

³ Result not reported as a hazard ratio.

⁴ Downgraded by 1 increment because majority of evidence had indirect outcomes, and downgraded by 2 increments if the majority of the evidence had very indirect outcomes (this is a surrogate outcome for ED attendance)

Appendix G: Excluded clinical studies

Table 8: Studies excluded from the clinical review

Study	Exclusion reason
Andersen 2015 ⁴	Incorrect intervention. The study investigated the levels of interleukin (IL)-23 in patients with early rheumatoid arthritis and the effect of anti-tumour necrosis factor treatment on IL-23 levels.
Andreeva 2012 ⁵	Abstract
Anon 1984 ¹	Incorrect interventions. Narrative paper. Use of serological tests in the EPI.
Anon 2005 ²	Article not in English
Bjerrum 2004 ⁸	Observational study
Bjerrum 2006 ⁷	Before-After study
Bjerrum 2011 ⁹	Before-After audit based study
Cadth 2013 ¹¹	Incorrect interventions. A review of the clinical effectiveness of point of care testing technologies compared with central laboratory methods to assess patients' white blood cell counts.
Cals 2007 ¹⁶	Study protocol
Cals 2008 ¹²	Study protocol
Cals 2013 ¹⁵	No outcomes of interest
Chandrayay 2016 ¹⁸	Incorrect study design- prospective cohort study (RCT evidence available). Incorrect intervention- evaluation of the effect of clinical validation of out of hours critical laboratory results
Cook2015A ¹⁹	Narrative review of primary care point-of-care testing and anti-bacterial use in respiratory tract infection. RCTs included in this review have already been included in our evidence review.
Do2016 ²³	Incorrect setting- primary health care centres in the community
Engel 2012 ²⁴	Systematic review- screened for relevant references
Grodzinsky 2004 ²⁵	Observational study (RCT data available)
Hanrahan 2015 ²⁶	Incorrect intervention. The study evaluated the effect of Xpert (MTB/RIF assay to diagnose TB rapidly) either at point of care or at an off-site laboratory for diagnosis of pulmonary TB. Tests for diagnosis of TB not included intervention of interest in our protocol.
Holm 2007 ²⁷	Observational study (RCT evidence available)
Hopstaken 2003 ²⁹	Observational study (RCT evidence available)
Hopstaken 2006 ²⁸	Observational study
Huang 2013 ³¹	Systematic review- screened for relevant references
Jakobsen 2010 ³³	Observational study (RCT evidence available)
Joshi 2013 ³⁴	Review paper checked for references
Kavanagh 2011 ³⁵	Observational study (RCT evidence available)

Leber 2015 ³⁷	Incorrect intervention. This study assessed rapid HIV testing which was not included as an intervention of interest in our protocol.
Llor 2012 ⁴⁰	Before-After audit based study
Llor 2012 ⁴²	Before-After audit based study
Llor 2013 ⁴¹	Cross-sectional study
Llor 2013 ³⁹	Observational study
Llor 2014 ⁴³	Before- After audit based study
Mueller 2004 ⁴⁵	Incorrect setting (patients in Emergency department)
Neumark 2010 ⁵⁶	Observational study (RCT evidence available)
Oosterheert 2005 ⁵⁷	Incorrect intervention and setting. Intervention is real time polymerase chain reaction (PCR) and setting is University hospital.
Peters 2013 ⁶⁰	Case control study
Pluddemann 2011 ⁶¹	Review article
Rebnord 2015 ⁶²	Incorrect study design- observational study (RCT evidence available)
Strykowski 2015 ⁶⁵	Incorrect study design- before and after study (RCT evidence available)

Appendix H: Excluded economic studies

Table 9: Studies excluded from the health economic review

Reference	Reason for exclusion
Cals 2011 ¹³	This study was assessed as partially applicable with potentially serious limitations. However, given that 2 cost-utility analyses of CRP testing were available ^{32,58} including 1 set in the UK, this study was selectively excluded.

- 1 Uses of serologic tests in the EPI. EPI Newsletter. 1984; 6(2):6-8
- 2 RCT of point of care C-reactive protein test and enhanced communication skills for managing acute cough due to lower respiratory tract infection in general practice: cost effectiveness and effect on diagnostic testing, antibiotic prescribing and recovery. 2005. Available from: http://erj.ersjournals.com/content/40/Suppl_56/P720.full.pdf+html
- 3 Aabenhus R, Jensen Jens-Ulrik S, Jørgensen KJ, Hróbjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. Cochrane Database of Systematic Reviews. 2014; Issue 11:CD010130. DOI:10.1002/14651858.CD010130.pub2
- 4 Andersen T, Hvid M, Johansen C, Stengaard-Pedersen K, Hetland ML, Horslev-Petersen K et al. Interleukin-23 in early disease development in rheumatoid arthritis. Scandinavian Journal of Rheumatology. 2015; 44(6):438-442
- 5 Andreeva E, Melbye H. The usefulness of point-of-care-testing for C-reactive protein in lower respiratory tract infection/acute cough. European Respiratory Journal. 2012; 40(Suppl 56):117s
- 6 Andreeva E, Melbye H. Usefulness of C-reactive protein testing in acute cough/respiratory tract infection: an open cluster-randomized clinical trial with C-reactive protein testing in the intervention group. BMC Family Practice. 2014; 15:80
- 7 Bjerrum L, Cots JM, Llor C, Molist N, Munck A. Effect of intervention promoting a reduction in antibiotic prescribing by improvement of diagnostic procedures: a prospective, before and after study in general practice. European Journal of Clinical Pharmacology. 2006; 62(11):913-918
- 8 Bjerrum L, Gahrn-Hansen B, Munck AP. C-reactive protein measurement in general practice may lead to lower antibiotic prescribing for sinusitis. British Journal of General Practice. 2004; 54(506):659-662
- 9 Bjerrum L, Munck A, Gahrn-Hansen B, Hansen MP, Jarbol DE, Cordoba G et al. Health Alliance for prudent antibiotic prescribing in patients with respiratory tract infections (HAPPY AUDIT) - impact of a non-randomised multifaceted intervention programme. BMC Family Practice. 2011; 12:52
- 10 Burri E, Hochholzer K, Arenja N, Martin-Braschler H, Kaestner L, Gekeler H et al. B-type natriuretic peptide in the evaluation and management of dyspnoea in primary care. Journal of Internal Medicine. 2012; 272(5):504-513

- 11 CADTH. Point of care testing compared to laboratory testing for the assessment of white blood cell counts and differentials: a review of the clinical effectiveness, diagnostic precision and accuracy, cost-effectiveness, and guidelines. Canadian Agency for Drugs and Technologies in Health (CADTH), 2013. Available from: <https://www.cadth.ca/sites/default/files/pdf/htis/nov-2013/RC0489%20POC%20WBC%20Final.pdf>
- 12 Cals J, Butler C, Hopstaken R, Hood K, Dinant G-J. Effect of C-reactive protein point of care testing and clinical communication skills training on antibiotic use and patient recovery in lower respiratory tract infections: a cluster randomised trial. European Respiratory Society Annual Congress, Berlin, Germany, October 4-8. 2008;3500
- 13 Cals JWL, Ament AJHA, Hood K, Butler CC, Hopstaken RM, Wassink GF et al. C-reactive protein point of care testing and physician communication skills training for lower respiratory tract infections in general practice: economic evaluation of a cluster randomized trial. *Journal of Evaluation in Clinical Practice*. 2011; 17(6):1059-1069
- 14 Cals JWL, Butler CC, Hopstaken RM, Hood K, Dinant GJ. Effect of point of care testing for C reactive protein and training in communication skills on antibiotic use in lower respiratory tract infections: cluster randomised trial. *BMJ*. 2009; 338:b1374
- 15 Cals JWL, de Bock L, Beckers PJ, Francis NA, Hopstaken RM, Hood K et al. Enhanced communication skills and C-reactive protein point-of-care testing for respiratory tract infection: 3.5-year follow-up of a cluster randomized trial. *Annals of Family Medicine*. 2013; 11(2):157-164
- 16 Cals JWL, Hopstaken RM, Butler CC, Hood K, Severens JL, Dinant GJ. Improving management of patients with acute cough by C-reactive protein point of care testing and communication training (IMPAC3T): study protocol of a cluster randomised controlled trial. *BMC Family Practice*. 2007; 8:15
- 17 Cals JWL, Schot MJC, de Jong SAM, Dinant GJ, Hopstaken RM. Point-of-care C-reactive protein testing and antibiotic prescribing for respiratory tract infections: a randomized controlled trial. *Annals of Family Medicine*. 2010; 8(2):124-133
- 18 Chandrajay D, Narayanan D, Barth JH. Evaluation of the effect of clinical validation of out of hours critical laboratory results. *Annals of Clinical Biochemistry*. 2016; 53(Pt 2):274-278
- 19 Cook EJ, Randhawa G, Guppy A, Large S. A study of urgent and emergency referrals from NHS Direct within England. *BMJ Open*. 2015; 5(5):e007533
- 20 Cooke J, Butler C, Hopstaken R, Dryden MS, McNulty C, Hurding S et al. Narrative review of primary care point-of-care testing (POCT) and antibacterial use in respiratory tract infection (RTI). *BMJ Open Respiratory Research*. 2015; 2(1):e000086
- 21 Dahler-Eriksen BS, Lauritzen T, Lassen JF, Lund ED, Brandslund I. Near-patient test for C-reactive protein in general practice: assessment of clinical, organizational, and economic outcomes. *Clinical Chemistry*. 1999; 45(4):478-485
- 22 Diederichsen HZ, Skamling M, Diederichsen A, Grinsted P, Antonsen S, Petersen PH et al. Randomised controlled trial of CRP rapid test as a guide to treatment of respiratory infections in general practice. *Scandinavian Journal of Primary Health Care*. 2000; 18(1):39-43
- 23 Do NTT, Ta NTD, Tran NTH, Than HM, Vu BTN, Hoang LB et al. Point-of-care C-reactive protein testing to reduce inappropriate use of antibiotics for non-severe acute respiratory infections in

- Vietnamese primary health care: a randomised controlled trial. *Lancet Global Health*. 2016; 4(9):e633-e641
- 24 Engel MF, Paling FP, Hoepelman AIM, van der Meer V, Oosterheert JJ. Evaluating the evidence for the implementation of C-reactive protein measurement in adult patients with suspected lower respiratory tract infection in primary care: a systematic review. *Family Practice*. 2012; 29(4):383-393
 - 25 Grodzinsky E, Wirehn AB, Fremner E, Haglund S, Larsson L, Persson LG et al. Point-of-care testing has a limited effect on time to clinical decision in primary health care. *Scandinavian Journal of Clinical and Laboratory Investigation*. 2004; 64(6):547-551
 - 26 Hanrahan CF, Clouse K, Bassett J, Mutunga L, Selibas K, Stevens W et al. The patient impact of point-of-care vs. laboratory placement of Xpert() MTB/RIF. *International Journal of Tuberculosis and Lung Disease*. 2015; 19(7):811-816
 - 27 Holm A, Pedersen SS, Nexoe J, Obel N, Nielsen LP, Koldkjaer O et al. Procalcitonin versus C-reactive protein for predicting pneumonia in adults with lower respiratory tract infection in primary care. *British Journal of General Practice*. 2007; 57(540):555-560
 - 28 Hopstaken RM, Butler CC, Muris JW, Knottnerus JA, Kester AD, Rinkens PE et al. Do clinical findings in lower respiratory tract infection help general practitioners prescribe antibiotics appropriately? An observational cohort study in general practice. *Family Practice*. 2006; 23(2):180-187
 - 29 Hopstaken RM, Muris JW, Knottnerus JA, Kester AD, Rinkens PE, Dinant GJ. Contributions of symptoms, signs, erythrocyte sedimentation rate, and C-reactive protein to a diagnosis of pneumonia in acute lower respiratory tract infection. *British Journal of General Practice*. 2003; 53(490):358-364
 - 30 Howick J, Cals JW, Jones C, Price CP, Pluddemann A, Heneghan C et al. Current and future use of point-of-care tests in primary care: an international survey in Australia, Belgium, The Netherlands, the UK and the USA. *BMJ Open*. 2014; 4(8):e005611
 - 31 Huang Y, Chen R, Wu T, Wei X, Guo A. Association between point-of-care CRP testing and antibiotic prescribing in respiratory tract infections: a systematic review and meta-analysis of primary care studies. *British Journal of General Practice*. 2013; 63(616):e787-e794
 - 32 Hunter R. Cost-effectiveness of point-of-care C-reactive protein tests for respiratory tract infection in primary care in England. *Advances in Therapy*. 2015; 32(1):69-85
 - 33 Jakobsen KA, Melbye H, Kelly MJ, Ceynowa C, Molstad S, Hood K et al. Influence of CRP testing and clinical findings on antibiotic prescribing in adults presenting with acute cough in primary care. *Scandinavian Journal of Primary Health Care*. 2010; 28(4):229-236
 - 34 Joshi A, Perin DP, Gehle A, Nsiah-Kumi PA. Feasibility of using C-reactive protein for point-of-care testing. *Technology and Health Care*. 2013; 21(3):233-240
 - 35 Kavanagh KE, O'Shea E, Halloran R, Cantillon P, Murphy AW. A pilot study of the use of near-patient C-reactive protein testing in the treatment of adult respiratory tract infections in one Irish general practice. *BMC Family Practice*. 2011; 12:93
 - 36 Kind P, Hardman G, and Macran S. UK population norms for EQ-5D. University of York, 1999. Available from:

<http://www.york.ac.uk/media/che/documents/papers/discussionpapers/CHE%20Discussion%20Paper%20172.pdf>

- 37 Leber W, McMullen H, Anderson J, Marlin N, Santos AC, Bremner S et al. Promotion of rapid testing for HIV in primary care (RHIVA2): a cluster-randomised controlled trial. *The Lancet HIV*. 2015; 2(6):e229-e235
- 38 Little P, Stuart B, Francis N, Tonkin-Crine S, Douglas E, Anthierens S. The effect of web-based training in communication skills and an interactive patient booklet and the use of a CRP point of care test in acute respiratory tract infection (RTI): a multi-national cluster randomised factorial controlled trial. *The Lancet*. 2015; 382(9899):1175-1182
- 39 Llor C, Hernandez S, Cots JM, Bjerrum L, Gonzalez B, Garcia G et al. Physicians with access to point-of-care tests significantly reduce the antibiotic prescription for common cold. *Revista Espanola De Quimioterapia*. 2013; 26(1):12-20
- 40 Llor C, Bjerrum L, Arranz J, Garcia G, Cots JM, Gonzalez Lopez-Valcarcel B et al. C-reactive protein testing in patients with acute rhinosinusitis leads to a reduction in antibiotic use. *Family Practice*. 2012; 29(6):653-658
- 41 Llor C, Bjerrum L, Munck A, Hansen MP, Cordoba GC, Strandberg EL et al. Predictors for antibiotic prescribing in patients with exacerbations of COPD in general practice. *Therapeutic Advances in Respiratory Disease*. 2013; 7(3):131-137
- 42 Llor C, Cots JM, Lopez-Valcarcel BG, Arranz J, Garcia G, Ortega J et al. Interventions to reduce antibiotic prescription for lower respiratory tract infections: Happy Audit study. *European Respiratory Journal*. 2012; 40(2):436-441
- 43 Llor C, Cots JM, Hernandez S, Ortega J, Arranz J, Monedero MJ et al. Effectiveness of two types of intervention on antibiotic prescribing in respiratory tract infections in Primary Care in Spain. Happy Audit Study. *Atencion Primaria*. 2014; 46(9):492-500
- 44 Melbye H, Aaraas I, Fleten N, Kolstrup N, Mikalsen JI. The value of C-reactive protein testing in suspected lower respiratory tract infections. A study from general practice on the effect of a rapid test on antibiotic research and course of the disease in adults. *Tidsskrift for Den Norske Laegeforening : Tidsskrift for Praktisk Medicin, Ny Raekke*. 1995; 115(13):1610-1615
- 45 Mueller C, Laule-Kilian K, Scholer A, Frana B, Rodriguez D, Schindler C et al. Use of B-type natriuretic peptide for the management of women with dyspnea. *American Journal of Cardiology*. 2004; 94(12):1510-1514
- 46 National Clinical Guideline Centre. Chronic heart failure: the management of chronic heart failure in adults in primary and secondary care. NICE clinical guideline 108. London. National Clinical Guideline Centre, 2010. Available from: <http://guidance.nice.org.uk/CG108/>
- 47 National Clinical Guideline Centre. Venous thromboembolic diseases: the management of venous thromboembolic diseases and the role of thrombophilia testing. NICE clinical guideline 144. London. National Clinical Guideline Centre, 2012. Available from: <http://guidance.nice.org.uk/CG144>
- 48 National Clinical Guideline Centre. Acute kidney injury: prevention, detection and management of acute kidney injury up to the point of renal replacement therapy. NICE clinical guideline 169. London. National Clinical Guideline Centre, 2013. Available from: <http://guidance.nice.org.uk/CG169>

- 49 National Clinical Guideline Centre. Acute heart failure: diagnosing and managing acute heart failure in adults. NICE clinical guideline 187. London. National Clinical Guideline Centre, 2014. Available from: <http://guidance.nice.org.uk/CG187>
- 50 National Clinical Guideline Centre. Pneumonia: Diagnosis and management of community- and hospital-acquired pneumonia in adults. NICE clinical guideline CG191. London. National Clinical Guideline Centre, 2014. Available from: <http://guidance.nice.org.uk/CG191>
- 51 National Institute for Health and Care Excellence. Myocardial infarction (acute): Early rule out using high-sensitivity troponin tests (Elecsys Troponin T high-sensitive, ARCHITECT STAT High Sensitive Troponin-I and AccuTnI+3 assays). NICE diagnostic guidance 15. London. National Institute for Health and Care Excellence (NICE), 2014. Available from: <http://guidance.nice.org.uk/DG15>
- 52 National Institute for Health and Care Excellence. Antimicrobial stewardship: systems and processes for effective antimicrobial medicine use. NICE guideline 15. Manchester. National Institute for Health and Care Excellence, 2015. Available from: <https://www.nice.org.uk/guidance/ng15>
- 53 National Institute for Health and Care Excellence and Clinical Knowledge Summaries. Pulmonary embolism, 2015. Available from: <https://cks.nice.org.uk/pulmonary-embolism>
- 54 National Institute for Health and Clinical Excellence. Respiratory tract infections - antibiotic prescribing: prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care, 2008. Available from: <https://www.nice.org.uk/guidance/cg69/resources/guidance-respiratory-tract-infections-antibiotic-prescribing-pdf>
- 55 Nayer J, Aggarwal P, Galwankar S. Utility of point-of-care testing of natriuretic peptides (brain natriuretic peptide and n-terminal pro-brain natriuretic peptide) in the emergency department. *International Journal of Critical Illness and Injury Science*. 2014; 4(3):209-215
- 56 Neumark T, Brudin L, Molstad S. Use of rapid diagnostic tests and choice of antibiotics in respiratory tract infections in primary healthcare--a 6-y follow-up study. *Scandinavian Journal of Infectious Diseases*. 2010; 42(2):90-96
- 57 Oosterheert JJ, Loon AM, Schuurman R, Hoepelman AI, Hak E, Thijsen S et al. Impact of rapid detection of viral and atypical bacterial pathogens by real-time polymerase chain reaction for patients with lower respiratory tract infection. *Clinical Infectious Diseases*. 2005; 41(10):1438-1444
- 58 Oppong R, Jit M, Smith RD, Butler CC, Melbye H, Molstad S et al. Cost-effectiveness of point-of-care C-reactive protein testing to inform antibiotic prescribing decisions. *British Journal of General Practice*. 2013; 63(612):e465-e471
- 59 Organisation for Economic Co-operation and Development (OECD). Purchasing power parities (PPP), 2007. Available from: <http://www.oecd.org/std/ppp>
- 60 Peters CM, Schouwenaars FM, Haagsma E, Evenhuis HM, Echteld MA. Antibiotic prescribing and C-reactive protein testing for pulmonary infections in patients with intellectual disabilities. *British Journal of General Practice*. 2013; 63(610):e326-e330

- 61 Pluddemann A, Heneghan C, Price CP, Wolstenholme J, Thompson M. Point-of-care blood test for ketones in patients with diabetes: primary care diagnostic technology update. *British Journal of General Practice*. 2011; 61(589):530-531
- 62 Rebnord IK, Hunskaar S, Gjesdal S, Hetlevik O. Point-of-care testing with CRP in primary care: a registry-based observational study from Norway. *BMC Family Practice*. 2015; 16:170
- 63 Smith R, Coast J. The true cost of antimicrobial resistance. *BMJ*. 2013; 346:f1493
- 64 Stokes NR, Dietz BW, Liang JJ. Cardiopulmonary laboratory biomarkers in the evaluation of acute dyspnea. *Open Access Emergency Medicine : OAEM*. 2016; 8:35-45
- 65 Strykowski DF, Nielsen ABS, Llor C, Siersma V, Bjerrum L. An intervention with access to C-reactive protein rapid test reduces antibiotic overprescribing in acute exacerbations of chronic bronchitis and COPD. *Family Practice*. 2015; 32(4):395-400