) • HTA Searches will be restricted by: • Date limitations (2006 to date) • English language • Human studies • Observational studies Conference abstracts will be excluded from the search results Other searches: • Citation searching The full search strategies for MEDLINE database will be published in the final review.
5.	Condition or domain being studied	Urinary tract infection (UTI) is an important cause of serious bacterial illness in children. The accurate and timely diagnosis of UTI is important in order to prevent unnecessary short-term suffering and help to prevent more serious longer-term consequences including recurrent infection of the urinary tract and kidney growth impairment or damage.
6.	Population	Inclusion: babies, children, or young people from birth to under 16 years old. Exclusion:

		• babies, children or young people under 16 years old who have already had a diagnostic test for urinary tract infection and are being selected for inclusion based on this positive or negative diagnosis. • babies, children or young people under 16 years old who have already had a diagnostic test for urinary tract infection and the clinician is aware of this test result. • babies, children or young people under 16 years old who have been treated with an antimicrobial with the course being completed in the 48hrs preceding presentation (not including prophylactic antibiotic treatment for recurrent UTIs).
7.	Test	Symptoms and signs including but not limited to: • abdominal pain/crying • pain or crying when voiding • headache • jaundice • haematuria • high fever over 38 or 39 degrees • shivering • rigors • vomiting • lethargy/malaise • irritability • poor feeding

		• failure to thrive • offensive or smelly urine • loin tenderness • frequency (of passing urine) or holding urine in • dysuria • dysfunctional voiding • diarrhoea • changes in continence • cloudy urine • cough or ear symptoms • sore throat • skin mottling • skin rash • redness in perineal area • parental suspicion of a UTI • previous UTI Or a combination of symptoms and signs (for example as an algorithm).
8.	Reference standard	Microbiologically confirmed urinary tract infection (microscopy, culture, and sensitivity). Reference standards may include:

		• a pure (single) or predominant growth of a microorganism at ≥10^5 colony-forming units (CFU)/mL [a UK definition] • a pure microorganism growth: >50,000 CFU/mL with a leukocyte count of ≥25/mm3 on microscopy or leukocyte positive (threshold at nil/trace) on dipstick [a US definition] Method of reference sample collection may include clean catch, nappy pad, bladder catheterisation and suprapubic aspirate samples preferably obtained within 24 hours but not more than 48 hours after the index test is performed.
9.	Types of study to be included	• Cross-sectional studies • Cohort studies (prospective and retrospective) • Systematic reviews of these studies
10.	Other exclusion criteria	• All other study types. • Studies reporting data without confidence intervals or data that cannot be used to calculate confidence intervals. • Studies that are not published in English. • Studies that use urine samples that have been collected from cotton wool balls, gauze and sanitary towels.
11.	Context	This is an update of existing NICE guidance (CG54) on symptoms and signs to suggest a UTI in under 16s that dates from 2007 (literature search conducted June 2006). The current update is being undertaken based on identification of the DUTY study (Hay et al 2016) by the NICE surveillance team, which was judged to have the potential to alter the existing recommendations.

		Reference: Hay, Alastair D, Sterne, Jonathan A C, Hood, Kerenza et al. (2016) Improving the Diagnosis and Treatment of Urinary Tract Infection in Young Children in Primary Care: Results from the DUTY Prospective Diagnostic Cohort Study. Annals of family medicine 14(4): 325-36.
12.	Outcome measures	Diagnostic association measures: • Odds ratio. Diagnostic accuracy metrics: • Positive and negative likelihood ratio (LRs) • Sensitivity and specificity. • AUC (for diagnostic prediction models only)
13.	Secondary outcomes	Not applicable
14.	Data extraction (selection and coding)	All references identified by the searches and from other sources will be uploaded into EPPI reviewer and de-duplicated. 10% of the abstracts will be reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. This review will make use of the priority screening functionality within the EPPI-reviewer software. At least 50% of the data set will be screened and we will stop screening after that if we screen more than 500 records without an include. However, if the data set contains less than or equal to 3,000 references it will be screened in its entirety. The full text of potentially eligible studies will be retrieved and will be assessed in line with the criteria outlined above. A standardised form will be used to extract data from studies

		(see Developing NICE guidelines: the manual section 6.4). Study investigators may be contacted for missing data where time and resources allow.
15.	Risk of bias (quality) assessment	Risk of bias will be assessed using the checklists described in Developing NICE guidelines: the manual for each study type of interest. Diagnostic test accuracy studies will be assessed using the QUADAS-2 checklist; systematic reviews will be assessed using the ROBIS checklist; clinical prediction studies for diagnosis will be assessed using PROBAST and diagnostic association studies will be assessed using the QUIPS checklist.
16.	Strategy for data synthesis	**Approach to meta-analysis for association data** Where appropriate, pairwise meta-analyses will be performed in Cochrane Review Manager V5.3. A pooled odds ratio will be calculated for using the Mantel-Haenszel method. Adjusted odds ratios from multivariate models will only be pooled if the same set of factors were used across multiple studies and if the same thresholds to measure factors were used across studies. Random effects models will be fitted when there is significant between-study heterogeneity in methodology, population, intervention or comparator identified by the reviewer in advance of data analysis. For all other syntheses, fixed- and random-effects models will be fitted, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models are the preferred choice to report, but in situations where the assumption of a

		shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses are conducted, random-effects results are presented. **Approach to GRADE for association data** The line of no effect will be used as the clinical decision threshold for the purpose of rating imprecision in GRADE. Data from cohort and cross-sectional studies will be initially rated as high quality, with the quality of the evidence for each outcome then downgraded or not from this initial point using a modified form of GRADE. **Approach to meta-analysis for diagnostic accuracy data** Meta-analysis of diagnostic accuracy data will be conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

		Where five or more studies are available for all included strata, a bivariate model will be fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data is not available (2-4 studies), separate independent pooling will be performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity, using Microsoft Excel. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010). Random-effects models (der Simonian and Laird) will be fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010). **Approach to GRADE for diagnostic accuracy data** Evidence from diagnostic accuracy studies will initially be rated as high-quality, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness).

		Likelihood ratios will be used as the primary outcome for decision making to define clinical decision thresholds in GRADE. In all cases, the downstream effects of diagnostic accuracy on patient- important outcomes will be considered. This will be done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results. In reviews where a decision model is being carried (for example, as part of an economic analysis), these consequences will be incorporated here in addition.
17.	Analysis of sub-groups	• Reference standard • Method of collecting reference sample • Age of baby, child or young person (under 16 years old) • Previous UTI versus first UTI • Recent antimicrobial treatment (including prophylactic antibiotic treatment)
18.	Type and method of review	☐ Intervention ☒ Diagnostic

		☐ Prognostic ☐ Qualitative ☐ Epidemiologic ☐ Service Delivery ☐ Other (please specify)		
19.	Language	English		
20.	Country	England		
21.	Anticipated or actual start date	8/02/2022		
22.	Anticipated completion date	Date by which the guideline is expected to be published. To be determined		
23.	Stage of review at time of this submission	**Review stage**	**Started**	**Completed**
		Preliminary searches	☑	☐

		Piloting of the study selection process	☐	☐
		Formal screening of search results against eligibility criteria	☐	☐
		Data extraction	☐	☐
		Risk of bias (quality) assessment	☐	☐
		Data analysis	☐	☐
24.	Named contact	**5a. Named contact** Centre for Guidelines, NICE. **5b Named contact e-mail** uti.update@nice.org.uk		

		5c Organisational affiliation of the review National Institute for Health and Care Excellence (NICE) and NICE Guideline Development Team.
25.	Review team members	From the Guideline Development Team: • Marie Harrisingh, Technical adviser • Greg Moran, Medicines analyst • Syed Mohiuddin, Health economist adviser • Jeremy Dietz, Health economist analyst • Andrea Heath, Information specialist • Ruth Garnett, Medicines adviser
26.	Funding sources/sponsor	This systematic review is being completed by the Guideline Development Team which receives funding from NICE.
27.	Conflicts of interest	All guideline committee members and anyone who has direct input into NICE guidelines (including the evidence review team and expert witnesses) must declare any potential conflicts of interest in line with NICE's code of practice for declaring and dealing with conflicts of interest. Any relevant interests, or changes to interests, will also be declared publicly at the start of each guideline committee meeting. Before each meeting, any potential conflicts of interest will be considered by the guideline committee Chair and a senior member of the development team. Any decisions to exclude a person from all or part of a meeting will be documented. Any changes to a member's declaration of interests will be recorded in the minutes of the meeting. Declarations of interests will be published with the final guideline.
28.	Collaborators	Development of this systematic review will be overseen by an advisory committee who will use the review to inform the development of evidence-based recommendations in line with section 3 of

		Developing NICE guidelines: the manual. Members of the guideline committee are available on the NICE website: Urinary tract infection in under 16s: diagnosis and management.
29.	Other registration details	none
30.	Reference/URL for published protocol	none
31.	Dissemination plans	NICE may use a range of different methods to raise awareness of the guideline. These include standard approaches such as: • notifying registered stakeholders of publication • publicising the guideline through NICE's newsletter and alerts • issuing a press release or briefing as appropriate, posting news articles on the NICE website, using social media channels, and publicising the guideline within NICE.
32.	Keywords	Signs and symptoms; urinary tract infection; babies, children and young people under 16 years old.
33.	Details of existing review of same topic by same authors	Not applicable
34.	Current review status	☒ Ongoing ☐ Completed but not published ☐ Completed and published ☐ Completed, published and being updated ☐ Discontinued

35..	Additional information	None
36.	Details of final publication	www.nice.org.uk

Appendix B – Literature search strategies

Search design and peer review

A NICE information specialist conducted the literature searches for the evidence review. The searches were run on 02/02/2022. This search report is compliant with the requirements of PRISMA-S.

The MEDLINE strategy below was quality assured (QA) by a trained NICE information specialist. All translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

The principal search strategy was developed in MEDLINE (Ovid interface) and adapted, as appropriate, for use in the other sources listed in the protocol, taking into account their size, search functionality and subject coverage.

Review management

The search results were managed in EPPI-Reviewer v5. Duplicates were removed in EPPI-R5 using -step process. First, automated deduplication is performed using a high-value algorithm. Second, manual deduplication is used to assess 'low-probability' matches. All decisions made for the review can be accessed via the deduplication history.

Prior work

The search strategy was based on the terms used for the former CG54 NICE guideline and the NICE surveillance search for this guideline. Modifications were made to these original search strategies for the specifications in the review protocol.

Limits and restrictions

English language limits were applied in adherence to standard NICE practice and the review protocol.

Limits to exclude letters, editorials, news, conferences were applied in adherence to standard NICE practice and the review protocol. Case reports were also excluded in adherence to the review protocol.

The search was limited from June 2006 to current as defined in the review protocol.

The limit to remove animal studies in the searches was the standard NICE practice, which has been adapted from: Dickersin, K., Scherer, R., & Lefebvre, C. (1994). Systematic Reviews: Identifying relevant studies for systematic reviews. *BMJ*, 309(6964), 1286.

Search filters

- Observational studies

The terms used for observational studies are standard NICE practice that have been developed in house.

Cost effectiveness searches

The following search filters were applied to the search strategies in MEDLINE and Embase to identify cost-effectiveness studies:

- Glanville J et al. (2009) Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Alberta: Canadian Agency for Drugs and Technologies in Health (CADTH)

Several modifications have been made to these filters over the years that are standard NICE practice.

Key decisions

The International Database of HTA (INAHTA) was searched from 2018 because records have not been added to Centre for Reviews and Dissemination (CRD) HTA since 2018.

The INAHTA strategy was modified to two sets – UTI population and Signs & Symptoms terms because of the low number of results.

Searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
Cochrane Central Register of Controlled Trials (CENTRAL)	2/02/22	Wiley	Cochrane Central Register of Controlled Trials Issue 2 of 12, February 2022	426
Cochrane Database of Systematic Reviews (CDSR)	2/02/22	Wiley	Cochrane Database of Systematic Reviews Issue 2 of 12, February 2022	29
Embase	2/02/22	Ovid	Embase <1974 to 2022 February 01>	3800
Emcare	2/02/22	Ovid	Ovid Emcare <1995 to 2022 Week 4>	820
MEDLINE	2/02/22	Ovid	Ovid MEDLINEI <1946 to February 01, 2022>	2764
MEDLINE-in-Process	2/02/22	Ovid	Ovid MEDLINEI In-Process & In-Data-Review Citations <1946 to February 01, 2022>	28
MEDLINE Epub Ahead-of-Print	2/02/22	Ovid	Ovid MEDLINEI Epub Ahead of Print <February 01, 2022>	29
DARE	2/02/22	CRD	N/A	14
HTA	2/02/22	CRD	N/A	2
INAHTA	7/02/22	INAHTA	N/A	6

Additional method	Date searched	No. of results downloaded
Forwards citation searching	03/02/22	77

Search strategy history

Database name: Centre for Reviews and Dissemination (CRD) DARE and HTA

1 MeSH DESCRIPTOR Infant EXPLODE ALL TREES
2 MeSH DESCRIPTOR Infant health
3 MeSH DESCRIPTOR Infant welfare

4 ((92llness92t* or pre-matur* or 92llness92ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*))
5 MeSH DESCRIPTOR Child EXPLODE ALL TREES
6 MeSH DESCRIPTOR Child behavior EXPLODE ALL TREES
7 MeSH DESCRIPTOR Child health
8 MeSH DESCRIPTOR Child welfare
9 MeSH DESCRIPTOR Minors
10 ((child* or minor or minors or boy* or girl* or kid or kids or young*))
11 MeSH DESCRIPTOR pediatrics EXPLODE ALL TREES
12 ((pediatric* or paediatric* or peadiatric*))
13 MeSH DESCRIPTOR adolescent
14 MeSH DESCRIPTOR Adolescent Behavior
15 MeSH DESCRIPTOR Adolescent health
16 MeSH DESCRIPTOR Puberty
17 ((adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 92llness* or 92llness92ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*))
18 MeSH DESCRIPTOR Schools
19 MeSH DESCRIPTOR Child Day Care Centers
20 MeSH DESCRIPTOR Nurseries, Infant EXPLODE ALL TREES
21 MeSH DESCRIPTOR Schools, Nursery
22 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*))
23 (("under 16*" or "under sixteen*"))
24 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25 MeSH DESCRIPTOR urinary tract infections EXPLODE ALL TREES
26 (((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj4 infect*))
27 ((UTI or UTIs))
28 (((upper or lower) adj4 urin*))
29 MeSH DESCRIPTOR cystitis EXPLODE ALL TREES
30 (cystitis)
31 ((bladder* adj4 (ulcer* or ulcus or 92llness*)))
32 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
33 MeSH DESCRIPTOR Proteinuria
34 (92llness92ty92*)
35 MeSH DESCRIPTOR Albuminuria
36 (Albuminuri*)
37 MeSH DESCRIPTOR Bacteriuria
38 (Bacteriuria*)
39 (((bacteria* or microbial*) adj4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)))
40 MeSH DESCRIPTOR Pyuria
41 (pyuri*)
42 (((protein* or albumin*) adj4 urin*))
43 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42
44 MeSH DESCRIPTOR Vesico-ureteral reflux
45 (((vesicorenal* or vesico?ureteral* or vesicour*) adj reflux*))
46 (VUR)

47 (((backflow* or bladder* or cystoureteral* or ureter* or urether*) adj4 reflux*))
48 #44 OR #45 OR #46 OR #47
49 MeSH DESCRIPTOR Pyelonephritis
50 ((pyelonephriti* or pyonephrosi* or pyelocystiti*))
51 #49 OR #50
52 #32 OR #43 OR #48 OR #51
53 MeSH DESCRIPTOR Signs and Symptoms
54 ((sign* adj2 symptom*)):TI
55 ((sign or signs or symptom* or complain*)):TI
56 ((clinical adj2 (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)))
57 ((presenting adj2 (feature? Or finding? Or factor? Or symptom?)))
58 (presentation?):TI
59 ((physical adj2 (manifestation? Or characteristic? Or feature? Or finding?)))
60 (red flag*)
61 (((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 infect* adj3 (indicat* or manifest* or present* or symptom*)))
62 #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61
63 MeSH DESCRIPTOR urinary tract infections WITH QUALIFIER DI
64 #62 OR #63
65 #24 AND #52 AND #64
66 (#65) IN DARE FROM 2006 TO 2022
67 (#65) IN HTA FROM 2006 TO 2022

Database name: Cochrane Central Register of Controlled Trials (CENTRAL)

#1 MeSH descriptor: [Infant] explode all trees 34223
#2 MeSH descriptor: [Infant Health] this term only 60
#3 MeSH descriptor: [Infant Welfare] this term only 83
#4 (93llness93t* or pre-matur* or 93llness93ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*):ti,ab,kw 99887
#5 MeSH descriptor: [Child] explode all trees 60126
#6 MeSH descriptor: [Child Behavior] explode all trees 2288
#7 MeSH descriptor: [Child Health] this term only 140
#8 MeSH descriptor: [Child Welfare] this term only 341
#9 MeSH descriptor: [Minors] this term only 10
#10 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab,kw 298865
#11 MeSH descriptor: [Pediatrics] explode all trees 718
#12 (pediatric* or paediatric* or peadiatric*):ti,ab,kw 38335
#13 MeSH descriptor: [Adolescent] this term only 109121
#14 MeSH descriptor: [Adolescent Behavior] this term only 1469
#15 MeSH descriptor: [Adolescent Health] this term only 38
#16 MeSH descriptor: [Puberty] this term only 311
#17 (adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 93llness* or 93llness93ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*):ti,ab,kw 152725
#18 MeSH descriptor: [Schools] this term only 2394
#19 MeSH descriptor: [Child Day Care Centers] this term only 262
#20 MeSH descriptor: [Nurseries, Infant] explode all trees 11
#21 MeSH descriptor: [Schools, Nursery] this term only 40
#22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab,kw 110464

#23 ("under 16*" or "under sixteen*"):ti,ab,kw 140
#24 {OR #1-#23} 449355
#25 MeSH descriptor: [Urinary Tract Infections] 3 tree(s) exploded 2651
#26 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) near4 infect*):ti,ab,kw 140521
#27 (UTI or UTIs):ti,ab,kw 2306
#28 ((upper or lower) near/4 urin*):ti,ab,kw 4419
#29 MeSH descriptor: [Cystitis] 2 tree(s) exploded 115
#30 cystitis:ti,ab,kw 1716
#31 (bladder* near/4 (ulcer* or ulcus or 94llness*)):ti,ab,kw 59
#32 {OR #25-#31} 145375
#33 MeSH descriptor: [Proteinuria] this term only 1059
#34 proteinuri*:ti,ab,kw 5622
#35 MeSH descriptor: [Albuminuria] this term only 1353
#36 Albuminuri*:ti,ab,kw 2985
#37 MeSH descriptor: [Bacteriuria] this term only 507
#38 Bacteriuria*:ti,ab,kw 1191
#39 ((bacteria* or microbial*) near/4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)):ti,ab,kw 553
#40 MeSH descriptor: [Pyuria] this term only 37
#41 pyuri*:ti,ab,kw 272
#42 ((protein* or albumin*) near/4 urin*)ti,ab,kw 49
#43 {OR #33-#42} 9888
#44 MeSH descriptor: [Vesico-Ureteral Reflux] this term only 144
#45 ((vesicorenal* or vesico?ureteral* or vesicour*) next reflux*):ti,ab,kw 403
#46 VUR:ti,ab,kw 165
#47 ((backflow* or bladder* or cystoureteral* or ureter* or urether*) near/4 reflux*) 234
#48 {OR #44-#47} 437
#49 MeSH descriptor: [Pyelonephritis] this term only 258
#50 (pyelonephriti* or pyonephrosi* or pyelocystiti*):ti,ab,kw 1045
#51 #49 or #50 1045
#52 #32 or #43 or #48 or #51 153260
#53 MeSH descriptor: [Signs and Symptoms] this term only 122
#54 (sign* near/2 symptom*):ti,kw 1362
#55 (sign or signs or symptom* or complain*):ti 32287
#56 (clinical next (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)):ti 923
#57 (presenting next (feature? Or finding? Or factor? Or symptom?)):ti,ab,kw 467
#58 presentation?:ti,kw 1561
#59 (physical near/2 (manifestation? Or characteristic? Or feature? Or finding?)):ti,ab,kw 1640
#60 red flag*:ti,ab,kw 183
#61 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) near/3 infect* near/3 (indicat* or manifest* or present* or symptom*)):ti,ab,kw 594
#62 {OR #53-#61} 37903
#63 MeSH descriptor: [Urinary Tract Infections] this term only and with qualifier(s): [diagnosis – DI] 109
#64 #62 or #63 37987
#65 #24 and #52 and #64 with Cochrane Library publication date Between Jun 2006 and Jan 2022, in Cochrane Reviews, Cochrane Protocols 29

#66 #24 and #52 and #64 with Publication Year from 2006 to 2022, in Trials 709
#67 "conference":pt or (clinicaltrials or trialsearch):so 584219
#68 #66 not #67 426

Database name: Cochrane Database of Systematic Reviews (CDSR)

#1 MeSH descriptor: [Infant] explode all trees 34223
#2 MeSH descriptor: [Infant Health] this term only 60
#3 MeSH descriptor: [Infant Welfare] this term only 83
#4 (95llness95t* or pre-matur* or 95llness95ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*):ti,ab,kw 99887
#5 MeSH descriptor: [Child] explode all trees 60126
#6 MeSH descriptor: [Child Behavior] explode all trees 2288
#7 MeSH descriptor: [Child Health] this term only 140
#8 MeSH descriptor: [Child Welfare] this term only 341
#9 MeSH descriptor: [Minors] this term only 10
#10 (child* or minor or minors or boy* or girl* or kid or kids or young*):ti,ab,kw 298865
#11 MeSH descriptor: [Pediatrics] explode all trees 718
#12 (pediatric* or paediatric* or peadiatric*):ti,ab,kw 38335
#13 MeSH descriptor: [Adolescent] this term only 109121
#14 MeSH descriptor: [Adolescent Behavior] this term only 1469
#15 MeSH descriptor: [Adolescent Health] this term only 38
#16 MeSH descriptor: [Puberty] this term only 311
#17 (adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 95llness* or 95llness95ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*):ti,ab,kw 152725
#18 MeSH descriptor: [Schools] this term only 2394
#19 MeSH descriptor: [Child Day Care Centers] this term only 262
#20 MeSH descriptor: [Nurseries, Infant] explode all trees 11
#21 MeSH descriptor: [Schools, Nursery] this term only 40
#22 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*):ti,ab,kw 110464
#23 ("under 16*" or "under sixteen*"):ti,ab,kw 140
#24 {OR #1-#23} 449355
#25 MeSH descriptor: [Urinary Tract Infections] 3 tree(s) exploded 2651
#26 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) near4 infect*):ti,ab,kw 140521
#27 (UTI or UTIs):ti,ab,kw 2306
#28 ((upper or lower) near/4 urin*):ti,ab,kw 4419
#29 MeSH descriptor: [Cystitis] 2 tree(s) exploded 115
#30 cystitis:ti,ab,kw 1716
#31 (bladder* near/4 (ulcer* or ulcus or 95llness*)):ti,ab,kw 59
#32 {OR #25-#31} 145375
#33 MeSH descriptor: [Proteinuria] this term only 1059
#34 proteinuri*:ti,ab,kw 5622
#35 MeSH descriptor: [Albuminuria] this term only 1353
#36 Albuminuri*:ti,ab,kw 2985
#37 MeSH descriptor: [Bacteriuria] this term only 507
#38 Bacteriuria*:ti,ab,kw 1191
#39 ((bacteria* or microbial*) near/4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)):ti,ab,kw 553

#40 MeSH descriptor: [Pyuria] this term only 37
#41 pyuri*:ti,ab,kw 272
#42 ((protein* or albumin*) near/4 urin*)ti,ab,kw 49
#43 {OR #33-#42} 9888
#44 MeSH descriptor: [Vesico-Ureteral Reflux] this term only 144
#45 ((vesicorenal* or vesico?ureteral* or vesicour*) next reflux*):ti,ab,kw 403
#46 VUR:ti,ab,kw 165
#47 ((backflow* or bladder* or cystoureteral* or ureter* or urether*) near/4 reflux*) 234
#48 {OR #44-#47} 437
#49 MeSH descriptor: [Pyelonephritis] this term only 258
#50 (pyelonephriti* or pyonephrosi* or pyelocystiti*):ti,ab,kw 1045
#51 #49 or #50 1045
#52 #32 or #43 or #48 or #51 153260
#53 MeSH descriptor: [Signs and Symptoms] this term only 122
#54 (sign* near/2 symptom*):ti,kw 1362
#55 (sign or signs or symptom* or complain*):ti 32287
#56 (clinical next (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)):ti 923
#57 (presenting next (feature? Or finding? Or factor? Or symptom?)):ti,ab,kw 467
#58 presentation?:ti,kw 1561
#59 (physical near/2 (manifestation? Or characteristic? Or feature? Or finding?)):ti,ab,kw 1640
#60 red flag*:ti,ab,kw 183
#61 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) near/3 infect* near/3 (indicat* or manifest* or present* or symptom*)):ti,ab,kw 594
#62 {OR #53-#61} 37903
#63 MeSH descriptor: [Urinary Tract Infections] this term only and with qualifier(s): [diagnosis – DI] 109
#64 #62 or #63 37987
#65 #24 and #52 and #64 with Cochrane Library publication date Between Jun 2006 and Feb 2022, in Cochrane Reviews, Cochrane Protocols 29

Database name: Embase

1 exp infant/ or infant welfare/ (1056105)
2 prematurity/ or postmaturity/ or newborn/ or newborn period/ (630658)
3 (96llness96t* or pre-matur* or 96llness96ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1381201)
4 child welfare/ or exp child/ or child health care/ or child behavior/ or child health/ (2877473)
5 “minor (person)”/ (778)
6 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3961808)
7 exp pediatrics/ (116302)
8 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1678638)
9 adolescent behavior/ or adolescent health/ or adolescent/ (1648013)
10 puberty/ (27936)
11 (adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 96llness* or 96llness96ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*).ti,ab,in,jn. (721914)
12 school/ (67008)
13 nursery/ or nursery school/ or child day care/ or day care/ or kindergarten/ (20055)

14 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (772351)
15 ("under 16*" or "under sixteen*").ti,ab. (2377)
16 or/1-15 (6991692)
17 exp urinary tract infection/ (124574)
18 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj4 infect*).ti,ab. (104293)
19 (UTI or UTIs).ti,ab. (24001)
20 ((upper or lower) adj4 urin*).ti,ab. (44447)
21 exp cystitis/ (26450)
22 cystitis.ti,ab. (17763)
23 (bladder* adj4 (ulcer* or ulcus or 97llness*)).ti,ab. (2564)
24 or/17-23 (229189)
25 proteinuria/ (82118)
26 proteinuri*.ti,ab. (65707)
27 albuminuria/ (18606)
28 Albuminuri*.ti,ab. (17808)
29 bacteriuria/ (7334)
30 Bacteriuria*.ti,ab. (7362)
31 ((bacteria* or microbial*) adj4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)).ti,ab. (8423)
32 pyuria/ (4114)
33 pyuri*.ti,ab. (2894)
34 ((protein* or albumin*) adj4 urin*).ti,ab. (46732)
35 or/25-34 (162622)
36 vesicoureteral reflux/ (13499)
37 ((vesicorenal* or vesico?ureteral* or vesicour*) adj reflux*).ti,ab. (8324)
38 VUR.ti,ab. (3805)
39 ((backflow* or bladder* or cystoureteral* or ureter* or urether*) adj4 reflux*).ti,ab. (4256)
40 or/36-39 (15964)
41 exp pyelonephritis/ (22779)
42 (pyelonephriti* or pyonephrosi* or pyelocystiti*).ti,ab. (16507)
43 41 or 42 (26379)
44 or/24,35,40,43 (392922)
45 physical disease by body function/ (12479)
46 symptom/ (154200)
47 (sign* adj2 symptom*).ti,kw. (4051)
48 (sign or signs or symptom* or complain*).ti,ab. /freq=2 (1019919)
49 (clinical adj2 (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)).ti,ab. (453991)
50 (presenting adj2 (feature? Or finding? Or factor? Or symptom?)).ti,ab. (44060)
51 presentation?.ti,ab. /freq=2 (144267)
52 (physical adj2 (manifestation? Or characteristic? Or feature? Or finding?)).ti,ab. (31352)
53 red flag*.ti,ab. (4101)
54 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 infect* adj3 (indicat* or manifest* or present* or symptom*)).ti,ab. (4648)
55 or/45-54 (1660370)
56 urinary tract infection/di [Diagnosis] (8504)
57 55 or 56 (1667425)
58 and/16,44,57 (18661)
59 (97llness97t: or predictive value:).mp. or 97llness97:.tw. (2863775)

60 Clinical study/ (157140)
61 Case control study/ (183356)
62 Family study/ (25374)
63 Longitudinal study/ (166916)
64 Retrospective study/ (1194045)
65 comparative study/ (934491)
66 Prospective study/ (742075)
67 Randomized controlled trials/ (219331)
68 66 not 67 (733517)
69 Cohort analysis/ (800913)
70 cohort analy*.tw. (15929)
71 (Cohort adj (study or studies)).tw. (376645)
72 (Case control* adj (study or studies)).tw. (154285)
73 (follow up adj (study or studies)).tw. (68257)
74 (observational adj (study or studies)).tw. (208502)
75 (epidemiologic* adj (study or studies)).tw. (114340)
76 (cross sectional adj (study or studies)).tw. (276160)
77 case series.tw. (125334)
78 prospective.tw. (975470)
79 retrospective.tw. (1059829)
80 or/60-65,68-79 (4694383)
81 59 or 80 (7039118)
82 58 and 81 (7553)
83 limit 82 to 98llness language (6944)
84 limit 83 to dc=20060601-20220228 (5828)
85 nonhuman/ not (human/ and nonhuman/) (4925871)
86 84 not 85 (5792)
87 (conference abstract or conference paper or “conference review” or editorial or letter or note).pt. (7886507)
88 86 not 87 (3800)

Database name: Emcare

1 exp infant/ or infant welfare/ (211759)
2 prematurity/ or postmaturity/ or newborn/ or newborn period/ (120484)
3 (98llness98t* or pre-matur* or 98llness98ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*).ti,ab,in,jn. (322444)
4 child welfare/ or exp child/ or child health care/ or child behavior/ or child health/ (729998)
5 “minor (person)”/ (211)
6 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (1112364)
7 exp pediatrics/ (37250)
8 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (439218)
9 adolescent behavior/ or adolescent health/ or adolescent/ (376464)
10 puberty/ (5843)
11 (adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 98llness* or 98llness98ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*).ti,ab,in,jn. (267550)
12 school/ (56472)
13 nursery/ or nursery school/ or child day care/ or day care/ or kindergarten/ (10971)
14 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (349148)

15 ("under 16*" or "under sixteen*").ti,ab. (575)
16 or/1-15 (1801575)
17 exp urinary tract infection/ (26314)
18 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj4 infect*).ti,ab. (15692)
19 (UTI or UTIs).ti,ab. (4032)
20 ((upper or lower) adj4 urin*).ti,ab. (5285)
21 exp cystitis/ (3896)
22 cystitis.ti,ab. (1852)
23 (bladder* adj4 (ulcer* or ulcus or 99llness*)).ti,ab. (252)
24 or/17-23 (38650)
25 proteinuria/ (12401)
26 proteinuri*.ti,ab. (6879)
27 albuminuria/ (3396)
28 Albuminuri*.ti,ab. (3142)
29 bacteriuria/ (1086)
30 Bacteriuria*.ti,ab. (1065)
31 ((bacteria* or microbial*) adj4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)).ti,ab. (904)
32 pyuria/ (809)
33 pyuri*.ti,ab. (356)
34 ((protein* or albumin*) adj4 urin*).ti,ab. (5900)
35 or/25-34 (23122)
36 vesicoureteral reflux/ (2082)
37 ((vesicorenal* or vesico?ureteral* or vesicour*) adj reflux*).ti,ab. (1252)
38 VUR.ti,ab. (684)
39 ((backflow* or bladder* or cystoureteral* or ureter* or urether*) adj4 reflux*).ti,ab. (397)
40 or/36-39 (2309)
41 exp pyelonephritis/ (3467)
42 (pyelonephriti* or pyonephrosi* or pyelocystiti*).ti,ab. (1753)
43 41 or 42 (3739)
44 or/24,35,40,43 (61550)
45 physical disease by body function/ (7406)
46 symptom/ (38543)
47 (sign* adj2 symptom*).ti,kw. (1129)
48 (sign or signs or symptom* or complain*).ti,ab. /freq=2 (246663)
49 (clinical adj2 (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)).ti,ab. (75701)
50 (presenting adj2 (feature? Or finding? Or factor? Or symptom?)).ti,ab. (7697)
51 presentation?.ti,ab. /freq=2 (26307)
52 (physical adj2 (manifestation? Or characteristic? Or feature? Or finding?)).ti,ab. (8294)
53 red flag*.ti,ab. (1340)
54 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 infect* adj3 (indicat* or manifest* or present* or symptom*)).ti,ab. (777)
55 or/45-54 (366303)
56 [urinary tract infection/di [Diagnosis]] (0)
57 55 or 56 (366303)
58 and/16,44,57 (2315)
59 (99llness99t: or predictive value:).mp. or 99llness99:.tw. (526347)
60 Clinical study/ (49896)
61 Case control study/ (39837)

62 Family study/ (11147)
63 Longitudinal study/ (65509)
64 Retrospective study/ (251285)
65 comparative study/ (134052)
66 Prospective study/ (192832)
67 Randomized controlled trials/ (77035)
68 66 not 67 (190207)
69 Cohort analysis/ (214189)
70 cohort analy*.tw. (4235)
71 (Cohort adj (study or studies)).tw. (122442)
72 (Case control* adj (study or studies)).tw. (38993)
73 (follow up adj (study or studies)).tw. (17267)
74 (observational adj (study or studies)).tw. (63151)
75 (epidemiologic* adj (study or studies)).tw. (28087)
76 (cross sectional adj (study or studies)).tw. (110184)
77 case series.tw. (32707)
78 prospective.tw. (256181)
79 retrospective.tw. (236483)
80 or/60-65,68-79 (1113953)
81 59 or 80 (1516704)
82 58 and 81 (1027)
83 limit 82 to 100llness language (991)
84 limit 83 to dc=20060601-20220228 (844)
85 nonhuman/ not (human/ and nonhuman/) (443979)
86 84 not 85 (841)
87 (conference abstract o r conference paper or “conference review” or editorial or letter or note).pt. (1136793)
88 86 not 87 (820)

Database name: International HTA Database (INAHTA)

	Limit to English language and records from 2018-2022	6
13 and 23	(((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect*) AND (indicat* or manifest* or present* or symptom*)) OR ((red flag*)) OR ((physical) AND (manifestation? Or characteristic? Or feature? Or finding?)) OR ((presentation?)) OR ((presenting) AND (feature? Or finding? Or factor? Or symptom?)) OR ((clinical) AND (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)) OR ((sign or signs or symptom* or complain*)) OR ((sign* and symptom*)[Title]) OR ((Signs and Symptoms)[mh])) AND (((backflow* or bladder* or cystoureteral* or ureter* or urether*) AND (reflux*)) OR ((vesicorenal* or vesico?ureteral* or vesicour*) AND (reflux)) OR ((protein* or albumin*) AND (urin*)) OR ((bacteria* or microbial*) AND (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)) OR ((bladder*) AND (ulcer* or ulcus or 100llness*)) OR ((100llness100ty100* or Albuminuri* or Bacteriuria* or pyuri* or VUR or pyelonephriti* or pyonephrosi* or pyelocystiti*)) OR ((cystitis)) OR ((cystitis)[mh]) OR ((upper or lower) AND (urin*)) OR ((UTI or UTIs)) OR ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect*)) OR ((urinary tract infections)[mh]))	124

or/14-22	((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect*) AND (indicat* or manifest* or present* or symptom*)) OR ((red flag*)) OR ((physical) AND (manifestation? Or characteristic? Or feature? Or finding?)) OR ((presentation?)) OR ((presenting) AND (feature? Or finding? Or factor? Or symptom?)) OR ((clinical) AND (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)) OR ((sign or signs or symptom* or complain*)) OR ((sign* and symptom*)[Title]) OR ((Signs and Symptoms)[mh])	2213
22	(bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect*) AND (indicat* or manifest* or present* or symptom*)	69
21	(red flag*)	2
20	(physical) AND (manifestation? Or characteristic? Or feature? Or finding?)	19
19	(presentation?)	106
18	(presenting) AND (feature? Or finding? Or factor? Or symptom?)	32
17	(clinical) AND (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)	558
16	(sign or signs or symptom* or complain*)	1673
15	(sign* and symptom*)[Title]	2
14	(Signs and Symptoms)[mh]	1
or/1-12	((backflow* or bladder* or cystoureteral* or ureter* or urether*) AND (reflux*)) OR ((vesicorenal* or vesico?ureteral* or vesicour*) AND (reflux)) OR ((protein* or albumin*) AND (urin*)) OR ((bacteria* or microbial*) AND (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)) OR ((bladder*) AND (ulcer* or ulcus or 101llness*)) OR ((101llness101ty101* or Albuminuri* or Bacteriuria* or pyuri* or VUR or pyelonephriti* or pyonephrosi* or pyelocystiti*)) OR ((cystitis)) OR ((cystitis)[mh]) OR ((upper or lower) AND (urin*)) OR ((UTI or UTIs)) OR ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect*)) OR ((urinary tract infections)[mh])	216
12	(backflow* or bladder* or cystoureteral* or ureter* or urether*) AND (reflux*)	1
11	(vesicorenal* or vesico?ureteral* or vesicour*) AND (reflux)	1
10	(protein* or albumin*) AND (urin*)	29
9	(bacteria* or microbial*) AND (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)	15
8	(bladder*) AND (ulcer* or ulcus or 101llness*)	6
7	(101llness101ty101* or Albuminuri* or Bacteriuria* or pyuri* or VUR or pyelonephriti* or pyonephrosi* or pyelocystiti*)	23

6	(cystitis)	10
5	(cystitis)[mh]	7
4	(upper or lower) AND (urin*)	55
3	(UTI or UTIs)	14
2	(bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect*)	122
1	(urinary tract infections)[mh]	37

Database name: MEDLINE

1 exp Infant/ or Infant Health/ or Infant Welfare/ (1205894)
2 (102llness102t* or pre-matur* or 102llness102ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*).ti,ab,in,jn. (999890)
3 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (2054040)
4 Minors/ (2717)
5 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2653802)
6 exp pediatrics/ (61972)
7 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (971878)
8 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2155961)
9 Puberty/ (13916)
10 (adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 102llness* or 102llness102ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*).ti,ab,in,jn. (486853)
11 Schools/ (46070)
12 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7458)
13 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (527218)
14 (“under 16*” or “under sixteen*”).ti,ab. (1528)
15 or/1-14 (5704733)
16 exp Urinary tract infections/ (48927)
17 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj4 infect*).ti,ab. (63600)
18 (UTI or UTIs).ti,ab. (10452)
19 ((upper or lower) adj4 urin*).ti,ab. (26687)
20 exp cystitis/ (10140)
21 cystitis.ti,ab. (10750)
22 (bladder* adj4 (ulcer* or ulcus or 102llness*)).ti,ab. (1539)
23 or/16-22 (119102)
24 Proteinuria/ (24923)
25 proteinuri*.ti,ab. (38422)
26 Albuminuria/ (15825)
27 Albuminuri*.ti,ab. (10746)
28 Bacteriuria/ (7858)
29 Bacteriuria*.ti,ab. (5789)
30 ((bacteria* or microbial*) adj4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)).ti,ab. (5633)
31 Pyuria/ (1165)

32 pyuri*.ti,ab. (1761)
33 ((protein* or albumin*) adj4 urin*).ti,ab. (27621)
34 or/24-33 (92609)
35 Vesico-ureteral reflux/ (8480)
36 ((vesicorenal* or vesico?ureteral* or vesicour*) adj reflux*).ti,ab. (5846)
37 VUR.ti,ab. (2143)
38 ((backflow* or bladder* or cystoureteral* or ureter* or urether*) adj4 reflux*).ti,ab. (3344)
39 or/35-38 (11148)
40 Pyelonephritis/ (14327)
41 (pyelonephriti* or pyonephrosi* or pyelocystiti*).ti,ab. (12932)
42 40 or 41 (19123)
43 or/23,34,39,42 (213922)
44 "Signs and Symptoms"/ (407)
45 (sign* adj2 symptom*).ti,kw. (2771)
46 (sign or signs or symptom* or complain*).ti,ab. /freq=2 (575361)
47 (clinical adj2 (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)).ti,ab. (279789)
48 (presenting adj2 (feature? Or finding? Or factor? Or symptom?)).ti,ab. (23641)
49 presentation?.ti,ab. /freq=2 (66770)
50 (physical adj2 (manifestation? Or characteristic? Or feature? Or finding?)).ti,ab. (20210)
51 red flag*.ti,ab. (1982)
52 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 infect* adj3 (indicat* or manifest* or present* or symptom*)).ti,ab. (2839)
53 or/44-52 (911150)
54 Urinary Tract Infections/di [Diagnosis] (6336)
55 53 or 54 (916529)
56 and/15,43,55 (10075)
57 (103llness103t: or predictive value:).mp. or 103llness103:.tw. (2074068)
58 Observational Studies as Topic/ (7431)
59 Observational Study/ (120052)
60 Epidemiologic Studies/ (8988)
61 exp Case-Control Studies/ (1279713)
62 exp Cohort Studies/ (2289768)
63 Cross-Sectional Studies/ (409861)
64 Controlled Before-After Studies/ (678)
65 Historically Controlled Study/ (218)
66 Interrupted Time Series Analysis/ (1513)
67 Comparative Study.pt. (1907879)
68 case control$.tw. (126873)
69 case series.tw. (72068)
70 (cohort adj (study or studies)).tw. (222725)
71 cohort analy$.tw. (8522)
72 (follow up adj (study or studies)).tw. (48667)
73 (observational adj (study or studies)).tw. (111206)
74 longitudinal.tw. (241773)
75 prospective.tw. (567079)
76 retrospective.tw. (541532)
77 cross sectional.tw. (355667)
78 or/58-77 (4813006)
79 57 or 78 (6317701)
80 56 and 79 (5093)

81 limit 80 to 104llness language (4476)
82 limit 81 to ed=20060601-20220228 (2891)
83 Animals/ not humans/ (4919018)
84 82 not 83 (2873)
85 limit 84 to (letter or historical article or clinical conference or comment or editorial or news or case reports) (109)
86 84 not 85 (2764)

Database name: Medline in Process and Medline ePubs

1 (104llness104t* or pre-matur* or 104llness104ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*).ti,ab,in,jn. (7314)
2 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (24483)
3 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (12723)
4 (adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 104llness* or 104llness104ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*).ti,ab,in,jn. (4803)
5 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (3108)
6 ("under 16*" or "under sixteen*").ti,ab. (5)
7 or/1-6 (34611)
8 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj4 infect*).ti,ab. (479)
9 (UTI or UTIs).ti,ab. (128)
10 ((upper or lower) adj4 urin*).ti,ab. (245)
11 cystitis.ti,ab. (65)
12 (bladder* adj4 (ulcer* or ulcus or 104llness*)).ti,ab. (13)
13 proteinuri*.ti,ab. (331)
14 Albuminuri*.ti,ab. (148)
15 Bacteriuria*.ti,ab. (23)
16 ((bacteria* or microbial*) adj4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)).ti,ab. (45)
17 pyuri*.ti,ab. (5)
18 ((protein* or albumin*) adj4 urin*).ti,ab. (243)
19 ((vesicorenal* or vesico?ureteral* or vesicour*) adj reflux*).ti,ab. (38)
20 VUR.ti,ab. (25)
21 ((backflow* or bladder* or cystoureteral* or ureter* or urether*) adj4 reflux*).ti,ab. (12)
22 (pyelonephriti* or pyonephrosi* or pyelocystiti*).ti,ab. (37)
23 or/8-22 (1421)
24 (sign* adj2 symptom*).ti,kw. (15)
25 (sign or signs or symptom* or complain*).ti,ab. /freq=2 (4651)
26 (clinical adj2 (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)).ti,ab. (2506)
27 (presenting adj2 (feature? Or finding? Or factor? Or symptom?)).ti,ab. (131)
28 presentation?.ti,ab. /freq=2 (607)
29 (physical adj2 (manifestation? Or characteristic? Or feature? Or finding?)).ti,ab. (132)
30 red flag*.ti,ab. (28)
31 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 infect* adj3 (indicat* or manifest* or present* or symptom*)).ti,ab. (20)
32 or/24-31 (7576)
33 and/7,23,32 (63)

34 (105llness105t: or predictive value:).mp. or 105llness105:.tw. (14594)
35 case control*.tw. (1198)
36 case series.tw. (873)
37 (cohort adj (study or studies)).tw. (4449)
38 cohort analy*.tw. (163)
39 (follow up adj (study or studies)).tw. (248)
40 (observational adj (study or studies)).tw. (1885)
41 longitudinal.tw. (3049)
42 prospective.tw. (5653)
43 retrospective.tw. (7686)
44 cross sectional.tw. (4506)
45 or/35-44 (22392)
46 34 or 45 (34752)
47 33 and 46 (28)
48 limit 47 to 105llness language (28)
49 limit 48 to dt=20060601-20220228 (28)

Additional search methods

Source name: Citationchaser

Citationchaser was used for Forward citation searching.

Haddaway, N. R., Grainger, M. J., Gray, C. T. (2021) citationchaser: An R package and Shiny app for forward and backward citations chasing in academic searching. Doi: 10.5281/zenodo.4543513

The following three papers were selected for citation searching:

Improving the Diagnosis and Treatment of Urinary Tract Infection in Young Children in Primary Care: Results from the DUTY Prospective Diagnostic Cohort Study

Alastair D. Hay, Jonathan A. C. Sterne et al

The Annals of Family Medicine Jul 2016, 14 (4) 325-336

Hay AD, Birnie K, Busby J, et al.; on behalf of the DUTY team. The Diagnosis of Urinary Tract infection in Young children (DUTY): a diagnostic prospective observational study to derive and validate a clinical algorithm for the diagnosis of urinary tract infection in children presenting to primary care with an acute illness. Southampton (UK): NIHR Journals Library; 2016 Jul. (Health Technology Assessment, No. 20.51.)

Butler CC, Sterne JA, Lawton M, O'Brien K, Wootton M, Hood K, Hollingworth W, Little P, Delaney BC, van der Voort J, Dudley J, Birnie K, Pickles T, Waldron CA, Downing H, Thomas-Jones E, Lisles C, Rumsby K, Durbaba S, Whiting P, Harman K, Howe R, MacGowan A, Fletcher M, Hay AD. Nappy pad urine samples for investigation and treatment of UTI in young children: the 'DUTY' prospective diagnostic cohort study. Br J Gen Pract. 2016 Jul;66(648):e516-24.

Cost-effectiveness searches

Main search – Databases

Database	Date searched	Database Platform	Database segment or version	No. of results downloaded
EconLit	07/02/22	OVID	Econlit <1886 to January 27, 2022>	0
EED	07/02/22	CRD	N/A	11
Embase	07/02/22	Ovid	Embase <1974 to 2022 February 04>	992
HTA	02/02/22	CRD	N/A	2
INAHTA	07/02/22	INAHTA	N/A	21
MEDLINE	07/02/22	Ovid	<1946 to February 04, 2022>	542
MEDLINE-in-Process	07/02/22	Ovid	Ovid MEDLINEI In-Process & In-Data-Review Citations <1946 to February 04, 2022>	9
MEDLINE Epub Ahead-of-Print	07/02/22	Ovid	Epub Ahead of Print <February 04, 2022>	14

Search strategy history

Database name: Centre for Reviews and Dissemination (CRD) HTA

1 MeSH DESCRIPTOR Infant EXPLODE ALL TREES
2 MeSH DESCRIPTOR Infant health
3 MeSH DESCRIPTOR Infant welfare
4 ((106llness106t* or pre-matur* or 106llness106ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*))
5 MeSH DESCRIPTOR Child EXPLODE ALL TREES
6 MeSH DESCRIPTOR Child behavior EXPLODE ALL TREES
7 MeSH DESCRIPTOR Child health
8 MeSH DESCRIPTOR Child welfare
9 MeSH DESCRIPTOR Minors
10 ((child* or minor or minors or boy* or girl* or kid or kids or young*))
11 MeSH DESCRIPTOR pediatrics EXPLODE ALL TREES
12 ((pediatric* or paediatric* or peadiatric*))
13 MeSH DESCRIPTOR adolescent
14 MeSH DESCRIPTOR Adolescent Behavior
15 MeSH DESCRIPTOR Adolescent health
16 MeSH DESCRIPTOR Puberty

17 ((adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 107llness* or 107llness107ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*))
18 MeSH DESCRIPTOR Schools
19 MeSH DESCRIPTOR Child Day Care Centers
20 MeSH DESCRIPTOR Nurseries, Infant EXPLODE ALL TREES
21 MeSH DESCRIPTOR Schools, Nursery
22 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*))
23 (("under 16*" or "under sixteen*"))
24 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25 MeSH DESCRIPTOR urinary tract infections EXPLODE ALL TREES
26 (((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj4 infect*))
27 ((UTI or UTIs))
28 (((upper or lower) adj4 urin*))
29 MeSH DESCRIPTOR cystitis EXPLODE ALL TREES
30 (cystitis)
31 ((bladder* adj4 (ulcer* or ulcus or 107llness*)))
32 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
33 MeSH DESCRIPTOR Proteinuria
34 (107llness107ty107*)
35 MeSH DESCRIPTOR Albuminuria
36 (Albuminuri*)
37 MeSH DESCRIPTOR Bacteriuria
38 (Bacteriuria*)
39 (((bacteria* or microbial*) adj4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)))
40 MeSH DESCRIPTOR Pyuria
41 (pyuri*)
42 (((protein* or albumin*) adj4 urin*))
43 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42
44 MeSH DESCRIPTOR Vesico-ureteral reflux
45 (((vesicorenal* or vesico?ureteral* or vesicour*) adj reflux*))
46 (VUR)
47 (((backflow* or bladder* or cystoureteral* or ureter* or urether*) adj4 reflux*))
48 #44 OR #45 OR #46 OR #47
49 MeSH DESCRIPTOR Pyelonephritis
50 ((pyelonephriti* or pyonephrosi* or pyelocystiti*))
51 #49 OR #50
52 #32 OR #43 OR #48 OR #51
53 MeSH DESCRIPTOR Signs and Symptoms
54 ((sign* adj2 symptom*)):TI
55 ((sign or signs or symptom* or complain*)):TI
56 ((clinical adj2 (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)))
57 ((presenting adj2 (feature? Or finding? Or factor? Or symptom?)))
58 (presentation?):TI
59 ((physical adj2 (manifestation? Or characteristic? Or feature? Or finding?)))
60 (red flag*)

61 (((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 infect* adj3 (indicat* or manifest* or present* or symptom*)))
62 #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61
63 MeSH DESCRIPTOR urinary tract infections WITH QUALIFIER DI
64 #62 OR #63
65 #24 AND #52 AND #64
66 (#65) IN DARE FROM 2006 TO 2022
67 (#65) IN HTA FROM 2006 TO 2022

Database name: Centre for Reviews and Dissemination (CRD) NHS EED

1 MeSH DESCRIPTOR Infant EXPLODE ALL TREES
2 MeSH DESCRIPTOR Infant health
3 MeSH DESCRIPTOR Infant welfare
4 ((108llness108t* or pre-matur* or 108llness108ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*))
5 MeSH DESCRIPTOR Child EXPLODE ALL TREES
6 MeSH DESCRIPTOR Child behavior EXPLODE ALL TREES
7 MeSH DESCRIPTOR Child health
8 MeSH DESCRIPTOR Child welfare
9 MeSH DESCRIPTOR Minors
10 ((child* or minor or minors or boy* or girl* or kid or kids or young*))
11 MeSH DESCRIPTOR pediatrics EXPLODE ALL TREES
12 ((pediatric* or paediatric* or peadiatric*))
13 MeSH DESCRIPTOR adolescent
14 MeSH DESCRIPTOR Adolescent Behavior
15 MeSH DESCRIPTOR Adolescent health
16 MeSH DESCRIPTOR Puberty
17 ((adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 108llness* or 108llness108ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*))
18 MeSH DESCRIPTOR Schools
19 MeSH DESCRIPTOR Child Day Care Centers
20 MeSH DESCRIPTOR Nurseries, Infant EXPLODE ALL TREES
21 MeSH DESCRIPTOR Schools, Nursery
22 ((pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*))
23 ((“under 16*” or “under sixteen*”))
24 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23
25 MeSH DESCRIPTOR urinary tract infections EXPLODE ALL TREES
26 (((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj4 infect*))
27 ((UTI or UTIs))
28 (((upper or lower) adj4 urin*))
29 MeSH DESCRIPTOR cystitis EXPLODE ALL TREES
30 (cystitis)
31 ((bladder* adj4 (ulcer* or ulcus or 108llness*)))
32 #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
33 MeSH DESCRIPTOR Proteinuria
34 (108llness108ty108*)

35 MeSH DESCRIPTOR Albuminuria
36 (Albuminuri*)
37 MeSH DESCRIPTOR Bacteriuria
38 (Bacteriuria*)
39 (((bacteria* or microbial*) adj4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)))
40 MeSH DESCRIPTOR Pyuria
41 (pyuri*)
42 (((protein* or albumin*) adj4 urin*))
43 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42
44 MeSH DESCRIPTOR Vesico-ureteral reflux
45 (((vesicorenal* or vesico?ureteral* or vesicour*) adj reflux*))
46 (VUR)
47 (((backflow* or bladder* or cystoureteral* or ureter* or urether*) adj4 reflux*))
48 #44 OR #45 OR #46 OR #47
49 MeSH DESCRIPTOR Pyelonephritis
50 ((pyelonephriti* or pyonephrosi* or pyelocystiti*))
51 #49 OR #50
52 #32 OR #43 OR #48 OR #51
53 MeSH DESCRIPTOR Signs and Symptoms
54 ((sign* adj2 symptom*)):TI
55 ((sign or signs or symptom* or complain*)):TI
56 ((clinical adj2 (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)))
57 ((presenting adj2 (feature? Or finding? Or factor? Or symptom?)))
58 (presentation?):TI
59 ((physical adj2 (manifestation? Or characteristic? Or feature? Or finding?)))
60 (red flag*)
61 (((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 infect* adj3 (indicat* or manifest* or present* or symptom*)))
62 #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61
63 MeSH DESCRIPTOR urinary tract infections WITH QUALIFIER DI
64 #62 OR #63
65 #24 AND #52 AND #64
66 (#65) IN NHSEED FROM 2006 TO 2022

Database name: Econlit

1 (109llness109t* or pre-matur* or 109llness109ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*).ti,ab,in,jn. (6527)
2 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (53142)
3 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (199)
4 (adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 109llness* or 109llness109ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*).ti,ab,in,jn. (10221)
5 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (55197)
6 (“under 16*” or “under sixteen*”).ti,ab. (9)
7 or/1-6 (105970)
8 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj4 infect*).ti,ab. (16)
9 (UTI or UTIs).ti,ab. (13)

10 ((upper or lower) adj4 urin*).ti,ab. (4)
11 cystitis.ti,ab. (2)
12 (bladder* adj4 (ulcer* or ulcus or 110llness*)).ti,ab. (0)
13 proteinuri*.ti,ab. (1)
14 Albuminuri*.ti,ab. (1)
15 Bacteriuria*.ti,ab. (0)
16 ((bacteria* or microbial*) adj4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)).ti,ab. (2)
17 pyuri*.ti,ab. (0)
18 ((protein* or albumin*) adj4 urin*).ti,ab. (0)
19 ((vesicorenal* or vesico?ureteral* or vesicour*) adj reflux*).ti,ab. (0)
20 VUR.ti,ab. (0)
21 ((backflow* or bladder* or cystoureteral* or ureter* or urether*) adj4 reflux*).ti,ab. (0)
22 (pyelonephriti* or pyonephrosi* or pyelocystiti*).ti,ab. (2)
23 or/8-22 (35)
24 (sign* adj2 symptom*).ti,kw. (1)
25 (sign or signs or symptom* or complain*).ti,ab. /freq=2 (1623)
26 (clinical adj2 (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)).ti,ab. (43)
27 (presenting adj2 (feature? Or finding? Or factor? Or symptom?)).ti,ab. (55)
28 presentation?.ti,ab. /freq=2 (389)
29 (physical adj2 (manifestation? Or characteristic? Or feature? Or finding?)).ti,ab. (281)
30 red flag*.ti,ab. (54)
31 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 infect* adj3 (indicat* or manifest* or present* or symptom*)).ti,ab. (0)
32 or/24-31 (2440)
33 and/7,23,32 (0)

Database name: Embase

1 exp infant/ or infant welfare/ (1056810)
2 prematurity/ or postmaturity/ or newborn/ or newborn period/ (631078)
3 (110llness110t* or pre-matur* or 110llness110ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1382064)
4 child welfare/ or exp child/ or child health care/ or child behavior/ or child health/ (2879395)
5 “minor (person)”/ (782)
6 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (3965057)
7 exp pediatrics/ (116336)
8 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (1680063)
9 adolescent behavior/ or adolescent health/ or adolescent/ (1649627)
10 puberty/ (27955)
11 (adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 110llness* or 110llness110ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*).ti,ab,in,jn. (722736)
12 school/ (67134)
13 nursery/ or nursery school/ or child day care/ or day care/ or kindergarten/ (20037)
14 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (773200)
15 (“under 16*” or “under sixteen*”).ti,ab. (2378)
16 or/1-15 (6997255)
17 exp urinary tract infection/ (124684)

18 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj4 infect*).ti,ab. (104346)
19 (UTI or UTIs).ti,ab. (24018)
20 ((upper or lower) adj4 urin*).ti,ab. (44469)
21 exp cystitis/ (26471)
22 cystitis.ti,ab. (17770)
23 (bladder* adj4 (ulcer* or ulcus or 111lness*)).ti,ab. (2568)
24 or/17-23 (229367)
25 proteinuria/ (82191)
26 proteinuri*.ti,ab. (65741)
27 albuminuria/ (18625)
28 Albuminuri*.ti,ab. (17811)
29 bacteriuria/ (7335)
30 Bacteriuria*.ti,ab. (7363)
31 ((bacteria* or microbial*) adj4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)).ti,ab. (8430)
32 pyuria/ (4116)
33 pyuri*.ti,ab. (2895)
34 ((protein* or albumin*) adj4 urin*).ti,ab. (46763)
35 or/25-34 (162745)
36 vesicoureteral reflux/ (13504)
37 ((vesicorenal* or vesico?ureteral* or vesicour*) adj reflux*).ti,ab. (8348)
38 VUR.ti,ab. (3809)
39 ((backflow* or bladder* or cystoureteral* or ureter* or urether*) adj4 reflux*).ti,ab. (4257)
40 or/36-39 (15973)
41 exp pyelonephritis/ (22795)
42 (pyelonephriti* or pyonephrosi* or pyelocystiti*).ti,ab. (16514)
43 41 or 42 (26395)
44 or/24,35,40,43 (393220)
45 physical disease by body function/ (12478)
46 symptom/ (154338)
47 (sign* adj2 symptom*).ti,kw. (4056)
48 (sign or signs or symptom* or complain*).ti,ab. /freq=2 (1020843)
49 (clinical adj2 (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)).ti,ab. (454309)
50 (presenting adj2 (feature? Or finding? Or factor? Or symptom?)).ti,ab. (44087)
51 presentation?.ti,ab. /freq=2 (144368)
52 (physical adj2 (manifestation? Or characteristic? Or feature? Or finding?)).ti,ab. (31377)
53 red flag*.ti,ab. (4105)
54 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 infect* adj3 (indicat* or manifest* or present* or symptom*)).ti,ab. (4649)
55 or/45-54 (1661757)
56 urinary tract infection/di [Diagnosis] (8517)
57 55 or 56 (1668823)
58 and/16,44,57 (18678)
59 exp Health Economics/ (942796)
60 exp “Health Care Cost”/ (313583)
61 exp Pharmacoeconomics/ (216046)
62 Monte Carlo Method/ (45303)
63 Decision Tree/ (16618)
64 econom*.tw. (428635)

65 cba.tw. (13425)
66 cea.tw. (37883)
67 cua.tw. (1679)
68 markov*.tw. (34864)
69 (monte adj carlo).tw. (54513)
70 (decision adj3 (tree* or analys*)).tw. (29578)
71 (cost or costs or costing* or costly or costed).tw. (877219)
72 (price* or pricing*).tw. (64768)
73 budget*.tw. (42821)
74 expenditure*.tw. (82459)
75 (value adj3 (money or monetary)).tw. (3858)
76 (pharmacoeconomic* or (pharmaco adj economic*)).tw. (9151)
77 or/59-76 (1999237)
78 "Quality of Life"/ (540307)
79 Quality Adjusted Life Year/ (30776)
80 Quality of Life Index/ (2958)
81 Short Form 36/ (33888)
82 Health Status/ (138940)
83 quality of life.tw. (510331)
84 quality adjusted life.tw. (22986)
85 (qaly* or qald* or qale* or qtime*).tw. (23352)
86 disability adjusted life.tw. (5039)
87 daly*.tw. (4858)
88 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (45616)
89 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (2652)
90 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (10794)
91 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (64)
92 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (484)
93 (euroqol or euro qol or eq5d or eq 5d).tw. (25230)
94 (qol or hql or hqol or hrqol).tw. (113389)
95 (hye or hyes).tw. (149)
96 health* year* equivalent*.tw. (41)
97 utilit*.tw. (330442)
98 (hui or hui1 or hui2 or hui3).tw. (2704)
99 disutili*.tw. (1067)
100 rosser.tw. (134)
101 quality of wellbeing.tw. (59)
102 quality of well-being.tw. (530)
103 qwb.tw. (261)
104 willingness to pay.tw. (10759)
105 standard gamble*.tw. (1151)
106 time trade off.tw. (1867)
107 time tradeoff.tw. (307)
108 tto.tw. (1931)
109 or/78-108 (1132420)
110 77 or 109 (2950151)

111 58 and 110 (2057)
112 limit 111 to 113llness language (1940)
113 limit 112 to dc=20060601-20220228 (1659)
114 nonhuman/ not (human/ and nonhuman/) (4925844)
115 113 not 114 (1649)
116 (conference abstract or conference paper or “conference review” or editorial or letter or note).pt. (7890179)
117 115 not 116 (992)

Database name: International database of HTA

	Limit to English language and records from 2015-2022
13 and 23	(((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect*) AND (indicat* or manifest* or present* or symptom*)) OR ((red flag*)) OR ((physical) AND (manifestation? Or characteristic? Or feature? Or finding?)) OR ((presentation?)) OR ((presenting) AND (feature? Or finding? Or factor? Or symptom?)) OR ((clinical) AND (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)) OR ((sign or signs or symptom* or complain*)) OR ((sign* and symptom*)[Title]) OR ((Signs and Symptoms)[mh])) AND (((backflow* or bladder* or cystoureteral* or ureter* or urether*) AND (reflux*)) OR ((vesicorenal* or vesico?ureteral* or vesicour*) AND (reflux)) OR ((protein* or albumin*) AND (urin*)) OR ((bacteria* or microbial*) AND (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)) OR ((bladder*) AND (ulcer* or ulcus or 113llness*)) OR ((113llness113ty113* or Albuminuri* or Bacteriuria* or pyuri* or VUR or pyelonephriti* or pyonephrosi* or pyelocystiti*)) OR ((cystitis)) OR ((cystitis)[mh]) OR ((upper or lower) AND (urin*)) OR ((UTI or UTIs)) OR ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect*)) OR ((urinary tract infections)[mh]))
or/14-22	((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect*) AND (indicat* or manifest* or present* or symptom*)) OR ((red flag*)) OR ((physical) AND (manifestation? Or characteristic? Or feature? Or finding?)) OR ((presentation?)) OR ((presenting) AND (feature? Or finding? Or factor? Or symptom?)) OR ((clinical) AND (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)) OR ((sign or signs or symptom* or complain*)) OR ((sign* and symptom*)[Title]) OR ((Signs and Symptoms)[mh])
22	(bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect*) AND (indicat* or manifest* or present* or symptom*)
21	(red flag*)
20	(physical) AND (manifestation? Or characteristic? Or feature? Or finding?)
19	(presentation?)
18	(presenting) AND (feature? Or finding? Or factor? Or symptom?)
17	(clinical) AND (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)
16	(sign or signs or symptom* or complain*)

15	(sign* and symptom*)[Title]
14	(Signs and Symptoms)[mh]
or/1-12	((backflow* or bladder* or cystoureteral* or ureter* or urether*) AND (reflux*)) OR ((vesicorenal* or vesico?ureteral* or vesicour*) AND (reflux)) OR ((protein* or albumin*) AND (urin*)) OR ((bacteria* or microbial*) AND (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)) OR ((bladder*) AND (ulcer* or ulcus or 114llness*)) OR ((114llness114ty114* or Albuminuri* or Bacteriuria* or pyuri* or VUR or pyelonephriti* or pyonephrosi* or pyelocystiti*)) OR ((cystitis)) OR ((cystitis)[mh]) OR ((upper or lower) AND (urin*)) OR ((UTI or UTIs)) OR ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect*)) OR ((urinary tract infections)[mh])
12	(backflow* or bladder* or cystoureteral* or ureter* or urether*) AND (reflux*)
11	(vesicorenal* or vesico?ureteral* or vesicour*) AND (reflux)
10	(protein* or albumin*) AND (urin*)
9	(bacteria* or microbial*) AND (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)
8	(bladder*) AND (ulcer* or ulcus or 114llness*)
7	(114llness114ty114* or Albuminuri* or Bacteriuria* or pyuri* or VUR or pyelonephriti* or pyonephrosi* or pyelocystiti*)
6	(cystitis)
5	(cystitis)[mh]
4	(upper or lower) AND (urin*)
3	(UTI or UTIs)
2	(bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) AND (infect*)
1	(urinary tract infections)[mh]

Database name: MEDLINE

1 exp Infant/ or Infant Health/ or Infant Welfare/ (1206445)
2 (114llness114t* or pre-matur* or 114llness114ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*).ti,ab,in,jn. (1000650)
3 exp Child/ or exp Child Behavior/ or Child Health/ or Child Welfare/ (2055279)
4 Minors/ (2718)
5 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (2656314)
6 exp pediatrics/ (61988)
7 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (973254)
8 Adolescent/ or Adolescent Behavior/ or Adolescent Health/ (2156825)
9 Puberty/ (13921)

10 (adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 115llness* or 115llness115ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*).ti,ab,in,jn. (487358)
11 Schools/ (46112)
12 Child Day Care Centers/ or exp Nurseries/ or Schools, Nursery/ (7459)
13 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (527614)
14 ("under 16*" or "under sixteen*").ti,ab. (1529)
15 or/1-14 (5708619)
16 exp Urinary tract infections/ (48950)
17 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj4 infect*).ti,ab. (63644)
18 (UTI or UTIs).ti,ab. (10469)
19 ((upper or lower) adj4 urin*).ti,ab. (26716)
20 exp cystitis/ (10147)
21 cystitis.ti,ab. (10757)
22 (bladder* adj4 (ulcer* or ulcus or 115llness*)).ti,ab. (1539)
23 or/16-22 (119187)
24 Proteinuria/ (24935)
25 proteinuri*.ti,ab. (38448)
26 Albuminuria/ (15838)
27 Albuminuri*.ti,ab. (10761)
28 Bacteriuria/ (7860)
29 Bacteriuria*.ti,ab. (5791)
30 ((bacteria* or microbial*) adj4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)).ti,ab. (5636)
31 Pyuria/ (1165)
32 pyuri*.ti,ab. (1761)
33 ((protein* or albumin*) adj4 urin*).ti,ab. (27661)
34 or/24-33 (92684)
35 Vesico-ureteral reflux/ (8485)
36 ((vesicorenal* or vesico?ureteral* or vesicour*) adj reflux*).ti,ab. (5867)
37 VUR.ti,ab. (2148)
38 ((backflow* or bladder* or cystoureteral* or ureter* or urether*) adj4 reflux*).ti,ab. (3347)
39 or/35-38 (11163)
40 Pyelonephritis/ (14329)
41 (pyelonephriti* or pyonephrosi* or pyelocystiti*).ti,ab. (12934)
42 40 or 41 (19125)
43 or/23,34,39,42 (214081)
44 "Signs and Symptoms"/ (407)
45 (sign* adj2 symptom*).ti,kw. (2775)
46 (sign or signs or symptom* or complain*).ti,ab. /freq=2 (575932)
47 (clinical adj2 (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)).ti,ab. (280075)
48 (presenting adj2 (feature? Or finding? Or factor? Or symptom?)).ti,ab. (23655)
49 presentation?.ti,ab. /freq=2 (66846)
50 (physical adj2 (manifestation? Or characteristic? Or feature? Or finding?)).ti,ab. (20224)
51 red flag*.ti,ab. (1984)
52 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 infect* adj3 (indicat* or manifest* or present* or symptom*)).ti,ab. (2841)
53 or/44-52 (912034)

54 Urinary Tract Infections/di [Diagnosis] (6343)
55 53 or 54 (917419)
56 and/15,43,55 (10086)
57 Economics/ (27415)
58 exp "Costs and Cost Analysis"/ (253818)
59 Economics, Dental/ (1920)
60 exp Economics, Hospital/ (25488)
61 exp Economics, Medical/ (14324)
62 Economics, Nursing/ (4012)
63 Economics, Pharmaceutical/ (3054)
64 Budgets/ (11564)
65 exp Models, Economic/ (16030)
66 Markov Chains/ (15570)
67 Monte Carlo Method/ (30823)
68 Decision Trees/ (11857)
69 econom*.tw. (281115)
70 cba.tw. (10192)
71 cea.tw. (22260)
72 cua.tw. (1080)
73 markov*.tw. (20697)
74 (monte adj carlo).tw. (33477)
75 (decision adj3 (tree* or analys*)).tw. (17152)
76 (cost or costs or costing* or costly or costed).tw. (529000)
77 (price* or pricing*).tw. (38195)
78 budget*.tw. (26371)
79 expenditure*.tw. (55428)
80 (value adj3 (money or monetary)).tw. (2450)
81 (pharmacoeconomic* or (pharmaco adj economic*)).tw. (3732)
82 or/57-81 (1048416)
83 "Quality of Life"/ (232775)
84 quality of life.tw. (273208)
85 "Value of Life"/ (5780)
86 Quality-Adjusted Life Years/ (14340)
87 quality adjusted life.tw. (13147)
88 (qaly* or qald* or qale* or qtime*).tw. (10771)
89 disability adjusted life.tw. (3559)
90 daly*.tw. (3158)
91 Health Status Indicators/ (24020)
92 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (25028)
93 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (1469)
94 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (5847)
95 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (31)
96 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (405)
97 (euroqol or euro qol or eq5d or eq 5d).tw. (11634)
98 (qol or hql or hqol or hrqol).tw. (53269)
99 (hye or hyes).tw. (63)

100 health* year* equivalent*.tw. (38)
101 utilit*.tw. (198670)
102 (hui or hui1 or hui2 or hui3).tw. (1482)
103 disutili*.tw. (461)
104 rosser.tw. (98)
105 quality of wellbeing.tw. (24)
106 quality of well-being.tw. (411)
107 qwb.tw. (195)
108 willingness to pay.tw. (5807)
109 standard gamble*.tw. (825)
110 time trade off.tw. (1141)
111 time tradeoff.tw. (248)
112 tto.tw. (1036)
113 or/83-112 (570854)
114 82 or 113 (1539715)
115 56 and 114 (877)
116 limit 115 to 117llness language (787)
117 limit 116 to ed=20060601-20220228 (561)
118 Animals/ not humans/ (4921016)
119 117 not 118 (557)
120 limit 119 to (letter or historical article or clinical conference or comment or editorial or news or case reports) (15)
121 119 not 120 (542)

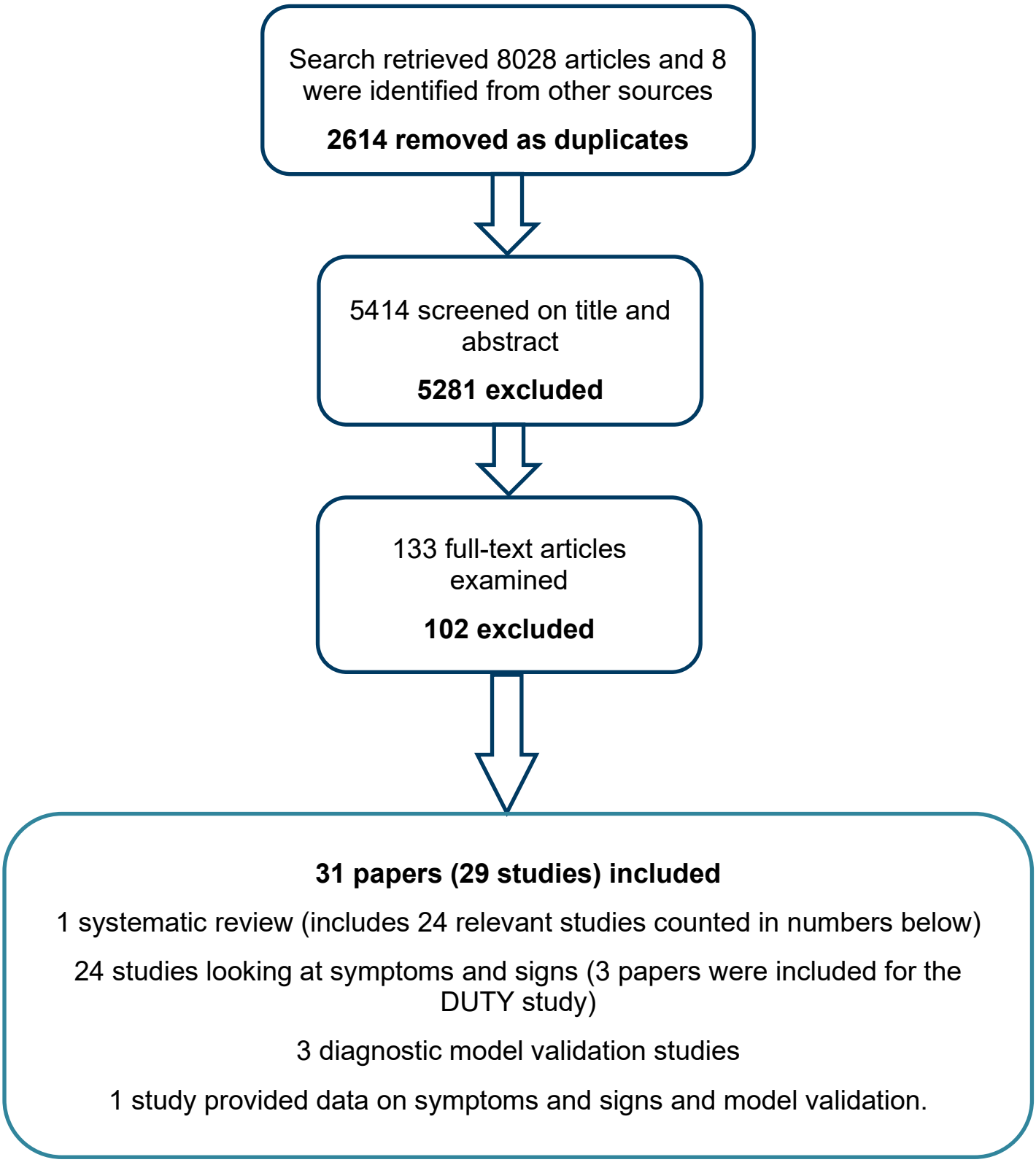
Database name: Medline in Process and Medline ePubs

1 (117llness117t* or pre-matur* or 117llness117ty* or post-matur* or preterm* or pre-term* or infan* or newborn* or new-born* or perinat* or peri-nat* or neonat* or neo-nat* or postnat* or post-nat* or baby* or babies or toddler*).ti,ab,in,jn. (15787)
2 (child* or minor or minors or boy* or girl* or kid or kids or young*).ti,ab,in,jn. (50178)
3 (pediatric* or paediatric* or peadiatric*).ti,ab,in,jn. (22232)
4 (adolescen* or preadolescen* or pre-adolescen* or pubescen* or prepubescen* or pre-pubescen* or 117llness* or 117llness117ty* or pre-pubert* or teen* or preteen* or pre-teen* or juvenil* or youth* or under*age* or underage*).ti,ab,in,jn. (12069)
5 (pre-school* or preschool* or kindergar* or daycare or day-care or nurser* or school* or pupil* or student*).ti,ab,jn. (13126)
6 (“under 16*” or “under sixteen*”).ti,ab. (30)
7 or/1-6 (75654)
8 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj4 infect*).ti,ab. (847)
9 (UTI or UTIs).ti,ab. (242)
10 ((upper or lower) adj4 urin*).ti,ab. (347)
11 cystitis.ti,ab. (129)
12 (bladder* adj4 (ulcer* or ulcus or 117llness*)).ti,ab. (28)
13 proteinuri*.ti,ab. (394)
14 Albuminuri*.ti,ab. (160)
15 Bacteriuria*.ti,ab. (48)
16 ((bacteria* or microbial*) adj4 (bladder* or genitourin* or kidney* or renal* or ureter* or ureth* or urin* or urolog* or urogen*)).ti,ab. (70)
17 pyuri*.ti,ab. (12)
18 ((protein* or albumin*) adj4 urin*).ti,ab. (278)
19 ((vesicorenal* or vesico?ureteral* or vesicour*) adj reflux*).ti,ab. (58)

20 VUR.ti,ab. (27)
21 ((backflow* or bladder* or cystoureteral* or ureter* or urether*) adj4 reflux*).ti,ab. (19)
22 (pyelonephriti* or pyonephrosi* or pyelocystiti*).ti,ab. (78)
23 or/8-22 (2047)
24 (sign* adj2 symptom*).ti,kw. (47)
25 (sign or signs or symptom* or complain*).ti,ab. /freq=2 (14248)
26 (clinical adj2 (manifestation? Or feature? Or finding? Or aspect? Or marker? Or predict*)).ti,ab. (5065)
27 (presenting adj2 (feature? Or finding? Or factor? Or symptom?)).ti,ab. (440)
28 presentation?.ti,ab. /freq=2 (1462)
29 (physical adj2 (manifestation? Or characteristic? Or feature? Or finding?)).ti,ab. (359)
30 red flag*.ti,ab. (85)
31 ((bladder* or genitourin* or kidney* or pyelo* or renal* or ureter* or ureth* or urin* or urolog* or urogen*) adj3 infect* adj3 (indicat* or manifest* or present* or symptom*)).ti,ab. (37)
32 or/24-31 (20329)
33 and/7,23,32 (130)
34 econom*.tw. (8570)
35 cba.tw. (57)
36 cea.tw. (243)
37 cua.tw. (16)
38 markov*.tw. (652)
39 (monte adj carlo).tw. (873)
40 (decision adj3 (tree* or analys*)).tw. (621)
41 (cost or costs or costing* or costly or costed).tw. (13293)
42 (price* or pricing*).tw. (1163)
43 budget*.tw. (590)
44 expenditure*.tw. (1130)
45 (value adj3 (money or monetary)).tw. (77)
46 (pharmacoeconomic* or (pharmaco adj economic*)).tw. (51)
47 or/34-46 (23333)
48 quality of life.tw. (8096)
49 quality adjusted life.tw. (446)
50 (qaly* or qald* or qale* or qtime*).tw. (375)
51 disability adjusted life.tw. (109)
52 daly*.tw. (97)
53 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw. (454)
54 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw. (40)
55 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw. (162)
56 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw. (0)
57 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw. (3)
58 (euroqol or euro qol or eq5d or eq 5d).tw. (486)
59 (qol or hql or hqol or hrqol).tw. (1658)
60 (hye or hyes).tw. (1)
61 health* year* equivalent*.tw. (0)
62 utilit*.tw. (4593)
63 (hui or hui1 or hui2 or hui3).tw. (35)

64 disutili*.tw. (17)
65 rosser.tw. (0)
66 quality of wellbeing.tw. (2)
67 quality of well-being.tw. (8)
68 qwb.tw. (4)
69 willingness to pay.tw. (236)
70 standard gamble*.tw. (4)
71 time trade off.tw. (21)
72 time tradeoff.tw. (2)
73 tto.tw. (28)
74 or/48-73 (13072)
75 47 or 74 (34475)
76 33 and 75 (16)
77 limit 76 to 119llness language (16)
78 limit 77 to yr=”2006 -Current” (14)

Appendix C –Diagnostic evidence study selection



Appendix D –Diagnostic evidence

Systematic review

Boon, 2021

Bibliographic Reference	Boon, Hanne A; Van den Bruel, Ann; Struyf, Thomas; Gillemot, Andreas; Bullens, Dominique; Verbakel, Jan Y; Clinical Features for the Diagnosis of Pediatric Urinary Tract Infections: Systematic Review and Meta-Analysis.; Annals of family medicine; 2021; vol. 19 (no. 5); 437-446

Study Characteristics

Study design	Systematic review
Study details	Dates searched • from inception to January 27, 2020 Databases searched • PubMed, Embase, Web of Science, Cumulative Index to Nursing and Allied Health Literature, Cochrane Central Register of Controlled Trials, Health Technology Assessment, and Database of Abstracts of Reviews of Effects Sources of funding • None
Inclusion criteria	≥18 years of age Used urine culture as the reference standard Study design • Eligible study designs included prospective cross-sectional diagnostic accuracy studies, diagnostic nested case-control studies, and retrospective cohort studies. Study took place in ambulatory care setting • defined as outpatient medical care and included family practices, emergency departments, walk-in clinics, health centres, and outpatient hospital departments.
Exclusion criteria	• case-control studies with differential sampling scheme for case and control • reviews • letters • comments and conference abstracts • sample sizes <50 children • high-risk samples such as children who are premature or malnourished
Symptoms and signs	• vomiting • nausea • diarrhoea • poor feeding • abdominal pain • previous UTI • irritability • shivering • jaundice

	• fever duration • haematuria • cloudy urine • smelly urine • frequency • loin tenderness • dysuria • no nappy rash

Models looking at combinations of symptoms and signs	• DUTY model (clean catch)
	  ○ Pain while urinating (2p), malodorous urine (2p), history of UTI (1p), absence of cough (2p), severe illness (2p)
	• DUTY score (diaper)
	  ○ Female (1p), malodorous urine (2p), darker urine (1p), absence of diaper rash (3p)
	• UTIcalc
	  ○ Age <12 mo, temperature ≥39°C, non–African American, female, uncircumcised male, other fever source
	• Gorelick scale
	  ○ Age <12 mo, temperature ≥39°C, White, fever ≥2 days, absence of other fever source
	• Yale observation scale
	  ○ Quality of cry, reaction to parents, arousability, skin colour, hydration, social response
	• NICE traffic light
	  ○ Colour, activity, respiratory, circulation and hydration, other

Outcome(s)	Diagnosis of UTI confirmed by urine culture
Studies included in our review from Boon 2021	• Bonadio 1991 • Craig 2010 • De 2013 • Diaz 2016 • Dobbs and Fleming 1987 • Duong 2016 • Festo 2011 • Gauthier 2012 • Gorelick 2000 • Hay et al 2016 • Hoberman 1993 • Kanegaye 2014 • Kartika 2006 • Lizama – paper not in English- used data from Boon 2021 only • Mitiku 2018 • Msaki 2012 • Musa-Aisen 2003 • Newman 2002 • O'Brien 2013 • Pylkkanen 1979 • Shaw 1998 • Velasco 2015 • Verbakel 2016 • Zorc 2005
Studies excluded from our review that	• Bulloch 2000 - conference abstract • Chaudhari 2017 - - study does not provide data on UTI diagnosis • Chaudhari 2018 - - study does not provide data on UTI diagnosis • Chen and Baker 2006 - study does not provide data on UTI diagnosis

are included in Boon 20221	• Dickinson 1979 - data not in an extractable format (not possible to calculate a contingency table for the data provided) • Felt 2017 - study does not contain any relevant index tests for UTI diagnosis • Gorelick 2003 – not a relevant study design (nested case-control study) • Lagos 1994- Not English language publication • Shaikh 2018 - not a relevant study design (nested case-control design) • Shaikh 2019 - study does not provide data on UTI diagnosis • Tzimenatos 2018 - study does not contain any relevant index tests for UTI diagnosis
Additional comments	Additional data was extracted directly from the following studies (signs/symptoms in brackets): • Bonadio 1991 (degree of fever) • Dobbs and Fleming 1987 (symptoms for 9 days or less) • Duong 2016 (degree of fever) • Festo 2011 (degree of fever, failure to thrive) • Hoberman 1993 (vomiting, diarrhoea, poor feeding, irritability, degree of fever) • Msaki 2012 (degree of fever) • Newman 2002 (decreased feeding, initial appearance, degree of fever, increased sleepiness, decreased social interaction, decreased activity) • O'Brien 2013 (poor feeding, muscle aches or pains) • Pylkkanen 1979 (fever alone) • Shaw 1998 (degree of fever) All other data was extracted from Boon 2021 and back calculated to 2x2 table format for re-analysis.

Risk of bias – systematic review - ROBIS

Section	Question	Answer
Study eligibility criteria	Concerns regarding specification of study eligibility criteria	Low
Identification and selection of studies	Concerns regarding methods used to identify and/or select studies	Low *(Authors also checked the references of primary studies and reviews for additional studies.)*
Data collection and study appraisal	Concerns regarding methods used to collect data and appraise studies	Low
Synthesis and findings	Concerns regarding the synthesis and findings	Low
Overall study ratings	Overall risk of bias	Low
Overall study ratings	Applicability as a source of data	Fully applicable *(Our review is interested in <16 years and this SR looks at <18 years, but most included studies*

Section	Question	Answer
		are within our age range and the in the only study which included participants <18 years most were < 2 years old.

Overall risk of bias and applicability for studies contained within Boon 2021 systematic review.

The Guideline development team used the QUADAS-2 domain ratings for the risk of bias and applicability from within the Boon 2021 systematic review to inform their judgement of overall risk of bias and applicability using the following rules: if 1 risk of bias domain was red (high), or there were 3 yellow (unclear) domains then we judged the study to be at high risk of bias. If there were 2 yellow (unclear) domains, then we judged the study to be at moderate risk of bias and if there was 1 yellow (unclear) domain or all domains were green (low risk) then we judged the study to be at low risk of bias.

Study name	Risk of bias	Reason for downgrading (taken from Boon 2021 systematic review unless stated otherwise)	Applicability (with reason if not directly applicable)
Bonadio 1991	High	**Patient selection domain**: Retrospective sampling	Directly applicable
Craig 2010	High	**Flow and timing domain:** Urine sample only collected from a small proportion of included children	Directly applicable
De 2013	High	**Flow and timing domain**: Urine sample only collected from a small proportion of included children	Directly applicable
Diaz 2016	High	**Patient selection domain**: Retrospective sampling **Reference standard domain**: Reference standard positivity threshold not adapted to sampling method	Directly applicable
Dobbs 1987	High	**Patient selection domain:** Included only a narrow spectrum of participants **Reference standard domain**: Reference standard positivity threshold lower than recommended threshold **Flow and timing domain**: Inappropriate exclusion from analysis	Directly applicable
Duong 2016	Low	Not applicable	Directly applicable
Festo 2011	Low	Not applicable	Directly applicable
Gauthier 2012	High	**Patient selection domain:** Included only a narrow spectrum of participants	Directly applicable
Gorelick 2000	Low	Not applicable	Directly applicable
Hay 2016	Low	Not applicable	Directly applicable
Hoberman 1993	Low	Not applicable	Directly applicable
Kanegaye 2014	High	**Patient selection domain:** Convenience/non-consecutive sampling	Directly applicable

Kartika 2006	High	**Patient selection domain:** Included only a narrow spectrum of participants **Reference standard domain**: Reference standard positivity threshold lower than recommended threshold	Directly applicable
Lizama 2005	High	**Patient selection domain:** Retrospective sampling	Directly applicable
Mitiku 2018	Low	Not applicable	Directly applicable
Msaki 2012	Low	Not applicable	Directly applicable
Musa Aisien 2003	High	**Reference standard domain**: Reference standard positivity threshold not adapted to sampling method	Directly applicable
Newman 2002	Low	Not applicable	Directly applicable
O'Brien 2013	Low	Not applicable	Directly applicable
Pylkkanen 1979	High	**Patient selection domain:** Included only a narrow spectrum of participants. Additional GDT comment: results not reported for all participants.	Partially applicable – GDT judgement (study included participants <18 years, but GDT are interested in <16s)
Shaw 1998	Low	Not applicable	Directly applicable
Velasco 2015	High	**Reference standard domain**: Reference standard positivity threshold not adapted to sampling method	Directly applicable
Verbakel 2015	High	**Flow and timing domain**: Urine sample only collected from a small proportion of included children	Directly applicable
Zorc 2005	High	**Patient selection domain:** Convenience/non-consecutive sampling	Directly applicable

Primary studies looking at symptoms and signs

Bonadio, 1991

Bibliographic Reference	Bonadio WA; McElroy K; Jacoby PL; Smith D; Relationship of fever magnitude to rate of serious bacterial infections in infants aged 4-8 weeks.; Clinical pediatrics; 1991; vol. 30 (no. 8)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Wisconsin, Milwaukee, USA • Setting Hospital emergency department • Study dates 1986 to 1990 • Sources of funding Not reported
Study type	Retrospective cohort study

	Consecutive infants
Inclusion criteria	• Fever • Evaluated for sepsis • Aged 30 - 60 days
Exclusion criteria	• History of antibiotic treatment or use of antimalarials • Preadmission antibiotic medication within 72 hours • History of antipyretic treatment • Preadmission antipyretic treatment within 4 hours
Number of participants	N=683
Index test(s)	fever
Reference standard (s)	≥100,000 colony forming units (cfu) per millilitre (mL) (single pathogen)
Method of reference standard collection	Not reported

Butler, 2016

Bibliographic Reference	Butler, Christopher C; Sterne, Jonathan Ac; Lawton, Michael; O'Brien, Kathryn; Wootton, Mandy; Hood, Kerenza; Hollingworth, William; Little, Paul; Delaney, Brendan C; van der Voort, Judith; Dudley, Jan; Birnie, Kate; Pickles, Timothy; Waldron, Cherry-Ann; Downing, Harriet; Thomas-Jones, Emma; Lisles, Catherine; Rumsby, Kate; Durbaba, Stevo; Whiting, Penny; Harman, Kim; Howe, Robin; MacGowan, Alasdair; Fletcher, Margaret; Hay, Alastair D; Nappy pad urine samples for investigation and treatment of UTI in young children: the 'DUTY' prospective diagnostic cohort study.; The British journal of general practice : the journal of the Royal College of General Practitioners; 2016; vol. 66 (no. 648); e516-24

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.

Reports details of the nappy pad cohort from the Hay et al 2016 HTA.

Additional comments	For further details of the DUTY study see the Hay et al 2016 HTA summary

Craig, 2010

Bibliographic Reference	Craig, Jonathan C; Williams, Gabrielle J; Jones, Mike; Codarini, Miriam; Macaskill, Petra; Hayen, Andrew; Irwig, Les; Fitzgerald, Dominic A; Isaacs, David; McCaskill, Mary; The accuracy of clinical symptoms and signs for the diagnosis of serious bacterial infection in young febrile children: prospective cohort study of 15 781 febrile illnesses.; BMJ (Clinical research ed.); 2010; vol. 340; c1594

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.

Study details	• Study location Westmead, Australia • Setting Children's hospital emergency department • Study dates 1 July 2004 to 30 June 2006 • Sources of funding This trial was funded by the National Health and Medical Research Council of Australia (programme grant numbers 211205 and 402764). The funding source had no influence on study design, data collection, analysis, interpretation of data, writing of the report, or on the decision to submit the paper for publication.
Study type	Prospective cohort study Consecutive children
Inclusion criteria	• Unwell/febrile child o a measured axillary temperature of ≥38.0°C; parental report of a temperature of ≥38.0°Cmeasured at home within the previous 24 hours; a parental report that the child “felt hot” in the previous 24 hours; or a presenting problem related to fever (10th revision of the international classification of diseases, Australian modification codesR50, R50.0, R50.1,R50.9, and R56.0), as determined by a triage nurse. • Aged less than 5 years
Exclusion criteria	• Known acquired or congenital immunodeficiency or other major chronic condition • children transferred from another hospital • Possibility of physical or sexual abuse
Number of participants	n=15781
Length of follow-up	All eligible febrile children were followed up until they fulfilled the case definition for serious bacterial infection or until the fever had resolved for ≥24 hours.
Loss to follow-up	Febrile children [illnesses] with a clinically diagnosed infection or without evidence of an infection, unable to contact (n=1158 [n=1114]). The effect of children whose parents were unable to be contacted (loss to follow-up) was explored by the inclusion of their data in the analysis with the assumption of no serious bacterial infection as well as by their exclusion from the analyses (sensitivity analysis).
Index test(s)	• fever • diarrhoea • urinary symptoms • fluid intake • general appearance • felt hot • capillary refill time • crying • tachycardia • chest crackles • breathing difficulty • tachypnoea • abnormal chest sounds • respiratory symptoms • abnormal ENT • cough • bulging fontanelle • rash

	• wheeze • stridor
Reference standard (s)	• UTI diagnosis Definite urinary tract infection was defined as ≥10(8) colony forming units (cfu) per litre of a single type of organism in a voided sample, ≥10(7) cfu/l of a single organism in a catheter sample, or any growth of a single organism in a suprapubic bladder tap sample. Probable urinary tract infection was defined as ≥10(7) cfu/l of a single organism in a voided sample, ≥10(6) cfu/l of a single organism in a catheter sample, ≥10(8) cfu/l of two organisms in a voided sample, or ≥10(7) cfu/l of two organisms from a catheter sample.
Method of reference standard collection	Voided, catheter or suprapubic aspiration further details not provided

Dobbs, 1987

Bibliographic Reference	Dobbs FF; Fleming DM; A simple scoring system for evaluating symptoms, history and urine dipstick testing in the diagnosis of urinary tract infection.; The Journal of the Royal College of General Practitioners; 1987; vol. 37 (no. 296)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Birmingham, UK • Setting Health centre • Study dates November 1984 to June 1985 • Sources of funding Not reported
Study type	Cross-sectional study Prospective
Inclusion criteria	• Symptoms suggestive of urinary tract infection • Aged 0 to 14 years (subgroup of larger study population)
Exclusion criteria	Incomplete data available
Number of participants	N=521, of these 75 were aged 0 to 14 years
Index test(s)	• urinary frequency • dysuria • urgency • smelly urine • urinary symptoms • for 9 days or less • nocturia • haematuria • nausea
Reference standard (s)	UTI diagnosis A colony count exceeding 100 000 organisms per ml with a pure urine culture or a count of 10 000-100 000 organisms per ml plus a minimum of 100 leucocytes per

	mm3. Urines containing bacterial inhibitors, and in which mixed growths were cultured were excluded.
Method of reference standard collection	Not reported

Duong, 2016

Bibliographic Reference	Duong HP; Wissing KM; Tram N; Mascart G; Lepage P; Ismaili K; Accuracy of Automated Flow Cytometry-Based Leukocyte Counts To Rule Out Urinary Tract Infection in Febrile Children: a Prospective Cross-Sectional Study.; Journal of clinical microbiology; 2016; vol. 54 (no. 12)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Brussels, Belgium • Setting Children's hospital emergency department • Study dates July 2006 and July 2008 • Sources of funding This study was funded by the Department of Pediatric Nephrology of the Hôpital Universitaire des Enfants Reine Fabiola in Brussels, Belgium.
Study type	Cross-sectional study Consecutive
Inclusion criteria	• Fever • Aged up to 16 years
Exclusion criteria	• Incomplete data available • 51 children with positive urine cultures were excluded from the study because of incomplete urinalysis and/or clinical data
Number of participants	N=1247
Index test(s)	fever
Reference standard (s)	≥100,000 colony forming units per millilitre (single pathogen) by clean catch or bladder catheterisation, for suprapubic urine aspiration samples, any growth of pathogen was considered significant
Method of reference standard collection	For children younger than 24 months, urine samples were obtained by suprapubic aspiration or bladder catheterisation. For older children, samples were obtained by clean catch or bladder catheterisation.

Epaphura Festo, Benson R Kidenya, Aldofina Hokororo, 2011

Bibliographic Reference	Epaphura Festo, Benson R Kidenya, Aldofina Hokororo SEM; Predictors of Urinary tract infection among febrile children attending at Bugando Medical Centre Northwestern, Tanzania; Archives of Clinical Microbiology; 2011; vol. 2; 7 pages

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.

Study details	Study location Northwest Tanzania Setting Medical centre, tertiary hospital Study dates October 2010 to February 2011 Sources of funding Not reported, but authors state funding was limited.
Study type	Cross-sectional study consecutive
Inclusion criteria	• Unwell/febrile child • Aged 2 to 60 months
Exclusion criteria	Indwelling catheter
Number of participants	N=370
Index test(s)	• fever • vomiting • diarrhoea • dysuria • flank pain • irritability
Reference standard (s)	≥100,000 colony forming units per millilitre for midstream urine, for suprapubic aspiration samples any growth of pathogen was considered significant
Method of reference standard collection	Mid-stream clean catch urine (MSU) was obtained in all children above 2 and those below 2 years who were able to provide MSU. Suprapubic aspiration was done for children below 2 years.

Gauthier, 2012

Bibliographic Reference	Gauthier M; Gouin S; Phan V; Gravel J; Association of malodorous urine with urinary tract infection in children aged 1 to 36 months.; Pediatrics; 2012; vol. 129 (no. 5)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Montreal, Canada • Setting Children's hospital emergency department • Study dates 31 July 2009 to 30 April 2011 • Sources of funding Funded by Fonds d'operation pour les projets de recherche clinique appliquee. CHU Sainte-Justine, Montreal
Study type	Prospective cohort study States consecutive recruitment, but recruitment only took place on weekdays from 10 am to 6 pm.
Inclusion criteria	• Aged up to 36 months • Fever without source • Fever at home or in the ED >38.5 degrees Celsius rectally

	• Unexplained irritability • Vomiting
Exclusion criteria	• Urinary tract anomalies • Chronic illness • Ongoing antibacterial treatment • Other than prophylaxis given in the previous 48 hours • Incomplete data available • Indwelling catheter
Number of participants	N=331
Index test(s)	• fever • vomiting • abdominal pain • diarrhoea • dysuria • smelly urine • previous UTI

Reference standard (s)	• UTI diagnosis
	  ○ ≥50X10(6) of a single pathogen (bladder catheterisation samples), ≥10X10(6) of pseudomonas spp. or ≥100X10(6) of a single pathogen in clean-catch or midstream void.
	  ○ For samples obtained by suprapubic aspiration, any growth of pathogen was considered significant
	  ○ For Gram negative bacteria. Or greater than or equal to 10X10(6) of Gram-positive bacteria.

Method of reference standard collection	Clean-catch, midstream void, catheterisation, suprapubic aspiration. Samples from urine bag collection were excluded *a posteriori*

Gorelick, 2000

Bibliographic Reference	Gorelick MH; Shaw KN; Clinical decision rule to identify febrile young girls at risk for urinary tract infection.; Archives of pediatrics & adolescent medicine; 2000; vol. 154 (no. 4)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Philadelphia, USA • Setting Children's hospital emergency department • Study dates Study conducted over a 12-month period (date range not reported) • Sources of funding This study was supported by grant MCJ-420648 from the Maternal and Child Health Bureau (Title V, Social Security Act), Health Resources and Services Administration, US Department of Health and Human Services, Rockville, Md.
Study type	Prospective cohort study consecutive
Inclusion criteria	• Fever • Greater than or equal to 38.3 degrees Celsius • Boys younger than 1 year and girls aged less than 2 years

Exclusion criteria	Known acquired or congenital immunodeficiency or other major chronic condition diagnosis of serious bacterial infection already made
Number of participants	N=1469
Index test(s)	• fever • vomiting • diarrhoea • irritability • poor feeding
Reference standard (s)	UTI diagnosis Pure growth of ≥10(4) colonies/mL of a pathogenic species.
Method of reference standard collection	Urinary catheterisation
Additional information	Note due to the small number of boys with UTI the paper restricts itself to analysis of data from girls

Hay, 2016a

Bibliographic Reference	Hay, Alastair D.; Downing, Harriet; Harman, Kim; Birnie, Kate; Busby, John; Hollingworth, William; Lawton, Michael; Sterne, Jonathan A. C.; Whiting, Penny; Delaney, Brendan; Dudley, Jan; Durbaba, Stevo; Fletcher, Margaret; Hood, Kerenza; Lisles, Catherine; Pickles, Timothy; Thomas-Jones, Emma; Waldron, Cherry-Ann; Howe, Robin; Wootton, Mandy; Little, Paul; Rumsby, Kate; MacGowan, Alasdair; O'Brien, Kathryn; van der Voort, Judith; Butler, Christopher C.; The Diagnosis of Urinary Tract infection in Young children (DUTY): A diagnostic prospective observational study to derive and validate a clinical algorithm for the diagnosis of urinary tract infection in children presenting to primary care with an acute illness; Health Technology Assessment; 2016; vol. 20 (no. 51); 1-197

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location UK • Setting Multiple primary care (general practices, walk-in centers, and children's emergency departments) in England and Wales. • Study dates 7 April 2010 until 30 April 2012 • Sources of funding Funded by the National Institute for Health Research (NIHR) HTA programme - project number 08/66/01
Study type	Prospective cohort study
Inclusion criteria	Fever • Unwell/febrile child (<28 days duration) • Aged less than 5 years • Symptoms suggestive of urinary tract infection • At least one urinary symptom identified by NICE as a potential marker of UTI – that is, abdominal pain, jaundice (children < 3 months only), haematuria, offensive urine, cloudy urine, loin pain, frequency, apparent pain on passing urine and changes to continence. • Unexplained irritability

	• Vomiting • Lethargy/malaise • Poor feeding or failure to thrive
Exclusion criteria	• History of antibiotic treatment or use of antimalarials within last 7 days • Urinary tract anomalies • Known acquired or congenital immunodeficiency or other major chronic condition • Indwelling catheter • Known neurogenic (e.g., spina bifida) or surgically reconstructed bladder or urinary permanent or intermittent catheterisation • Presenting with trauma • Children referred by a GP or other setting
Number of participants	Clean-catch N=2740, Nappy pad N=2277
Index test(s)	• vomiting • abdominal pain • diarrhoea • urinary frequency • dysuria • urgency • smelly urine • chills • Shivering • general appearance • abnormal ENT • cough • rash • nappy rash • haematuria • previous UTI • poor feeding • DUTY score • loin tenderness • suprapubic tenderness • darker and/or cloudy urine • oliguria • bed wetting • poor weight gain • constipation
Reference standard (s)	UTI diagnosis Either the pure (single) or predominant growth of a uropathogen (Enterobacteriaceae) at ≥10(5) colony-forming units (CFU)/mL. The study defined predominant growth as ≥10(5) CFU/mL of a uropathogen with a 3-log10 (1,000-fold) or greater difference between the growth of this and the next species.
Method of reference standard collection	Clean-catch and nappy pads
Subgroup analyses	Clean-catch Nappy pad

Hay, 2016b

Bibliographic Reference	Hay, Alastair D; Sterne, Jonathan A C; Hood, Kerenza; Little, Paul; Delaney, Brendan; Hollingworth, William; Wootton, Mandy; Howe, Robin; MacGowan, Alasdair; Lawton, Michael; Busby, John; Pickles, Timothy; Birnie, Kate; O'Brien, Kathryn; Waldron, Cherry-Ann; Dudley, Jan; Van Der Voort, Judith; Downing, Harriet; Thomas-Jones, Emma; Harman, Kim; Lisles, Catherine; Rumsby, Kate; Durbaba, Stevo; Whiting, Penny; Butler, Christopher C; Improving the Diagnosis and Treatment of Urinary Tract Infection in Young Children in Primary Care: Results from the DUTY Prospective Diagnostic Cohort Study.; Annals of family medicine; 2016; vol. 14 (no. 4); 325-36

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics. Reports clean-catch results from Hay et al 2016 HTA	
Additional comments	For further details of the DUTY study see Hay et al 2016a HTA summary

Hoberman, 1993

Bibliographic Reference	Hoberman A; Chao HP; Keller DM; Hickey R; Davis HW; Ellis D; Prevalence of urinary tract infection in febrile infants.; The Journal of pediatrics; 1993; vol. 123 (no. 1)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Pittsburgh, USA • Setting Children's hospital emergency department (ED) • Study dates February 1990 through January 1991 • Sources of funding Not reported
Study type	Cross-sectional study Consecutive recruitment.
Inclusion criteria	• Fever • Rectal temperature ≥38.3°C (100.9°F) recorded in the ED, or a history of a rectal temperature ≥38.3°C or axillary temperature ≥37.4°C having been recorded within the previous 24 hours • Aged up to 12 months
Exclusion criteria	• History of antibiotic treatment or use of antimalarials within the previous 24 hours • Indwelling catheter • Catheterised within 48 hours
Number of participants	N=945
Index test(s)	• fever • vomiting • diarrhoea

	• irritability • poor feeding
Reference standard (s)	UTI diagnosis Results of both standard quantitative and dipslide cultures were considered positive if greater than or equal to 10,000 colony forming units of a single type of organism per millilitre were present
Method of reference standard collection	All urine specimens were obtained by bladder catheterization

Ibeneme, 2014

Bibliographic Reference	Ibeneme, C A; Oguonu, T; Okafor, H U; Ikefuna, A N; Ozumba, U C; Urinary tract infection in febrile under five children in Enugu, South Eastern Nigeria.; Nigerian journal of clinical practice; 2014; vol. 17 (no. 5); 624-8

Study Characteristics

Study details	• Study location Nigeria • Setting Single hospital centre • Study dates February 2010 - April 2010
Study type	Cross-sectional study
Inclusion criteria	• Aged 1 - 59 months • Fever • Axillary temperature ≥37.6°C.
Exclusion criteria	• History of antibiotic treatment or use of antimalarials in 7 days prior to enrolment • Urologic manipulation such as use catheterization • Urinary tract anomalies • Chronic illness ○ Such as severe protein energy malnutrition, sickle cell disease, malignancies, nephrotic syndrome, glomerulonephritis, chronic renal failure and human immunodeficiency. Virus/acquired immunodeficiency and people on immunosuppressive drugs were also excluded.
Number of participants	200
Index test(s)	• fever • vomiting • abdominal pain • diarrhoea • urinary frequency • renal angle tenderness • dysuria • urgency
Reference standard (s)	UTI diagnosis A pure growth of ≥10(5) colony forming units/mL
Method of reference standard collection	Suprapubic aspiration for children aged <2 years and by mid-stream specimen in older children

Participant Characteristics

Characteristic	Study (N = 200)
% Female Nominal	44
Mean age (SD) (Months) Mean (SD)	31.1 (18)
Mean (SD) temparature (degree Celsius) Mean (SD)	38.3 (0.69)
% fever for 7 days or more Nominal	26

Risk of bias – QUADAS-2

Section	Question	Answer
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Kanegaye, 2014

Bibliographic Reference	Kanegaye JT; Jacob JM; Malicki D; Automated urinalysis and urine dipstick in the emergency evaluation of young febrile children.; Pediatrics; 2014; vol. 134 (no. 3)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location San Diego, California, USA • Setting Children's hospital • Study dates May 15, 2009, to May 15, 2010 • Sources of funding

	No external funding
Study type	Prospective cohort study Convenience sampling
Inclusion criteria	• Fever Temperatures ≥38°C in the ED or tactile or documented fevers at home within 24 hours • Symptoms suggestive of urinary tract infection • Aged up to 48 months
Exclusion criteria	• Urologic manipulation • Urinary tract anomalies • Known acquired or congenital immunodeficiency or other major chronic condition • Ongoing antibacterial treatment within 24 hours • Incomplete data available
Number of participants	N=342
Index test(s)	previous UTI
Reference standard (s)	UTI diagnosis Positive urine culture result was defined as growth of ≥50 000 CFU/mL of a urinary pathogen
Method of reference standard collection	Bladder catheterisation

Kartika, 2006

Bibliographic Reference	Kartika, I Damanik, MP, S Yati Soenarto; Diagnostic test of urine clarity in urinary tract infection; Paediatrica Indonesiana; 2006; vol. 46 (No, 7-8); 170-73

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Yogyakarta, Indonesia • Setting Hospital emergency and outpatient departments and children's ward • Study dates July 2004 to August 2005 • Sources of funding Not reported
Study type	Prospective cohort study
Inclusion criteria	• Symptoms suggestive of urinary tract infection • Aged 2 years to 15 months
Exclusion criteria	• Urinary tract anomalies • Ongoing antibacterial treatment • Indwelling catheter or intermittent catheterisation in neurogenic bladder
Number of participants	N=205
Index test(s)	Darker and/or cloudy urine

Reference standard (s)	UTI diagnosis Urine culture single pathogen, not further defined
Method of reference standard collection	Clean-catch and mid-stream collection

Lizama, 2005

Bibliographic Reference	Lizama MC, LUCO MI., CRISTINA REICHHARD T. y TAMARA HIRSCH B.; Infección del tracto urinario en un servicio de urgencia pediátrico: Frecuencia y características clínicas; Rev Chil Infect; 2005; vol. 22 (no. 3); 235-241

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Santiago, Chile • Setting Paediatric emergency department • Study dates Unclear • Sources of funding Unclear
Study type	Retrospective cohort study Consecutive recruitment
Inclusion criteria	Specimen available (reported in Boon et al) no further detail reported
Exclusion criteria	Not known (study not in English)
Number of participants	N=1173
Index test(s)	• abdominal pain • diarrhoea • urinary frequency • dysuria • respiratory symptoms
Reference standard (s)	UTI diagnosis urine culture any colony forming unit/mL (cfu/mL) for suprapubic aspiration samples, ≥10(4) cfu/ml for catheter samples and ≥10(5) cfu/ml for mid-stream samples
Method of reference standard collection	Suprapubic aspiration, midstream and catheter samples
Additional information	English language paper included in the Boon et al review.

Mitiku, 2018

Bibliographic Reference	Mitiku E; Amsalu A; Tadesse BT; Pediatric Urinary Tract Infection as a Cause of Outpatient Clinic Visits in Southern Ethiopia: A Cross Sectional Study.; Ethiopian journal of health sciences; 2018; vol. 28 (no. 2)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Hawassa, Ethiopia • Setting Outpatient department of a Specialist Hospital • Study dates May to September 2015 • Sources of funding No external funding
Study type	Cross-sectional study Consecutive recruitment
Inclusion criteria	• Fever Axillary temperature of 37.5 °C or higher at presentation • Symptoms suggestive of urinary tract infection • Urgency, loin pain or tenderness, frequency and dysuria • Vomiting • Aged up to 15 years
Exclusion criteria	History of antibiotic treatment or use of antimalarials within 2 weeks
Number of participants	N=269
Index test(s)	previous UTI
Reference standard (s)	UTI diagnosis urine culture ≥10(5) colony forming unit/mL for mid-stream samples
Method of reference standard collection	Midstream urine specimens

Msaki, 2012

Bibliographic Reference	Msaki BP; Mshana SE; Hokororo A; Mazigo HD; Morona D; Prevalence and predictors of urinary tract infection and severe malaria among febrile children attending Makongoro health centre in Mwanza city, North-Western Tanzania.; Archives of public health = Archives belges de sante publique; 2012; vol. 70 (no. 1)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Mwanza city, North-Western Tanzania • Setting Health centre • Study dates February to June 2011 • Sources of funding supported from research grant of Ministry of Health and Social Welfare
Study type	Cross-sectional study Consecutive recruitment
Inclusion criteria	• Unwell/febrile child Defined as axillary temperature ≥37.5°C

	• Aged 2 to 60 months
Exclusion criteria	History of antibiotic treatment or use of antimalarials in past 7 days
Number of participants	N=231
Index test(s)	• fever • abdominal pain • dysuria
Reference standard (s)	UTI diagnosis Urine culture any colony forming unit/mL (cfu/ml) for suprapubic aspiration samples, ≥10(5) cfu/ml for mid-stream samples, reported in Boon et al (other diagnostic thresholds not reported)
Method of reference standard collection	Urethral catheterization methods were used in infants and pre-toilet trained children to collect urine samples. For the other group of children (>2 years), a clean catch method of the mid-stream urine was used to obtain the samples

Musa-Aisien, 2003

Bibliographic Reference	Musa-Aisien AS; Ibadin OM; Ukoh G; Akpede GO; Prevalence and antimicrobial sensitivity pattern in urinary tract infection in febrile under-5s at a children's emergency unit in Nigeria.; Annals of tropical paediatrics; 2003; vol. 23 (no. 1)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Benin city, Nigeria • Setting Children's emergency room in teaching hospital • Study dates 1 April and 30 September 1999 • Sources of funding Not reported
Study type	Prospective cohort study Consecutive recruitment
Inclusion criteria	• Fever Core temperature ≥38.0°C • Aged 1 to 60 months
Exclusion criteria	• History of antibiotic treatment or use of antimalarials in past 7 days • Urologic manipulation • Urinary tract anomalies • Known acquired or congenital immunodeficiency or other major chronic condition
Number of participants	N=306
Index test(s)	• fever • vomiting • abdominal pain • diarrhoea • irritability • poor feeding

	• jaundice • convulsions
Reference standard (s)	UTI diagnosis counts >10(5) colony forming unit/mL were considered diagnostic
Method of reference standard collection	Clean-catch method/mid-stream urine (MSU) or suprapubic urine aspirate (SPA)

Newman, 2002

Bibliographic Reference	Newman TB; Bernzweig JA; Takayama JI; Finch SA; Wasserman RC; Pantell RH; Urine testing and urinary tract infections in febrile infants seen in office settings: the Pediatric Research in Office Settings' Febrile Infant Study.; Archives of pediatrics & adolescent medicine; 2002; vol. 156 (no. 1)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Multiple sites from USA • Setting Offices of paediatric practitioners • Study dates February 28, 1995, to April 25, 1998 • Sources of funding This study was supported by grant R01 HS06485 from the Agency for Health Care Policy and Research, Rockville, Md, and grant MCJ-177022 from the Health Resources and Services Administration Maternal and Child Health Bureau, Rockville.
Study type	Prospective cohort study
Inclusion criteria	• Fever Axillary, rectal, or tympanic temperatures of ≥38°C at assessment or at home in the previous 24 hours • Aged up to 3 months
Exclusion criteria	Not known
Number of participants	N=1666
Index test(s)	• vomiting • altered consciousness • fluid intake • general appearance • breathing difficulty • abnormal chest sounds • abnormal ENT • cough • poor feeding • darker and/or cloudy urine • oliguria • runny nose • social interaction

Reference standard (s)	UTI diagnosis Urine culture single pathogen ≥10(2) colony forming unit/mL (cfu/ml) for suprapubic aspiration samples, ≥2x10(4) cfu/ml for catheter samples, ≥10(5) cfu/ml for bag specimen and clean-catch samples
Method of reference standard collection	Catheter, urine collection bag, clean-catch

O'Brien, 2013

Bibliographic Reference	O'Brien K; Edwards A; Hood K; Butler CC; Prevalence of urinary tract infection in acutely unwell children in general practice: a prospective study with systematic urine sampling.; The British journal of general practice : the journal of the Royal College of General Practitioners; 2013; vol. 63 (no. 607)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Multiple sites in Wales, UK • Setting General practices • Study dates March 2008 and July 2010 • Sources of funding This study was funded by a Welsh Government National Institute for Health and Social Care Research (NISCHR)/Medical Research Council Health Research Partnership Award. The Southeast Wales Trials Unit is funded by the National Institute for Social Care and Health Research. Further support was from the Wales School of Primary Care research, funded by NISCHR, and by the NISCHR Clinical Research Centre.
Study type	Prospective cohort study
Inclusion criteria	• Unwell/febrile child <28 days duration • Aged 1 to 60 months
Exclusion criteria	Known acquired or congenital immunodeficiency or other major chronic condition ongoing antibacterial treatment
Number of participants	N=597
Index test(s)	• urinary frequency • dysuria • irritability • poor feeding • bed wetting • muscle aches or pains
Reference standard (s)	UTI diagnosis A positive culture was defined as pure or predominant bacterial growth of >10(5) colony-forming units (cfu)/ml on culture.
Method of reference	A urine sample was sought from all children. Clean catch was the preferred method but if this was not feasible, a nappy pad was used

standard collection	

Pylkkänen, 1979

Bibliographic Reference	Pylkkänen J; Vilska J; Koskimies O; Diagnostic value of symptoms and clean-voided urine specimen in childhood urinary tract infection.; Acta paediatrica Scandinavica; 1979; vol. 68 (no. 3)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Helsinki, Finland • Setting General outpatient clinic • Study dates Not reported • Sources of funding This study was supported by the Foundation of Pediatric Research, Sigrid Juselius Foundation and Orion Pharmaceutical Co.
Study type	Prospective cohort study
Inclusion criteria	• Symptoms suggestive of urinary tract infection • Aged <18 years
Exclusion criteria	Not known
Number of participants	N= 477, but data for only 200
Index test(s)	• fever • vomiting • abdominal pain • diarrhoea • urinary frequency • dysuria • smelly urine • haematuria • bed wetting • constipation • convulsions • muscle aches or pains
Reference standard (s)	UTI diagnosis Urine culture any colony forming unit/mL
Method of reference standard collection	Suprapubic aspiration or clean-catch
Additional information	Study recruited 477 participants, but only provided data for 200 without explanation.

Shaw, 1998

Bibliographic Reference	Shaw KN; Gorelick M; McGowan KL; Yakscoe NM; Schwartz JS; Prevalence of urinary tract infection in febrile young children in the emergency department.; Pediatrics; 1998; vol. 102 (no. 2)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Philadelphia, Pennsylvania, USA • Setting Children's hospital emergency department • Study dates February 2, 1995, to February 14, 1996 • Sources of funding This work was supported by the Maternal and Child Health Bureau (Title V, Social Security Act), Health Resource and Services Administration, Department of Health and Human Services.
Study type	Cross-sectional study Consecutive recruitment
Inclusion criteria	• Fever Rectal temperature ≥38.5°C • Boys younger than 1 year and girls aged less than 2 years
Exclusion criteria	• Known acquired or congenital immunodeficiency or other major chronic condition • diagnosis of serious bacterial infection already made • Ongoing antibacterial treatment
Number of participants	N=2411
Index test(s)	• fever • urinary symptoms • general appearance • previous UTI
Reference standard (s)	UTI diagnosis A positive result was defined as growth of a single urinary tract pathogen at ≥10(4) colony forming unit/mL
Method of reference standard collection	Urethral catheter

Struthers, 2003

Bibliographic Reference	Struthers S, Scanlon J, Parker K, Goddard J HR; Parental reporting of smelly urine and urinary tract infection; Arch Dis Child; 2003; vol. 3 (no. 88); 250-2

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location UK • Setting

	Acute paediatric admissions unit of single centre • Study dates September 2000 - May 2001 • Sources of funding Not reported
Study type	Prospective cohort study
Inclusion criteria	• Unwell/febrile child It was unit policy that all unwell or febrile young children should have a urine sample collected. This included children with symptoms of UTI, such as urinary frequency, and more commonly children with non-specific signs and symptoms such as pyrexia, irritability, and abdominal pain. • Aged less than 6 years
Number of participants	N=110
Index test(s)	• smelly urine Parents of admitted children were given a questionnaire regarding child's urine, asking them to: 1) assess the smell ('mildly offensive', 'very offensive', 'strong', 'fishy' or 'infected') 2) describe the smell
Reference standard (s)	UTI diagnosis The diagnosis of a UTI was defined as a pure growth of >10(5) organisms/ml. Mixed growths or pure growths of <10(4) were regarded as negative. Results were analysed using the Fisher exact test (two tailed) and predictive values, sensitivities, and specificities for the replies were calculated.
Method of reference standard collection	The method of collection is specific to the age group and follows unit guidelines. Clean catch (often with parental assistance) is the most common method, although suprapubic aspiration, catheter (“in/out”) specimen, or mid-stream catch are other methods used. “Bag” urine collection is rarely used. Urine samples are sent to the pathology laboratory for microscopy, culture, and sensitivity. Initial microscopy results are phoned back to the ward, normally within one hour.

Participant Characteristics

Characteristic	**Study (N =110)**
Mean (range) age (Months) Mean (95% CI)	23 (0 to 62)
% clean catch as method of collection Nominal	95.5

Risk of bias – QUADAS-2

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	Low
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low =
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low

Section	Question	Answer
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	Low
Overall risk of bias and directness	Directness	Directly applicable

Velasco, 2015

Bibliographic Reference	Velasco R; Benito H; Mozun R; Trujillo JE; Merino PA; de la Torre M; Gomez B; ; Using a urine dipstick to identify a positive urine culture in young febrile infants is as effective as in older patients.; Acta paediatrica (Oslo, Norway : 1992); 2015; vol. 104 (no. 1)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Multiple locations in Spain • Setting paediatric emergency departments • Study dates October 2011 and September 2013 • Sources of funding Not reported
Study type	Prospective cohort study
Inclusion criteria	• Fever without source Axillary or rectal temperature ≥ 38°C (100.4°F) registered either at home or at paediatric emergency department • Aged younger than 90 days
Exclusion criteria	Incomplete data available
Number of participants	N=3401
Index test(s)	general appearance irritability
Reference standard (s)	UTI diagnosis The threshold for considering a urine culture as positive was the growth of ≥50 000 colony forming unit/mL of a single pathogen in a urine culture collected by a sterile method (urethral catheterization, suprapubic aspiration)
Method of reference standard collection	Urethral catheterisation or suprapubic aspiration

Verbakel, 2016

Bibliographic Reference	Verbakel JY; Lemiengre MB; De Burghgraeve T; De Sutter A; Aertgeerts B; Shinkins B; Perera R; Mant D; Van den Bruel A; Buntinx F; Should all acutely ill children in primary care be tested with point-of-care CRP: a cluster randomised trial.; BMC medicine; 2016; vol. 14 (no. 1)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics. Included	
Study details	• Study location Multiple locations in Belgium • Setting General practices • Study dates February 15, 2013, to February 28, 2014 • Sources of funding This study was funded by the National Institute for Health and Disability Insurance (RIZIV, Belgium) under reference CGV n° 2012/235 and the Research Foundation Flanders (FWO) under reference n° G067509N. AVDB and BS were funded by the NIHR Diagnostic Evidence Co-operative Oxford.
Study type	Cluster randomised controlled trial
Inclusion criteria	• Unwell/febrile child Acutely unwell for maximum of 5 days • Aged up to 16 years
Exclusion criteria	• Chronic illness • Presenting with trauma
Number of participants	N=756
Index test(s)	• abdominal pain • respiratory symptoms • DUTY score
Reference standard (s)	UTI diagnosis urine culture ≥10(5) colony forming unit/mL
Method of reference standard collection	Not reported

Williams-Smith, 2020

Bibliographic Reference	Williams-Smith, J A; Fougere, Y; Pauchard, J-Y; Asner, S; Gehri, M; Crisinel, P A; Risk factors for urinary tract infections in children aged 0-36months presenting with fever without source and evaluated for risk of serious bacterial infections.; Archives de pediatrie : organe officiel de la Societe francaise de pediatrie; 2020; vol. 27 (no. 7); 372-379

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Switzerland

	• Setting Emergency department of single centre • Study dates October 2015 - October 2017
Study type	Prospective cohort study
Inclusion criteria	• Aged up to 36 months • Evaluated for risk of serious bacterial infection • Fever without source Defined as a temperature of ≥38 degrees C at home or in the emergency room with no identified infectious source during physical examination at the hospital; under 10 days in duration
Exclusion criteria	• Returning travellers • Known acquired or congenital immunodeficiency or other major chronic condition • Diagnosis of serious bacterial infection already made • Ongoing antibacterial treatment
Number of participants	N=173
Index test(s)	• fever • duration of fever >2 days; • temperature >39 degrees Celsius • chills • altered consciousness
Reference standard (s)	UTI diagnosis within 10 days follow-up period. UTI was defined as the presence of ≥10(4) colony forming units per milliliter of a single uropathogen, cultured from a urine specimen obtained by bladder catheterization
Method of reference standard collection	Bladder catheterisation

Participant Characteristics

Characteristic	**Study (N =173)**
% Female Nominal	46
Median (IQR) age (Months) Median (IQR)	4.4 (2.1 to 11)
median (IQR) duration of fever (days) Median (IQR)	1 (0 to 2)

Risk of bias – QUADAS-2

Section	**Question**	**Answer**
Patient selection: risk of bias	Could the selection of patients have introduced bias?	High *(of initial cohort of 400 participants, 155 were lost due to increased patient flow to ED during that period. Those patients not captured in records may be distinct from those that were.)*
Patient selection: applicability	Are there concerns that included patients do not match the review question?	Low

Section	Question	Answer
Index tests: risk of bias	Could the conduct or interpretation of the index test have introduced bias?	Low
Index tests: applicability	Are there concerns that the index test, its conduct, or interpretation differ from the review question?	Low
Reference standard: risk of bias	Could the reference standard, its conduct, or its interpretation have introduced bias?	Low
Reference standard: applicability	Is there concern that the target condition as defined by the reference standard does not match the review question?	Low
Flow and timing: risk of bias	Could the patient flow have introduced bias?	Low
Overall risk of bias and directness	Risk of Bias	High *(risk of bias due to issues surrounding patient selection)*
Overall risk of bias and directness	Directness	Directly applicable

Zorc, 2005

Bibliographic Reference	Zorc JJ; Levine DA; Platt SL; Dayan PS; Macias CG; Krief W; Schor J; Bank D; Shaw KN; Kuppermann N; ; Clinical and demographic factors associated with urinary tract infection in young febrile infants.; Pediatrics; 2005; vol. 116 (no. 3)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location USA • Setting Paediatric emergency departments • Study dates 1991 to 2001 • Sources of funding This study was supported in part by research grants from Roche Pharmaceuticals and Medimmune Pharmaceuticals. This study was also supported in part by General Clinical Research Center National Institutes of Health National Center for Research Resources Grant M01 RR00096.
Study type	Cross-sectional study
Inclusion criteria	• Fever Rectal temperatures ≥38°C by history or in the ED • Aged up to 60 days
Exclusion criteria	• History of antibiotic treatment or use of antimalarial within 48 hours of presentation
Number of participants	N=1005

Index test(s)	• fever • general appearance • Yale observation scale
Reference standard (s)	UTI diagnosis Growth of a single known pathogen with colony counts meeting 1 of 3 criteria: (1) ≥1000 colony forming units (cfu)/mL for urine cultures obtained by suprapubic aspiration, (2) ≥50 000 cfu/mL from a catheterized specimen, or (3) ≥10 000 cfu/mL from a catheterized specimen in association with a positive urinalysis
Method of reference standard collection	Bladder catheterization or suprapubic aspiration

Primary studies looking at diagnostic models

Boon, 2022

Bibliographic Reference	Boon, Hanne Ann; Verbakel, Jan Y; De Burghgraeve, Tine; Bruel, Ann Van den; Clinical prediction rules for childhood UTIs: a cross-sectional study in ambulatory care.; BJGP open; 2022

Participant characteristics

Study design	Cross-sectional study • Post-hoc analysis of a cross-sectional study
Study details	Study location • Belgium Study setting • 39 general practices and 2 emergency departments Study dates • March 2019 - March 2020 Sources of funding • Funded by the Research Foundation Flanders (Fonds Wetenschappelijk Onderzoek (FWO), Odysseus Program, grant number G0H8518N) and by a KU Leuven starting grant (grant number ERX-D5331-STG/18/008 [to HB])

Inclusion criteria	• Overall sample inclusion criteria between 3 months to 18 years with an acute illness ≤10 days duration.
	• DUTY model inclusion criteria
	  ○ <5 years of age
	• UTIcalc model inclusion criteria
	  ○ Febrile children (≥38°C), <2 years old without urinary tract abnormalities
	• Gorelick model inclusion criteria
	  ○ Febrile children (≥38°C) <2 years old.

Exclusion criteria	• traumatic injury • urinary catheter • critically unstable • referred to the hospital • been on immunosuppressive medication in previous 30 days • been on antibiotics in previous 7 days
Number of participants and recruitment methods	575 in total sample. DUTY score tested on 297 participants, Gorelick score on 100 participants and UTIcalc on 96. All participants were enrolled in the ERNIE4 study, a multicentre, prospective cross-sectional study.

Sample characteristics	Median (IQR) age 6 (4-10) years
Outcome(s) of interest	Diagnosis of UTI • UTI was defined as a single pathogen ≥10^5 colony-forming units per milliliter (cfu/mL) on urine culture. • Contamination was defined as multiple pathogens or one pathogen <10^5 cfu/mL. Samples were excluded if there was no result for culture or if the sample was received >72 hours after inclusion in the laboratory. For the DUTY models, the reference standard was one pathogen ≥10^5 cfu/mL; for the Gorelick score, a pathogen ≥5x10^4cfu/mL; and for the UTIcalc, a pathogen ≥5x10^4cfu/mL with pyuria, e.g. LE ≥trace or white blood cells (WBC)(≥5/high-powerfield (hpf) or ≥10/microliter(µl)).
Diagnostic factors or risk factor(s) or sign(s)/symptom(s)	• DUTY score (high risk if 5 or more points): Dysuria (2 points), malodorous urine (2 points), history of UTI (1 point), absence of severe cough (2 points), severity of illness (2 points when >6 on a scale of 0-10). • Gorelick score (high risk if 2 or more variables are present): Age <12 months, Caucasian, Fever ≥39°C, fever 2 or more days, fever without source* • UTIcalc (high risk if 2% risk or greater on online calculator): Age < 12months, Fever ≥39°C, non-African American ethnicity, female gender, uncircumcised male, fever without source. * defined in the original study as discharge diagnoses: 'fever', 'fever without source' or 'viral infection'. ** defined in the original study as no upper respiratory tract infection, no bronchiolitis, no pneumonia, no acute otitis media, no gastroenteritis, no meningitis and no viral syndrome.
Additional information	Study looked at validating a number of models but did not refit them based on the results. The PROBAST checklist was used to assess risk of bias for diagnostic model studies but this was designed for prediction models and many of the domains are not relevant where an existing model is being tested and not refitted.

Participant characteristics

	DUTY sample (n=297)	Gorelick sample (n=100)	UTIcalc sample (n=96)
Median (IQR) age	2.60 (1.12-3.75)	0.94 (0.56-1.49)	0.94 (0.56-1.49)
Female %	55%	62%	62%
Fever %	84%	100%	100%
Median (IQR) duration of illness, days	2.00 (1.00-3.00)	2.00 (1.00-3.00)	2.00 (1.00-3.00)
Dysuria %	4%	1%	1%
Malodorous urine %	3%	3%	3%
Abdominal pain %	14%	5%	5%
History of UTI	8%	10%	9%

%			

Risk of bias - PROBAST tool

Section	Question	Answer
Selection of participants	Overall risk of bias for selection of participants domain	Low
Selection of participants	Concerns for applicability for selection of participants domain	Low
Predictors or their assessment	Overall risk of bias for predictors or their assessment domain	Low *(Although it was unclear whether all predictor variables were routinely assessed in each centre, there is a low level of missing data.)*
Predictors or their assessment	Concerns for applicability for predictors or their assessment domain	Low
Outcome or its determination	Overall risk of bias for outcome or its determination domain	Low *(Samples were excluded if there was no result for culture or if the sample was received >72 hours after inclusion in the laboratory. Sensitivity analyses were conducted examining the accuracy of the model at different urine culture positivity thresholds.)*
Outcome or its determination	Concerns for applicability for outcome or its determination domain	Low
Analysis	Overall risk of bias for analysis domain	Low
Overall Risk of bias and Applicability	Risk of bias	Low
Overall Risk of bias and Applicability	Concerns for applicability	Low

De, 2013

Bibliographic Reference	De S; Williams GJ; Hayen A; Macaskill P; McCaskill M; Isaacs D; Craig JC; Accuracy of the "traffic light" clinical decision rule for serious bacterial infections in young children with fever: a retrospective cohort study.; BMJ (Clinical research ed.); 2013; vol. 346

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Westmead, Australia • Setting Children's hospital emergency department

	• Study dates 1 July 2004 and 30 June 2006 • Sources of funding This is a sub-study of FEVER, which was funded by the National Health and Medical Research Council of Australia (grant Nos 211205 and 402764).
Study type	Retrospective cohort study Retrospective analysis of data from a two-year prospective cohort study (see Craig et al 2010)
Inclusion criteria	• Unwell/febrile child • Aged less than 5 years See also Craig et al 2010
Exclusion criteria	Known acquired or congenital immunodeficiency or other major chronic condition children transferred from another hospital
Number of participants	N=15781
Length of follow-up	All eligible children were followed up until they fulfilled the case definition for serious bacterial infection or until the fever had resolved for over 24 hours
Loss to follow-up	see Craig et al 2010
Index test(s)	The traffic light system developed by the National Institute for Health and Clinical Excellence (NICE)) for detecting three common serious bacterial infections (urinary tract infection, pneumonia, and bacteraemia)
Method of reference standard collection	see Craig et al 2010

Díaz, 2016

Bibliographic Reference	Díaz MG; García RP; Gamero DB; González-Tomé MI; Romero PC; Ferrer MM; Contreras JR; Lack of Accuracy of Biomarkers and Physical Examination to Detect Bacterial Infection in Febrile Infants.; Pediatric emergency care; 2016; vol. 32 (no. 10)

Study Characteristics

Study included in Boon 2021 systematic review. See this review for more study characteristics.	
Study details	• Study location Madrid, Spain • Setting Hospital children's emergency department • Study dates July 2008 and January 2012 • Sources of funding Not reported
Study type	Retrospective cohort study
Inclusion criteria	• Fever without source • Fever was defined as an axillary temperature of ≥38°C (100.4°F) measured at home and/or in the ED. • Aged younger than 90 days
Exclusion criteria	• Urinary tract anomalies

	• Known acquired or congenital immunodeficiency or other major chronic condition • Ongoing antibacterial treatment • Preterm neonates • Previously hospitalised
Number of participants	N=318
Index test(s)	Yale observation scale
Reference standard (s)	UTI diagnosis At least 50,000 colony-forming units/mL of a uropathogen cultured from the urine specimen
Method of reference standard collection	Urine culture collected by urinary catheterization or suprapubic puncture

Zorc, 2005

Bibliographic Reference	Zorc JJ; Levine DA; Platt SL; Dayan PS; Macias CG; Krief W; Schor J; Bank D; Shaw KN; Kuppermann N; ; Clinical and demographic factors associated with urinary tract infection in young febrile infants.; Pediatrics; 2005; vol. 116 (no. 3)

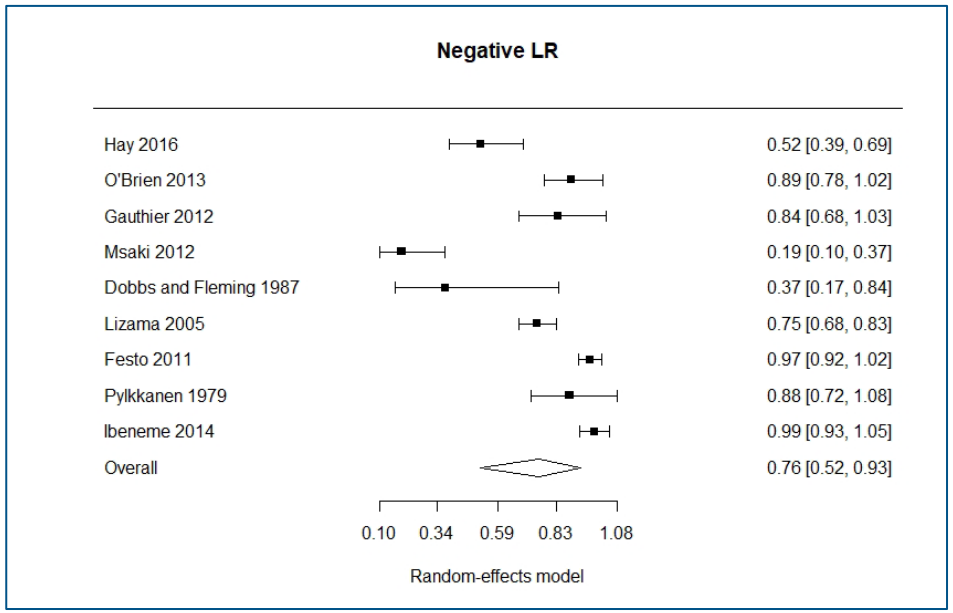
Study Characteristics

See table in section on signs and symptoms above

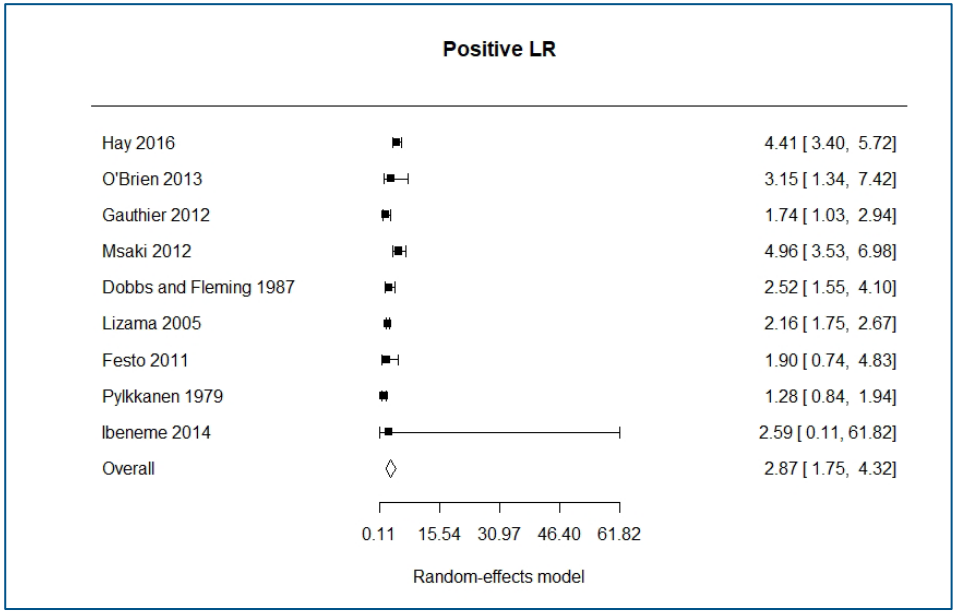
Appendix E – Forest plots

Dysuria – main analysis

Likelihood ratios for dysuria (< 14 years)

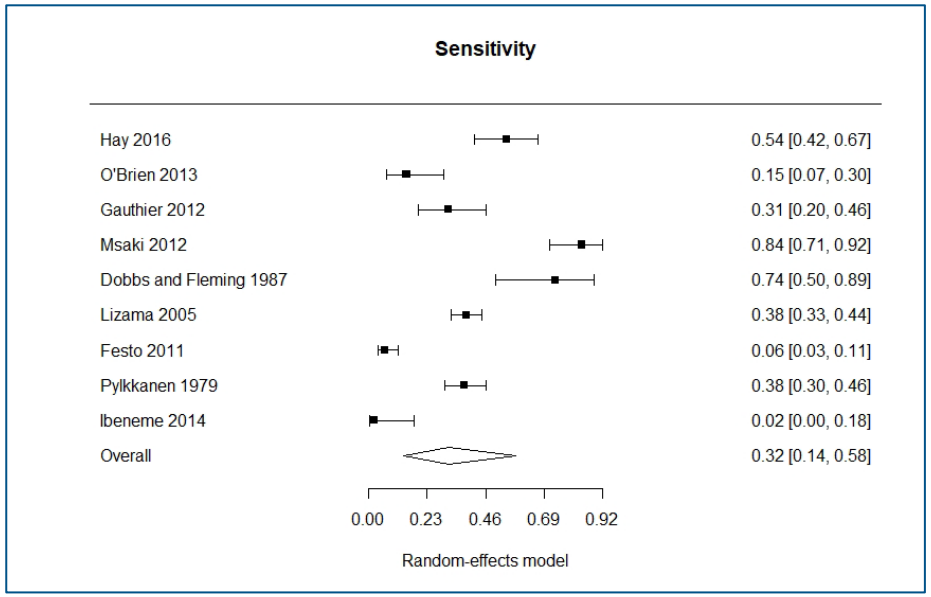


I^2 for negative LR for dysuria = 88.0%

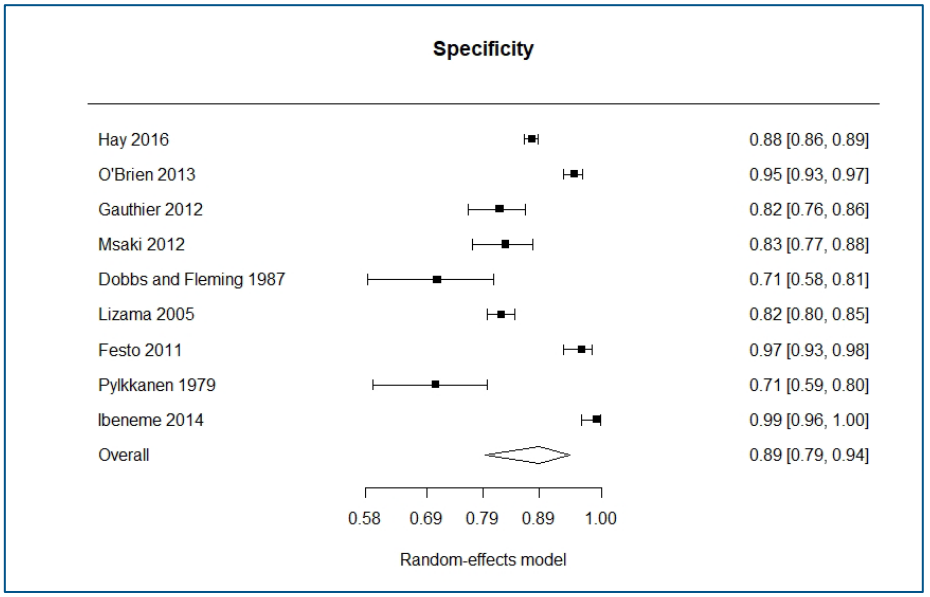


I^2 for positive LR for dysuria = 82.4%

Sensitivity and specificity for dysuria (< 14 years)

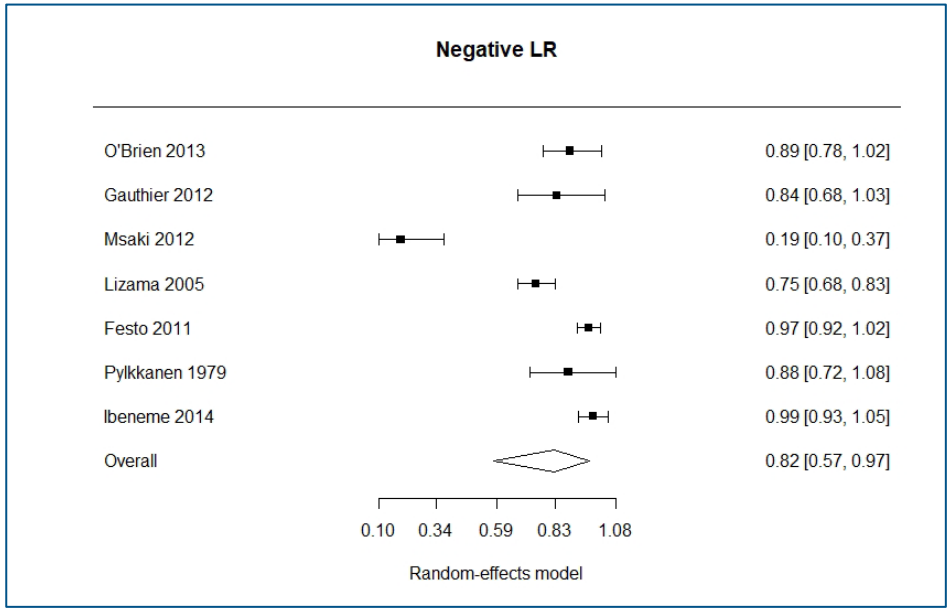


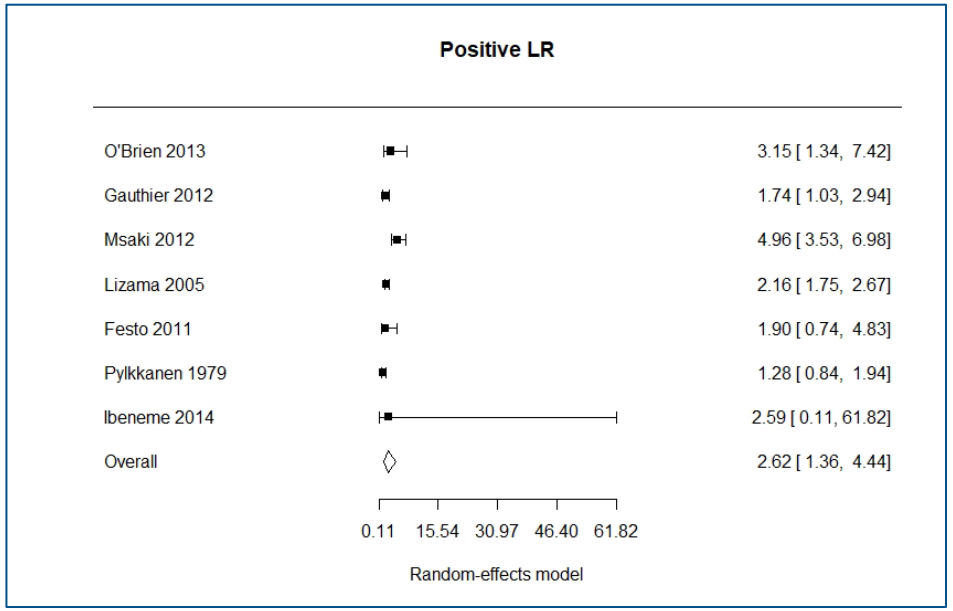
I^2 for sensitivity for dysuria = 91.9%



I^2 for specificity for dysuria = 92.7%

Likelihood ratios for dysuria (<2 years)

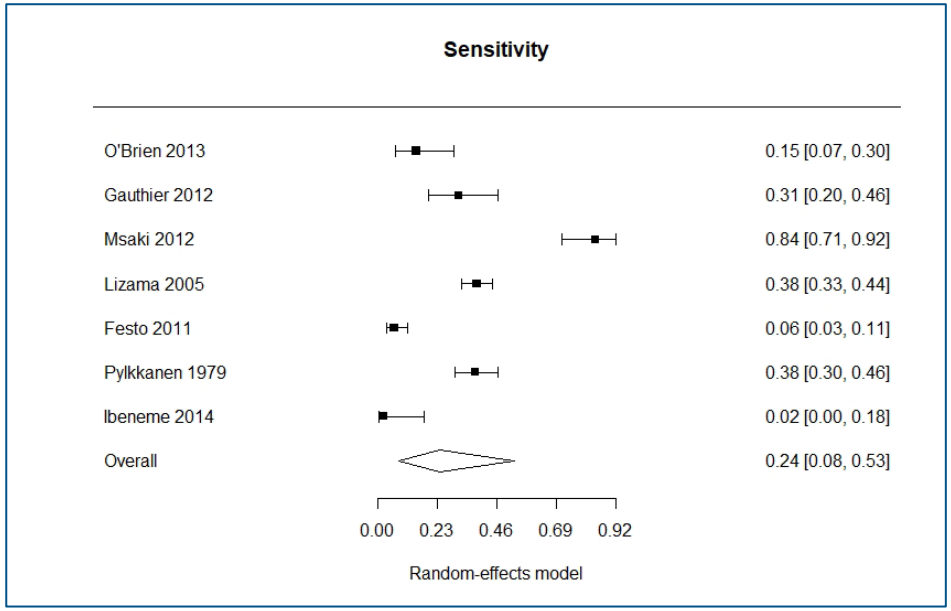


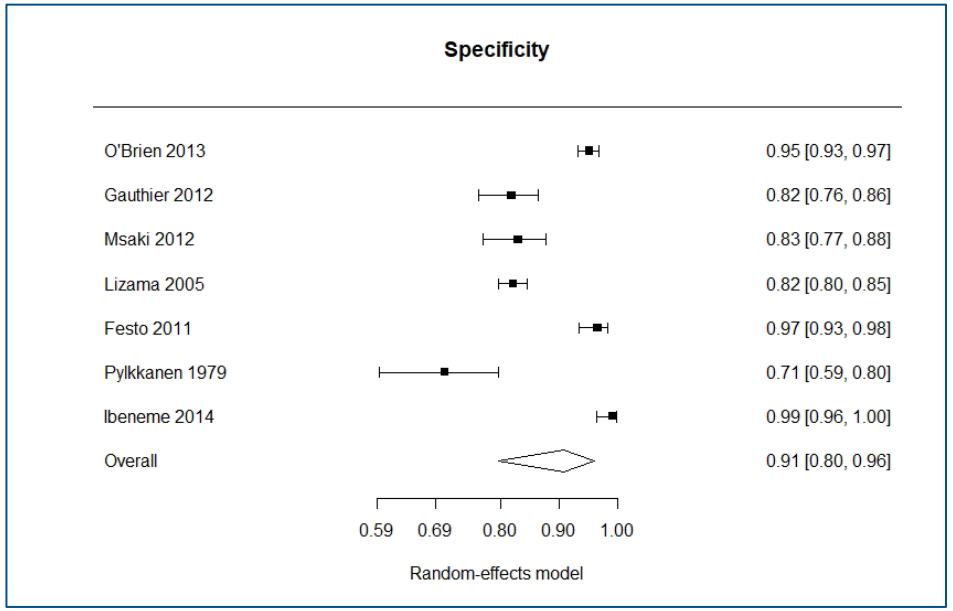


I^2 for negative LR for dysuria = 87.1%

I^2 for positive LR for dysuria = 79.4%

Sensitivity and specificity for dysuria (<2 years)



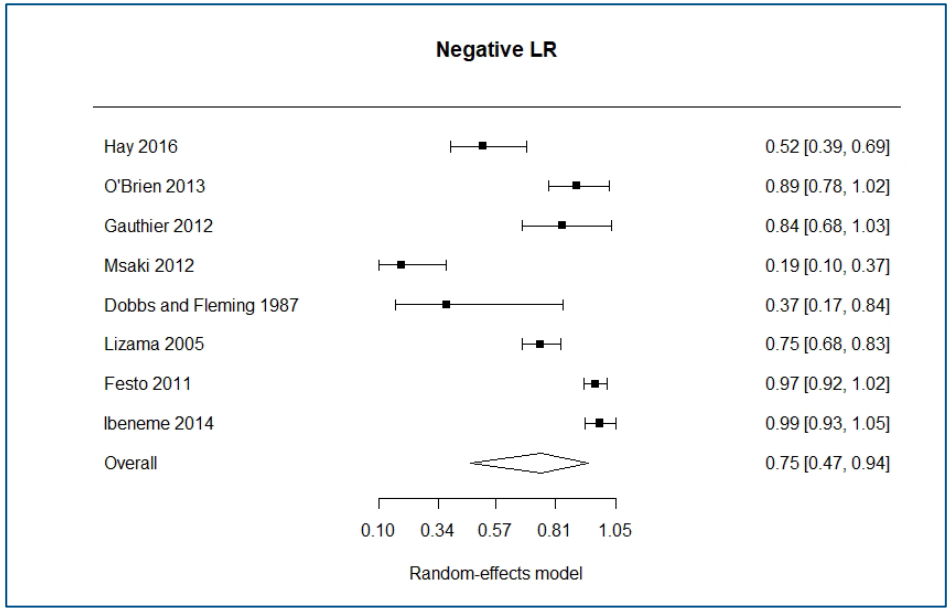


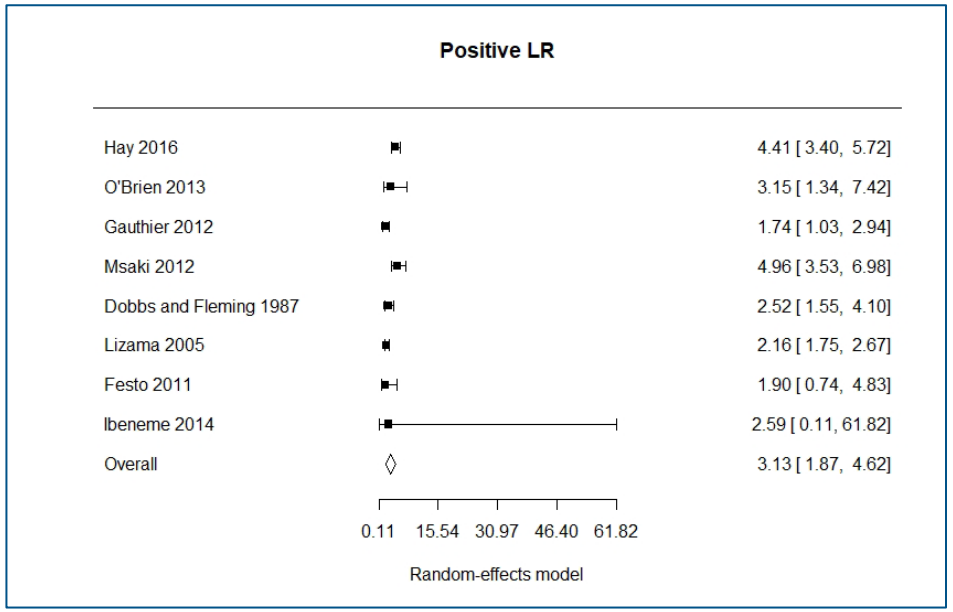
I^2 for sensitivity for dysuria = 92.8%

I^2 for specificity for dysuria = 93.5%

Dysuria – sensitivity analysis

Likelihood ratios for dysuria (< 14 years) (removing Pylkkanen 1979)

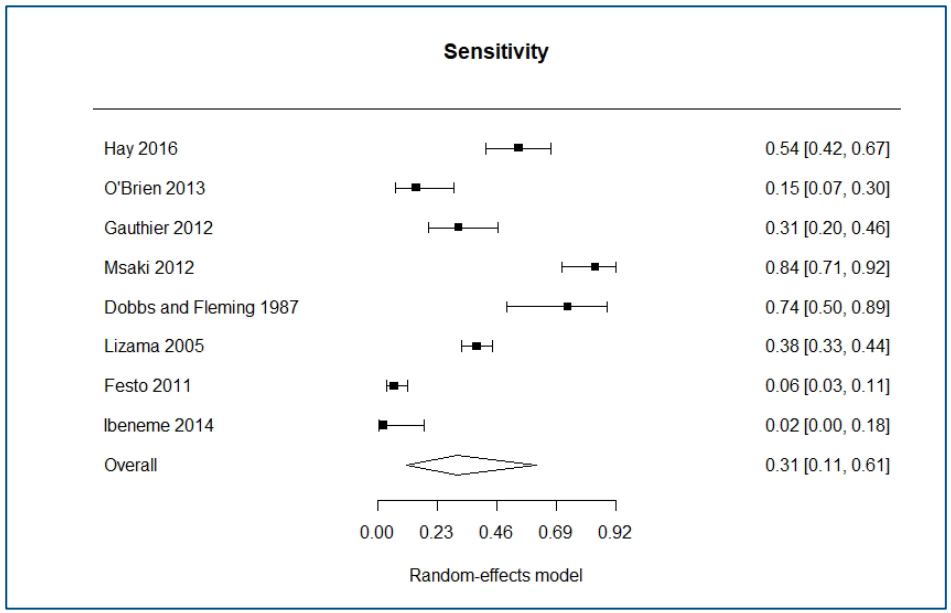


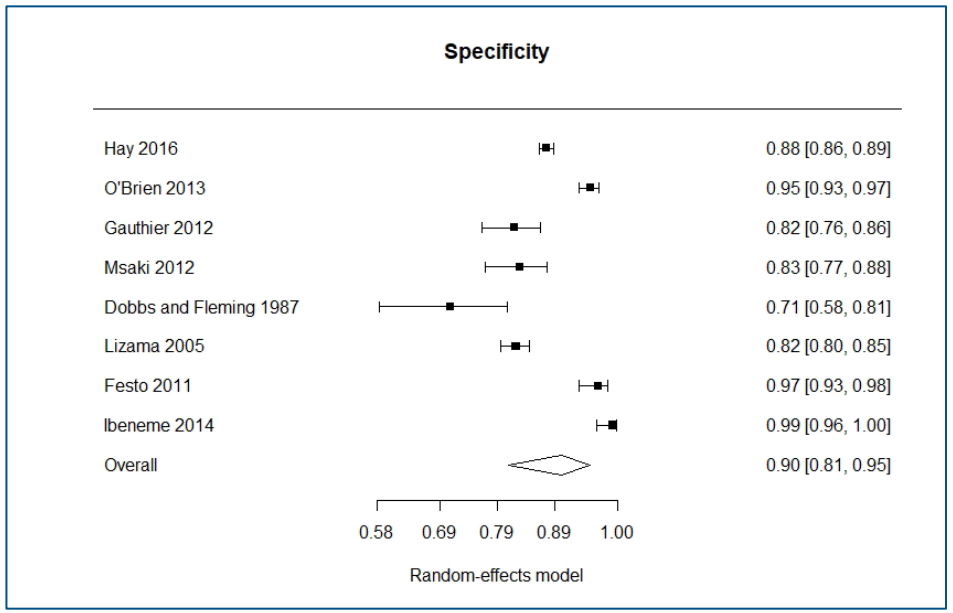


I^2 for negative LR for dysuria = 89.5%

I^2 for positive LR for dysuria = 77.9%

Sensitivity and specificity for dysuria (< 14 years) (removing Pylkkanen 1979)

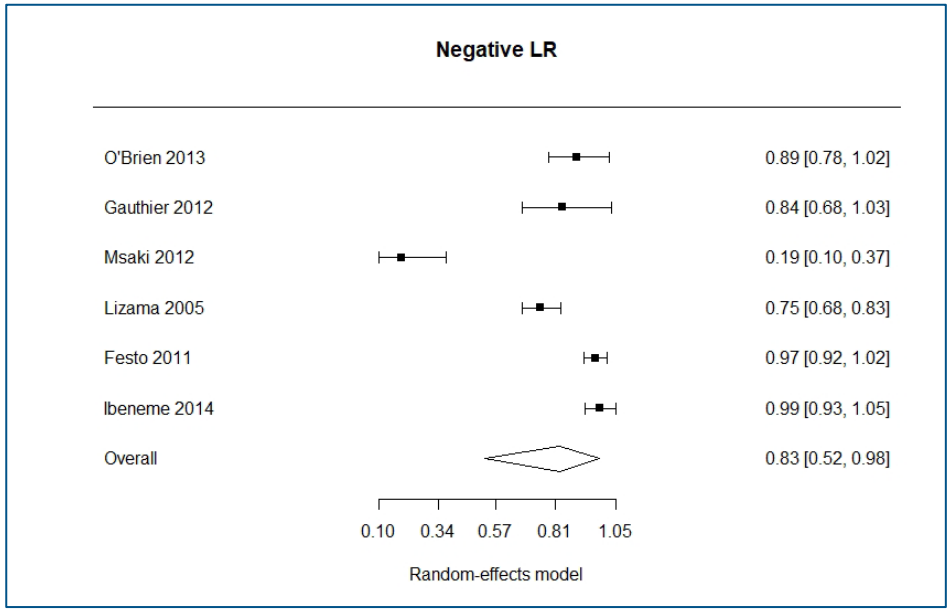


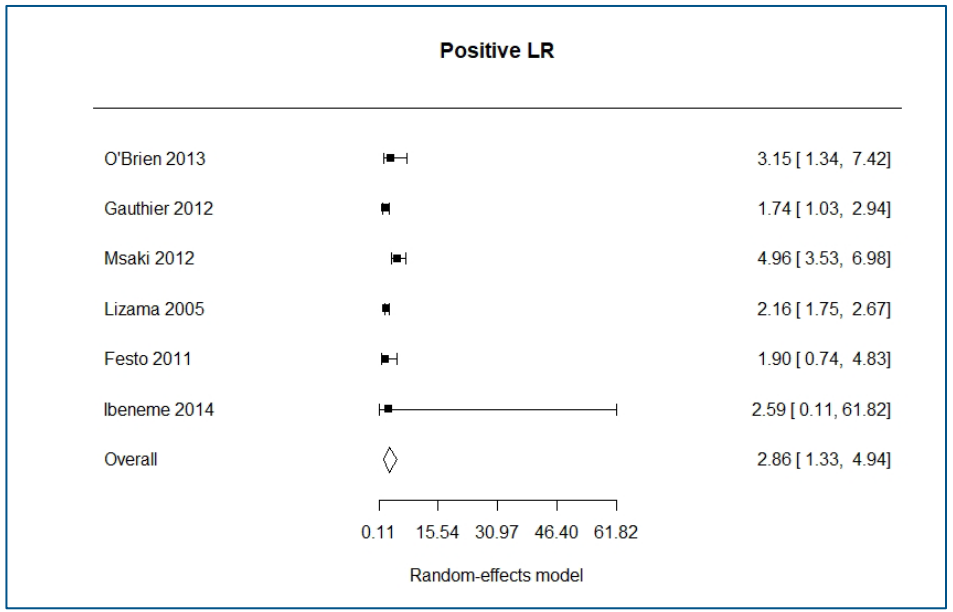


I^2 for sensitivity for dysuria = 92.9%

I^2 for specificity for dysuria = 92.7%

Likelihood ratios for dysuria (<2 years) (removing Pylkkanen 1979)

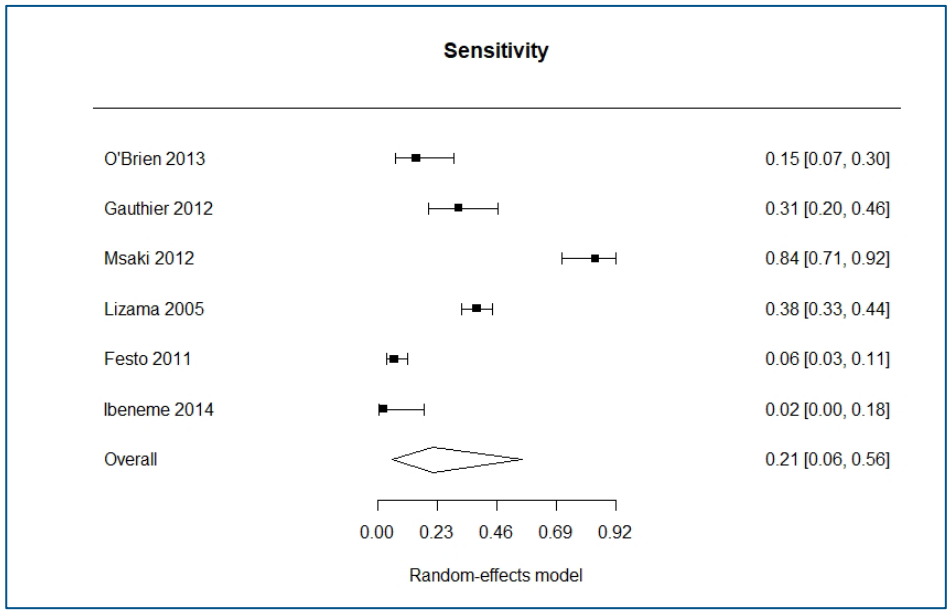


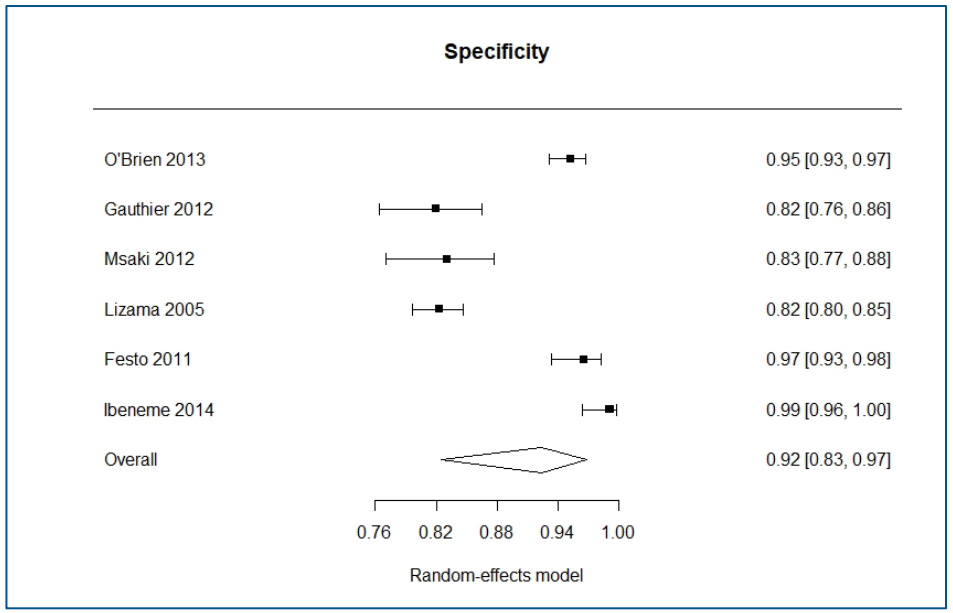


I^2 for negative LR for dysuria = 89.2%

I^2 for positive LR for dysuria = 75.0%

Sensitivity and specificity for dysuria (<2 years) (removing Pylkkanen 1979)



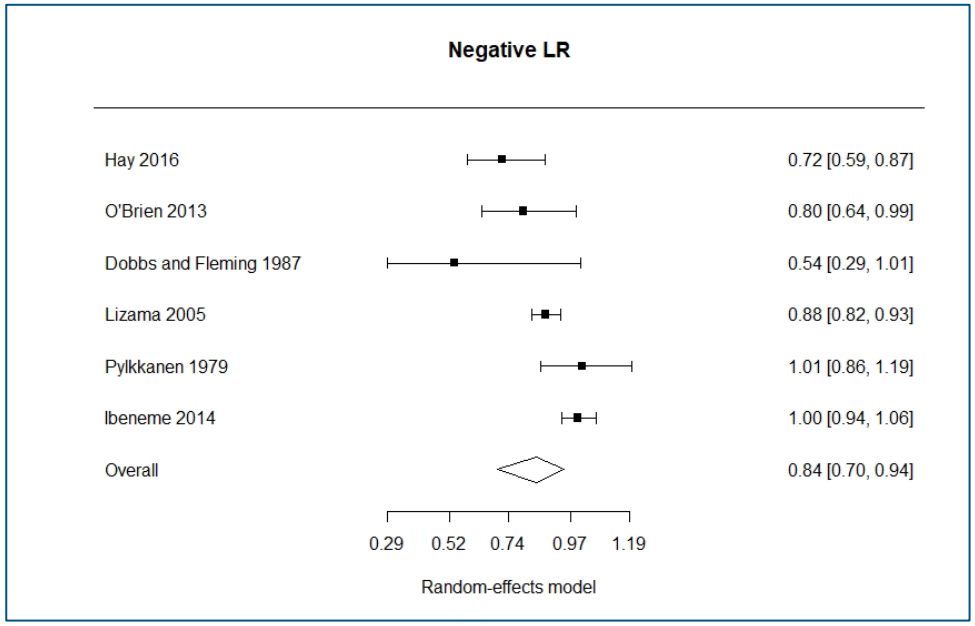


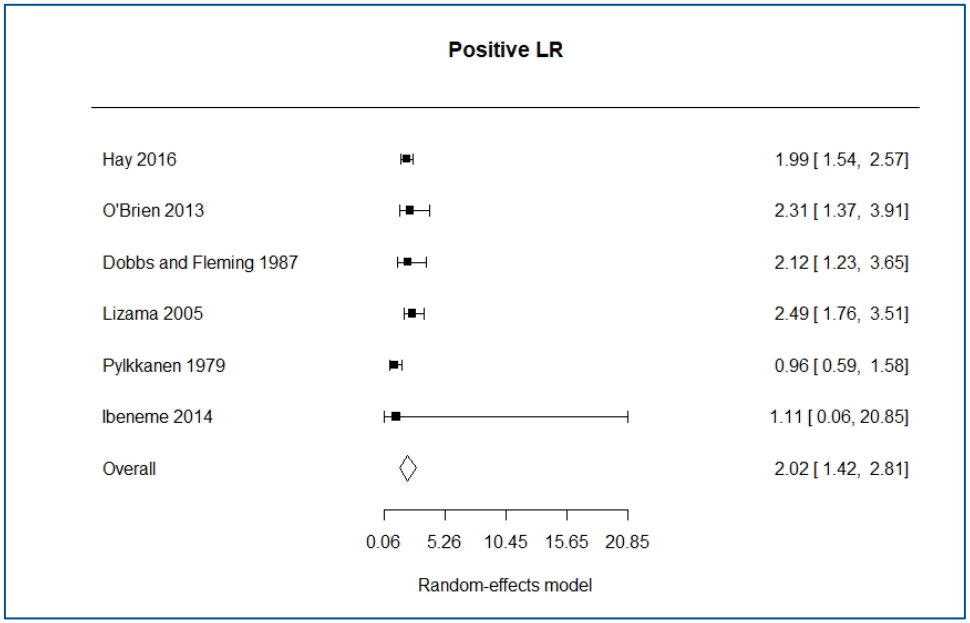
I^2 for sensitivity for dysuria = 94.0%

I^2 for specificity for dysuria = 93.8%

Frequency – main analysis

Likelihood ratios for frequency (< 14 years)

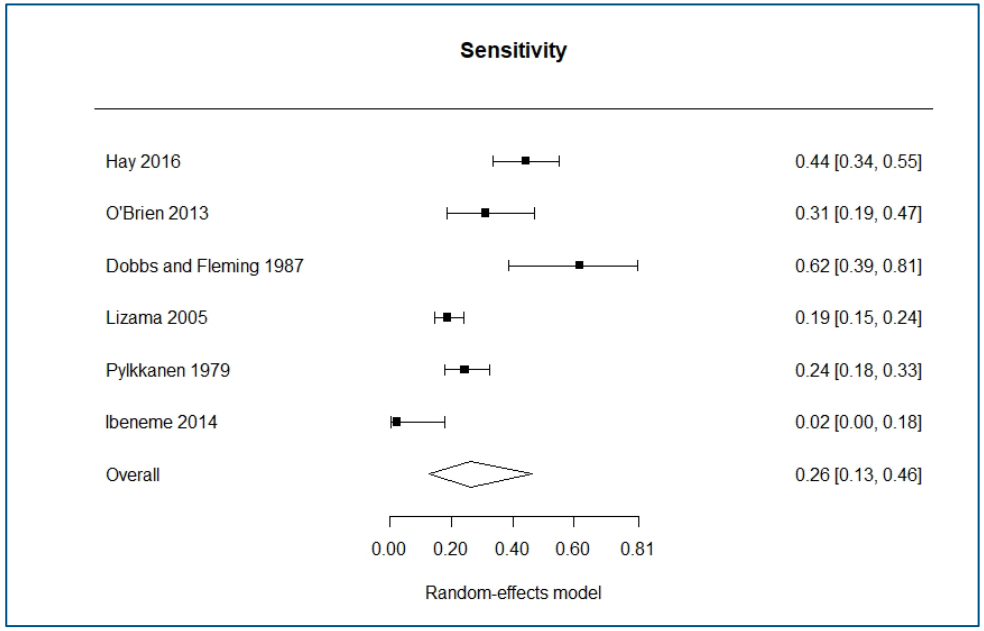


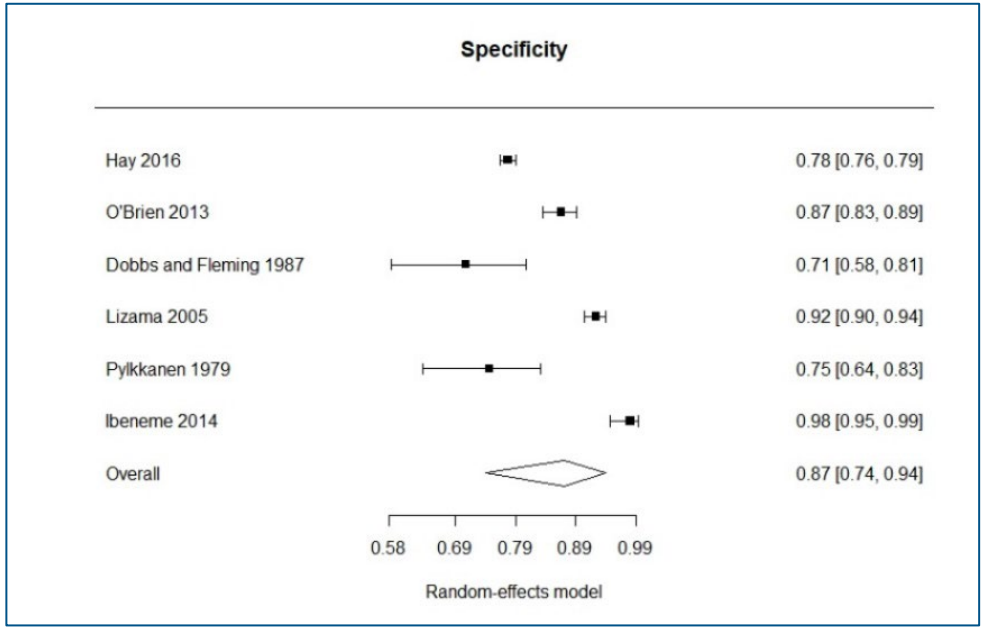


I^2 for negative LR for frequency = 74.6%

I^2 for positive LR for frequency = 49.6%

Sensitivity and specificity for frequency (< 14 years)

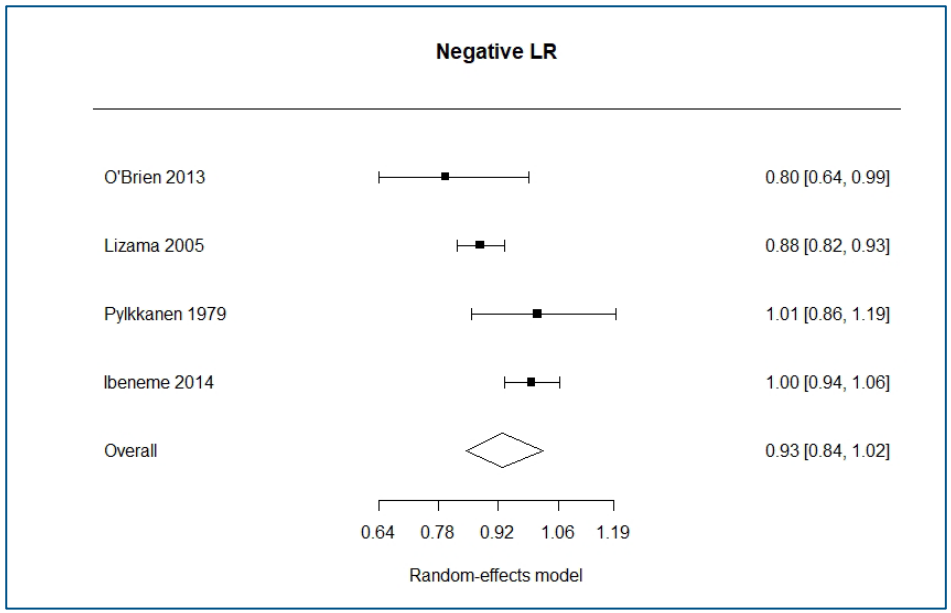




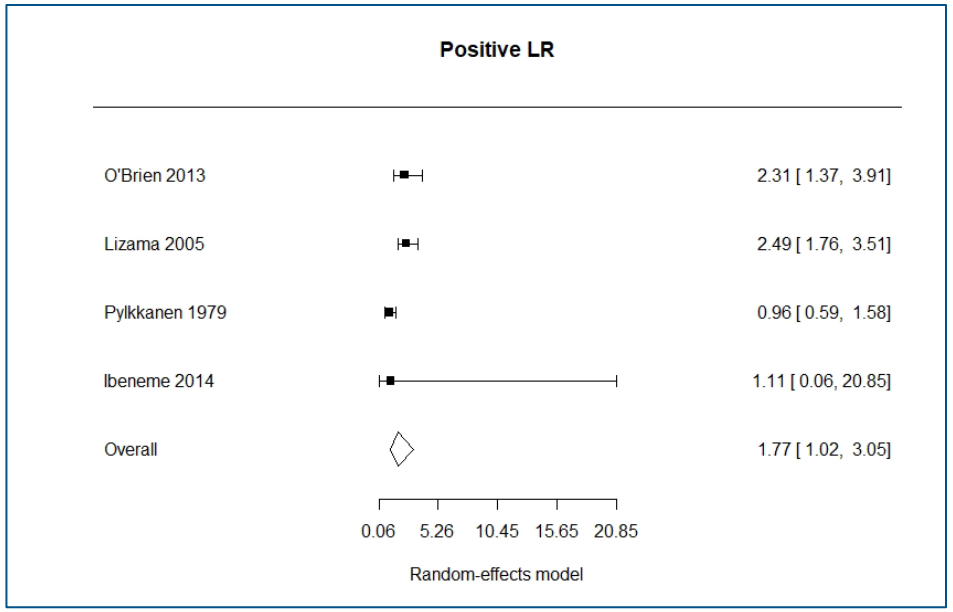
I^2 for sensitivity for frequency = 84.7%

I^2 for specificity for frequency = 96.2%

Likelihood ratios for frequency (<2 years)

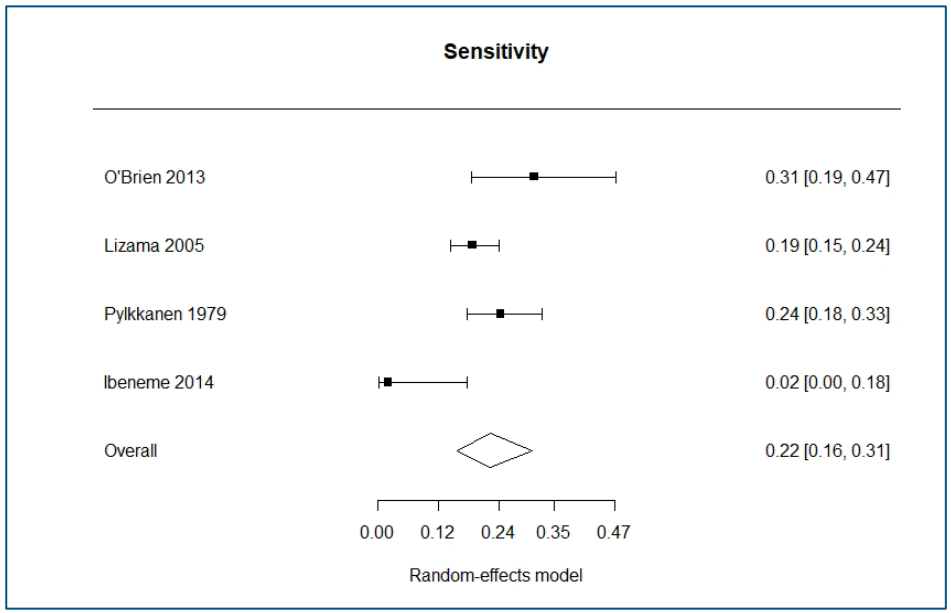


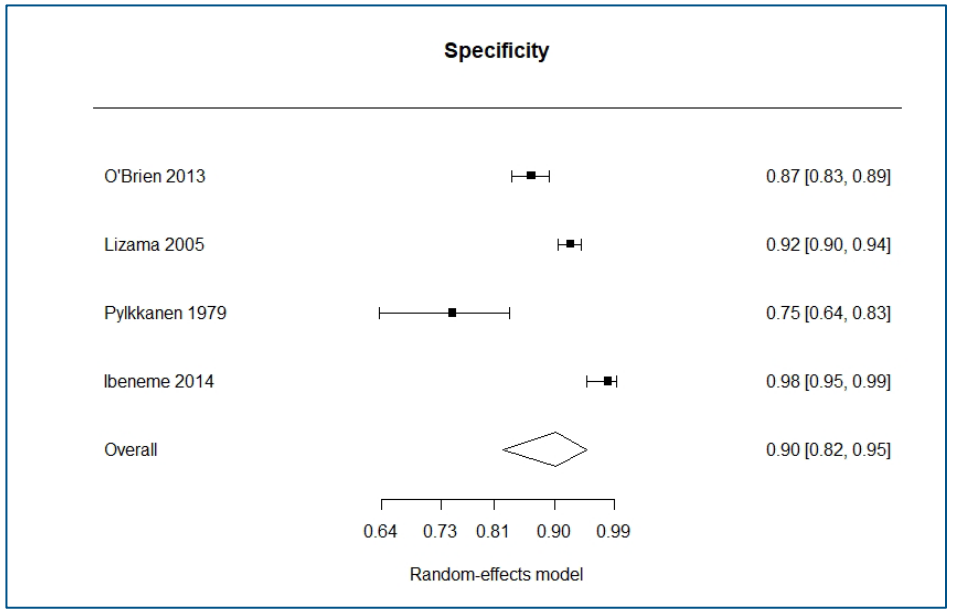
I^2 for negative LR for frequency = 71.2%



I^2 for positive LR for frequency = 69.2%

Sensitivity and specificity for frequency (<2 years)



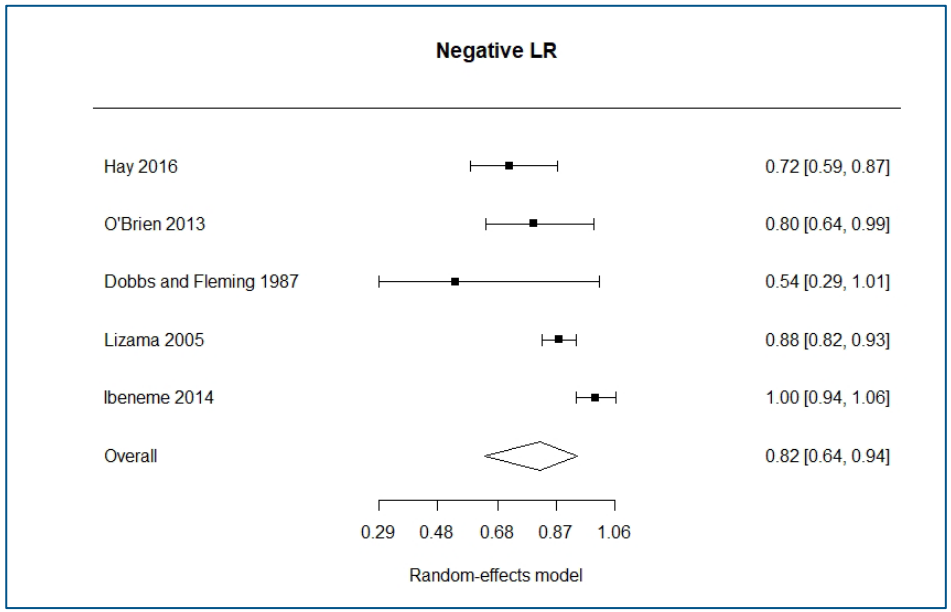


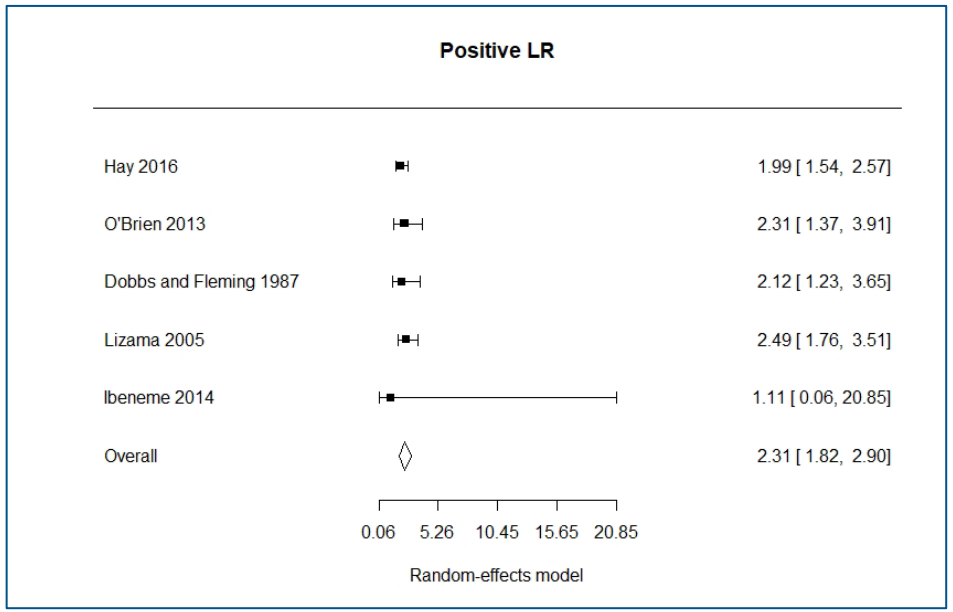
I^2 for sensitivity for frequency = 53.8%

I^2 for specificity for frequency = 92.2%

Frequency – sensitivity analysis

Likelihood ratios for frequency (< 14 years) (removing Pylkkanen 1979)

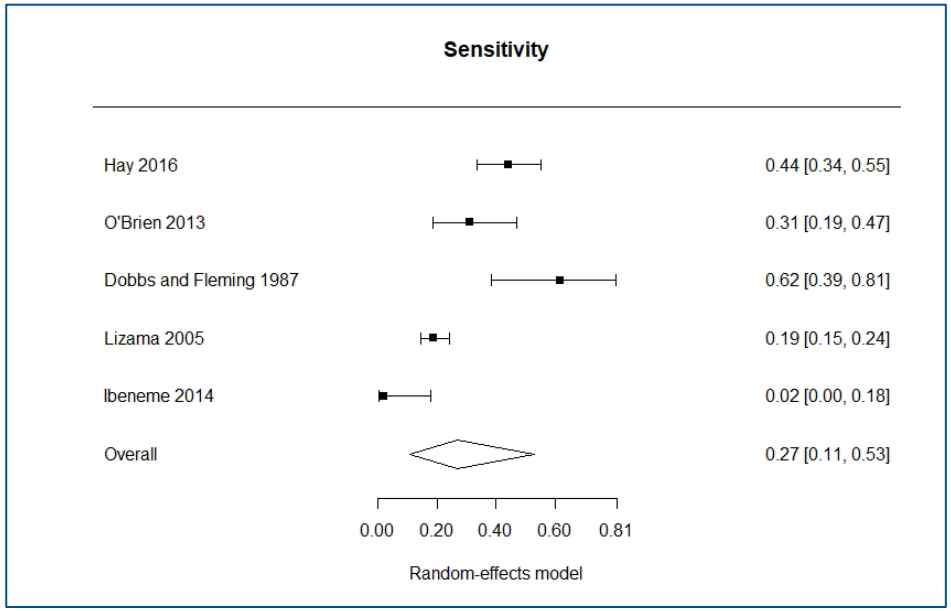


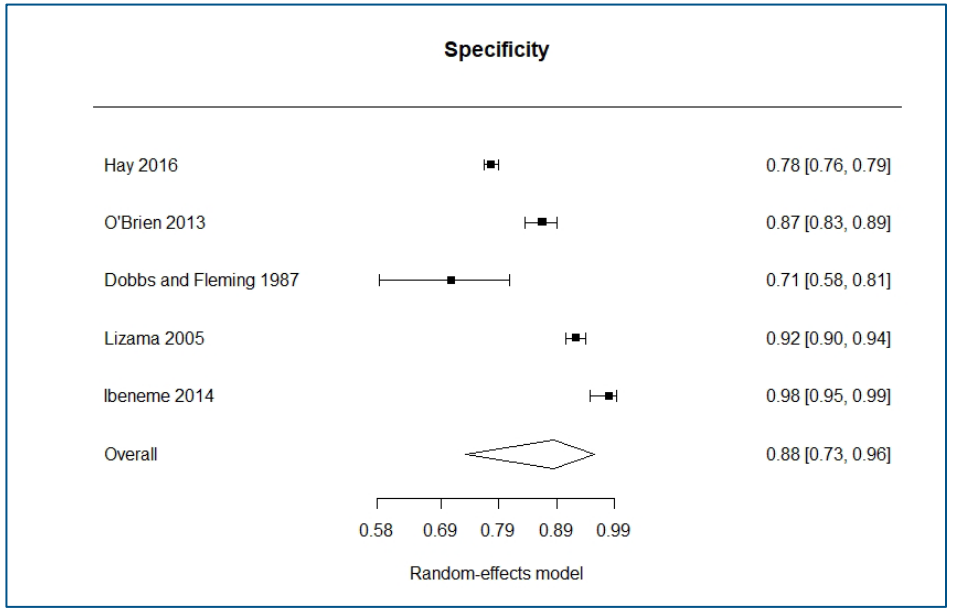


I^2 for negative LR for frequency = 78.2%

I^2 for positive LR for frequency = 0.0%

Sensitivity and specificity for frequency (< 14 years) (removing Pylkkanen 1979)

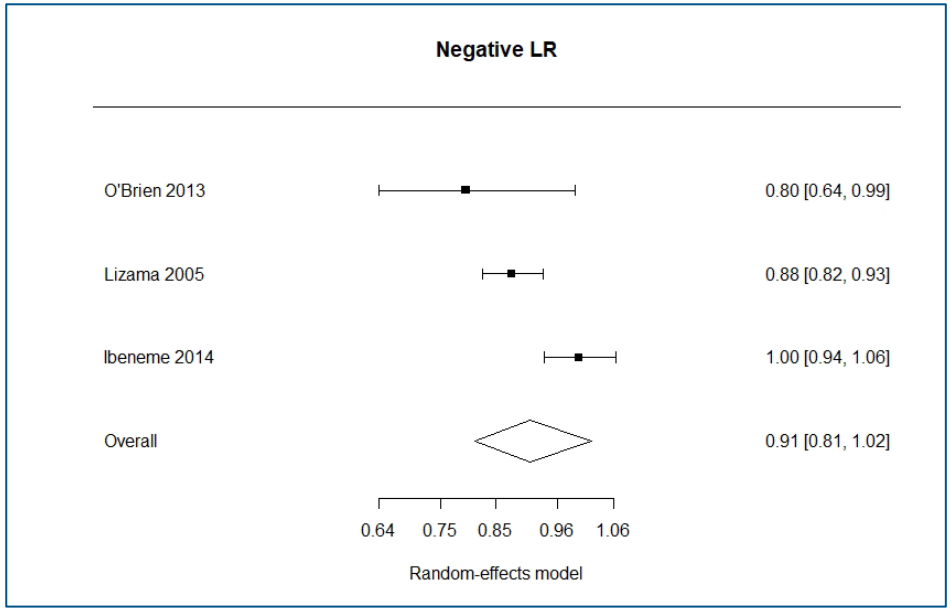


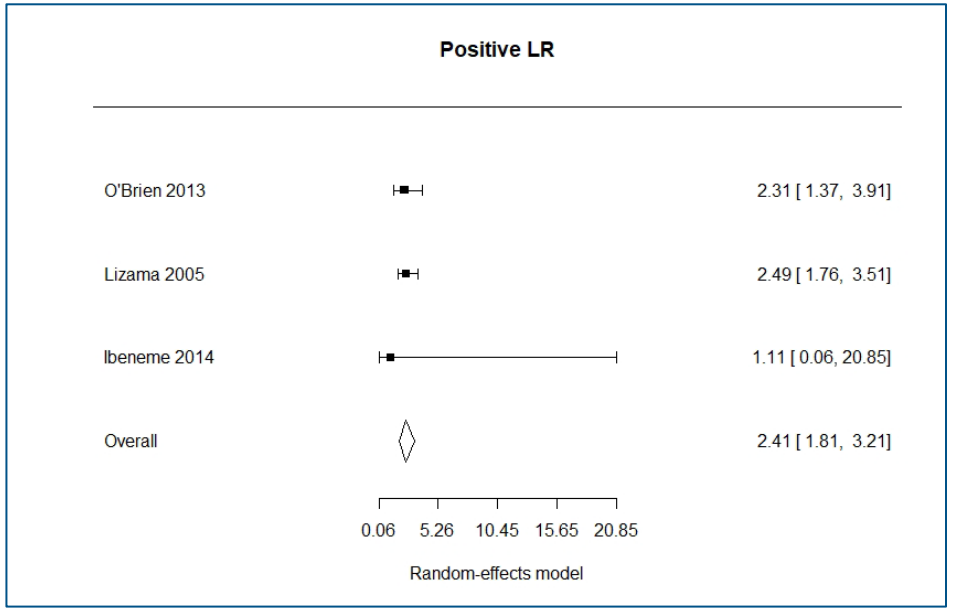


I^2 for sensitivity for frequency = 87.5%

I^2 for specificity for frequency = 96.9%

Likelihood ratios for frequency (<2 years) (removing Pylkkanen 1979)

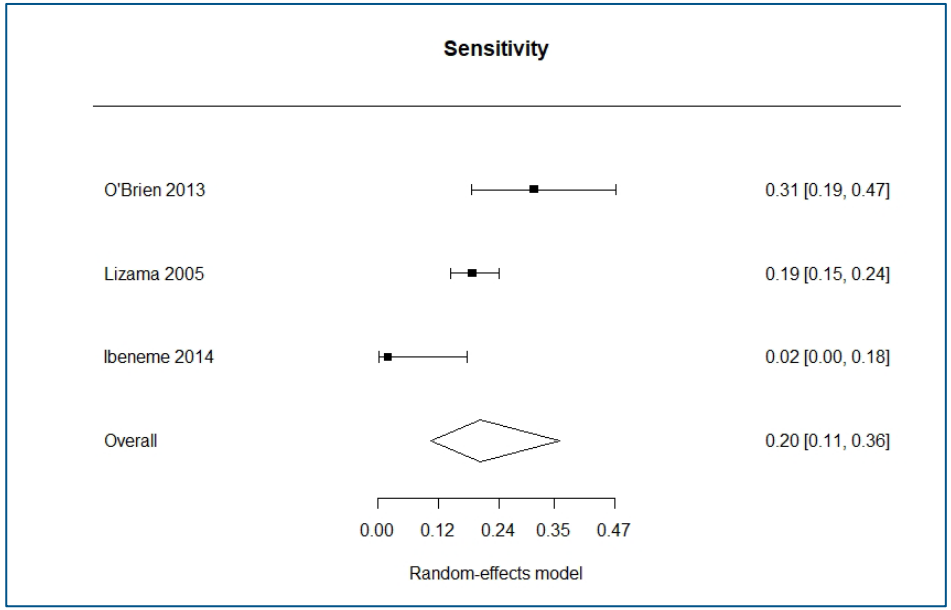


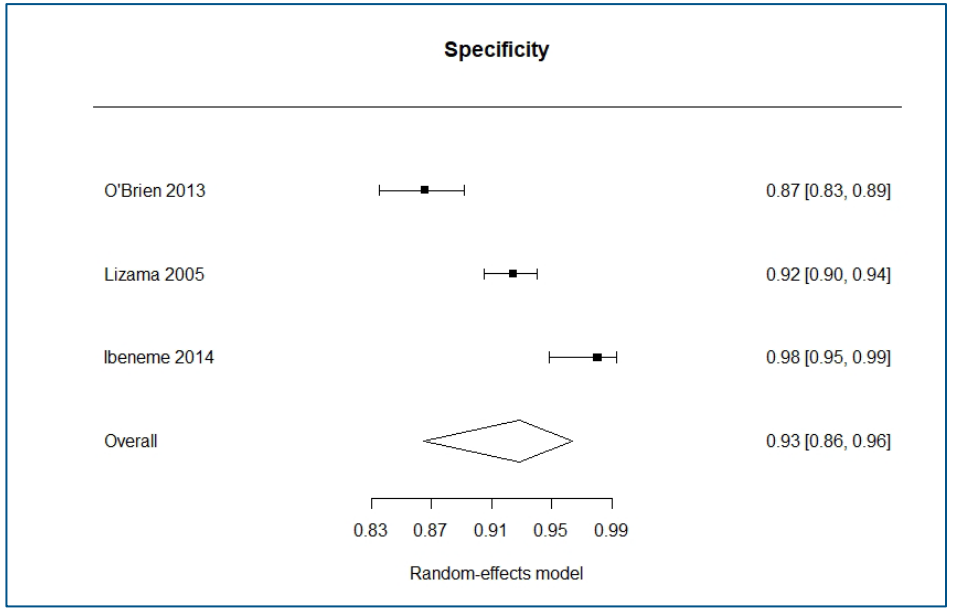


I^2 for negative LR for frequency = 79.0%

I^2 for positive LR for frequency = 0.0%

Sensitivity and specificity for frequency (<2 years) (removing Pylkkanen 1979)



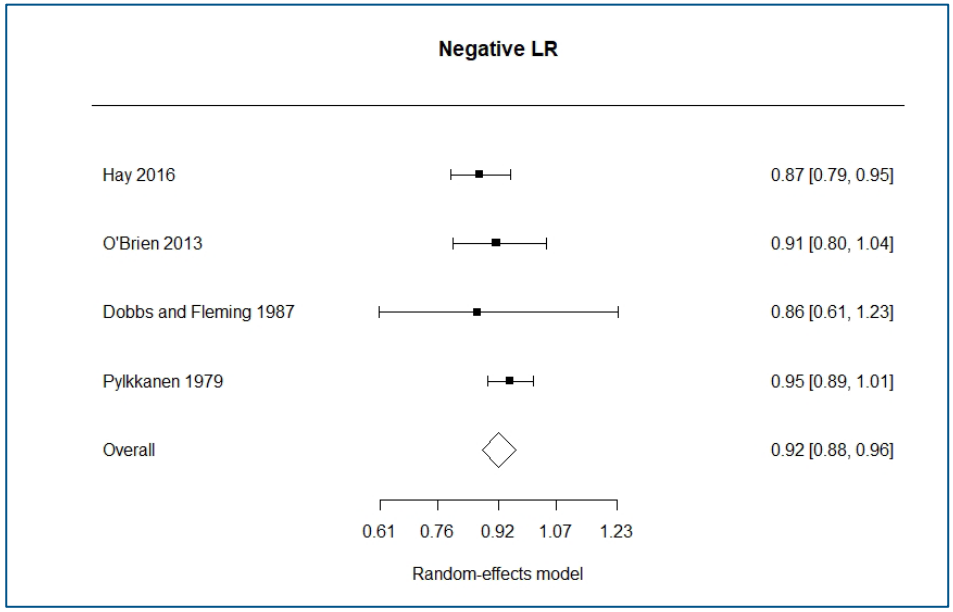


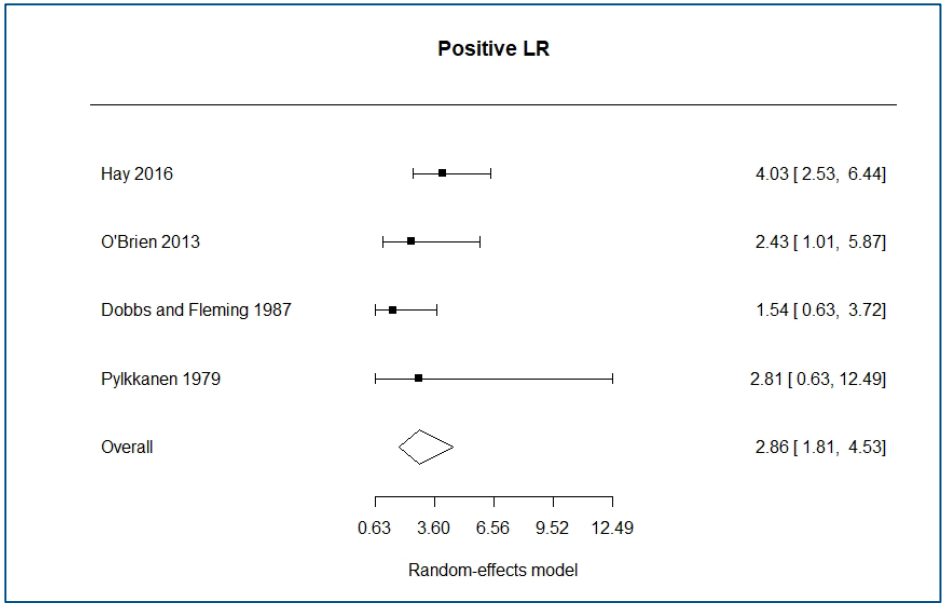
I^2 for sensitivity for frequency = 64.0%

I^2 for specificity for frequency = 91.3%

Bed wetting – main analysis

Likelihood ratios for bed wetting (< 14 years)

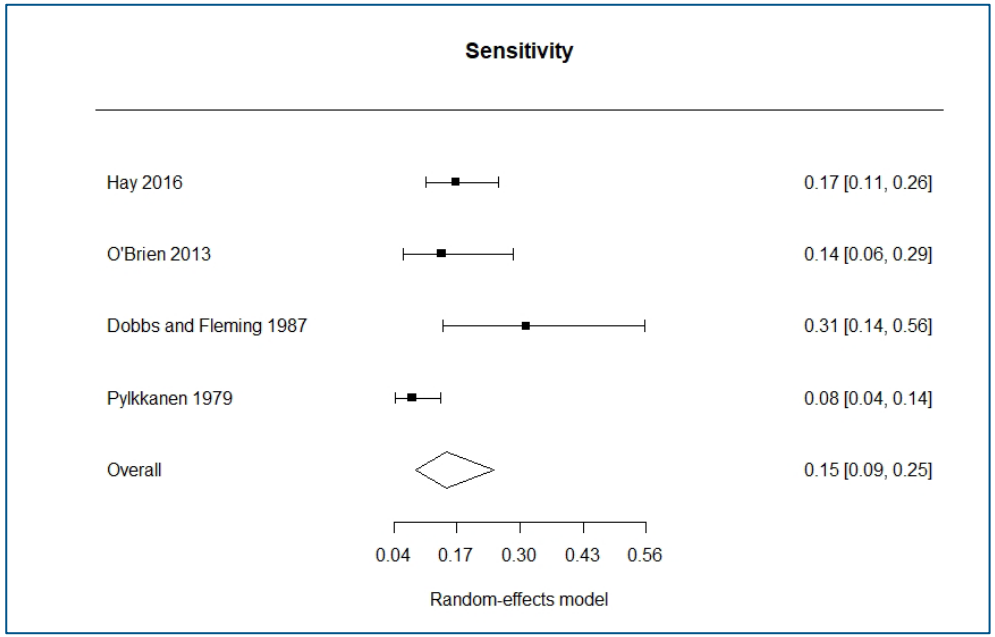


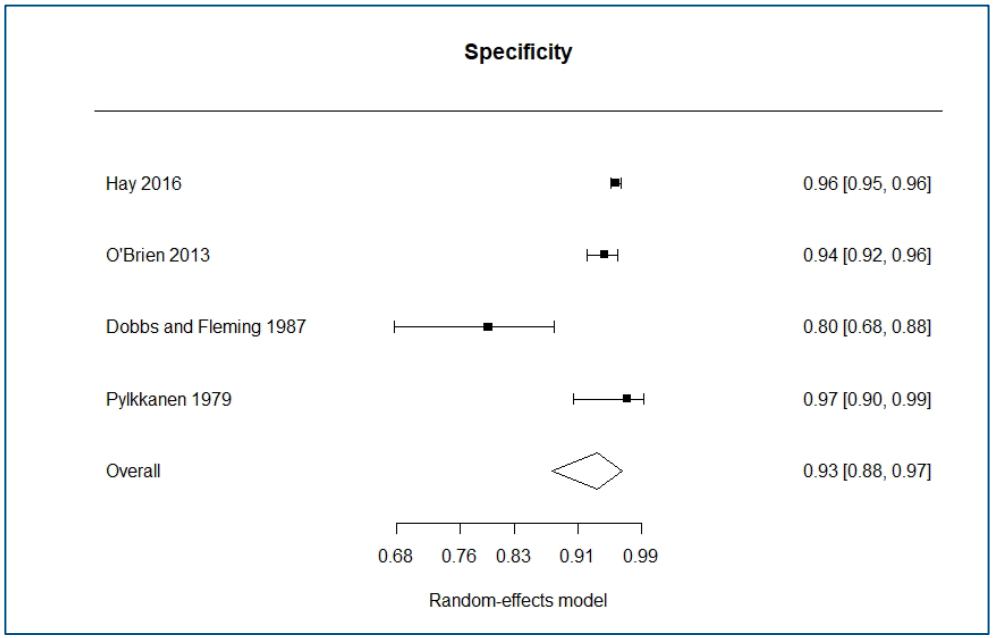


I^2 for negative LR for bedwetting = 0.0%

I^2 for positive LR for bedwetting = 23.8%

Sensitivity and specificity for bed wetting (< 14 years)

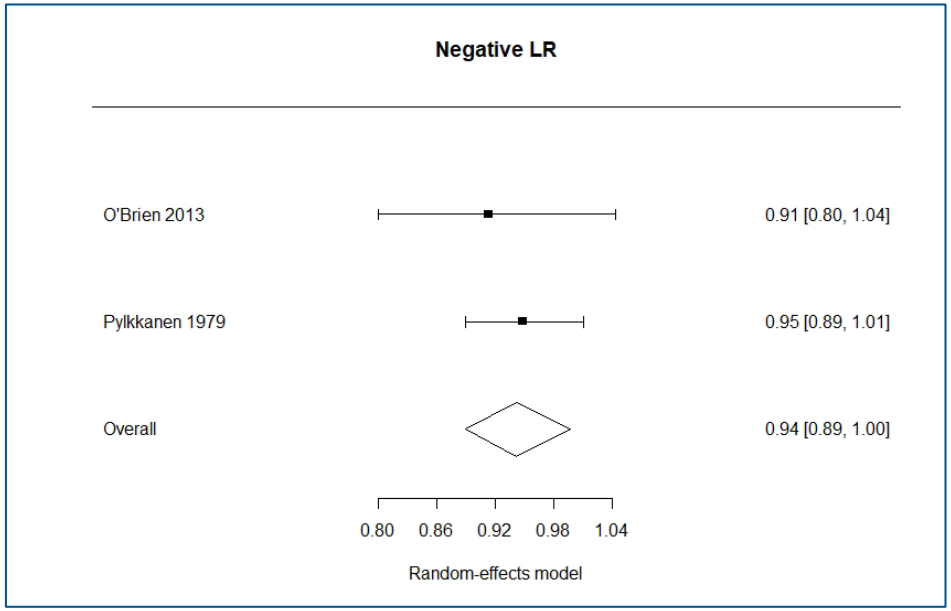


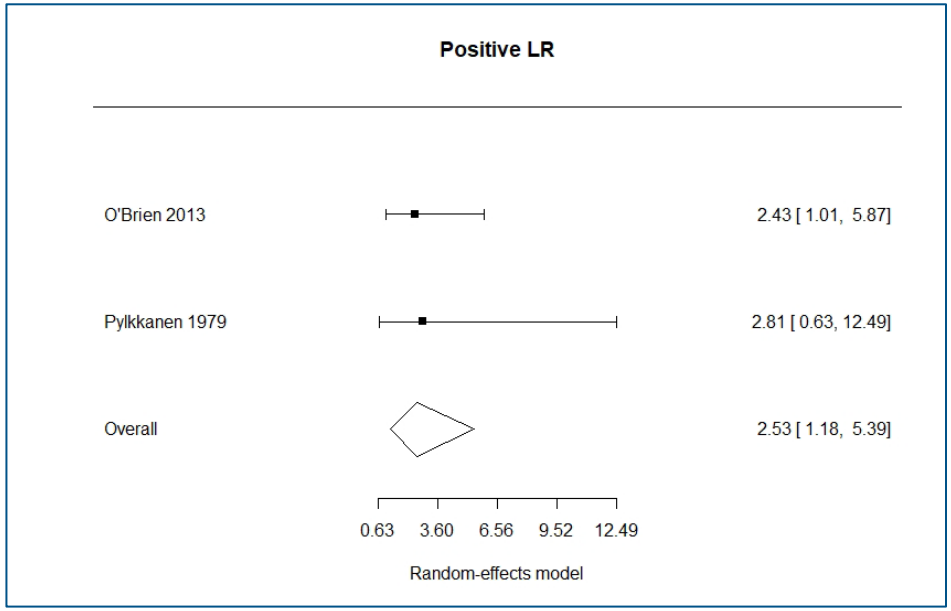


I^2 for sensitivity for bedwetting = 63.3%

I^2 for specificity for bedwetting = 90.2%

Likelihood ratios for bed wetting (<2 years)

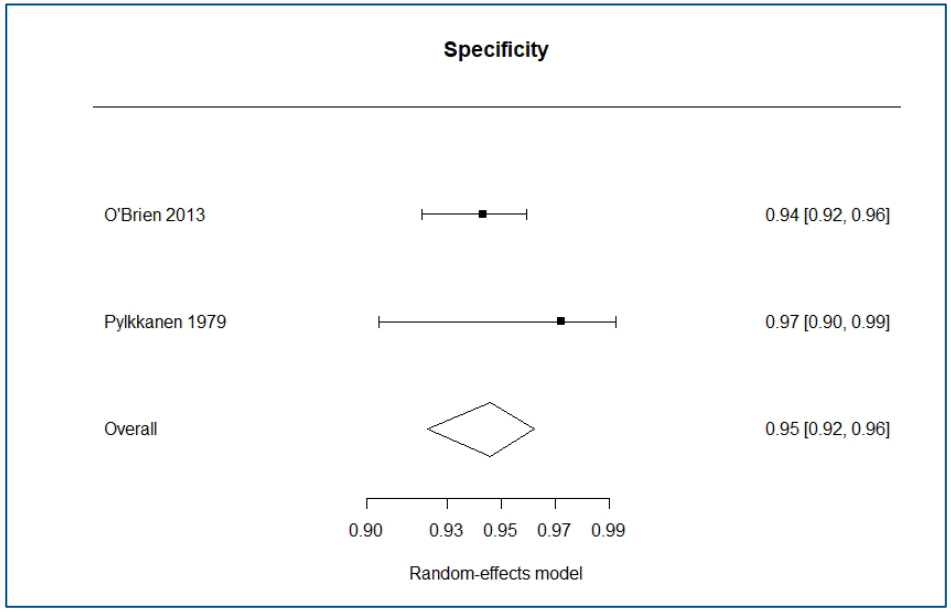


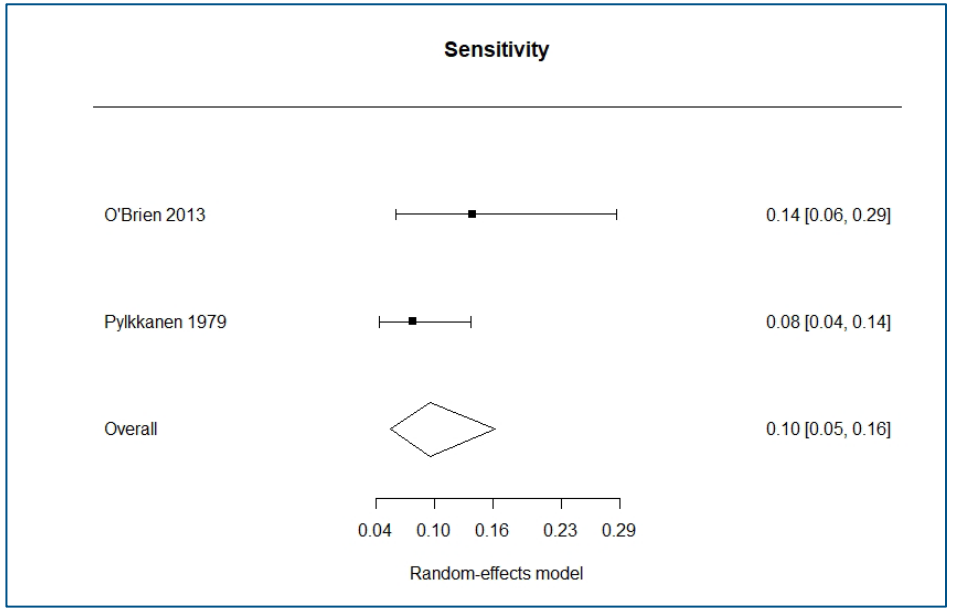


I^2 for negative LR for bedwetting = 0.0%

I^2 for positive LR for bedwetting = 0.0%

Sensitivity and specificity for bed wetting (<2 years)



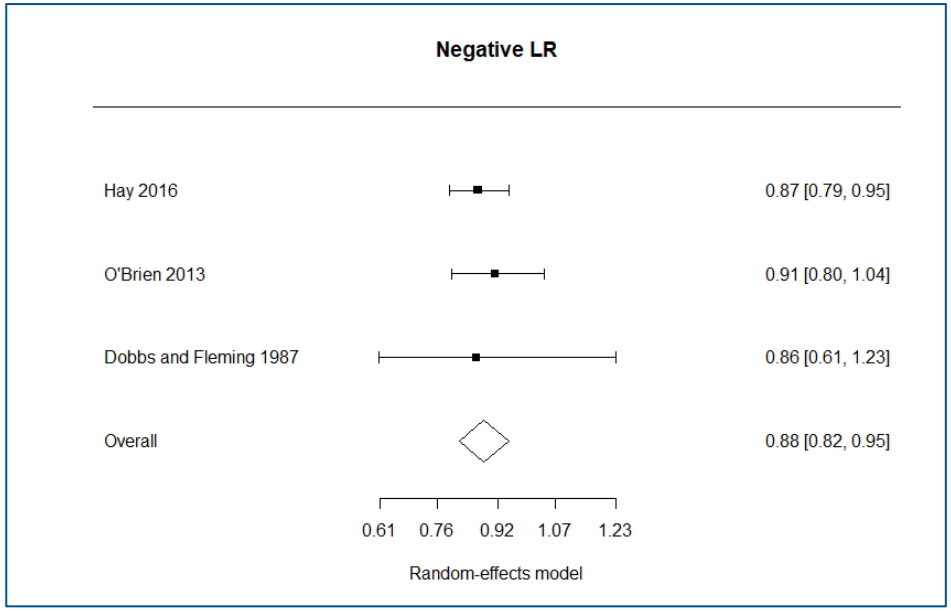


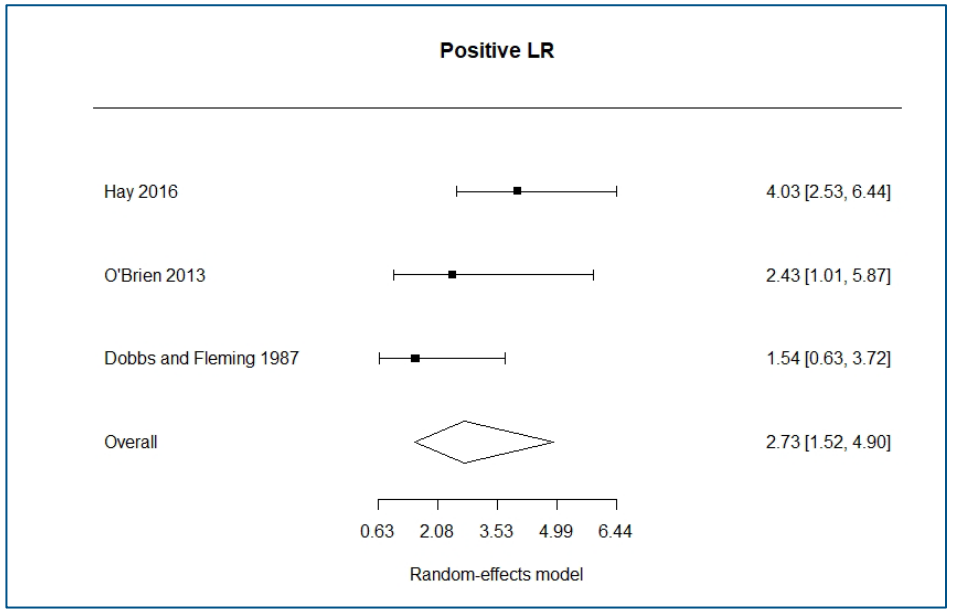
I^2 for sensitivity for bedwetting = 17.7%

I^2 for specificity for bedwetting = 2.7%

Bed wetting – sensitivity analysis

Likelihood ratios for bed wetting (< 14 years) (removing Pylkkanen 1979)

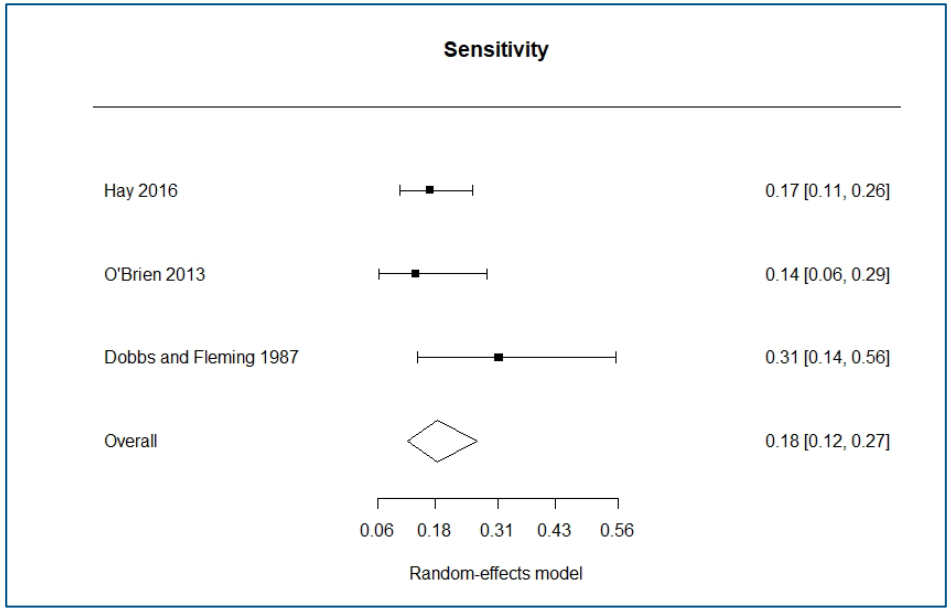


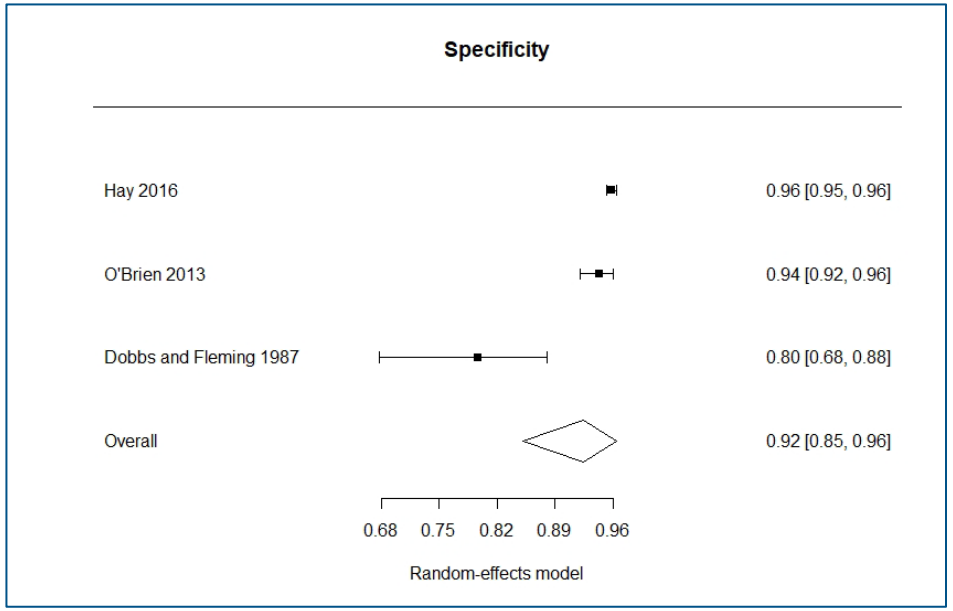


I^2 for negative LR for bedwetting = 0.0%

I^2 for positive LR for bedwetting = 49.0%

Sensitivity and specificity for bed wetting (< 14 years) (removing Pylkkanen 1979)



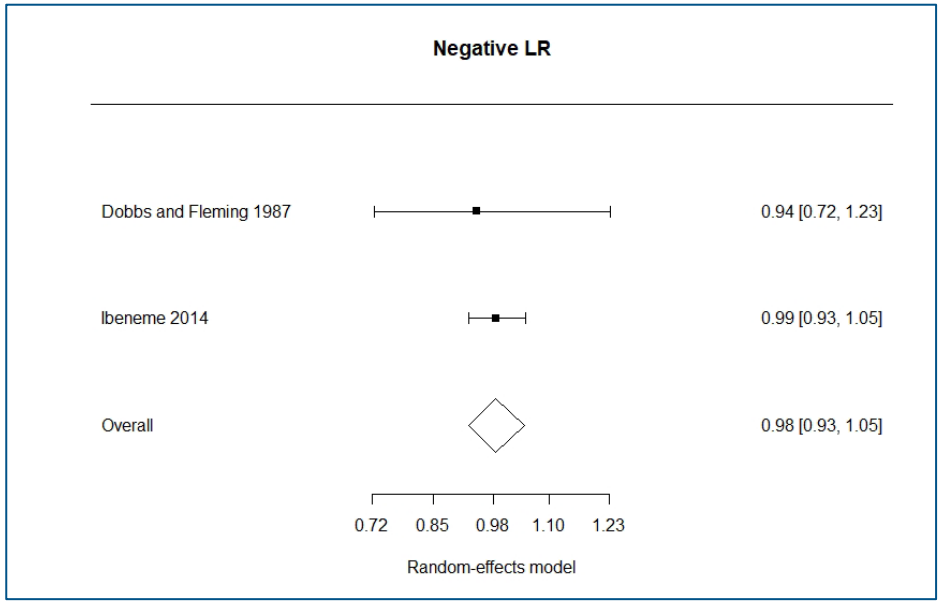


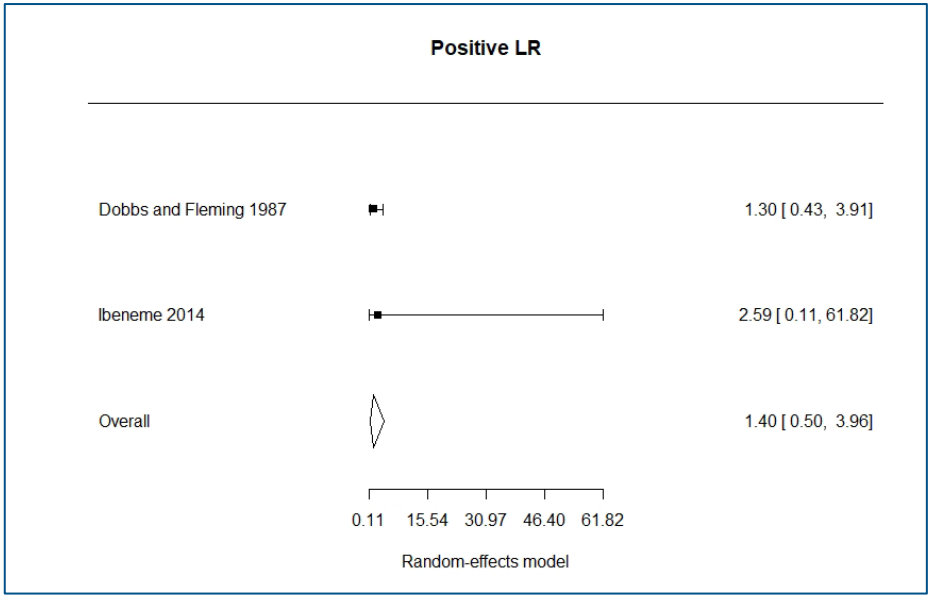
I^2 for sensitivity for bedwetting = 13.6%

I^2 for specificity for bedwetting = 93.3%

Urgency

Likelihood ratios for Urgency (< 14 years)

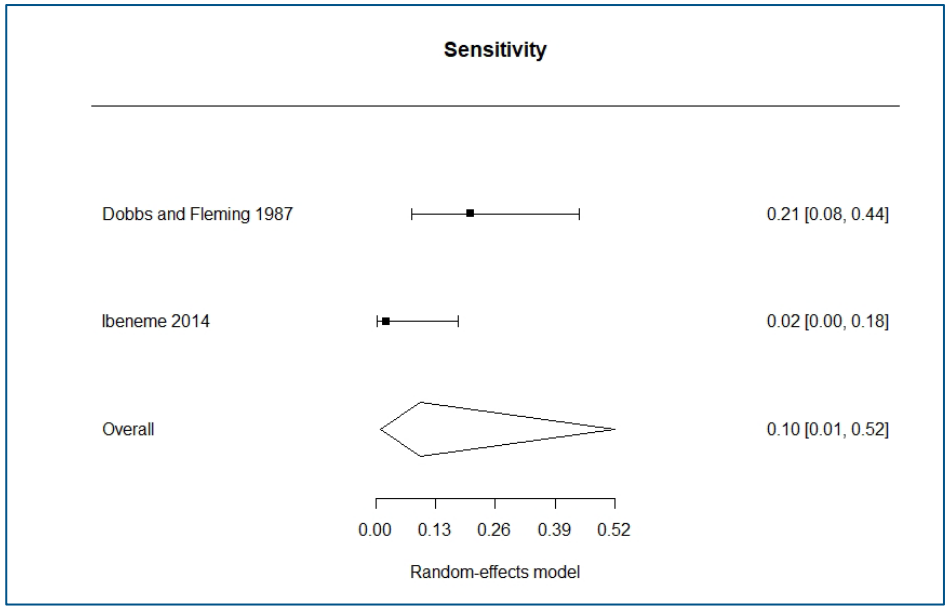


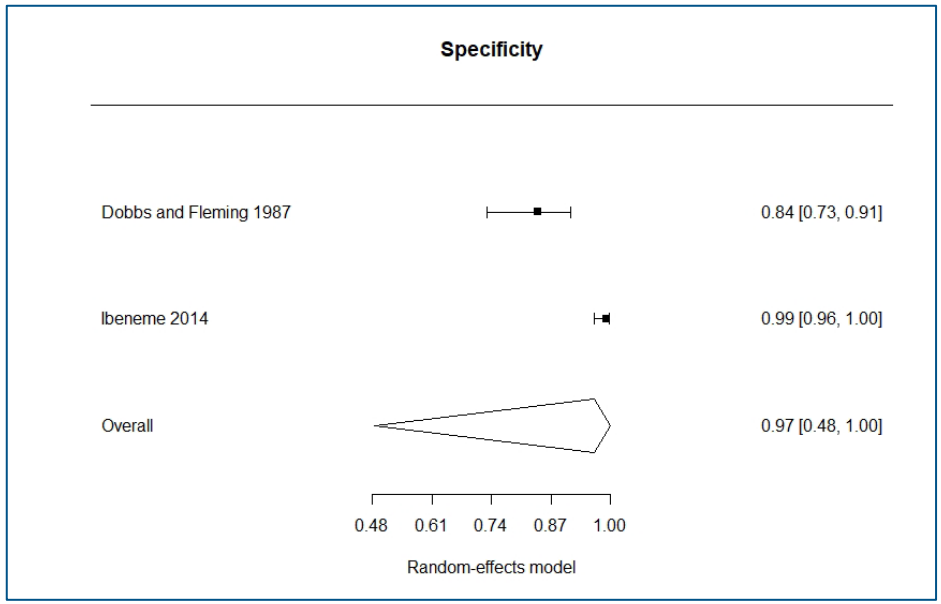


I^2 for negative LR for urgency = 0.0%

I^2 for positive LR for dysuria = 0.0%

Sensitivity and specificity for urgency (< 14 years)



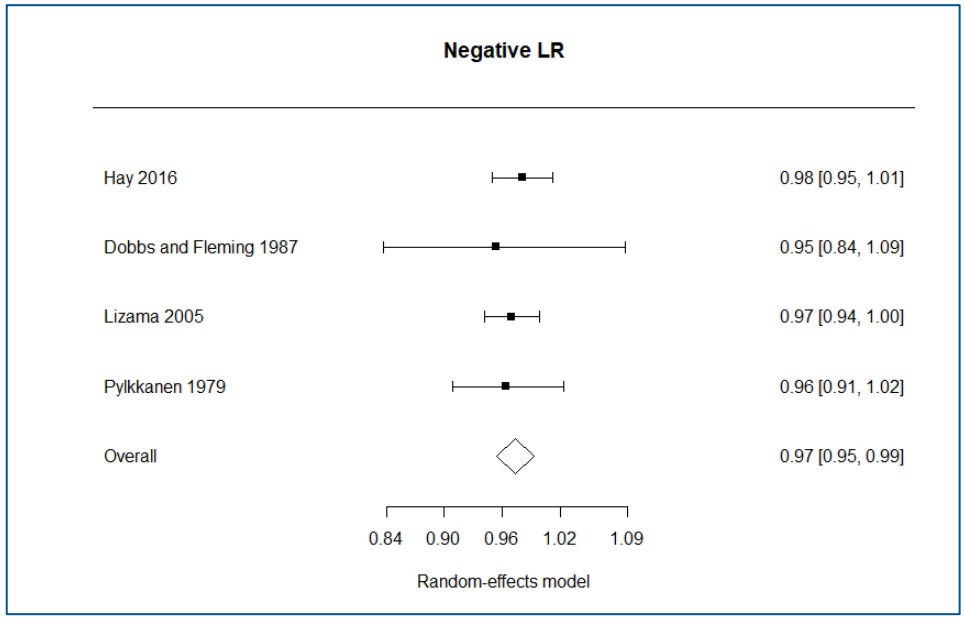


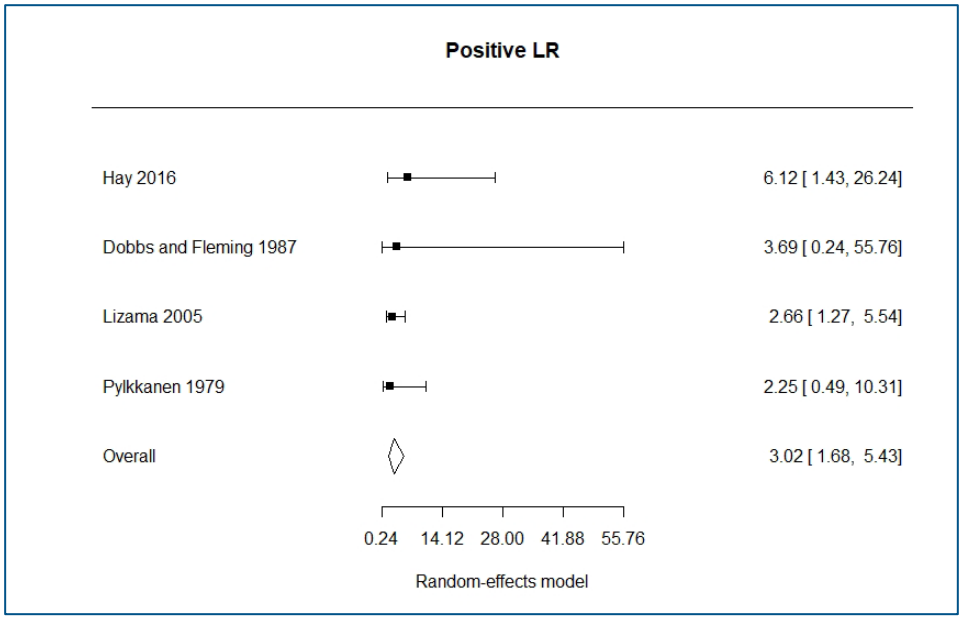
I^2 for sensitivity for urgency = 55.2%

I^2 for specificity for dysuria = 91.4%

Haematuria – main analysis

Likelihood ratios for Haematuria (< 14 years)

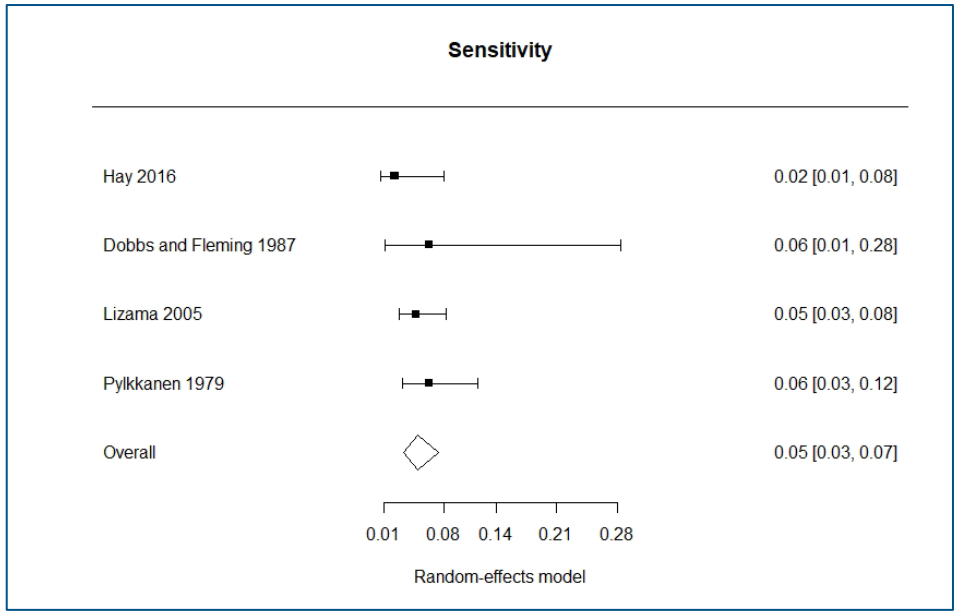


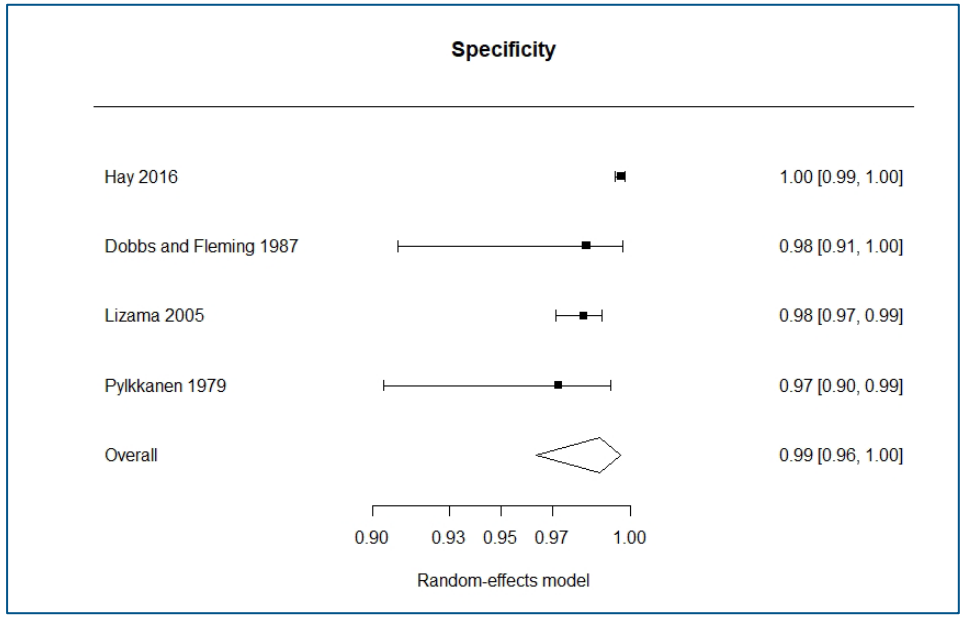


I^2 for negative LR for haematuria = 0.0%

I^2 for positive LR for haematuria = 0.0%

Sensitivity and specificity for haematuria (< 14 years)

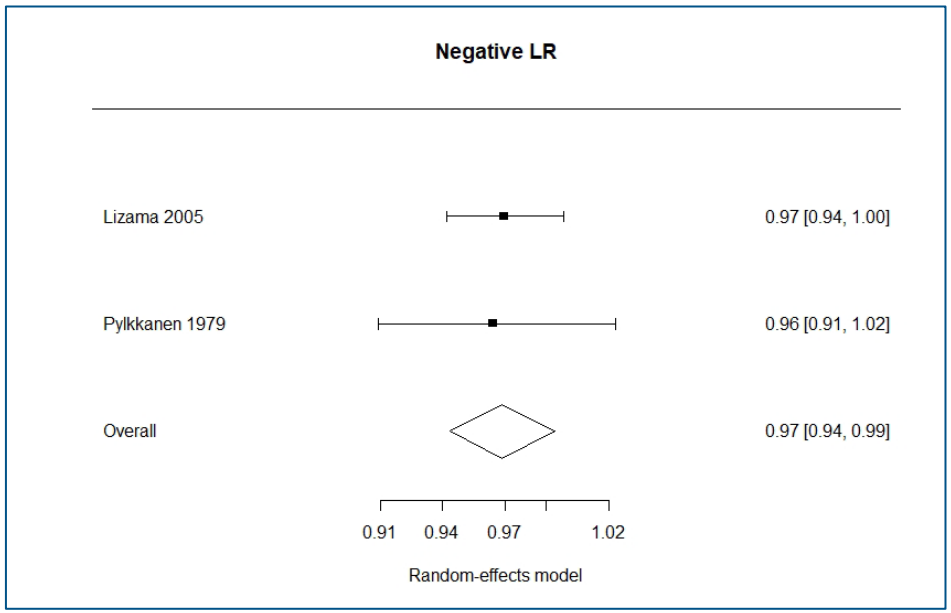


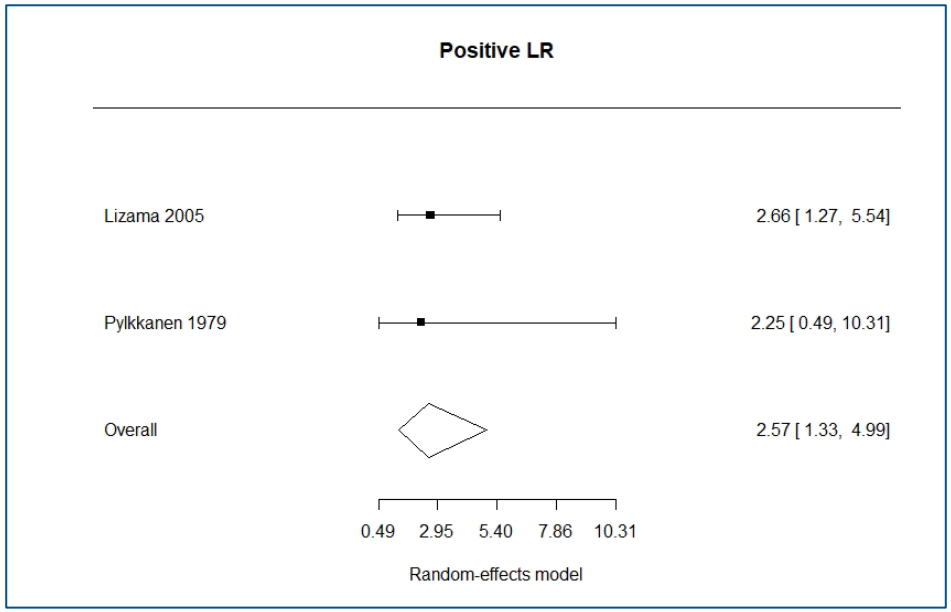


I^2 for sensitivity for haematuria = 0.0%

I^2 for specificity for haematuria = 87.2%

Likelihood ratios for Haematuria (<2 years)

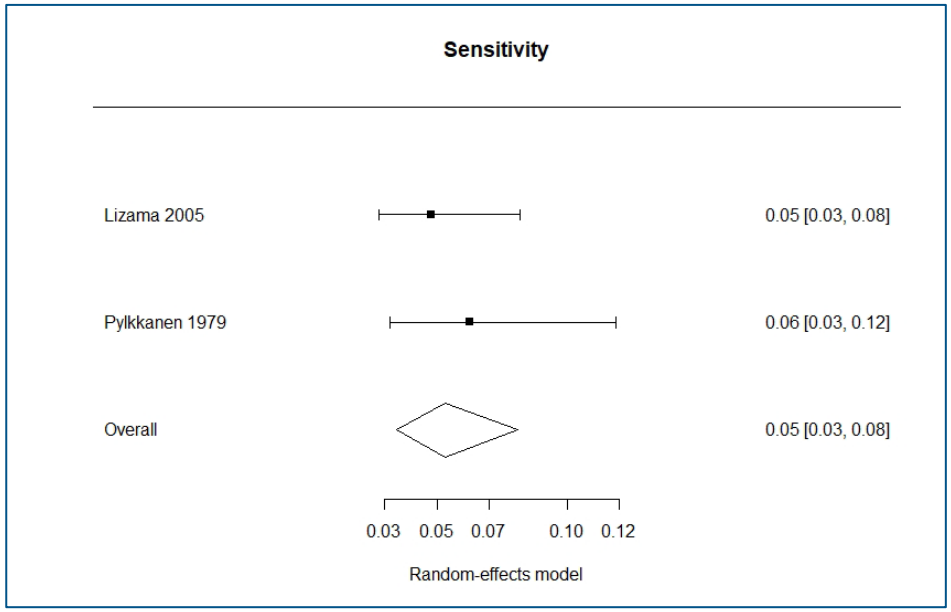




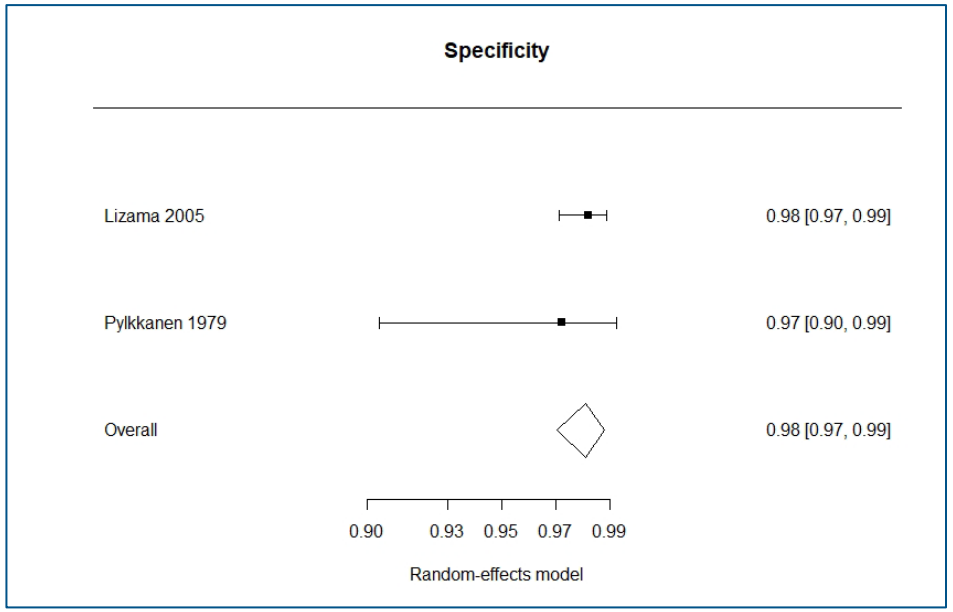
I^2 for negative LR for haematuria = 0.0%

I^2 for positive LR for haematuria = 0.0%

Sensitivity and specificity for haematuria (<2 years)



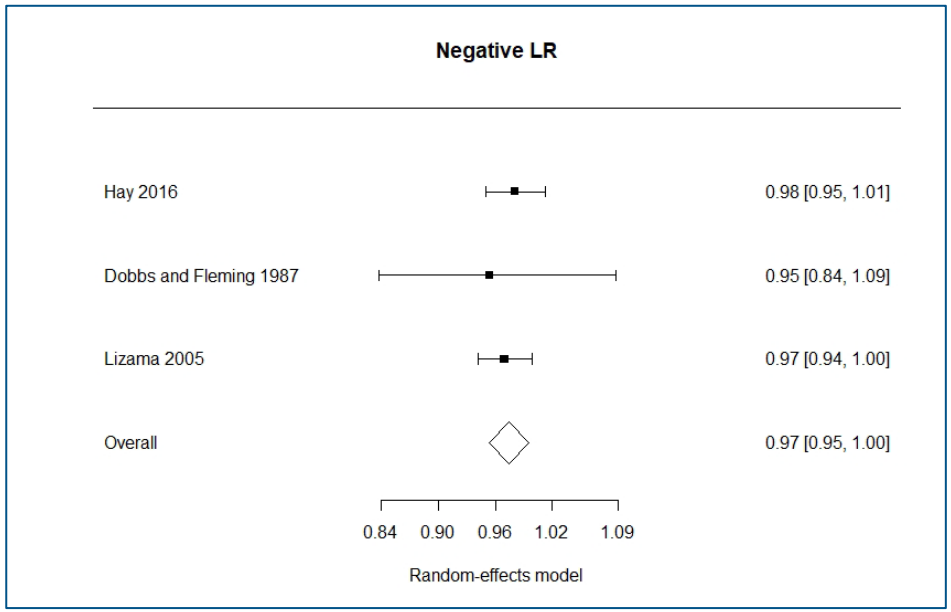
I^2 for sensitivity for haematuria = 0.0%

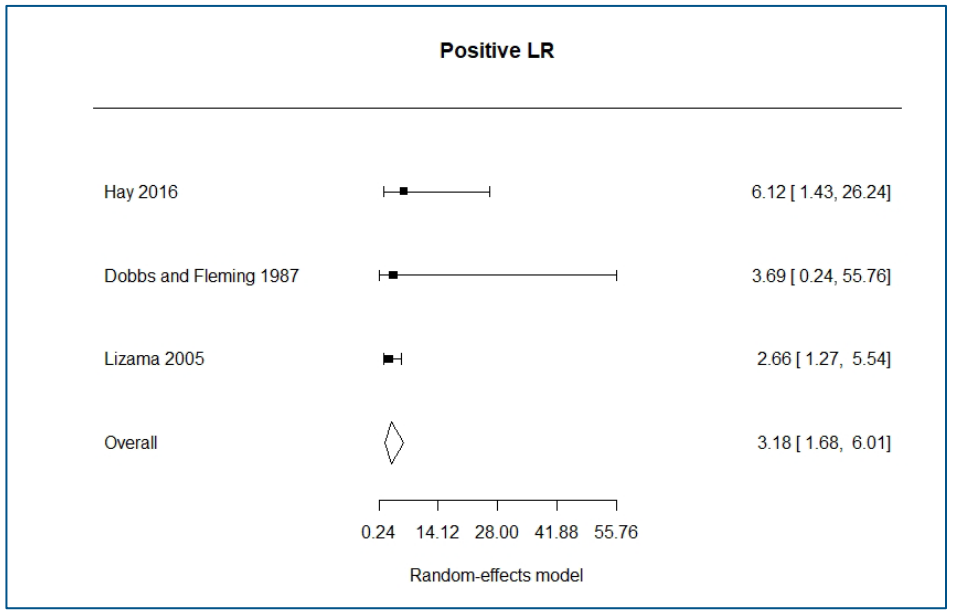


I^2 for specificity for haematuria = 0.0%

Haematuria – sensitivity analysis

Likelihood ratios for Haematuria (< 14 years) (removing Pylkkanen 1979)

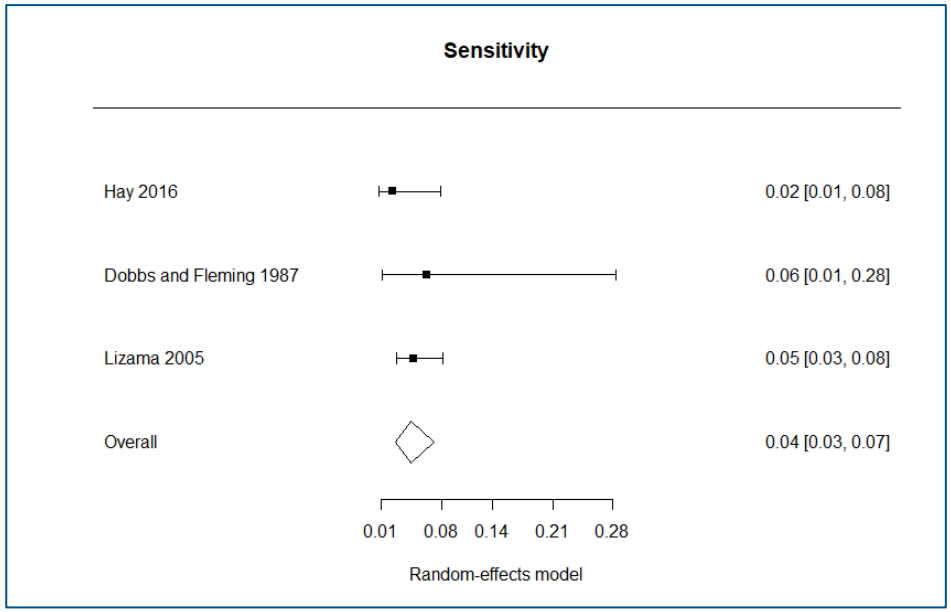


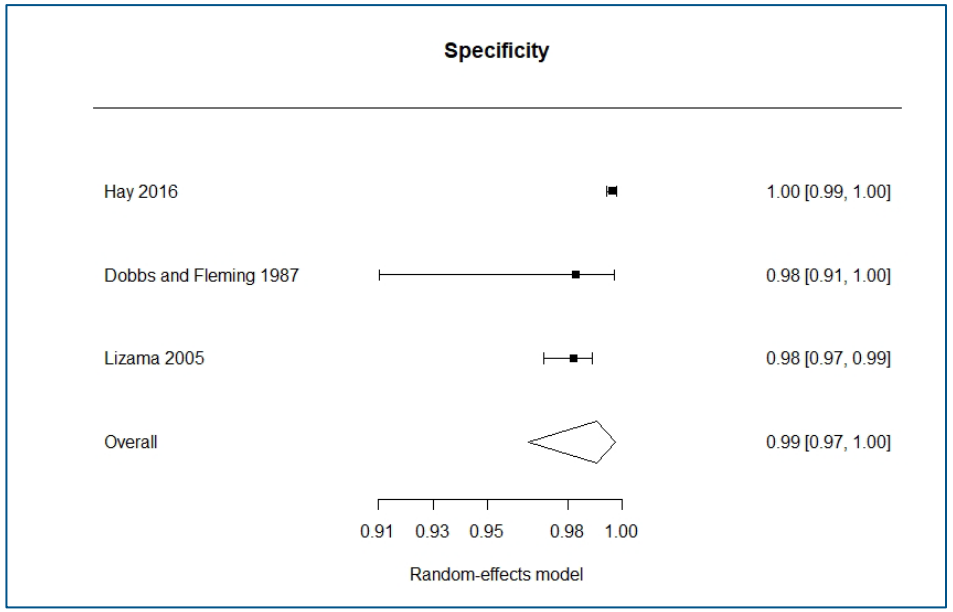


I^2 for negative LR for haematuria = 0.0%

I^2 for positive LR for haematuria = 0.0%

Sensitivity and specificity for haematuria (< 14 years) (removing Pylkkanen 1979)



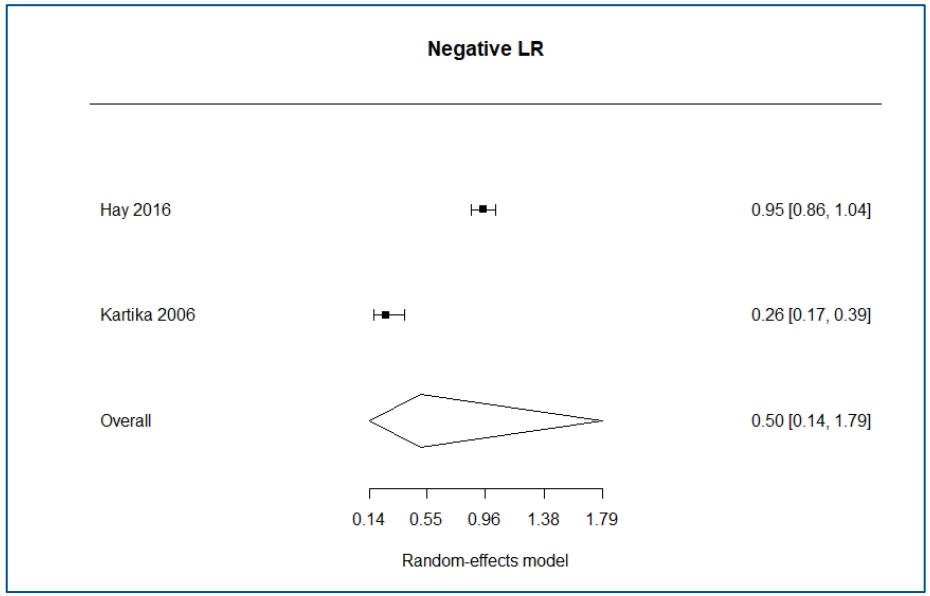


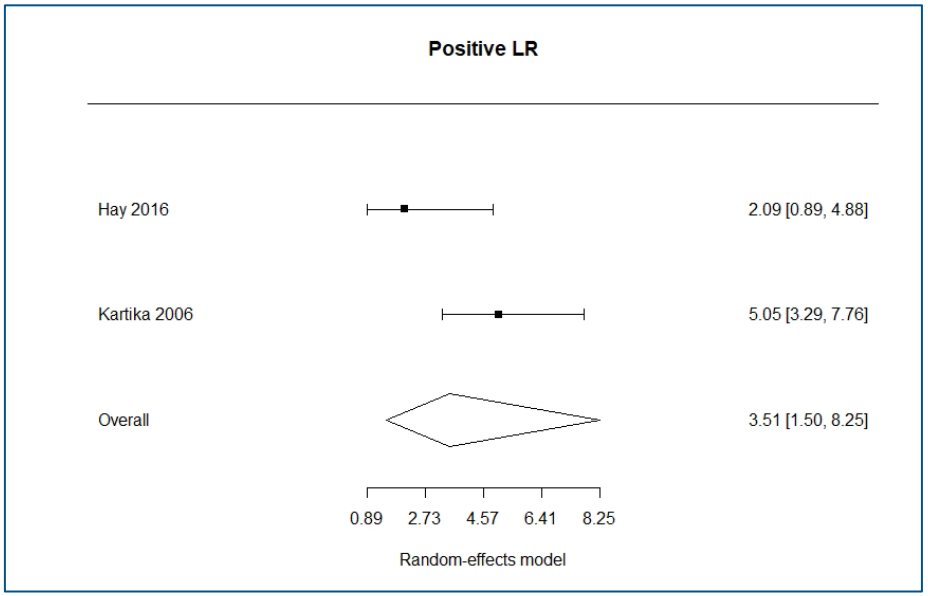
I^2 for sensitivity for haematuria = 0.0%

I^2 for specificity for haematuria = 90.3%

Cloudy urine

Likelihood ratios for cloudy urine (< 5 years)

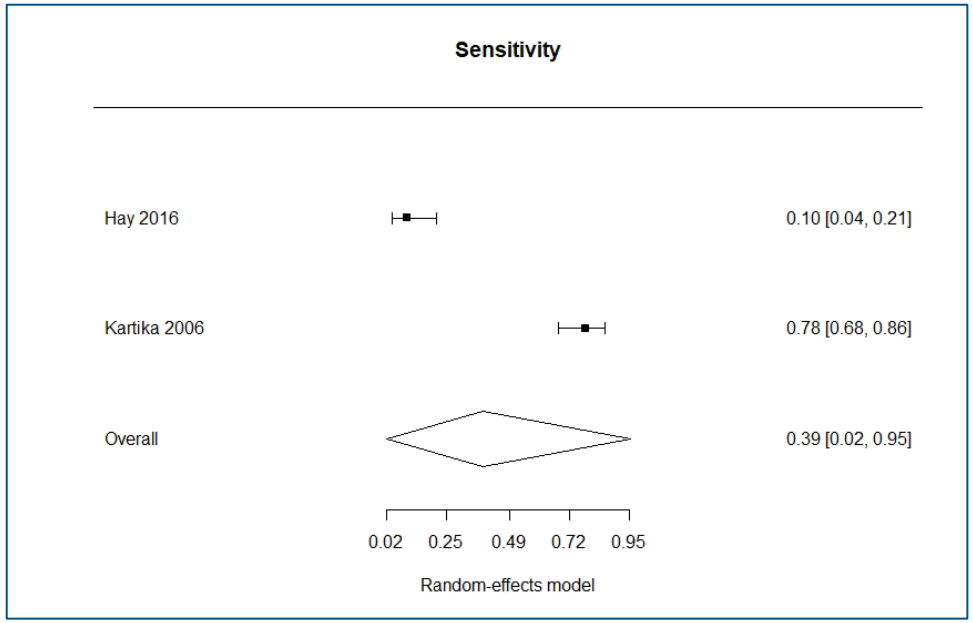


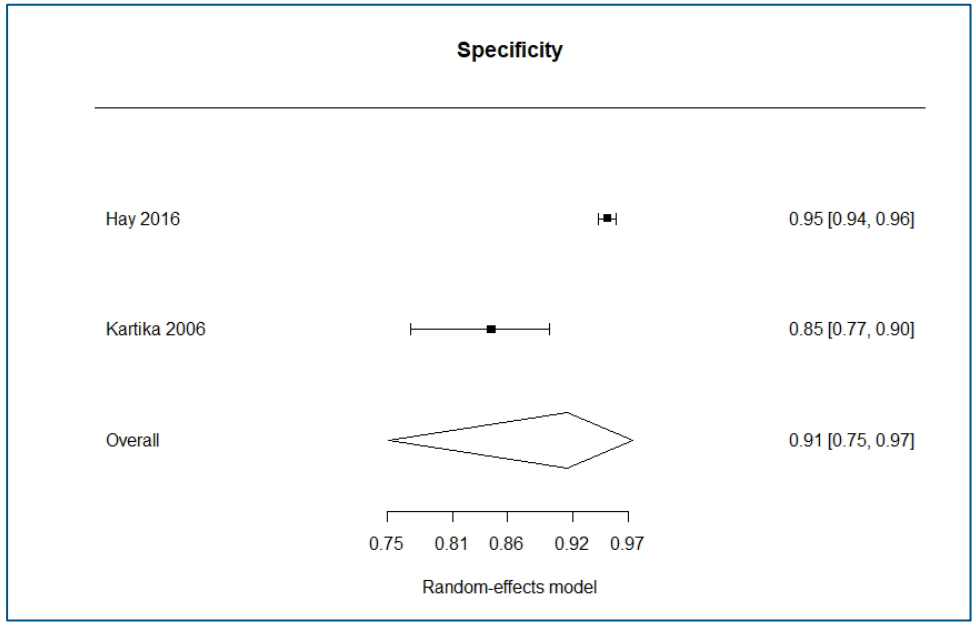


I^2 for negative LR for cloudy urine = 97.2%

I^2 for positive LR for cloudy urine = 69.8%

Sensitivity and specificity for cloudy urine (< 5 years)



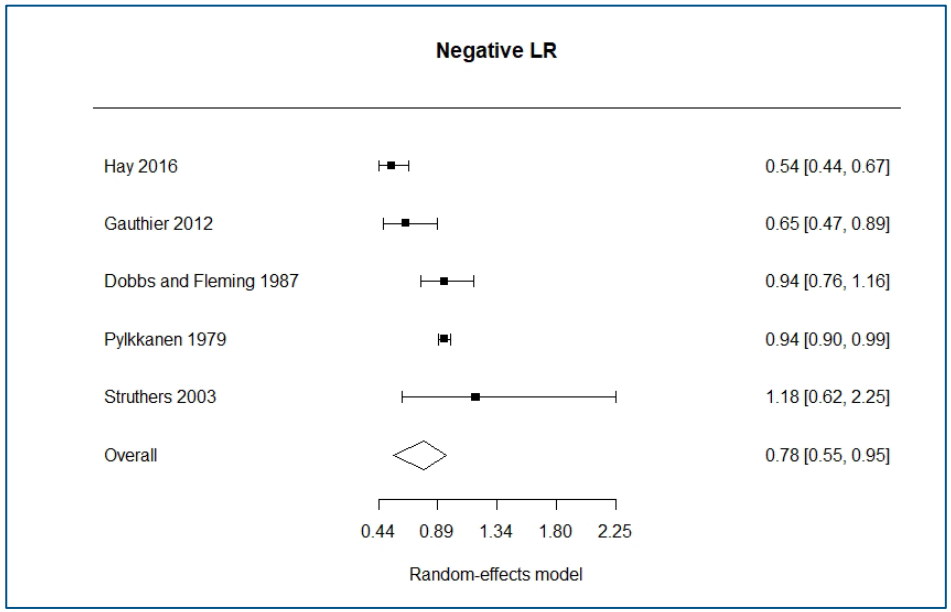


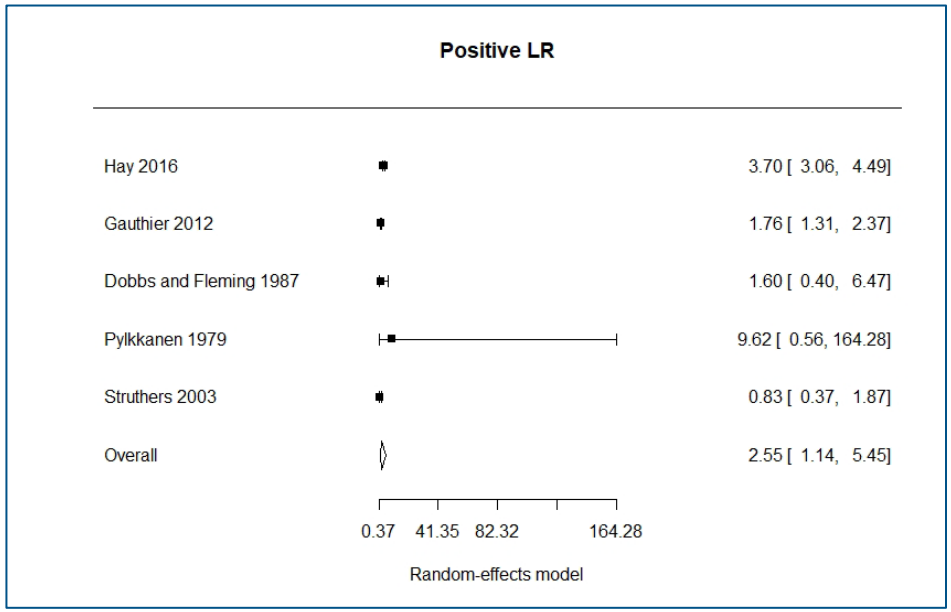
I^2 for sensitivity for cloudy urine = 97.6%

I^2 for specificity for cloudy urine = 95.7%

Malodorous urine – main analysis

Likelihood ratios for malodorous urine (< 14 years)

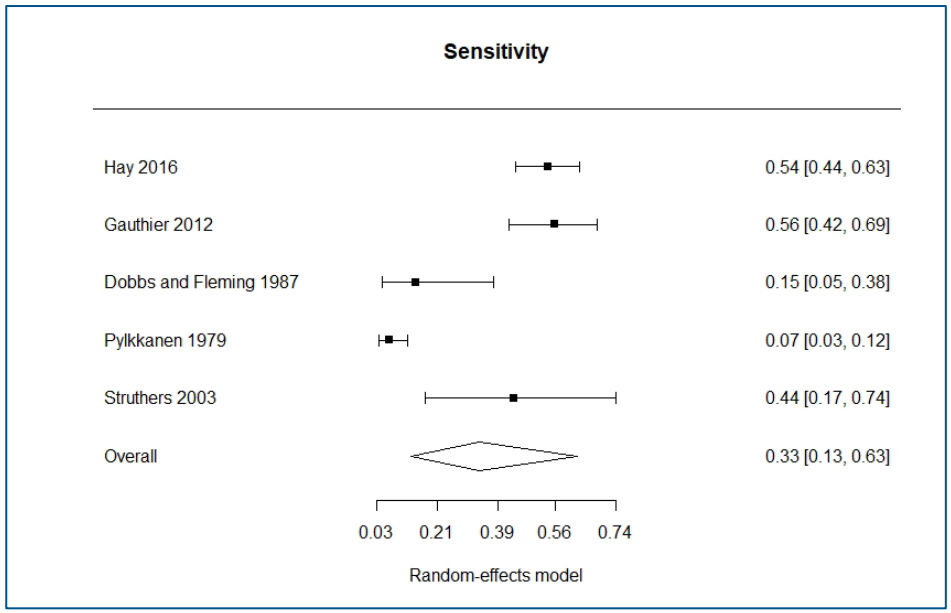


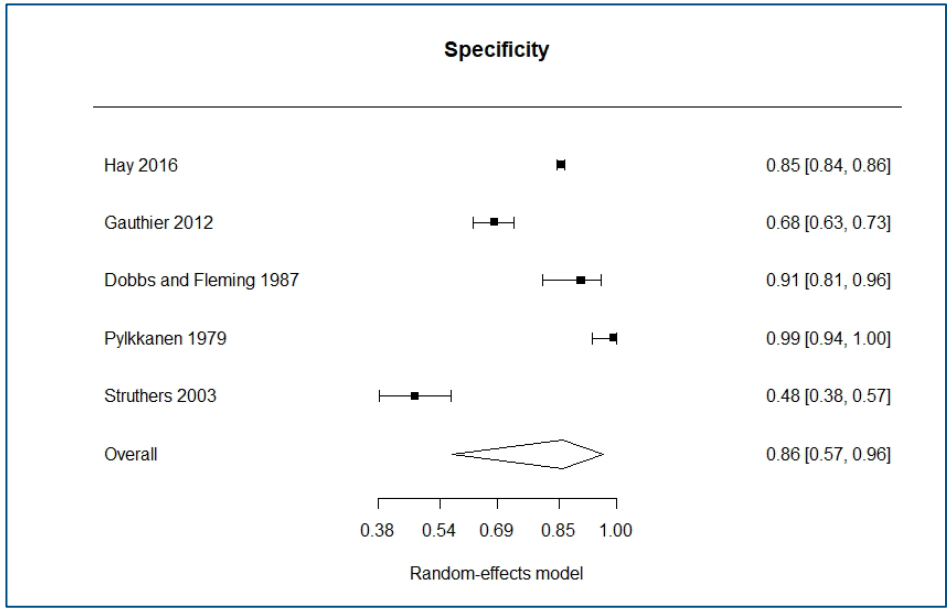


I^2 for negative LR for malodorous urine = 86.8%

I^2 for positive LR for malodorous urine = 84.7%

Sensitivity and specificity for malodorous urine (< 14 years)

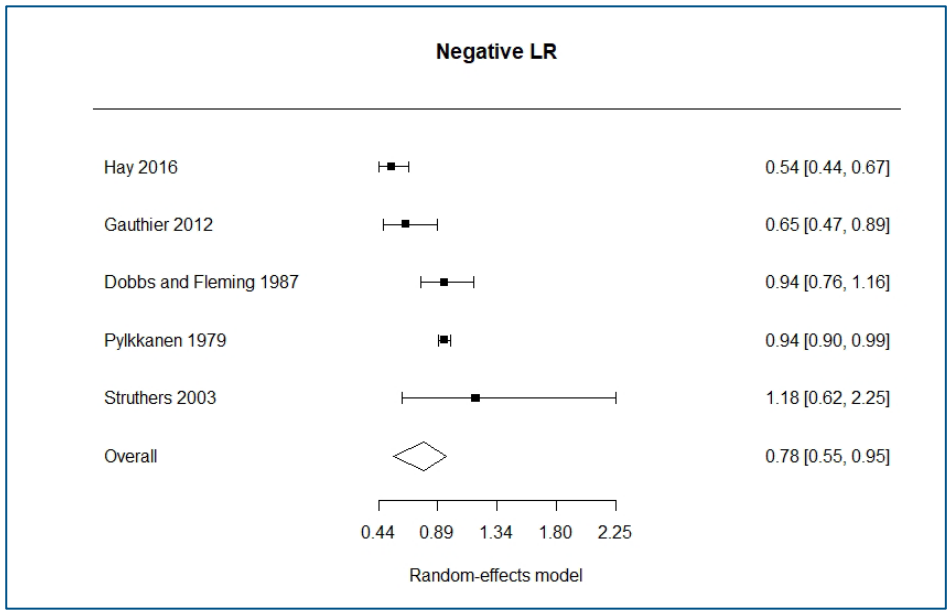


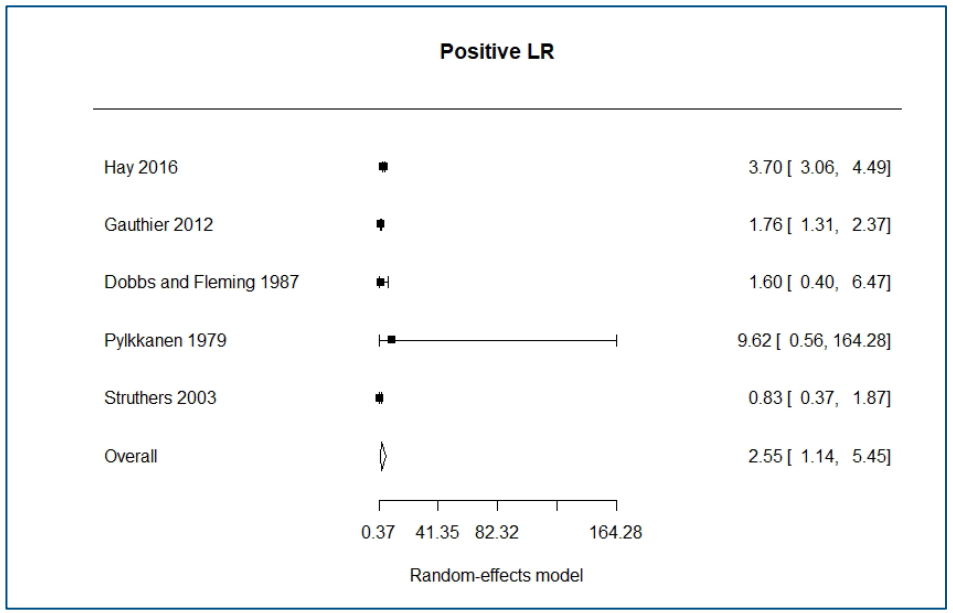


I^2 for sensitivity for malodorous urine = 93.0%

I^2 for specificity for malodorous urine = 97.2%

Likelihood ratios for malodorous urine (<2 years)

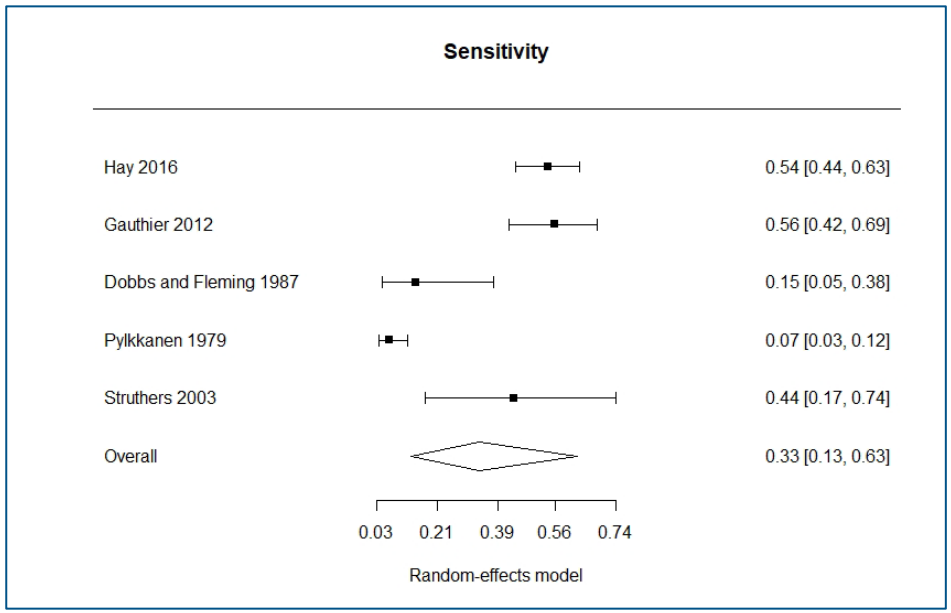


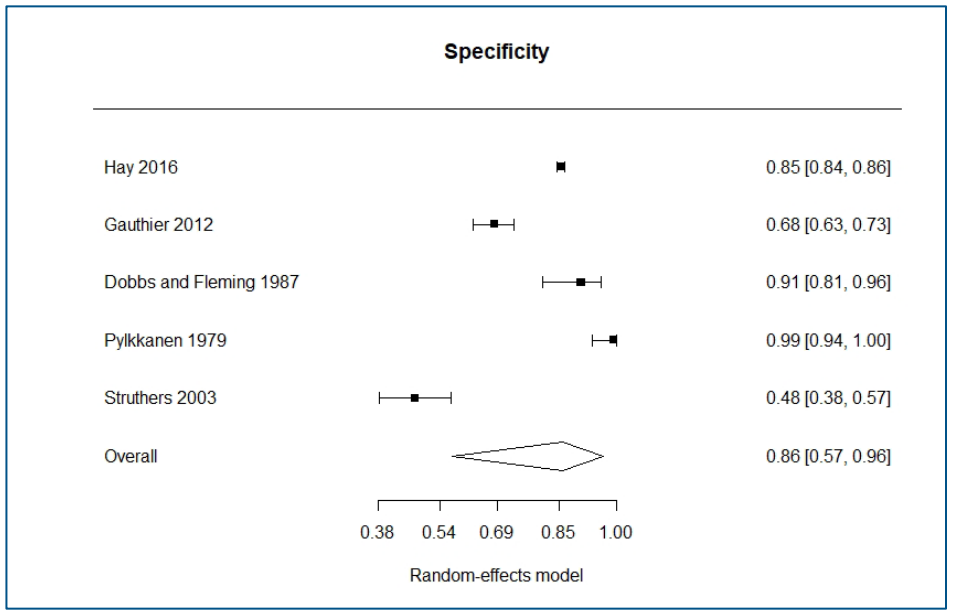


I^2 for negative LR for malodorous urine = 65.0%

I^2 for positive LR for malodorous urine = 51.9%

Sensitivity and specificity for malodorous urine (<2 years)



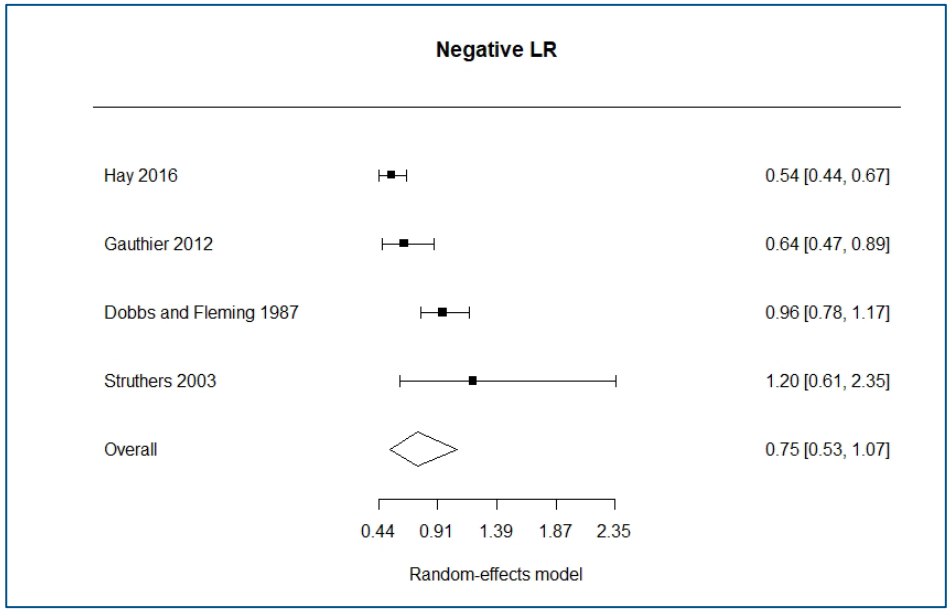


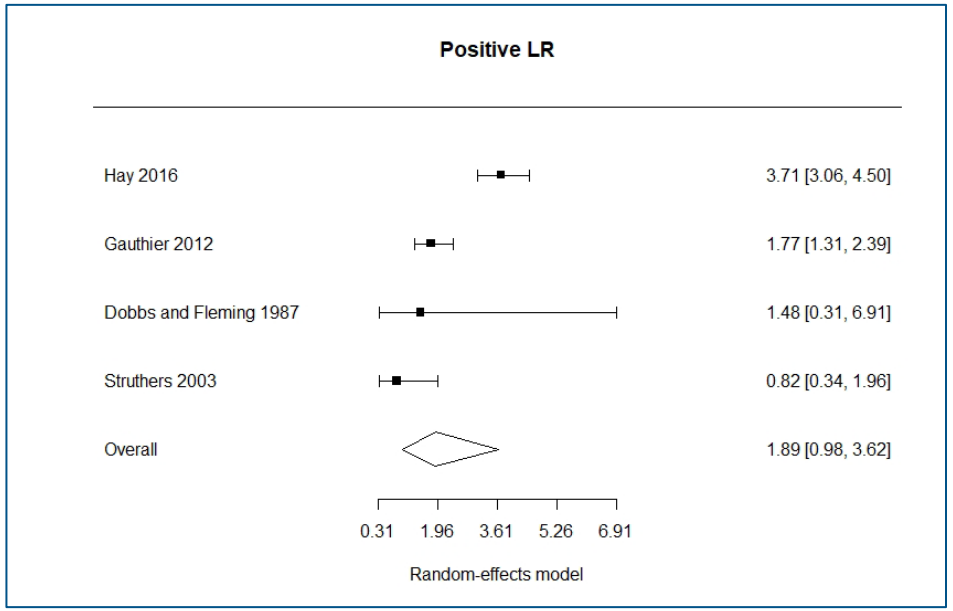
I^2 for sensitivity for malodorous urine = 95.1%

I^2 for specificity for malodorous urine = 91.4%

Malodorous urine – sensitivity analysis

Likelihood ratios for malodorous urine (< 14 years) (removing Pylkkanen 1979)

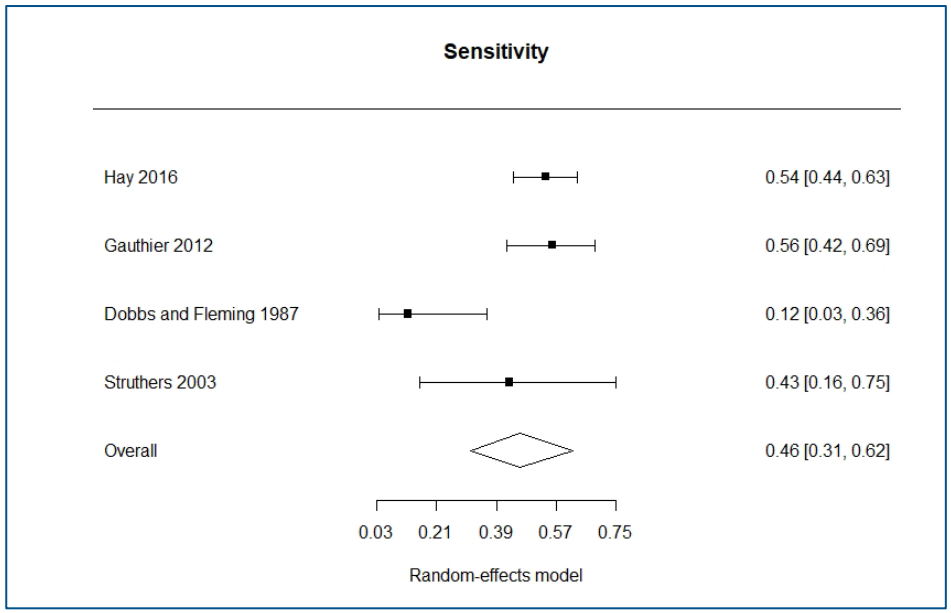


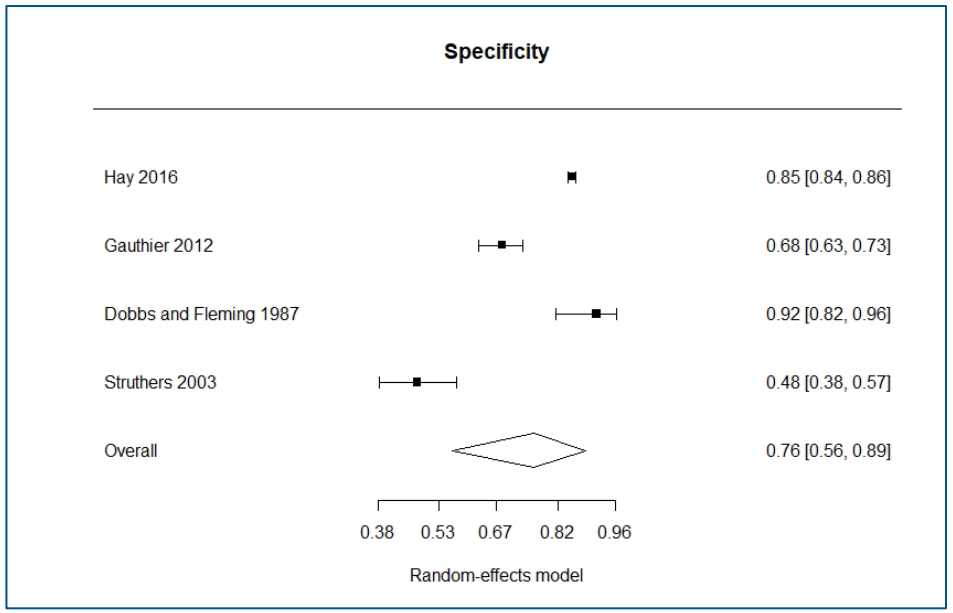


I^2 for negative LR for malodorous urine = 82.8%

I^2 for positive LR for malodorous urine = 88.2%

Sensitivity and specificity for malodorous urine (< 14 years) (removing Pylkkanen 1979)

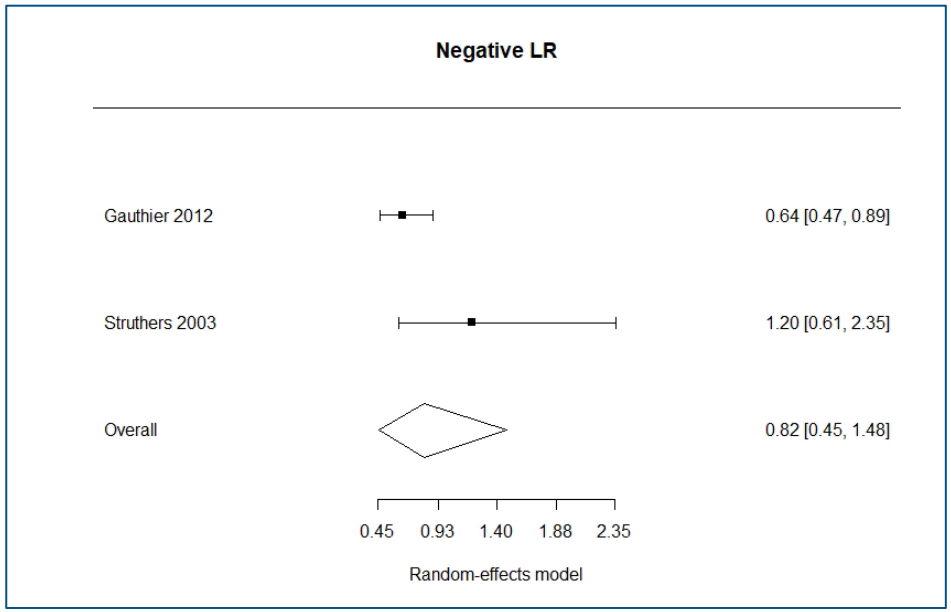


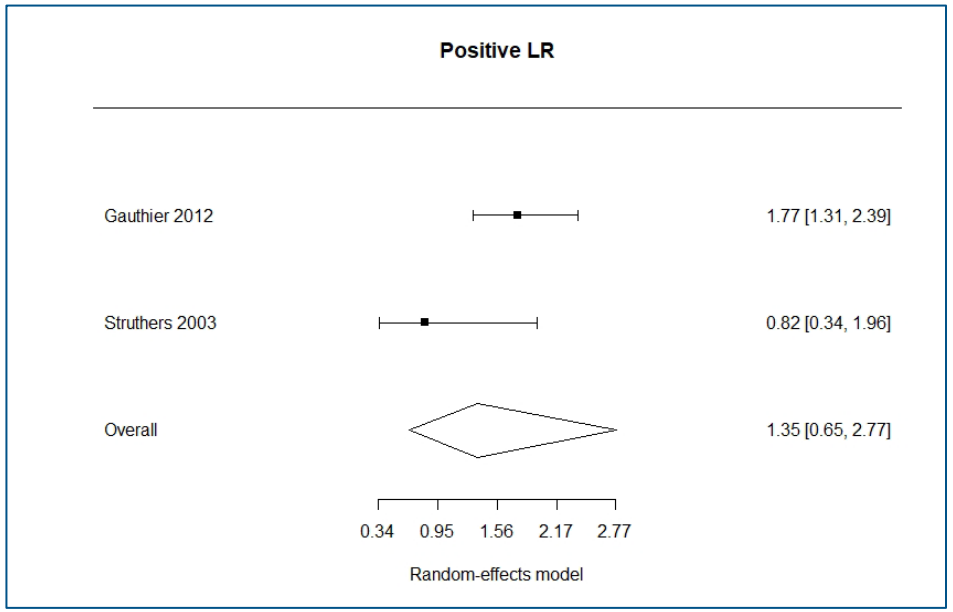


I^2 for sensitivity for malodorous urine = 62.0%

I^2 for specificity for malodorous urine = 97.8%

Likelihood ratios for malodorous urine (<2 years) (removing Pylkkanen 1979)

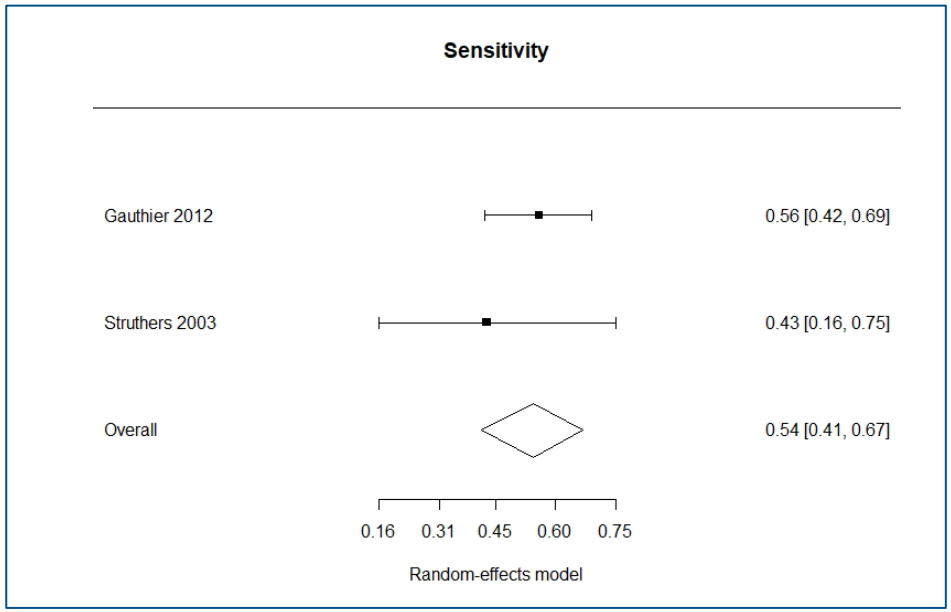


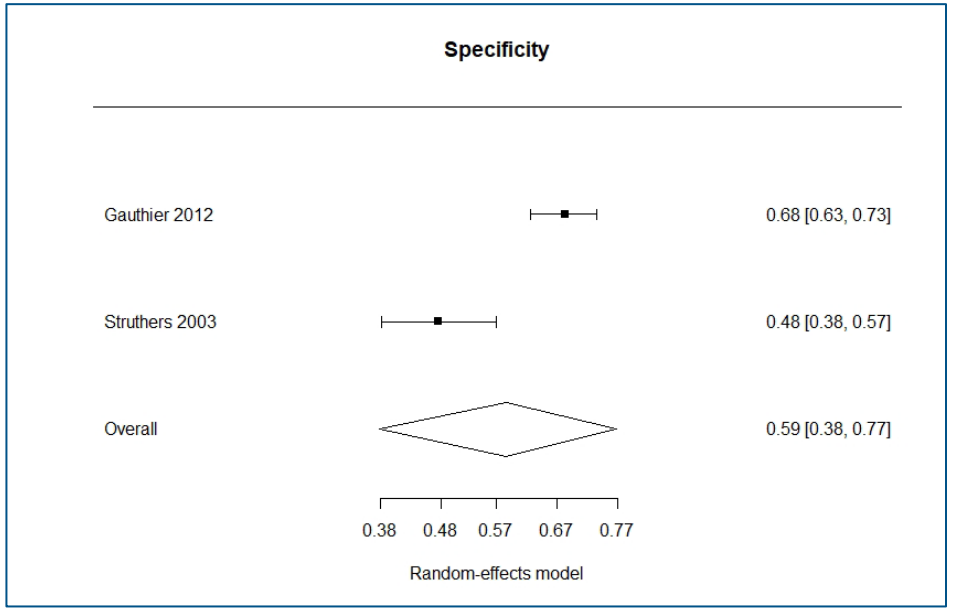


I^2 for negative LR for malodorous urine = 62.7%

I^2 for positive LR for malodorous urine = 62.6%

Sensitivity and specificity for malodorous urine (<2 years) (removing Pylkkanen 1979)



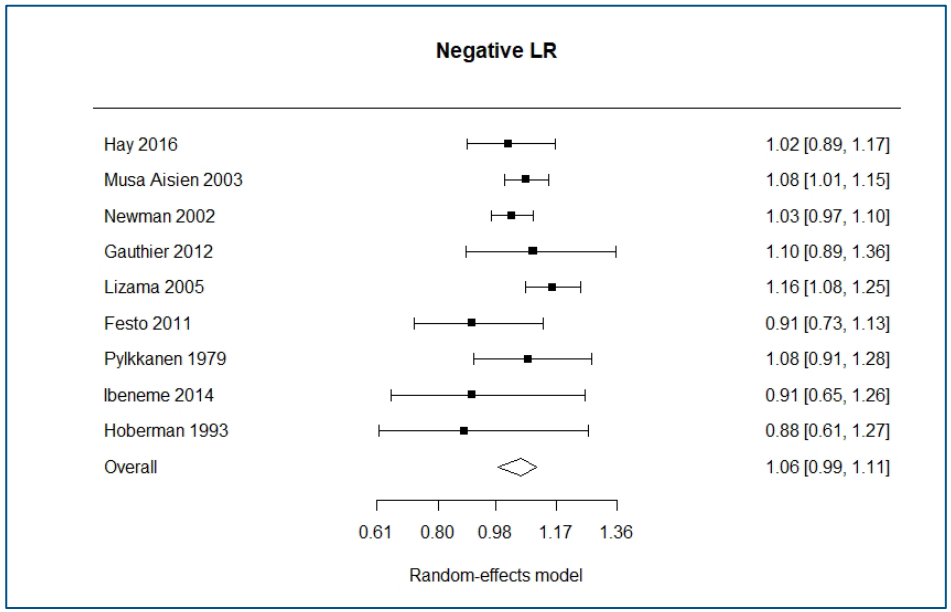


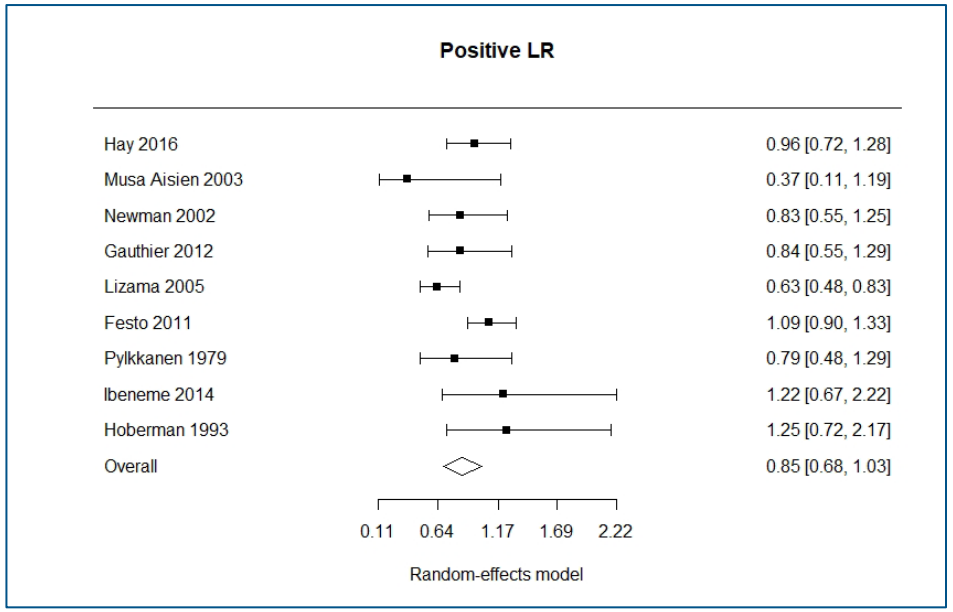
I^2 for sensitivity for malodorous urine = 0.0%

I^2 for specificity for malodorous urine = 92.6%

Vomiting – main analysis

Likelihood ratios for vomiting (< 5 years)

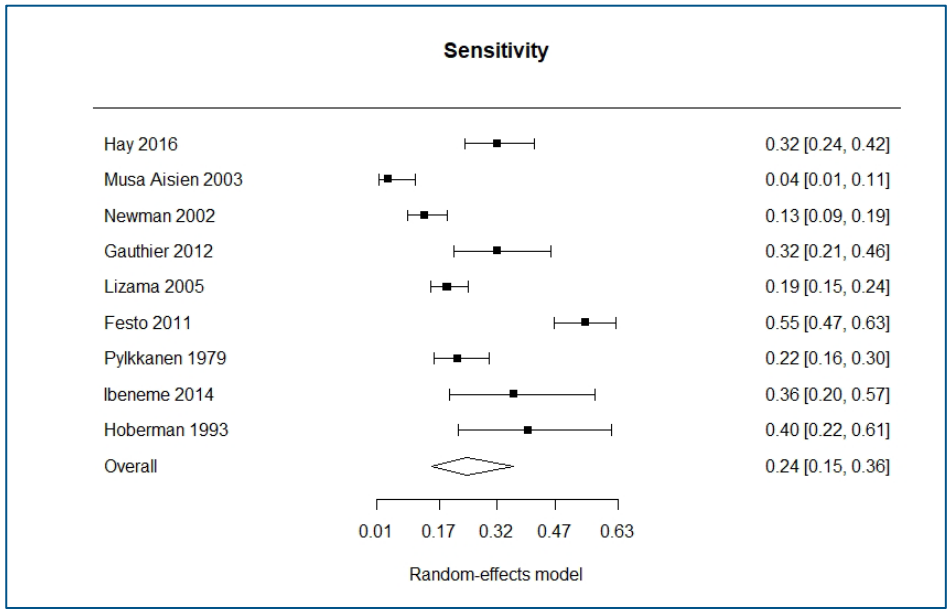


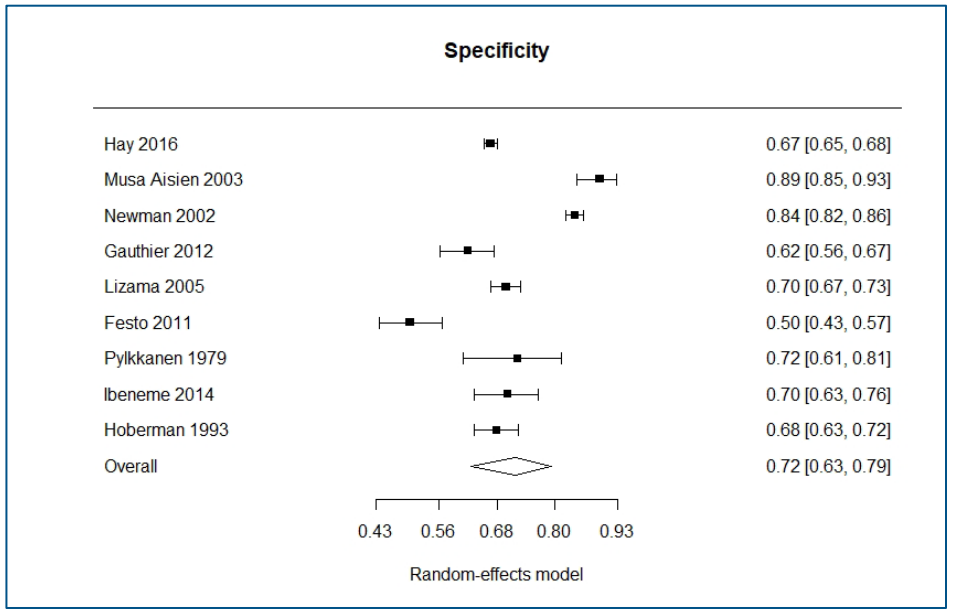


I^2 for negative LR for vomiting = 23.6%

I^2 for positive LR for vomiting = 47.7%

Sensitivity and specificity for vomiting (< 5 years)

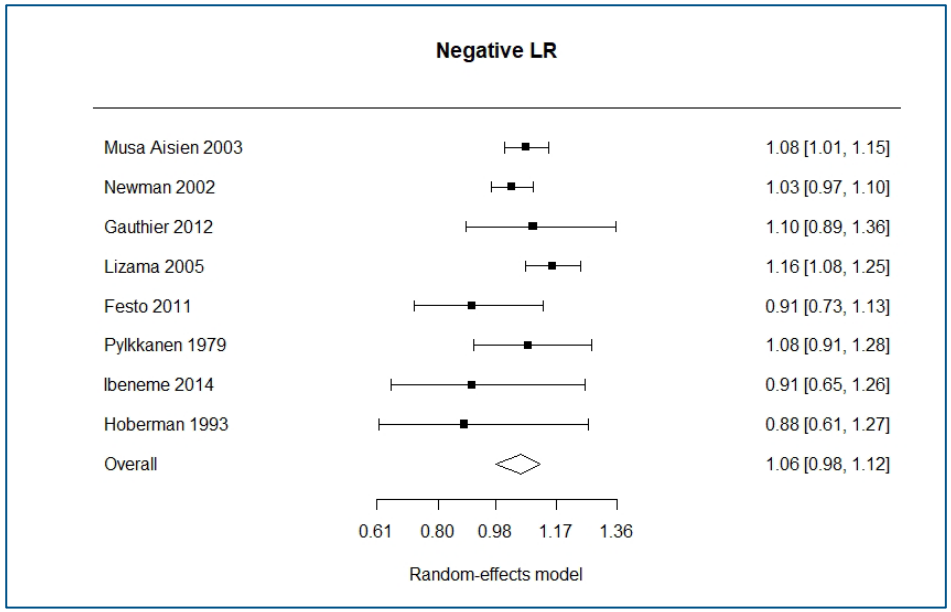


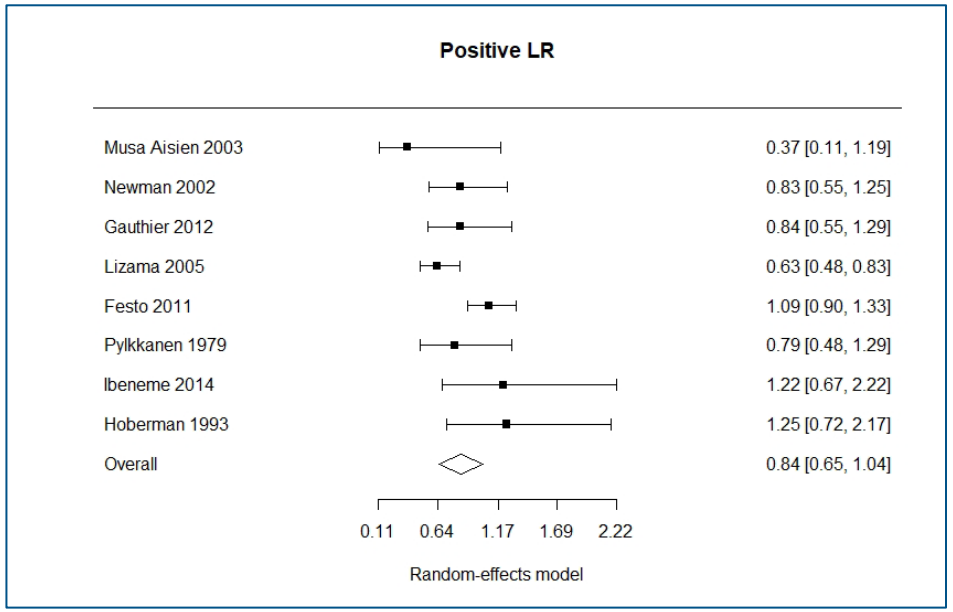


I^2 for sensitivity for vomiting = 91.5%

I^2 for specificity for vomiting = 96.7%

Likelihood ratios for vomiting (<2 years)

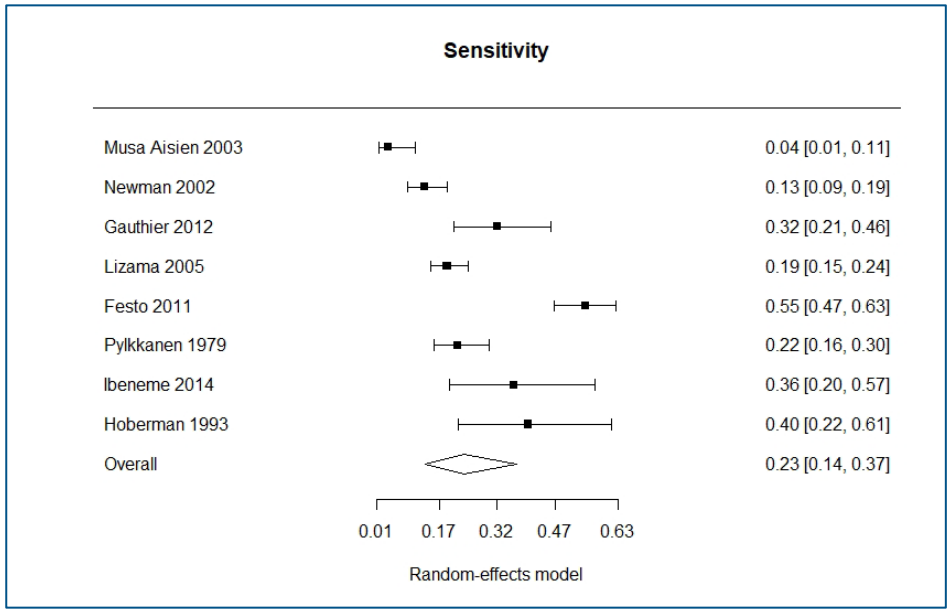


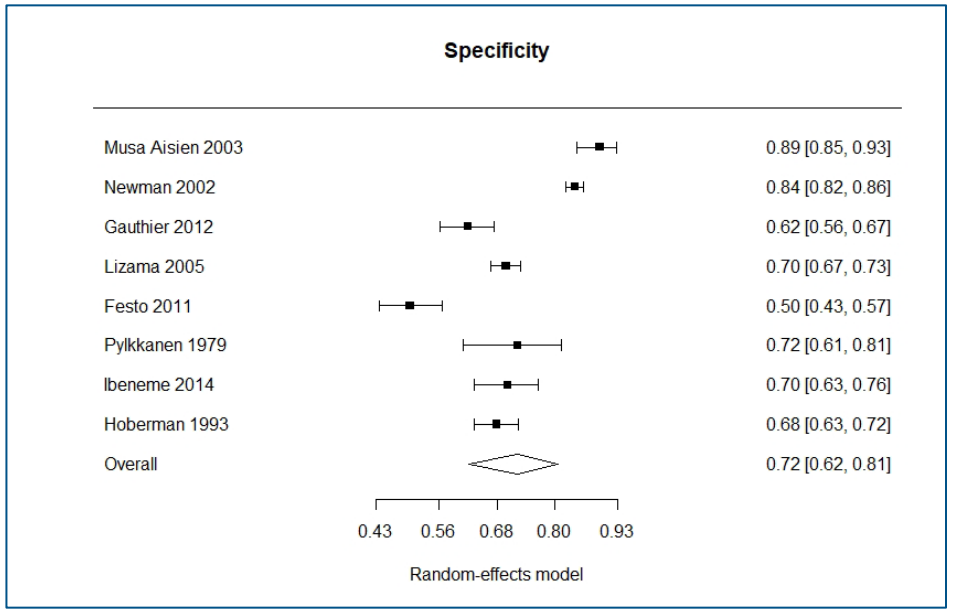


I^2 for negative LR for vomiting = 30.0%

I^2 for positive LR for vomiting = 53.8%

Sensitivity and specificity for vomiting (<2 years)



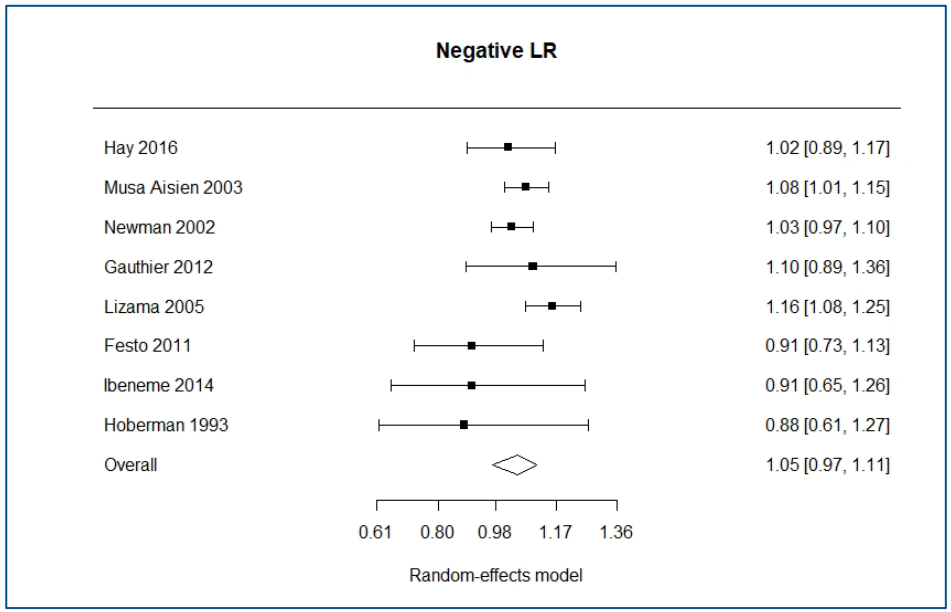


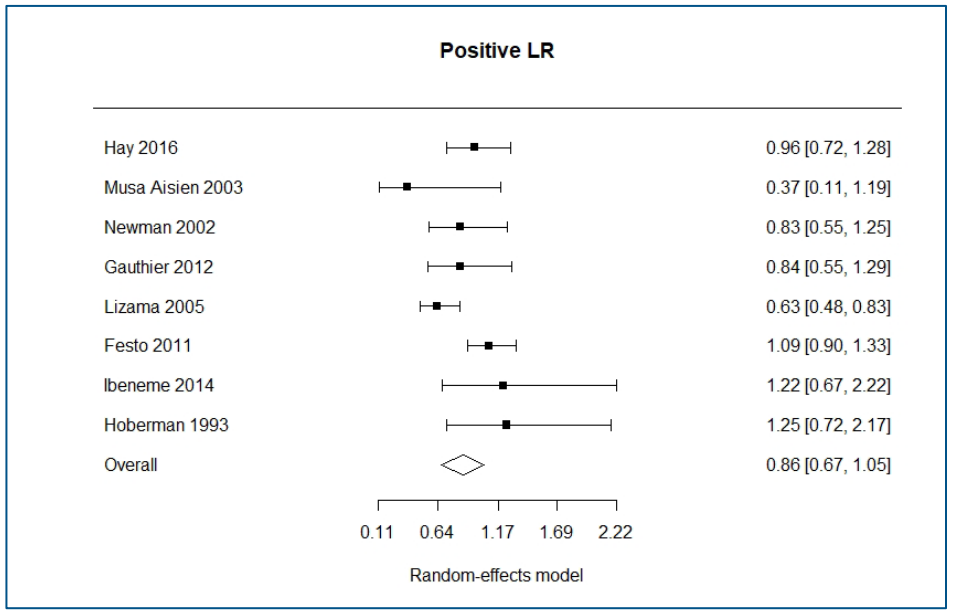
I^2 for sensitivity for vomiting = 92.5%

I^2 for specificity for vomiting = 96.5%

Vomiting – sensitivity analysis

Likelihood ratios for vomiting (< 5 years) (removing Pylkkanen 1979)

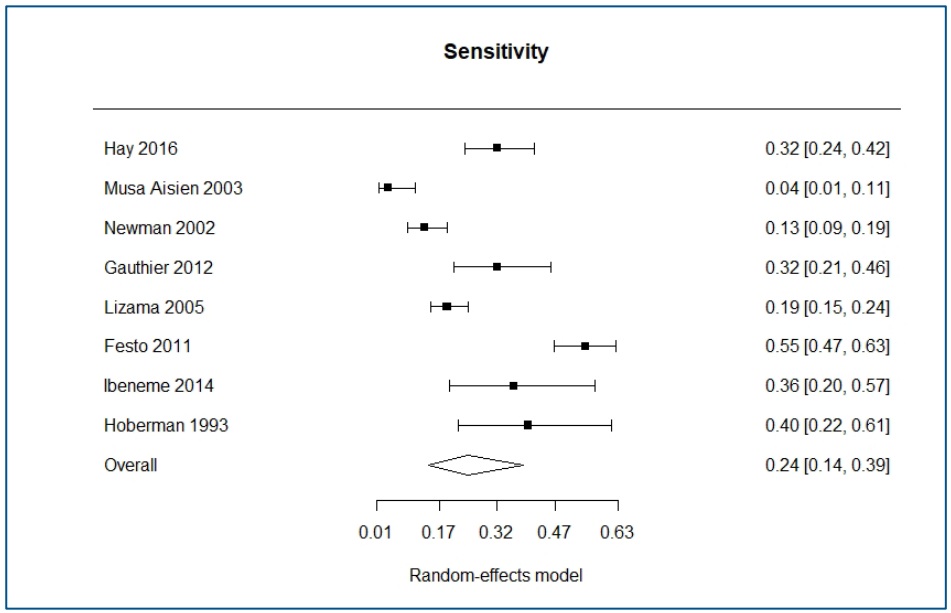


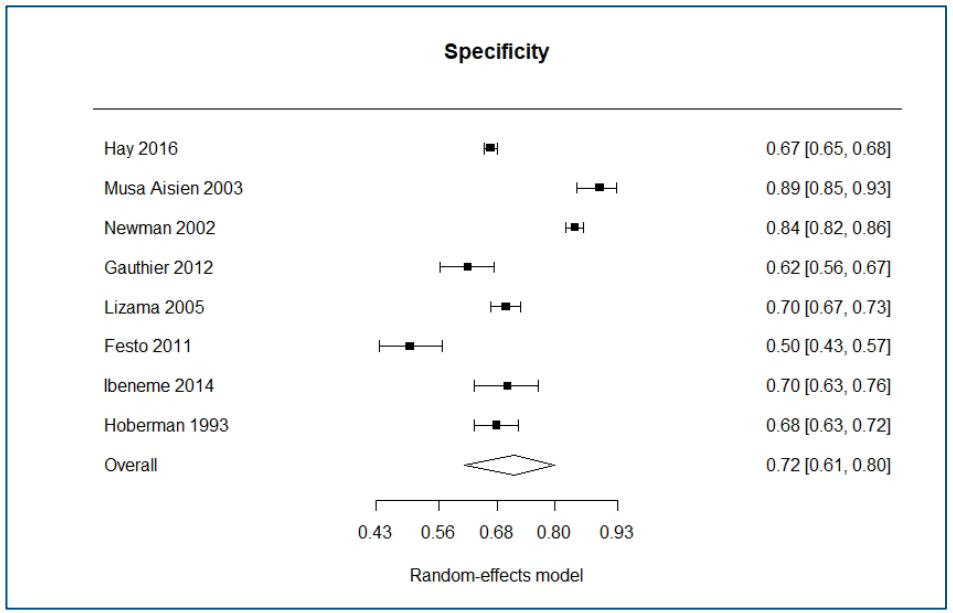


I^2 for negative LR for vomiting = 33.0%

I^2 for positive LR for vomiting = 53.1%

Sensitivity and specificity for vomiting (< 5 years) (removing Pylkkanen 1979)

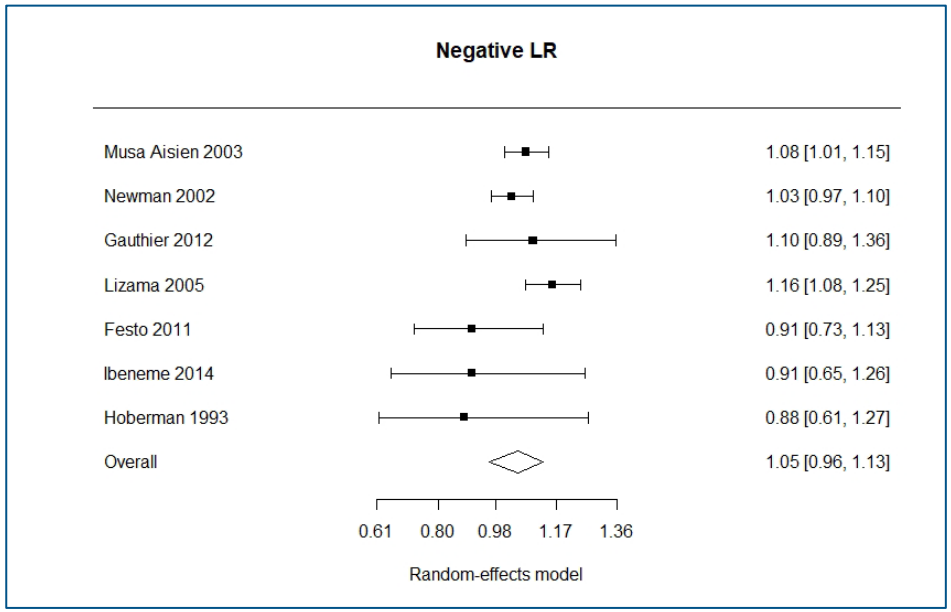


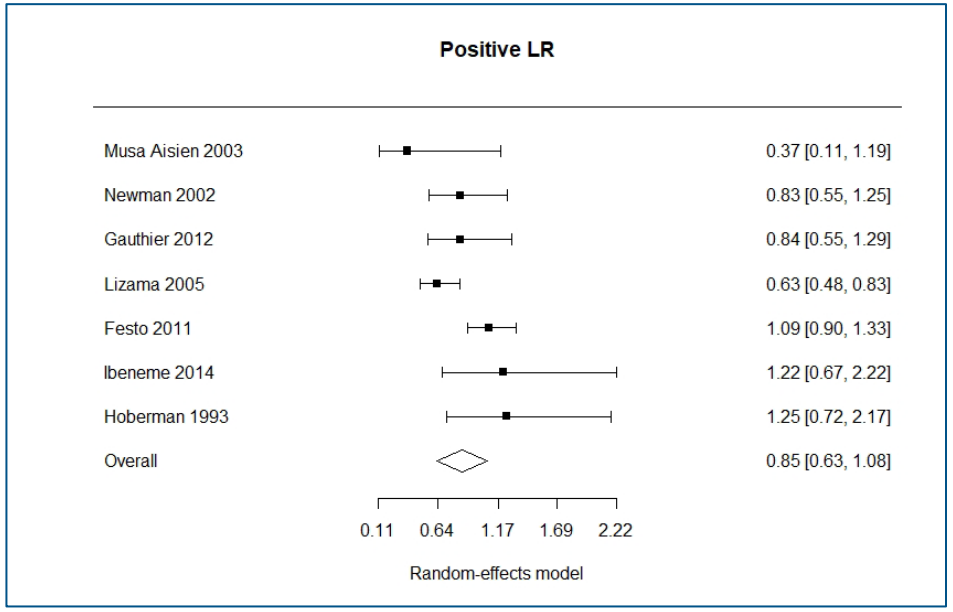


I^2 for sensitivity for vomiting = 92.3%

I^2 for specificity for vomiting = 97.1%

Likelihood ratios for vomiting (<2 years) (removing Pylkkanen 1979)

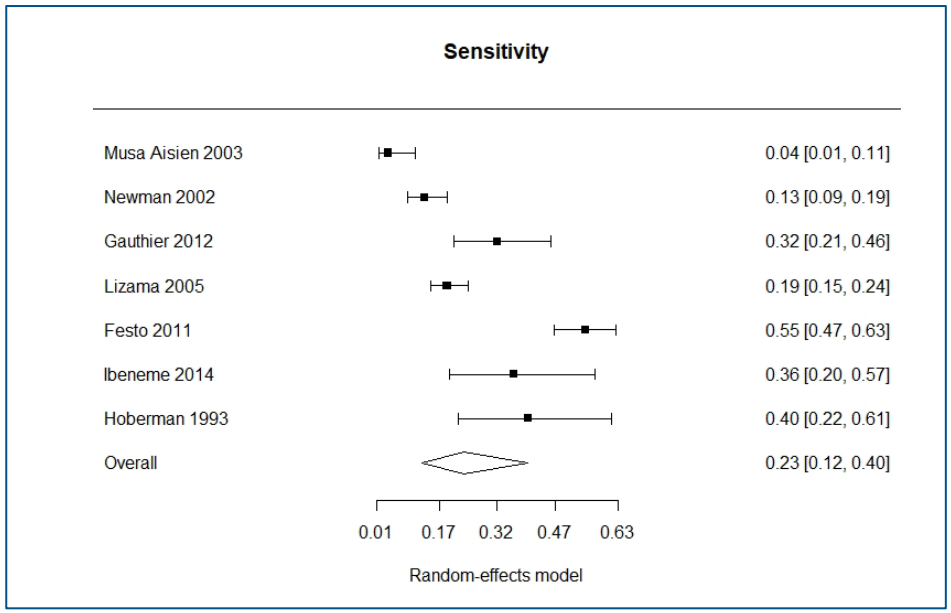


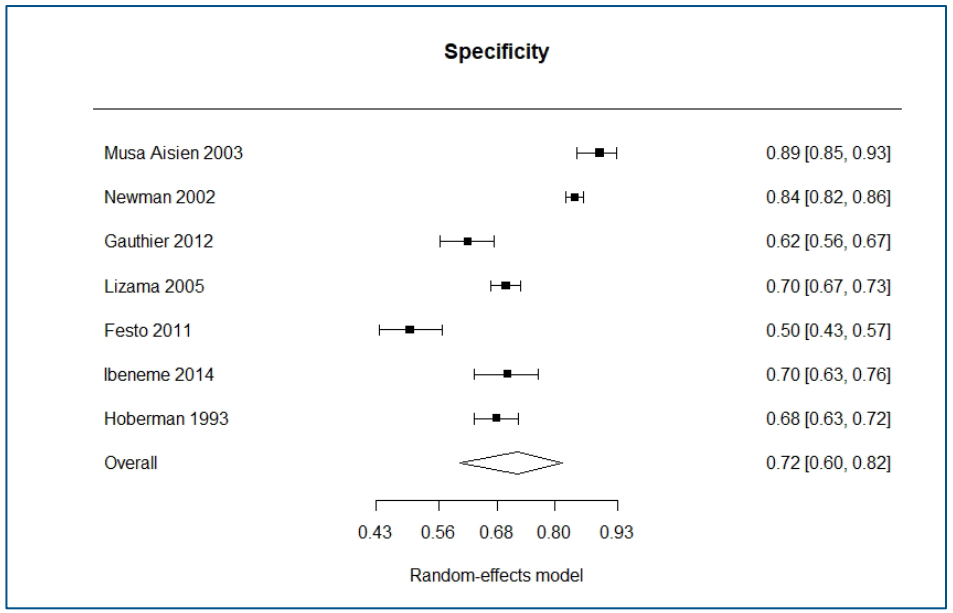


I^2 for negative LR for vomiting = 40.0%

I^2 for positive LR for vomiting = 59.6%

Sensitivity and specificity for vomiting (<2 years) (removing Pylkkanen 1979)



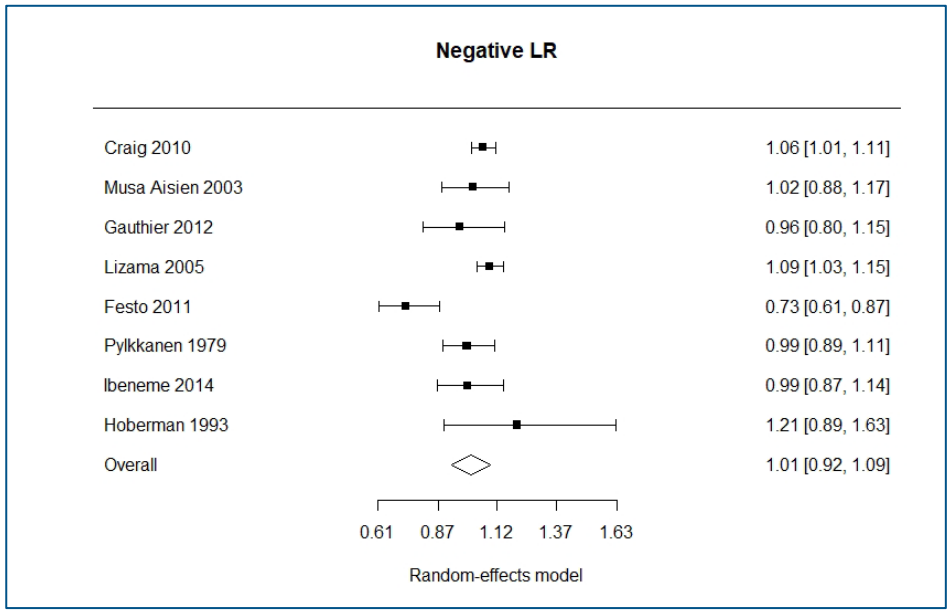


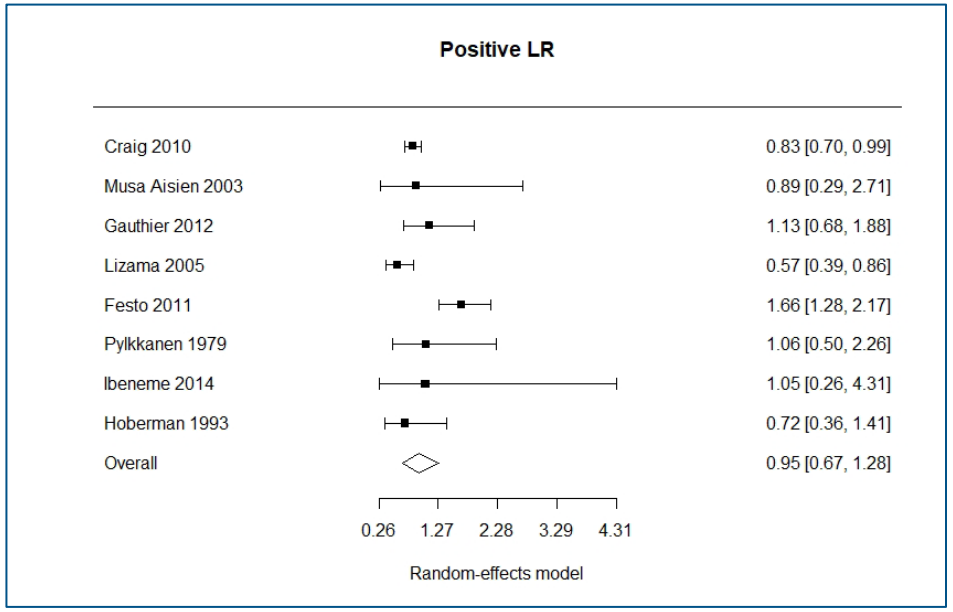
I^2 for sensitivity for vomiting = 93.4%

I^2 for specificity for vomiting = 97.0%

Diarrhoea – main analysis

Likelihood ratios for diarrhoea (< 5 years)

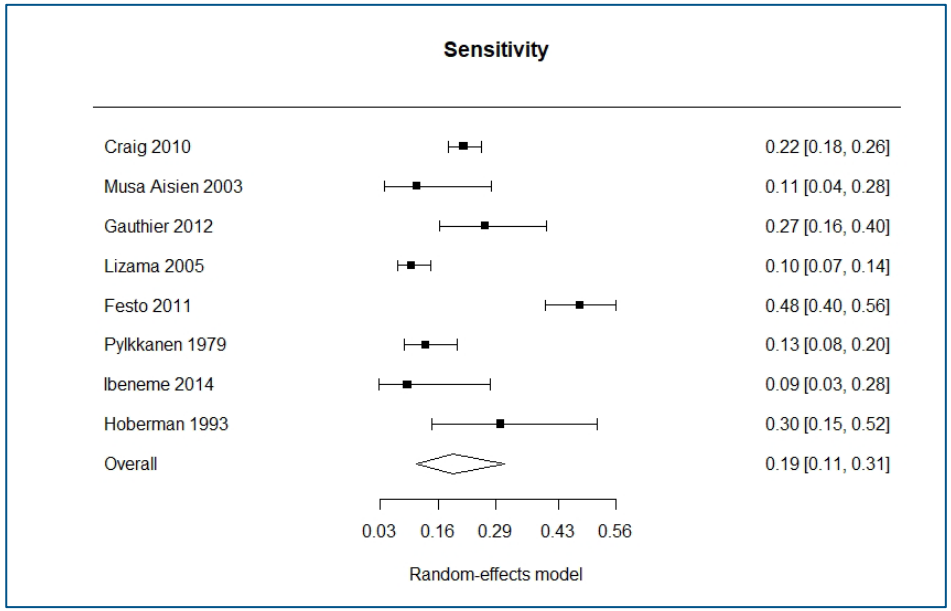


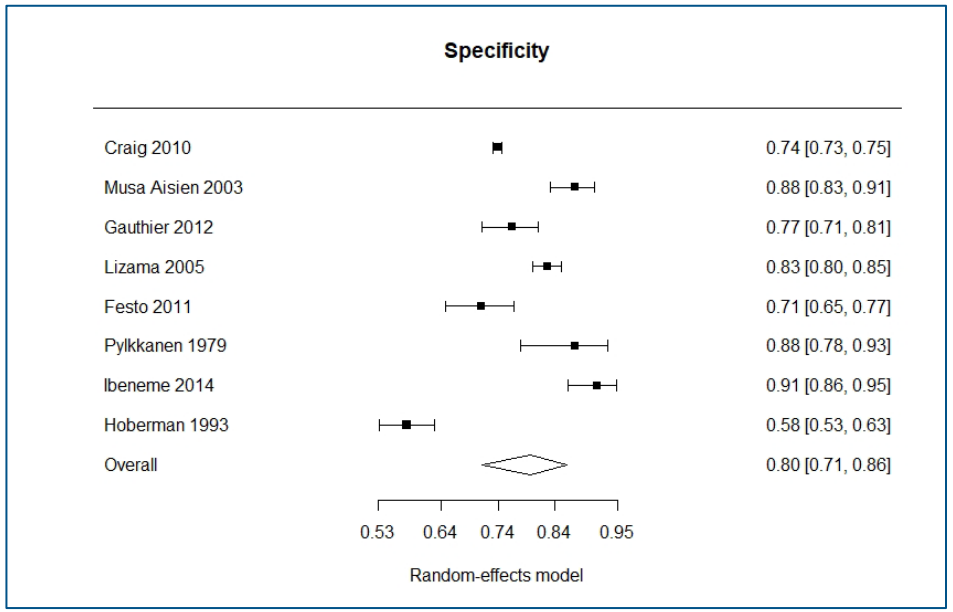


I^2 for negative LR for diarrhoea = 68.0%

I^2 for positive LR for diarrhoea = 73.6%

Sensitivity and specificity of diarrhoea (< 5 years)

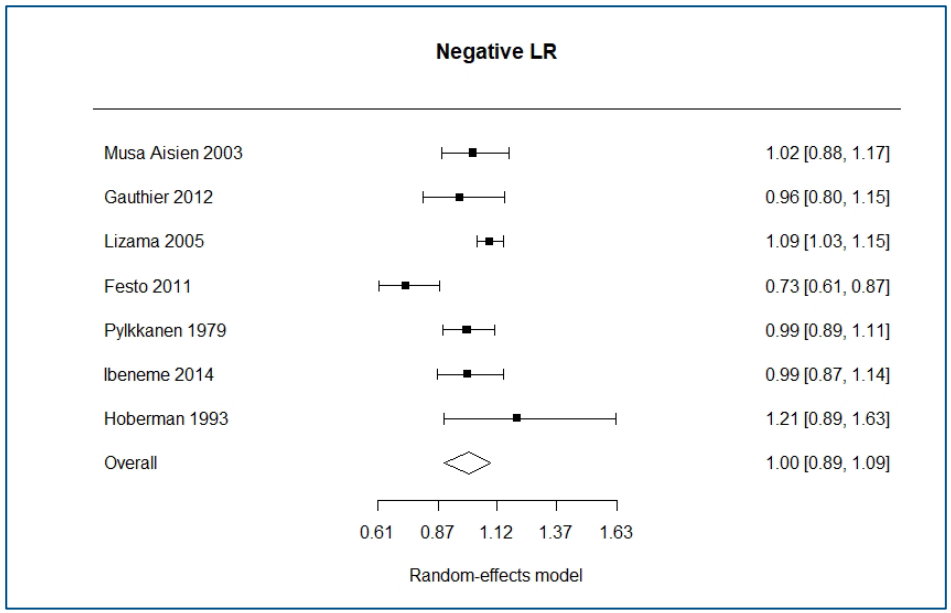




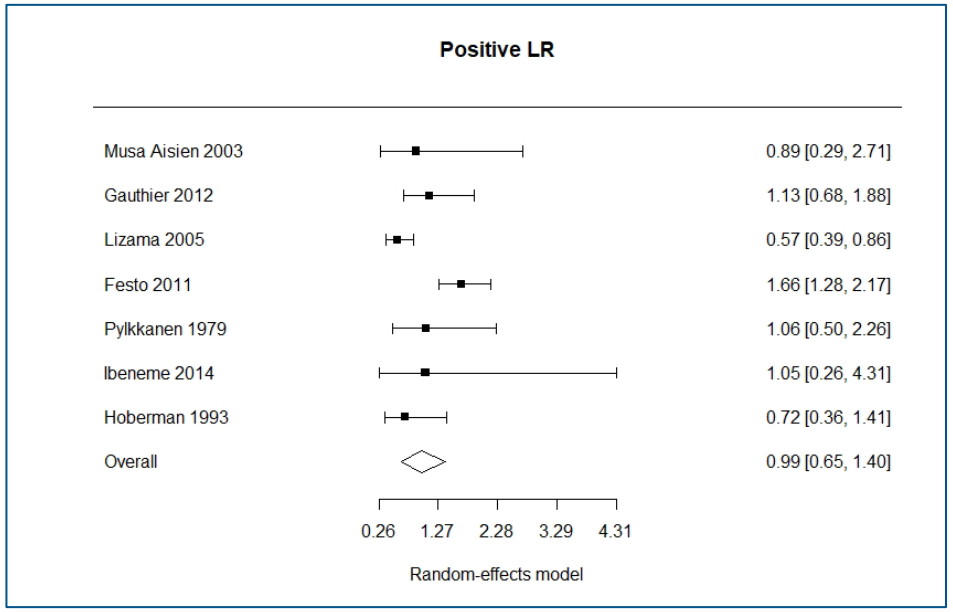
I^2 for sensitivity for diarrhoea = 91.4%

I^2 for specificity for diarrhoea = 95.0%

Likelihood ratios for diarrhoea (<2 years)

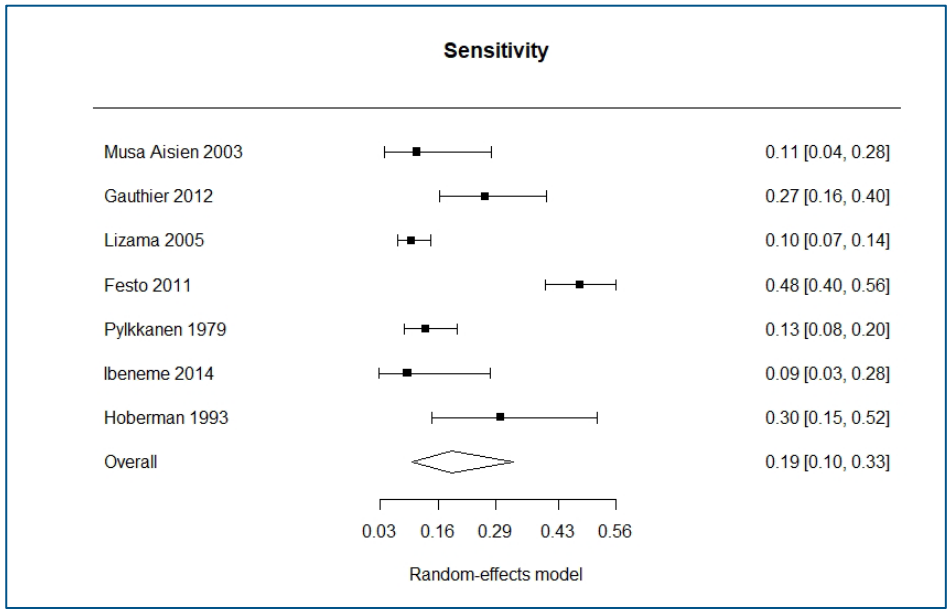


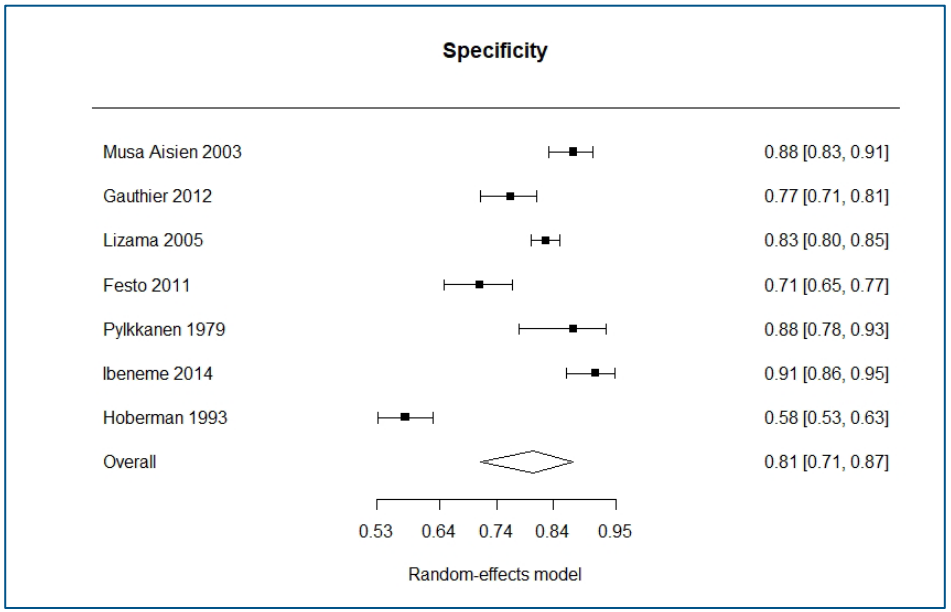
I^2 for negative LR for diarrhoea = 72.0%



I^2 for positive LR for diarrhoea = 71.6%

Sensitivity and specificity of diarrhoea (<2 years)



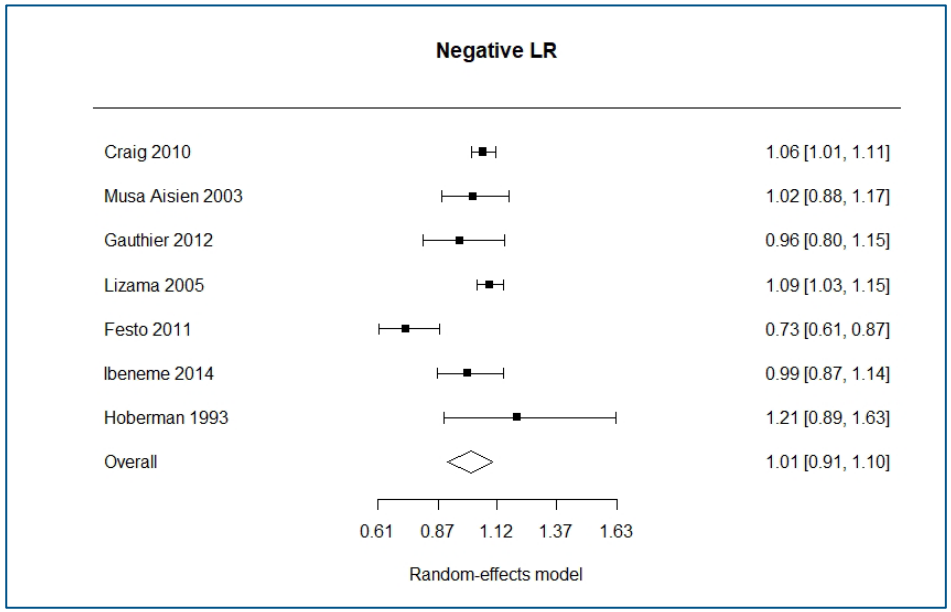


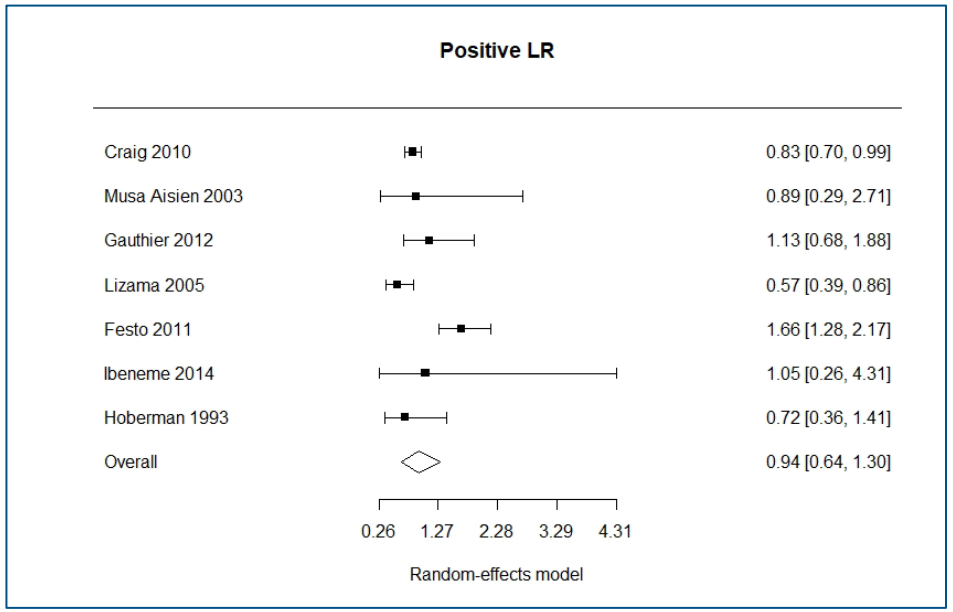
I^2 for sensitivity for diarrhoea = 92.5%

I^2 for specificity for diarrhoea = 95.5%

Diarrhoea – sensitivity analysis

Likelihood ratios for diarrhoea (< 5 years) (removing Pylkkanen 1979)

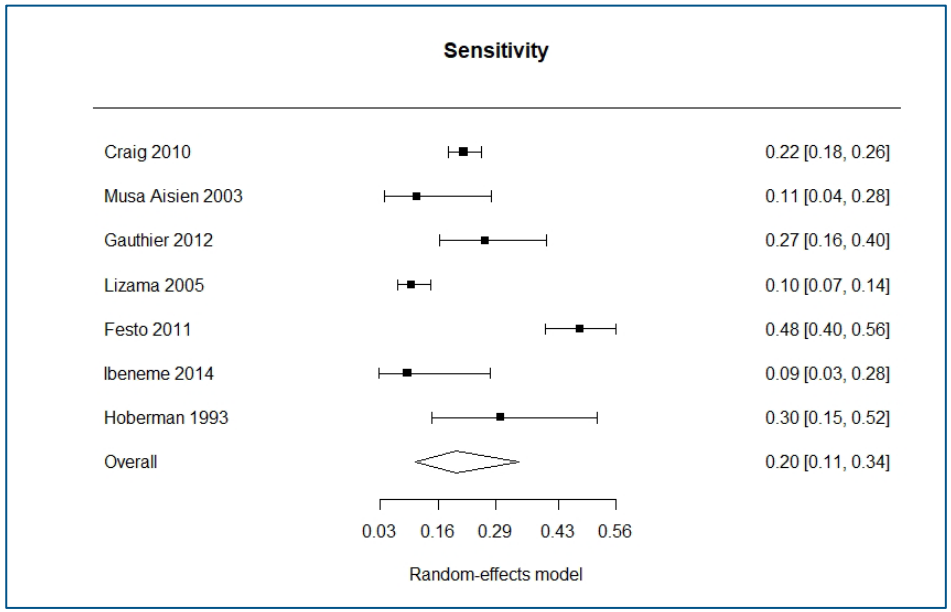


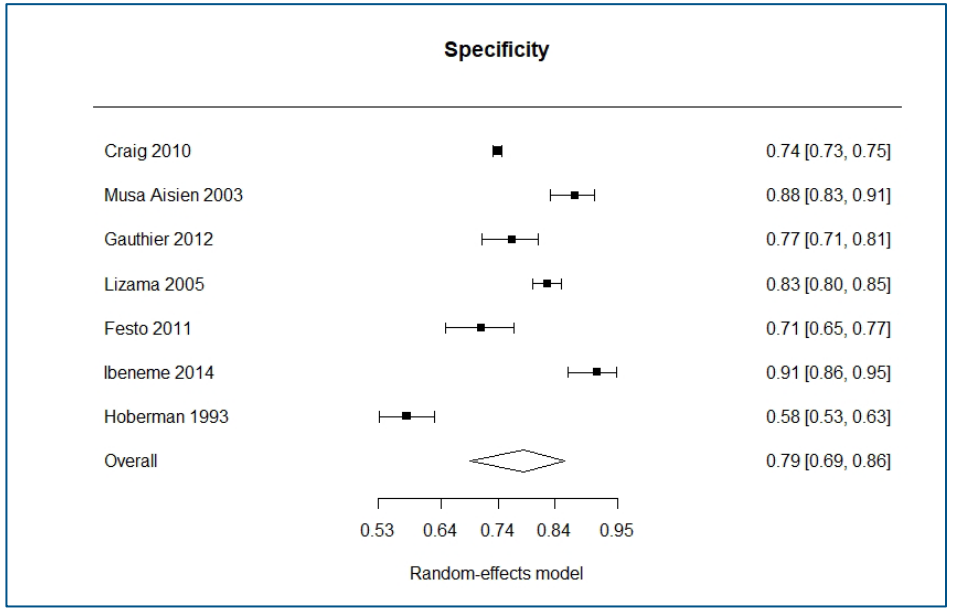


I^2 for negative LR for diarrhoea = 71.3%

I^2 for positive LR for diarrhoea = 77.3%

Sensitivity and specificity of diarrhoea (< 5 years) (removing Pylkkanen 1979)

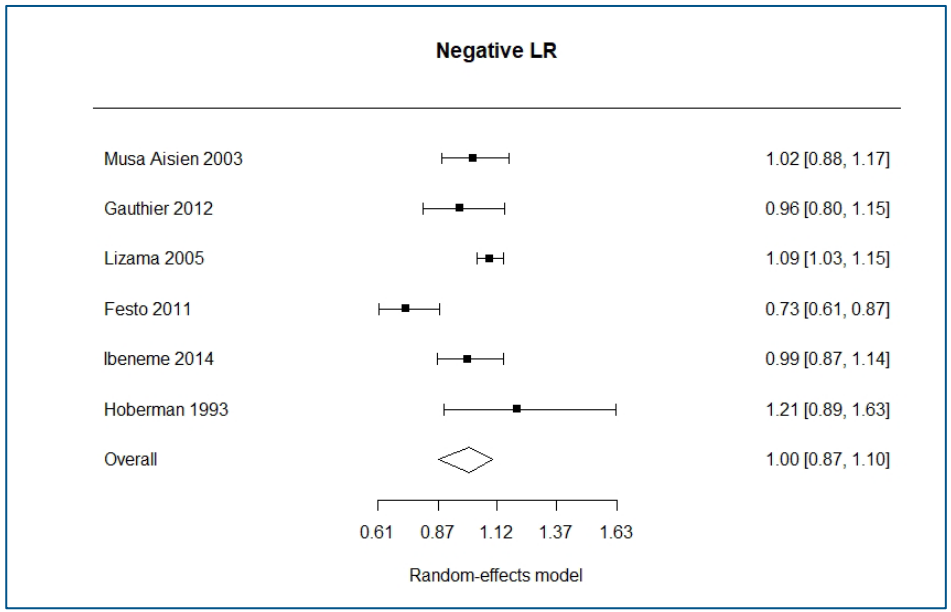


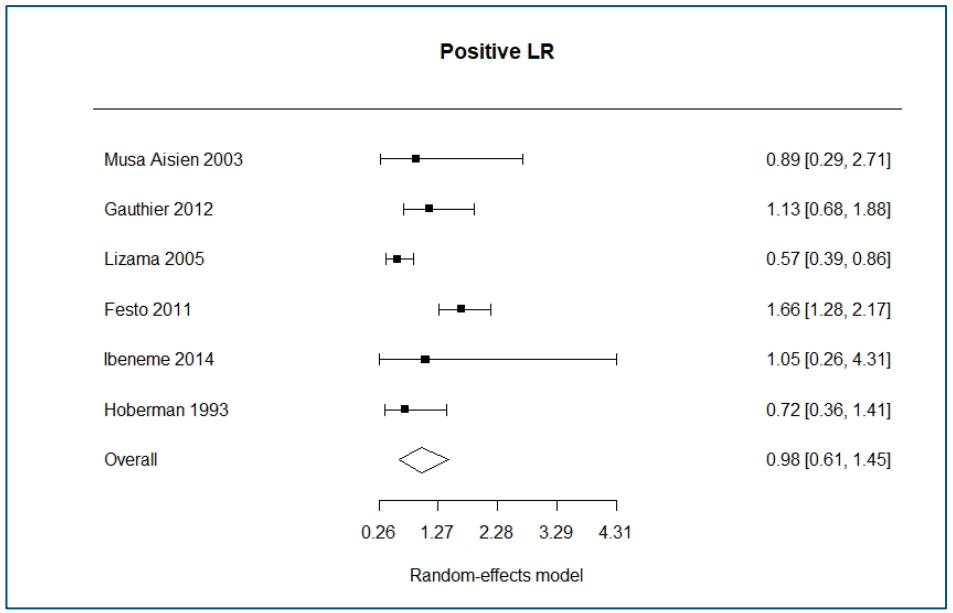


I^2 for sensitivity for diarrhoea = 91.9%

I^2 for specificity for diarrhoea = 95.5%

Likelihood ratios for diarrhoea (<2 years) (removing Pylkkanen 1979)

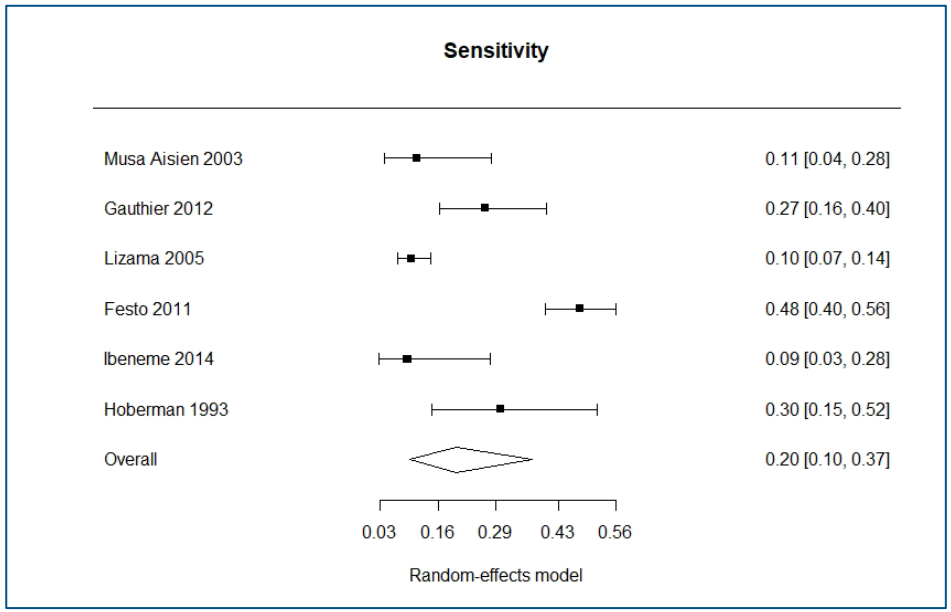


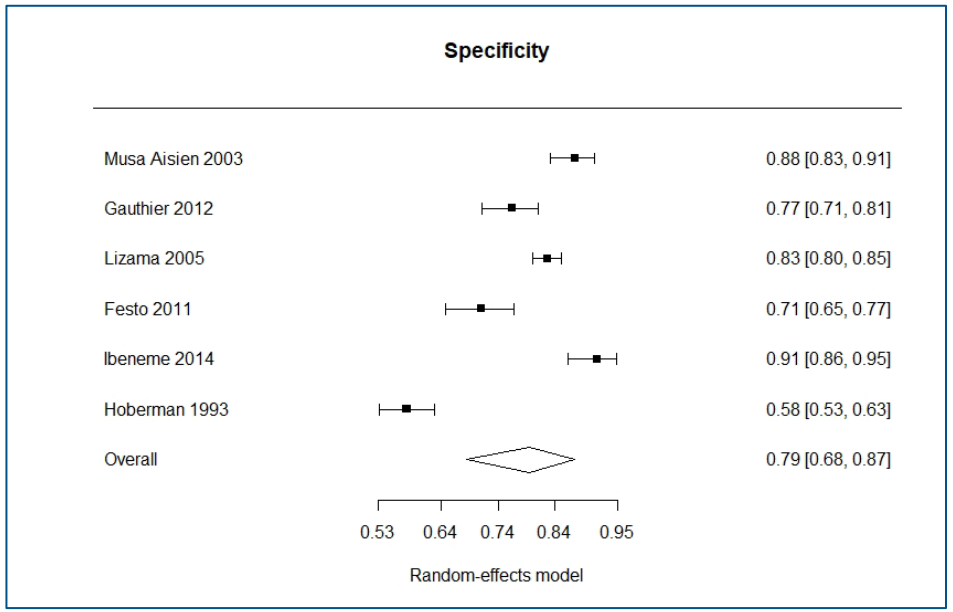


I^2 for negative LR for diarrhoea = 75.9%

I^2 for positive LR for diarrhoea = 76.3%

Sensitivity and specificity of diarrhoea (<2 years) (removing Pylkkanen 1979)



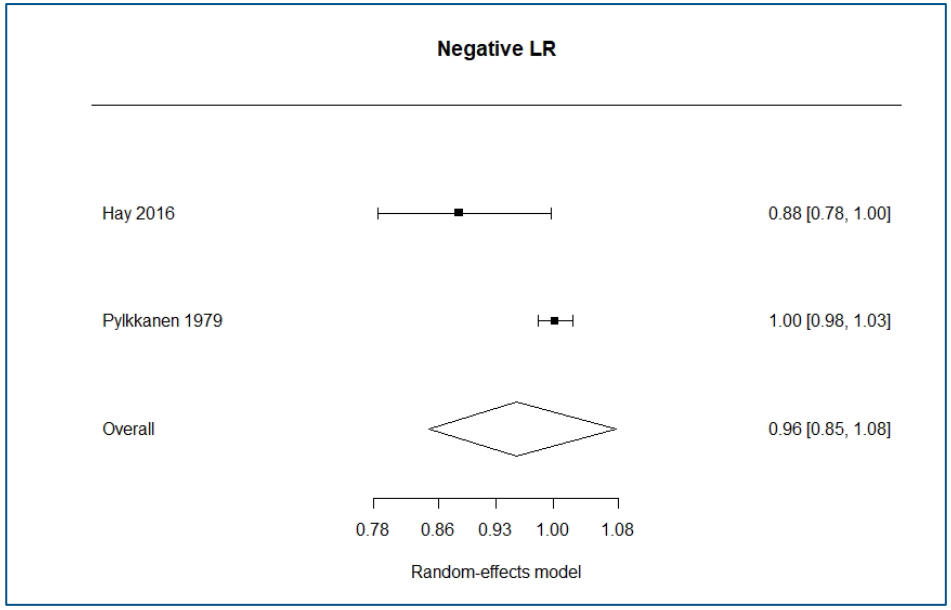


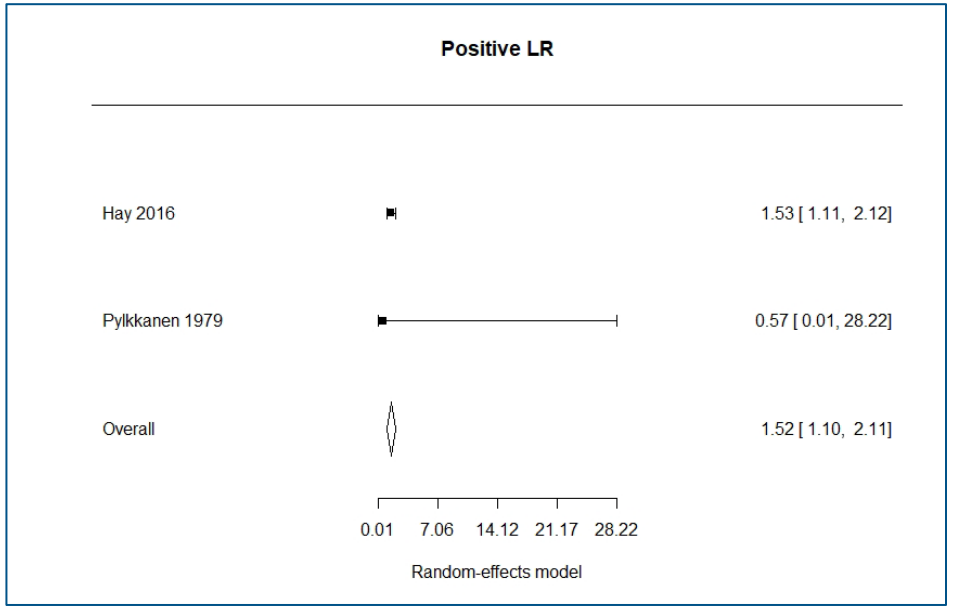
I^2 for sensitivity for diarrhoea = 92.8%

I^2 for specificity for diarrhoea = 96.1%

Constipation

Likelihood ratios for constipation (< 5 years)

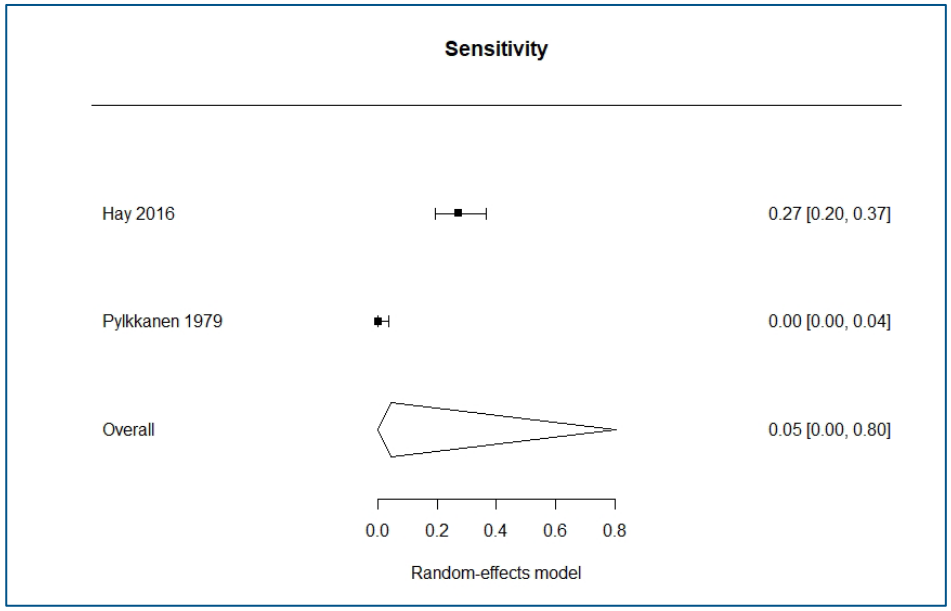


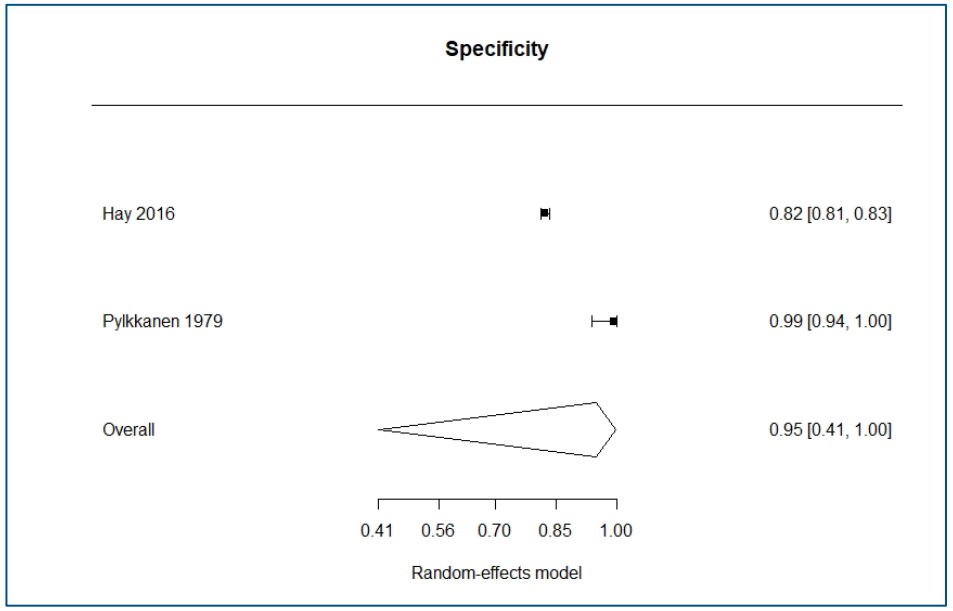


I^2 for negative LR for constipation = 74.2%

I^2 for positive LR for constipation = 0.0%

Sensitivity and specificity for constipation (< 5 years)



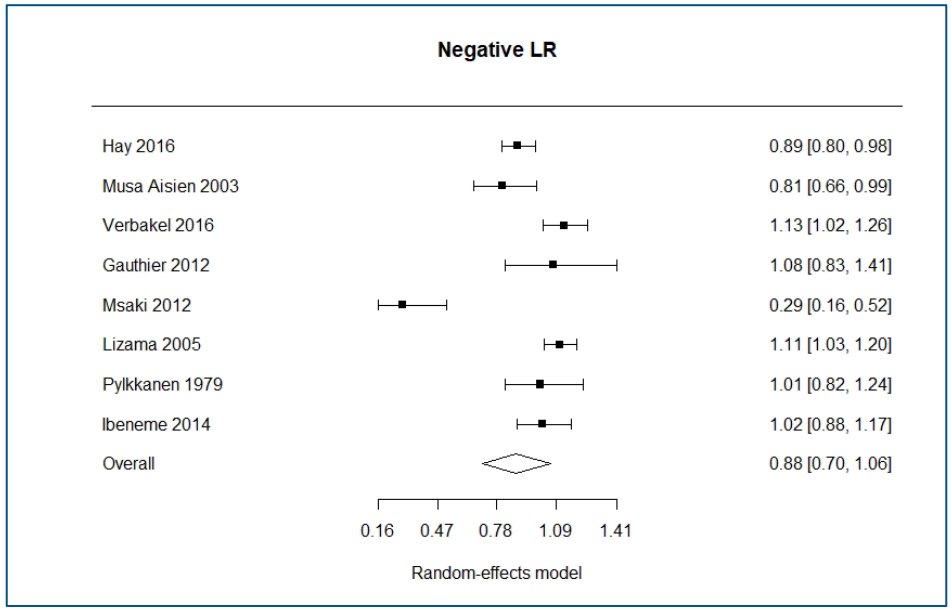


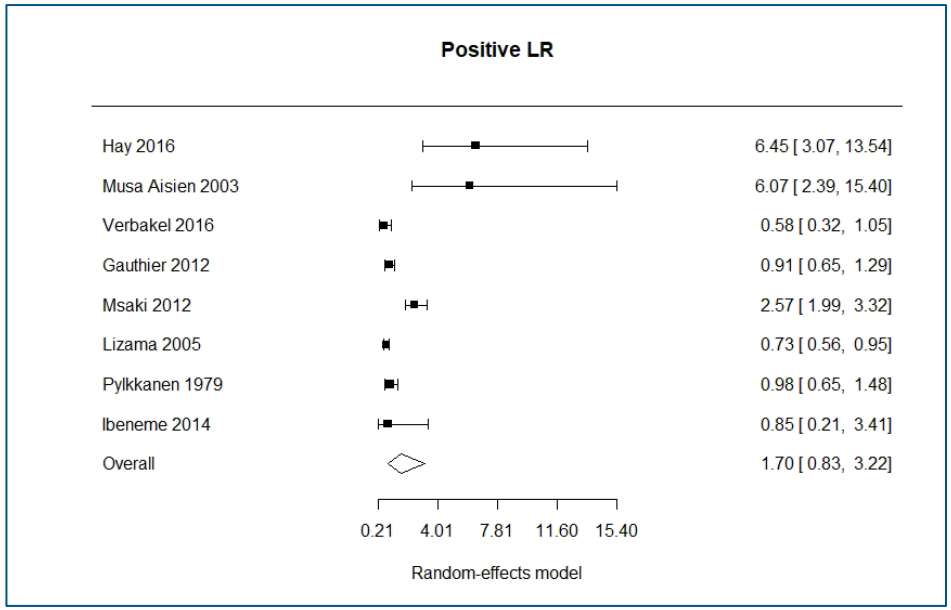
I^2 for sensitivity for constipation = 90.1%

I^2 for specificity for constipation = 83.0%

Abdominal pain – main analysis

Likelihood ratios for abdominal pain (< 5 years)

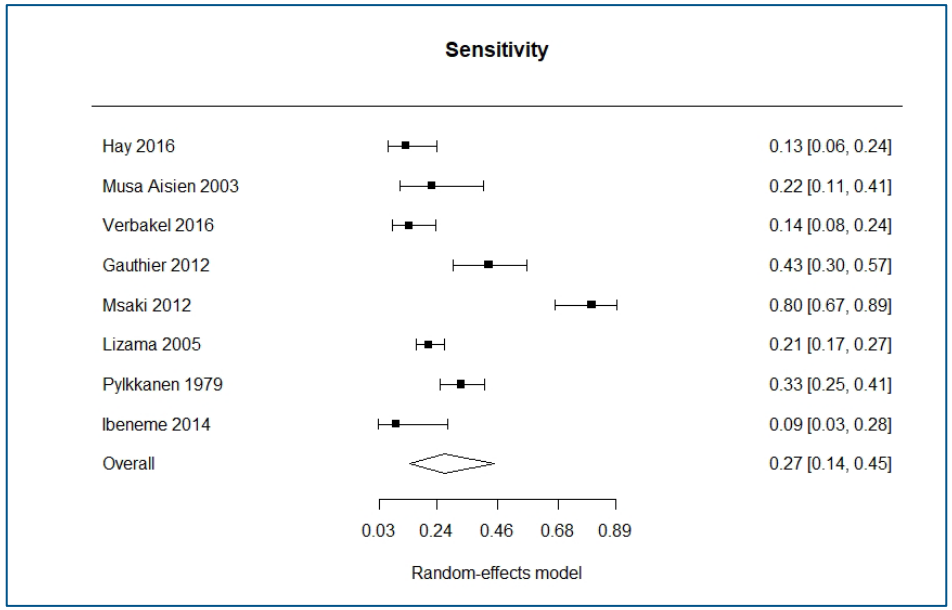


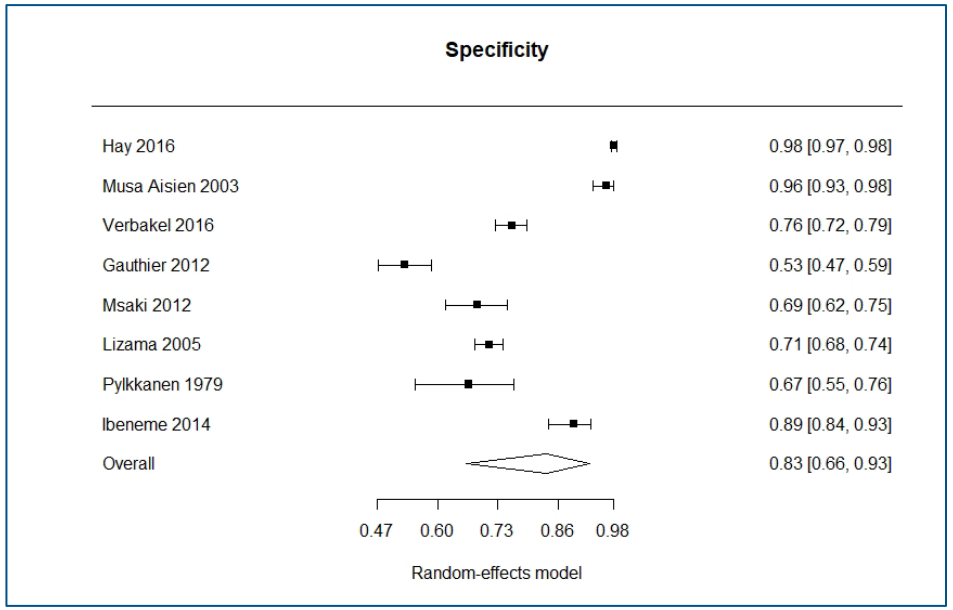


I^2 for negative LR for abdominal pain = 81.8%

I^2 for positive LR for abdominal pain = 92.0%

Sensitivity and specificity for abdominal pain (< 5 years)

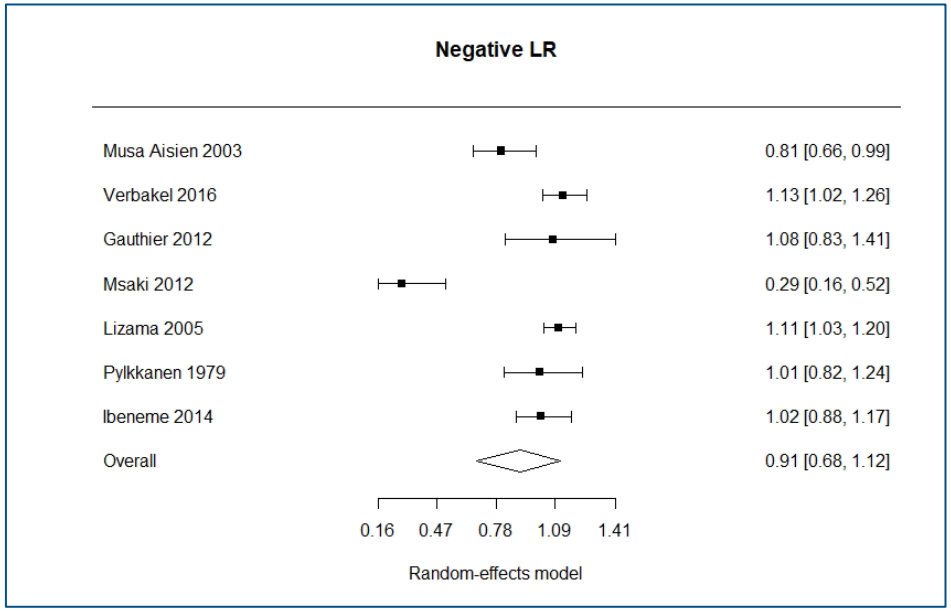


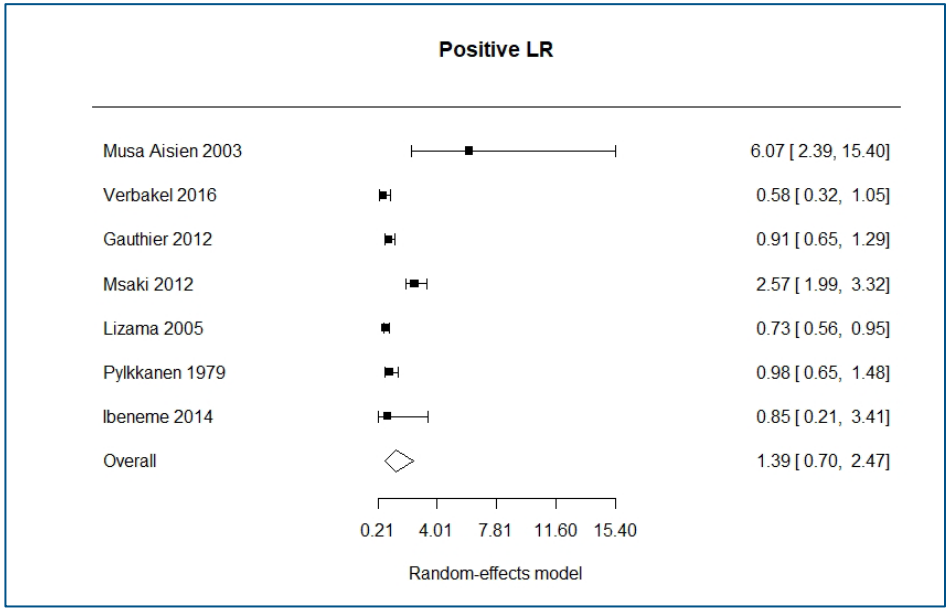


I^2 for sensitivity for abdominal pain = 89.9%

I^2 for specificity for abdominal pain = 98.7%

Likelihood ratios for abdominal pain (<2 years)

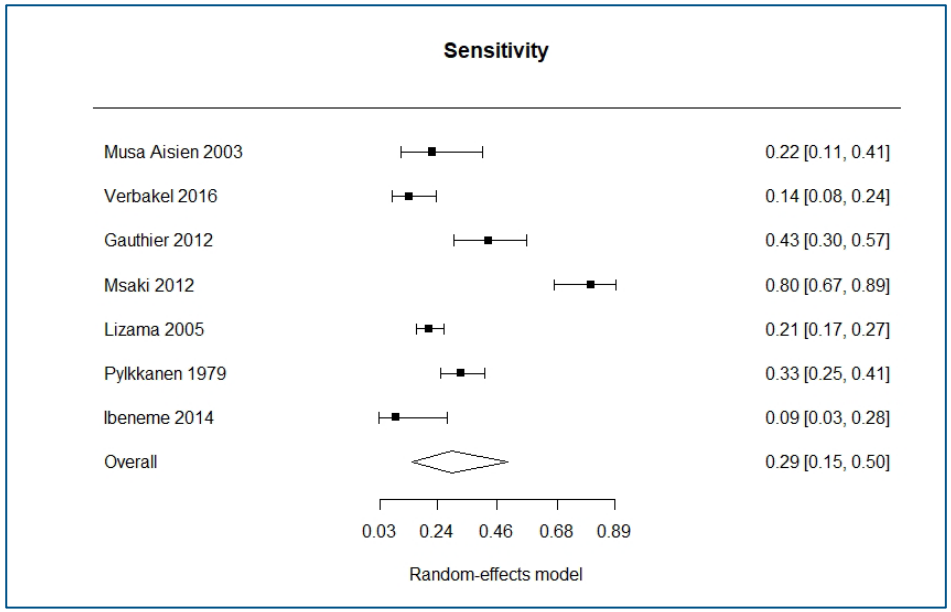


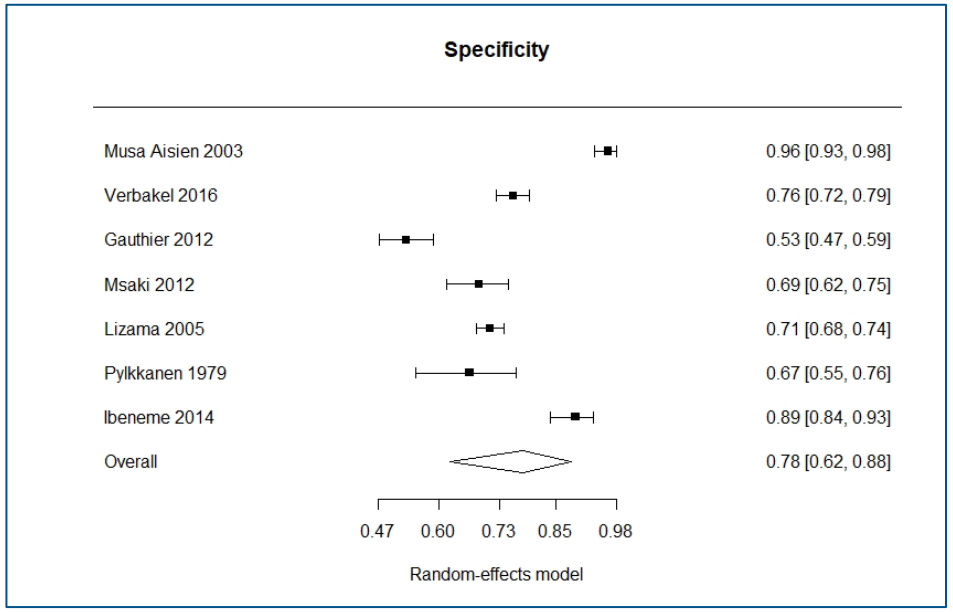


I^2 for negative LR for abdominal pain = 79.5%

I^2 for positive LR for abdominal pain = 91.3%

Sensitivity and specificity for abdominal pain (<2 years)



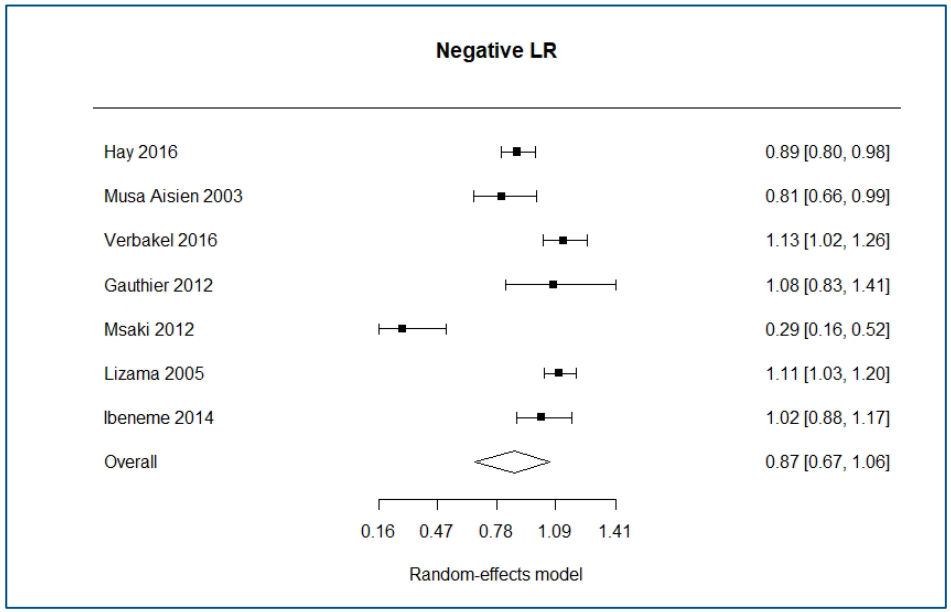


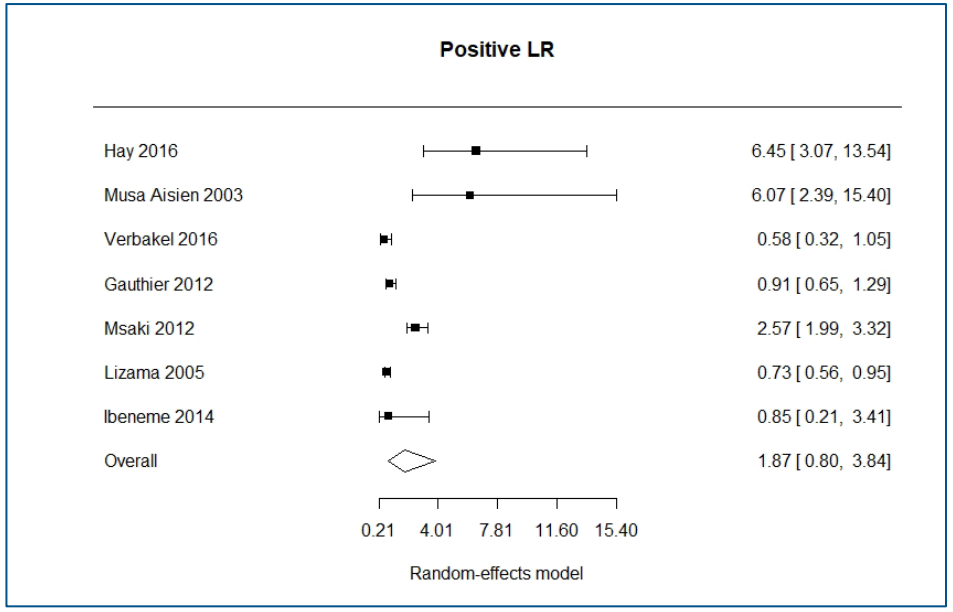
I^2 for sensitivity for abdominal pain = 90.5%

I^2 for specificity for abdominal pain = 95.4%

Abdominal pain – sensitivity analysis

Likelihood ratios for abdominal pain (< 5 years) (removing Pylkkanen 1979)

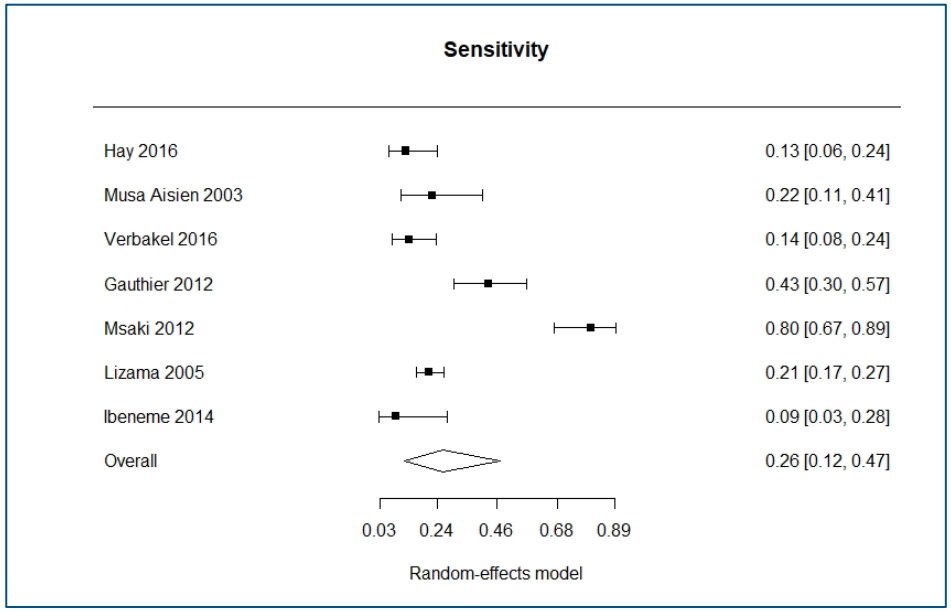


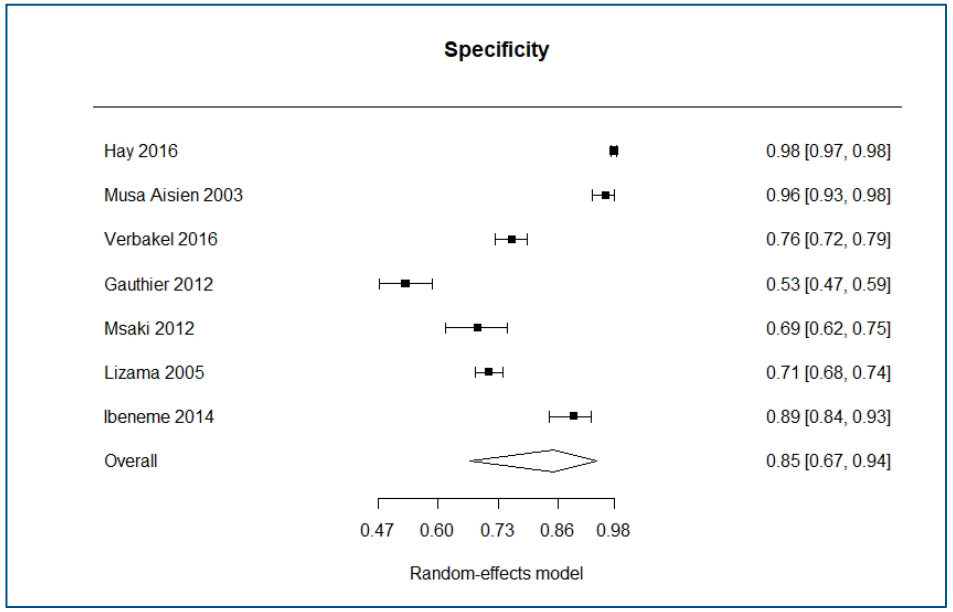


I^2 for negative LR for abdominal pain = 84.4%

I^2 for positive LR for abdominal pain = 93.0%

Sensitivity and specificity for abdominal pain (< 5 years) (removing Pylkkanen 1979)

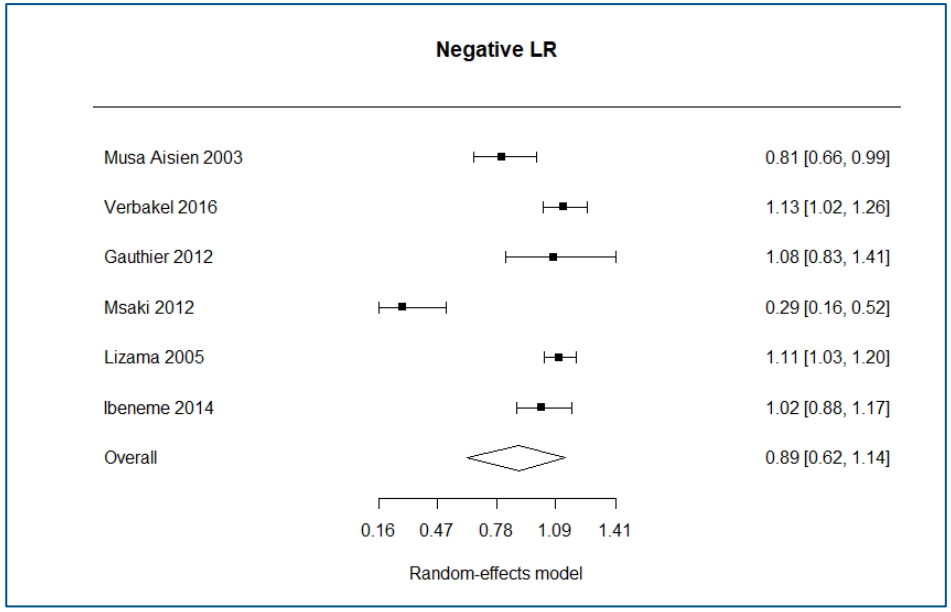


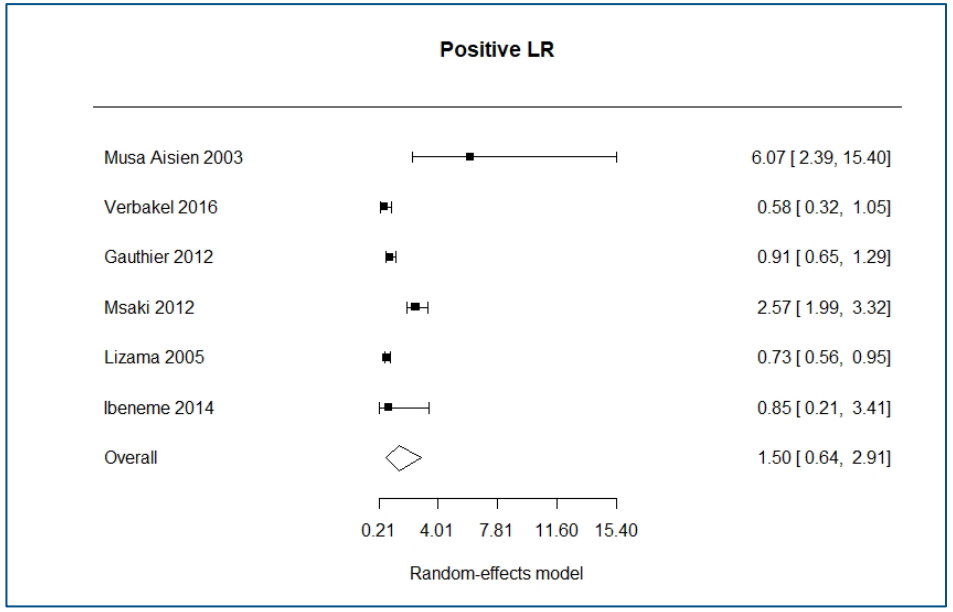


I^2 for sensitivity for abdominal pain = 91.0%

I^2 for specificity for abdominal pain = 98.9%

Likelihood ratios for abdominal pain (<2 years) (removing Pylkkanen 1979)

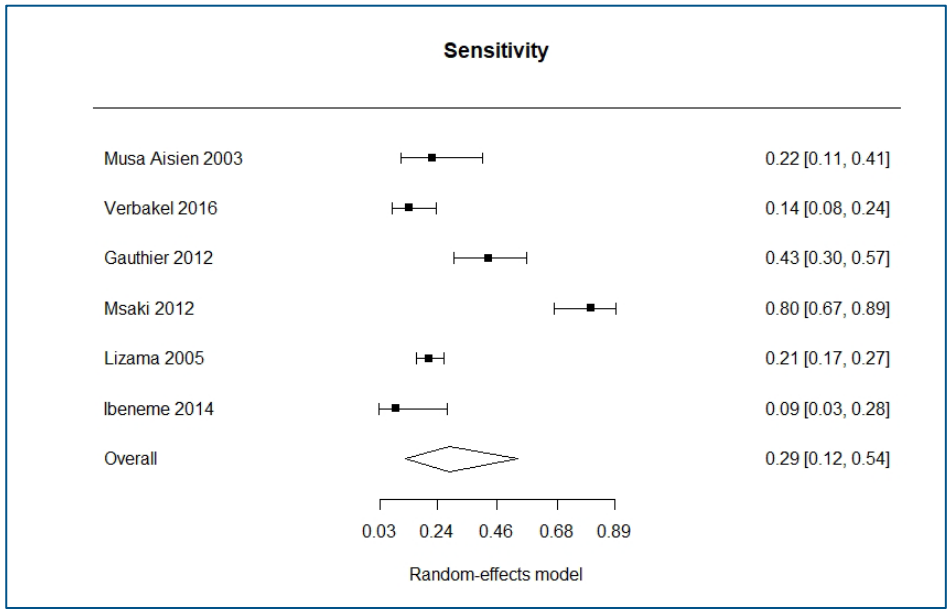


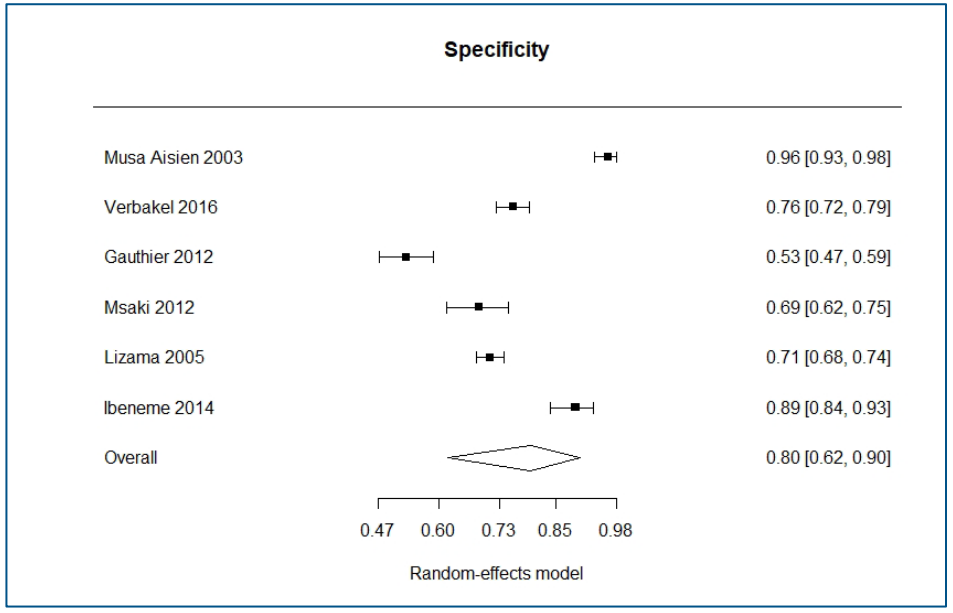


I^2 for negative LR for abdominal pain = 82.7%

I^2 for positive LR for abdominal pain = 92.6%

Sensitivity and specificity for abdominal pain (<2 years) (removing Pylkkanen 1979)



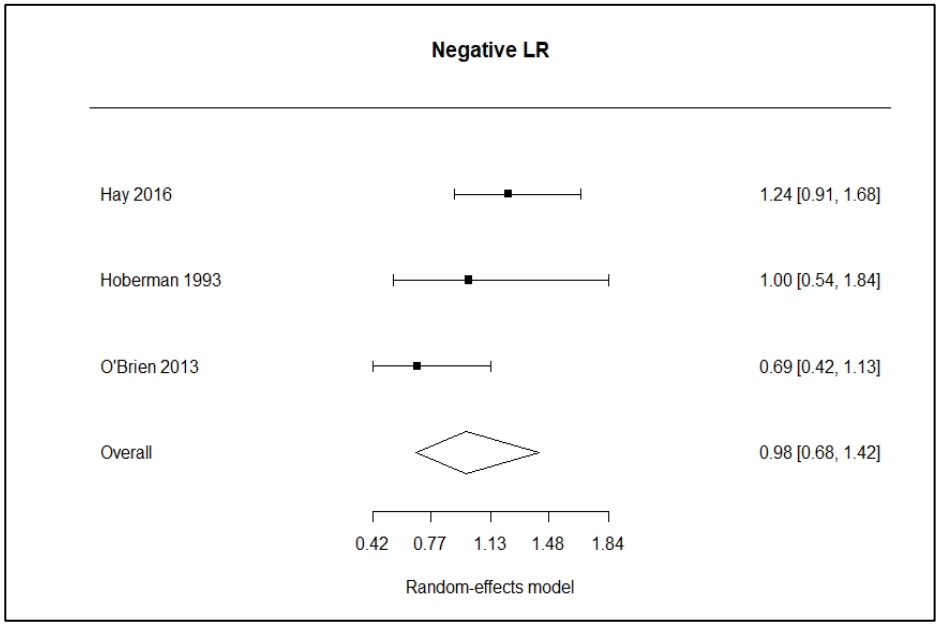


I^2 for sensitivity for abdominal pain = 91.9%

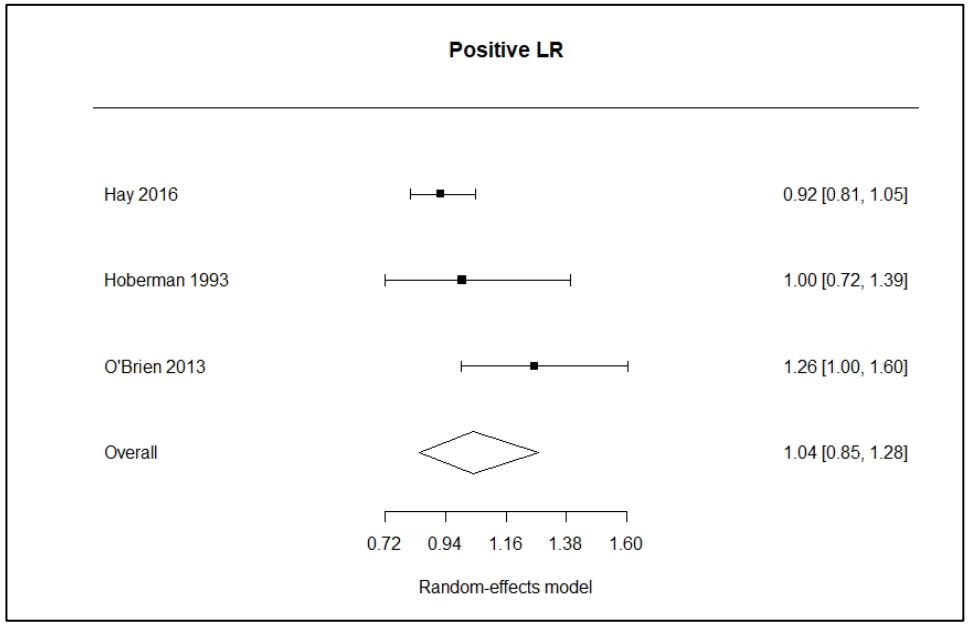
I^2 for specificity for abdominal pain = 96.1%

Poor feeding

Likelihood ratios for poor feeding (< 5 years)

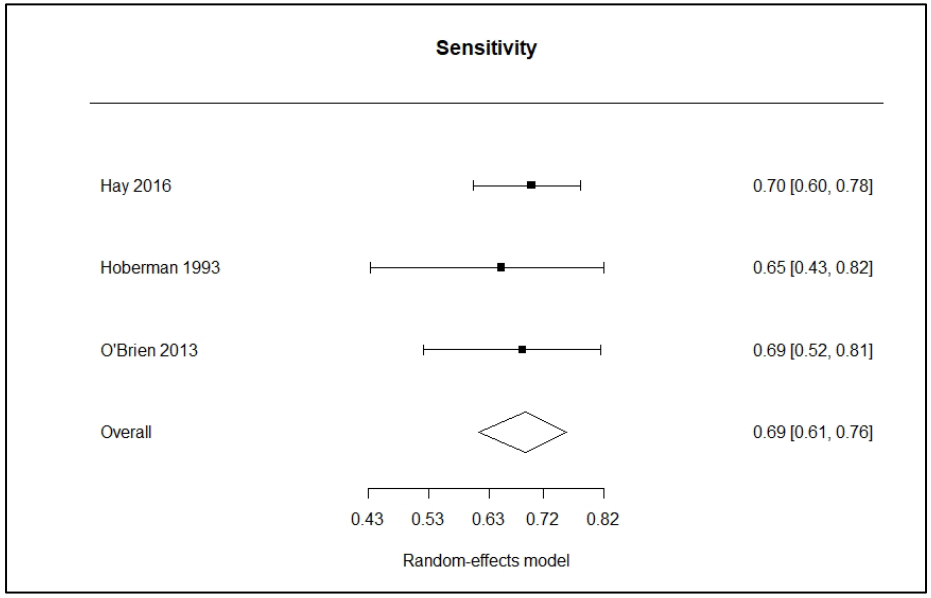


I^2 for negative LR for poor feeding = 49.2%

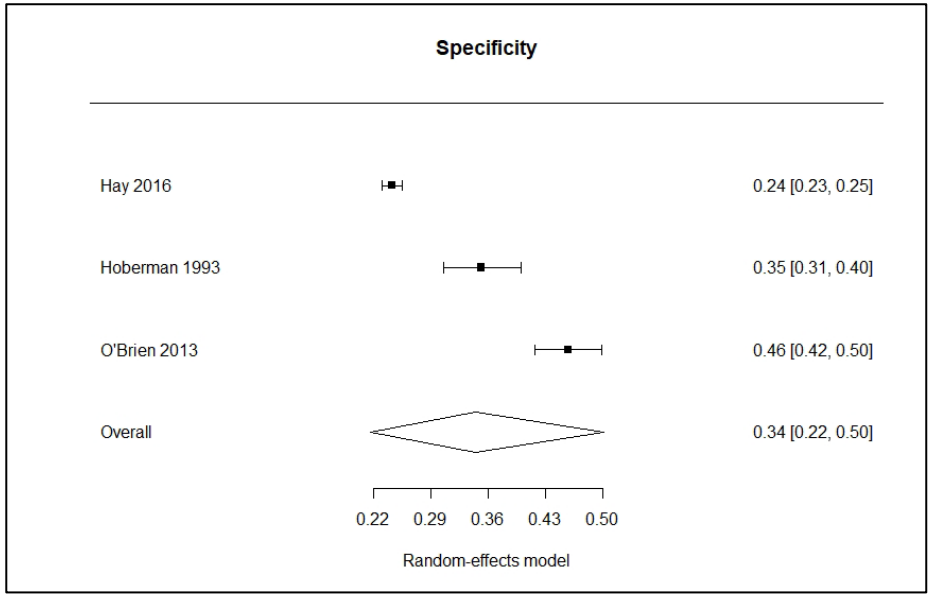


I^2 for positive LR for poor feeding = 61.3%

Sensitivity and specificity of poor feeding (< 5 years)

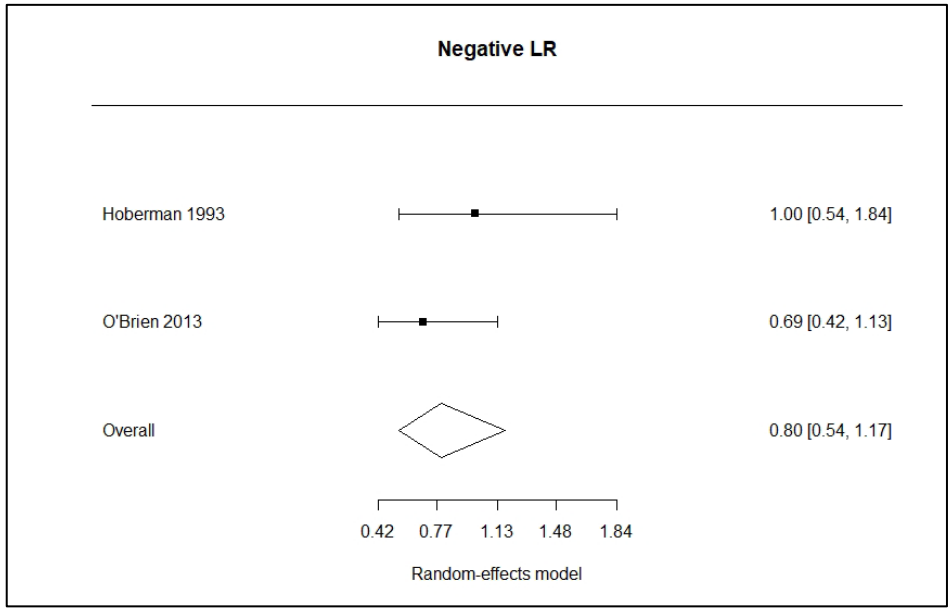


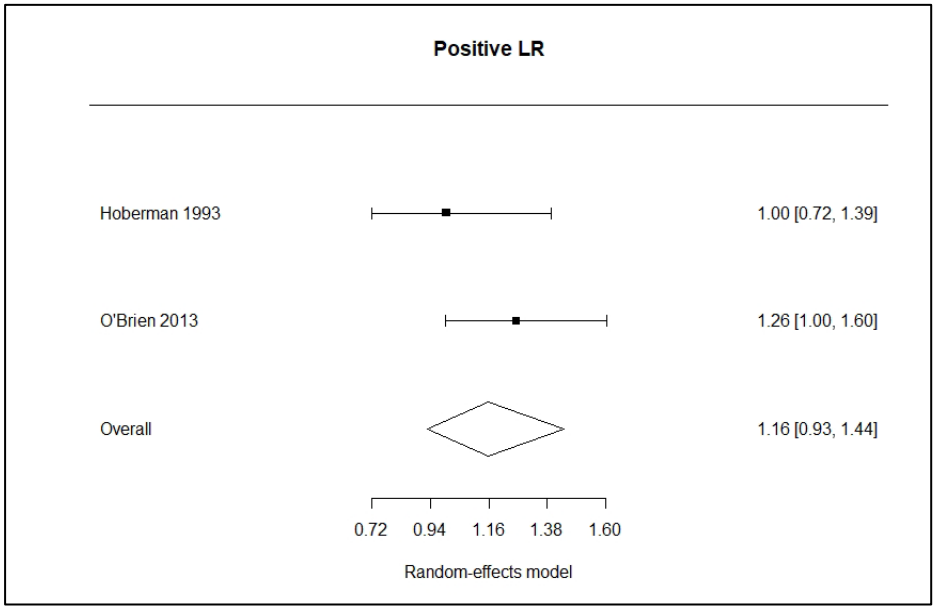
I^2 for sensitivity for poor feeding = 0.0%



I^2 for specificity for poor feeding = 98.4%

Likelihood ratios for poor feeding (<2 years)

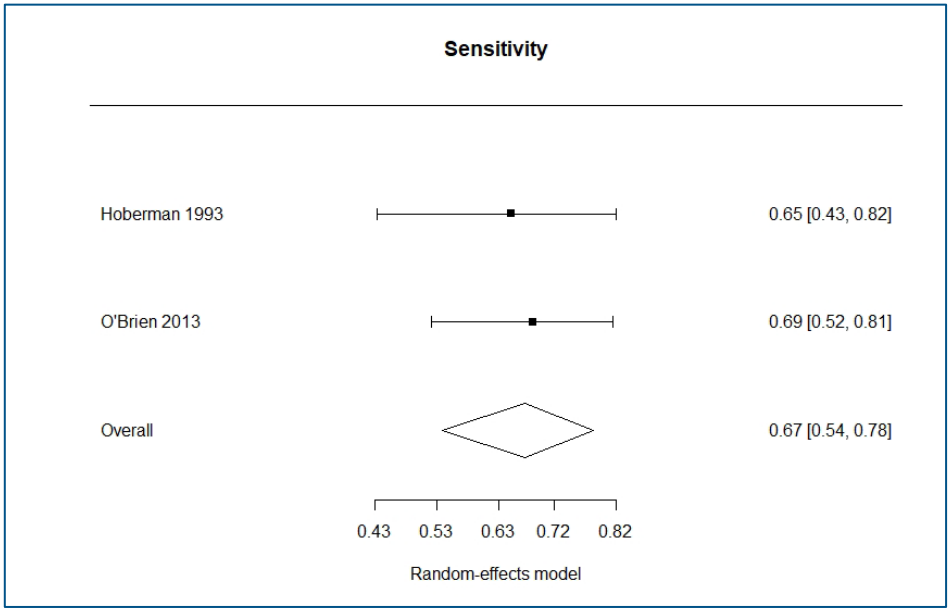




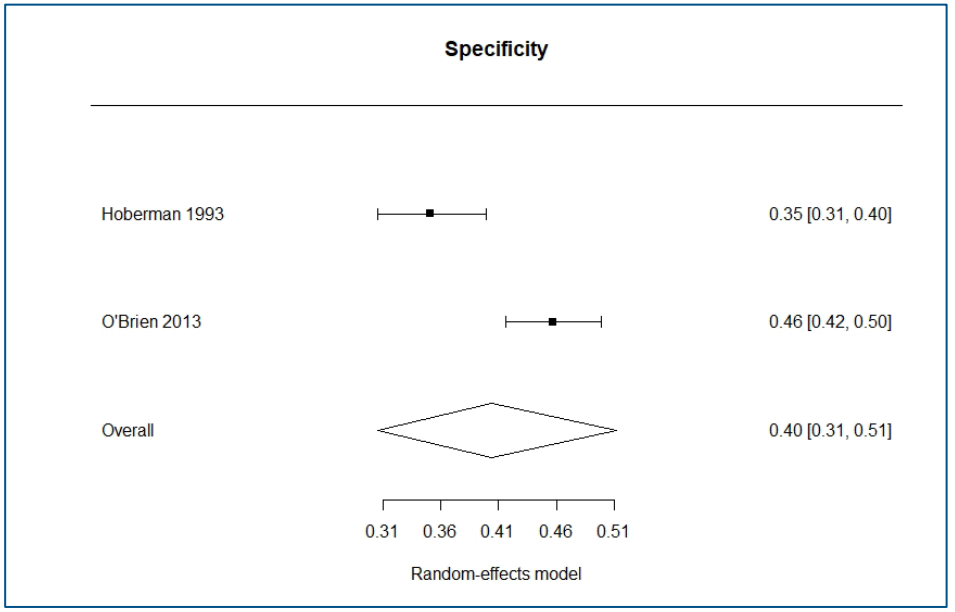
I^2 for negative LR for poor feeding = 0.0%

I^2 for positive LR for poor feeding = 20.6%

Sensitivity and specificity of poor feeding (<2 years)



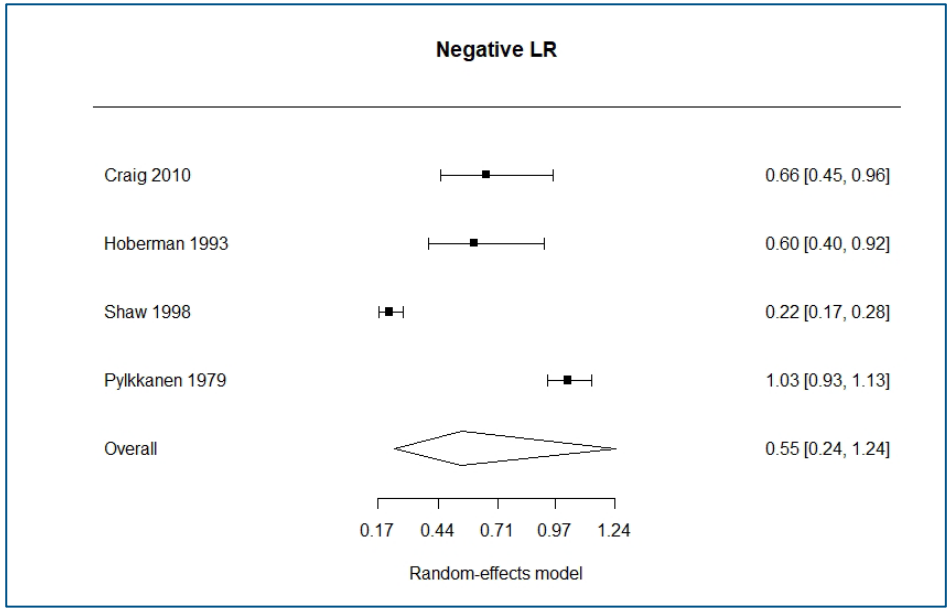
I^2 for sensitivity for poor feeding = 0.0%



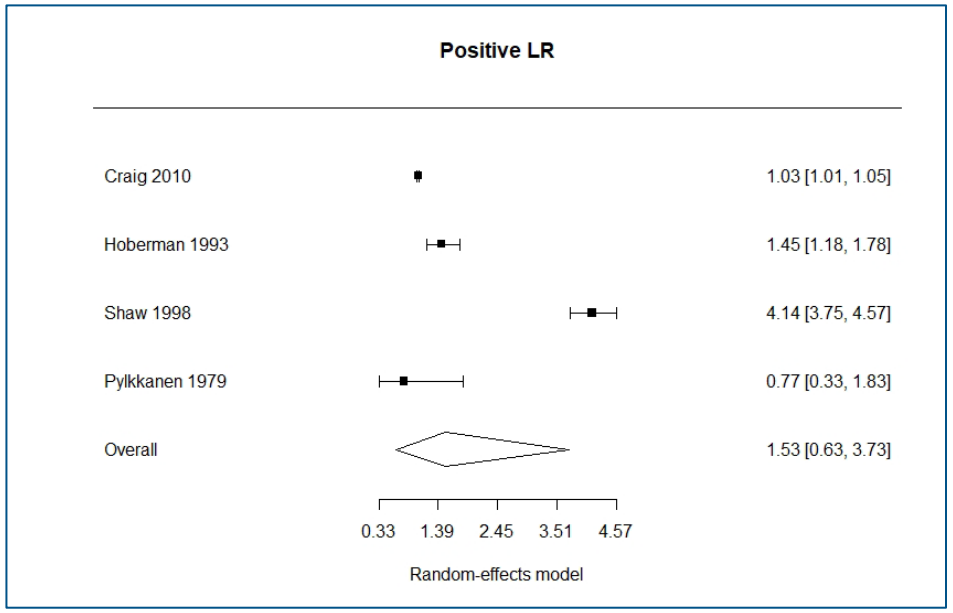
I^2 for specificity for poor feeding = 90.7%

No source of fever – main analysis

Likelihood ratios for no source of fever (< 5 years)

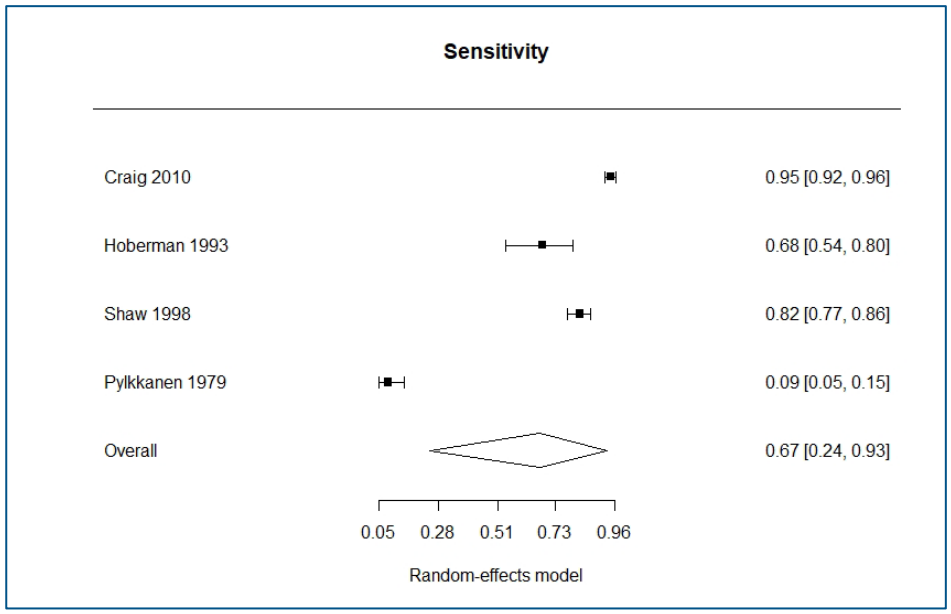


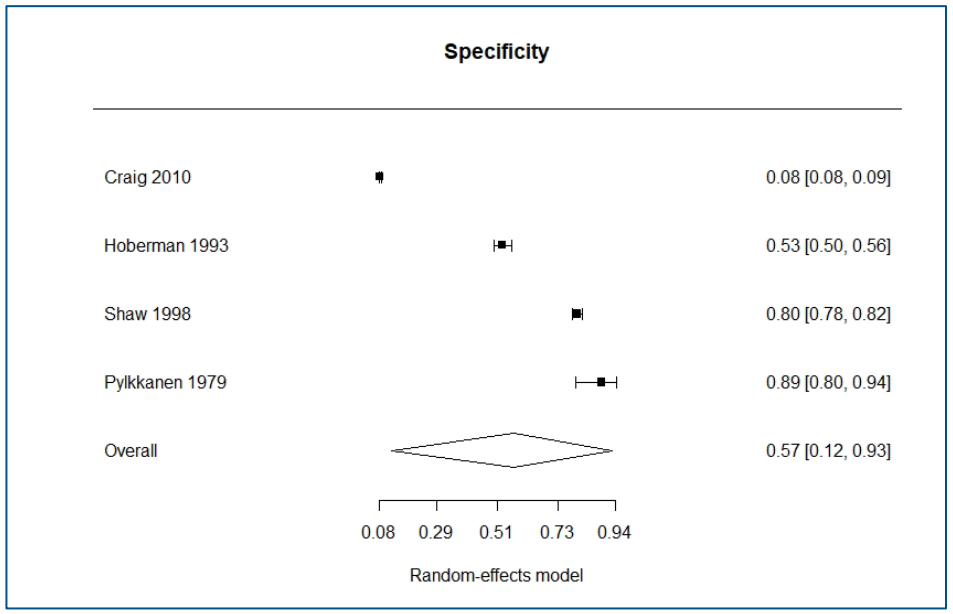
I^2 for negative LR for no source of fever = 97.6%



I^2 for positive LR for no source of fever = 99.6%

Sensitivity and specificity for no source of fever (< 5 years)

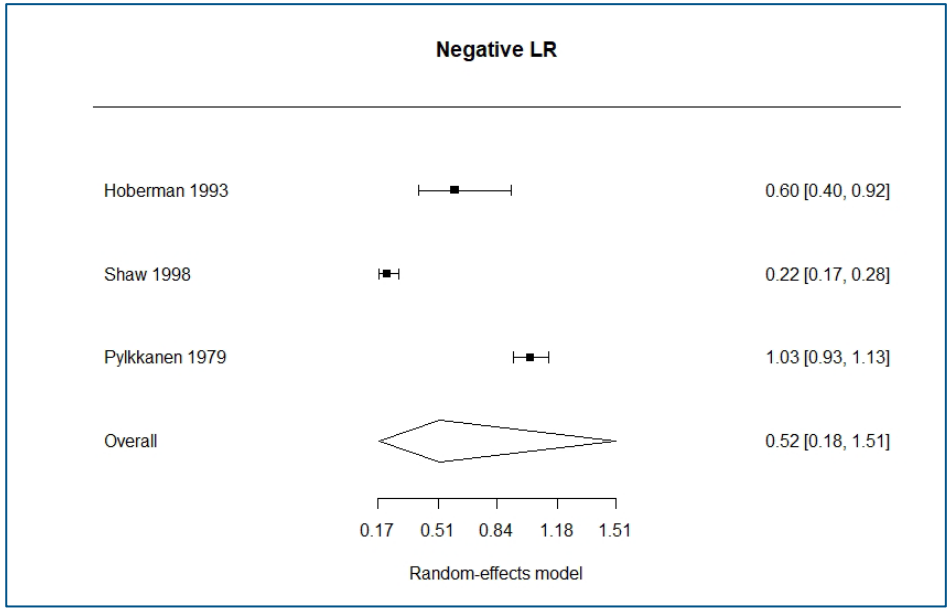


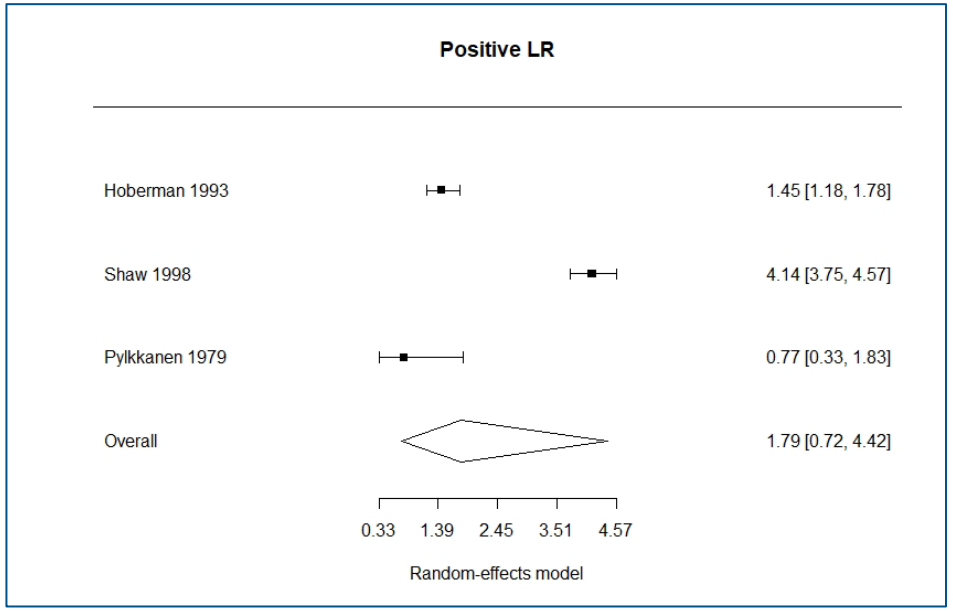


I^2 for sensitivity for no source of fever = 98.5%

I^2 for specificity for no source of fever = 99.9%

Likelihood ratios for no source of fever (<2 years)

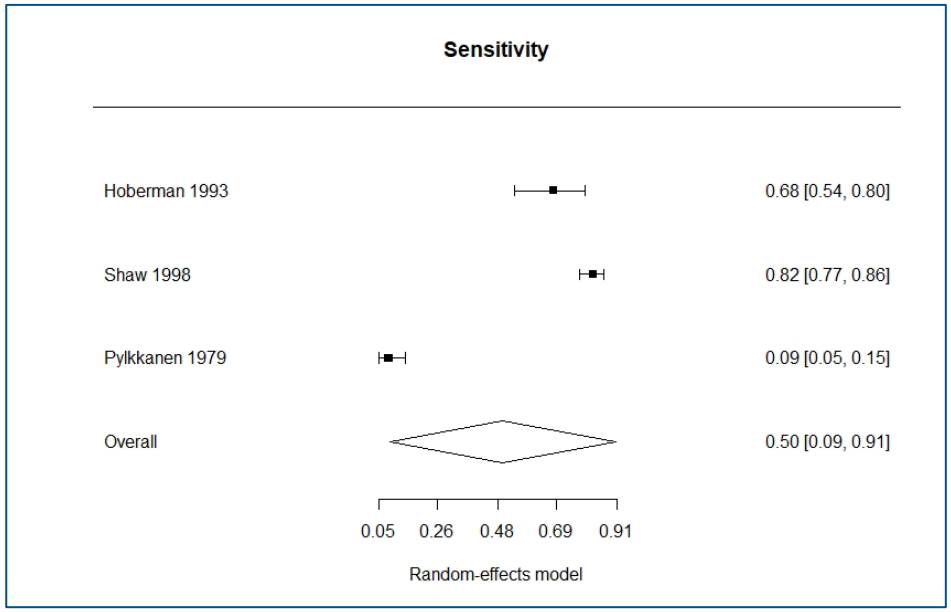


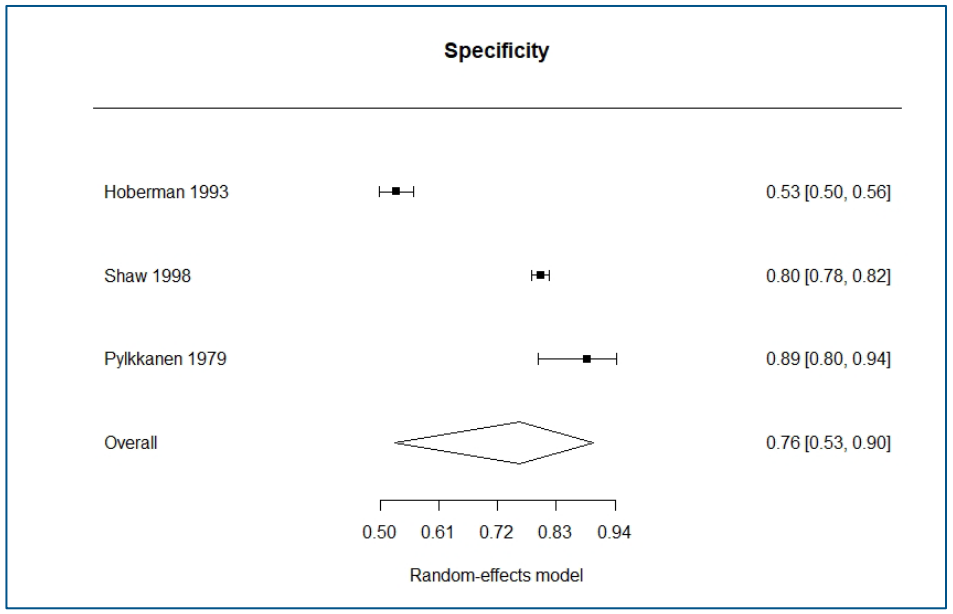


I^2 for negative LR for no source of fever = 98.4%

I^2 for positive LR for no source of fever = 97.8%

Sensitivity and specificity for no source of fever (<2 years)



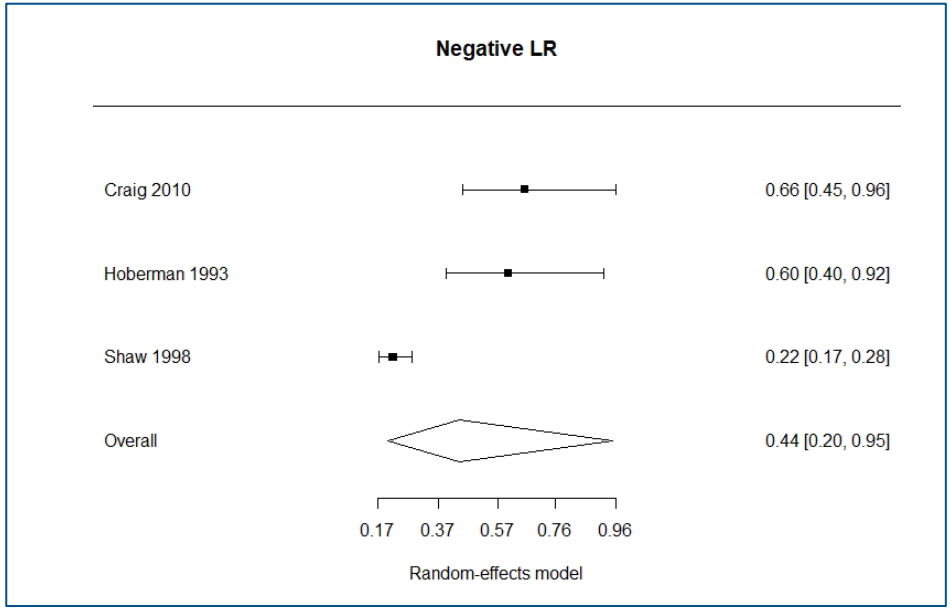


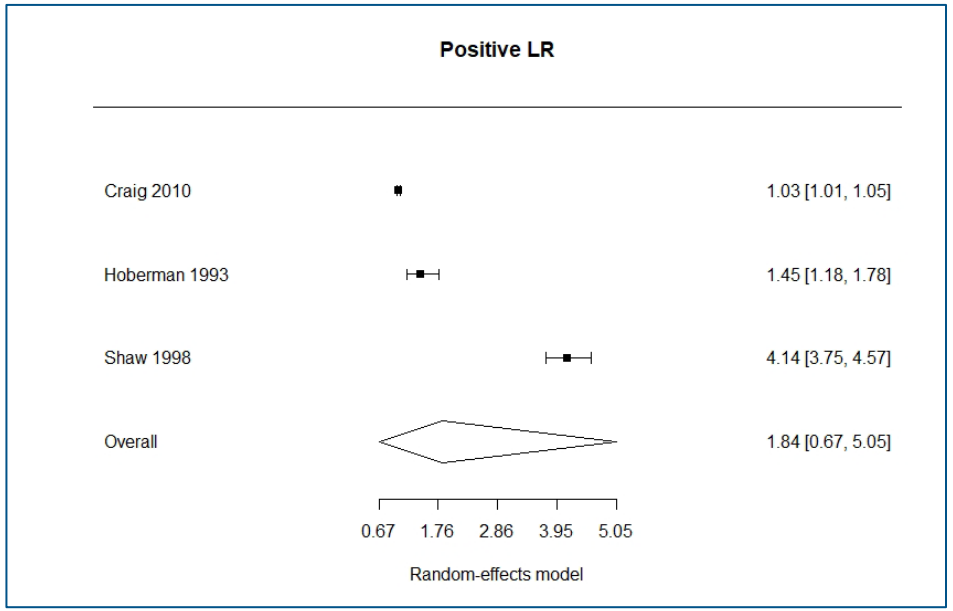
I^2 for sensitivity for no source of fever = 98.4%

I^2 for specificity for no source of fever = 99.1%

No source of fever – sensitivity analysis

Likelihood ratios for no source of fever (< 5 years) (removing Pylkkanen 1979)

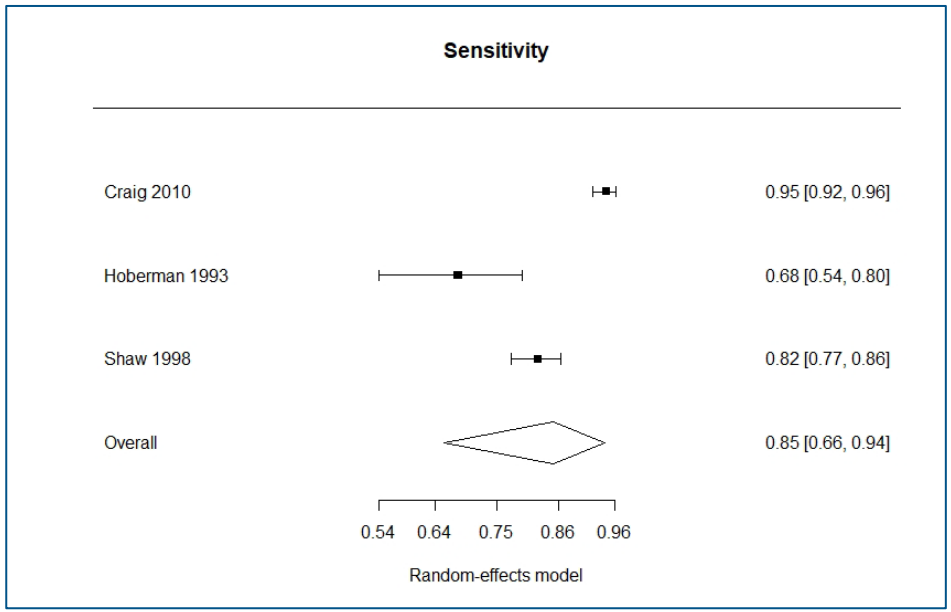


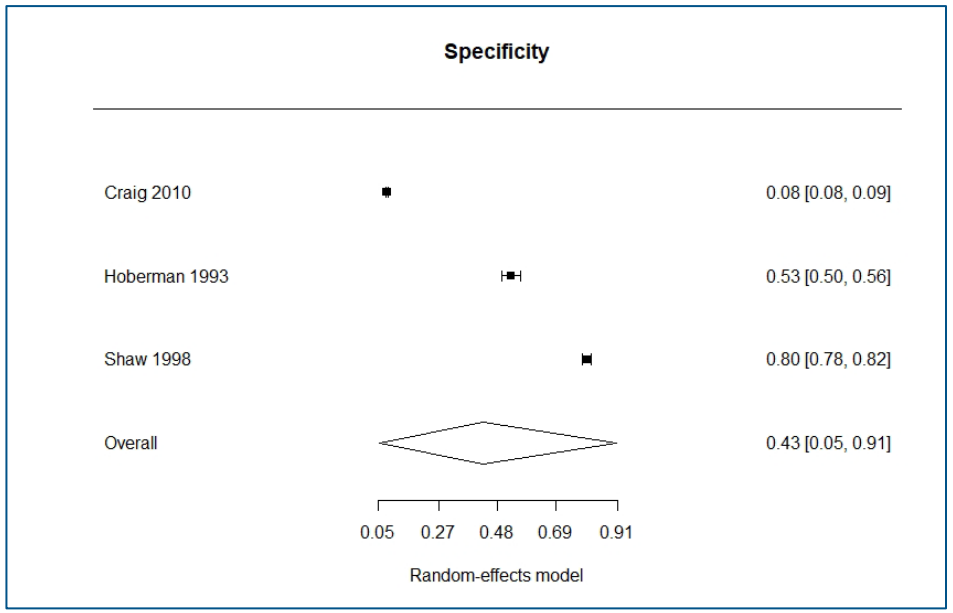


I^2 for negative LR for no source of fever = 93.3%

I^2 for positive LR for no source of fever = 99.7%

Sensitivity and specificity for no source of fever (< 5 years) (removing Pylkkanen 1979)

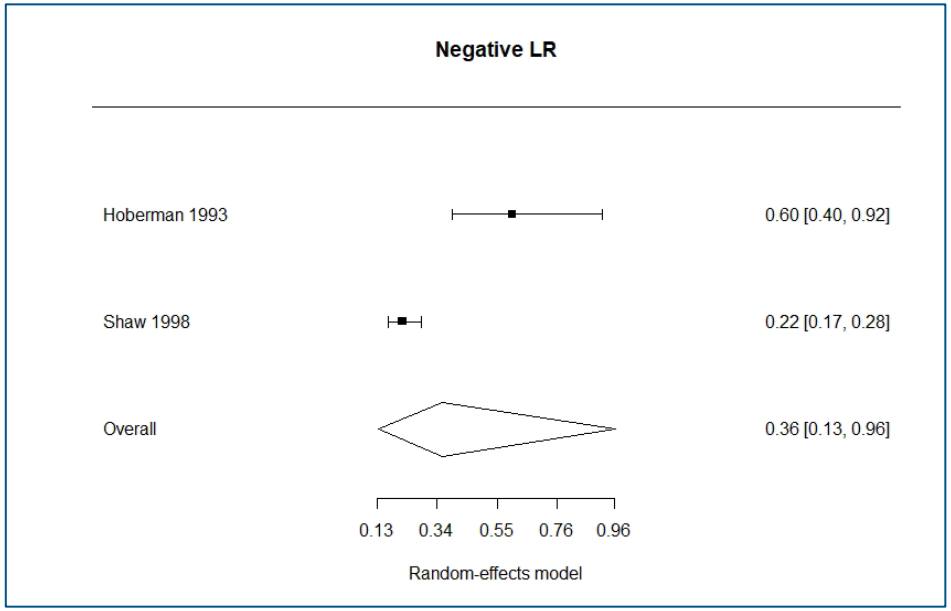


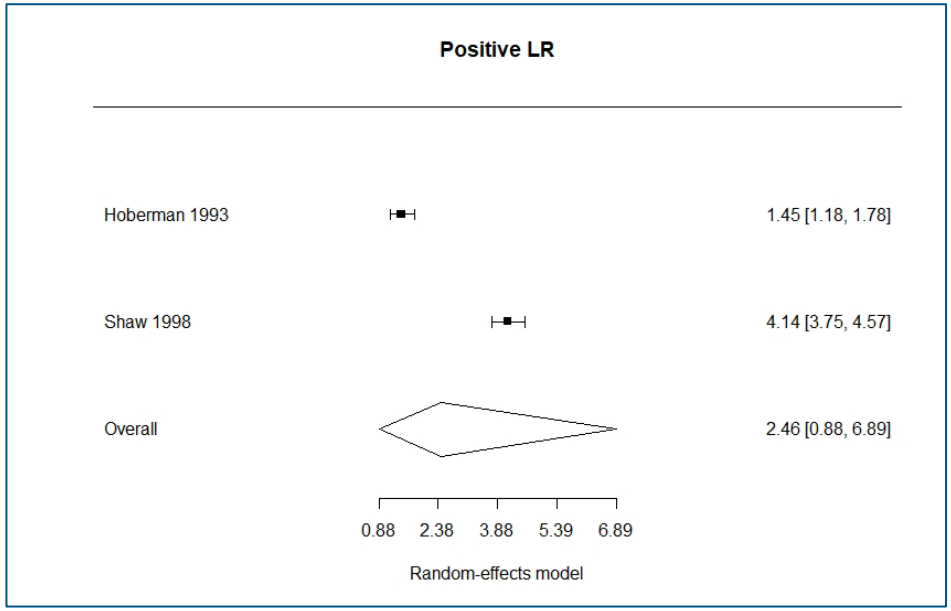


I^2 for sensitivity for no source of fever = 95.1%

I^2 for specificity for no source of fever = 100.0%

Likelihood ratios for no source of fever (<2 years) (removing Pylkkanen 1979)

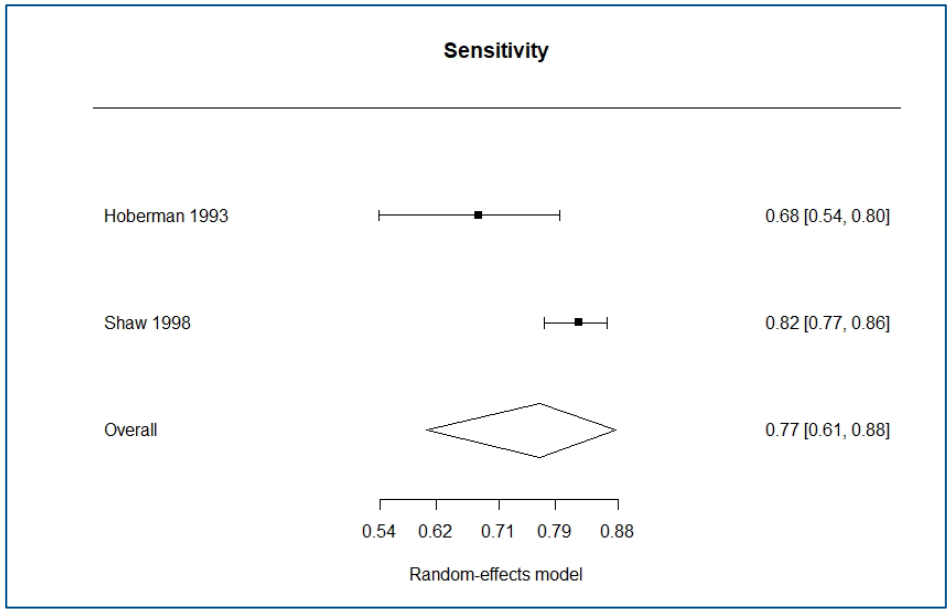


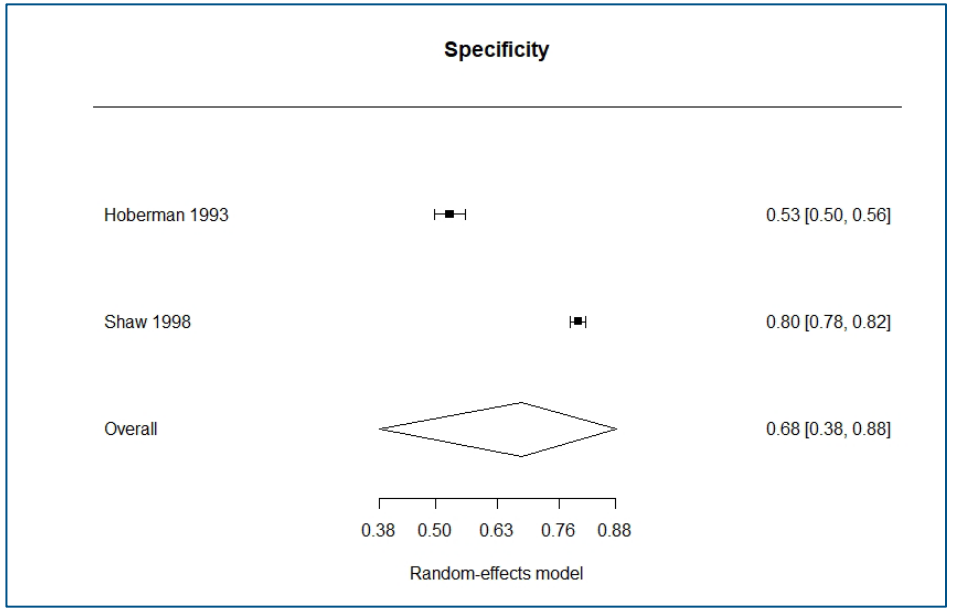


I^2 for negative LR for no source of fever = 93.8%

I^2 for positive LR for no source of fever = 98.8%

Sensitivity and specificity for no source of fever (<2 years) (removing Pylkkanen 1979)



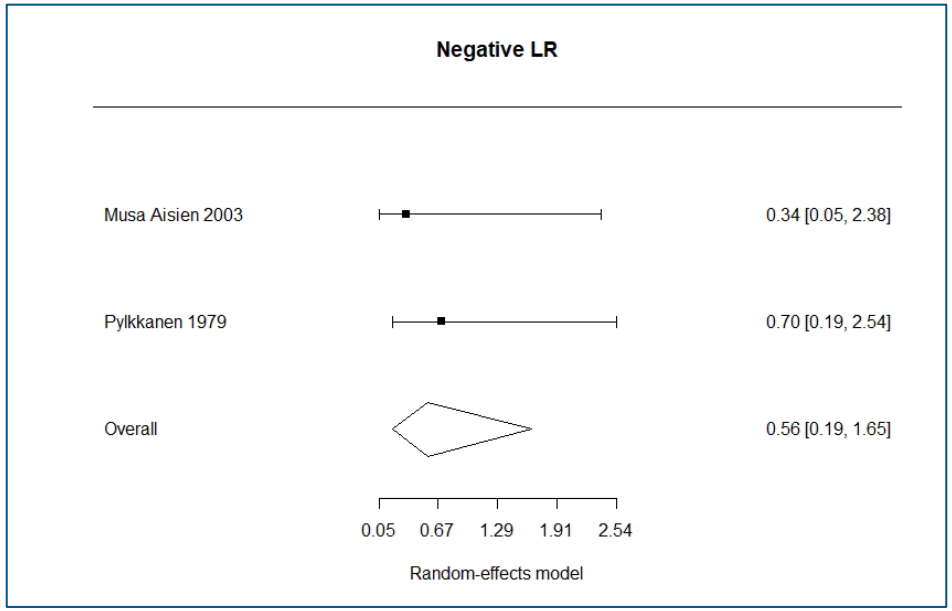


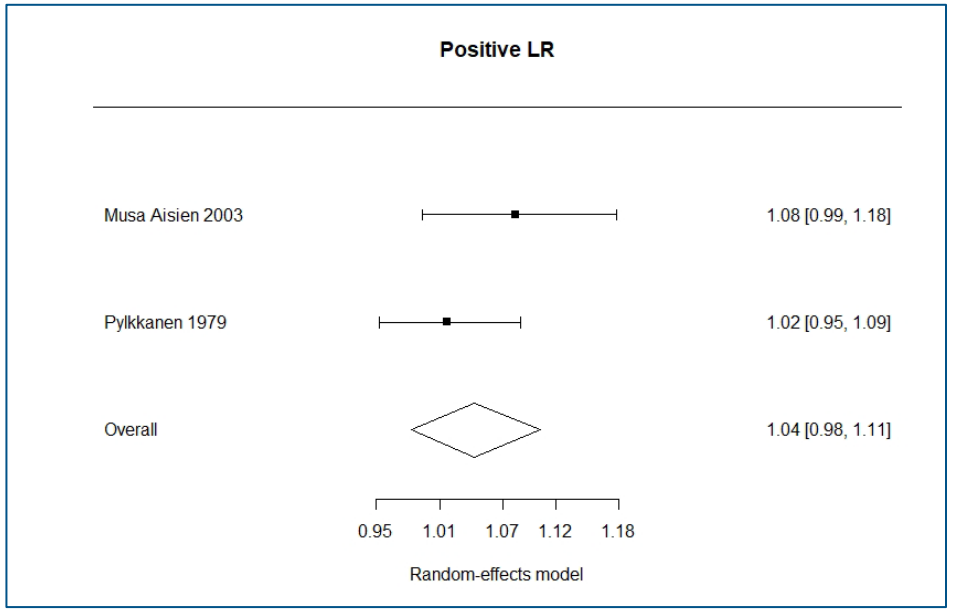
I^2 for sensitivity for no source of fever = 80.0%

I^2 for specificity for no source of fever = 99.6%

No convulsions

Likelihood ratios for no convulsions (data only reported for <2 years)

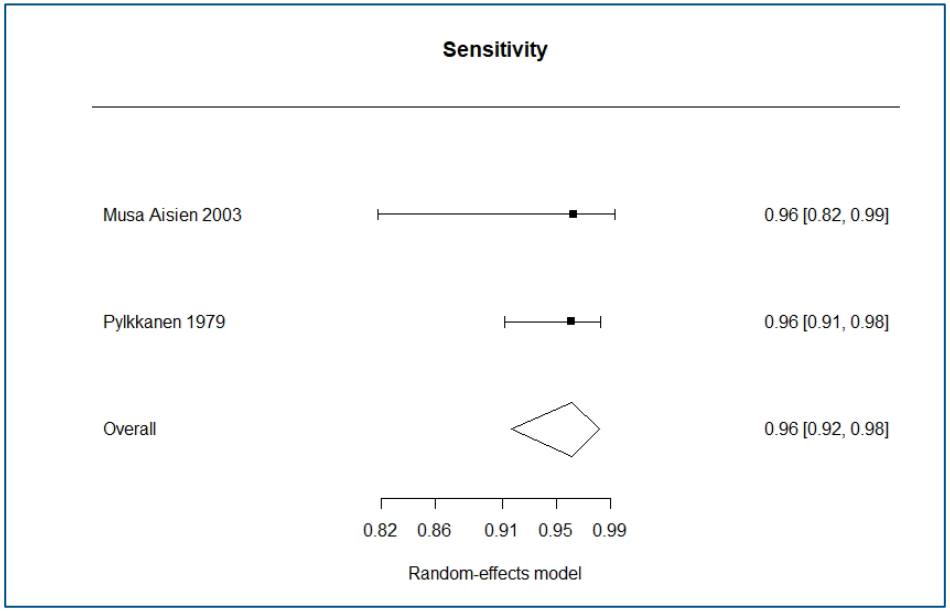




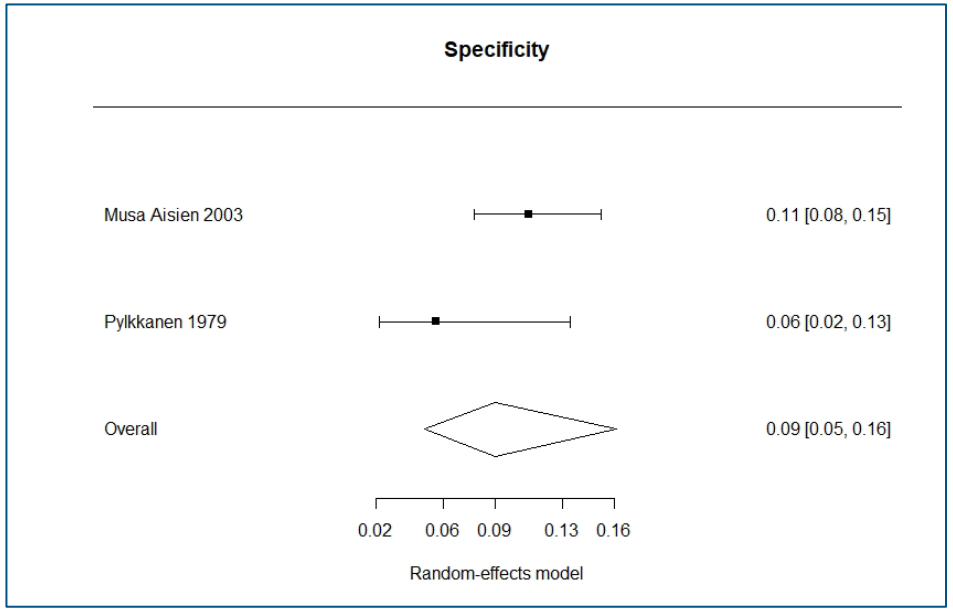
I^2 for negative LR for no convulsions = 0.0%

I^2 for positive LR for no convulsions = 20.0%

Sensitivity and specificity for no convulsions (data only reported for <2 years)



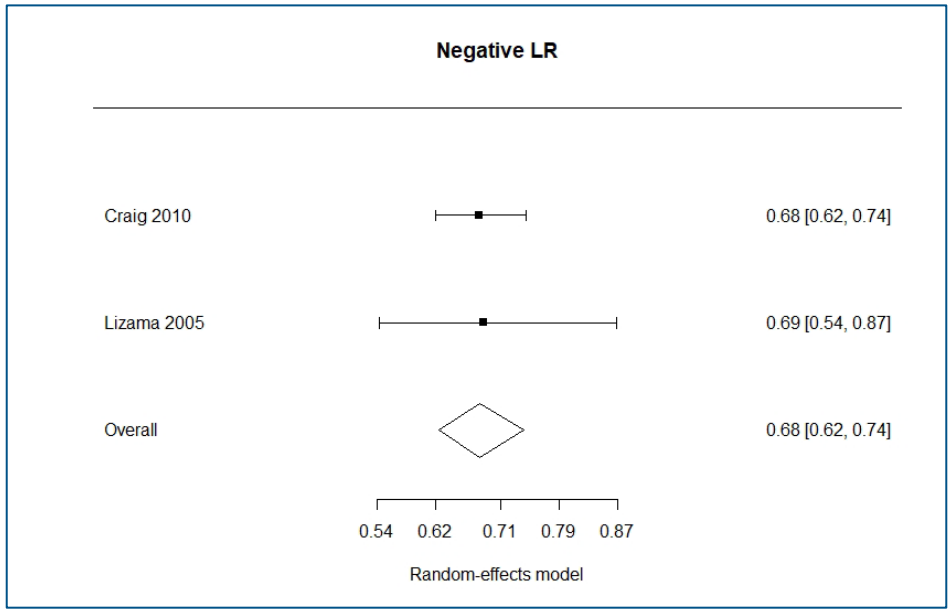
I^2 for sensitivity for no convulsions = 0.0%

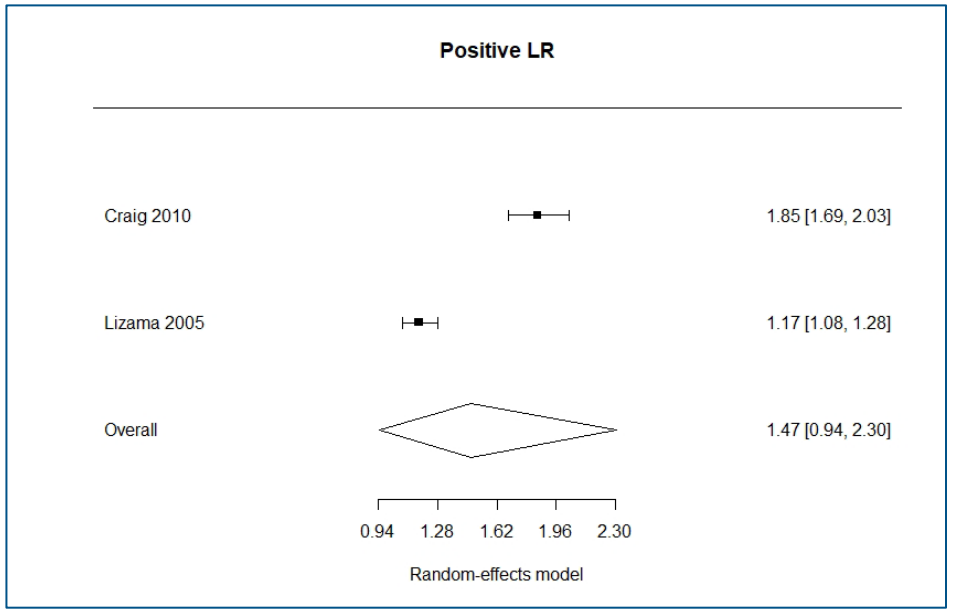


I^2 for specificity for no convulsions = 45.0%

No respiratory symptoms

Likelihood ratios for no respiratory symptoms (< 5 years)

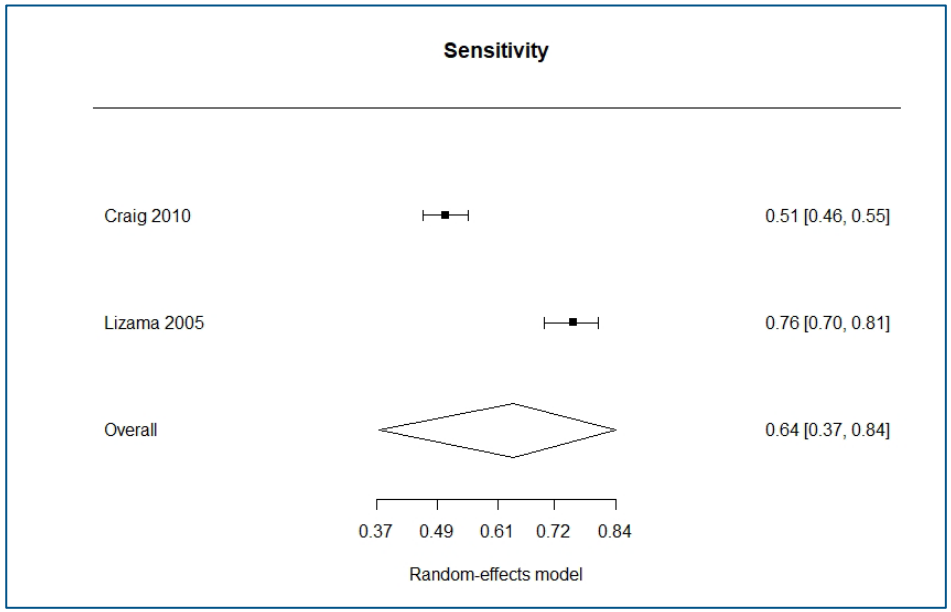


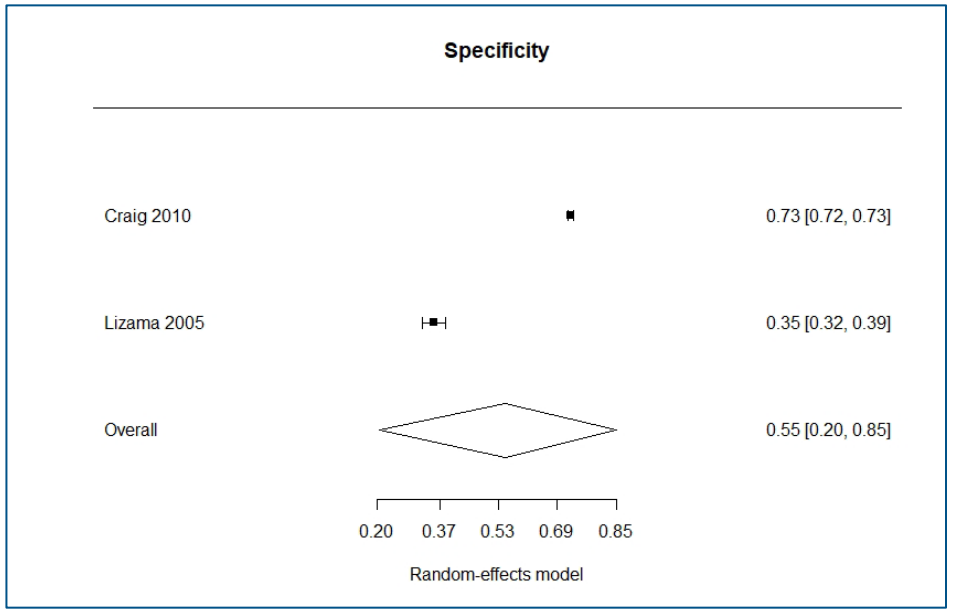


I^2 for negative LR for no respiratory symptoms = 0.0%

I^2 for positive LR for no respiratory symptoms = 98.0%

Sensitivity and specificity for no respiratory symptoms (< 5 years)



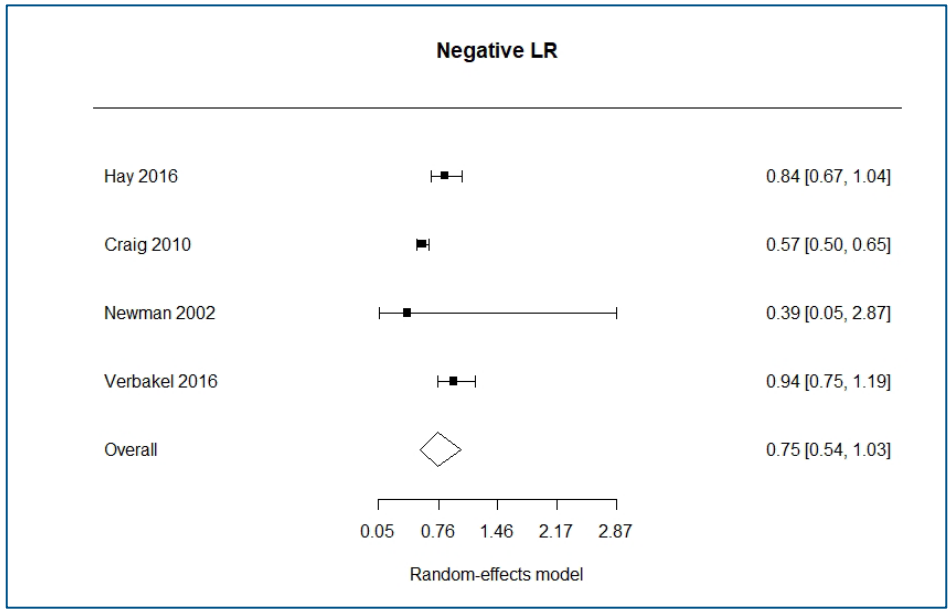


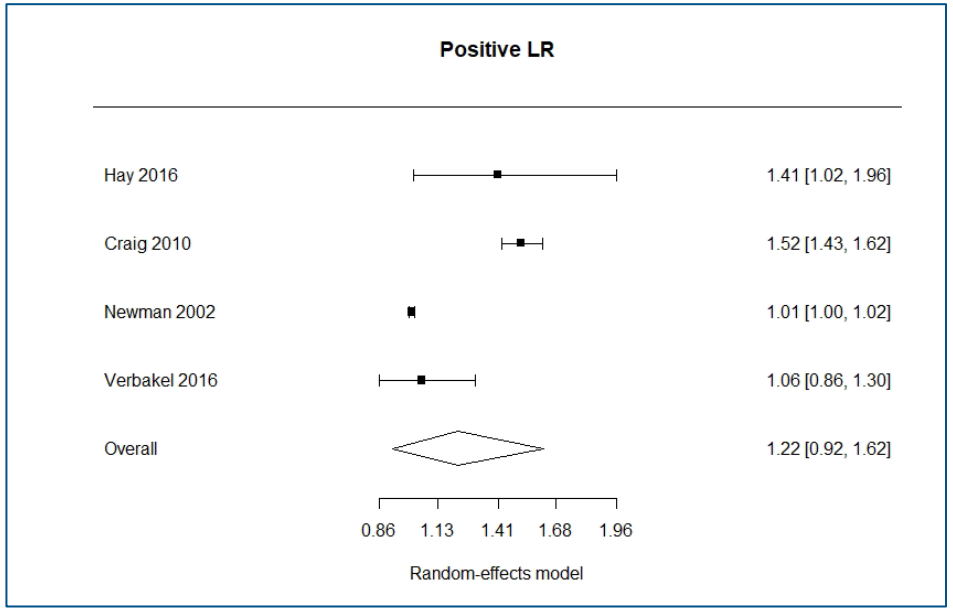
I^2 for sensitivity for no respiratory symptoms = 97.6%

I^2 for specificity for no respiratory symptoms = 99.8%

No cough

Likelihood ratios for no cough (< 5 years)

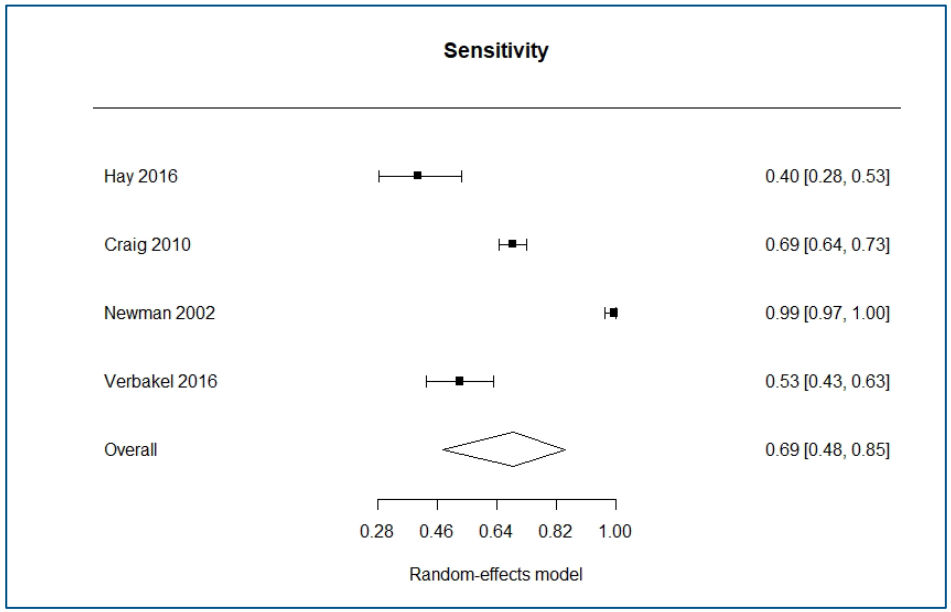


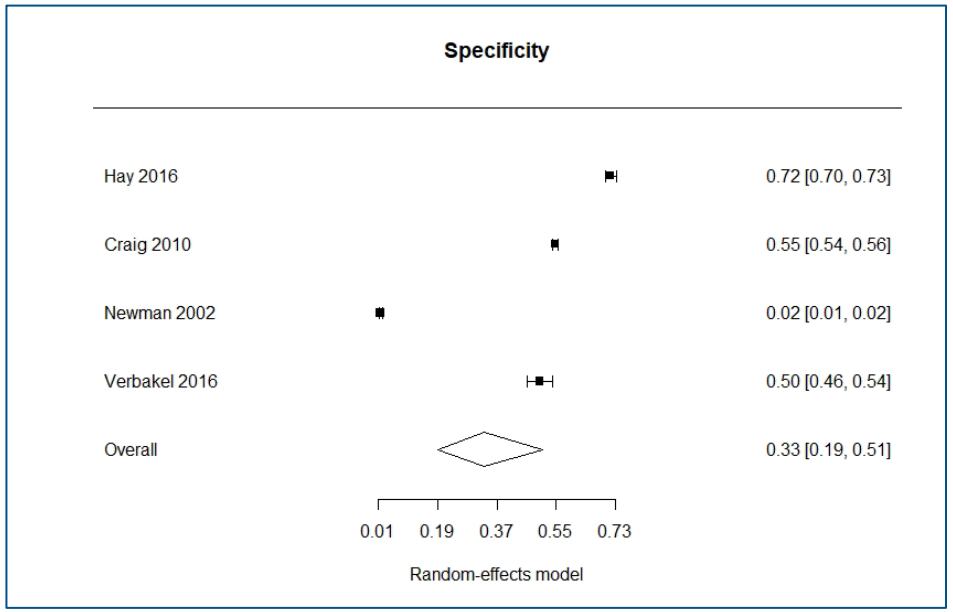


I^2 for negative LR for no cough = 83.3%

I^2 for positive LR for no cough = 98.1%

Sensitivity and specificity for no cough (< 5 years)

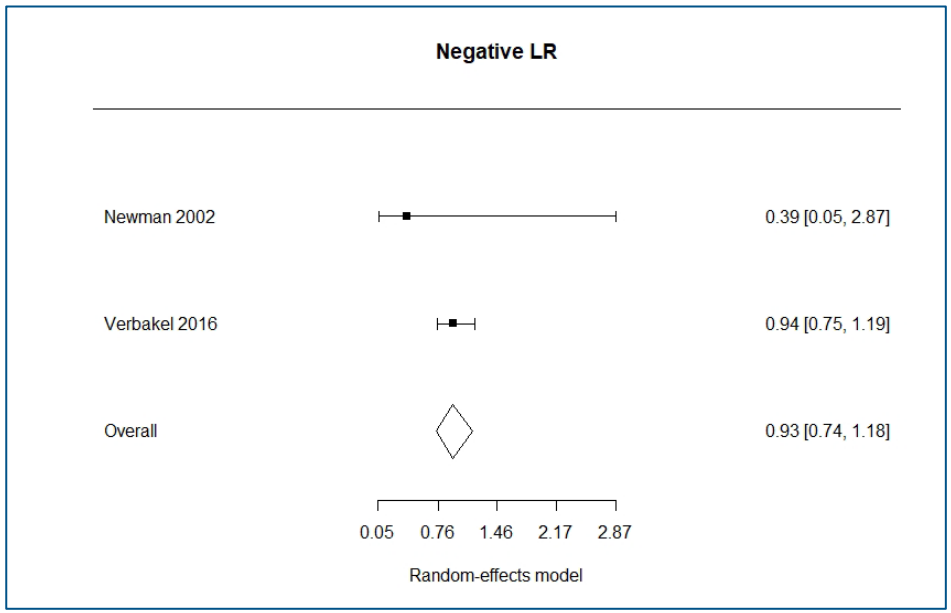


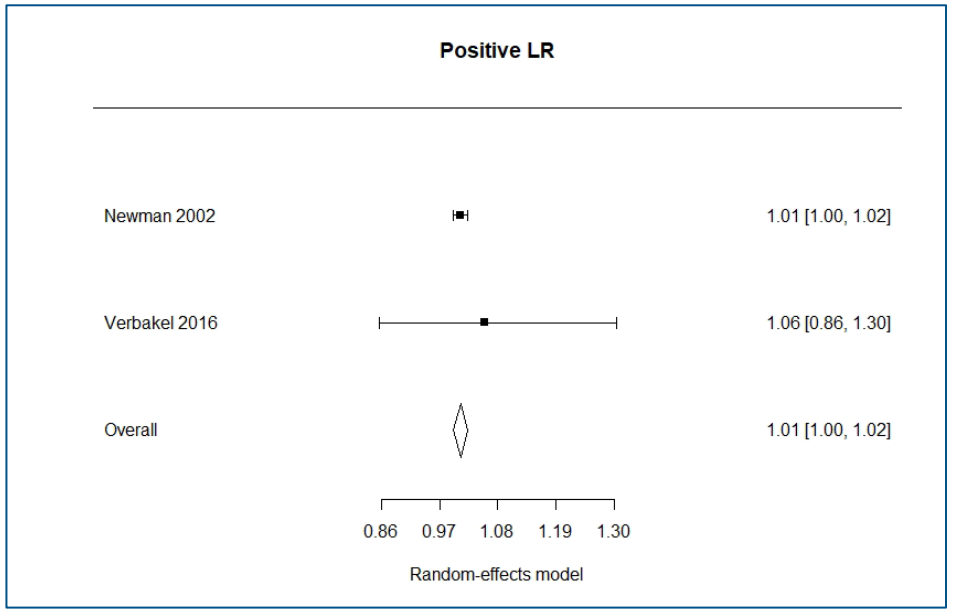


I^2 for sensitivity for no cough = 92.9%

I^2 for specificity for no cough = 99.6%

Likelihood ratios for no cough (<2 years)

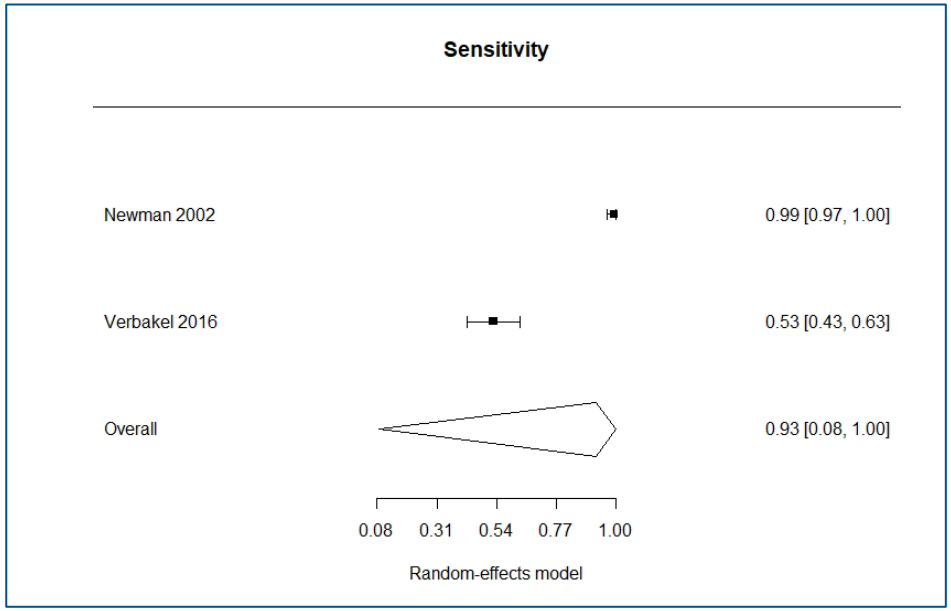


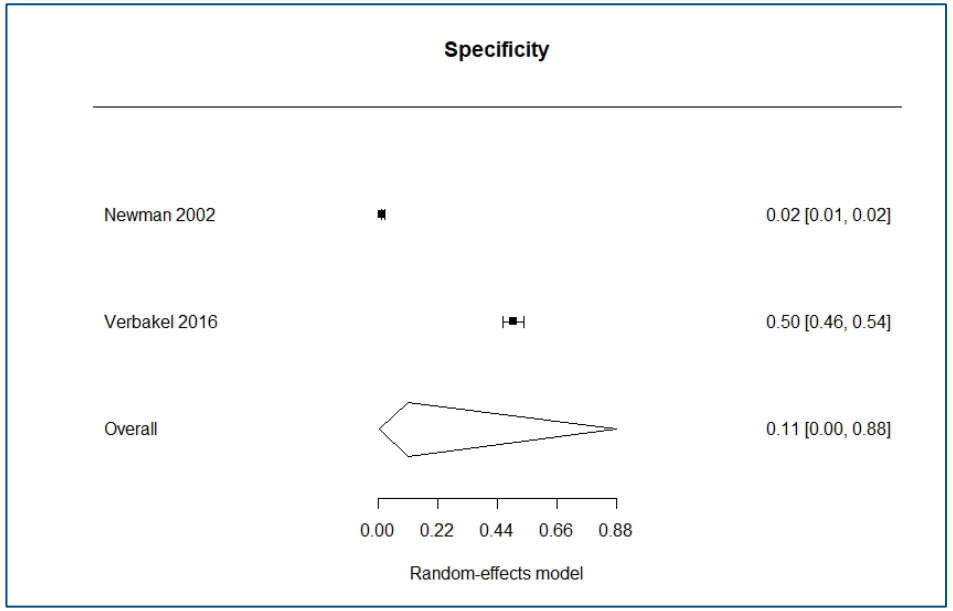


I^2 for negative LR for no cough = 0.0%

I^2 for positive LR for no cough = 0.0%

Sensitivity and specificity for no cough (<2 years)



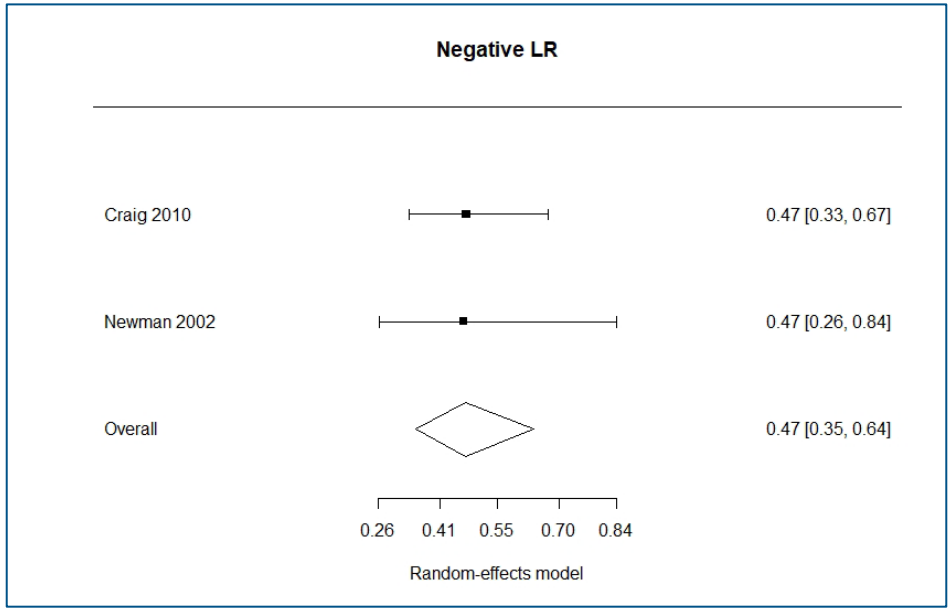


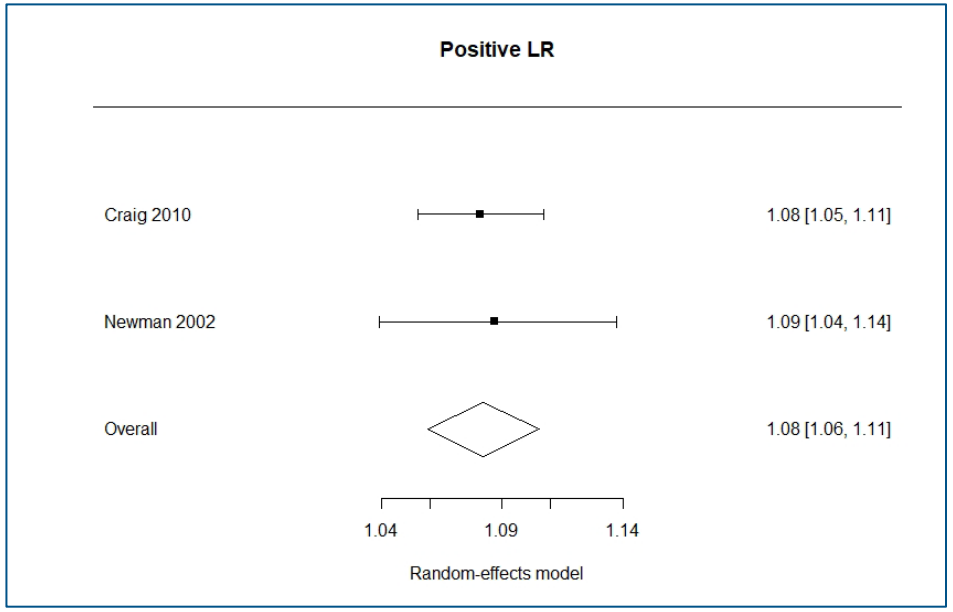
I^2 for sensitivity for no cough = 95.8%

I^2 for specificity for no cough = 99.7%

No breathing difficulty

Likelihood ratios for no breathing difficulty (< 5 years)

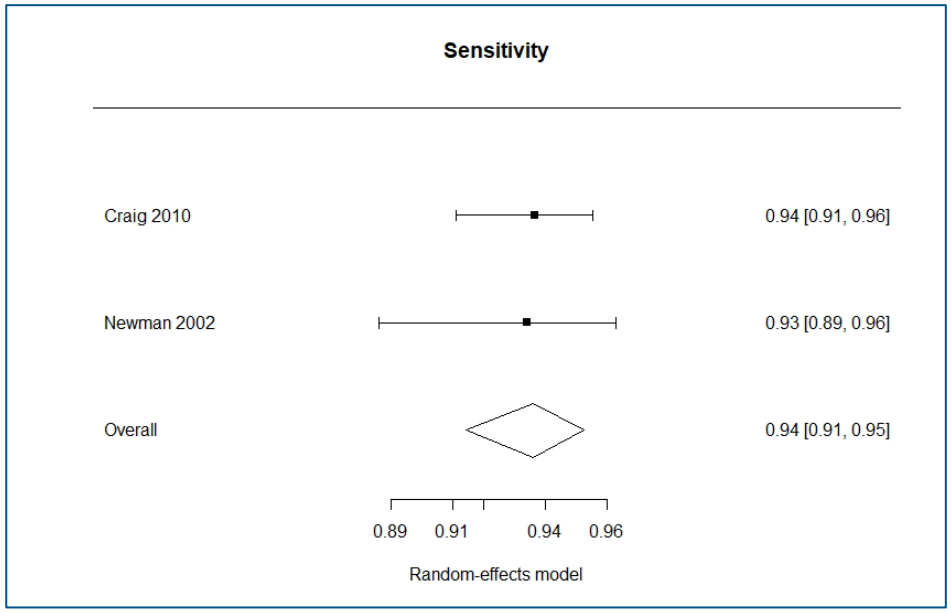


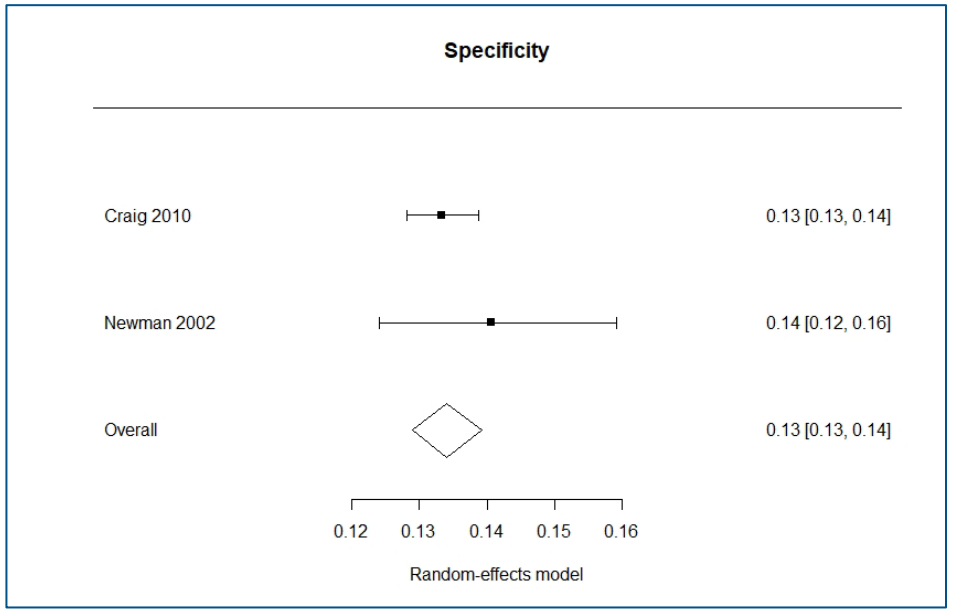


I^2 for negative LR for no breathing difficulty = 0.0%

I^2 for positive LR for no breathing difficulty = 0.0%

Sensitivity and specificity for no breathing difficulty (< 5 years)



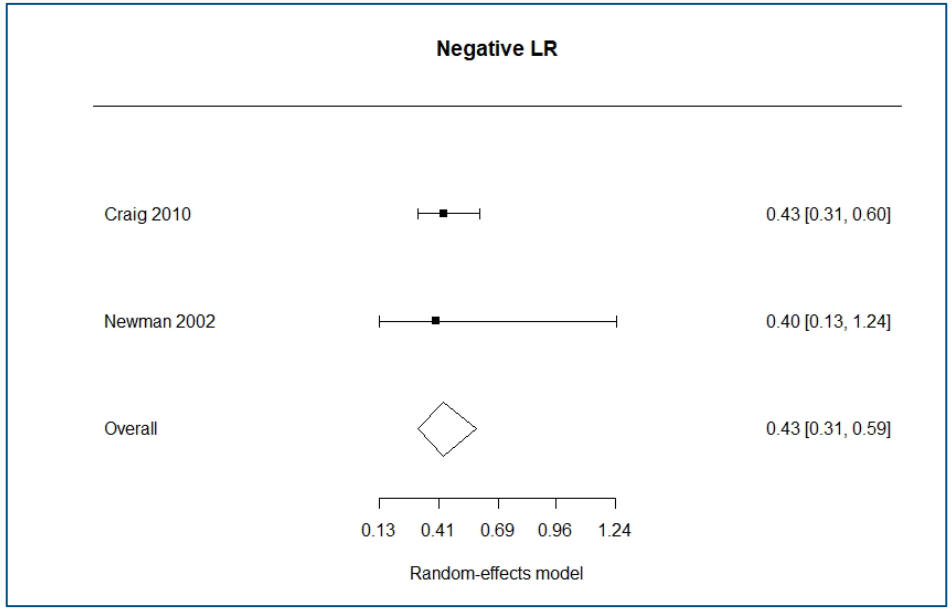


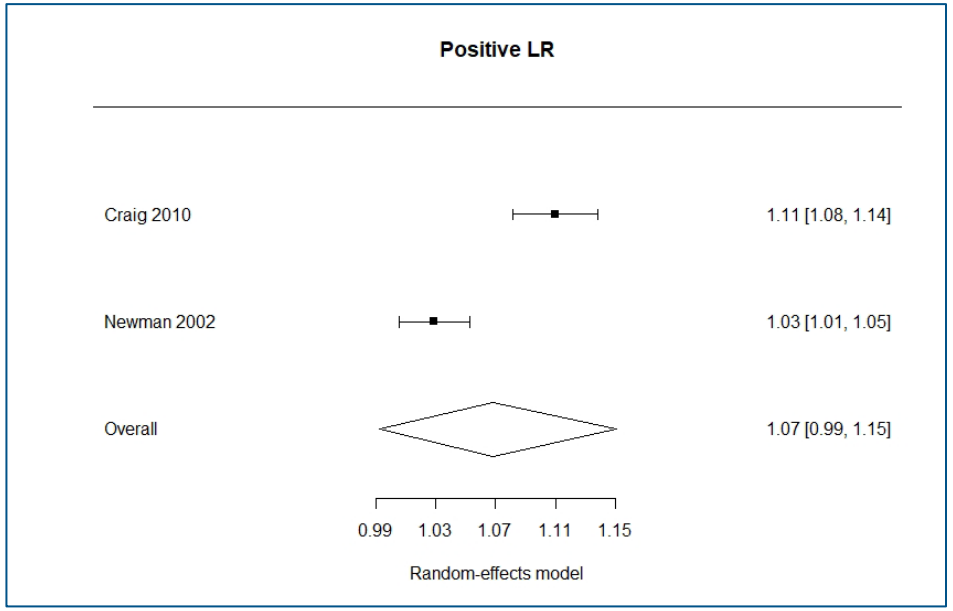
I^2 for sensitivity for no breathing difficulty = 0.0%

I^2 for specificity for no breathing difficulty = 0.0%

No abnormal chest sounds

Likelihood ratios for no abnormal chest sounds (< 5 years)

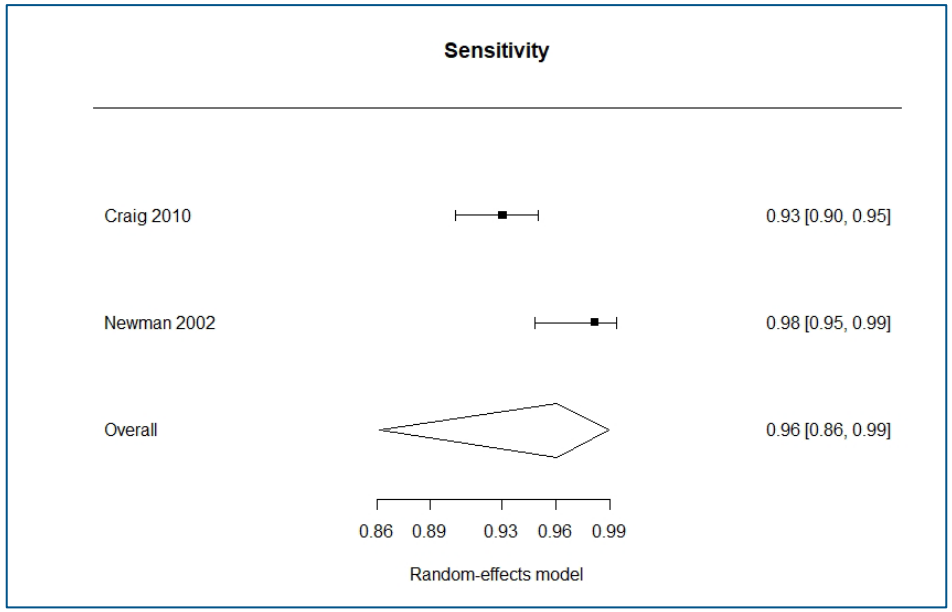


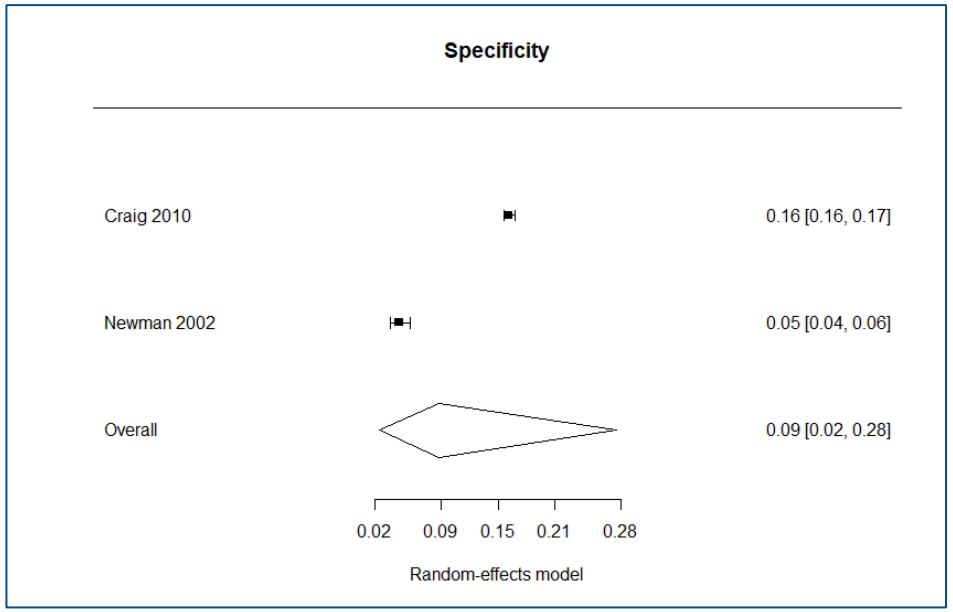


I^2 for negative LR for no abnormal chest sounds = 0.0%

I^2 for positive LR for no abnormal chest sounds = 94.6%

Sensitivity and specificity for no abnormal chest sounds (< 5 years)



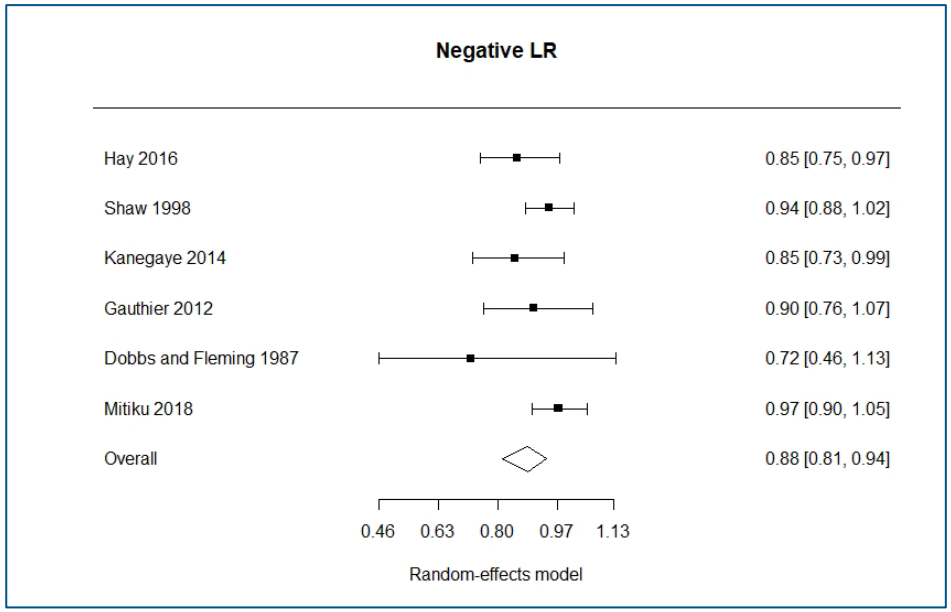


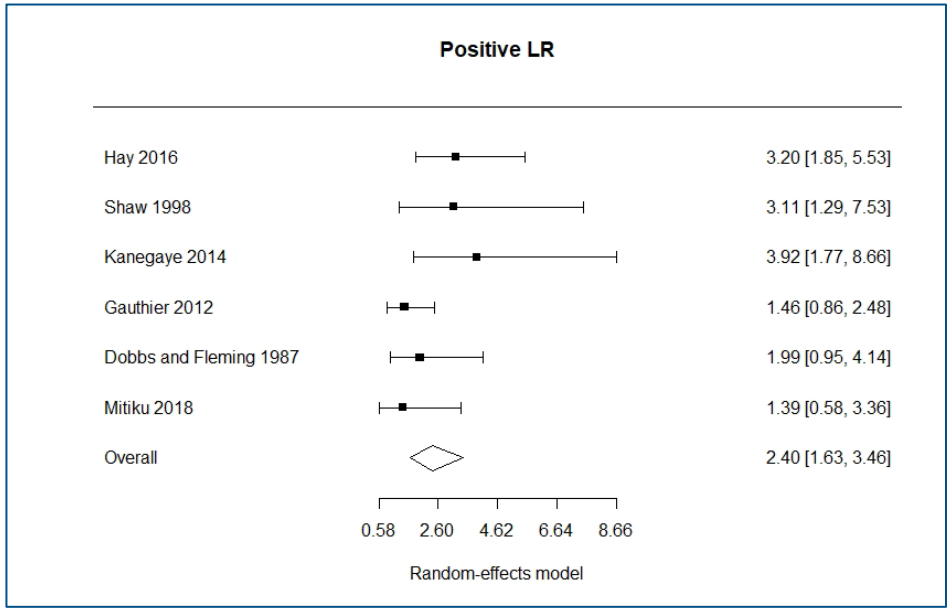
I^2 for sensitivity for no abnormal chest sounds = 81.3%

I^2 for specificity for no abnormal chest sounds = 99.2%

Previous urinary tract infection

Likelihood ratios for previous UTI (< 15 years)

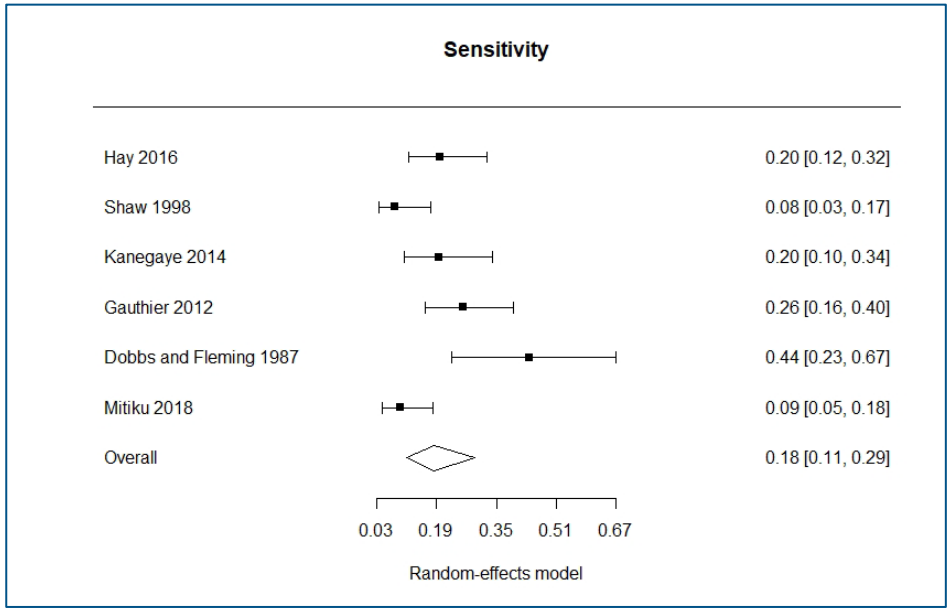


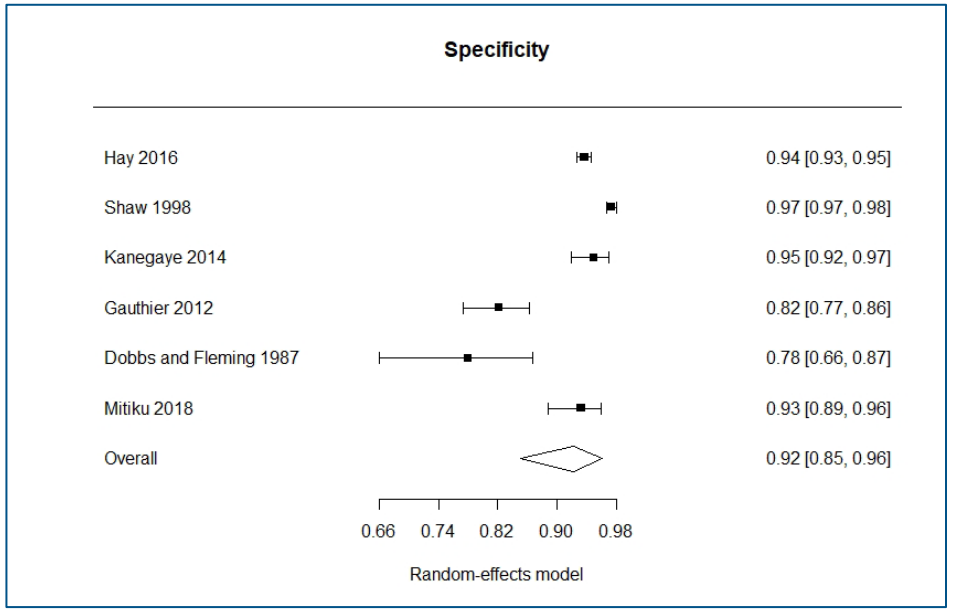


I^2 for negative LR for previous UTI = 11.6%

I^2 for positive LR for previous UTI = 35.6%

Sensitivity and specificity for previous UTI (< 15 years)

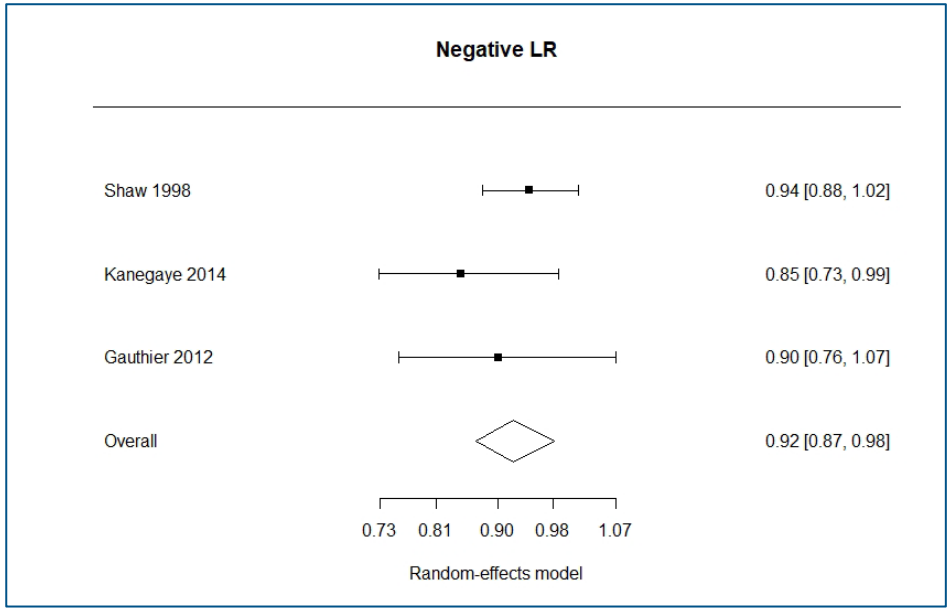


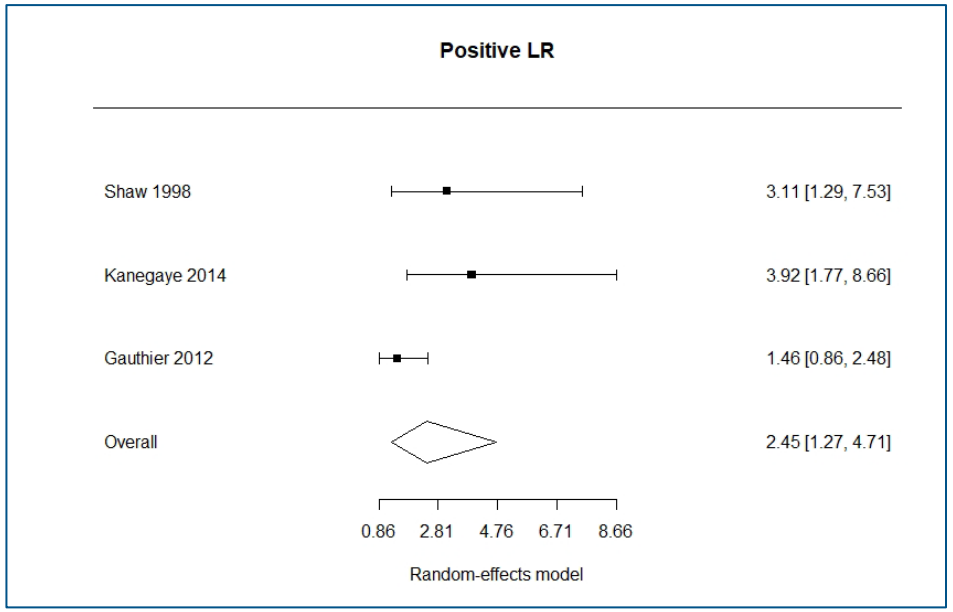


I^2 for sensitivity for previous UTI = 69.1%

I^2 for specificity for previous UTI = 95.9%

Likelihood ratios for previous UTI (<2 years)

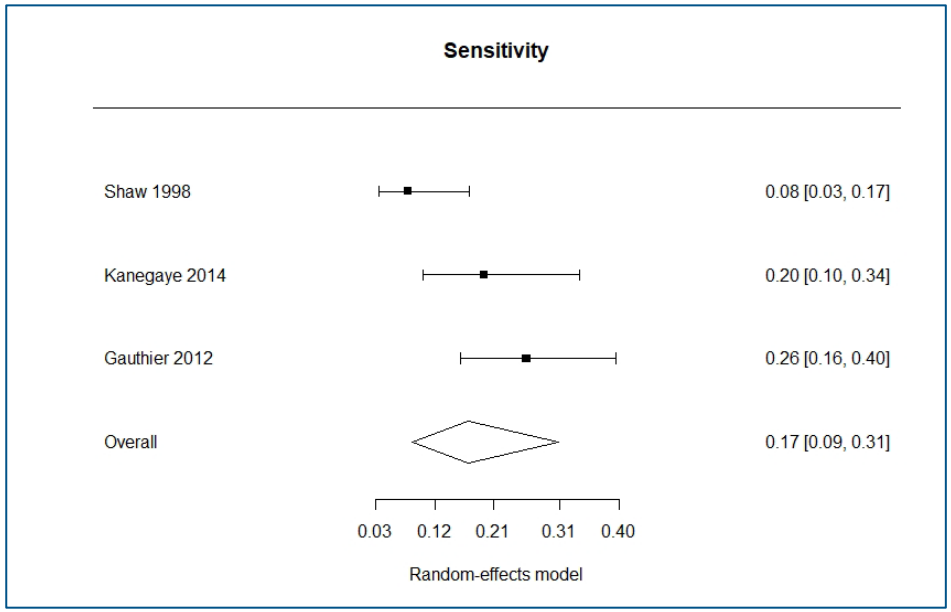


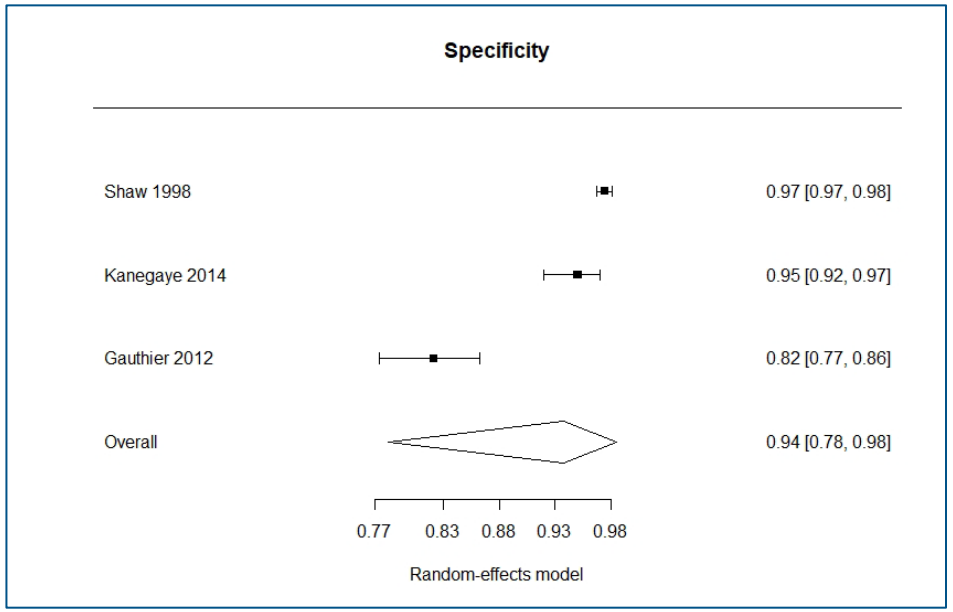


I^2 for negative LR for previous UTI = 0.0%

I^2 for positive LR for previous UTI = 59.2%

Sensitivity and specificity for previous UTI (<2 years)

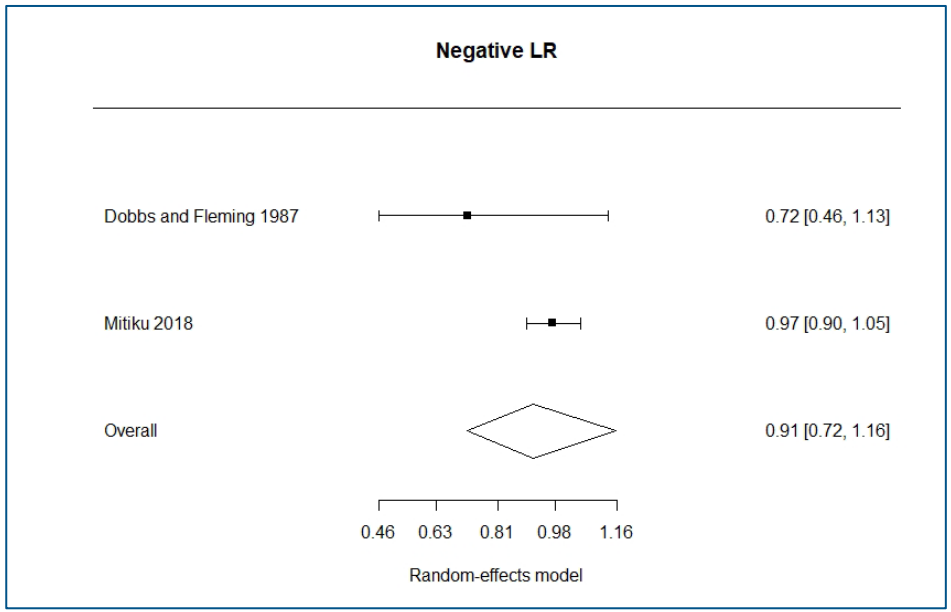


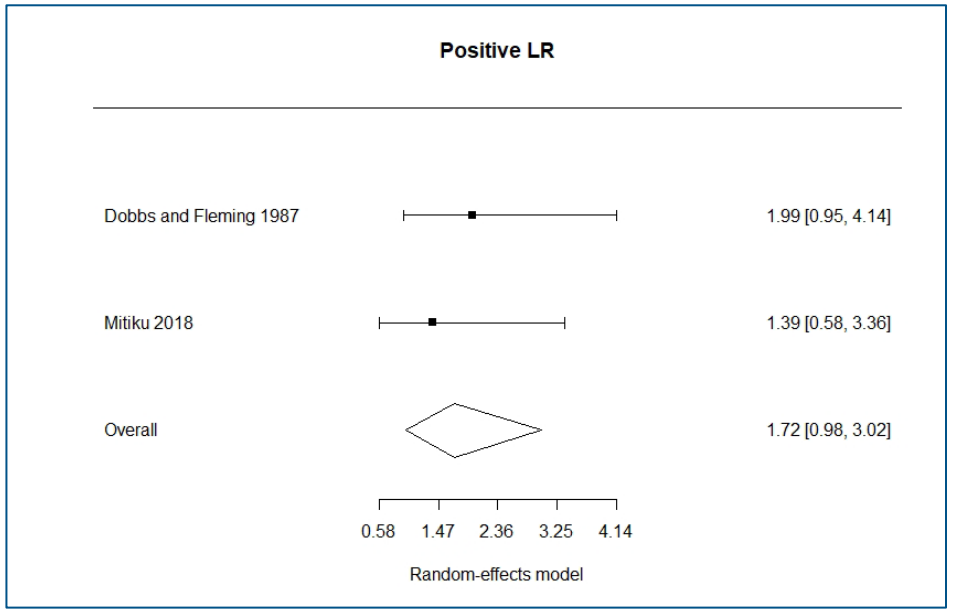


I^2 for sensitivity for previous UTI = 67.6%

I^2 for specificity for previous UTI = 98.0%

Likelihood ratios for previous UTI (<15 years)

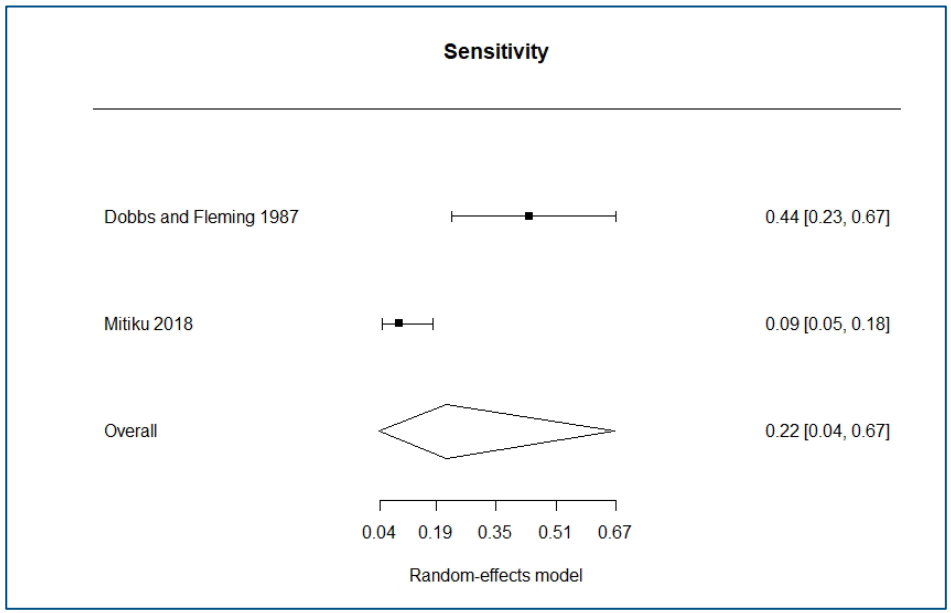


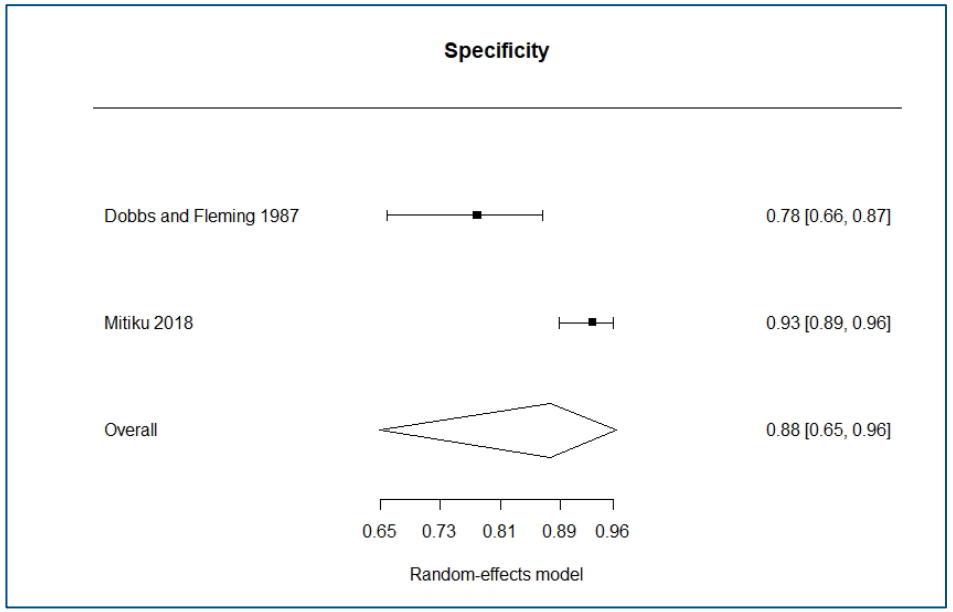


I^2 for negative LR for previous UTI = 37.8%

I^2 for positive LR for previous UTI = 0.0%

Sensitivity and specificity for previous UTI (<15 years)



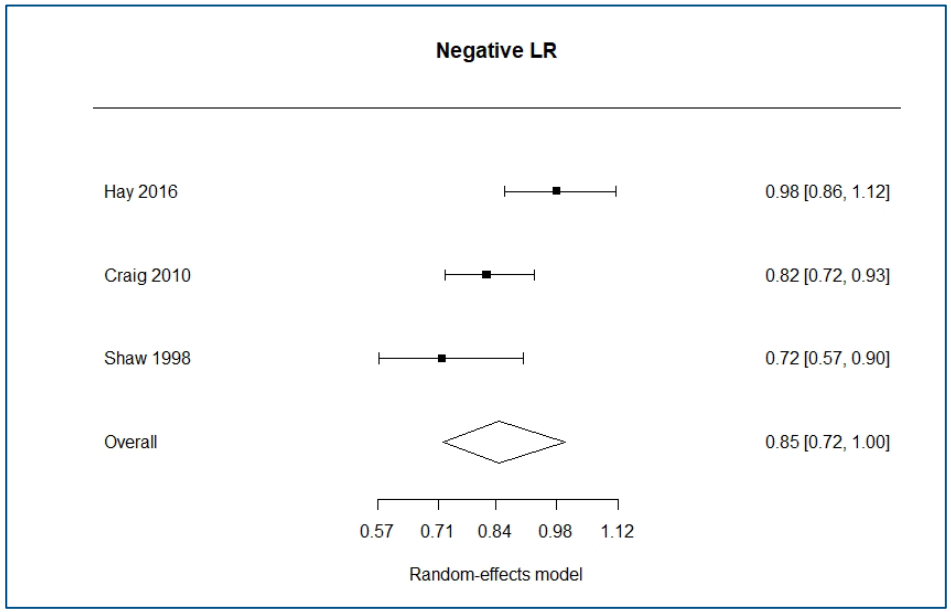


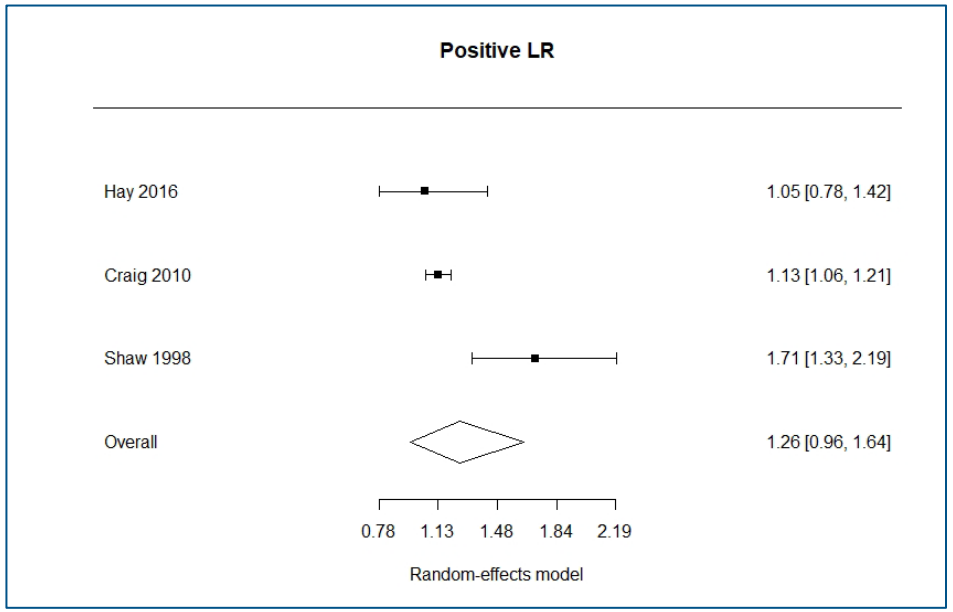
I^2 for sensitivity for previous UTI = 89.9%

I^2 for specificity for previous UTI = 90.3%

Abnormal general appearance

Likelihood ratios for abnormal general appearance (< 5 years)

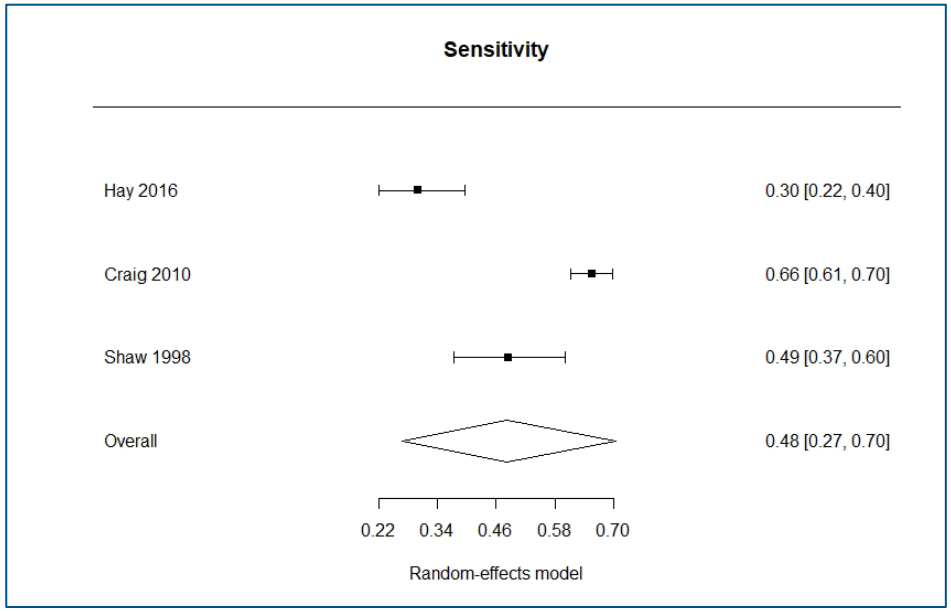


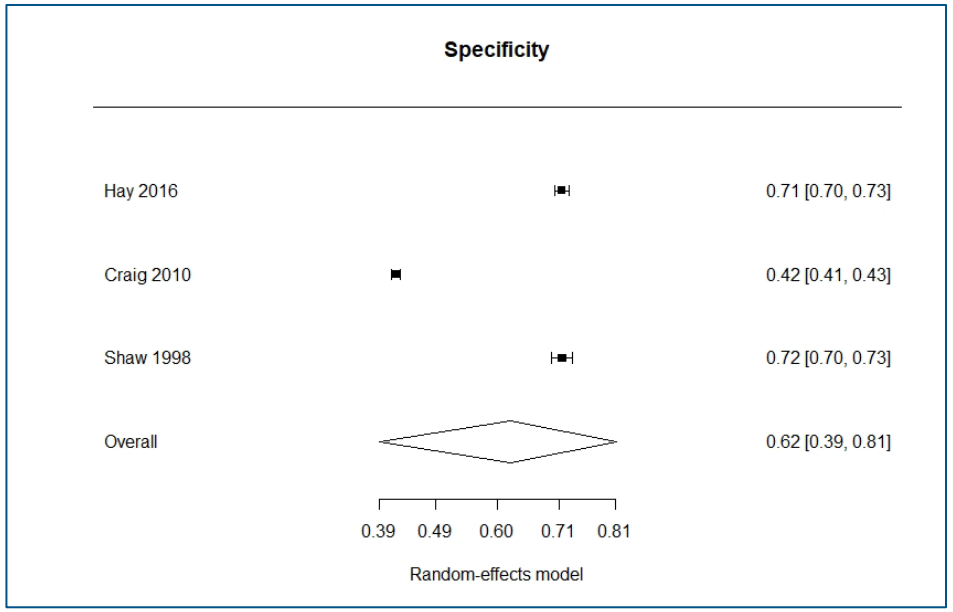


I^2 for negative LR for abnormal general appearance = 70.4%

I^2 for positive LR for abnormal general appearance = 80.4%

Sensitivity and specificity for abnormal general appearance (< 5 years)

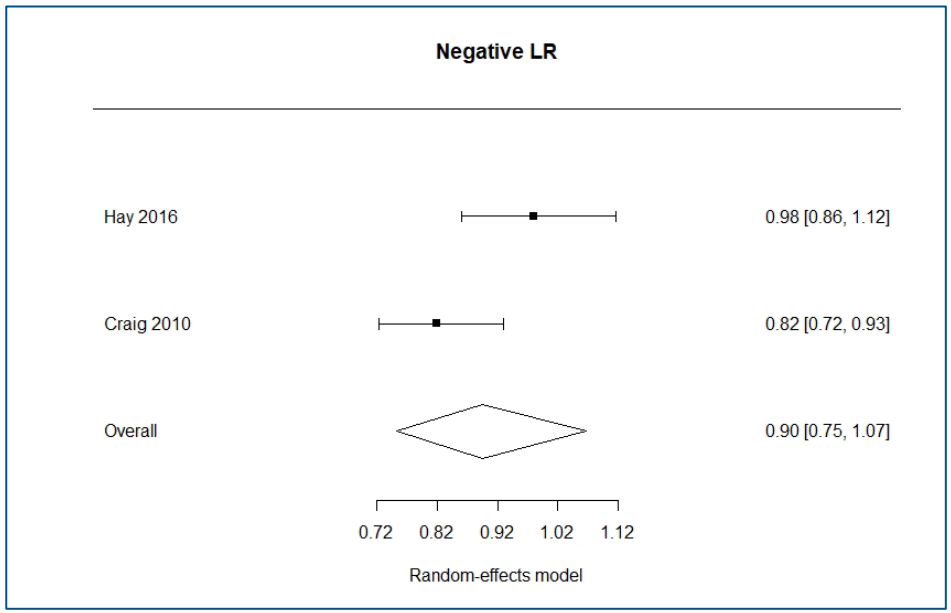


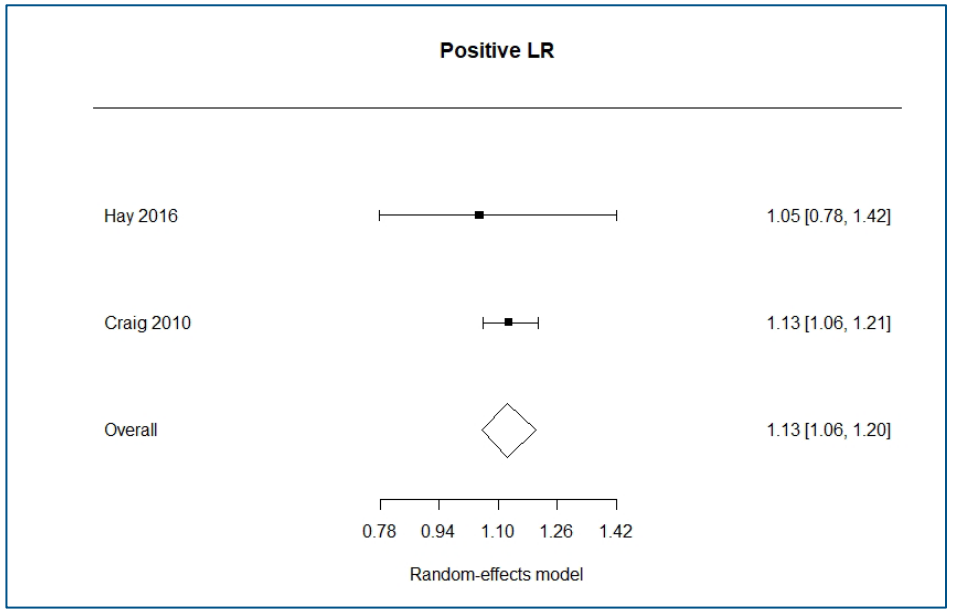


I^2 for sensitivity for abnormal general appearance = 95.3%

I^2 for specificity for abnormal general appearance = 99.9%

Likelihood ratios for abnormal general appearance (<5 years)

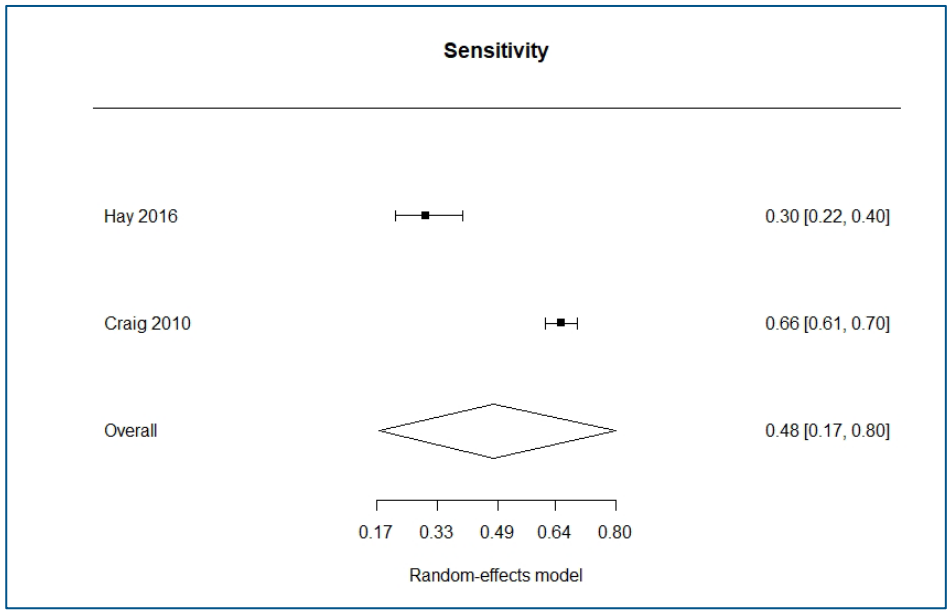


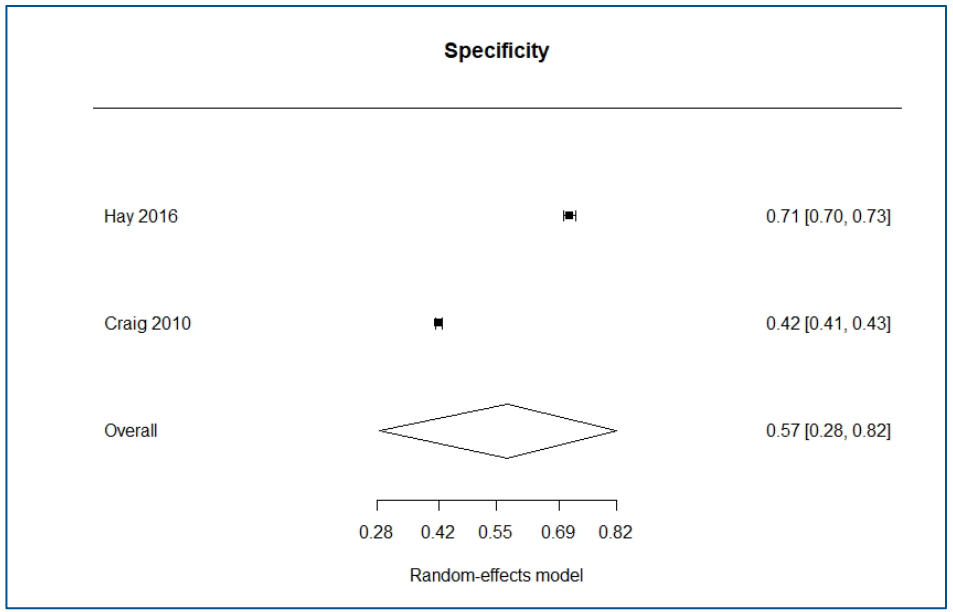


I^2 for negative LR for abnormal general appearance = 73.3%

I^2 for positive LR for abnormal general appearance = 0.0%

Sensitivity and specificity for abnormal general appearance (<5 years)



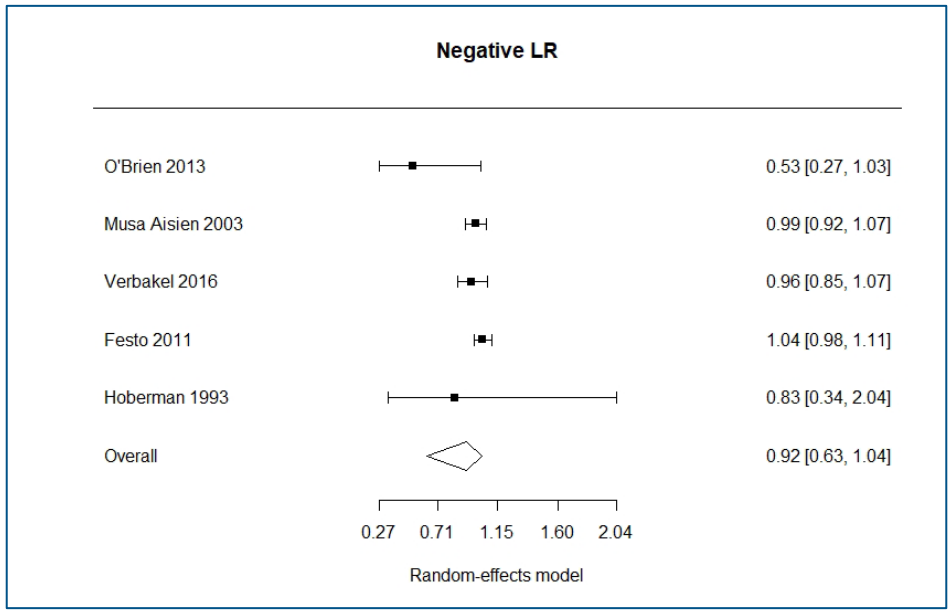


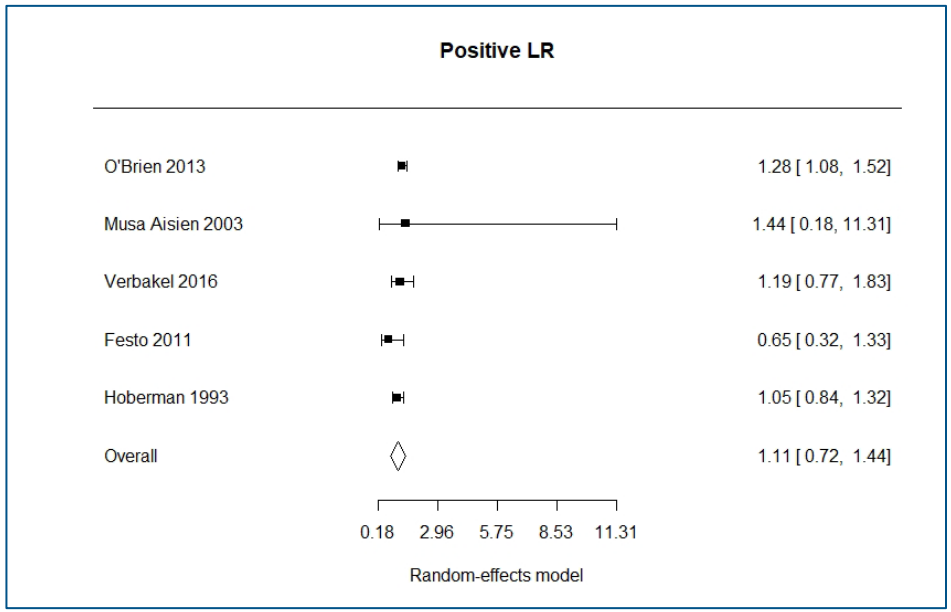
I^2 for sensitivity for abnormal general appearance = 97.4%

I^2 for specificity for abnormal general appearance = 99.9%

Irritability

Likelihood ratios for irritability (data only reported for <2 years)

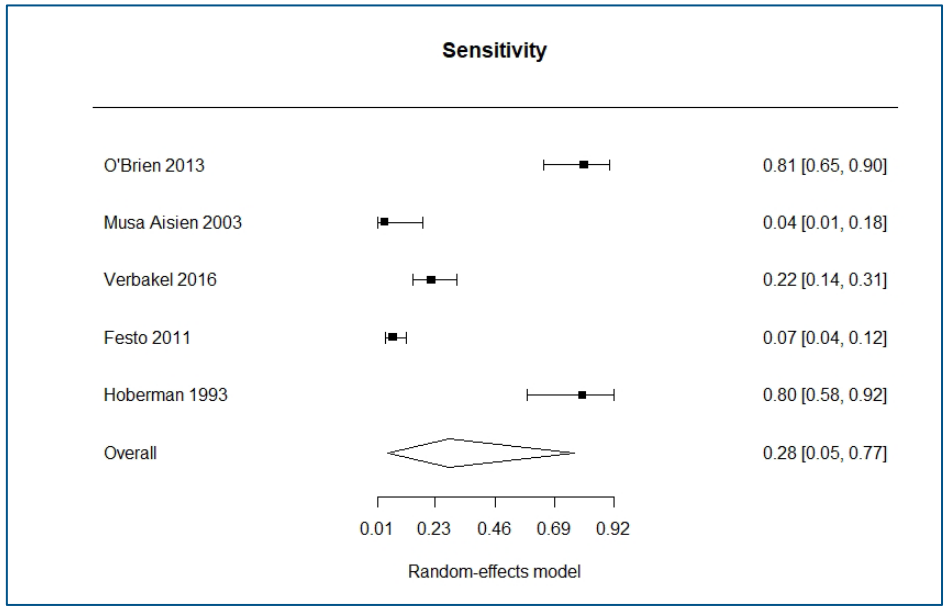


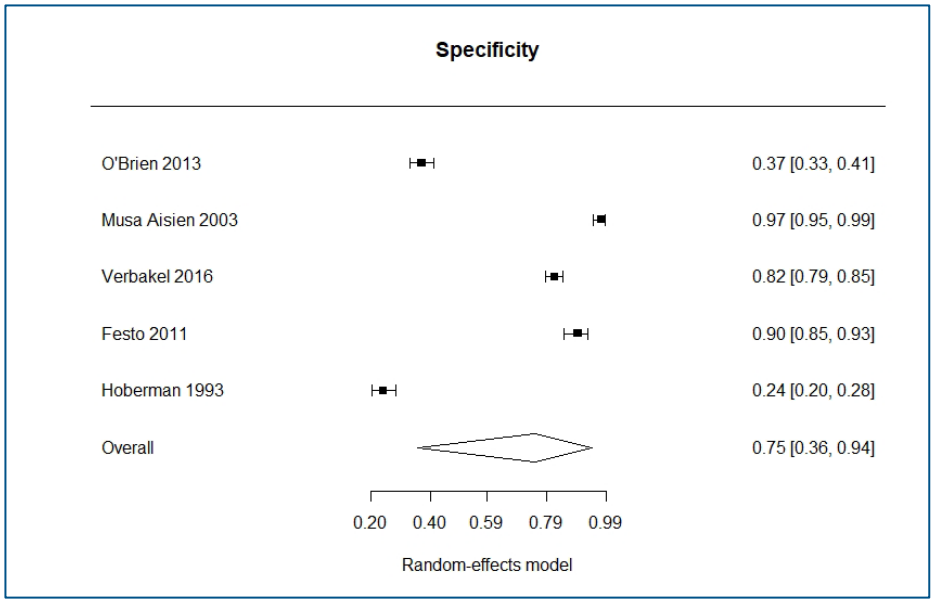


I^2 for negative LR for irritability = 30.5%

I^2 for positive LR for irritability = 11.0%

Sensitivity and specificity for irritability (data only reported for <2 years)



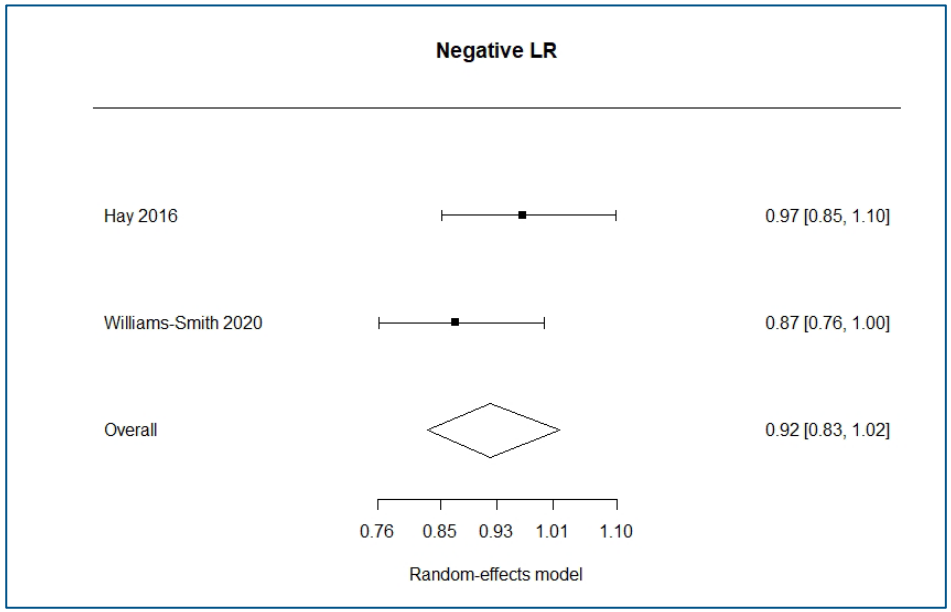


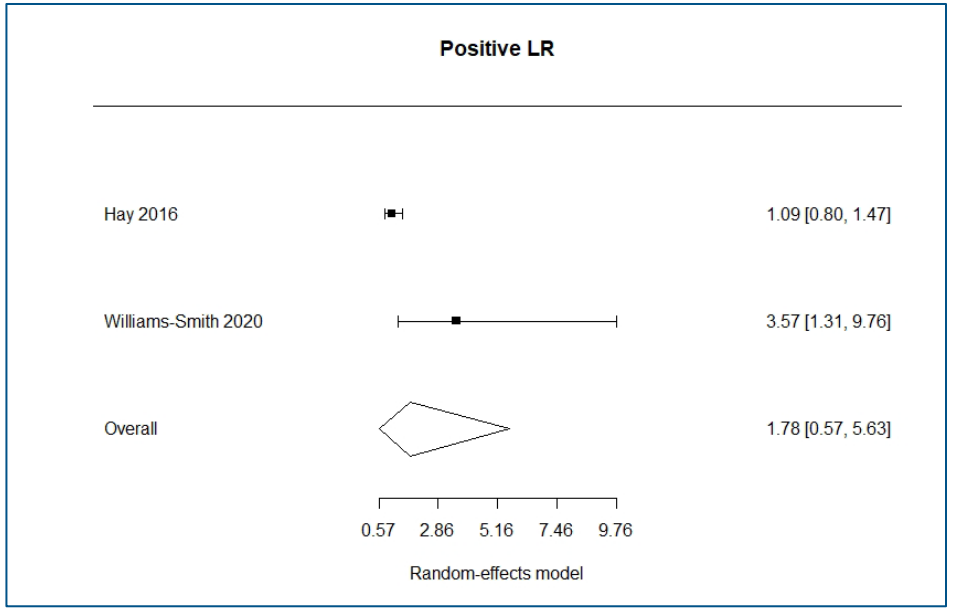
I^2 for sensitivity for irritability = 95.1%

I^2 for specificity for irritability = 99.2%

Shivering/chills

Likelihood ratios for shivering/chills (< 5 years)

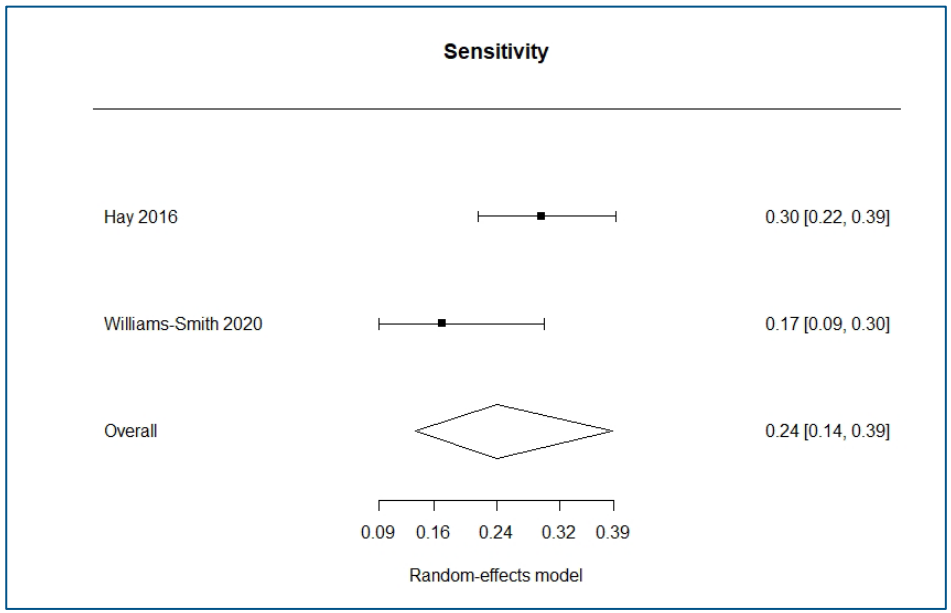


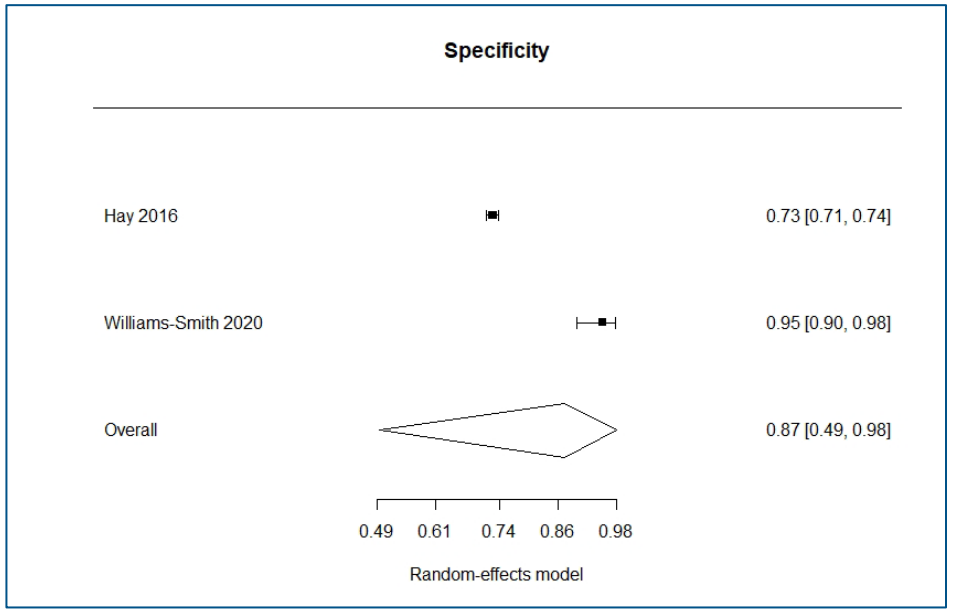


I^2 for negative LR for shivering/chills = 16.5%

I^2 for positive LR for shivering/chills = 79.7%

Sensitivity and specificity for shivering/chills (< 5 years)



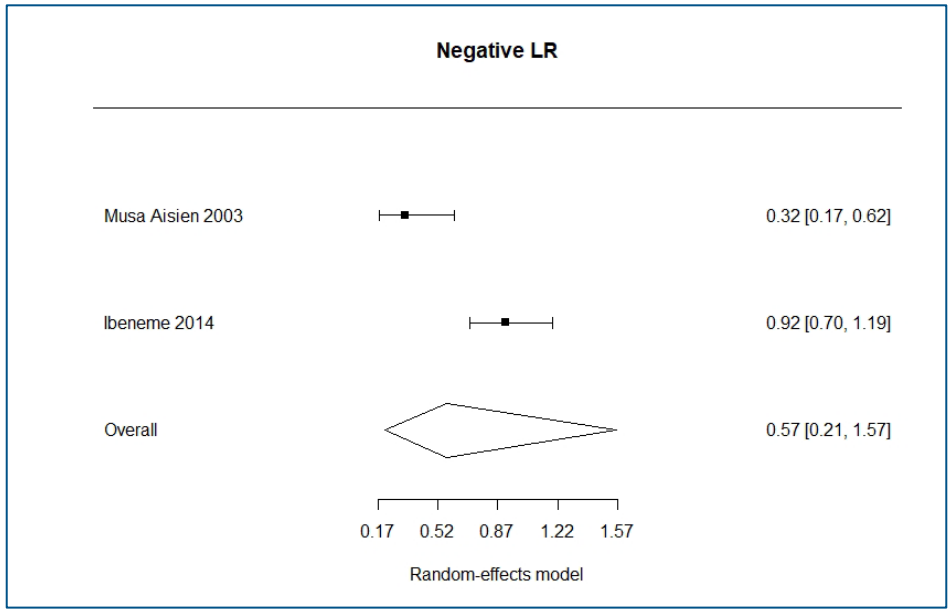


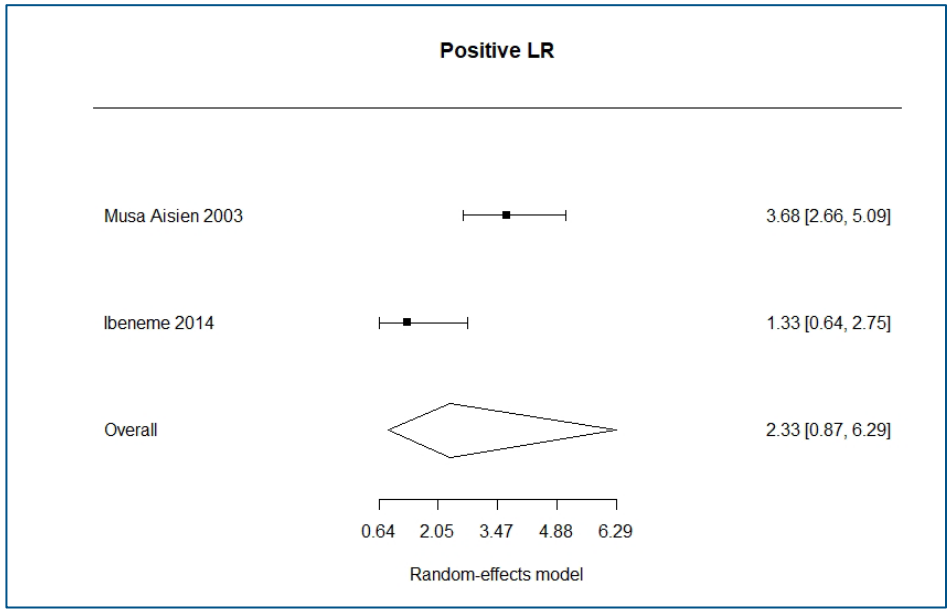
I^2 for sensitivity for shivering/chills = 62.1%

I^2 for specificity for shivering/chills = 95.7%

Fever duration >1 week

Likelihood ratios for fever duration >1 week (data only reported for <5 years)

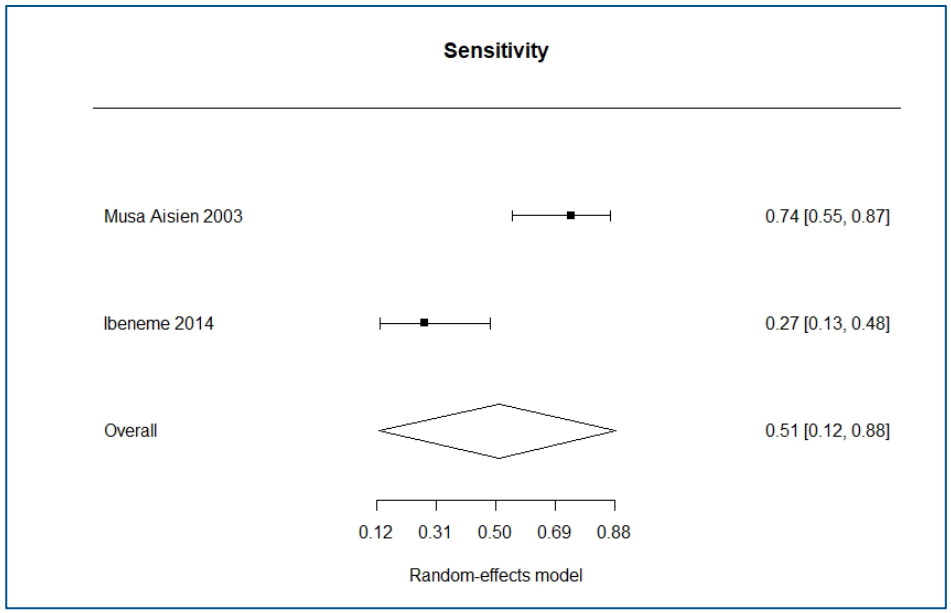


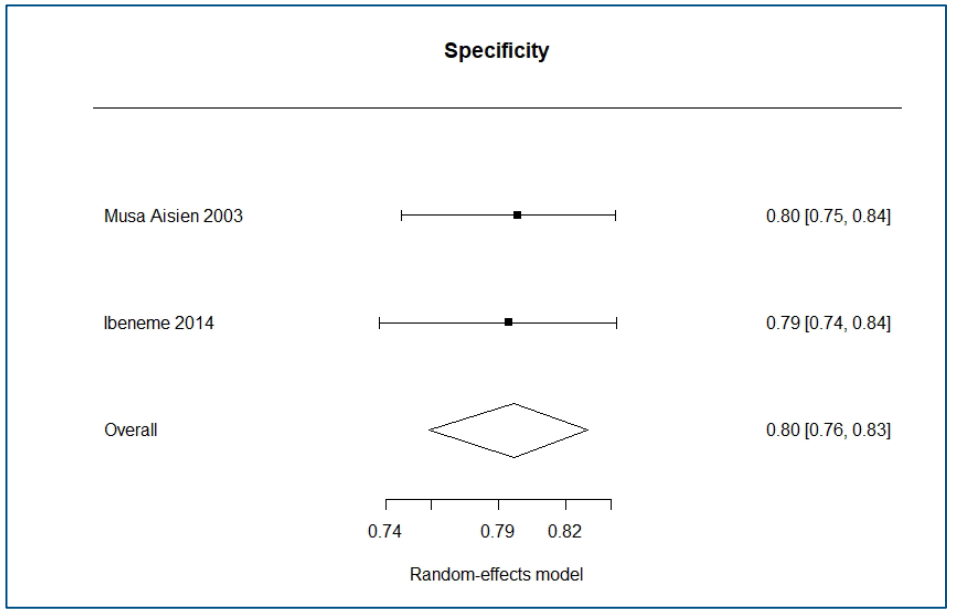


I^2 for negative LR for fever >1 week = 88.4%

I^2 for positive LR for fever >1 week = 84.0%

Sensitivity and specificity for fever duration >1 week (data only reported for <5 years)



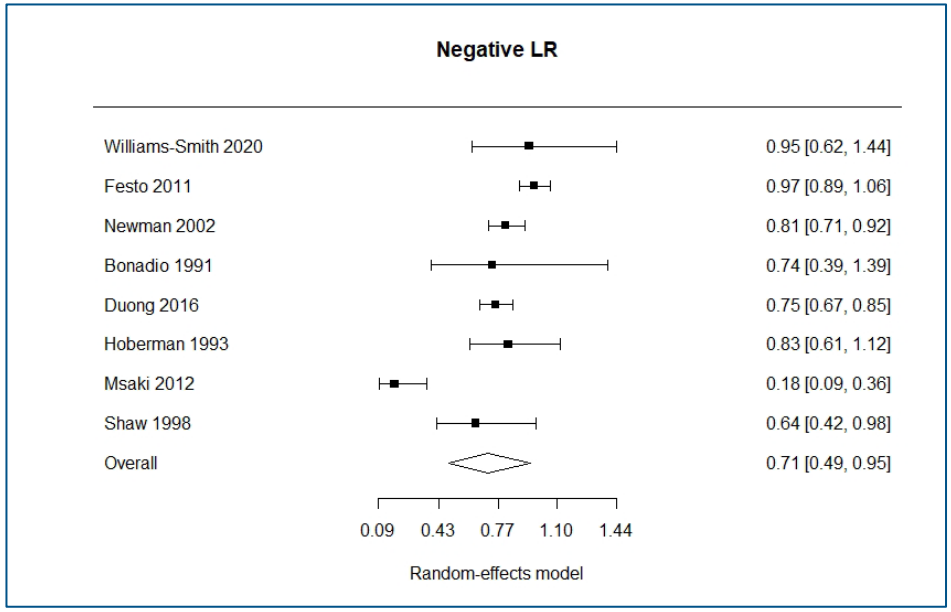


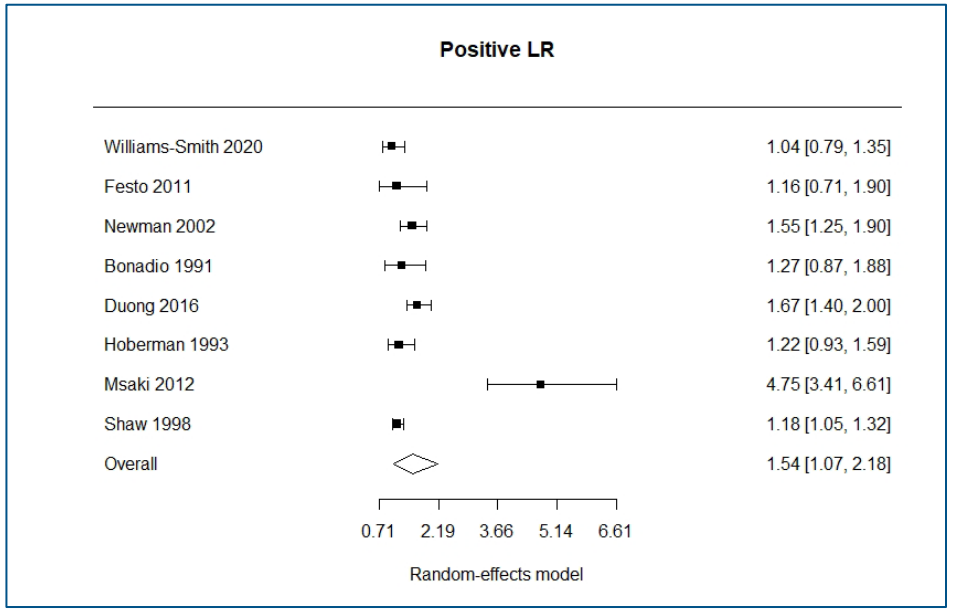
I^2 for sensitivity for fever >1 week = 89.8%

I^2 for specificity for fever >1 week = 0.0%

Degree of fever (temperature ≥39°C)

Likelihood ratios for degree of fever (< 5 years)

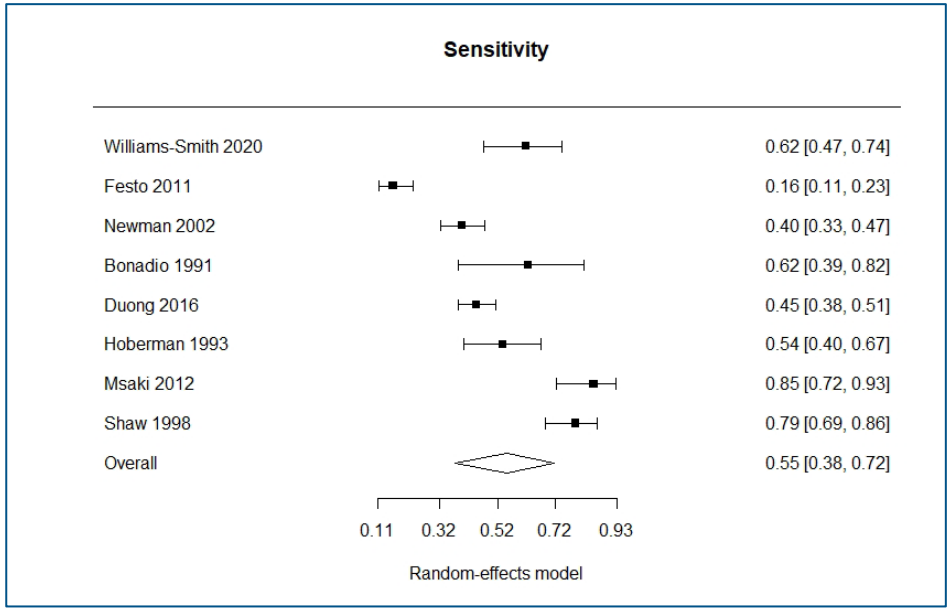


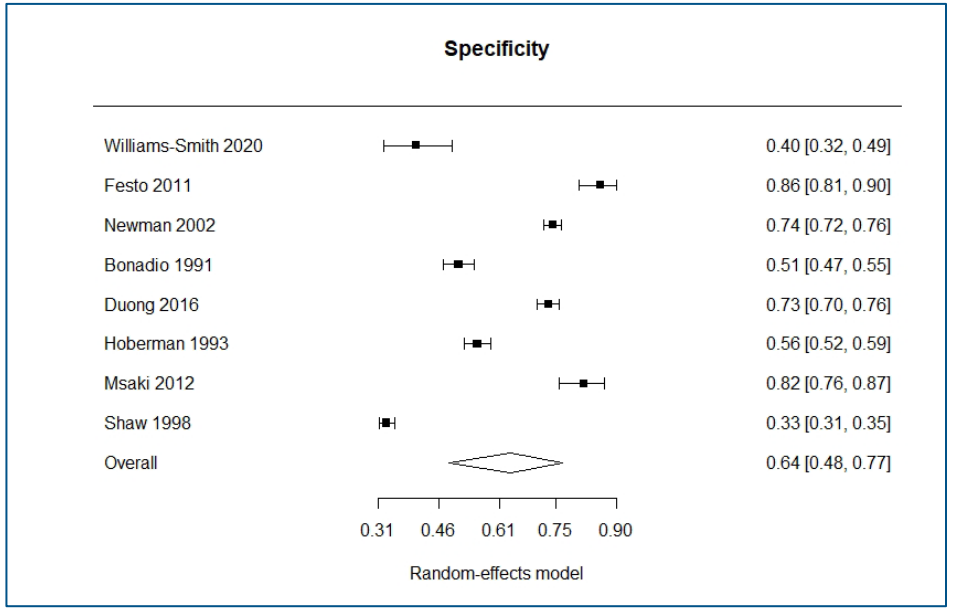


I^2 for negative LR for degree of fever = 79.8%

I^2 for positive LR for degree of fever = 90.3%

Sensitivity and specificity of degree of fever (< 5 years)

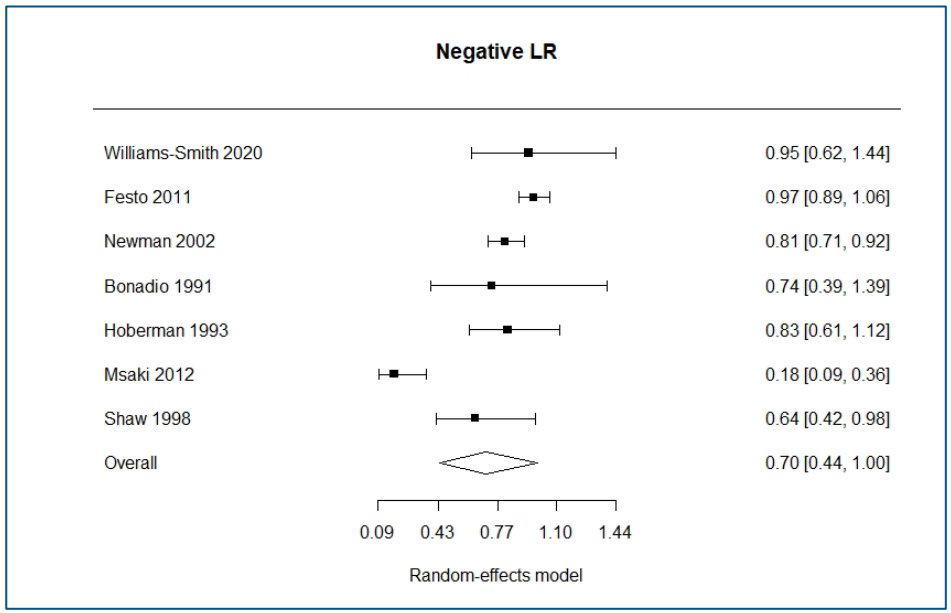


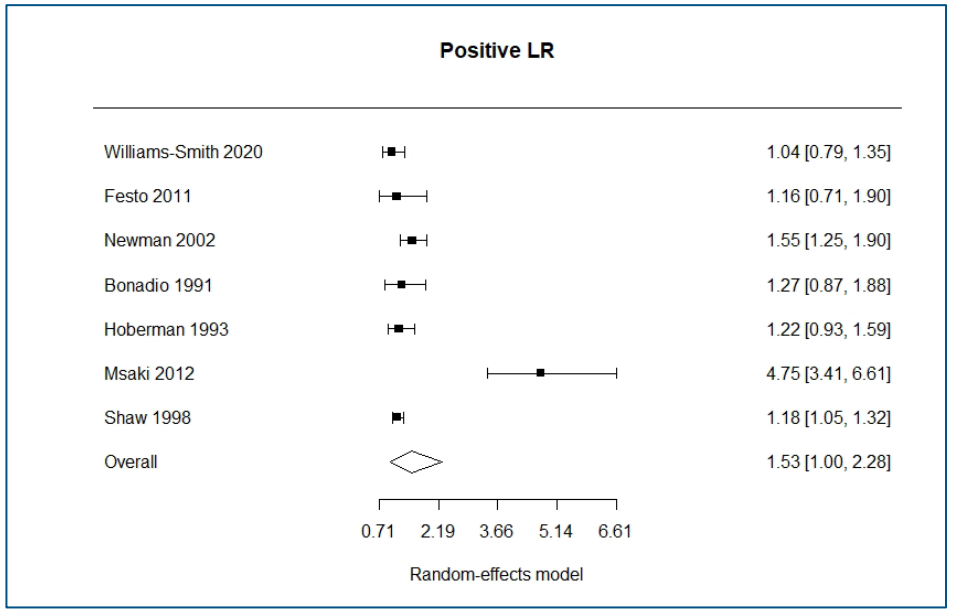


I^2 for sensitivity for degree of fever = 93.3%

I^2 for specificity for degree of fever = 99.2%

Likelihood ratios for degree of fever (<2 years)

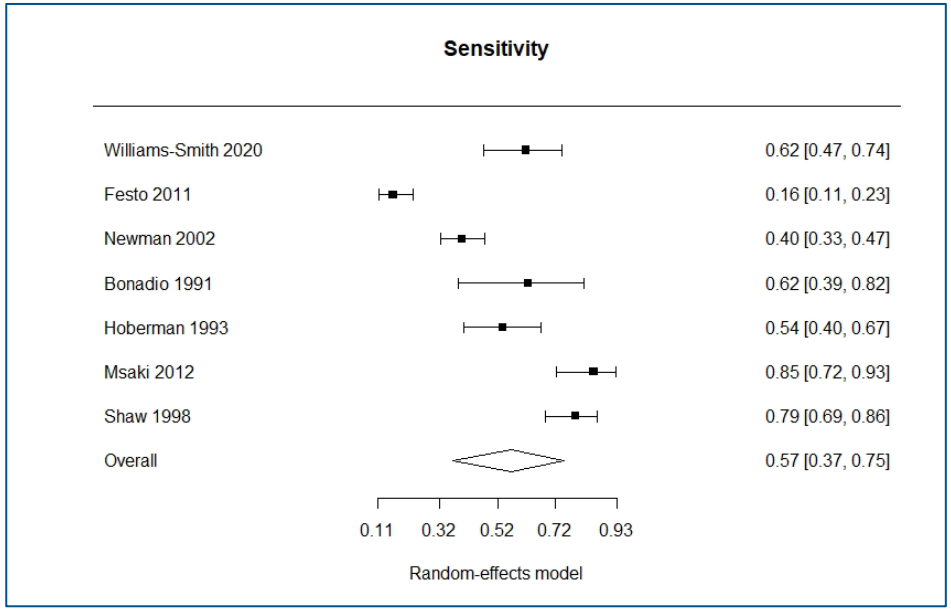


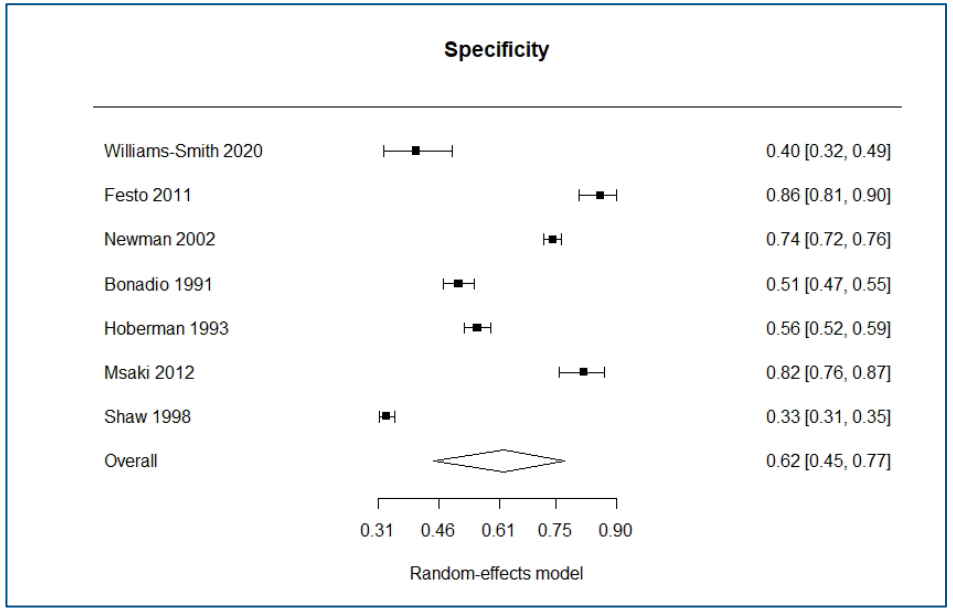


I^2 for negative LR for degree of fever = 79.6%

I^2 for positive LR for degree of fever = 91.0%

Sensitivity and specificity of degree of fever (<2 years)





I^2 for sensitivity for degree of fever = 94.3%

I^2 for specificity for degree of fever = 99.2%

Appendix F – GRADE tables

Symptoms and signs individually – main analysis

Table 10 GRADE table for symptoms and signs individually

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Urinary symptoms (< 5 years)										
1 (Craig 2010)	Prospective - cross sectional	15801	0.08 (0.06, 0.1)	0.98 (0.98, 0.98)	LR+ 4.38 (3.21, 5.97)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.94 (0.92, 0.96)	Very serious [1]	Not serious	Not applicable	Not serious	Low
Dysuria (< 14 years)										
9 [a]	Prospective - cross sectional Retrospective - cohort	5813	0.32 (0.14, 0.58)	0.89 (0.79, 0.94)	LR+ 2.87 (1.75, 4.32)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 0.76 (0.52, 0.93)	Very serious [1]	Not serious	Very serious [2]	Not serious	Very low
Dysuria (< 2 years)										
7 [b]	Prospective - cross sectional Retrospective - cohort	3000	0.24 (0.08, 0.53)	0.91 (0.80, 0.96)	LR+ 2.62 (1.36, 4.44)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 0.82 (0.57, 0.97)	Very serious [1]	Not serious	Very serious [2]	Not serious	Very low
Dysuria (2 to <5 years)										
1 (Hay 2016)	Prospective - cross sectional	2740	0.55 (0.41, 0.67)	0.88 (0.86, 0.89)	LR+ 4.42 (3.41, 5.75)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.52 (0.39, 0.69)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Dysuria (< 14 years)										
1 (Dobbs		75	0.75 (0.49, 0.9)	0.71 (0.58, 0.81)	LR+ 2.6 (1.59, 4.25)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
and Fleming 1987)	Prospective - cross sectional				LR- 0.35 (0.15, 0.83)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Frequency (< 14 years)										
6 [c]	Prospective - cross sectional Retrospective - cohort	6068	0.26 (0.13, 0.46)	0.87 (0.74, 0.94)	LR+ 2.02 (1.42, 2.81)	Very serious [1]	Not serious	Serious [4]	Serious [3]	Very low
					LR- 0.84 (0.70, 0.94)	Very serious [1]	Not serious	Very serious [2]	Not serious	Very low
Frequency (< 2 years)										
4 (O'Brien 2013, Lizama 2005, Pylkkanen 1979, Ibeneme 2014)	Prospective - cross sectional Retrospective - cohort	2139	0.22 (0.16, 0.31)	0.90 (0.82, 0.95)	LR+ 1.77 (1.02, 3.05)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 0.93 (0.84, 1.02)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
Frequency (< 5 years)										
1 (Hay 2016)	Prospective - cross sectional	3856	0.44 (0.34, 0.55)	0.78 (0.76, 0.79)	LR+ 1.99 (1.53, 2.57)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.72 (0.59, 0.88)	Not serious	Not serious	Not applicable	Not serious	High
Frequency (< 14 years)										
1 (Dobbs and Fleming 1987)	Prospective - cross sectional	75	0.63 (0.38, 0.82)	0.71 (0.58, 0.81)	LR+ 2.17 (1.25, 3.77)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
					LR- 0.53 (0.27, 1.01)	Very serious [1]	Not serious	Not applicable	Very serious [5]	Very low
Bed wetting (< 14 years)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
4 (Hay 2016, O'Brien 2013, Dobbs and Fleming 1987 and Pylkkanen 1979)	Prospective - cross sectional	5636	0.15 (0.09, 0.25)	0.93 (0.88, 0.97)	LR+ 2.86 (1.81, 4.53)	Not serious	Not serious	Not serious	Serious [3]	Moderate
					LR- 0.92 (0.88, 0.96)	Very serious [1]	Serious [6]	Not serious	Not serious	Very low
Bed wetting (< 2 years)										
2 (O'Brien 2013 and Pylkkanen 1979)	Prospective - cross sectional	797	0.10 (0.05, 0.16)	0.95 (0.92, 0.96)	LR+ 2.53 (1.18, 5.39)	Not serious	Not serious	Not serious	Serious [3]	Moderate
					LR- 0.94 (0.89, 1.00)	Very serious [1]	Serious [6]	Not serious	Serious [3]	Very low
Bed wetting (< 5 years)										
1 (Hay 2016)	Prospective - cross sectional	4764	0.17 (0.11, 0.26)	0.96 (0.95, 0.96)	LR+ 4.03 (2.53, 6.44)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.87 (0.79, 0.95)	Not serious	Not serious	Not applicable	Not serious	High
Bed wetting (< 14 years)										
1 (Dobbs and Fleming 1987)	Prospective - cross sectional	75	0.31 (0.14, 0.57)	0.8 (0.68, 0.88)	LR+ 1.54 (0.63, 3.72)	Very serious [1]	Not serious	Not applicable	Very serious [5]	Very low
					LR- 0.86 (0.61, 1.23)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Urgency (< 14 years)										
2 (Dobbs		275	0.10 (0.01, 0.52)	0.97 (0.48, 1.00)	LR+ 1.40 (0.50, 3.96)	Very serious [1]	Not serious	Not serious	Very serious [5]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
and Fleming 1987 and Ibeneme 2014)	Prospective - cross sectional				LR- 0.98 (0.93, 1.05)	Not serious	Not serious	Not serious	Serious [3]	Moderate
Urgency (< 5 years)										
1 (Ibeneme 2014)	Prospective - cross sectional	200	0.02 (0, 0.27)	0.99 (0.96, 1.0)	LR+ 2.59 (0.11, 61.82)	Not serious	Not serious	Not applicable	Very serious[5]	Low
					LR- 0.99 (0.93, 1.05)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Urgency (< 14 years)										
1 (Dobbs and Fleming 1987)	Prospective - cross sectional	75	0.19 (0.06, 0.45)	0.85 (0.73, 0.92)	LR+ 1.23 (0.38, 4.02)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
					LR- 0.96 (0.74, 1.24)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Oliguria (≤ 3 months)										
1 (Newman 2002)	Prospective - cross sectional	1666	0.18 (0.13, 0.25)	0.85 (0.83, 0.87)	LR+ 1.23 (0.85, 1.77)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.96 (0.90, 1.04)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Haematuria (< 14 years) ***unclear if blood visible to child or parent, or whether a dipstick was used for detection in all studies***										
4 (Hay 2016, Dobbs and Fleming 1987, Lizama 2005 and	Prospective - cross sectional Retrospective - cohort	5815	0.05 (0.03, 0.07)	0.99 (0.96, 1.00)	LR+ 3.02 (1.68, 5.43)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
					LR- 0.97 (0.95, 0.99)	Very serious [1]	Not serious	Not serious	Not serious	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Pylkkanen 1979)										
Haematuria (< 2 years) ***unclear if blood visible to child or parent, or whether a dipstick was used for detection in all studies***										
2 (Lizama 2005 and Pylkkanen 1979)	Prospective - cross sectional Retrospective - cohort	1340	0.05 (0.03, 0.08)	0.98 (0.97, 0.99)	LR+ 2.57 (1.33, 4.99)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
					LR- 0.97 (0.94, 0.99)	Very serious [1]	Not serious	Not serious	Not serious	Low
Haematuria (< 5 years) ***unclear if blood visible to child or parent, or whether a dipstick was used for detection in all studies***										
1 (Hay 2016)	Prospective - cross sectional	4400	0.02 (0.01, 0.09)	1.0 (0.99, 1.0)	LR+ 6.13 (1.43, 26.24)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.98 (0.95, 1.01)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Haematuria (< 14 years) ***unclear if blood visible to child or parent, or whether a dipstick was used for detection in all studies***										
1 (Dobbs and Fleming 1987)	Prospective - cross sectional	75	0.06 (0.01, 0.34)	0.98 (0.89, 1.0)	LR+ 3.69 (0.24, 55.76)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
					LR- 0.95 (0.84, 1.09)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Cloudy urine (< 5 years)										
2 (Hay 2016, Kartika 2006)	Prospective - cross sectional	2717	0.39 (0.02, 0.95)	0.91 (0.75, 0.97)	LR+ 3.51 (1.50, 8.25)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 0.50 (0.14, 1.79)	Very serious [1]	Not serious	Very serious [2]	Very serious[5]	Very low
Cloudy urine (2 to < 5 years)										
1 (Hay 2016)	Prospective - cross sectional	2512	0.10 (0.04, 0.22)	0.95 (0.94, 0.96)	LR+ 2.09 (0.89, 4.88)	Not serious	Not serious	Not applicable	Very serious[5]	Low
					LR- 0.95 (0.86, 1.04)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Cloudy urine (< 5 years)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Kartika 2006)	Prospective - cross sectional	205	0.78 (0.68, 0.86)	0.85 (0.77, 0.9)	LR+ 5.05 (3.29, 7.76)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.26 (0.17, 0.39)	Very serious [1]	Not serious	Not applicable	Not serious	Low
Darker urine (< 2 years)										
1 (Hay 2016)	Prospective - cross sectional	2277	0.22 (0.09, 0.43)	0.95 (0.94, 0.95)	LR+ 3.81 (1.82, 7.96)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.84 (0.71, 1.01)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Malodorous urine (< 14 years)										
5 [d]	Prospective - cross sectional	5735	0.33 (0.13, 0.63)	0.86 (0.57, 0.96)	LR+ 2.55 (1.14, 5.45)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 0.78 (0.55, 0.95)	Very serious [1]	Not serious	Very serious [2]	Not serious	Very low
Malodorous urine (< 2 years)										
3 (Gauthier 2012, Pylkkanen 1979, Struthers 2003)	Prospective - cross sectional	643	0.28 (0.04, 0.77)	0.70 (0.45, 0.86)	LR+ 1.49 (0.72, 3.08)	Very serious [1]	Not serious	Serious [4]	Very serious [5]	Very low
					LR- 0.86 (0.65, 1.15)	Very serious [1]	Serious [6]	Serious [4]	Serious [3]	Very low
Malodorous urine (< 5 years)										
1 (Hay 2016)	Prospective - cross sectional	5017	0.54 (0.44, 0.63)	0.85 (0.84, 0.86)	LR+ 3.71 (3.06, 4.50)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.54 (0.44, 0.67)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Malodorous urine (< 14 years)										
1 (Dobbs		75	0.13 (0.03, 0.39)	0.92 (0.81, 0.96)	LR+ 1.48 (0.31, 6.91)	Very serious [1]	Not serious	Not applicable	Very serious [5]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
and Fleming 1987)	Prospective - cross sectional				LR- 0.96 (0.78, 1.17)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
No diaper rash (< 2 years)										
1 (Hay 2016)	Prospective - cross sectional	2277	0.96 (0.75, 0.99)	0.25 (0.23, 0.27)	LR+ 1.29 (1.20, 1.38)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.13 (0.02, 0.92)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Suprapubic tenderness (< 5 years)										
1 (Hay 2016)	Prospective - cross sectional	4199	0.06 (0.02, 0.14)	0.99 (0.99, 1.0)	LR+ 7.94 (3.18, 19.86)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.95 (0.89, 1.00)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Loin tenderness (2 to <5 years)										
1 (Hay 2016)	Prospective – cross sectional	2300	0.02 (0, 0.14)	1.0 (1.0, 1.0)	LR+ 16.63 (3.30, 83.86)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.97 (0.92, 1.02)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Renal angle tenderness (<5 years)										
1 (Ibenem e 2014)	Prospective - cross sectional	200	0.07 (0.01, 0.27)	1 (0.96, 1)	LR+ 23.35 (0.98, 556.42)	Not serious	Not serious	Not applicable	Very serious[5]	Low
					LR- 0.94 (0.84, 1.05)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Flank pain (< 2 years)										
1 (Festo 2011)	Prospective - cross sectional	373	0.14 (0.09, 0.21)	0.79 (0.74, 0.84)	LR+ 0.69 (0.43, 1.12)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 1.08 (0.98, 1.18)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Back pain (< 2 years)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Pylkkanen 1979)	Prospective - cross sectional	200	0.02 (0.01, 0.07)	0.99 (0.91, 1)	LR+ 1.72 (0.18, 16.28)	Very serious [1]	Serious [6]	Not applicable	Very serious[5]	Very low
					LR- 0.99 (0.95, 1.03)	Very serious [1]	Serious [6]	Not applicable	Serious [3]	Very low
Vomiting (< 5 years)										
9 [e]	Prospective - cross sectional Retrospective - cohort	9635	0.24 (0.15, 0.36)	0.72 (0.63, 0.79)	LR+ 0.85 (0.68, 1.03)	Very serious [1]	Not serious	Serious [4]	Serious [3]	Very low
					LR- 1.06 (0.99, 1.11)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
Vomiting (< 2 years)										
8 [f]	Prospective - cross sectional Retrospective - cohort	4623	0.23 (0.14, 0.37)	0.72 (0.62, 0.81)	LR+ 0.84 (0.65, 1.04)	Very serious [1]	Not serious	Serious [4]	Serious [3]	Very low
					LR- 1.06 (0.98, 1.12)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
Vomiting (< 5 years)										
1 (Hay 2016)	Prospective - cross sectional	5012	0.32 (0.24, 0.42)	0.67 (0.65, 0.68)	LR+ 0.96 (0.72, 1.28)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 1.02 (0.89, 1.17)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Nausea (< 14 years)										
1 (Dobbs and Fleming 1987)	Prospective – cross sectional	75	0.06 (0.01, 0.34)	0.8 (0.68, 0.88)	LR+ 0.31 (0.04, 2.19)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
					LR- 1.18 (0.98. 1.41)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Diarrhoea (< 5 years)										
8 [g]		18753	0.19 (0.11, 0.31)	0.80 (0.71, 0.86)	LR+ 0.95 (0.67, 1.28)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
	Prospective – cross sectional Retrospective – cohort				LR- 1.01 (0.92, 1.09)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
Diarrhoea (< 2 years)										
7 [h]	Prospective – cross sectional Retrospective – cohort	2952	0.19 (0.10, 0.33)	0.81 (0.71, 0.87)	LR+ 0.99 (0.65, 1.40)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 1.00 (0.89, 1.09)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
Diarrhoea (< 5 years)										
1 (Craig 2010)	Prospective - cross sectional	15801	0.22 (0.18, 0.26)	0.74 (0.73, 0.75)	LR+ 0.83 (0.70, 0.99)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 1.06 (1.01, 1.11)	Very serious [1]	Not serious	Not applicable	Not serious	Low
Constipation (< 5 years)										
2 (Hay 2016, Pylkkanen 1979)	Prospective – cross sectional	5212	0.05 (0.00, 0.80)	0.95 (0.41, 1.00)	LR+ 1.52 (1.10, 2.11)	Not serious	Not serious	Not serious	Serious [3]	Moderate
					LR- 0.96 (0.85, 1.08)	Very serious [1]	Serious [6]	Very serious [2]	Serious [3]	Very low
Constipation (< 2 years)										
1 (Pylkkanen 1979)	Prospective - cross sectional	200	0 (0, 0.06)	0.99 (0.9, 1.0)	LR+ 0.57 (0.01, 28.22)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
					LR- 1.0 (0.98, 1.03)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Constipation (< 5 years)										
1 (Hay 2016)	Prospective - cross sectional	5012	0.27 (0.19, 0.37)	0.82 (0.81, 0.83)	LR+ 1.52 (1.10, 2.11)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.89 (0.79, 1.0)	Not serious	Not serious	Not applicable	Serious [3]	Moderate

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Abdominal pain (< 5 years)										
8 [i]	Prospective - cross sectional Retrospective - cohort	5797	0.27 (0.14, 0.45)	0.83 (0.66, 0.93)	LR+ 1.70 (0.83, 3.22)	Very serious [1]	Not serious	Very serious [2]	Very serious [5]	Very low
					LR- 0.88 (0.70, 1.06)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
Abdominal pain (< 2 years)										
7 [j]	Prospective - cross sectional Retrospective - cohort	3056	0.29 (0.15, 0.50)	0.78 (0.62, 0.88)	LR+ 1.39 (0.70, 2.47)	Very serious [1]	Not serious	Very serious [2]	Very serious [5]	Very low
					LR- 0.91 (0.68, 1.12)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
Abdominal pain (2 to < 5 years)										
1 (Hay 2016)	Prospective – cross sectional	2740	0.13 (0.06, 0.24)	0.98 (0.97, 0.98)	LR+ 6.45 (3.07, 13.54)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.89 (0.80, 0.98)	Not serious	Not serious	Not applicable	Not serious	High
Poor feeding (< 5 years)										
3 (Hay 2016, Hoberman 1993 and O'Brien 2014)	Prospective - cross sectional	6025	0.69 (0.61, 0.76)	0.34 (0.22, 0.50)	LR+ 1.04 (0.85, 1.28)	Not serious	Not serious	Serious [4]	Serious [3]	Low
					LR- 0.98 (0.68, 1.42)	Not serious	Not serious	Serious [4]	Serious [3]	Low
Poor feeding (< 2 years)										
2 (Hoberman 1993, O'Brien 2013)	Prospective - cross sectional	1013	0.67 (0.54, 0.78)	0.40 (0.31, 0.51)	LR+ 1.16 (0.93, 1.44)	Not serious	Not serious	Not serious	Serious [3]	Moderate
					LR- 0.80 (0.54, 1.17)	Not serious	Not serious	Not serious	Serious [3]	Moderate
Poor feeding (< 5 years)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Hay 2016)	Prospective - cross sectional	5012	0.7 (0.6, 0.78)	0.24 (0.23, 0.25)	LR+ 0.92 (0.81, 1.05)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 1.24 (0.91, 1.68)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Decreased feeding (≤ 3 months)										
1 (Newman 2002)	Prospective - cross sectional	1666	0.37 (0.30, 0.44)	0.63 (0.60, 0.65)	LR+ 0.98 (0.79, 1.21)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 1.01 (0.89, 1.15)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Poor weight gain (< 5 years)										
1 (Hay 2016)	Prospective - cross sectional	3607	0.13 (0.07, 0.22)	0.85 (0.83, 0.86)	LR+ 0.81 (0.44, 1.5)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 1.03 (0.95, 1.13)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
No source of fever (< 5 years)										
4 (Craig 2010, Hoberman 1993, Shaw 1998, Pylkkanen 1979)	Prospective - cross sectional	19476	0.67 (0.24, 0.93)	0.57 (0.12, 0.93)	LR+ 1.53 (0.63, 3.73)	Very serious [1]	Not serious	Very serious [2]	Very serious[5]	Very low
					LR- 0.55 (0.24, 1.24)	Very serious [1]	Not serious	Very serious [2]	Very serious[5]	Very low
No source of fever (< 2 years)										
3 (Hoberman 1993, Shaw 1998, Pylkkanen 1979)	Prospective - cross sectional	3675	0.50 (0.09, 0.91)	0.76 (0.53, 0.90)	LR+ 1.79 (0.72, 4.42)	Not serious	Not serious	Very serious [2]	Very serious[5]	Very low
					LR- 0.52 (0.18, 1.51)	Very serious [1]	Serious [6]	Very serious [2]	Very serious[5]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
No source of fever (< 5 years)										
1 (Craig 2010)	Prospective - cross sectional	15801	0.95 (0.92, 0.96)	0.08 (0.08, 0.09)	LR+ 1.03 (1.01, 1.05)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.66 (0.45, 0.96)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
No convulsions (data only reported < 2 years)										
2 (Musa Aisien 2003, Pylkkanen 1979)	Prospective - cross sectional	500	0.96 (0.92, 0.98)	0.09 (0.05, 0.16)	LR+ 1.04 (0.98, 1.11)	Very serious [1]	Serious [6]	Not serious	Serious [3]	Very low
					LR- 0.56 (0.19, 1.65)	Very serious [1]	Serious [6]	Not serious	Very serious [5]	Very low
No bulging fontanelle (< 5 years)										
1 (Craig 2010)	Prospective - cross sectional	9339	1 (0.98, 1)	0 (0, 0)	LR+ 1 (1, 1)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
					LR- 23.91 (0.48, 1203.31)	Very serious [1]	Not serious	Not applicable	Very serious [5]	Very low
No respiratory symptoms (< 5 years)										
2 (Craig 2010, Lizama 2005)	Prospective - cross sectional Retrospective - cohort	16941	0.64 (0.37, 0.84)	0.55 (0.20, 0.85)	LR+ 1.47 (0.94, 2.30)	Very serious [1]	Not serious	Very serious [2]	Very serious	Very low
					LR- 0.68 (0.62, 0.74)	Very serious [1]	Not serious	Not serious	Not serious	Low
No respiratory symptoms (< 2 years)										
1 (Lizama 2005)	Retrospective - cohort	1140	0.76 (0.70, 0.81)	0.35 (0.32, 0.39)	LR+ 1.17 (1.08, 1.28)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.69 (0.54, 0.87)	Very serious [1]	Not serious	Not applicable	Not serious	Low
No respiratory symptoms (< 5 years)										
1 (Craig 2010)		15801	0.51 (0.46, 0.55)	0.73 (0.72, 0.73)	LR+ 1.85 (1.69, 2.03)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
	Prospective - cross sectional				LR- 0.68 (0.62, 0.74)	Very serious [1]	Not serious	Not applicable	Not serious	Low
No cough (< 5 years)										
4 (Hay 2016, Craig 2010, Newman 2002, Verbakel 2016)	Prospective - cross sectional	20946	0.69 (0.48, 0.85)	0.33 (0.19, 0.51)	LR+ 1.22 (0.92, 1.62)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 0.75 (0.54, 1.03)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
No cough (< 2 years)										
2 (Newman 2002, Verbakel 2015)	Prospective - cross sectional	2405	0.93 (0.08, 1.00)	0.11 (0.00, 0.88)	LR+ 1.01 (1.00, 1.02)	Not serious	Not serious	Not serious	Serious [3]	Moderate
					LR- 0.93 (0.74, 1.18)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
No cough (2 to < 5 years)										
1 (Hay 2016)	Prospective - cross sectional	2740	0.40 (0.28, 0.53)	0.72 (0.70, 0.73)	LR+ 1.41 (1.02, 1.96)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.84 (0.67, 1.04)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
No cough (< 5 years)										
1 (Craig 2010)	Prospective - cross sectional	15801	0.69 (0.64, 0.73)	0.55 (0.54, 0.56)	LR+ 1.52 (1.43, 1.62)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.57 (0.50, 0.65)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
No breathing difficulty (< 5 years)										
2 (Craig 2010,		17467	0.94 (0.91, 0.95)	0.13 (0.13, 0.14)	LR+ 1.08 (1.06, 1.11)	Very serious [1]	Not serious	Not serious	Not serious	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Newman 2002)	Prospective - cross sectional				LR- 0.47 (0.35, 0.64)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
No breathing difficulty (≤ 3 months)										
1 (Newman 2002)	Prospective - cross sectional	1666	0.93 (0.88, 0.96)	0.14 (0.12, 0.16)	LR+ 1.09 (1.04, 1.14)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.47 (0.26, 0.84)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
No breathing difficulty (< 5 years)										
1 (Craig 2010)	Prospective - cross sectional	15801	0.94 (0.91, 0.96)	0.13 (0.13, 0.14)	LR+ 1.08 (1.05, 1.11)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.47 (0.33, 0.67)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
No chest crackles (< 5 years)										
1 (Craig 2010)	Prospective - cross sectional	15801	0.96 (0.94, 0.98)	0.08 (0.08, 0.09)	LR+ 1.05 (1.03, 1.07)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.45 (0.28, 0.71)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
No abnormal chest sounds (< 5 years)										
2 (Craig 2010, Newman 2002)	Prospective - cross sectional	17467	0.96 (0.86, 0.99)	0.09 (0.02, 0.28)	LR+ 1.07 (0.99, 1.15)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 0.43 (0.31, 0.59)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
No abnormal chest sounds (≤ 3 months)										
1 (Newman 2002)	Prospective - cross sectional	1666	0.98 (0.95, 0.99)	0.05 (0.04, 0.06)	LR+ 1.03 (1.01, 1.05)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.40 (0.13, 1.24)	Not serious	Not serious	Not applicable	Very serious[5]	Low
No abnormal chest sounds (< 5 years)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Craig 2010)	Prospective - cross sectional	15801	0.93 (0.9, 0.95)	0.16 (0.16, 0.17)	LR+ 1.11 (1.08, 1.14)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.43 (0.31, 0.60)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
No stridor (< 5 years)										
1 (Craig 2010)	Prospective - cross sectional	15801	1 (0.99, 1)	0.01 (0.01, 0.01)	LR+ 1.01 (1.01, 1.01)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.17 (0.02, 1.22)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
No wheezing (< 5 years)										
1 (Craig 2010)	Prospective - cross sectional	15801	0.99 (0.97, 0.99)	0.06 (0.06, 0.07)	LR+ 1.05 (1.04, 1.06)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.24 (0.11, 0.49)	Very serious [1]	Not serious	Not applicable	Not serious	Low
Normal ENT (< 5 years)										
1 (Craig 2010)	Prospective - cross sectional	15801	0.63 (0.59, 0.68)	0.55 (0.54, 0.56)	LR+ 1.4 (1.3, 1.5)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.67 (0.59, 0.75)	Very serious [1]	Not serious	Not applicable	Not serious	Low
Normal ear examination (2 to <5 years)										
1 (Hay 2016)	Prospective - cross sectional	2740	0.93 (0.82, 0.97)	0.23 (0.22, 0.25)	LR+ 1.21 (1.12, 1.31)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.31 (0.12, 0.8)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Normal tympanic membranes (≤ 3 months)										
1 (Newman 2002)	Prospective - cross sectional	1666	0.96 (0.92, 0.98)	0.01 (0, 0.01)	LR+ 0.97 (0.94, 1.0)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 4.93 (1.85, 13.15)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
No runny nose (≤ 3 months)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Newman 2002)	Prospective - cross sectional	1666	0.95 (0.91, 0.98)	0.1 (0.09, 0.12)	LR+ 1.06 (1.02, 1.1)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.47 (0.23, 0.93)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Previous UTI (< 15 years)										
6 [k]	Prospective - cross sectional	5860	0.18 (0.11, 0.29)	0.92 (0.85, 0.96)	LR+ 2.40 (1.63, 3.46)	Very serious [1]	Not serious	Serious [4]	Serious [3]	Very low
					LR- 0.88 (0.81, 0.94)	Not serious	Not serious	Not serious	Not serious	High
Previous UTI (< 2 years)										
3 (Shaw 1998, Kanegaye 2014, Gauthier 2012)	Prospective - cross sectional	2776	0.17 (0.09, 0.31)	0.94 (0.78, 0.98)	LR+ 2.45 (1.27, 4.71)	Very serious [1]	Not serious	Serious [4]	Serious [3]	Very low
					LR- 0.92 (0.87, 0.98)	Not serious	Not serious	Not serious	Not serious	High
Previous UTI (2 to < 5 years)										
1 (Hay 2016)	Prospective - cross sectional	2740	0.2 (0.11, 0.33)	0.94 (0.93, 0.95)	LR+ 3.2 (1.85, 5.53)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.85 (0.75, 0.97)	Not serious	Not serious	Not applicable	Not serious	High
Previous UTI (< 15 years)										
2 (Dobbs and Fleming 1987, Mitiku 2018)	Prospective - cross sectional	344	0.22 (0.04, 0.67)	0.88 (0.65, 0.96)	LR+ 1.72 (0.98, 3.02)	Very serious [1]	Not serious	Not serious	Very serious[5]	Very low
					LR- 0.91 (0.72, 1.16)	Not serious	Not serious	Serious[4]	Serious [3]	Low
Abnormal general appearance (< 5 years)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
3 (Hay 2016, Craig 2010, Shaw 1998)	Prospective - cross sectional	23124	0.48 (0.27, 0.70)	0.62 (0.39, 0.81)	LR+ 1.26 (0.96, 1.64)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 0.85 (0.72, 1.00)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
Abnormal general appearance (< 2 years)										
1 (Shaw 1998)	Prospective - cross sectional	2331	0.49 (0.37, 0.6)	0.72 (0.7, 0.73)	LR+ 1.71 (1.33, 2.19)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.72 (0.57, 0.9)	Not serious	Not serious	Not applicable	Not serious	High
Abnormal general appearance (< 5 years)										
2 (Hay 2016, Craig 2010)	Prospective – cross sectional	20793	0.48 (0.17, 0.80)	0.57 (0.28, 0.82)	LR+ 1.13 (1.06, 1.20)	Very serious [1]	Not serious	Not serious	Not serious	Low
					LR- 0.90 (0.75, 1.07)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
Initial appearance (moderately or very ill) (≤ 3 months)										
1 (Newman 2002)	Prospective – cross sectional	1666	0.39 (0.31, 0.46)	0.64 (0.62, 0.67)	LR+ 1.08 (0.88, 1.33)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.95 (0.84, 1.09)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Irritability (data only reported < 2 years)										
5 [l]	Prospective – cross sectional	2411	0.28 (0.05, 0.77)	0.75 (0.36, 0.94)	LR+ 1.11 (0.72, 1.44)	Not serious	Not serious	Not serious	Serious [3]	Moderate
					LR- 0.92 (0.63, 1.04)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
Shivering/chills (< 5 years)										
1 (Hay 2016,		5186	0.24 (0.14, 0.39)	0.87 (0.49, 0.98)	LR+ 1.78 (0.57, 5.63)	Very serious [1]	Not serious	Very serious [2]	Very serious[5]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Williams-Smith 2020)	Prospective - cross sectional				LR- 0.92 (0.83, 1.02)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
Shivering/chills (< 5 years)										
1 (Hay 2016)	Prospective - cross sectional	5012	0.3 (0.22, 0.39)	0.73 (0.71, 0.74)	LR+ 1.09 (0.8, 1.47)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.97 (0.85, 1.1)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Chills (< 2 years)										
1 (Williams-Smith 2020)	Prospective – cross sectional	173	0.17 (0.09, 0.31)	0.95 (0.9, 0.98)	LR+ 3.57 (1.31, 9.76)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
					LR- 0.87 (0.76, 1.00)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Dehydrated (≤ 3 months)										
1 (Newman 2002)	Prospective - cross sectional	1666	0.05 (0.03, 0.1)	0.92 (0.91, 0.93)	LR+ 0.68 (0.35, 1.32)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 1.03 (0.99, 1.07)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Not alert (≤ 3 months)										
1 (Newman 2002)	Prospective - cross sectional	1666	0.19 (0.13, 0.25)	0.76 (0.74, 0.78)	LR+ 0.77 (0.56, 1.08)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 1.07 (0.99, 1.16)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Pale colour (≤ 3 months)										
1 (Newman 2002)	Prospective - cross sectional	1666	0.1 (0.06, 0.16)	0.91 (0.89, 0.92)	LR+ 1.12 (0.7, 1.81)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.99 (0.94, 1.04)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Capillary refill time >3 seconds (< 5 years)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Craig 2010)	Prospective - cross sectional	15801	0.01 (0.01, 0.03)	1 (1, 1)	LR+ 4.85 (2.07, 11.38)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.99 (0.98, 1.00)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Capillary refill time ≥2 seconds (< 2 years)										
1 (Williams-Smith 2020)	Prospective - cross sectional	173	0.34 (0.22, 0.49)	0.79 (0.71, 0.86)	LR+ 1.65 (0.98, 2.79)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
					LR- 0.83 (0.66, 1.04)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Elevated heart rate (< 5 years)										
1 (Craig 2010)	Prospective – cross sectional	15801	0.51 (0.47, 0.56)	0.58 (0.57, 0.59)	LR+ 1.22 (1.12, 1.33)	Very serious [1]	Not serious	Not applicable	Not serious	Low
					LR- 0.84 (0.77, 0.92)	Very serious [1]	Not serious	Not applicable	Not serious	Low
Jaundice (< 5 years)										
1 (Musa Aisien 2003)	Prospective - cross sectional	300	0.04 (0.01, 0.22)	0.98 (0.96, 0.99)	LR+ 2.02 (0.25, 16.68)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
					LR- 0.98 (0.91, 1.06)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
No fluid intake (< 5 years)										
1 (Craig 2010)	Prospective - cross sectional	15801	0.01 (0.01, 0.03)	1 (1, 1)	LR+ 4.31 (1.85, 10.06)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
					LR- 0.99 (0.98, 1.00)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Fever duration >24 hours (≤ 3 months)										
1 (Newman 2002)	Prospective - cross sectional	1666	0.19 (0.14, 0.26)	0.9 (0.88, 0.91)	LR+ 1.88 (1.33, 2.65)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.9 (0.83, 0.97)	Not serious	Not serious	Not applicable	Not serious	High
Fever duration >48 hours (< 2 years)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1 (Williams-Smith 2020)	Prospective - cross sectional	173	0.23 (0.13, 0.38)	0.90 (0.84, 0.95)	LR+ 2.46 (1.16, 5.18)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
					LR- 0.85 (0.72, 1.00)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Fever duration >72 hours (< 2 years)										
1 (Gauthier 2012)	Prospective - cross sectional	330	0.48 (0.35, 0.62)	0.64 (0.58, 0.69)	LR+ 1.34 (0.96, 1.85)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
					LR- 0.81 (0.61, 1.07)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Fever duration >5 days (< 5 years)										
1 (Festo 2011)	Prospective - cross sectional	370	0.43 (0.35, 0.51)	0.68 (0.62, 0.74)	LR+ 1.33 (1.02, 1.74)	Not serious	Not serious	Not applicable	Not serious	High
					LR- 0.84 (0.72, 1.00)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Fever duration >1 week (< 5 years)										
2 (Musa Aisien 2003, Ibeneme 2014)	Prospective - cross sectional	500	0.51 (0.12, 0.88)	0.80 (0.76, 0.83)	LR+ 2.33 (0.87, 6.29)	Very serious [1]	Not serious	Very serious [2]	Very serious[5]	Very low
					LR- 0.57 (0.21, 1.57)	Very serious [1]	Not serious	Very serious [2]	Very serious[5]	Very low
Degree of fever (≥39°C) (< 5 years)										
8 [m]	Prospective - cross sectional	7726	0.55 (0.38, 0.72)	0.64 (0.48, 0.77)	LR+ 1.54 (1.07, 2.18)	Not serious	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 0.71 (0.49, 0.95)	Not serious	Not serious	Very serious [2]	Serious [3]	Very low
Degree of fever (≥39°C) (< 2 years)										
7 [n]	Prospective - cross sectional	6478	0.57 (0.37, 0.75)	0.62 (0.45, 0.77)	LR+ 1.53 (1.00, 2.28)	Not serious	Not serious	Very serious [2]	Very serious[5]	Very low
					LR- 0.70 (0.44, 1.00)	Not serious	Not serious	Very serious [2]	Serious [3]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Degree of fever (≥39°C) (< 5 years)										
1 (Duong 2016)	Prospective - cross sectional	1247	0.45 (0.38, 0.51)	0.73 (0.70, 0.76)	LR+ 1.67 (1.4, 2.00)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.75 (0.67, 0.85)	Not serious	Not serious	Not applicable	Not serious	High
Tachypnoea (< 2 years)										
1 (Williams-Smith 2020)	Prospective - cross sectional	173	0.3 (0.19, 0.44)	0.82 (0.74, 0.88)	LR+ 1.63 (0.92, 2.9)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
					LR- 0.86 (0.7, 1.05)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Tachycardia (< 2 years)										
1 (Williams-Smith 2020)	Prospective - cross sectional	173	0.32 (0.2, 0.46)	0.75 (0.67, 0.82)	LR+ 1.3 (0.77, 2.18)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
					LR- 0.9 (0.72, 1.12)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Cyanosis (< 2 years)										
1 (Williams-Smith 2020)	Prospective - cross sectional	173	0.01 (0, 0.15)	0.99 (0.94, 1)	LR+ 0.88 (0.04, 21.28)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
					LR- 1 (0.97, 1.04)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Altered consciousness (< 2 years)										
1 (Williams-Smith 2020)	Prospective - cross sectional	173	0.01 (0, 0.15)	0.98 (0.93, 0.99)	LR+ 0.53 (0.03, 10.82)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
					LR- 1.01 (0.97, 1.05)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Purpura (< 2 years)										
1 (William	Prospective - cross sectional	173	0.01 (0, 0.15)	1 (0.94, 1)	LR+ 2.65 (0.05, 131.48)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
s-Smith 2020)					LR- 0.99 (0.96, 1.02)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Grunting (< 2 years)										
1 (William s-Smith 2020)	Prospective - cross sectional	173	0.06 (0.02, 0.18)	0.96 (0.91, 0.98)	LR+ 1.61 (0.4, 6.47)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
					LR- 0.97 (0.9, 1.06)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
Failure to thrive (< 5 years)										
1 (Festo 2011)	Prospective - cross sectional	370	0.01 (0, 0.05)	0.99 (0.96, 1)	LR+ 1.5 (0.21, 10.53)	Not serious	Not serious	Not applicable	Very serious[5]	Low
					LR- 1 (0.97, 1.02)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Increased sleepiness (≤ 3 months)										
1 (Newma n 2002)	Prospective - cross sectional	1666	0.34 (0.27, 0.41)	0.7 (0.68, 0.72)	LR+ 1.12 (0.89, 1.41)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.95 (0.85, 1.06)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Decreased social interaction (≤ 3 months)										
1 (Newma n 2002)	Prospective – cross sectional	1666	0.23 (0.17, 0.3)	0.74 (0.71, 0.76)	LR+ 0.87 (0.65, 1.17)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 1.05 (0.96, 1.14)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Decreased activity (≤ 3 months)										
1 (Newma n 2002)	Prospective - cross sectional	1666	0.17 (0.12, 0.24)	0.82 (0.8, 0.83)	LR+ 0.94 (0.66, 1.34)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 1.01 (0.94, 1.09)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Symptoms for 9 days or less (< 14 years)										
1 (Dobbs		75	0.94 (0.66, 0.99)	0.34 (0.23, 0.47)	LR+ 1.42 (1.14, 1.77)	Very serious [1]	Not serious	Not applicable	Not serious	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
and Fleming 1987)	Prospective - cross sectional				LR- 0.18 (0.03, 1.27)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low
Fever alone (< 2 years)										
1 (Pylkkanen 1979)	Prospective - cross sectional	200	0.1 (0.06, 0.17)	0.88 (0.78, 0.93)	LR+ 0.83 (0.37, 1.85)	Very serious [1]	Serious [6]	Not applicable	Very serious[5]	Very low
					LR- 1.02 (0.92, 1.14)	Very serious [1]	Serious [6]	Not applicable	Serious [3]	Very low
Muscle aches or pains (< 5 years)										
1 (O'Brien 2013)	Prospective - cross sectional	597	0.01 (0, 0.19)	0.9 (0.87, 0.92)	LR+ 0.14 (0.01, 2.23)	Not serious	Not serious	Not applicable	Very serious[5]	Low
					LR- 1.09 (1.04, 1.15)	Not serious	Not serious	Not applicable	Not serious	High

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality

GRADE domains

1. >33.3% of weighted data from studies at high risk of bias
2. i-squared >66.7%
3. 95% confidence interval for likelihood ratio crosses 1.0 or either 0.5 or 2
4. i-squared between 33.3% and 66.7%
5. 95% confidence interval for likelihood ratio crosses both 1.0 and either 0.5 or 2
6. >33.3% of weighted data from indirect or partially indirect studies
7. >33.3% of weighted data from studies at moderate or high risk of bias

References

a. Hay 2016, O'Brien 2013, Gauthier 2012, Msaki 2012, Dobbs and Fleming 1987, Lizama 2005, Festo 2011, Pylkkanen 1979 and Ibeneme 2014
b. O'Brien 2013, Gauthier 2012, Msaki 2012, Lizama 2005, Festo 2011, Pylkkanen 1979, Ibeneme 2014
c. Hay 2016, O'Brien 2013, Dobbs and Fleming 1987, Lizama 2005, Pylkkanen 1979 and Ibeneme 2014
d. Hay 2016, Gauthier 2012, Dobbs and Fleming 1987, Pylkkanen 1979, Struthers 2003
e. Hay 2016, Musa Aisien 2003, Newman 2002, Gauthier 2012, Lizama 2005, Festo 2011, Pylkkanen 1979, Ibeneme 2014 and Hoberman 1993
f. Musa Aisien 2003, Newman 2002, Gauthier 2012, Lizama 2005, Festo 2011, Pylkkanen 1979, Ibeneme 2014, Hoberman 1993
g. Craig 2010, Musa Aisien 2003, Gauthier 2012, Lizama 2005, Festo 2011, Pylkkanen 1979, Ibeneme 2014 and Hoberman 1993
h. Musa Aisien 2003, Gauthier 2012, Lizama 2005, Festo 2011, Pylkkanen 1979, Ibeneme 2014 and Hoberman 1993
i. Hay 2016, Musa Aisien 2003, Verbakel 2015, Gauthier 2012, Msaki 2012, Lizama 2005, Pylkkanen 1979, Ibeneme 2014
j. Musa Aisien 2003, Verbakel 2015, Gauthier 2012, Msaki 2012, Lizama 2005, Pylkkanen 1979, Ibeneme 2014
k. Hay 2016, Shaw 1998, Kanegaye 2014, Gauthier 2012, Dobbs and Fleming 1987, Mitiku 2018
l. O'Brien 2013, Musa Aisien 2003, Verbakel 2016, Festo 2011 and Hoberman 1993
m. Williams-Smith 2020, Festo 2011, Newman 2002, Bonadio 1991, Duong 2016, Hoberman 1993, Msaki 2012 and Shaw 1998
n. Williams-Smith 2020, Festo 2011, Newman 2002, Bonadio 1991, Hoberman 1993, Msaki 2012, Shaw 1998

Symptoms and signs individually – sensitivity analysis (removing Pylkkanen 1979 at committee request)

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
Dysuria (< 14 years)										
8 [a]	Prospective - cross sectional Retrospective - cohort	5615	0.31 (0.11, 0.61)	0.90 (0.81, 0.95)	LR+ 3.13 (1.87, 4.62)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 0.75 (0.47, 0.94)	Not serious	Not serious	Very serious [2]	Serious [3]	Very low
Dysuria (< 2 years)										
6 [b]	Prospective - cross sectional Retrospective - cohort	2800	0.21 (0.06, 0.56)	0.92 (0.83, 0.97)	LR+ 2.86 (1.33, 4.94)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 0.83 (0.52, 0.98)	Very serious [1]	Not serious	Very serious [2]	Not serious	Very low
Frequency (< 14 years)										
5 [c]	Prospective - cross sectional Retrospective - cohort	5870	0.27 (0.11, 0.53)	0.88 (0.73, 0.96)	LR+ 2.31 (1.82, 2.90)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
					LR- 0.82 (0.64, 0.94)	Very serious [1]	Not serious	Very serious [2]	Not serious	Very low
Frequency (< 2 years)										
3 (O'Brien 2013, Lizama 2005, Ibeneme 2014)	Prospective - cross sectional Retrospective - cohort	1939	0.20 (0.11, 0.36)	0.93 (0.86, 0.96)	LR+ 2.41 (1.81, 3.21)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
					LR- 0.91 (0.81, 1.02)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
Bed wetting (< 14 years)										
3 (Hay 2016,		5436	0.18 (0.12, 0.27)	0.92 (0.85, 0.96)	LR+ 2.73 (1.52, 4.90)	Not serious	Not serious	Serious [4]	Serious [3]	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
O'Brien 2013, Dobbs and Fleming 1987)	Prospective - cross sectional				LR- 0.88 (0.82, 0.95)	Not serious	Not serious	Not serious	Not serious	High
Bed wetting (< 2 years)										
1 (O'Brien 2013)	Prospective - cross sectional	597	0.14 (0.06, 0.29)	0.94 (0.92, 0.96)	LR+ 2.43 (1.01, 5.87)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.91 (0.8, 1.04)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Haematuria (< 14 years) ***unclear if blood was visible or on dipstick in all studies***										
3 (Hay 2016, Dobbs and Fleming 1987, Lizama 2005)	Prospective - cross sectional Retrospective - cohort	5615	0.04 (0.03, 0.07)	0.99 (0.97, 1.00)	LR+ 3.18 (1.68, 6.01)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
					LR- 0.97 (0.95, 1.00)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
Haematuria (< 2 years) ***unclear if blood was visible or on dipstick in all studies***										
1 (Lizama 2005)	Retrospective - cohort	1140	0.05 (0.03, 0.08)	0.98 (0.97, 0.99)	LR+ 2.66 (1.27, 5.54)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
					LR- 0.97 (0.94, 1.00)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
Malodorous urine (< 14 years)										
4 (Hay 2016, Gauthier 2012, Dobbs and Fleming	Prospective - cross sectional	5533	0.46 (0.31, 0.62)	0.76 (0.56, 0.89)	LR+ 1.89 (0.98, 3.62)	Very serious [1]	Not serious	Very serious [2]	Very serious [5]	Very low
					LR- 0.75 (0.53, 1.07)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
1987, Struthers 2003)										
Malodorous urine (< 2 years)										
2 (Gauthier 2012, Struthers 2003)	Prospective - cross sectional	441	0.54 (0.41, 0.67)	0.59 (0.38, 0.77)	LR+ 1.35 (0.65, 2.77)	Very serious [1]	Not serious	Serious [4]	Very serious[5]	Very low
					LR- 0.82 (0.45, 1.48)	Very serious [1]	Not serious	Serious [4]	Very serious[5]	Very low
Vomiting (< 5 years)										
8 [d]	Prospective - cross sectional Retrospective - cohort	9435	0.24 (0.14, 0.39)	0.72 (0.61, 0.80)	LR+ 0.86 (0.67, 1.05)	Not serious	Not serious	Serious [4]	Serious [3]	Low
					LR- 1.05 (0.97, 1.11)	Very serious [1]	Not serious	Not serious	Serious [3]	Very low
Vomiting (< 2 years)										
7 [e]	Prospective - cross sectional Retrospective - cohort	4423	0.23 (0.12, 0.40)	0.72 (0.60, 0.82)	LR+ 0.85 (0.63, 1.08)	Very serious [1]	Not serious	Serious [4]	Serious [3]	Very low
					LR- 1.05 (0.96, 1.13)	Very serious [1]	Not serious	Serious [4]	Serious [3]	Very low
Diarrhoea (< 5 years)										
7 [f]	Prospective – cross sectional Retrospective – cohort	18553	0.20 (0.11, 0.34)	0.79 (0.69, 0.86)	LR+ 0.94 (0.64, 1.30)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 1.01 (0.91, 1.10)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
Diarrhoea (< 2 years)										

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
6 [g]	Prospective – cross sectional Retrospective – cohort	2752	0.20 (0.10, 0.37)	0.79 (0.68, 0.87)	LR+ 0.98 (0.61, 1.45)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
					LR- 1.00 (0.87, 1.10)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
Constipation (< 5 years)										
1 (Hay 2016)	Prospective – cross sectional	5012	0.27 (0.19, 0.37)	0.82 (0.81, 0.83)	LR+ 1.52 (1.10, 2.11)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
					LR- 0.89 (0.79, 1.00)	Not serious	Not serious	Not applicable	Serious [3]	Moderate
Abdominal pain (< 5 years)										
7 [h]	Prospective - cross sectional Retrospective - cohort	5597	0.26 (0.12, 0.47)	0.85 (0.67, 0.94)	LR+ 1.87 (0.80, 3.84)	Very serious [1]	Not serious	Very serious [2]	Very serious[5]	Very low
					LR- 0.87 (0.67, 1.06)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
Abdominal pain (< 2 years)										
6 [i]	Prospective - cross sectional Retrospective - cohort	2856	0.29 (0.12, 0.54)	0.80 (0.62, 0.90)	LR+ 1.50 (0.64, 2.91)	Very serious [1]	Not serious	Very serious [2]	Very serious[5]	Very low
					LR- 0.89 (0.62, 1.14)	Very serious [1]	Not serious	Very serious [2]	Serious [3]	Very low
No source of fever (< 5 years)										
3 (Craig 2010, Hoberman 1993, Shaw 1998)	Prospective - cross sectional	19276	0.85 (0.66, 0.94)	0.43 (0.05, 0.91)	LR+ 1.84 (0.67, 5.05)	Very serious [1]	Not serious	Very serious [2]	Very serious[5]	Very low
					LR- 0.44 (0.20, 0.95)	Not serious	Not serious	Very serious [2]	Not serious	Low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Indirectness	Inconsistency	Imprecision	Quality
No source of fever (< 2 years)										
2 (Hoberman 1993, Shaw 1998)	Prospective - cross sectional	3475	0.77 (0.61, 0.88)	0.68 (0.38, 0.88)	LR+ 2.46 (0.88, 6.89)	Not serious	Not serious	Very serious [2]	Very serious[5]	Very low
					LR- 0.36 (0.13, 0.96)	Not serious	Not serious	Very serious [2]	Not serious	Low
No convulsions (data only reported < 2 years)										
1 (Musa Aisien 2003)	Prospective - cross sectional	300	0.96 (0.78, 0.99)	0.11 (0.08, 0.15)	LR+ 1.08 (0.99, 1.18)	Very serious [1]	Not serious	Not applicable	Serious [3]	Very low
					LR- 0.34 (0.05, 2.38)	Very serious [1]	Not serious	Not applicable	Very serious[5]	Very low

GRADE domains

1. >33.3% of weighted data from studies at high risk of bias
2. i-squared >66.7%
3. 95% confidence interval for likelihood ratio crosses 1.0 or either 0.5 or 2.
4. i-squared between 33.3% and 66.7%
5. 95% confidence interval for likelihood ratio crosses both 1.0 and either 0.5 or 2

References

a. Hay 2016, O'Brien 2013, Gauthier 2012, Msaki 2012, Dobbs and Fleming 1987, Lizama 2005, Festo 2011, Ibeneme 2014
b. O'Brien 2013, Gauthier 2012, Msaki 2012, Lizama 2005, Festo 2011, Ibeneme 2014
c. Hay 2016, O'Brien 2013, Dobbs and Fleming 1987, Lizama 2005, Ibeneme 2014
d. Hay 2016, Musa Aisien 2003, Newman 2002, Gauthier 2012, Lizama 2005, Festo 2011, Ibeneme 2014, Hoberman 1993
e. Musa Aisien 2003, Newman 2002, Gauthier 2012, Lizama 2005, Festo 2011, Ibeneme 2014, Hoberman 1993
f. Craig 2010, Musa Aisien 2003, Gauthier 2012, Lizama 2005, Festo 2011, Ibeneme 2014, Hoberman 1993
g. Musa Aisien 2003, Gauthier 2012, Lizama 2005, Festo 2011, Ibeneme 2014, Hoberman 1993
h. Hay 2016, Musa Aisien 2003, Verbakel 2015, Gauthier 2012, Msaki 2012, Lizama 2005, Ibeneme 2014
i. Musa Aisien 2003, Verbakel 2015, Gauthier 2012, Msaki 2012, Lizama 2005, Ibeneme 2014

Diagnostic models combining symptoms and signs

Sensitivity, specificity and likelihood ratios

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
UTIcalc score≥ 2% (<2 years)										
1 (Boon 2022)	Cross-sectional study	96	0.75 (0.19, 0.99)	0.16 (0.09, 0.25)	LR+ 0.90 (0.51, 1.59)	Not serious	Not applicable	Not serious	Serious[2]	Moderate
					LR- 1.53 (0.26, 8.91)	Not serious	Not applicable	Not serious	Very serious[3]	Low
Gorelick score ≥ 2 variables (<2 years)										
1 (Boon 2022)	Cross-sectional study	100	0.91 (0.72, 0.99)	0.08 (0.03, 0.16)	LR+ 0.99 (0.86, 1.14)	Not serious	Not applicable	Not serious	Serious[2]	Moderate
					LR- 1.12 (0.24, 5.16)	Not serious	Not applicable	Not serious	Very serious[3]	Low
DUTY score (signs and symptoms) ≥ 5 points (< 5 years)										
1 (Boon 2022)	Cross-sectional study	297	0.08 (0.01, 0.25)	0.99 (0.96, 1.00)	LR+ 6.95 (1.22, 39.72)	Not serious	Not applicable	Not serious	Serious[2]	Moderate
					LR- 0.93 (0.84, 1.04)	Not serious	Not applicable	Not serious	Serious[2]	Moderate
Yale Observation scale ≥ 10 points (<3 months)										
1 (Zorc 2005) [a]	Prospective, cross-	995		0.93 (0.91, 0.95)	LR+ 0.59 (0.22, 1.59)	Serious[1]	Not applicable	Not serious	Very serious[3]	Very low

No. of studies	Study design	Sample size	Sensitivity (95%CI)	Specificity (95%CI)	Effect size (95%CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
	sectional study		0.04 (0.02, 0.11)		LR- 1.03 (0.98, 1.08)	Serious[1]	Not applicable	Not serious	Serious[2]	Low
Yale Observation scale > 7 points (<3 months)										
1 (Diaz 2016) [a]	Retrospective cohort	314	0.13 (0.07, 0.23)	0.86 (0.81, 0.90)	LR+ 0.92 (0.48, 1.18)	Serious[1]	Not applicable	Not serious	Very serious[3]	Very low
					LR- 1.01 (0.92, 1.12)	Serious[1]	Not applicable	Not serious	Serious[2]	Low
NICE traffic light system-amber or red positive (< 5 years)										
1 (De 2013) [a]	Prospective cohort study (post hoc analysis)	3653	0.79 (0.74, 0.82)	0.25 (0.23 to 0.26)	LR+ 1.04 (0.98, 1.10)	Serious[1]	Not applicable	Not serious	Serious[2]	Low
					LR- 0.88 (0.72, 1.08)	Serious[1]	Not applicable	Not serious	Serious[2]	Low

1. Study was at moderate risk of bias
2. 95% confidence interval for likelihood ratio crosses 1.0 or either 0.5 or 2
3. 95% confidence interval for likelihood ratio crosses 1.0 and either 0.5 or 2

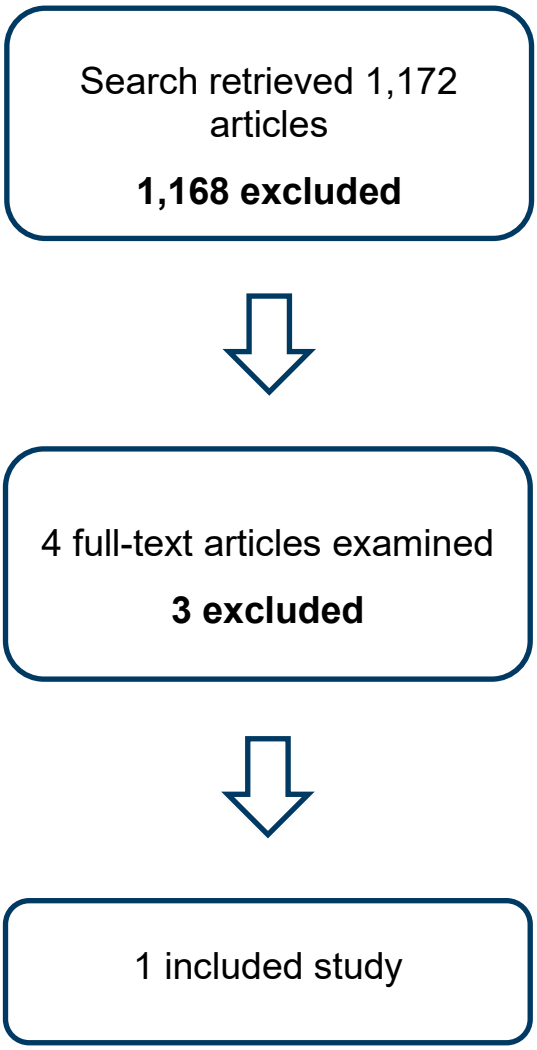
a. LR data was extracted from the Boon 2021 systematic review and back calculated to give 2x2 data using the Cochrane RevMan calculator.

c-statistics

No. of studies	Study design	Sample size	Effect size (95% CI)	Risk of bias	Inconsistency	Indirectness	Imprecision	Quality
DUTY Score (signs and symptoms model) ≥ 5 points (< 5 years)								
Boon (2022)	Cross-sectional study	297	AUC 0.55 (0.43-0.68)	Not serious	N/A	Not serious	Very serious[1]	Low

1. 95% confidence interval spans two categories of test effectiveness.

Appendix G – Economic evidence study selection



Appendix H – Economic evidence tables

Table 11: Hay et al. (2016)

Hay et al. (2016). The Diagnosis of Urinary Tract infection in Young children (DUTY): a diagnostic prospective observational study to derive and validate a clinical algorithm for the diagnosis of urinary tract infection in children presenting to primary care with an acute illness.[1]

Study details

Analysis: Cost utility analysis

Approach to analysis: Multiple models using both decision trees and Markov models to compare both the short-term as well as the medium- and long-term benefits, harms and costs of different urine sampling strategies for acutely unwell children <5 years old presenting to primary care. Different strategies were compared for both clean-catch and nappy pad samples.

UTI related complications considered: short- and medium-term models (UTI with or without pyelonephritic attack, vesicoureteral reflux), long term (infection-related renal scarring, end stage renal disease, dialysis, renal transplant)

Time horizon: short term (diagnosis and acute illness; up to 21 days), medium term (recurrent UTI; up to 3 years) and long term (long-term sequelae; lifetime)

Discounting: 3.5%

Interventions

Intervention 1: Sample none
Intervention 2: Clinical judgement
Intervention 3: DUTY 5%
Intervention 4: DUTY 10%
Intervention 5: DUTY 20%
Intervention 6: Sample all
Intervention 7: DUTY points ≥ 6
Intervention 7: DUTY points ≥ 5
Intervention 7: DUTY points ≥ 4
Intervention 7: DUTY points ≥ 3

Population

Population: Acutely unwell children <5 years old presenting to primary care

Data sources

Baseline/natural history: Biologically confirmed UTI based on laboratory test results from the DUTY study.

Effectiveness: Risk stratification for the different sampling strategies were obtained from the results from the DUTY study.

Resource use & Costs: Short-term resource use from DUTY RCT, expert opinion, UK reference costs, published sources and a prescription cost analysis. Medium- and long-term resource use from DUTY RCT, a UK study on nephrology management and UK reference costs.

QoL: Authors conducted a search of the cost-effectiveness analysis registry for studies reporting utilities for unwell infants. No studies reported estimates for infants with UTI. Therefore, rotavirus was used as a proxy measure given its symptoms were deemed to closely match UTI symptoms. Base case utility estimates were elicited from caregivers of children <3 years old in Canada using the Health Utilities Index (HUI2). Sensitivity analysis explored the impact of using GP EQ-5D derived utility scores. Utility values for pyelonephritis came from reported values for adults in the literature. Long-term utilities for dialysis and renal transplant estimated from a time-trade-off exercise of transplant and haemodialysis patients.

Base-case results

Short-term costs and benefits

Analysis	Intervention	Absolute		Incremental		
		Costs (£)	QALDs	Costs (£)	QALDs	INMB
Clean catch	Clinical judgement	£45.02	20.709	-	-	-
	Sample none	£43.64	20.708	-£1.38	-0.001	1.34 (1.32 to 1.36)
	DUTY 5%	£44.28	20.709	-£0.74	0	0.74 (0.72 to 0.76)
	DUTY 10%	£45.01	20.709	-£0.01	0	0.02 (0.01 to 0.04)
	DUTY 20%	£46.59	20.709	£1.57	0	-1.54 (-1.56 to -1.51)
	Sample all	£60.23	20.710	£15.21	0.001	-15.14 (-15.25 to -15.03)
	DUTY points ≥ 6	NR	20.708	NR	-0.001	0.79 (0.77 to 0.81)
	DUTY points ≥ 5	NR	20.709	NR	0	0.42 (0.40 to 0.44)

Hay et al. (2016). The Diagnosis of Urinary Tract infection in Young children (DUTY): a diagnostic prospective observational study to derive and validate a clinical algorithm for the diagnosis of urinary tract infection in children presenting to primary care with an acute illness.[1]

	DUTY points ≥ 4	NR	20.709	NR	0	-1.76 (-1.79 to -1.74)
	DUTY points ≥ 3	NR	20.709	NR	0	-2.40 (-2.42 to -2.37)
Nappy pad	Clinical judgement	£44.10	20.708	-	-	-
	Sample none	£43.64	20.708	-£0.46	0	0.44 (0.42 to 0.47)
	DUTY 5%	£44.54	20.709	£0.44	0.001	-0.42 (-0.44 to -0.39)
	DUTY 10%	£45.38	20.709	£1.28	0.001	-1.25 (-1.27 to -1.23)
	DUTY 20%	£46.99	20.709	£2.89	0.001	-2.84 (-2.87 to -2.82)
	Sample all	£62.10	20.710	£18.00	0.002	-17.91 (-18.05 to -17.78)

Medium- and long-term costs and benefits

Analysis	Intervention	Absolute		Incremental		
		Costs (£)	QALYs	Costs (£)	QALYs	INMB
Clean catch	Clinical judgement	£200.16	25.722	-	-	-
	Sample none	£196.13	25.722	-£4.03	0	3.94 (3.90 to 3.96)
	DUTY 5%	£197.92	25.722	-£2.24	0	2.24 (2.22 to 2.26)
	DUTY 10%	£200.10	25.722	-£0.06	0	0.09 (0.08 to 0.11)
	DUTY 20%	£204.85	25.722	£4.69	0	-4.63 (-4.67 to -4.59)
	Sample all	£245.99	25.722	£45.83	0	-45.73 (-45.99 to -45.41)
	DUTY points ≥ 6	£197.77	25.722	-£2.39	0	2.35 (2.33 to 2.37)
	DUTY points ≥ 5	£198.94	25.722	-£1.22	0	1.22 (1.20 to 1.24)
	DUTY points ≥ 4	£205.54	25.722	£5.38	0	-5.34 (-5.38 to -5.29)
	DUTY points ≥ 3	£207.43	25.722	£7.27	0	-7.23 (-7.29 to -7.17)
Nappy pad	Clinical judgement	£197.47	25.722	-	-	-
	Sample none	£196.13	25.722	-£1.34	0	1.31 (1.29 to 1.32)
	DUTY 5%	£198.75	25.722	£1.28	0	-1.24 (-1.26 to -1.22)
	DUTY 10%	£201.31	25.722	£3.84	0	-3.78 (-3.81 to -3.74)
	DUTY 20%	£206.23	25.722	£8.76	0	-8.68 (-8.74 to -8.62)
	Sample all	£252.44	25.722	£54.97	0	-54.81 (-55.17 to -54.44)

Sensitivity analyses

Deterministic: Sensitivity analysis for short-term results showed that for clean catch samples, the sample none and DUTY 5% strategies were not sensitive to any 1 parameter: that is to say more conservative approaches to urine sampling strategies represented an effective use of NHS resources, assuming QALDs are valued at £20,000 each. Although not presented, authors report similar results were found for deterministic analysis using nappy pad samples.

Probabilistic: Regarding short-term results, both clean-catch and nappy pad samples, the sample none strategy had the greatest probability (99.9% and 100% respectively) of being an effective use of NHS resources, assuming QALYs are valued at £20,000 each. Regarding medium- and long-term results, both

Hay et al. (2016). The Diagnosis of Urinary Tract infection in Young children (DUTY): a diagnostic prospective observational study to derive and validate a clinical algorithm for the diagnosis of urinary tract infection in children presenting to primary care with an acute illness.[1]	
	clean-catch and nappy pad samples, the sample none strategy had the greatest probability (100% for both) of being an effective use of NHS resources, assuming QALYs are valued at £20,000 each.
Comments	**Source of funding:** National Institute for Health Research (NIHR) **Limitations:** Minor limitations (Table 12)

Abbreviations: EQ-5D, Euro-qol five dimensions; GP, general practitioners; INMB, incremental net monetary benefit; NHS, National Health Service; QALDs, quality-adjusted life days; QALYs, quality-adjusted life years; QoL, quality of life; RCT, randomized controlled trial; UK, United Kingdom; UTI, urinary tract infection

Table 12: Economic evaluation checklist Hay et al. (2016)

Category	Rating	Comments
Applicability		
1.1 Is the study population appropriate for the review question?	Yes	
1.2 Are the interventions appropriate for the review question?	Yes	
1.3 Is the system in which the study was conducted sufficiently similar to the current UK context?	Yes	
1.4 Is the perspective for costs appropriate for the review question?	Yes	
1.5 Is the perspective for outcomes appropriate for the review question?	Yes	Quality-adjusted life-years (QALYs) or life-days (QALDs)
1.6 Are all future costs and outcomes discounted appropriately?	Yes	
1.7 Are QALYs, derived using NICE's preferred methods, or an appropriate social care-related equivalent used as an outcome? If not, describe rationale and outcomes used in line with analytical perspectives taken (item 1.5 above).	Partly	Authors found no studies reporting estimates of quality of life for infants with UTI. Therefore, it was agreed to use rotavirus as a proxy for UTI because the symptoms most closely matched UTI. In the base case, caregiver-reported HUI2-derived utility scores for rotavirus used. GP EQ-5D-derived utility scores for rotavirus used as a sensitivity analysis.
1.8 OVERALL JUDGEMENT	**DIRECTLY APPLICABLE**	
Limitations		
2.1 Does the model structure adequately reflect the nature of the topic under evaluation?	Yes	
2.2 Is the time horizon sufficiently long to reflect all important differences in costs and outcomes?	Yes	
2.3 Are all important and relevant outcomes included?	Yes	

Category	Rating	Comments
2.4 Are the estimates of baseline outcomes from the best available source?	Partly	Some parameters are assumptions (i.e. MCUG for VUR) or informed by expert opinion (effect of resistance on symptom resolution rates). However, most parameters are informed by trial evidence.
2.5 Are the estimates of relative intervention effects from the best available source?	Yes	
2.6 Are all important and relevant costs included?	Yes	
2.7 Are the estimates of resource use from the best available source?	Yes	
2.8 Are the unit costs of resources from the best available source?	Yes	
2.9 Is an appropriate incremental analysis presented or can it be calculated from the data?	Yes	
2.10 Are all important parameters whose values are uncertain subjected to appropriate sensitivity analysis?	Partly	All costs were included in the model as uniform distributions, with a lower bound 50% lower than the estimated mean and an upper bound 50% greater than the estimated mean. All utilities were included in the model as uniform distributions, with a lower bound 20% lower than the estimated mean and an upper bound 20% greater than the estimated mean. Although such assumptions are better than assuming fixed values for parameters, it would be preferrable if better data was available by which to estimate a parameter and its distribution.
2.11 Has no potential financial conflict of interest been declared?	Yes	
2.12 OVERALL ASSESSMENT	**MINOR LIMITATIONS**	

Appendix I – Health economic model

This question was not prioritised for original economic analysis.

Appendix J – Excluded studies

Clinical studies

Author	Reason for exclusion
Abuzeyad, Feras Husain, Ashraf, Muhammad Kashif, Ebrahim, Appas et al. (2020) Clinical presentation, culture and sensitivity pattern of urinary tract infection. Bahrain Medical Bulletin 42(1): 20-23	- Not a relevant study design *Only culture positive children were included in the study. Therefore, not possible to assess diagnostic value of the symptoms and signs reported.*
Afroz, Shireen, Khan, Anwar Hossain, Roy, Dilip Kumar et al. (2008) Risk factors of Urinary Tract Infection (UTI) in children with nephrotic syndrome. Bangladesh Renal Journal 27(2): 28-32	- Full text paper not available *Advised paper was not obtainable.*
Akagawa, Yuko, Kimata, Takahisa, Akagawa, Shohei et al. (2020) Optimal bacterial colony counts for the diagnosis of upper urinary tract infections in infants. Clinical and experimental nephrology 24(3): 253-258	- Study does not provide data on UTI diagnosis *Background paper on culture cut-offs*
Al-Otaibi, Fawzia E and Bukhari, Elham E (2013) Clinical and laboratory profiles of urinary tract infections caused by extended-spectrum beta-lactamase-producing Escherichia coli in a tertiary care center in central Saudi Arabia. Saudi medical journal 34(2): 171-6	- Incorrect population *The study population included adults, and everyone had a diagnosis of a UTI.* - Study does not contain any relevant index tests
Aldridge, Patrick, Rao, Arjun, Sethumadavan, Rebecca et al. (2018) Fever under 3 months and the full septic screen: Time to think again? A retrospective cohort study at a tertiary-level paediatric hospital. Journal of paediatrics and child health 54(3): 272-278	- Study does not provide data on UTI diagnosis *Outcome was serious bacterial infection, data for UTI was not presented separately*
Amin, Ezzat K, Abo Zaid, Ali M, I Kotb, Abd El Rahman et al. (2020) Incidence, risk factors and causative bacteria of urinary tract infections and their antimicrobial sensitivity patterns in toddlers and children: A report from two tertiary care hospitals. Saudi journal of kidney diseases and transplantation : an official publication of the Saudi Center for Organ Transplantation, Saudi Arabia 31(1): 200-208	- Incorrect population *The study did not exclude children on antibiotics and included a prolonged antibiotic category that was not defined.*
Amin, Omayma, Prestel, Christopher, Gonzalez, Mark D et al. (2020) Urinary Tract Infections	- Not a relevant study design

Author	Reason for exclusion
With Extended-spectrum-beta-lactamase-producing Bacteria: Case-control Study. The Pediatric infectious disease journal 39(3): 211-216	*Nested case-control study*
Arica, Vefik, Tutanc, Murat, Arica, Secil et al. (2012) Analysis of children admitted to emergency department with acute abdominal pain in Van. Duzce Medical Journal 14(1): 14-18	- Study not reported in English
Bahagon, Y., Raveh, D., Schlesinger, Y. et al. (2007) Prevalence and predictive features of bacteremic urinary tract infection in emergency department patients. European Journal of Clinical Microbiology and Infectious Diseases 26(5): 349-352	- Incorrect population *Participants all had a diagnosis of UTI*
Bari, Attia, Saeed, Sara, Javed, Humera et al. (2021) Clinical utility and accuracy of UTI calculator for estimating the probability of urinary tract infection in young febrile children. Pakistan Paediatric Journal 45(4): 405-410	- Not possible to calculate a contingency table from the data provided *Missing participants so table cannot be calculated accurately.*
Bin Salleeh, Hashim, McGillivray, David, Martin, Mitch et al. (2010) Duration of fever affects the likelihood of a positive bag urinalysis or catheter culture in young children. The Journal of pediatrics 156(4): 629-33	- Not a relevant study design *Participants with a negative dipstick test did not undergo any further reference (urine culture) testing.*
Birnie, Kate, Hay, Alastair D, Wootton, Mandy et al. (2017) Comparison of microbiological diagnosis of urinary tract infection in young children by routine health service laboratories and a research laboratory: Diagnostic cohort study. PloS one 12(2): e0171113	- Study does not provide data on UTI diagnosis *DUTY study paper, but no outcomes of interest to the NICE review reported in this paper.*
Bitsori, M, Maraki, S, Koukouraki, S et al. (2012) Pseudomonas aeruginosa urinary tract infection in children: risk factors and outcomes. The Journal of urology 187(1): 260-4	- Incorrect population *Participants all had a diagnosis of UTI*
Bolivar, Patricia, de Ponga, Pilar, Granda, Elena et al. (2020) Prevalence of Urinary Tract Infection in Febrile Infants With Upper Respiratory Tract Symptomatology. The Pediatric infectious disease journal 39(11): e380-e382	- Not a relevant study design *Only participants with a positive dipstick test went on to receive a culture*
Boon, Hanne A., De Burghgraeve, Tine, Verbakel, Jan Y et al. (2021) Point-of-care tests for pediatric urinary tract infections in general	- Study does not contain any relevant index tests

Author	Reason for exclusion
practice: a diagnostic accuracy study. Family practice na(na): na-na	*Point of care medical tests not symptoms or signs.*
Brkic, Selmira, Mustafic, Sehveta, Nuhbegovic, Sabina et al. (2010) Clinical and epidemiology characteristics of urinary tract infections in childhood. Medicinski arhiv 64(3): 135-8	- Reference standard in study does not match that specified in protocol *No reference standard is quoted only UTI present or not present.*
Bulloch B, Bausher JC, Pomerantz WJ et al. (2000) Can urine clarity exclude the diagnosis of urinary tract infection?. Pediatrics 106(5): E60	- Conference abstract
Butler, Christopher C, O'Brien, Kathryn, Pickles, Timothy et al. (2015) Childhood urinary tract infection in primary care: a prospective observational study of prevalence, diagnosis, treatment, and recovery. The British journal of general practice : the journal of the Royal College of General Practitioners 65(633): e217-23	- Study does not provide data on UTI diagnosis *No data provided in this paper for index tests compared to a reference test in this DUTY study paper*
Chaudhari, Pradip P; Monuteaux, Michael C; Bachur, Richard G (2018) Microscopic Bacteriuria Detected by Automated Urinalysis for the Diagnosis of Urinary Tract Infection. The Journal of pediatrics 202: 238-244e1	- Study does not provide data on UTI diagnosis *No data provided in this paper for index tests compared to a reference test in this study.*
Chaudhari, Pradip P, Monuteaux, Michael C, Shah, Pinkey et al. (2017) The Importance of Urine Concentration on the Diagnostic Performance of the Urinalysis for Pediatric Urinary Tract Infection. Annals of emergency medicine 70(1): 63-71e8	- Study does not provide data on UTI diagnosis *No data provided in this paper for index tests compared to a reference test in this study.*
Chen L and Baker MD (2006) Racial and ethnic differences in the rates of urinary tract infections in febrile infants in the emergency department. Pediatric emergency care 22(7): 485-487	- Study does not provide data on UTI diagnosis *No data provided in this paper for index tests compared to a reference test in this study.*
Clyne, Melanie (2014) Paediatrics: dipstick adequate for febrile UTI test. Nature reviews. Urology 11(6): 304	- Not a relevant study design *Narrative review*
Colborn, Kathryn L, Bronsert, Michael, Hammermeister, Karl et al. (2019) Identification of urinary tract infections using electronic health record data. American journal of infection control 47(4): 371-375	- Incorrect population *Not a study in children, and no data presented for children.*

Author	Reason for exclusion
de Salis, Isabel, Whiting, Penny, Sterne, Jonathan A C et al. (2013) Using qualitative research to inform development of a diagnostic algorithm for UTI in children. Family practice 30(3): 325-31	- Not a relevant study design *Narrative review*
De Santis, Olga, Kilowoko, Mary, Kyungu, Esther et al. (2017) Predictive value of clinical and laboratory features for the main febrile diseases in children living in Tanzania: A prospective observational study. PloS one 12(5): e0173314	- Not a relevant study design *Case control study*
De, Sukanya, Williams, Gabrielle J, Hayen, Andrew et al. (2013) Accuracy of the "traffic light" clinical decision rule for serious bacterial infections in young children with fever: a retrospective cohort study. BMJ (Clinical research ed.) 346: f866	- Duplicate reference
Diaz, Marta German, Garcia, Rosa Pavo, Gamero, Daniel Blazquez et al. (2016) Lack of Accuracy of Biomarkers and Physical Examination to Detect Bacterial Infection in Febrile Infants. Pediatric emergency care 32(10): 664-668	- Study does not contain any relevant index tests
Dickinson JA (1979) Incidence and outcome of symptomatic urinary tract infection in children. British medical journal 1(6174): 1330-1332	- Not possible to calculate a contingency table from the data provided
Doern, Christopher D. and Richardson, Susan E. (2016) Diagnosis of urinary tract infections in children. Journal of Clinical Microbiology 54(9): 2233-2242	- Review article but not a systematic review
Downing, Harriet, Thomas-Jones, Emma, Gal, Micaela et al. (2012) The diagnosis of urinary tract infections in young children (DUTY): protocol for a diagnostic and prospective observational study to derive and validate a clinical algorithm for the diagnosis of UTI in children presenting to primary care with an acute illness. BMC infectious diseases 12: 158	- Not possible to calculate a contingency table from the data provided *Study protocol paper only*
Elkhunovich, Marsha A and Wang, Vincent J (2015) Assessing the Utility of Urine Testing in Febrile Infants Aged 2 to 12 Months With Bronchiolitis. Pediatric emergency care 31(9): 616-20	- Study does not provide data on UTI diagnosis *Does not include symptoms or signs for UTI diagnosis.*

Author	Reason for exclusion
Eun, So Hyun, Kang, Ji-Man, Ahn, Jong Gyun et al. (2020) Clinical features of and antibiotic resistance in recurrent urinary tract infection in children with vesicoureteral reflux. Pediatric Infection and Vaccine 27(1): 35-44	- Study does not contain any relevant index tests *Does not include symptoms or signs for UTI diagnosis.*
Fahimi, Daryoosh, Khedmat, Leila, Afshin, Azadeh et al. (2021) Clinical manifestations, laboratory markers, and renal ultrasonographic examinations in 1-month to 12-year-old Iranian children with pyelonephritis: a six-year cross-sectional retrospective study. BMC infectious diseases 21(1): 189	- Incorrect population *Only included children with a diagnosis of acute pyelonephritis.*
Fan, Nai-Chia, Chen, Hsin-Hang, Chen, Chyi-Liang et al. (2014) Rise of community-onset urinary tract infection caused by extended-spectrum beta-lactamase-producing Escherichia coli in children. Journal of microbiology, immunology, and infection = Wei mian yu gan ran za zhi 47(5): 399-405	- Not a relevant study design *Case-control design*
Felt, Jon R, Yurkovich, Chelsey, Garshott, Danielle M et al. (2017) The Utility of Real-Time Quantitative Polymerase Chain Reaction Genotype Detection in the Diagnosis of Urinary Tract Infections in Children. Clinical pediatrics 56(10): 912-919	- Study does not contain any relevant index tests for UTI diagnosis *Does not include symptoms or signs for UTI diagnosis.*
Foglia, E.E. and Lorch, S.A. (2012) Clinical predictors of urinary tract infection in the neonatal intensive care unit. Journal of Neonatal-Perinatal Medicine 5(4): 327-333	- Incorrect setting *Neonatal intensive care unit.*
Forster, C S, Haslam, D B, Jackson, E et al. (2017) Utility of a routine urinalysis in children who require clean intermittent catheterization. Journal of pediatric urology 13(5): 488e1-488e5	- Incorrect population *Study of children with neurogenic bladder (out-of-scope population).*
Forster, Catherine S and Wang, Jichuan (2020) Symptom- and urinalysis-based approach to diagnosing urinary tract infections in children with neuropathic bladders. Pediatric nephrology (Berlin, Germany) 35(5): 807-814	- Incorrect population *Study of children with neurogenic bladder (out-of-scope population).*
Freedman, Stephen B; Al-Harthy, Nesrin; Thull-Freedman, Jennifer (2009) The crying infant: diagnostic testing and frequency of serious underlying disease. Pediatrics 123(3): 841-8	- Study does not contain any relevant index tests for UTI diagnosis *Not symptoms or signs.*

Author	Reason for exclusion
Gauthier, Marie, Gouin, Serge, Phan, Veronique et al. (2012) Association of malodorous urine with urinary tract infection in children aged 1 to 36 months. Pediatrics 129(5): 885-90	- Duplicate reference
Geurts, Dorien H F, Vos, Willem, Moll, Henriette A et al. (2014) Impact analysis of an evidence-based guideline on diagnosis of urinary tract infection in infants and young children with unexplained fever. European journal of pediatrics 173(4): 463-8	- Study does not contain any relevant index tests *Not symptoms or signs.*
Ghaemi, Sedigheh; Fesharaki, Reyhaneh Jafari; Kelishadi, Roya (2007) Late onset jaundice and urinary tract infection in neonates. Indian journal of pediatrics 74(2): 139-41	- Not possible to calculate a contingency table from the data provided
Goldman, Michael, Rosenfeld-Yehoshua, Noa, Lerner-Geva, Liat et al. (2008) Clinical features of community-acquired Pseudomonas aeruginosa urinary tract infections in children. Pediatric nephrology (Berlin, Germany) 23(5): 765-8	- Incorrect population *Included children with urinary tract malformation (out-of-scope) and did not appear exclude children prescribed antibiotics.*
Goodlet, Kellie J.; Fairman, Kathleen A.; Afolabi, Titilola M. (2020) Association of Antibiotic Treatment Duration With Recurrence of Uncomplicated Urinary Tract Infection in Pediatric Patients. Annals of Pharmacotherapy 54(8): 757-766	- Incorrect population *Participants all had a diagnosis of UTI*
Gorelick MH, Hoberman A, Kearney D et al. (2003) Validation of a decision rule identifying febrile young girls at high risk for urinary tract infection. Pediatric emergency care 19(3): 162-164	- Not a relevant study design *Model validation study with a case control design*
Guri, Alex, Hurvitz Florenthal, Michal, Scheier, Eric et al. (2021) Contamination rates of different methods of urine culture collection in children: A retrospective cohort study. Journal of paediatrics and child health 57(8): 1281-1287	- Study does not provide data on UTI diagnosis *Not symptoms or signs of UTI*
Hay, Alastair D (2018) UTICalc may enhance UTI risk-estimation in young children. The Journal of pediatrics 200(na): 291-294	- Not a relevant study design *Letter.*
Heale WF, Weldon AP HA (1973) Reflux Nephropathy: Presentation of urinary infection in	- Not a relevant study design

Author	Reason for exclusion
childhood. The Medical Journal of Australia 23(9): 1138-40	*Splits symptoms and signs into localizing and non-localizing and presents data for combinations of symptoms chosen not a priori.*
Hidas, Guy, Billimek, John, Nam, Alexander et al. (2015) Predicting the Risk of Breakthrough Urinary Tract Infections: Primary Vesicoureteral Reflux. The Journal of urology 194(5): 1396-401	- Study does not provide data on UTI diagnosis *Not symptoms or signs*
Hollingworth, William, Busby, John, Butler, Christopher C et al. (2017) The Diagnosis of Urinary Tract Infection in Young Children (DUTY) Study Clinical Rule: Economic Evaluation. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 20(4): 556-566	- Not a relevant study design *Economic evaluation study (see economic studies section)*
Hsiao AL, Chen L BM (2006) Incidence and predictors of serious bacterial infections among 57- to 180-day-old infants. Pediatrics 5(117): 1695-701	- Index test results cannot be related to UTI diagnosis *Study looks at serious bacterial infections rather than UTIs.*
Kanellopoulos, Theodoros A, Salakos, Christos, Spiliopoulou, Iris et al. (2006) First urinary tract infection in neonates, infants and young children: a comparative study. Pediatric nephrology (Berlin, Germany) 21(8): 1131-7	- Incorrect population *Participants had a diagnosis of UTI at point of inclusion to study.*
Karavanaki, Kyriaki A, Soldatou, Alexandra, Koufadaki, Athina Maria et al. (2017) Delayed treatment of the first febrile urinary tract infection in early childhood increased the risk of renal scarring. Acta paediatrica (Oslo, Norway : 1992) 106(1): 149-154	- Study does not provide data on UTI diagnosis *Not symptoms and signs of UTI*
Kasmire, Kathryn E, Vega, Carolina, Bennett, Nicholas J et al. (2021) Hypothermia: A Sign of Sepsis in Young Infants in the Emergency Department?. Pediatric emergency care 37(3): e124-e128	- Reference standard in study does not match that specified in protocol *Reference standard for UTI diagnosis not reported or sample method.*
Khassawneh, Mohammad; Khriesat, Wadah; Khader, Yousef (2008) Clinical features of urinary tract infection in infants born preterm. Journal of Pediatric Infectious Diseases 3(4): 245-248	- Incorrect population *All participants had a diagnosis of UTI at point of inclusion to study.*
Kim, Yun Hee; Yang, Eun Mi; Kim, Chan Jong (2017) Urinary tract infection caused by	- Study does not provide data on UTI diagnosis

Author	Reason for exclusion
community-acquired extended-spectrum beta-lactamase-producing bacteria in infants. Jornal de Pediatria 93(3): 260-266	*Not symptoms or signs of UTI.*
Krober MS, Bass JW, Powell JM, Smith FR SD (1985) Bacterial and viral pathogens causing fever in infants less than 3 months old. Am J Dis Child 9(139): 889-92	- Study does not contain any relevant index tests for UTI diagnosis *Not symptoms or signs of UTI*
Lagos Zuccone R, Carter JS HP (1994) Utilidad de una tira reactiva y del aspecto macroscópico de la orina para descartar la sospecha clínica de infección del tracto urinario en niños ambulatorios. Rev Chil Pediatr 2(65): 88-94	- Study not reported in English - Incorrect population *Included a cohort of children likely to be out-of-scope for this update (immunosuppressed).*
Lee, Ha Ni, Kwak, Young Ho, Jung, Jae Yun et al. (2019) Are parents' statements reliable for diagnosis of serious bacterial infection among children with fever without an apparent source?: A retrospective study. Medicine 98(42): e17530	- Diagnosis under investigation does not match that specified in the protocol *Diagnosis was Serious Bacterial Infection (SBI includes UTI), but UTI was not presented separately.*
Lendner, Idan, Justman, Naphtali, Givon-Lavi, Noga et al. (2019) Urine dipstick low sensitivity for UTI diagnosis in febrile infants *. Infectious diseases (London, England) 51(10): 764-771	- Not a relevant study design *Case control study and incorrect index test (dipstick test) which is out-of-scope.*
Leung, Alexander K C, Wong, Alex H C, Leung, Amy A M et al. (2019) Urinary Tract Infection in Children. Recent patents on inflammation & allergy drug discovery 13(1): 2-18	- Not a relevant study design *Narrative review which includes diagnosis but does not present data for the included symptoms or signs.*
Lo, Denise Swei, Rodrigues, Larissa, Koch, Vera Hermina Kalika et al. (2018) Clinical and laboratory features of urinary tract infections in young infants. Jornal brasileiro de nefrologia : 'orgao oficial de Sociedades Brasileira e Latino-Americana de Nefrologia 40(1): 66-72	- Incorrect population *All participants had a diagnosis of UTI at the point of inclusion to the study.*
Lo, Yu-Cheng, Tsai, Wan-Jung, Tsao, Pei-Chen et al. (2020) Relationship between infectious screening and early unconjugated hyperbilirubinemia in well-appearing neonates. Journal of the Chinese Medical Association : JCMA 83(4): 406-410	- Study does not provide data on UTI diagnosis *Not symptoms or signs of UTI.*
Madhi, Fouad, Jung, Camille, Timsit, Sandra et al. (2018) Febrile urinary-tract infection due to extended-spectrum beta-lactamase-producing	- Incorrect population *Included >20% population with congenital abnormality of the urinary tract (excluding VUR).*

Author	Reason for exclusion
Enterobacteriaceae in children: A French prospective multicenter study. PloS one 13(1): e0190910	
Magistro, G, Westhofen, T, Stief, C et al. (2018) Novel minimally invasive treatment options for male lower urinary tract symptoms. Aktuelle urologie 49(4): 339-345	- Study not reported in English
Marcus, Nir, Ashkenazi, Shai, Samra, Zmira et al. (2012) Community-acquired enterococcal urinary tract infections in hospitalized children. Pediatric nephrology (Berlin, Germany) 27(1): 109-14	- Not possible to calculate a contingency table from the data provided
McDaniel, Corrie E, Ralston, Shawn, Lucas, Brian et al. (2019) Association of Diagnostic Criteria With Urinary Tract Infection Prevalence in Bronchiolitis: A Systematic Review and Meta-analysis. JAMA pediatrics 173(3): 269-277	- Study does not provide data on UTI diagnosis *Not symptoms or signs of UTI*
Miller, Aaron S, Hall, Laura E, Jones, Katherine M et al. (2017) Afebrile Infants Evaluated in the Emergency Department for Serious Bacterial Infection. Pediatric emergency care 33(8): e15-e20	- Index test results cannot be related to UTI diagnosis *Paper looks at serious bacterial infection and the symptoms seen in both febrile and afebrile infants. Index test results are in presented in relation to presence of absence of fever.*
Mitiku, Enkosilassie; Amsalu, Anteneh; Tadesse, Birkneh Tilahun (2018) Pediatric Urinary Tract Infection as a Cause of Outpatient Clinic Visits in Southern Ethiopia: A Cross Sectional Study. Ethiopian journal of health sciences 28(2): 187-196	- Duplicate reference
Mohamed, Wael, Algameel, Alkassem, Bassyouni, Rasha et al. (2020) Prevalence and predictors of urinary tract infection in full-term and preterm neonates. Egyptian Pediatric Association Gazette 68(1): 12	- Incorrect setting *Neonatal intensive care unit setting (out-of-scope).*
Nijman, Ruud G, Vergouwe, Yvonne, Thompson, Matthew et al. (2013) Clinical prediction model to aid emergency doctors managing febrile children at risk of serious bacterial infections: diagnostic study. BMJ (Clinical research ed.) 346: f1706	- Diagnosis under investigation does not match that specified in the protocol *Only pneumonia reported as individual clinical outcome (UTI included with other SBI only, no separate data).*
Nji, Che Pantalius; Assob, Jules Clement Nguedia; Akoachere, Jane-Francis Tatah Kihla	- Not a relevant study design

Author	Reason for exclusion
(2020) Predictors of Urinary Tract Infections in Children and Antibiotic Susceptibility Pattern in the Buea Health District, South West Region, Cameroon. BioMed research international 2020: 2176569	*Case-control study*
Nosrati, Adi; Ben Tov, Amir; Reif, Shimon (2014) Diagnostic markers of serious bacterial infections in febrile infants younger than 90 days old. Pediatrics international : official journal of the Japan Pediatric Society 56(1): 47-52	- Diagnosis under investigation does not match that specified in the protocol *Study of SBI, UTI data not presented separately.*
O'Brien, Kathryn, Edwards, Adrian, Hood, Kerenza et al. (2013) Prevalence of urinary tract infection in acutely unwell children in general practice: a prospective study with systematic urine sampling. The British journal of general practice : the journal of the Royal College of General Practitioners 63(607): e156-64	- Duplicate reference
Ohnishi, Takuma, Mishima, Yoshinori, Takizawa, Shohei et al. (2020) Clinical Features of Febrile Urinary Tract Infection Caused by Extended-spectrum Beta-lactamase-producing Escherichia Coli in Children. The Keio journal of medicine 69(2): 43-47	- Study does not provide data on UTI diagnosis *No data on symptoms or signs, also population did not exclude children with recent antibiotic use.*
Oka, Hideharu, Nagamori, Tsunehisa, Yamamoto, Shiho et al. (2019) Non-invasive discrimination of acute focal bacterial nephritis with pyelonephritis. Pediatrics international : official journal of the Japan Pediatric Society 61(8): 777-780	- Study does not contain any relevant index tests for UTI diagnosis *Differential diagnosis rather than diagnosis of UTI.*
Park, Yun Seong, Kwon, Hyuksool, Suh, Dong Bum et al. (2021) A clinical prediction tool to predict urinary tract infection in pediatric febrile patients younger than 2 years old: a retrospective analysis of a fever registry. Clinical and Experimental Emergency Medicine 8(4): 314-324	- Not a relevant study design *Study was a case-control design*
Pathak, Ashish, Upadhayay, Radika, Mathur, Aditya et al. (2020) Incidence, clinical profile, and risk factors for serious bacterial infections in children hospitalized with fever in Ujjain, India. BMC infectious diseases 20(1): 162	- Study does not provide data on UTI diagnosis *SBI study which does not present outcome data for UTI separately.*
Phasuk, Nonthapan and Nurak, Awirut (2020) Etiology, Treatment, and Outcome of Children Aged 3 to 36 Months With Fever Without a	- Study does not provide data on UTI diagnosis *Not data on symptoms or signs other than fever (which was an entry criteria).*

Author	Reason for exclusion
Source at a Community Hospital in Southern Thailand. Journal of primary care & community health 11: 21501327209154O4	
Quinn, Brenna L, Solodiuk, Jean C, Morrill, Dominick et al. (2018) CE: Original Research: Pain in Nonverbal Children with Medical Complexity: A Two-Year Retrospective Study. The American journal of nursing 118(8): 28-37	- Incorrect population *Included children and adults up to 21 years.*
Ramgopal, Sriram, Walker, Lorne W, Vitale, Melissa A et al. (2019) Factors associated with serious bacterial infections in infants <=60days with hypothermia in the emergency department. The American journal of emergency medicine 37(6): 1139-1143	-Study does not provide data on UTI diagnosis *Serious bacterial infection study, does not present data for UTI separately*
Sandoval, Claudio, Sinaki, Banafsheh, Weiss, Robert et al. (2012) Urinary tract infections in pediatric oncology patients with fever and neutropenia. Pediatric hematology and oncology 29(1): 68-72	- Incorrect population *Included children and adults up to 21 years of age.*
Shaikh, Nader, Morone, Natalia E, Lopez, John et al. (2007) Does this child have a urinary tract infection?. JAMA 298(24): 2895-904	- More up to date systematic review has been identified and included
Shaikh N, Hoberman A, Hum SW et al. Development and Validation of a Calculator for Estimating the Probability of Urinary Tract Infection in Young Febrile Children. JAMA pediatrics 172(6): 550-556	- Duplicate reference
Shaikh N, Hoberman A, Hum SW et al. (2018) Development and Validation of a Calculator for Estimating the Probability of Urinary Tract Infection in Young Febrile Children. JAMA pediatrics 172(6): 550-556	- Not a relevant study design *Model validation study using a nested case-control design*
Shaikh, Nader, Hoberman, Alejandro, Alberty, Anastasia et al. (2018) Development and validation of a calculator for estimating the probability of urinary tract infection in young febrile children. JAMA Pediatrics 172(6): 550-556	- Not a relevant study design *Study was a case-control design*
Shaikh, Nader; Shope, Margaret F; Kurs-Lasky, Marcia (2019) Urine Specific Gravity and the Accuracy of Urinalysis. Pediatrics 144(5)	- Study does not provide data on UTI diagnosis *No symptoms or signs of UTI.*

Author	Reason for exclusion
Shaw, Kathy N., Levine, Deborah A., Dayan, Peter S. et al. (2005) Clinical and demographic factors associated with urinary tract infection in young febrile infants. Pediatrics 116(3): 644-648	- Not possible to calculate a contingency table from the data provided
Singh, S D and Madhup, S K (2013) Clinical profile and antibiotics sensitivity in childhood urinary tract infection at Dhulikhel Hospital. Kathmandu University medical journal (KUMJ) 11(44): 319-24	- Incorrect population *All participants had a diagnosis of UTI at point of inclusion to study.*
Sorrentino, F, Cartwright, R, Digesu, GA et al. (2015) Associations between individual lower urinary tract symptoms and bacteriuria in random urine samples in women. Neurourology and urodynamics 34(5): 429-433	- Incorrect population *Adult women.*
Steadman, S, Ahmed, I, McGarry, K et al. (2016) Is screening for urine infection in well infants with prolonged jaundice required? Local review and meta-analysis of existing data. Archives of disease in childhood 101(7): 614-9	- Incorrect setting *Neonatal intensive care unit setting (out-of-scope).*
Troche, Avelina Victoria, Martinez-Pico, Marlene, Gomez, Nidia et al. (2019) Symptomatic and asymptomatic bacteriuria in a pediatric cohort of kidney transplants from a hospital in paraguay. Electronic Journal of General Medicine 16(5): em152	- Incorrect population *Includes those aged over 16 years and who had received kidney transplant and asymptomatic bacteriuria.*
Troesch, Victoria L, Wald, Moshe, Bonnett, Megan A et al. (2021) The additive impact of the distal ureteral diameter ratio in predicting early breakthrough urinary tract infections in children with vesicoureteral reflux. Journal of pediatric urology 17(2): 208e1-208e5	- Study does not provide data on UTI diagnosis *Not symptoms or signs of UTI*
Tullus, Kjell and Shaikh, Nader (2020) Urinary tract infections in children. Lancet (London, England) 395(10237): 1659-1668	- Review article but not a systematic review *Inconsistent presentation of findings from included studies of diagnosis.*
Tzimenatos, Leah, Mahajan, Prashant, Dayan, Peter S et al. (2018) Accuracy of the Urinalysis for Urinary Tract Infections in Febrile Infants 60 Days and Younger. Pediatrics 141(2)	- Study does not contain any relevant index tests for UTI diagnosis *No index tests of interest to the NICE review reported.*
Uyar Aksu, Nihal, Ekinci, Zelal, Dundar, Devrim et al. (2017) Childhood urinary tract infection	- Not a relevant study design *Appears to be a case-control design.*

Author	Reason for exclusion
caused by extended-spectrum beta-lactamase-producing bacteria: Risk factors and empiric therapy. Pediatrics international : official journal of the Japan Pediatric Society 59(2): 176-180	
Van den Bruel, Ann, Aertgeerts, Bert, Bruyninckx, Rudi et al. (2007) Signs and symptoms for diagnosis of serious infections in children: a prospective study in primary care. The British journal of general practice : the journal of the Royal College of General Practitioners 57(540): 538-46	- Study does not provide data on UTI diagnosis *Outcome was serious infection; pyelonephritis was included but data was not presented separately.*
Velasco, Roberto, Gomez, Borja, Benito, Javier et al. (2021) Accuracy of PECARN rule for predicting serious bacterial infection in infants with fever without a source. Archives of Disease in Childhood 106(2): 143-148	- Study does not provide data on UTI diagnosis *Outcome was serious bacterial infection not UTI.*
Yankova, Lyubina C, Neuman, Mark I, Wang, Marie E et al. (2020) Febrile Infants <=60 Days Old With Positive Urinalysis Results and Invasive Bacterial Infections. Hospital pediatrics 10(12): 1120-1125	- Study does not provide data on UTI diagnosis *Invasive bacterial infections no mention of symptoms and signs of UTI.*
Yilmaz, S, Pekdemir, M, Aksu, N M et al. (2012) A multicenter case-control study of diagnostic tests for urinary tract infection in the presence of urolithiasis. Urological research 40(1): 61-5	- Incorrect population *Adult population over 18 years.*
Zanetta, Vitor C, Rosman, Brian M, Rowe, Courtney K et al. (2013) Predicting anatomical urological abnormalities in children who present with their first urinary tract infection. Clinical pediatrics 52(8): 739-46	- Incorrect population *All participants had a diagnosis of UTI at point of inclusion to study.*
Zarkesh, Marjaneh, Hashemian, Houman, Momtazbakhsh, Mohammad et al. (2011) Assessment of febrile neonates according to low risk criteria for serious bacterial infection. Iranian Journal of Pediatrics 21(4): 436-440	- Study does not provide data on UTI diagnosis Outcome was serious bacterial infection, UTI was not presented separately.

Economic studies

Study	Reason for exclusion
Hollingworth W, Busby J, Butler CC, O'Brien K, Sterne JA, Hood K, Little P, Lawton M, Birnie K,	- A longer more comprehensive version of this economic evaluation is published in full,

Study	Reason for exclusion
Thomas-Jones E, Harman K. The Diagnosis of Urinary Tract Infection in Young Children (DUTY) study clinical rule: economic evaluation. Value in Health. 2017 Apr 1;20(4):556-66.	therefore the more comprehensive version is included instead of this version.
Kaufman J, Knight AJ, Bryant PA, Babl FE, Dalziel K. Liquid gold: the cost-effectiveness of urine sample collection methods for young precontinent children. Archives of Disease in Childhood. 2020 Mar 1;105(3):253-9.	- Not a cost-utility study.
Noorbakhsh KA, Ramgopal S, Rixe NS, Dunnick J, Smith KJ. Risk-stratification in febrile infants 29 to 60 days old: a cost-effectiveness analysis. BMC pediatrics. 2022 Dec;22(1):1-1.	- Study includes diagnostic testing as part of its approach to risk stratification. Given this update is dealing with signs and symptoms before diagnostic testing for UTI, this article is not consistent with the PICO criteria for this review question

Appendix K – Research recommendations – full details

K.1.1 Research recommendation 1

What are the symptoms and signs of UTI in children and young people aged from 5 to under 16 years?

K.1.2 Why this is important

Only 7 included studies in the current review included children aged over 5 years, however in 6 of these studies the average age or majority of those study participants were aged <6 years, the remaining study did not report this information. Additionally, none of these studies was carried out in general practice setting (mostly emergency and outpatient department settings) and only 1 was a UK study. Currently, therefore, there is a paucity of good information about which symptoms and signs are useful in determining which children in these age groups should have urine samples taken for further testing and treatment.

In addition, most of the evidence came from studies that recruited unwell babies, children and young people based on them having fever, and the committee agreed that this might have skewed the population away from those with lower UTIs, where fever may not be present. Although many of the symptoms and signs listed could be relevant for babies, children and young people under 16 with lower UTIs, the committee agreed that it would be useful to know more about the specific symptoms and signs of lower UTI. Therefore, they included the request to report symptoms and signs separately for lower and upper UTIs.

K.1.3 Rationale for research recommendation

Importance to 'patients' or the population	There is relevance to the patient (child or young person) in terms of preventable suffering and more serious renal complications if a diagnosis of UTI is delayed or missed. Further a false positive test (symptom or sign) places the patient at risk of unnecessary further tests and treatment with antibiotics and any side effects or antimicrobial resistance at an individual level. The importance to the population is that overtreatment with antibiotics is a leading cause of population level antimicrobial resistance.
Relevance to NICE guidance	Research on the identified age gaps would enable the committee to make recommendations on which symptoms or signs are useful for ruling in or ruling out which children should go onto have further diagnostic testing and treatment with decreased uncertainty.
Relevance to the NHS	The current level of diagnostic uncertainty in those age children aged between 5 to 16 years is likely to be leading to over treatment with antibiotics and less than optimum use of diagnostic resources (point of care tests such as dipstick and laboratory culture tests).
National priorities	Antimicrobial resistance is a national priority area and there is a UK 5-year action plan for tackling antimicrobial resistance (2019 to 2024).
Current evidence base	The committee identified several gaps in the evidence. Most of the studies included in this review look at symptoms and signs of UTI in

	babies and children under 5 years old and those that included older children in their study participants still had average ages closer to 5 than 16 and did not present data separately for older children.
Equality considerations	Urinary tract infections are more common in female children affecting around 4 times as many girls compared to boys by the age of seven years. The committee identified that it would be important to have include (and separately report data for) certain subgroups for which no evidence was found in the search. These included children with cognitive or learning disability or other groups with communication difficulties who may find it difficult to communicate or verbalise symptoms of UTI. Similarly, the committee identified that no evidence on symptoms or signs of UTI was identified for female children with genital mutilation (FGM).

K.1.4 Modified PICO table

Population	Children and young people aged 5 to under 16 years who are unwell
Index tests	Symptoms and signs including but not limited to: • abdominal pain/crying • pain or crying when voiding • headache • jaundice • high fever over 38 or 39 degrees • shivering • rigors • vomiting • lethargy/malaise • irritability • poor feeding • failure to thrive • offensive or smelly urine • loin tenderness • frequency (of passing urine) or holding urine in • dysuria • dysfunctional voiding • diarrhoea • changes in continence • cough or ear symptoms • sore throat • skin mottling • skin rash • redness in perineal area • parental suspicion of a UTI • previous UTI

Reference test	Microscopy, culture and sensitivity or validated novel diagnostic tests for confirmation of presence of UTI.
Outcome measures	Data that can be used to construct a 2x2 contingency table, diagnostic test accuracy measures such as likelihood ratios, sensitivity and specificity, NPV and PPV, and association measures such as odds ratios.
Study design	Prospective cross-sectional, or prospective cohort design
Timeframe	Long term
Additional information	• Separate results by final diagnosis (upper or lower UTI) as this negates the need for separate studies in primary and secondary care (or other settings) which may affect the likelihood of type of illness. • The entry criteria for the study should be unwell child rather than presence of specific symptoms (such as fever). • Sample collection method should be detailed for babies (for example SPA, in-and-out catheterisation, nappy pad or bag collection). • Subgroups of interest include children and young people with cognitive or learning disability or other groups with communication difficulties who may find it difficult to communicate or verbalise symptoms of UTI. Another subgroup of interest would females who have had genital mutilation (FGM).

K.1.5 Research recommendation 2

K.1.6 Do the symptoms and signs of UTI in babies, children and young people aged under 16 years differ in those with a history of recurrent UTIs compared with those without a history of recurrent UTI?

K.1.7 Why this is important

None of the included studies in the current review were solely conducted in participants with recurrent UTI (which may include children taking antibiotic prophylaxis) or reported separate data for these individuals. Indeed, many studies in the review excluded children with chronic illness or major chronic illness which may have included recurrent UTI but as the details of what the study authors defined as chronic illness or major chronic illness were rarely reported it is uncertain whether children with recurrent UTI were included in these studies. One study (Shaw et al 1998) excluded children who already had a diagnosis of bacterial infection and many others excluded children who had a recent history of taking antibiotics (no exemptions or caveats such as for recurrent UTI were reported). Currently, therefore, there is a paucity of good information about which symptoms and signs are useful in determining which children should have urine samples taken for further testing and treatment and whether these symptoms and signs are different to acute UTI. Rationale for research recommendation

Importance to 'patients' or the population	There is relevance to the patient (baby, child, or young person) in terms of possible preventable suffering including a loss of quality of life and potentially more serious renal complications if a recurrence of UTI is delayed or missed. It may be that, particularly in children taking antibiotic prophylaxis, that symptoms or signs may be absent or qualitatively different (less specific) and may lead to delayed or missed diagnoses.

Relevance to NICE guidance	This may lead to a separate recommendation or table of symptoms and signs for babies, children, and young people with recurrent UTI leading to less diagnostic uncertainty and greater awareness of diagnostic concerns for babies, children, and young people with recurrent UTI.
Relevance to the NHS	Up to one half of children who have a UTI will suffer from at least one recurrence. The paucity of information on symptoms and signs of multiple recurrent UTI in babies, children, and young people with this condition means that children may undergo other invasive tests or procedures and treatments which may not be warranted and at cost to the service.
National priorities	Antimicrobial resistance is a national priority area and there is a UK 5-year action plan for tackling antimicrobial resistance (2019 to 2024).
Current evidence base	The committee identified several gaps in the evidence. None of the included studies in the current review were conducted in participants with recurrent UTI or reported separate data for these people. Many excluded children with chronic illness or major chronic illness but it is uncertain whether children with recurrent UTI were excluded. The included studies also often excluded children who had a diagnosis of bacterial infection or who had a recent history of taking antibiotics.
Equality considerations	Urinary tract infections are more common in female children affecting around 4 times as many girls compared to boys by the age of seven years.

K.1.8 Modified PICO table

Population	Babies, children and young people under 16 years with a recurrent UTI.
Index tests	Symptoms and signs including but not limited to: • abdominal pain/crying • pain or crying when voiding • headache • jaundice • high fever over 38 or 39 degrees • shivering • rigors • vomiting • lethargy/malaise • irritability • poor feeding • failure to thrive • offensive or smelly urine • loin tenderness • frequency (of passing urine) or holding urine in

	• dysuria • dysfunctional voiding • diarrhoea • changes in continence • cough or ear symptoms • sore throat • skin mottling • skin rash • redness in perineal area • parental suspicion of a UTI • previous UTI
Reference test	Microscopy, culture and sensitivity.
Outcome measures	Data that can be used to construct a 2x2 contingency table, diagnostic test accuracy measures such as likelihood ratios, sensitivity and specificity, NPV and PPV, and association measures such as odds ratios.
Study design	Cross-sectional, cohort or case control design (we expect the prevalence of recurrent UTI to be lower than that of acute UTI, therefore a case-control design may be more feasible).
Timeframe	Long term
Additional information	• Recurrence should be defined, for example consider using the European Association of Urology guidelines definition of a repeated UTI with a frequency of 2 or more UTIs in the last 6 months or 3 or more UTIs in the last 12 months. • Sample collection method should be detailed for babies (for example SPA, in-and-out catheterisation, nappy pad or bag collection). • Babies, children and young people taking antibiotic prophylaxis for recurrent UTI would be a subgroup of interest.

K.1.9 Research recommendation 3

What symptoms and signs do children and young people with long-term (chronic) UTI report and what do they perceive is the impact on their health and quality of life?

K.1.10 Why this is important

The NHS is now recognising that in some people, antibiotics do not work, or urine tests do not pick up an infection, even though they may have UTI symptoms. This is being described by the NHS as a long term (chronic) UTI that is not picked up by current urine tests. There is more information known about this condition in adults, while for children and young people there is more uncertainty about its presentation, epidemiology and natural history.

It is unclear if the symptoms and signs experienced by children and young people with long term (chronic) UTI are the same as those with acute or recurrent UTI. None of the studies identified in this evidence review reported whether they included children and young people with long term (chronic) UTI. The lack of research is probably because this population is still being defined and there is currently no agreed diagnostic definition.

This research recommendation is aimed at providing information at a higher level about the lived experiences of children and young people with long term (chronic) UTI including the persistent symptoms and signs of a UTI that they experience. This is aimed at helping to define the population and facilitate future quantitative research.

K.1.11 Rationale for research recommendation

Importance to 'patients' or the population	There is relevance to the patient (child or young person) in terms of possible preventable suffering and more serious renal complications if a diagnosis of long term (chronic) UTI is delayed or missed, and the continued presence of symptoms might mean other causes are investigated before an long term UTI is successfully diagnosed. However, given the refractory to treatment nature of a persistent infection it may not always be possible to prevent these poorer outcomes.
Relevance to NICE guidance	Children and young people with suspected long term (chronic) UTI would currently still undergo the same diagnostic tests as for acute or recurrent UTI in the first instance as it is likely that, as with the current evidence for acute UTI, a single symptom or sign would not necessarily be considered diagnostic of an ongoing infection. However, the committee discussed that there may be subtle differences in presenting symptoms or signs between acute UTI and that might raise a possibility of a long term (chronic) infection especially if the child remained unwell after treatment.
Relevance to the NHS	Unclear, there is a clear paucity of information available on the prevalence and incidence of long term (chronic)) UTI in children. The paucity of information on symptoms and signs of long term (chronic) UTI in children and young people with this condition means that they may undergo ineffective treatment, other invasive tests or procedures and extensive delays in effective care which may not be warranted and at cost to the service.
National priorities	Antimicrobial resistance is a national priority area and there is a UK 5-year action plan for tackling antimicrobial resistance (2019 to 2024).
Current evidence base	The committee identified several gaps in the evidence. None of the included studies in the current review were specifically conducted in participants with long term (chronic) UTI or reported separate data for this group. Many excluded children with chronic illness or major chronic illness but it is uncertain whether children with long term UTI were excluded. The included studies also often excluded children who had a diagnosis of bacterial infection or who had a recent history of taking antibiotics. Uncertainty around the diagnostic criteria for long term (chronic) UTI makes it harder for quantitative research to be carried out at this time.
Equality considerations	Urinary tract infections are more common in female children affecting around 4 times as many girls compared to boys by the age of seven years.

K.1.12 SPIDER table

Sample	Children and young people aged under 16 years with long term (chronic) UTI and/ or parents/ carers (as appropriate) of children and young people aged under 16 years with ongoing (chronic) UTI
Phenomenon of interest	The symptoms and signs of long term (chronic) UTI in children and young people aged under 16 years and the impact on their health and quality of life.
Design	Individual interviews or focus group sessions (as appropriate depending on age and setting)
Evaluation	Symptoms and signs experienced Wider effects on education, sleep, social life and other quality of life indicators
Research type	Qualitative
Additional information	Long term (chronic) UTI could be defined as a persistence of symptoms of UTI lasting longer than 6 months after antibiotic options have been tried and other causes of UTI symptoms have been excluded. This should not be confused with recurrent UTI which can be defined as a repeated UTI with a frequency of 2 or more UTIs in the last 6 months or 3 or more UTIs in the last 12 months (according to the European Association of Urology guidelines).

Appendix L – Methods

Review protocols

Review protocols were developed with the guideline committee to outline the inclusion and exclusion criteria used to select studies for each evidence review. Where possible, review protocols were prospectively registered in the PROSPERO register of systematic reviews.

Search strategy methods

The searches for the effectiveness evidence were run on 02 02 2022. The following databases were searched: Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), DARE (CRD), Embase (Ovid), Emcase (Ovid), HTA (CRD), INAHTA (INAHTA), MEDLINE (Ovid), MEDLINE ePubs, MEDLINE-in-Process (Ovid), . Full search strategies for each database are provided in Appendix B.

The database searches were supplemented with additional search methods. Forwards citation searching were conducted on Citationchaser (LENS.org) Full details for this method are provided in Appendix B.

The searches for the cost effectiveness evidence were run on 07 02 2022. The following databases were searched: EconLit (Ovid), Embase (Ovid), HTA (CRD), INAHTA (INAHTA), MEDLINE (Ovid), MEDLINE ePubs, MEDLINE-in-Process (Ovid) and NHS Economic Evaluations Database (CRD). Full search strategies for each database are provided in Appendix B.

A NICE information specialist conducted the searches. The MEDLINE strategy was quality assured by a trained NICE information specialist and all translated search strategies were peer reviewed to ensure their accuracy. Both procedures were adapted from the 2016 PRESS Checklist.

Selecting studies for inclusion

All references identified by the literature searches and from other sources (for example, previous versions of the guideline or studies identified by committee members) were uploaded into EPPI reviewer software (version 5) and de-duplicated. Titles and abstracts were assessed for possible inclusion using the criteria specified in the review protocol. 10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer.

This evidence review made use of the priority screening functionality within the EPPI-reviewer software. This functionality uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being ‘includes’ or ‘excludes’ during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened. Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstracts can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. Due to the large number of symptoms and signs of interest and the variable study designs that contained them priority screening was not used to terminate sifting early and all references in the database were examined for inclusion.

The full text of potentially eligible studies was retrieved and assessed according to the criteria specified in the review protocol. A standardised form was used to extract data from included studies.

Incorporating published evidence syntheses

For review questions where a literature search was undertaken looking for a particular study design, published evidence syntheses (quantitative systematic reviews or qualitative evidence syntheses) containing studies of that design were also included. All included studies from those syntheses were screened to identify any additional relevant primary studies not found as part of the initial search. Evidence syntheses that were used solely as a source of primary studies were not formally included in the evidence review (as they did not provide additional data) and were not quality assessed.

If published evidence syntheses were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were considered for use as the primary source of data, rather than extracting information from primary studies. Systematic reviews considered for inclusion in this way were quality assessed to assess their suitability using the ROBIS appropriate checklist. Note that this quality assessment was solely used to assess the quality of the synthesis in order to decide whether it could be used as a source of data, as outlined in Table 13, not the quality of evidence contained within it, which was assessed in the usual way as outlined in the section on 'Appraising the quality of evidence'.

Each published evidence synthesis was classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.
- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each published evidence synthesis was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

The way that a published evidence synthesis was used in the evidence review depended on its quality and applicability, as defined in Table 13. When published evidence syntheses were used as a source of primary data, data from these evidence syntheses were quality assessed and presented in GRADE tables in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were checked to ensure none of the data had been double counted through this process.

Table 13 Criteria for using published evidence syntheses as a source of data

Quality	Applicability	Use of published evidence synthesis
High	Fully applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted.
High	Partially applicable	Data from the published evidence synthesis were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. If the review was considered up to date (following discussion with the guideline committee and NICE lead for quality assurance), no additional search was conducted. For other sections not covered by the evidence synthesis, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the evidence synthesis, searches were undertaken as normal.

Diagnostic test accuracy data

Methods of combining evidence

Diagnostic test accuracy (DTA) data are classified as any data in which a feature – be it a symptom, a risk factor, a test result or the output of some algorithm that combines many such features – is observed in some people who have the condition of interest at the time of the test and some people who do not. Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who, according to the reference standard, truly have the condition) and false positives and true negatives (in people who, according to the reference standard, do not).

The ‘raw’ 2x2 data can be summarised in a variety of ways. Those that were used for decision making in this guideline were as follows:

- **Positive likelihood ratios** describe how many times more likely positive features are in people with the condition compared to people without the condition. Values greater than 1 indicate that a positive result makes the condition more likely.
  - LR^+ = (TP/[TP+FN])/(FP/[FP+TN])
- **Negative likelihood ratios** describe how many times less likely negative features are in people with the condition compared to people without the condition. Values less than 1 indicate that a negative result makes the condition less likely.
  - LR^- = (FN/[TP+FN])/(TN/[FP+TN])
- **Sensitivity** is the probability that the feature will be positive in a person with the condition.
  - sensitivity = TP/(TP+FN)
- **Specificity** is the probability that the feature will be negative in a person without the condition.
  - specificity = TN/(FP+TN)

Meta-analysis of diagnostic accuracy data was conducted with reference to the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

Where five or more studies were available for all included strata, a bivariate model was fitted using the mada package in R v3.4.0, which accounts for the correlations between positive and negative likelihood ratios, and between sensitivities and specificities. Where sufficient data were not available (2-4 studies), separate independent pooling was performed for positive likelihood ratios, negative likelihood ratios, sensitivity and specificity. This approach is conservative as it is likely to somewhat underestimate test accuracy, due to failing to account for the correlation and trade-off between sensitivity and specificity (see Deeks 2010).

Random-effects models (der Simonian and Laird) were fitted for all syntheses, as recommended in the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy (Deeks et al. 2010).

Appraising the quality of evidence: diagnostic accuracy studies

Individual diagnostic accuracy studies were quality assessed using the QUADAS-2 tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard.

- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard.

GRADE

Evidence from diagnostic accuracy studies was initially rated as high-quality, and then downgraded according to the standard GRADE criteria (risk of bias, inconsistency, imprecision and indirectness) as detailed in Table 15 below.

The choice of primary outcome for decision making was determined by the committee and GRADE assessments were undertaken based on these outcomes.

In all cases, the downstream effects of diagnostic accuracy on patient- important outcomes were considered. This was done explicitly during committee deliberations and reported as part of the discussion section of the review detailing the likely consequences of true positive, true negative, false positive and false negative test results. In reviews where a decision model is being carried (for example, as part of an economic analysis), these consequences were incorporated here in addition.

Using likelihood ratios as the primary outcomes

The following schema (Table 14), adapted from the suggestions of Jaeschke et al. (1994), was used to interpret the likelihood ratio findings from diagnostic test accuracy reviews.

Table 14 Interpretation of likelihood ratios

Value of likelihood ratio	Interpretation
LR ≤ 0.1	**Very large** decrease in probability of disease
0.1 < LR ≤ 0.2	**Large** decrease in probability of disease
0.2 < LR ≤ 0.5	**Moderate** decrease in probability of disease
0.5 < LR ≤ 1.0	**Slight** decrease in probability of disease
1.0 < LR < 2.0	**Slight** increase in probability of disease
2.0 ≤ LR < 5.0	**Moderate** increase in probability of disease
5.0 ≤ LR < 10.0	**Large** increase in probability of disease
LR ≥ 10.0	**Very large** increase in probability of disease

The schema above has the effect of setting a clinical decision threshold for positive likelihoods ratio at 2, and a corresponding clinical decision threshold for negative likelihood ratios at 0.5. Likelihood ratios (whether positive or negative) falling between these thresholds were judged to indicate no meaningful change in the probability of disease.

GRADE assessments were only undertaken for positive and negative likelihood ratios but results for sensitivity and specificity are also presented alongside those data.

The committee were consulted to set 2 clinical decision thresholds for each measure: the likelihood ratio above (or below for negative likelihood ratios) which a test would be recommended, and a second below (or above for negative likelihood ratios) which a test would be considered of no clinical use. These were used to judge imprecision (see below). The committee decided to use 2 for LR+, with 0.5 for LR- as above, with 1 (the line of no effect) as the second threshold for both.

If studies could not be pooled in a meta-analysis, GRADE assessments were undertaken for each study individually and reported as separate lines in the GRADE profile.

Table 15 Rationale for downgrading quality of evidence for diagnostic accuracy data

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.
Imprecision	If the 95% confidence interval for the outcome crossed one of the clinical decision thresholds, the outcome was downgraded one level. If the 95% confidence interval spanned both thresholds, the outcome was downgraded twice. See the sections on 'Using sensitivity and specificity as the primary outcome' and 'Using likelihood ratios as the primary outcome' for a description of how clinical decision thresholds were agreed. The committee decided to use MIDs of 1, 2 for LRs with a point estimate of over 1 and 0.5, 1 for LRs with a point estimate of under 1. This would usually, but not always, correspond to LR+ and LR- respectively.

GRADE criteria	Reasons for downgrading quality
Publication bias	If the review team became aware of evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

Diagnostic models

For the purpose of this review diagnostic models are classified as any data in which any combination of symptoms and signs or features are used to predict whether a person has a condition of interest at that point in time. Only models with external validation studies were included in this review.

Such data either explicitly provide, or can be manipulated to generate, a 2x2 classification of true positives and false negatives (in people who have the condition) and false positives and true negatives (in people who do not).

Studies developing or evaluating diagnostic models

Individual studies developing or validating diagnostic models were assessed using the PROBAST checklist. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, index features and/or reference standard/outcome to be predicted in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, index feature and/or reference standard/outcome to be predicted.
- Partially indirect – Important deviations from the protocol in one of the population, index feature and/or reference standard/outcome to be predicted.
- Indirect – Important deviations from the protocol in at least two of the population, index feature and/or reference standard/outcome to be predicted.

Modified GRADE for diagnostic models

GRADE has not been developed for use with data from diagnostic models, therefore a modified approach was applied using the GRADE framework. The approach taken depended on the outcome data produced by the decision model. Accuracy data (from a 2x2 table) was assessed as described in the section on using GRADE for other diagnostic test accuracy studies reporting 2*2 data (Table 15).

Methods for combining c-statistics

C-statistics were assessed in a similar manner to likelihood ratios using the categories in Table 16 below.

Table 16 Interpretation of c-statistics

Value of c-statistic	Interpretation
c-statistic <0.6	**Poor** classification accuracy
0.6 ≤ c-statistic <0.7	**Adequate** classification accuracy
0.7 ≤ c-statistic <0.8	**Good** classification accuracy
0.8 ≤ c-statistic <0.9	**Excellent** classification accuracy
0.9 ≤ c-statistic < 1.0	**Outstanding** classification accuracy

A modified version of GRADE was carried out to assess the quality of the c-statistics as follows in Table 17.

Table 17 Rationale for downgrading quality of evidence for diagnostic model data

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded.

GRADE criteria	Reasons for downgrading quality
	Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.
Imprecision	If the 95% confidence interval for the outcome crossed one of the clinical decision thresholds, the outcome was downgraded one level. If the 95% confidence interval spanned both thresholds, the outcome was downgraded twice.
Publication bias	If the review team became aware of evidence of publication bias (for example, evidence of unpublished trials where there was evidence that the effect estimate differed in published and unpublished data), the outcome was downgraded once. If no evidence of publication bias was found for any outcomes in a review (as was often the case), this domain was excluded from GRADE profiles to improve readability.

If studies could not be pooled in a meta-analysis, GRADE assessments were undertaken for each study individually and reported as separate lines in the GRADE profile.

Appendix M– R code used for the diagnostic test accuracy meta-analysis

```
setwd("Q://3. Guidelines/3. In Development/UTI/3. Development/13. TA working/Analysis/R code and tools")
rm(list = ls())
detach(package:mada)
library("metafor")
library("mada")

data = read.csv("Diag test.csv",header=TRUE)
Bivariate_minimum_sample=5
continuity_correction_type="all"
continuity_correction_value=0.5
isquared_required=1

if (length(data$Study)>=Bivariate_minimum_sample && Bivariate_minimum_sample!=-1)
{

model=madad(data,correction=continuity_correction_value,correction.control=continuity_correction_type)

model2=reitsma(data,correction=continuity_correction_value,correction.control=continuity_correction_type)

  meansens=coef(summary(model2))[3,1]
  lowsens=coef(summary(model2))[3,5]
  highsens=coef(summary(model2))[3,6]

  meanspec=1-coef(summary(model2))[4,1]
  lowspec=1-coef(summary(model2))[4,6]
  highspec=1-coef(summary(model2))[4,5]

  model3=SummaryPts(model2)

  meanneglr=summary(model3)[2,1]
  lowneglr=summary(model3)[2,3]
  highneglr=summary(model3)[2,4]

  meanposlr=summary(model3)[1,1]
  lowposlr=summary(model3)[1,3]
  highposlr=summary(model3)[1,4]

  model$sens$sens = c(model$sens$sens,meansens)
  model$sens$sens.ci=rbind(model$sens$sens.ci,c(lowsens,highsens))

  model$spec$spec = c(model$spec$spec,meanspec)
  model$spec$spec.ci=rbind(model$spec$spec.ci,c(lowspec,highspec))

  model$negLR$negLR = c(model$negLR$negLR,meanneglr)
  model$negLR$negLR.ci=rbind(model$negLR$negLR.ci,c(lowneglr,highneglr))

  model$posLR$posLR = c(model$posLR$posLR,meanposlr)
  model$posLR$posLR.ci=rbind(model$posLR$posLR.ci,c(lowposlr,highposlr))
```

```
  model$DOR$DOR = c(model$DOR$DOR,0)
  model$DOR$DOR.ci=rbind(model$DOR$DOR.ci,c(0,0))

  snames=c(as.character(data$Study),"Overall")
  poly=rep(FALSE,length(data$Study))
  poly=c(poly,TRUE)
  axis_label="Random-effects model"
}

if (length(data$Study)<Bivariate_minimum_sample || Bivariate_minimum_sample==-1)
{
  if (continuity_correction_type=="single")
  {
    continuity_correction_type2="only0"
  }
  if (continuity_correction_type=="all")
  {
    continuity_correction_type2="if0all"
  }

model=madad(data,correction=continuity_correction_value,correction.control=continuity_corr
ection_type)

model2a=madauni(data,type="posLR",correction=continuity_correction_value,correction.cont
rol=continuity_correction_type)

model2b=madauni(data,type="negLR",correction=continuity_correction_value,correction.cont
rol=continuity_correction_type)

data3a=escalc(measure="PLO",xi=TP,ni=TP+FN,data=data,add=continuity_correction_value
,to=continuity_correction_type2)

data3b=escalc(measure="PLO",xi=TN,ni=TN+FP,data=data,add=continuity_correction_value
,to=continuity_correction_type2)
  model3a=rma.uni(yi,vi,data=data3a,method="DL")
  model3b=rma.uni(yi,vi,data=data3b,method="DL")

  meansens=exp(as.numeric(model3a[1]))/(1+exp(as.numeric(model3a[1])))
  lowsens=exp(as.numeric(model3a[6]))/(1+exp(as.numeric(model3a[6])))
  highsens=exp(as.numeric(model3a[7]))/(1+exp(as.numeric(model3a[7])))

  meanspec=exp(as.numeric(model3b[1]))/(1+exp(as.numeric(model3b[1])))
  lowspec=exp(as.numeric(model3b[6]))/(1+exp(as.numeric(model3b[6])))
  highspec=exp(as.numeric(model3b[7]))/(1+exp(as.numeric(model3b[7])))

  meanneglr=summary(model2b)$CIcoef[1,1]
  lowneglr=summary(model2b)$CIcoef[1,2]
  highneglr=summary(model2b)$CIcoef[1,3]

  meanposlr=summary(model2a)$CIcoef[1,1]
  lowposlr=summary(model2a)$CIcoef[1,2]
  highposlr=summary(model2a)$CIcoef[1,3]

  model$sens$sens = c(model$sens$sens,meansens)
```

```
  model$sens$sens.ci=rbind(model$sens$sens.ci,c(lowsens,highsens))

  model$spec$spec = c(model$spec$spec,meanspec)
  model$spec$spec.ci=rbind(model$spec$spec.ci,c(lowspec,highspec))

  model$negLR$negLR = c(model$negLR$negLR,meanneglr)
  model$negLR$negLR.ci=rbind(model$negLR$negLR.ci,c(lowneglr,highneglr))

  model$posLR$posLR = c(model$posLR$posLR,meanposlr)
  model$posLR$posLR.ci=rbind(model$posLR$posLR.ci,c(lowposlr,highposlr))

  model$DOR$DOR = c(model$DOR$DOR,0)
  model$DOR$DOR.ci=rbind(model$DOR$DOR.ci,c(0,0))

  snames=c(as.character(data$Study),"Overall")
  poly=rep(FALSE,length(data$Study))
  poly=c(poly,TRUE)
  axis_label="Random-effects model"
}

print("Sensitivities, specificities and likelihood ratios for all primary studies, and the pooled
result (which is in the final row)")
model$names=snames
model ##Outputs results for the 4 summary measures (sensitivity, specificity and likelihood
ratios

if (isquared_required==1)
{
  print("i-squared statistics")
  isquared=matrix(nrow=4,ncol=2)
  isquared[1,1]="Sensitivity"
  isquared[2,1]="Specificity"
  isquared[3,1]="Positive likelihood ratio"
  isquared[4,1]="Negative likelihood ratio"

model2a=madauni(data,method="MH",type="posLR",correction=continuity_correction_value,
correction.control=continuity_correction_type)

model2b=madauni(data,method="MH",type="negLR",correction=continuity_correction_value,
correction.control=continuity_correction_type)

data3a=escalc(measure="PLO",xi=TP,ni=TP+FN,data=data,add=continuity_correction_value
,to=continuity_correction_type2)

data3b=escalc(measure="PLO",xi=TN,ni=TN+FP,data=data,add=continuity_correction_value
,to=continuity_correction_type2)
  model3a=rma.uni(yi,vi,data=data3a,method="DL")
  model3b=rma.uni(yi,vi,data=data3b,method="DL")
  isquared[1,2]=model3a$I2
  isquared[2,2]=model3b$I2
  isquared[3,2]=max(0,(100*(as.numeric(model2a$CQ[1])-
as.numeric(model2a$CQ[3]))/as.numeric(model2a$CQ[1])))
  isquared[4,2]=max(0,(100*(as.numeric(model2b$CQ[1])-
as.numeric(model2b$CQ[3]))/as.numeric(model2b$CQ[1])))
  print(isquared) ##Outputs i-squared values (if requested)
```

```
}

forest(model,type="sens",snames=snames,cipoly=poly,xlab=axis_label,main="Sensitivity")
##Outputs forest plot for sensitivities
forest(model,type="spec",snames=snames,cipoly=poly,xlab=axis_label,main="Specificity")
##Outputs forest plot for specificities
forest(model,type="posLR",snames=snames,cipoly=poly,xlab=axis_label,main="Positive
LR") ##Outputs forest plot for positive likelihood ratios
forest(model,type="negLR",snames=snames,cipoly=poly,xlab=axis_label,main="Negative
LR") ##Outputs forest plot for negative likelihood ratios
```