Antimicrobial resistance: changing risk-related behaviours in the general population

A systematic review protocol

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RAND Europe

Final Version

November 2014

Prepared for the Centre for Public Health (CPH) at the National Institute for Health and Care Excellence (NICE)

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Abbreviations

AMR	Antimicrobial Resistance
BMJ	British Medical Journal
HIV	Human Immunodeficiency Virus
NICE	National Institute for Health and Care Excellence
RCT	Randomised Controlled Trial
SR	Systematic Review
TB	Tuberculosis
WHO	World Health Organization

1. Introduction

1.1. Summary of proposed project

The National Institute for Health and Care Excellence (NICE) has been asked by the Department of Health to develop a public health guideline aimed at delaying antimicrobial resistance. The scope for this guideline was published on the NICE website in October 2014[1] and the text presented in this document (protocol) is largely based on this scope. Overall, the guideline will focus on public education about:

- the importance of using antimicrobials correctly;
- the dangers associated with their overuse and misuse;
- changes in behaviour that can avert the problems associated with the misuse of antimicrobials, such as infection prevention and control measures.

In order to inform this guideline ('Antimicrobial resistance: changing risk-related behaviours in the general population'), RAND Europe has been commissioned by NICE to conduct a systematic review of the effectiveness and cost-effectiveness of educational interventions to change people's behaviour in order (1) to ensure appropriate demand for, and correct use of, antimicrobials; and (2) to prevent infection and reduce the spread of antimicrobial resistance. This guideline will provide recommendations for good practice at the local, regional and population level. It will be aimed at commissioners, managers, professionals and professional bodies with a responsibility for prescribing and dispensing antimicrobials or with public health as part of their remit. These people may work within the NHS, social services, local authorities and the wider public, private, voluntary and community sectors. In addition, it may be of interest to people who are particularly vulnerable to infection (such as people with suppressed immune systems due to cancer treatment) and other members of the public.

This protocol details the steps required for conducting the systematic review. The review question is based on the NICE public health guideline scope[1], and the review methodology is based on the NICE guidelines manual[2].

[1] https://www.nice.org.uk/guidance/gid-phg89/documents/antimicrobial-resistance-changing-riskrelated-behaviours-in-the-general-population-final-scope2

[2] https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-the-manual.pdf

1.2. Background

The World Health Organization defines antimicrobial resistance (AMR) as 'resistance of a microorganism to an antimicrobial drug that was originally effective for treatment of infections caused by it' (http://www.who.int/mediacentre/factsheets/fs194/en/). Resistant microorganisms (including bacteria, fungi, viruses and parasites) are able to withstand attack by antimicrobials (for example, antibiotics, antifungals, antivirals and antimalarials). As a result, standard treatments become ineffective and infections persist, increasing the risk of them spreading. Resistance is a natural evolutionary phenomenon but the use (and misuse) of antimicrobials accelerates this process. Poor infection prevention and control practices, inadequate sanitary conditions and inappropriate food-handling encourage the further spread of AMR.

AMR poses a serious and growing threat to public health as infections from resistant strains of microbials are becoming increasingly more difficult and expensive to treat (Davies 2013; Howell 2013). Viruses (such as HIV), parasites (such as malaria) and fungi (for example, *candida*), are showing resistance to antivirals, antiparasitics and antifungals respectively. But antibiotic resistance is the main concern. Common bacteria such as *Escherichia coli*, *Klebsiella pneumoniae*, and Staphylococcus aureus have high rates of resistance. These bacteria cause many common infections, for example, urinary tract, wound and bloodstream infections and pneumonia (WHO, 2014). In the UK, the spread of multi-drug resistant tuberculosis (TB) and gonorhhoea is also a concern (Davies, 2012).

The World Health Organization (WHO) estimated that antimicrobials add, on average, 20 years to life expectancy[3] (WHO 2012). Although it has also been estimated that 25,000 people in Europe die each year because of antimicrobial *resistance*: equivalent to the number of deaths from road traffic accidents (WHO 2011) –translating to a cost of €1.5 billion annually (Davies et al. 2013). AMR, however, is largely considered to be tomorrow's problem; while current costs may be considered to be relatively low, a recent review in the BMJ has argued that future costs of AMR may be significantly underestimated – including a study that estimated a future cost of $55 billion per year in the US (Smith and Coast 2012; 2013). As antimicrobial resistance is increasing, the problem is confounded by the lack of development of new antimicrobials (Piddock 2012; Theuretzbacher 2012), which has occurred because their net present value is lower than that of other therapeutic treatments making antimicrobials an unattractive therapeutic investment (Mossialos et al. 2013). It is vital to ensure the antimicrobials that are still effective remain so for as long as possible, to allow time to research and develop new ones.

A review by Huttner et al. (2010) identified 22 public campaigns aimed at improving the use of antibiotics in outpatients. This included campaigns conducted at the national and regional level in high-income countries between 1990 and 2007. In most cases, health authorities were involved in the establishment of the campaigns, which predominantly targeted the general public. The campaigns usually used a multifaceted approach, with the most common intervention involving the distribution of informational material such as pamphlets to

[3] Broader environmental factors, such as improvements in nutrition, hygiene and sanitation and overcrowded housing also helped prevent and reduce the transmission of infectious diseases (Davies 2013).

patients. With respect to their results, the authors found that only a few campaigns have assessed their impact on resistance to antibiotics. Establishing a cause–effect relationship between the campaigns and a reduction in the use of antibiotics is further complicated by methodological limitations. According to the review, most campaigns did not have a control population and pre-intervention trends were rarely assessed.

Recent European surveys suggest that there continues to be room for an awareness campaign targeting the general public. According to a special edition of the Eurobarometer (2010), 83% of respondents believed that unnecessary use of antibiotics makes them become ineffective yet 53% of Europeans believed that antibiotics kill viruses and 47% of respondents believed that antibiotics are effective against cold and flu. Figures in the UK from Ipsos MORI (2013) suggest that 40% of respondents think that antibiotics can kill viruses, 16% wrongly believe that antibiotics are effective against coughs and colds. Strategies are therefore needed that encourage antimicrobials to be used more "*responsibly and less often*" to safeguard human health (DH 2013).

Thus, this review will aim to answer the following research questions that were set out in the scope for this guideline[1]:

1. Which educational interventions are effective and cost-effective in changing the public's behaviour to ensure they only ask for antimicrobials when appropriate and use them correctly?
2. Which educational interventions are effective and cost-effective in changing the public's behaviour to prevent infection and reduce the spread of antimicrobial resistance?

1.3. Objectives

The objectives of this systematic review will be to:

- Estimate the effectiveness of education interventions that elicit changes in knowledge, awareness and/or behaviour in people about how and when to take antimicrobials;
- Estimate the effectiveness of educational interventions that elicit behavioural change in people to prevent infections such as flu and TB, and more specifically, to reduce the spread of antimicrobial resistance;
- Estimate the cost-effectiveness of these educational interventions;
- Identify strengths and weaknesses in the literature, and identify whether there are any gaps in the literature that may need to be addressed in future studies.

2. Methods

2.1. Inclusion and exclusion criteria

To address the above research questions, the population(s), intervention(s), comparison(s), outcome(s), and study types of interest ('PICOS') are defined below and in Table 1.

2.1.1. Populations

For both questions above, studies of people of all ages, including children and young people, living at home, in the community and those who are in hospital, will be eligible for inclusion. There will be a particular focus on people who regularly take a lot of antibiotics, such as young children and older people, and people who misuse antibiotics (i.e. those who do not take the correct dose for the correct amount of time and via the correct route; those who keep antimicrobials to use another time; those who self-medicate [take antimicrobials without prescription or advice from a healthcare professional]; those who share antimicrobials with others; those who use counterfeit medications). We will also consider groups identified by McNulty et al. (2007a) (and others) who have demonstrated less knowledge about antibiotics, including males, and those with less formal educational qualifications - or those who may be more likely to misuse antibiotics (e.g. counterintuitively, highly educated young women [see McNulty et al. 2007b]).

Where appropriate, there will also be a focus on people whose social and economic circumstances or health puts them at greater risk of acquiring or transmitting infectious disease and antimicrobial strains. This includes (but is not limited to) people who:

- Are immunosuppressed (for example, due to cancer treatment or an organ transplant);
- Have a chronic disease;
- Live in crowded conditions[4]
- Are homeless;
- Have been in prison;

[4] Overcrowding has been defined as either having too many people sleeping in one room, or the amount of space in the house is too small for the number of people living in it (defined by Shelter: http://england.shelter.org.uk/get_advice/repairs_and_bad_conditions/common_problems/overcrowding)

- Have migrated from countries with a high prevalence of infectious diseases such as tuberculosis (e.g. South Asia and sub-Saharan Africa). Studies of populations living in low-income countries will not, however, be included.

2.1.2. Interventions and comparisons

This systematic review will focus on educational interventions – those that aim to change knowledge, awareness and behaviours regarding how, why and when to take antimicrobials, and those that aim to prevent the spread of infection and antimicrobial resistance.

To address question 1 above (Which educational interventions are effective and cost-effective in changing the public's behaviour to ensure they only ask for antimicrobials when appropriate and use them correctly?), studies that evaluate educational interventions that reduce the misuse of antimicrobials will be eligible for inclusion. This includes educating the general public about:

- When, why and how to use antimicrobials;
- The dangers of overuse and misuse (including self-medication, sharing medicines, not completing or missing doses, buying antimicrobials on the Internet, or using counterfeit antimicrobials;
- Suitable alternatives to antimicrobials (e.g. using over-the-counter medicines for the symptoms of a cold).

To address question 2 above (Which educational interventions are effective and cost-effective in changing the public's behaviour to prevent infection and reduce the spread of antimicrobial resistance?), studies that evaluate educational interventions on how to reduce the spread of infections, and antimicrobial resistance, at home and in the community, will be eligible for inclusion. This includes (but is not limited to) educating the general public about:

- Hand-washing to prevent infection;
- Using a tissue to cover the mouth when coughing and sneezing;
- Food-hygiene to prevent and reduce transmission of infection.

For both questions, we will include interventions that educate the general public about the type of healthcare they should ask for to prevent or treat infectious diseases, so they are clear that:

- Antibiotics should not be used for a cold or flu (e.g. for question 1);
- Vaccines or other protection, such as anti-malarial medication should be used when travelling abroad (e.g. for question 2).

For both questions, interventions that are delivered at the population, community, organisational or individual level in any setting and by any mode of delivery will be included (e.g. via the Internet, apps, face-to-face). Examples include:

- Individual level: prescribers and dispensers telling patients how important it is to use antimicrobials properly and the dangers of over- and misuse (e.g. for question 1);
- Population and community level: media campaigns on antibiotic appropriate antibiotic use (e.g. for question 1), or media campaigns on infection prevention (hand washing, food hygiene) (e.g. for question 2).

Studies will be excluded if they evaluate any of the following: national and international policy on AMR; surveillance to track antimicrobial use and resistance in bacteria; developing new drugs, treatments and diagnostics; education of prescribers about the diagnosis of infectious diseases and clinical decisions concerning whether to prescribe an antimicrobial; education of healthcare professionals about hygiene practices to prevent the spread of infectious diseases; environmental cleanliness and cleaning products; promoting safe sex; antimicrobial use in animals; antibiotic stewardship (i.e. studies that evaluate management or care of antibiotics – including prescribers or management at a higher level [hospital or government levels]); the use of herbal alternatives for antibiotics; or multi-component interventions where education is not the main component.

Included studies may or may not include a comparison group (e.g. baseline comparison, different educational strategies, or different modes of delivery).

2.1.3. Outcomes

For question 1, studies eligible for inclusion must evaluate one of the following outcomes:

- Knowledge and awareness of when, why and/or how antimicrobials should be used;
- Knowledge and awareness of antimicrobial resistance;
- Knowledge of the type of support people can expect from health professionals in relation to the use of antimicrobials;
- The ability and confidence of prescribers and dispensers to talk to people about the use and misuse of antimicrobials;
- Demand for antimicrobials (particularly antibiotics);
- Adherence to prescribed antimicrobials;
- Inappropriate antimicrobial use;
- Inappropriate antimicrobial prescribing by healthcare professionals.

For question 2, studies eligible for inclusion must evaluate one of the following outcomes:

- People's knowledge and awareness of how they can prevent infection and/or reduce the spread of antimicrobial resistant microbes;
- Hand washing behaviour;
- Behaviour to reduce the spread of airborne diseases such as TB and flu (for example, use and appropriate disposal of tissues when coughing and sneezing);
- Food hygiene practices.

Studies that address the above inclusion criteria and also report any cost data will also be included in the review.

2.1.4. Study designs

Initially, all types of studies will be eligible for inclusion, with the exception of letters, editorials and commentaries. If there are a large number of 'hits' (i.e. over 15,000) then we may restrict the included studies by study type, starting with randomised controlled trials, and then non-randomised controlled trials, etc. Any decisions to limit study designs will be discussed with the NICE team and the changes recorded in the protocol appendix. For all studies, those published as abstracts or conference presentations will be included in the

primary analysis if enough data are presented (and costs and outcomes are sufficiently disaggregated), and if the abstract is not linked to a full paper.

Table 1. Summary of inclusion/exclusion criteria

	Inclusion	Exclusion
Population	People of all ages, including children and young people, living at home, in the community and who are in hospital. Population groups will include: • people who regularly take a lot of antibiotics including, but not limited to, young children and older people; • people who misuse antibiotics including, but not limited to, those who: - do not take the correct dose for the correct amount of time and via the correct route; - keep antimicrobials to use another time; - self-medicate (i.e. take antimicrobials without prescription or advice from a healthcare professional); - share antimicrobials with others; - those who use counterfeit medications. • people whose social and economic circumstances or health puts them at greater risk of acquiring or transmitting infectious disease and antimicrobial strains. This includes, but is not limited to, people who: - are immunosuppressed; - have a chronic disease; - live in crowded conditions; - are homeless; - have been in prison; - are migrants from countries with a high prevalence of infectious diseases such as TB.	People living in low income countries
Intervention(s)	Question 1: Educational interventions that reduce the misuse of antimicrobials, particularly antibiotics. This includes educating the general public about: - When, why and how to use antimicrobials; - The dangers of overuse and misuse (including self-medication, sharing medicines, not completing or missing doses, buying antimicrobials on the Internet, or using counterfeit antimicrobials; - Suitable alternatives to antimicrobials (e.g. using over-the-counter medicines for the symptoms of a cold). Question 2: Interventions that educate the general public about how to reduce the spread of antimicrobial resistance at home and	- National and international policy on AMR. - Surveillance to track antimicrobial use and resistance in bacteria. - Developing new drugs, treatments and diagnostics. - Education of prescribers about the diagnosis of infectious diseases and clinical decisions concerning whether to prescribe an

	in the community. This includes interventions to prevent and reduce transmission of infection by targeting: • Hand-washing behaviour; • Respiratory etiquette, e.g. using a tissue to cover the mouth when coughing and sneezing; • Food hygiene practices. These studies may not necessarily be specifically aimed at preventing antimicrobial resistance. For both questions, we will include interventions that educate the general public about the type of healthcare they should ask for to prevent or treat infectious diseases. For example, so they are clear that: - Antibiotics should not be used for a cold or flu (e.g. for question 1); - Vaccines or other protection, such as anti-malarial medication should be used when travelling abroad (e.g. for question 2). For both questions, interventions that are delivered at the population, community, organisational or individual level in any setting and by any mode of delivery will be included (e.g. via the Internet, apps, face-to-face). Examples include: - Individual level: prescribers and dispensers telling patients how important it is to use antimicrobials properly and the dangers of over- and misuse (e.g. for question 1); - Population and community level: media campaigns on antibiotic appropriate antibiotic use (e.g. for question 1), or media campaigns on infection prevention (hand washing, food hygiene) (e.g. for question 2).	antimicrobial. - Education of healthcare professionals about hygiene practices to prevent the spread of infectious diseases. - Environmental cleanliness and cleaning products. - Promoting safe sex. - Antimicrobial use in animals. - Antibiotic stewardship. - The use of herbal alternatives for antibiotics. - Multi-component interventions where education is not the main component of the intervention[5].
Comparison(s)	Included studies may or may not include a comparison group (e.g. baseline comparison, different educational strategies, or different modes of delivery).	
Outcome(s)	Studies will be eligible for inclusion if they measure changes in: (For Research Question 1) - Knowledge and awareness of when, why and/or how antimicrobials should be used; - Knowledge and awareness of antimicrobial resistance; - Knowledge of the type of support people can expect	

[5] If any multi-component interventions are identified in the literature searches where education is not the main component, they will not be included – but will be categorised for reference (as well as being listed in an 'excluded studies' table).

	from health professionals in relation to the use of antimicrobials; - The ability and confidence of prescribers and dispensers to talk to people about the use and misuse of antimicrobials; - Demand for antimicrobials (particularly antibiotics); - Adherence to prescribed antimicrobials; - Inappropriate antimicrobial use; - Inappropriate antimicrobial prescribing by healthcare professionals. (For Research Question 2) - People's knowledge and awareness of how they can prevent infection and reduce the spread of antimicrobial resistant microbes; - Hand washing behaviour; - Behaviour to reduce the spread of airborne diseases such as TB and flu (for example, use and appropriate disposal of tissues when coughing and sneezing); - Food hygiene practices. For both questions, any studies which report cost data will also be eligible for inclusion.	
Studies design	All study types will be eligible for inclusion[6]. For the economic review, published economic evaluations, such as cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses, cost-minimisation analyses, and cost-consequence analyses will be eligible for inclusion.	Letters, editorials and commentaries will not be eligible for inclusion.

2.2. Search Strategy

One search will be conducted to address all three review questions. The literature search will be conducted in the following:

Databases:
Medline and Medline in process (Ovid)
Embase (Elsevier) (includes conference proceedings)
Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO)
Web of Science Core Collection*(Thomson Reuters)
*includes: Science Citation Index, Social Sciences Citation Index, Arts & Humanities Citation Index, Conference Proceedings Citation Index – Science, Conference Proceedings Citation Index – Social Sciences & Humanities

[6] If there are a large number of 'hits' (i.e. over 15,000) than we may restrict the included studies by study type, starting with randomised controlled trials, and then non-randomised controlled trials, etc. Any decisions to limit study designs will be discussed with the NICE team and the changes recorded in the protocol appendix.

Cochrane Library* (Wiley)
*includes: Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Database of Abstracts and Reviews (DARE), Health Technology Assessment Database(HTA), NHS Economic Evaluation Database (NHS EED)
PsycInfo (EBSCO)
Education Resources Information Center (ERIC)(EBSCO)
EconLit (EBSCO)
Sociological Abstracts (Proquest)
Social Sciences Abstracts (EBSCO)
Health Management Information Consortium (HMIC) (Ovid)
NIHR Health Technology Assessment (NIHR HTA and other NIHR journals)
NICE Technology appraisals

Registries:
CEA Registry (https://research.tufts-nemc.org/cear4/)
ClinicalTrials.gov (https://clinicaltrials.gov/)
International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
metaRegister of Controlled Trials (mRCT) (http://www.controlled-trials.com/mrct/)

URLs (for grey literature):
Oaister (www.oaister.org)
OpenGrey (www.opengrey.eu)
NYAM Grey Literature Report (www.greylit.org)

As presented above, economic evaluations and costs studies will be undertaken in the following economic databases:

- NHS Economic Evaluation Database (NHS EED);
- Health Economic Evaluation Database (HEED) (Wiley);
- EconLit; (EBCSO)
- CEA Registry.

Search limits

The searches will be restricted to:

- English language publications;
- Search dates from 2001 and onwards. This date has been chosen as it is the date of the publication of the WHO Global Strategy for Containment of Antimicrobial Resistance (http://www.who.int/drugresistance/WHO_Global_Strategy.htm/en/).

Additional searches

Additional techniques, typically used to identify evidence for systematic reviews will be applied:

- Checking the references within relevant papers and reviews (e.g. checking citations in the Huttner et al. 2010 review, and other reviews identified);
- Searching for specific trial/campaign names (e.g. of well-known public health campaigns identified by expert knowledge and google searches);
- Carrying out citation searches of key publications to identify subsequent publications which have cited those key publications (e.g. we will check references of

all included studies to make sure we haven't missed any potentially relevant studies in our searches).

Unpublished studies will be sought by searching through clinical trial registries and conference proceedings.

All of the results of the searches will be loaded together into EndNote bibliographic software.

The search below is for the Medline search, and will be slightly adapted to fit the search syntax for each of the other databases.

Table 2. Draft Search Terms

Ovid MEDLINE(R) 1948 to Present (including In-Process & Other Non-Indexed Citations) Searched 14 November 2014

1	exp Drug Resistance, Bacterial/ or exp Drug Resistance, Multiple/	76170
2	anti-infective agents/ad, tu or anti-bacterial agents/ad, tu or antibiotics, antitubercular/ad, tu or antitubercular agents/ad, tu or antifungal agents/ad, tu or anti-infective agents, local/ad, tu or antiparasitic agents/ad, tu or anthelmintics/ad, tu or antiprotozoal agents/ad, tu or antiviral agents/ad, tu or anti-retroviral agents/ad, tu	241302
3	(antibiotic$ or anti-biot$ or "anti biot$" or antimicrob$ or "anti microb$" or antibacter$ or anti-bacter$ or "anti bacter$" or antiviral$ or anti-viral$ or "anti viral$" or antiparasitic$ or anti-parasitic$ or "anti parasitic$" or antifungal$ or anti-fungal$ or "anti fungal$").ti,ab.	431777
4	Hand disinfection/ or Hand sanitizer/ or Hand hygiene/	4853
5	(skin care/ or Anti infective agents, local/) and (hand or hands or handwash$).tw.	872
6	((hand or hands or handwash$) adj3 (wash$ or disinfect$ or sanitiz$ or sanitis$ or scrub$ or clean$ or soap$ or hygiene$)).tw.	6100
7	((tissue$ or kleenex$ or handkerchief$ or hanky or hankie or hankies or hygiene or etiquette) adj3 (cough$ or sneez$)).tw.	56
8	Communicable Disease Control/ and (cough/ or sneezing/)	19
9	Communicable Disease Control/ and ((travel$ or holiday$ or tourist$ or tourism or vacation$ or journey$ or trip or trips or flight$) adj3 (oversea$ or foreign$ or international or abroad)).ti,ab.	162
10	exp Foodborne Diseases/pc or Food safety/ or Food contamination/ or exp Food handling/st, ae or Gastroenteritis/pc	37128
11	((food$ adj2 (disease$ or poison$ or contamin$) adj2 (prevent$ or reduc$ or decrease$ or discourag$)) or ((food$ or cook$) adj (safe$ or handl$ or hygiene$))).tw.	7295
12	exp *travel/ or travel medicine/	12703
13	or/1-12	672727
14	health education/ or health promotion/ or Patient Education as Topic/ or exp Programmed Instruction as Topic/ or Health Communication/ or Consumer Health Information/ or attitude to health/ or Patient Acceptance of Health Care/ or Patient Satisfaction/ or "Health Knowledge, Attitudes, Practice"/ or medication adherence/ or patient compliance/ or risk reduction	432567

	behavior/	
15	Public Health/ed	3994
16	Education/ or Models, Educational/ or Education, Distance/ or Education, Nonprofessional/ or Education, Continuing/ or Faculty/ or Universities/ or Patient Education Handout/ or Curriculum/ or Teaching materials/ or Teaching/ or health literacy/	163391
17	Pamphlets/ or exp Audiovisual aids/ or communications media/ or exp marketing/ or Advertising as Topic/ or Persuasive Communication/ or Social Networking/ or internet/	175110
18	Libraries/ or Library materials/ or Library Services/ or Information services/ or Information Dissemination/ or access to information/ or Information Literacy/ or Information Seeking Behavior/ or Decision Support Techniques/	45868
19	behavior therapy/ or self efficacy/	37600
20	physician-patient relations/ or professional-family relations/ or professional-patient relations/ or Inappropriate Prescribing/ae, pc	96949
21	((outreach or written or printed or oral or campaign$ or resource$ or disseminat$) adj1 information).ti,ab.	5841
22	(marketing or advertis$ or publicis$ or publiciz$ or publicity or mass media or media campaign$ or communication$ media).ti,ab.	37620
23	(internet$ or social media or social network$ or facebook or twitter or blog$ or SMS or short messaging service$ or smartphone$ or mobile app or mobile apps or mobile application$ or tweet or text messag$ or texting or emailing or podcast$ or ((mobile or cell$ or smart) adj (phone$ or telephone$))).ti,ab.	51129
24	computer-assisted instruction/	9720
25	((shared or informed) adj3 (decision$ or choice$)).ti,ab.	10449
26	or/14-25	899541
27	13 and 26	14490
28	(((counsel$ or educat$ or informat$ or communicat$ or pamphlet$ or handout$ or hand-out$ or hand out$ or booklet$ or leaflet$ or advice$ or advis$ or literacy or literature or video$ or audio$ or web$ or website$ or poster or posters or publication$ or curriculum$ or curricula$ or teach$ or trainer$ or training or program$ or intervention$ or resource$ or meeting$1 or session$1 or workshop$1 or visit$1 or material$1 or initiative$1 or outreach) adj3 (antibiotic$ or anti-biot$ or "anti biot$" or antimicrob$ or "anti microb$" or antibacter$ or anti-bacter$ or "anti bacter$" or	2937

	antiviral$ or anti-viral$ or "anti viral$" or antiparasitic$ or anti-parasitic$ or "anti parasitic$" or antifungal$ or anti-fungal$ or "anti fungal$" or "antimalarial$" or "anti-malarial$" or "anti malarial$")) and (misuse$ or overuse$ or "self medicat$" or "self-medicat$" or adhere$ or "missed dose" or counterfeit or prescri$ or resist$ or tolera$ or compliance)).tw.	
29	(((behavior$ or behaviour$) adj3 (change or changing or modification$ or modify or modifying or modifies or modified or therapy or therapies) adj3 (antibiotic$ or anti-biot$ or "anti biot$" or antimicrob$ or "anti microb$" or antibacter$ or anti-bacter$ or "anti bacter$" or antiviral$ or anti-viral$ or "anti viral$" or antiparasitic$ or anti-parasitic$ or "anti parasitic$" or antifungal$ or anti-fungal$ or "anti fungal$" or "antimalarial$" or "anti-malarial$" or "anti malarial$")) and (misuse$ or overuse$ or "self medicat$" or "self-medicat$" or adhere$ or "missed dose" or counterfeit or prescri$ or resist$ or tolera$ or compliance)).tw.	12
30	((travel$ or holiday$ or tourist$ or tourism or vacation$ or journeys or trip or trips or flight$) adj3 (oversea$ or foreign$ or international or abroad or vaccin$)).ti,ab.	4099
31	(counsel$ or educat$ or pamphlet$ or handout$ or hand-out$ or hand out$ or booklet$ or leaflet$ or advice$ or advis$ or video$ or audio$ or web$ or website$ or poster or posters or curriculum$ or curricula$ or teach$ or trainer$ or training or resource$ or meeting$1 or session$1 or workshop$1 or initiative$1 or outreach).tw.	1361778
32	30 and 31	975
33	27 or 28 or 29 or 32	17843
34	limit 33 to yr="2001 -Current"	13598
35	limit 34 to english language	12526
36	animals/ not humans/	3998174
37	35 not 36	12252
38	(comment or letter or editorial).pt.	1408064
39	37 not 38	11647

2.3. Study selection and data extraction

Titles and abstracts of identified studies will be independently[7] screened by two researchers for inclusion against the criteria specified in Table 1. This first screening phase will be conducted within Endnote – using inclusion/exclusion criteria for all three review questions. A consensus will be drawn on the papers to be considered for full paper review, consulting a third reviewer if necessary. At this point, if there appear to be any probable includes, we will choose some of these papers (for example UK studies) for early citation searching.

During the next stage, full papers of potentially relevant studies identified in the first pass will be obtained and screened by two RAND researchers working independently, and using the inclusion criteria as a reference. Again, if there are any discrepancies, the opinion of a third reviewer will be sought.

The number of studies identified by the search and excluded at various stages will be recorded and reported in a PRISMA study flow diagram (see Appendix A). After the second stage of screening, a table of excluded studies with detailed reasons for exclusion will be created and reported in an appendix in the final report.

An Excel spread sheet will be used for data extraction. The template will be developed based on the model provided in Appendix H of the NICE manual, and then will be piloted using two or three studies (or more if necessary). Data likely to be extracted from each study include:

- Bibliographic reference (authors, year, article title, journal, volume, pages);
- Study setting/country;
- Study type;
- Study quality;
- Key aims of the study (including the target audience);
- If the interventions are based on an underlying theory or conceptual model;
- Study inclusion/exclusion criteria;
- Comparator conditions evaluated (if any);
- Method of allocation;
- Number of participants;
- Population characteristics (age, sex, ethnic origin; socio-economic status, education, other descriptive characteristics such as if the population is immunosuppressed, have a chronic disease, live in crowded conditions, homeless; have been in prison; migrants, etc.);
- The number of individuals recruited to the study (total, per treatment group);
- Interventions evaluated (including setting, mode of delivery, who delivered the intervention, the intervention frequency, length, duration and intensity);
- Methods of analysis;

[7] If there are over 10,000 hits, we may agree with NICE that a certain percentage of title/abstracts are double reviewed (e.g. 20%). If there is good agreement (e.g. 90% agreement/ >0.60 Kappa) then the rest may not need to be double reviewed.

- Results (including any adverse or unintended effects);
- Any factors the authors identified that may prevent, or support, effective implementation of the intervention evaluated;
- Comments (e.g. whether the intervention is transferable for other settings; limitations identified by authors and/or by reviewers).
- Gaps and limitations.

Following identification of relevant economic studies, data will be extracted on:

- Costs;
- Health outcomes, or valuation of health effects (HRQL);
- Incremental cost-effectiveness.

2.4. Quality assessment

To assess the quality of the included studies, methodology checklists reported in Appendix H of the NICE guidelines manual will be used for the different study types.

To make a judgment about the overall quality of an included study (and also a collection of studies), an assessment will be made to determine which quality appraisal criteria from the checklist are the most important indicators of quality for the review questions[8]. The overall quality will be largely guided by whether or not the included studies adequately address these selected criteria (as described in the Cochrane Handbook).

Studies will be rated ('++', '+' or '–'). An overall quality rating of ++ means that all or most of the checklist criteria have been fulfilled, and where they have not been fulfilled the conclusions are very unlikely to alter. An overall quality rating of + means that some the checklist criteria have been fulfilled, and where they have not been fulfilled, or are not adequately described, the conclusions are unlikely to alter. An overall quality rating of – means that few or no checklist criteria have been fulfilled and the conclusions are likely or very likely to alter.

Quality assessments will be conducted by one reviewer and checked by a second reviewer, with any discrepancies resolved through discussion or by consulting a third reviewer.

2.5. Synthesising the evidence

For studies that report qualitative outcomes, thematic analysis techniques will be used, and reported in a narrative synthesis. For quantitative studies, meta-analysis will be undertaken where possible (using the RevMan program) provided that there is no clinical or statistical

[8] The rationale used to decide which quality criteria are most important will be presented in the final report.

heterogeneity[9] between studies. The results will be pooled using a fixed effect model and a random effects model – and the results compared using these different models. Results will be presented as risk ratios for dichotomous outcomes and mean differences for studies that evaluate continuous outcomes (means, or mean differences), and presented in forest plots. For those studies that use different scales, a standardised mean will be estimated, and also presented in forest plots. If the data cannot be pooled, we will summarise the evidence in text and tables (i.e. using a narrative synthesis).

The main results will be summarised into general themes, and any qualitative studies will be presented alongside the quantitative analysis (i.e. in a parallel synthesis). The quality of the included studies will also be reported alongside the results.

We envision that the data will be presented by intervention type and mode of delivery, study type, country, setting, and population group targeted. During the course of the review, other relevant variables on context, such as inequalities, may be identified and will be included in the results tables and in the text.

Where possible, results will be presented separately for people who are immunosuppressed; people who have a chronic disease; people who live in crowded conditions; people who are homeless; people who have been in prison; people who have migrated from countries with a high prevalence of infectious diseases (i.e. those people whose social and economic circumstances or health puts them at greater risk of acquiring or transmitting infectious diseases and antimicrobial resistant strains).

Cost-effectiveness or net benefit estimates from published or unpublished studies will be presented using an 'economic evidence profile' which includes relevant economic information (i.e. applicability, limitations, resource use, costs, cost-effectiveness and/or net benefit estimates as appropriate). It will be stated if the economic information is not available or if it is not thought to be relevant to the review question.

The final report will be typically structured as follows.

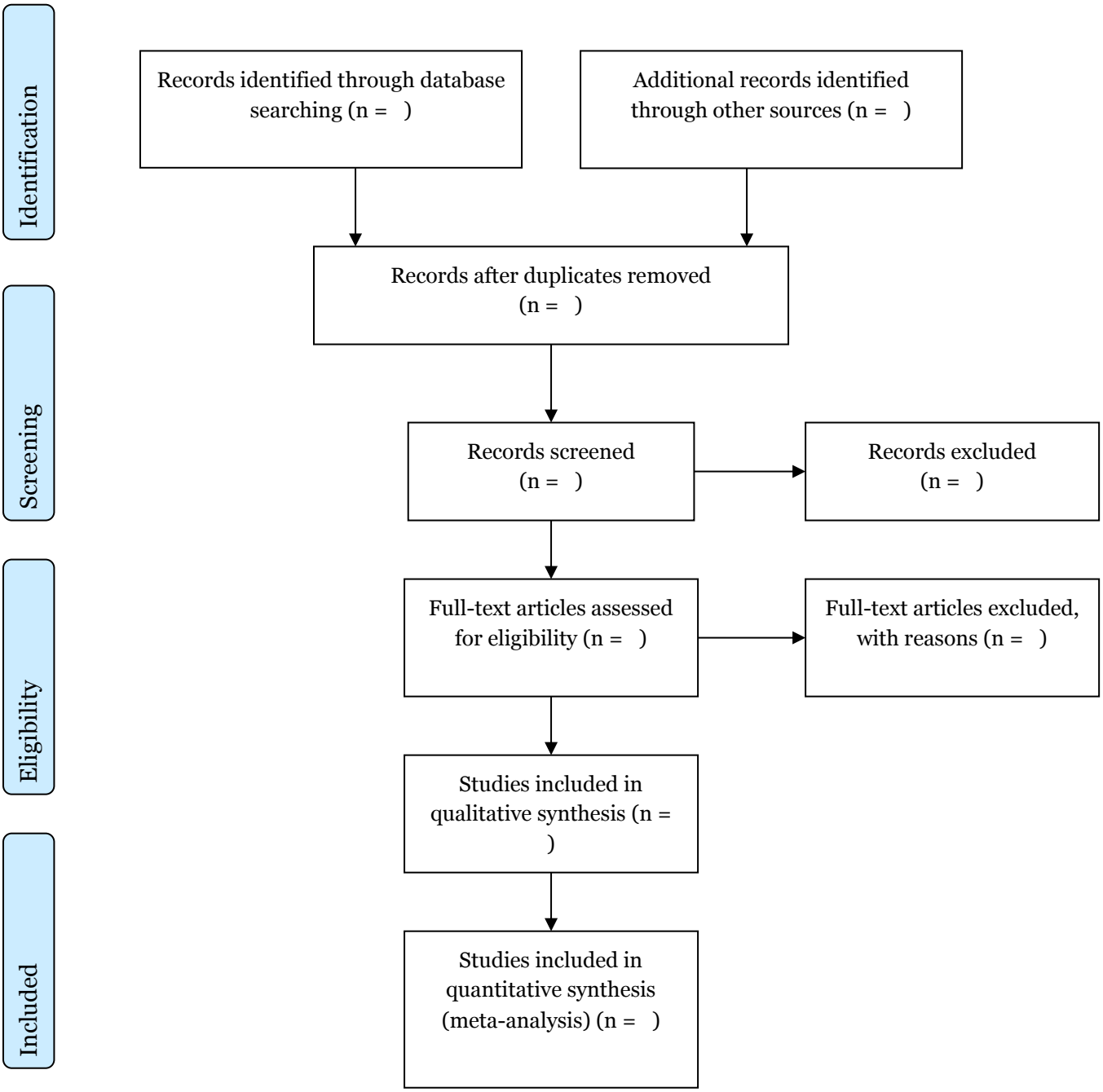
- Executive summary
- List of tables and figures;
- Introduction
    - Context in which the review is set
    - Aims and objectives of the review
    - Research questions
    - Operational definitions
    - Identification of possible equality and equity issues
    - Review team
- Methodology
    - Literature search and abstract appraisal

[9] Consistency between study effect estimates is investigated using the Chi2 test (significance set at $p<0.1$) and the I2 statistic (with a value of ≥ 50%). An I2 statistic < 25% is considered to be a low level of heterogeneity, 25% to 50% a moderate level and > 50% a high level. Subgroup analyses (i.e. grouping studies by factors such as age of participants or year of publication) may be conducted (specified a priori) to explore inconsistencies between study results that are unlikely to have arisen by chance alone. Sensitivity analyses may also be conducted (for example, omitting studies with lower quality from the analysis) to give an indication of the 'robustness' of the results.

    - Retrieval of data and full paper appraisal (including inclusion/exclusion criteria)
    - Selection of studies for inclusion (including flow diagram which is to be adapted from NICE template)
    - Quality assessment and applicability appraising
    - Methods of data extraction, synthesis and presentation (including formulation of evidence statements)
- Findings
    - Overview of studies for each research question
    - Narrative summary of the evidence for each selected theme
    - Evidence statements for each selected theme
    - Applicability of the evidence to the UK populations in the scope
    - Meta-analyses if applicable
- Discussion including findings in context, implications of findings, applicability of findings, limitations, gaps, etc.
- Conclusions and recommendations
- References
- Appendices
    - Search strategy
    - Bibliography of included and excluded studies (with reasons for exclusion)
    - Evidence tables
    - Example completed quality appraisal checklist.

Week commencing	20-Oct	27-Oct	03-Nov	10-Nov	17-Nov	24-Nov	01-Dec	08-Dec	15-Dec	22-Dec	29-Dec	05-Jan	12-Jan	19-Jan	26-Jan	02-Feb	09-Feb	16-Feb	23-Feb	02-Mar	09-Mar	16-Mar	23-Mar	30-Mar	06-Apr	13-Apr	20-Apr	27-Apr	04-May	11-May	18-May
Inception meeting 28/10/14																															
Joint protect meetings with NICE project team (biweekly red=phone, purple=face-to-face)																															
Stage 1. Protocol Development																															
Tasks:																															
Task 1. Protocol development																															
Task 2. Initial pilot testing																															
Outputs:																															
Output 1. Production of draft protocol for review 3/11/14																															
Output 2. Production and sign off of final protocol 17/11/14																															
Stage 2. Production of draft report																															
Tasks:																															
Task 1. Performing the full search																															
Task 2. Loading and de-duplicating records																															
Task 3. Study selection (first pass)																															
Task 4. Document processing (acquiring full papers)																															
Task 5. Record selection (second pass)																															
Task 6. Pilot data extraction form																															
Task 7. Data extraction and quality assessment																															
Task 8. Analysis and synthesis of studies																															
Task 9. Drafting of report																															
Task 10. Quality Assurance																															
Outputs:																															
Output 3. Progress report																															
Output 4. Production of draft evidence review to NICE team 9/3/15																															
Output 5. Submission of revised draft review 13/4/15																															
Payment:																															
Payment 1. Production of draft report £75,000.00 2/3/15																															
Stage 4. Presentation to PHAC																															
Tasks:																															
Task 1. Production of slides																															
Outputs:																															
Output 6. Submission of final slides to NICE 8/5/15																															
Output 7. Presentation of review to PHAC 12/5/15																															
Stage 5. Production of final report																															
Tasks:																															
Task 1. Drafting of final report																															
Task 2. Quality Assurance																															
Task 3. Copy editing																															
Outputs:																															
Output 1. Final report 22/5/15																															
Payment																															
Payment 2. Production of final report £3,785.00 1/12/15																															

Appendix A: PRISMA 2009 Flow Diagram



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