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Title: The effectiveness of interventions to improve the public's antimicrobial resistance awareness and behaviours associated with prudent use of antimicrobials: a systematic review

Running title: Effectiveness of AMR interventions: systematic review

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Synopsis

Background: A global antimicrobial resistance (AMR) awareness intervention targeting the general public has been prioritised.

Objectives: To evaluate the effectiveness of interventions which aim to change AMR awareness and subsequent stewardship behaviours amongst the public.

Methods: Five databases were searched between 2000 and 2016 for interventions to change the public's AMR awareness and/or antimicrobial stewardship behaviours. Study designs meeting the EPOC criteria: non-controlled before and after studies and prospective cohort studies were considered eligible. Participants recruited from healthcare settings and studies measuring stewardship behaviours of healthcare professionals were excluded. Quality of studies was assessed using EPOC risk of bias criteria. Data were extracted and synthesised narratively.

Results: Twenty studies were included in the review with nine meeting the EPOC criteria. The overall risk of bias was high. Nineteen studies were conducted in high-income countries. Mass media interventions were most common (n = 7), followed by school-based (n = 6) and printed materials interventions (n = 6). Seventeen studies demonstrated a significant effect on changing knowledge, attitudes, or the public's antimicrobial stewardship behaviours. Analysis showed that interventions targeting schoolchildren and parents have a notable potential but for the general public the picture is less clear.

Conclusions: Our work provides an in-depth examination of the effectiveness of AMR interventions for the public. However, the studies were heterogeneous and the quality of evidence was poor. Well-designed, experimental studies on behavioural outcomes of such interventions are required.

Registration: PROSPERO International prospective register of systematic reviews (PROSPERO 2016:CRD42016050343).

Introduction

The rise of antimicrobial resistance (AMR) is a rapidly developing global threat that greatly affects our ability to deliver effective healthcare and results in a financial burden.[1] AMR refers to the ability of a microorganism to adapt and grow despite the presence of antimicrobials. AMR threatens effective treatment of an ever-increasing range of infections.[1] Therefore, increasing AMR is becoming a major public health concern. Although AMR is a naturally occurring phenomenon, inappropriate use of antimicrobials is the main driver of AMR.[1] The demands for the use of antimicrobials are increasing worldwide and because of suboptimal management of these demands, huge quantities of antimicrobials are being misused.[2] Together these highlight the need for effective strategies encouraging prudent use of antimicrobials.

The O'Neil report emphasises the need for AMR awareness interventions directed towards the public and development of a uniform, globally consistent set of AMR messages that could be then tailored to meet the specific demands of local settings.[2] However, the report does not provide recommendations on components of such interventions.[2]

Previous evidence syntheses shows that the overall levels of knowledge and understanding of AMR amongst the public is generally low and members of the public often lack an understanding of their potential contribution to the development of AMR.[3-5] Although high-level evidence demonstrating the effectiveness of interventions in increasing public understanding of AMR exists,[5-7] these evaluations are methodologically diverse. It is therefore challenging to identify what interventions work, why and for whom in order to inform future interventions.

Thus, the aim of this systematic review is to provide the best quality evidence regarding the effectiveness of AMR interventions that change public awareness and their subsequent antimicrobial stewardship behaviours. Although, antimicrobial stewardship is most commonly thought of in medical settings, the word "stewardship" means "taking care of" particularly on behalf of others. Furthermore,

a One Health perspective requires the *collaborative* effort of all stakeholders to take the responsibility for the prudent use of antimicrobials. Therefore, within this work, we use the term "antimicrobial stewardship" to explore the public's behaviours related to their prudent use of antimicrobials (such as, but not limited to: adhering to prescribers' directions, not taking or demanding antimicrobial prescription for colds and flu and safe disposal of leftover antimicrobials). We believe an understanding of the public's antimicrobial stewardship is central to engaging them with their part to play in reducing the drivers of AMR on behalf of future generations, other key stakeholders such as prescribers, and the global community.

Methods

This review was prospectively registered on the PROSPERO International prospective register of systematic reviews (PROSPERO 2016:CRD42016050343 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42016050343), and is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[8]

Search strategy

CINAHL, Cochrane Library, EMBASE, MEDLINE and PsycINFO databases were searched for articles published between 2000 and 2016 using keywords associated with the following four concept areas: (1) population - general public; (2) intervention - interventions designed to increase antimicrobial awareness and/or to improve antimicrobial stewardship behaviour amongst the general public; (3) context - AMR or the public's antimicrobial stewardship; outcomes - all relevant short, medium or long-term outcomes related to the public's antimicrobial resistance and/or antimicrobial stewardship behaviours (knowledge/awareness, learning, public behavioural and cognition outcomes). The search strategy incorporated controlled vocabulary thesaurus terms and free text words contained in titles and abstracts. No restrictions were applied to language and publication status. The search strategy

was amended according to the functionality of each of the databases. An example of the search strategy applied to MEDLINE is presented in Table S1 (available at JAC Online).

In addition to the database search, the reference lists of included papers and previous systematic reviews were searched manually and citation searches were conducted through Web of Science in order to identify additional records.

Study selection

Cochrane's Effective Practice and Organization of Care (EPOC) recommendations[9] were used to initially select studies for inclusion in the review. Although, EPOC guidelines suggest the inclusion of Randomised controlled trials (RCT), Non-randomised controlled trials(NRT), controlled before and after studies (CBA), Interrupted time series studies (ITS) and repeated measures studies exclusively,[9] because of the limited number of eligible studies meeting the EPOC criteria, non-controlled before and after studies and prospective cohort studies were also deemed eligible to the review. Interventions targeting the general public population and designed to increase public antimicrobial awareness and/or to improve the public's antimicrobial stewardship were deemed eligible to the review. Furthermore, time bound geographical controls or no exposure comparators and all relevant short, medium or long-term outcomes related to antimicrobial resistance and/or the public's antimicrobial stewardship behaviours were included, while those related to antimicrobial prescribing were excluded as this was regarded as the behaviour of healthcare professionals rather than of the members of the general public. Eligibility criteria applied in this study are presented in detail in Table 1.

Titles and abstracts of identified records were screened against the eligibility criteria (Table 1) by one of three reviewers (MY, LG, FS) with a 30% sub-set of excluded studies independently checked by another reviewer (MY, LG or FS). The level of agreement on this sub-set was 99%. Disagreements were resolved with the involvement of another, experienced reviewer (LP). Full-texts of papers which appeared to meet the inclusion criteria, or where there was insufficient information within the title

and abstract were screened by two out of three independent reviewers (LG, MY, FS), with a fourth reviewer (LP) checking all decisions and resolving any discrepancies. Whenever possible, foreign-language papers were translated by members of the team who have a command in foreign languages (LG, JP), or were translated using Google Translate.

Data extraction and quality assessment

Two out of three reviewers (LG, MY, FS) independently extracted data from eligible studies using standardised tool, designed for the purpose of the study (Table S2, available at JAC online).

For studies that met the EPOC study design criteria (RT, NRT, CBA, ITS),[9] risk of bias was assessed across domains by one reviewer (MY, LG or FS) and checked by a second reviewer (MY, LG or FS) using standard EPOC risk of bias criteria.[9] Disagreements were resolved through consensus or, if necessary consulted with fourth reviewer (LP). Risk of bias assessments were not conducted for non-controlled before and after studies as it was assumed that the risk of bias of these studies was high. No studies were excluded based on quality assessment.

Data analysis

Given the heterogeneity of the study designs, populations, interventions and outcome measures, it was not possible to pool the results in a meta-analysis. Therefore, we applied an alternative, systematic approach to assessing complex interventions and carried out a narrative synthesis of evidence following the Cochrane Consumers and Communication Review Group's guidelines.[10] Individual study characteristics and findings were summarised and similarities, differences and patterns identified. Studies were grouped to those meeting or not meeting the EPOC criteria and categorised according to the target population. To identify discernible patterns of effectiveness, identified studies were mapped across five categories of intervention effectiveness. These categories were based upon both the strength of the evidence and the position of the primary outcome within the casual chain linking antecedents of behaviour to actual behaviour change. For example, knowledge

is understood to be a necessary but insufficient predictor of behaviour as people can develop good awareness and understanding of AMR yet still fail to implement the public's AMR stewardship. The five categories of a relative measure of effectiveness included (1) interventions indicative of clear positive behaviour change in the desired direction, (2) interventions indicative of some positive behaviour change in the desired direction, (3) interventions indicative of positive effect on the antecedent of behaviour, such as knowledge or awareness in the desired direction, (4) interventions indicative of no effect on behaviour or antecedents of behaviour, and (5) interventions indicative of negative effect on behaviour or antecedents of behaviour in a non-desired direction.

Results

Electronic search resulted in the total of 17,312 records. An additional 31 records were identified through reference and citation searching of the included papers. A total number of 60 studies that did not meet eligibility criteria were excluded during the full text reviewing stage. Articles were excluded for not meeting study design criteria, study participants being recruited from healthcare settings, context other than AMR, study outcomes not related to the public's AMR awareness or antimicrobial stewardship, full text record being unavailable, and other reasons such as record being a study protocol, conference abstract of already identified study, short report of already identified study, inability to translate non-English paper, or majority of participants recruited for the study being healthcare workers. A detailed list of excluded papers is presented in Table S3 (available at JAC Online). Following screening, 20 studies that matched the eligibility criteria were included in the review. A detailed process of study selection is presented in Figure 1.

Study characteristics

As shown in Table 2, study designs of the 20 reviewed studies included randomised controlled trials (n = 2),[11, 12] non-randomised controlled trials (n = 3),[13-15] controlled before-after studies (n = 4),[16-19] non-controlled before-after studies (n = 10)[20-29] and a prospective cohort study (n = 1).[30]

Apart from one study conducted in Moldova,[16] all studies were conducted in high-income countries, with the majority conducted in the United States (US) (n = 8),[11, 12, 14, 15, 19, 23, 28, 30] or in the United Kingdom (UK) (n = 5).[18, 22, 24, 26, 27] The remaining studies were conducted in Italy,[13] Portugal,[20] Poland,[25] New Zealand,[21] and Australia,[29] while one study was a multisite study conducted in the UK, Czech Republic and France[17] (Table 2).

As shown in Table 2, the most common types of interventions were mass media interventions.[13, 14, 18, 24, 25, 29, 30] Apart from Madle *et al*. (2008)[24] who used website only, all mass media interventions were multimodal and used a variety of outlets, such as billboards, radio, television, newspapers, magazines, websites, and printed resources such as, posters, brochures, pamphlets, leaflets, stickers or badges distributed to community sites or healthcare settings. Six studies used printed materials interventions, either alone,[12, 15, 21, 23] or in combination with educational presentations,[11, 19] while Stockwell *et al*. (2010)[28] delivered taught modules to Latino community parents. Other interventions were school based, and included a student peer-taught program,[16] e-bug web game,[22] interactive workshops,[27] school lessons delivered using the "Bug Investigators" pack[26] and presentation followed by discussion,[20] while the intervention delivered in the study by Lecky *et al*. (2010)[17] involved the delivery of a lesson, printed materials, interactive activities and question & answer session.

Comparators were similar across the ten controlled studies.[11-19, 30] With an exception of Lecky *et al*. (2010)[17] who compared the educational intervention to the usual school curriculum, control groups were not exposed to the interventions.

Table 2 shows that the most common outcome measure was change in knowledge, attitudes or beliefs, measured alone (n = 10)[11-13, 15, 17, 20, 22, 24, 26, 27] or in combination with change in the public's antimicrobial stewardship behaviour (n = 8).[16, 18, 19, 21, 23, 25, 28, 29] Two studies measured the public's antimicrobial stewardship behaviour outcomes exclusively (n = 2).[14, 30]

Quality of studies

Amongst the included studies, nine met the EPOC study design criteria.[9] As shown in Table 3, the overall risk of bias of the included studies was generally high. Apart from one study, [11] all had at least one item assessed as high risk with the number of high risk items ranging from one[15] to five. [18] High risk of bias was most commonly associated with generation of sequence allocation, risk of contamination and other risks.

For all studies that met the EPOC criteria, insufficient information was provided for at least 2 of the items which were regarded as unclear risk. None of the studies provided information regarding blinding, and in all studies reporting secondary outcomes, the risk of bias for incomplete secondary outcome data could not be assessed. [13-16] The number of low risk items ranged from one[17, 18] to five [16] with the "selective outcome reporting" item being most commonly assessed as low risk. None of the studies had a low risk score for any of the following items: "allocation concealment", "addressing incomplete secondary outcome data" and "blinding primary outcome data".

Risk of bias was not assessed for the non-controlled before-after studies [20-29] and a prospective cohort study. [30] These study designs did not meet the EPOC criteria;[9] therefore, it was assumed that the risk of bias of these studies was high.

Relative effectiveness of interventions

Reviewed interventions were grouped into five categories of relative measure of effectiveness. As shown in Table 4, six studies demonstrated a clear desired behaviour change following the intervention, while two studies resulted in some desired behaviour change. Desired effect on the antecedent of behaviour was reported in nine papers. One study showed no effect, while two studies demonstrated an increase in drivers of AMR following the intervention.

Effectiveness of interventions delivered to populations through the lifecycle

In 17 of the studies, the intervention had a significant effect on the outcome of interest amongst the populations through the lifecycle. These included schoolchildren, university students, parents and the general public.

Schoolchildren

All six school-based educational interventions that targeted schoolchildren aged between 9-15 years [16, 17, 20, 22, 26, 27] found a significant increase in knowledge following the educational intervention (Table 2). However, Farrell *et al*. (2011)[22] found a significant knowledge change in only 3 out of 21 questions ($p \leq 0.02$), and no overall change in knowledge. The three questions for which significant improvement was reported related to the valuableness of "good microbes", the presence of microbes despite inability to see them, and handwashing being an effective method of removing microbes from the hands. Only one study [16] measured behavioural outcome in addition to beliefs, and found that children in the intervention group were 3.2 times more likely than other students to report that they had not taken an antibiotic for a cold or flu ($p < 0.001$).

None of the studies measured long term outcomes of school-based interventions. Post-intervention outcomes were measured immediately following the intervention,[22] or between 1-8 weeks after the intervention. In addition, one study [17] found that the increase in knowledge was maintained at 6 week post intervention in junior but not for senior school students.

University Students

University students were targeted in one experimental study that aimed to investigate whether an educational intervention (information booklet) resulted in an increase of young adult consumers' preference for physicians who do not unnecessarily prescribe antibiotics for simple acute upper respiratory tract infections.[15] This study demonstrated, that exposure to the intervention significantly increased the mean preferred start date for antibiotics after the onset of an infection from 2.3.-3.9 days ($p < 0.1$) and preference for a physician who would not prescribe antibiotics at day 3 of an infection ($p < 0.1$). However, this was still well before recommended time of 10-14 days.

Parents

The effect of educational interventions delivered to parents on change in their AMR knowledge, attitudes or beliefs alone,[11, 12] or in combination with parents' antimicrobial stewardship behaviour outcomes [16, 19, 23, 28] was measured in six studies. The majority of these interventions were directed to parents or caregivers of children under the age of 6.[11, 12, 19, 28] In the remaining two studies, intervention was delivered to households with at least one children over 5 years old[23] and parents of children aged 12-13.[16]

As shown in Table 2, all studies showed a significant increase in knowledge following the interventions. In addition, four of the reviewed interventions also had a positive effect on changing parents' antimicrobial stewardship behaviour. Cebotarenco & Bush (2008)[16] found, that parents in the intervention group were 5.2 times more likely than other parents to indicate they had not taken an antibiotic for colds or flu ($p < 0.001$). In Trepka *et al*. (2001)[19], the proportion of parents who expected an antibiotic for their child and did not receive one declined in the intervention area from 14% to 9%, while it increased from 7% to 10% in the control area ($p = 0.003$) and the percentage of parents reporting that they brought their child to another physician because they did not receive an antibiotic decreased from 5% to 2% in the intervention area and increased from 2% to 4% in the control area ($p = 0.02$). Larson *et al*. (2009)[23] found that the percentage of participants reporting using alcohol hand

sanitizers has increased from 1.4% to 66.8% following the intervention (p = 0.001) while the percentage of those reporting that at least one member of their household had been vaccinated against influenza has increased from 63.7% to 73.9% (p = 0.001). Stockwell *et al*. (2010)[28] on the other hand, demonstrated that the number of parents reporting that they sought antibiotics without a prescription when their child was sick has decreased from 6 to 1 (p = 0.06).

General public

The general public were the population of interest in eight of the included studies.[13, 14, 18, 21, 24, 25, 29, 30] Apart from Curry *et al*. (2006)[21] who used printed materials in the form of posters and leaflets, all studies were mass media campaigns, including four studies that measured the effects of the national campaign intervention.[18, 21, 25, 29]

Five studies demonstrated a significant effect on the general public's knowledge and attitudes [14, 21, 24, 25, 29] (Table 2). With respect to antimicrobial stewardship behaviour amongst the public, four studies report a significant effect following the intervention.[14, 21, 25, 29]

Gonzales *et al*. (2008)[14] found that visits to paediatricians declined in the intervention group for all conditions but mostly for acute respiratory infections (p = 0.01). Similarly, Curry (2006)[21] demonstrated a significant decrease in the numbers of respondents who reported consulting a doctor for the common cold (p = 0.026). The results of Wutzke, (2006)[29] showed that significantly less participants reported using antibiotics for cough, cold or flu following the intervention (7.4%) in comparison to baseline data (10.8%; percentage point change = 3.4; 95% CI: 1.3–5.5). Mazinska & Hryniewicz, (2010)[25] on the other hand, demonstrated a significant increase in the percentage of respondents who have limited the use of antibiotics (from 27% at baseline to 43% post intervention), have become more disciplined and cautious in their use (from 3% to 24%), and who paid attention to the correct dosage (from 6% to 18%; no p values given).

The remaining three studies did not show a significant positive effect on outcomes of interest.[13, 18, 30] In Mainous *et al*. (2009),[30] intervention designed to decrease self-medication with antibiotics surprisingly resulted in significantly greater percentage of the intervention Latino community group using antibiotics without a prescription in comparison with the control group (OR = 1.81; 95% CI, 1.02-3.22). McNulty *et al*. (2010)[18] on the other hand, found no positive effect on participants' knowledge or antimicrobial stewardship behaviour following a national campaign, and there was a significant increase in the percentage of respondents from the intervention area who reported retaining leftover antibiotics ($p < 0.001$). Formoso *et al*. (2013)[13] reported that knowledge consistency with the national campaign messages either worsened ($p < 0.05$) or did not improve in both the intervention and control groups after the intervention.

Discussion

Main findings of this study

This systematic review provides an in-depth examination of the effectiveness of interventions that target the public to increase their knowledge, understanding of AMR and engagement with antimicrobial stewardship behaviours. We have also identified patterns between target populations and relative intervention effectiveness. The findings present a complex picture reflecting the heterogeneity of the studies.

Our analysis has shown that interventions targeting schoolchildren and parents have notable potential. All interventions that targeted schoolchildren or parents showed a significant effect on the outcome of interest. However, effective school-based interventions tended to only have effects of increasing knowledge. In addition, these studies measured only short-term outcomes. In contrast, interventions targeting parents demonstrated changes in behaviour in addition to knowledge, with the follow up period ranging from 2 weeks [28] to 3 years.[12]

With regards to the interventions targeting the general public, the picture is less clear. Although the majority (n = 5) of these studies demonstrated effectiveness of interventions in improving the public's AMR knowledge or their antimicrobial stewardship behaviour, three studied did not, with two showing a decrease in AMR knowledge[13] and in antimicrobial stewardship behaviour.[30] These findings highlight the need to examine differences in the content between these interventions targeting the general public.

Patterning of the effectiveness across the type of target population also suggests that different target populations should receive different interventions with different primary outcomes. Nevertheless, targeting children alone is unlikely to make a major contribution to AMR because attitudes and the public's antimicrobial stewardship behaviours may be passed down through generations. Thus, using the power of familial social influence and parental duty where children's AMR education within school is reinforced and boosted by parental interventions in the home, might be a more appropriate approach for the achievement of desired cultural change. This indicates the potential of a multimodal intervention or programmatic approach to AMR related interventions.

An ideal approach would be to address the entire population simultaneously, yet segmenting it to target sub-populations. Through such segmentation, or stratification of the general public, diverse tailored interventions addressing different sub-population, would be a strategic way to begin the process of cultural change required to reduce the drivers of AMR.

The nature of the increase in knowledge that is needed can also be specified by drawing on other evidence syntheses that has shown that the public's' AMR knowledge and understanding of their contribution to AMR is generally poor.[3] Therefore, in addition to changing the public's understanding of appropriate antimicrobial use, interventions should also target the public's understanding of AMR to enable the public to understand their central role in tackling AMR, and the risks for the intervention recipient, their loved ones and the wider population.

Findings in relation to other research

In their recent paper, Wells & Piddock (2017)[31] argued that amongst other actions, an urgent review of educational campaigns is required in order to fulfil UK and European AMR action plans. Our review addresses this need. Furthermore, to our knowledge this is the first systematic review that provides such an in-depth examination of the effectiveness of AMR related interventions that target the public specifically.

Previous literature focused on the level of the public's AMR knowledge and beliefs,[3, 4] communication interventions or interventions that target both, the public and healthcare professionals.[6] The latter found that multi-component interventions improve the public's knowledge of appropriate antimicrobial use, specifically in relation to antibiotics and that interventions including both, physician and public education appear to be effective in reducing antibiotic use.[6] Similarly, Cross *et al*. (2016)[32] reported that multi-modal communication interventions targeting both the public and clinicians can reduce antibiotic prescribing in high-income countries. Although, our review focused on the general public population specifically, the potential of multi-faceted interventions was also highlighted in our work.

Another previous systematic review by King *et al*. (2015)[7] reviewed the evidence of effectiveness and cost-effectiveness of interventions changing the public' risk related behaviours in relation to antimicrobial use. The review showed that direct contact education interventions were consistently more effective than mass media interventions.[7] This appears to explain our findings on the varying effectiveness of interventions targeting the general public, as majority of these studies used mass media interventions.

There is also a body of evidence on large-scale antibiotic campaigns that although were not eligible for inclusion in our review as the participants were both members of the public and healthcare professions. A literature review showed that there have been numerous multifaceted antibiotic awareness campaigns launched in high-income countries;[33] however, there was substantial

heterogeneity in outcomes, including knowledge and awareness, use of antibiotics and antimicrobial resistance, and the interventions themselves often lack a robust grounding in behavioural and social science theory. The majority of campaigns included in the review targeted both the general public and healthcare professionals simultaneously and they appeared to result in a reduction of antibiotic use.[33] It therefore appears that targeting different populations at the same time might result in desired outcomes as healthcare professional's prescribing decisions might also be influenced by the patient, while patient's behaviour might be affected by the prescriber's advice. One such campaign, conducted in the UK in 2014 simultaneously targeted members of the public and healthcare professionals who pledged as Antibiotic Guardians, and showed an increase in AMR knowledge and commitment to pledge behaviour in both surveyed sub-populations.[34] Another antibiotic awareness campaign conducted in Hong Kong, targeted the general public, patients and healthcare professionals in a segmented fashion, and resulted in a significant improvement ($p \leq 0.002$) in respondents' knowledge on prudent use of antibiotics following the campaign.[35] Yet another successful large-scale antibiotic awareness campaign segmented to target the general public and healthcare professionals was conducted in France.[36] The effectiveness of this campaign in reducing the number of antibiotic prescriptions was evaluated and showed a 26.5% (95% CI 33·5–19·6) decrease in the total number of antibiotic prescriptions following the campaign, with the greatest decrease of 35.8% (95% CI-48.3% to -23.2%) in prescriptions issued for children and young adults in the 21-25 years age group (24.1% decrease; CI not provided).[36] These findings further emphasise the potential of programmatic approach to AMR related interventions segmented to different target sub-populations, as suggested previously in our main findings section.

Strengths and limitations

We have conducted a rigorous search and systematic review accompanied by a narrative synthesis. Although, similar work concerning the effectiveness of interventions aimed to improve antibiotic use has been conducted previously,[32] our work focused on interventions targeting the general public

population exclusively and did not include outcomes related to healthcare professionals' AMR awareness or antimicrobial stewardship, such as antibiotic prescribing. Our analysis provides a sense of what is normative within this field, what has been attempted before and what could be repeated. It also provides a unique and valuable contribution to the available literature. However, the study also has limitations.

First, because the UK Antimicrobial Resistance Strategy and Action Plan was launched by the Department of Health (DH) in 2000[37], followed by the publication of the WHO Global Strategy for Containment of Antimicrobial Resistance in 2001[1], we limited our search to publications from 2000 onwards. This could result in omission of important, older papers. Second, the studies from low- and middle-income countries were underrepresented in our review. Thus, relevance and applicability of our findings to different geographical areas or resource contexts is limited. Third, the risk of bias was assessed only for studies that met the EPOC study design criteria. However, a suitable, validated tool for assessing the risk of bias of non-controlled before and after studies could not be identified. Furthermore, using different instrument could result in ambiguities in relation to the quality of stronger designs. The overall quality of the evidence was rather low. Major problems were associated with randomisation in experimental designs and the evaluation of mass media and other population level interventions. As these kinds of interventions aim for maximum population reach, it is difficult to attain adequate controls or indeed randomise at this population level. Therefore, good quality study designs are systematically less likely to be identified within this kind of population level intervention literature. Notwithstanding this, there was a considerable heterogeneity in outcomes. There are no standardised ways of measuring the public's AMR related knowledge or associated stewardship behaviours. Furthermore, change in knowledge, awareness or beliefs, which were the most common outcome measures across the included studies, might not necessary lead to desired behaviour change. As a result, it is particularly challenging to build cumulative knowledge regarding the effectiveness of interventions to increase the public's engagement with antimicrobial stewardship. Another limitation is that given the problems with the quality of primary research, our measure of relative effectiveness

should be treated with caution as this was based on our relative measure and are not equivalent of a strong evidence base within typical evidence based guidance. Finally, we did not conduct an analysis of the cost-effectiveness of reviewed interventions; however, for the majority of studies included in our review, cost effectiveness data was not reported.

Recommendations for future research

Although, our work demonstrated the potential of intervention, that targets particular sub-populations of the general public, taking into account the low quality of reviewed evidence, lack of cost-effectiveness evaluation and underrepresentation of studies from low- and middle-income countries, these findings must be treated with caution. There is a need for well-designed, randomised experimental studies focusing on behavioural outcomes of the interventions. Furthermore, measures of AMR knowledge and stewardship behaviours need to be standardised and there is a need for improvement of the reporting standards to ensure detailed and transparent reporting of intervention components. Finally, considering the underrepresentation of studies from low- and middle-income countries, there is a need for the development and evaluation of similar interventions within such settings.

Conclusions

Although some evidence on the effectiveness of interventions that target the general public to engage with the problem of AMR exists, the public's understanding of AMR and their role in combating this problem remains poor. Thus, there is a need for a cultural change and effective engagement of the public in addition to other key stakeholders. This need could be addressed through development of well-designed AMR related interventions robustly grounding within behavioural and social science theory. Our work provided an in-depth examination of the effectiveness of AMR related interventions targeting the members of the public specifically. We suggests that future policy makers should consider multimodal segmented population level intervention that tailors its core messages to

children, parents and the wider general public alike, particularly in high-income geographical areas. Future interventions should convey messages that elicit the public's motivation to make their own efforts to address AMR as a growing problem for all and a problem for the present as much as for the future.

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Transparency declarations

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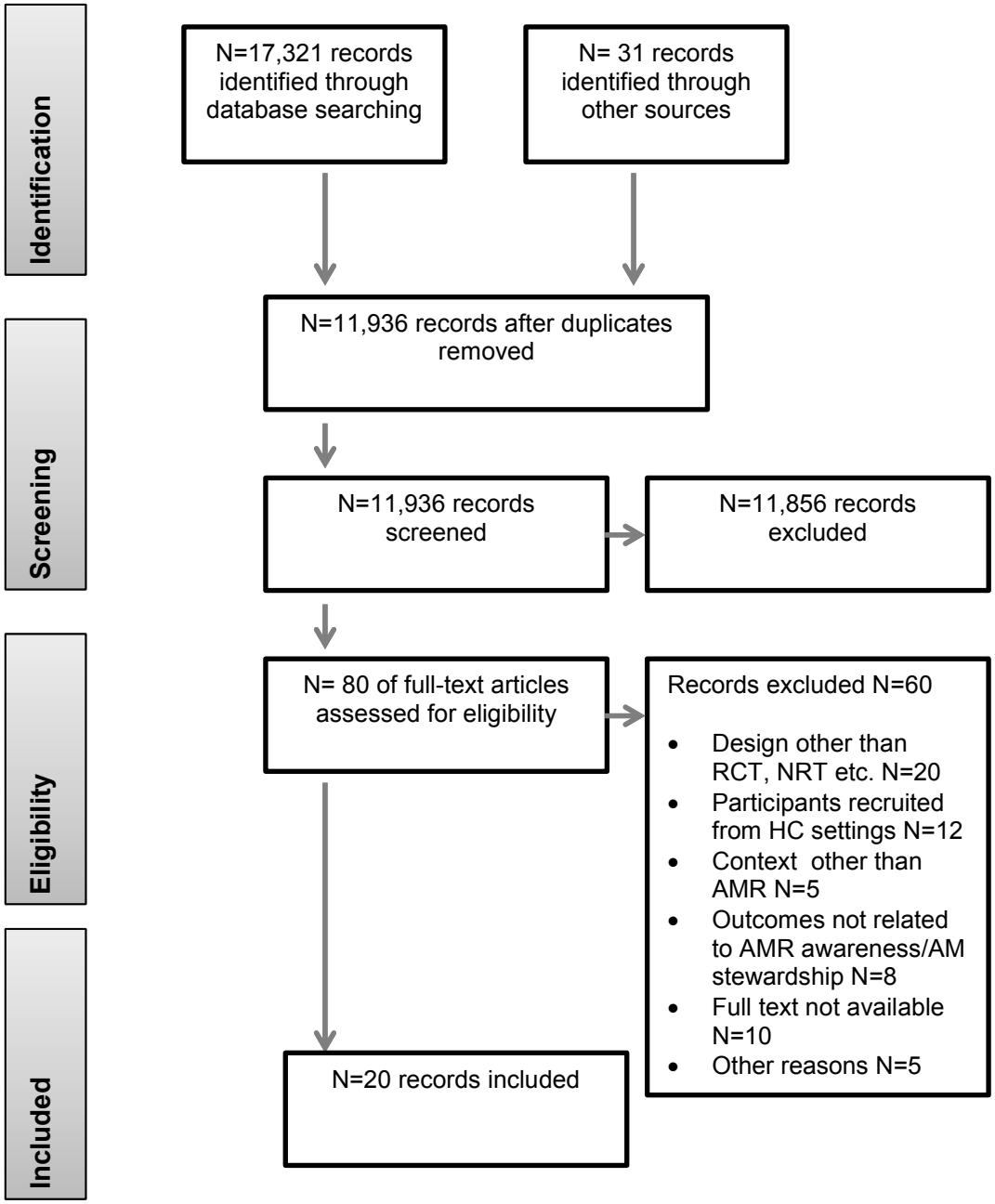
Figures and Tables

Figure 1. Study selection flowchart



518 Table 1. Review's eligibility criteria

	Inclusion criteria	Exclusion criteria
Design	Randomised controlled trials, non-randomised trial, interrupted time series studies, controlled before and after studies, non-controlled before and after studies and cohort studies.	-
Population	Members of the public	Participants recruited from healthcare settings
Intervention	Intervention designed to increase public antimicrobial awareness and/or to improve antimicrobial stewardship (through mass media, social marketing or printed media campaigns).	-
Comparator	Time bound, geographical controls or no exposure	-
Context	Non-healthcare settings; AMR or the public's antimicrobial stewardship	-
Outcomes	All relevant short, medium or long-term outcomes related to antimicrobial resistance and/or antimicrobial stewardship behaviours (knowledge/awareness, learning, public behavioural and cognition outcomes)	Antimicrobial prescribing
Publication date	Published after January 2000	Published before January 2000

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520 Table 2. Study characteristics and results of the included studies

Study	Country	Design	Sample	Nature of intervention(s)	Outcome measures	Significant results
Azevedo *et al.* (2013)[20]	Braga, Portugal	NCBA	N = 82 school children	School based presentation followed by discussion.	Knowledge & attitudes	Knowledge of the correct use of antibiotics for bacterial diseases rather than viral diseases rose from 43% to 76% in the post-test (p <0.01). Knowledge of the risk of bacterial resistance to antibiotics from their incorrect use rose from 48% to 74% in the post-test (p <0.05).
Cebotarenco & Bush, (2008)[16]	Chisinau, Moldova	CBA	N = 3586 school children & N = 2716 parents	Educational intervention about the use of antibiotics delivered by student volunteers trained as peer leaders delivered to their classmates & the classmates' parents.	Beliefs & behaviour	Students in both the intervention District & the Post-intervention phase were 3.2 (CI 2.065–4.909) times more likely than other students to indicate they had not taken an antibiotic.
Croft *et al.* (2007)[11]	Wisconsin, USA	RCT	N = 300 parents.	Distribution of printed materials to parents by child care staff; slide presentation delivered to staff.	Knowledge	In parents who were college graduates, the median knowledge scores were 7.0 at intervention centres & 6.5 at control centres (p <0.01).
Curry *et al.* (2006)[21]	Auckland, New Zealand	NCBA	N = 400 general public	National campaign "Wise use of antibiotics". Posters & leaflets delivered to the public attending pharmacies.	Knowledge & attitudes and behaviour	Patients who had ever been to the doctor for a common cold significantly decreased (45% vs 62%; p = 0.0006). They were significantly less likely to feel positive about antibiotics in 2003 for the treatment of a cold (16% versus 33%, p = 0.00001). The perception that antibiotics were beneficial for cold/flu symptoms significantly reduced from 1998 to 2003 (p <0.05); the perceived benefit of antibiotics for tonsillitis increased from 83% to 91% in 2003 (p = 0.014) Significantly less people reported ever attending a doctor for a cold in 2003 Vs 1998 (45% vs 62%; p = 0.0006); & the number of people who would usually see a doctor for a cold decreased from 24% to 15% (p = 0.026).

Farrell *et al.* (2011)[22]	Glasgow, Gloucester and London, UK	NCBA	N = 1736 children	E-Bug web game	Knowledge & attitudes	No overall change in knowledge. Significant knowledge change in 3 out of 21 questions (p ≤0.02).
Formoso *et al.* (2013)[13]	Emilia-Romagna, Italy	NRT	N = 1200 general public	Local mass media campaign (posters, brochures & advertisements on local media) delivered to general population to raise awareness of inappropriate use of antibiotics.	Knowledge	After the intervention, consistency with campaign messages worsened (or did not improve) similarly in both intervention and control areas, the only exception being knowledge on the presumptive antiviral activity of antibiotics, worsening in the intervention area more than control area
Gonzales *et al.* (2008)[14]	Colorado, USA	NRT	N = 1503 general public	Mass media intervention (outdoor & radio advertisements) delivered to general public about use of antibiotics.	Behaviour	Linear regression analysis showed a significant Net differences in monthly paediatric office visit rates between mass media & comparison communities before & after the campaign (p = 0.01).
Huang *et al.* (2007)[12]	Massachusetts, USA	RCT	N = 3142 parents	Community based educational intervention occurred through 3 successive cold & flu seasons. Printed materials: (mailed newsletters, posters, pamphlets, & fact sheets in the waiting rooms of local paediatric providers, pharmacies, & child care centres).	Knowledge & attitudes	The proportion of parents who answered 7 of 10 knowledge questions correctly increased significantly in both intervention (from 52% to 64%; p <0 .001) & control (from 54% to 61%; p <0.01) communities. Substantial improvements in percentage correct answers were seen for items on middle ear fluid (41% in 2000; 50% in 2003, p <0.001) & the general question of whether antibiotics were needed for colds & flu (66% in 2000; 77% in 2003, p <0.001)
Larson *et al.* (2009)[23]	Upper Manhattan, USA	NCBA	N = 422 households	Targeted Latino households. Educational materials (colouring book, pamphlets) based on knowledge, attitudes, & practices regarding prevention & treatment of upper respiratory tract infections. Program was delivered during home visits every 2 months.	Knowledge & attitudes and behaviour	After the intervention, the mean composite knowledge scores at baseline 7 end of study were 5.19 (SD = 1.60) & 5.91 (SD = 1.71) (p <0.001), respectively. With regard to reported practices, significantly more participants after the intervention reported using alcohol hand sanitizers (1.4% baseline & 66.8% post-intervention, p = 0.001). Significantly more also reported that one or more members in their household had received the influenza vaccination after the intervention (63.7% at baseline & 73.9% post-intervention, p = 0.001).

Lecky *et al.* (2010)[17]	Gloucestershire and London, England; Nice and Bordeaux, France; Prague and Ostrava, Czech Republic	CBA	N = 2724 school students	School based educational intervention (e-bug) regarding inappropriate antibiotic use delivered to classes of 9-11-year-old (junior) & 12-15 year old (senior) students in state schools Included 45 min lesson hand-outs, worksheets, factsheets, interactive activity 7 a follow-up plenary question &-answer session.	Knowledge	Junior school: Significant change in knowledge, & significant change in retention 6 weeks post-intervention, across countries. Little significant difference in knowledge change between intervention &control, with exception of Czech Republic. Senior school: Significant improvement in knowledge 6 weeks post intervention in Czech Republic. Significant - improvement in knowledge, & knowledge retention between control & intervention in England & Czech Republic
Madle *et al.* (2004)[24]	London, UK	NCBA	N = 177 general public	Open access to the National electronic Library of Infection Antimicrobial Resistance website on the use of antibiotics & antibiotic resistance. The site comprises frequently asked questions &links to evidence based resources.	Knowledge & attitudes	Significant improvements in knowledge about the use of antibiotics & antibiotic resistance in 2 out of 3 statements: (1) "people cannot become resistant to antibiotics" ($p < 0.001$, $X2 = 60.357$, 95% CI of change: 27.47 to 44.53); (2) "antibiotics do not cure most sore throats" ($p < 0.001$, $X2 = 19.22$, 95% CI of change: 8.62 to 27.38). Significant changes in the scores assigned by users for 3 out of 4 statements designed to test users' attitudes to the information on the site ($p \leq 0.003$). Expectations that antibiotics should be prescribed were significantly reduced after using the website ($p < 0.001$). Non-HCWs continued to have higher expectations of antibiotics being prescribed than HCW ($p = 0.0046$ before and $p = 0.0098$ after using the website).
Mainous III *et al.* (2009)[30]	South Carolina, USA	Prospective cohort study	N = 691 Self-identified Latinos	Mass media educational intervention (pamphlets, radio, newspapers) delivered to local Latino communities about use of antibiotics.	Behaviour	Numbers in the intervention group reporting that they had bought antibiotics without a prescription increased following the intervention compared to baseline (Chi sq test reported as significant but p value not given. The regression analysis showed the strongest predictor of purchase of antibiotics without a prescription in the previous 12 months was past purchase of antibiotics without a prescription outside the United States (OR = 5.72; 95% CI, 3.12-10.48). The regression analysis also showed the strongest predictor of likelihood of importing antibiotics into the United States was past purchase of antibiotics without a prescription outside the United States (OR = 3.01; 95% CI, 1.95-4.65).
Mazinska & Hryniewicz, (2010)[25]	Poland	NCBA	N = 1000 general public	Mass media educational intervention (posters, leaflets, billboards, TV, cinemas, radio, press, magazines, thematic exhibitions, internet) implemented across the country.	Knowledge, attitudes & behaviour	Significant increase in the percentage of people who have limited the use of antibiotics 27-43%, have become more disciplined and cautious in their use from 3-24%, as well as pay attention to the correct dosage 6-18% (no p values given).

McNulty *et al.* (2001)[27]	Gloucester, UK	NCBA	N = 38 year 5 school children.	School-based intervention to children aged 9-10years at a state school. Included two 90 minute interactive workshops entitled ``Antibiotics and your good bugs''.	Knowledge	Before the workshops 23% & 26% knew antibiotics do not kill viruses but kill good bacteria, compared with 47% & 69% afterwards (p = 0.03 & 0.0001). 45% before & 73% after the workshops correctly answered all the questions (p < 0.0001). Children thought antibiotics helped hay fever, this improved significantly after the workshop (correct answer 28% before, 77% after (p <0.0001). Overall score for 7 questions in the "where are bugs found" section was increased significantly from an average of 80.5% success to 93.2% success (p = 0.0002). The overall score improvement in the "How do bugs spread" section was significant (p = 0.00001).
McNulty *et al.* (2007)[26]	Gloucestershire, UK	NCBA	N = 198 year 5 and 6 school children	School based intervention. "Bug Investigators" pack about micro-organisms, hygiene & antibiotics The pack included 11 activity sheets, teachers' guide, poster & website.	Knowledge	Children's knowledge improved in all topic areas & was significant in 6 out of the 7 topic areas (p <0.005). Improved knowledge was most significant for what antibiotics do & how to use them (percent improvement 27 (CI 22.8, 31.1) & 31 (CI 23.4, 37.7), respectively; & the value of our own good bugs (16 percent improvement).
McNulty *et al.* (2010)[18]	England and Scotland, UK	CBA	N = 3718 general public	Mass media campaign about antibiotic use involving posters displayed in magazines & newspapers.	Knowledge & attitudes and behaviour	No positive effect of the campaigns.
Pontes & Pontes, (2005)[15]	Mid-Atlantic region, USA	NRT	N = 105 university students	University based educational intervention (information booklet) to increase young adult consumers' preference for physicians who do not unnecessarily prescribe antibiotics for simple acute upper respiratory tract infections.	Attitudes	Exposure to the intervention significantly increased the mean preferred start date for antibiotics after initiation of an infection from 2.3-3.9 days (p <0.1). Respondents' preferences were significantly greater for the physician who indicated he would not prescribe antibiotics in the intervention (M = 4.84) compared to control (M = 3.91, (p <0.01).
Stockwell *et al.* (2010)[28]	New York City, USA	NCBA	N = 10 parents	Health literacy intervention regarding upper respiratory tract infection delivered to parents on a "Early Head start" programme. Involved 3x 1.5 hour interactive sessions & provision of kit for care of a child with such an infection.	Knowledge & attitudes and behaviour	The mean composite knowledge/attitude score increased from 4.1 (total possible: 10) to 6.6 (p <0.05). Number of parents reporting that the last time their child was sick they sought antibiotics without a prescription instead of, or in addition to, seeing their health care provider has decreased from 6 to 1 (p = 0.06).

Trepka *et al.* (2001)[19]	Northern Wisconsin, USA	CBA	N = 365 parents	Nurse educators delivered parent-oriented presentations in community organisations, distributed information pamphlets & displayed posters. Topics covered included antibiotic resistance & use.	Knowledge & attitudes and behaviour	From baseline to post intervention the percentage of parents with high antibiotic resistance awareness significantly increased in the intervention (change: 14.3%: 95% confidence interval [CI]: 6.6, 22.0) but not in the control group (change: 4.3%; 95% CI: -4.1, 12.7; p = 0.015). The proportion of parents who expected an antibiotic for their child & did not receive one, declined in the intervention area (14% to 9%), while it increased in the control area (7% to 10%). The difference between the 2 area changes was -8.4% (95% CI: -13.9,-2.8; p = 0.003). The percentage of parents in the intervention area who brought their child to another physician because they did not receive an antibiotic decreased (5% to 2%), while it increased in the control area (2% to 4%). The difference between the 2 area changes was -4.5% (95% CI: -8.0,-.9; p = 0.02).
Wutzke *et al.* (2006)[29]	Australia	NCBA	N = 6217 general public	National mass media intervention for consumers delivered during winter months in 2001, 2002, 2003, & 2004. About the inappropriate use of antibiotics for upper respiratory tract infection. Strategies included newsletters & brochures, mass media activity using billboards, television, radio & magazines & small grants to promote local community education.	Knowledge & attitudes and behaviour	There was a significant decline in those who believe taking antibiotics for cold & flu is appropriate, from 28.7% pre-programme in 2002 to 21.7% in 2004 (percentage point change = 7.0; 95% CI: 3.5–10.5). Significant decrease in self-reported use of antibiotics to treat cough, cold or flu, from 10.8% in 1999 down to 7.4% in 2004 (percentage point change = 3.4; 95% CI: 1.3–5.5).

522 Table 3. Risk of bias of studies meeting the EPOC criteria.

Study ID	Allocation - sequence generation	Allocation - concealment	Baseline primary outcome	Baseline secondary outcome	Baseline characteristics	Incomplete primary outcome data	Incomplete secondary outcome data	Blinding primary outcome data	Blinding secondary outcome	Contamination	Selective reporting primary outcome	Selective reporting secondary outcome	Other risks of bias
Cebotarenco & Bush	H	H	U	U	L	U	U	U	U	L	L	L	L
Croft *et al.* (2007)[11]	L	U	U	n/a	U	L	n/a	U	n/a	U	L	n/a	L
Formoso *et al.* (2013)[13]	H	U	U	U	L	U	U	U	U	U	L	L	H
Gonzales *et al.* (2008)[14]	H	U	U	L	U	U	U	U	L	H	L	L	H
Huang *et al.* (2007)[12]	L	U	H	n/a	L	L	n/a	U	n/a	H	H	n/a	H
Lecky *et al.* (2010)[17]	H	U	U	n/a	U	H	n/a	U	n/a	H	L	n/a	H
McNulty *et al.* (2010)[18]	H	H	H	n/a	U	U	n/a	U	n/a	H	L	n/a	H
Pontes & Pontes	U	U	U	U	U	U	U	U	U	U	L	L	H
Trepka *et al.* (2001)[19]	H	U	L	n/a	U	L	n/a	U	n/a	H	L	n/a	H

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524 Table 4. Patterning of the effectiveness across the type of target population

Study	Interventions indicative of clear positive behaviour change in the desired direction	Interventions indicative of some positive behaviour change in the desired direction	Interventions indicative of positive effect on the antecedent of behavior in the desired direction	Interventions indicative of no effect on behaviour or antecedents of behaviour	Interventions indicative of negative effect on behaviour or antecedents of behaviour in a non-desired direction
Azevedo *et al.* (2013)[20]			School Children		
Cebotarenco & Bush, (2008)[16]		School Children			
Croft *et al.* (2007)[11]			Parents; Child Care Facilities		
Curry *et al.* (2006)[21]	General Public				
Farrell *et al.* (2011)[22]			School Children		
Formoso *et al.* (2013)[13]					General Public
Gonzales *et al.* (2008)[14]	General Public				
Huang *et al.* (2007)[12]			Parents		
Larson *et al.* (2009)[23]	Parents				
Lecky *et al.* (2010)[17]			School Children		
Madle *et al.* (2004)[24]			General Public		
Mainous *et al.* (2009)[30]					Latino Community, USA
Mazinska & Hryniewicz, (2010)[25]		General Public			
McNulty *et al.* (2001)[27]			School Children		
McNulty *et al.* (2007)[26]			School Children		
McNulty *et al.* (2010)[18]				General Public	
Pontes *et al.* (2005)[15]			Young Adults		
Stockwell *et al.* (2010)[28]	Latino Community Parents, USA				
Trepka *et al.* (2001)[19]	Parents				
Wutzke *et al.* (2006)[29]	General Public				

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Supplementary data

1. Supplementary Table S1. An example of search strategy applied for MEDLINE database
2. Supplementary Table S2. Data extraction tool designed for the purpose of the study
3. Supplementary Table S3. Excluded studies with rationale