Tackling antimicrobial resistance in primary health care through promoting the appropriate use of antibiotics in Estonia

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Evidence brief for policy

EVIPNet Europe

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ABSTRACT
This report is the second evidence brief for policy produced in Estonia within the framework of the WHO European Evidence-informed Policy Network. It was prepared by the Public Health Institute of University of Tartu in collaboration with the Ministry of Social Affairs of Estonia and WHO Country Office in Estonia. The working group identified, selected, appraised, and synthesized relevant research evidence on the problem, three options for tackling it and considerations in implementing them. The three options are: (1) Strengthening post-graduate education and continuing the education of primary care clinicians about the appropriate use of antibiotics and antimicrobial resistance (AMR); (2) Providing clinical decision support to PHCP (primary health care providers) for the prudent use of antibiotics; and (3) Using audit and feedback to improve prescribing behaviour.

KEY WORDS
DRUG RESISTANCE, RATIONAL USE; BENCHMARKING; ANTIMICROBIAL RESISTANCE, ANTIBIOTICS, PRIMARY HEALTH CARE, ESTONIA
CONTRIBUTORS AND ACKNOWLEDGEMENTS

WORLD HEALTH ORGANIZATION EVIDENCE-INFORMED POLICY NETWORK (EVIPNet)

EVIPNet promotes the systematic use of health research evidence in policy-making. EVIPNet promotes partnership at the country level among policy-makers, researchers and civil society to facilitate both policy development and policy implementation through using the best scientific evidence available. EVIPNet comprises networks that bring together country teams, which are coordinated at both the regional and global levels.

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MERIT REVIEW

This evidence brief for policy was reviewed by a small number of researchers and policymakers to ensure its scientific rigour and relevance for the health system. The authors are grateful to John Kopsidas from the Greece EVIPNet team; Mait Altmets from the Estonian Society for Infectious Diseases; Polly Mitchell, the Wellcome Trust Fellow at the WHO Regional Office for Europe, and Elizabeth Louise Stokle, independent consultant on antimicrobial resistance, infection prevention and health protection, for their valuable feedback. In addition, the authors thank Fadi el-Jardali and his team from the Knowledge to Policy Center (American University of Beirut) for their excellent training and continuous feedback and support throughout the development process of this evidence brief for policy. The views expressed in this brief do not necessarily represent those of the individuals named above.

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ABBREVIATIONS

AMR  antimicrobial resistance
AMS  antimicrobial stewardship
AMSTAR 2  A MeaSurement Tool to Assess Reviews
ARI  acute respiratory infections
AWaRe  Access, Watch, Reserve (AWaRe) classification of antibiotics
CDSS  clinical decision support system
CME  continuing medical education
CRT  cluster randomized trial
DDD  defined daily doses
DG SANTE  Directorate-General for Health and Food
EEA  European Economic Area
EC  European Commission
ECDC  European Centre for Disease Prevention and Control
EHIF  Estonian Health Insurance Fund
EHR  electronic health record
EU  European Union
HCP  health care providers
HCW  health care workers
PHCP  primary health care providers
RCT  randomized controlled trial
ROI  return on investment
UTI  urinary tract infections
Antimicrobial resistance (AMR) occurs when microorganisms change and become resistant to antimicrobial drugs used to treat them. There are different types of antimicrobials which work against different types of microorganisms, such as antibacterials or antibiotics against bacteria, antivirals against viruses, and antifungals against fungi. AMR is recognized as a major threat to public health globally. Overuse of antibiotics, especially the use of a broad-spectrum antibiotic in cases when the species of bacteria causing the disease is known and not resistant to a narrow-spectrum antibiotic, is like using a sledgehammer to crack a nut. It will not give a better result than a narrow-spectrum antibiotic, and yet enables the bacteria to develop a defense mechanism that is resistant to that antibiotic. The next time the use of this broad-spectrum antibiotic would be justified, it may no longer work, as the bacteria have already become familiar with it and have had time to develop resistance to it. This causes problems on an individual level but also for society, as the resistant pathogens spread and pass on the resistance genes to others. This will limit treatment options for anyone infected with them, in many cases making the treatment more expensive, and when the last-line antibiotics are no longer effective, it is extremely difficult, and in many cases impossible, to treat infected patients. Without effective antibiotics, common infections will become life-threatening and treatments such as surgical procedures and chemotherapy will not be possible.

While data show that antibiotics use and AMR in Estonia is low compared to other European countries, the consumption of broad-spectrum antibiotics is high and rising. As most antibiotics are used in the primary care sector, accounting for about 87% of the total consumption of antibiotics in 2019 in Estonia, the prescribing patterns in primary health care need to be changed to address this problem.

In order to improve the use and prescription of broad-spectrum antibiotics in primary care, this evidence brief for policy outlines the following three policy options:

- strengthening post-graduate education and continuing the education of primary care clinicians about the appropriate use of antibiotics and AMR through different
educational activities, such as educational materials, formal continued medical education activities, outreach visits, small discussion groups or online courses;

○ providing clinical decision support to primary health care providers (PHCP) for the prudent use of antibiotics, through a system or tool that integrates available clinical, patient, and reference information to assist evidence-based decision-making in the flow of patient care; and

○ using audit and feedback to improve prescribing behaviour.

Overall, the evidence suggests that the three policy options complement each other and combining them together could be the most effective course of action. While the policy options described in this evidence brief for policy are primarily focused at the level of PHCP, it is also known that awareness raising and educational programmes aimed at patients will help to reduce patients’ demand for using antibiotics.

What implementation considerations need to be borne in mind?

Pursuing any of the options set out in this evidence brief for policy will also require the development of a national guideline about antibiotic prescribing and use. In addition, Estonia needs to ramp up its development of a national action plan of AMR for human health and environment as well as finalize the overarching national One Health action plan to address AMR. Moreover, AMR itself needs more recognition and prioritization in the country, to ensure appropriate resource allocation to prevent AMR and promote appropriate prescribing of antibiotics.
EXECUTIVE SUMMARY

AMR is recognized as a major threat to public health globally. Antibiotic resistance is a subset of AMR as it applies to bacteria that has become resistant to antibiotics and is accelerated by the non-prudent use of antibiotics. Resistant microbes are more difficult to treat and require higher doses or alternative medications, which may prove more toxic. Alternative medications and treatments are often also more expensive, causing an inability to pay for the treatment and therefore an increase in the risk of disease spread, severe illness and death. More information can be found in Box 1, which provides a brief overview of antibiotic use and resistance.

**Box 1. Antibiotics, their use and antibiotic resistance**

**Antibiotics** are drugs designed to kill or inhibit the reproduction of bacteria and thus cure bacterial diseases. When a doctor anticipates that a disease is caused by bacteria, while the exact causative pathogen is unknown, the use of an antibiotic with a broad spectrum of action targeting all the potential species is justified. However, when the causative agent (the species of bacteria) is already known or known as soon as it is identified, including the information on antibiotic susceptibility, treatment should be optimized (by de-escalation or escalation as deemed necessary) with an antibiotic targeting exactly that species. In hospital care, starting with experience-based (empirical) antibiotic treatment is justified in urgent situations, such as with suspected sepsis, but treatment should be adjusted as soon as microbial culturing results become available. In outpatient settings, antibiotic treatment is often based on the suspected diagnosis of a bacterial disease, supported by relevant clinical guidelines.

**Broad-spectrum antibiotics** are effective against a wide range of disease-causing bacteria and are used when a bacterial infection is suspected but the group of bacteria is unknown or when infection with multiple groups of bacteria is suspected.

**Narrow-spectrum antibiotics** are effective only against specific group of bacteria.

The use of the optimal narrow-spectrum antibiotic can be hindered when a species has developed resistance, that is a defense mechanism to that exact antibiotic. **Antibiotic resistance** is a subset of AMR as it applies to bacteria that have become resistant to antibiotics. Resistance is one of the defense mechanisms that microbes develop to survive when attacked. This means that, in addition to bacteria, other microbes, such as fungi, viruses and protozoa, can evolve resistance. AMR is recognized as a major threat to public health globally. Resistant microbes are more difficult to treat and require higher doses or alternative medications, which may prove more toxic. These approaches may also be more expensive.
In Estonia, most antibiotics are used in the primary care sector, accounting for about 87% of the total consumption of antibiotics in 2019 (1). While data shows that antibiotics use and AMR in Estonia is low compared to other European Union (EU) countries, the consumption of broad-spectrum antibiotics, especially those falling into the WHO Watch category – which have higher resistance potential and should be used as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes – is rising in Estonia (2). Furthermore, the European Centre for Disease Prevention and Control (ECDC) quality indicators for antibiotic consumption in the community reveal that the ratio of consumption of broad-spectrum to that of narrow-spectrum penicillins, cephalosporins and macrolides in Estonia exceeded that of the Nordic countries (2). This indicates that these broad-spectrum antibiotics might be used without good explanation. Overall, while the current situation is still relatively good, there are hints that the AMR situation in the human health sector in Estonia might be evolving to pose a serious threat in the country in the future. In order to improve the current practices in antibiotic prescription, this evidence brief for policy focuses on the use of antibiotics by family doctors who prescribe most of the antibiotics in Estonia. The selection was made based on the fact that the general use of antibiotics is not seen as a problem in Estonia yet (given low use in the community compared to other EU countries and lower use than the EU average in hospitals) but the data indicates that the use of broad- to narrow-spectrum antibiotics is a problem. At the same time, the authors must highlight that there has not been any assessment of the appropriateness of antibiotic prescribing conducted in Estonia.

AMR causes problems on an individual level but also for society as the resistant pathogens spread and pass on resistance genes to others. This will limit treatment options for anyone infected with them, and when the last-line antibiotics are no longer effective, it is extremely difficult, and in many cases impossible, to treat infected patients. Without effective antibiotics, common infections will become life-threatening and treatments, such as surgical procedures and chemotherapy, may not be possible. The problem of using broad-spectrum antibiotics stems from a number of factors, including antibiotic prescribing patterns among Estonian doctors, pressure from patients to prescribe antibiotics, and current health care system arrangements – such as governance, financing and delivery-related arrangements – which may not promote appropriate prescribing of antibiotics.

In order to improve the use and prescription of broad-spectrum antibiotics in primary care, this evidence brief for policy outlines the following three policy options: 1) strengthening post-graduate education and continuing the education of primary care clinicians about the appropriate use of antibiotics and AMR; 2) providing clinical decision support to PHCP for the prudent use of antibiotics; and 3) using audit and feedback to improve prescribing behaviour. The three options are summarised below, and the methodology used for the policy brief can be found in Box 2. Although we did not explore it as a specific policy option, pursuing any of the options set in this evidence brief for policy will also require
the development of a national antibiotic prescribing and use guideline as there are no
national ones existing. In addition, Estonia needs to develop a national action plan of AMR
for human health and environment as well as finalize the overarching national One Health
action plan to address AMR.

Box 2. Background to the policy brief
This policy brief mobilizes both global and local research evidence about a problem,
three options for addressing the problem, and key implementation considerations.
Whenever possible, it summarizes research evidence drawn from systematic reviews
of the research literature and occasionally from single research studies. The chapter
about implementation considerations is mostly based on the team’s knowledge and
expertise that is validated through national stakeholder consultation as there was
not much written about implementation in the systematic reviews that we found.
A systematic review is a summary of studies addressing a clearly formulated question
that uses systematic and explicit methods to identify, select, and appraise research
studies and to synthesize data from the included studies. This evidence brief for policy
does not contain recommendations.

The preparation of this evidence brief for policy involved five steps.

1. A steering committee was convened, comprised of representatives from the
   University of Tartu, Ministry of Social Affairs, Health Board and WHO Country
   Office in Estonia.
2. The terms of reference for the evidence brief for policy were drafted and
   refined, particularly the framing of the problem and three viable options for
   addressing it.
3. The relevant research evidence about the problem, options, and implementation
   considerations was identified, selected, appraised, and synthesized.
4. The evidence brief for policy was drafted to present the global and local
   research evidence concisely and in accessible language.
5. It was finalized based on input from several merit reviewers.

The three options for addressing the problem were not designed to be mutually
exclusive. They could be pursued simultaneously, or elements could be drawn from
each option to create a new fourth option.

The policy brief was prepared to inform a policy dialogue where research evidence
is one of many considerations. Participants’ views and experiences and the tacit
knowledge they bring to the issues at hand are also important inputs to the dialogue.
One goal of the policy dialogue is to spark insights that can only come about when all
of those who will be involved in or affected by future decisions about the issue can
work through it together. A second goal of the policy dialogue is to generate action by
those who participate in the dialogue and by those who review the dialogue summary.
Options for addressing the problem

**Option 1. Strengthening post-graduate education and continuing the education of primary care clinicians about the appropriate use of antibiotics and AMR**

Option one includes the following observations.

» Educational interventions directed to prescribers are effective in reducing inappropriate antibiotic prescriptions.

» Some educational interventions have taken place within antimicrobial stewardship (AMS) programmes, and most provider education interventions were multifaceted and included seminars and workshops about current guidelines; educational outreach visits; small discussion groups; practice-based learning; and communication skills training.

» One systematic review found that digital educational interventions, which included personal digital assistants, short text messages, and online digital education, resulted in increased professional knowledge and reduced antibiotic prescribing compared to traditional education.

» The cost-effectiveness of educational programmes is difficult to estimate as there are many different forms of educational interventions, and educational interventions are mostly combined with other interventions. However, internet-based training in communication skills is a cost-effective intervention to reduce antibiotic prescribing for respiratory tract infections in primary care if the cost of AMR is accounted for.

» There is a paucity of evidence to support the use of educational interventions as a stand-alone intervention. However, reduced broad-spectrum antibiotic prescribing was seen after interventions where clinician education was combined with clinical decision support systems (CDSSs) or with audit and feedback.

» Educational interventions of prescribers should: support a larger AMS programme intervention; use interactive techniques for application, such as role playing; include feedback and/or periodic reinforcement; and focus on a single topic per session.

**Option 2. Providing clinical decision support to PHCP for the prudent use of antibiotics**

Option two includes the following observations.

» CDSSs are effective in reducing inappropriate antibiotic prescriptions, including overuse of broad-spectrum antibiotics.

» The most effective interventions are those which take place within AMS programmes, combining CDSS with education (based on local antibiotic treatment guidelines) and audit and feedback.
Combining CDSS with other interventions limits the ability to isolate its independent effect.

CDSS implementation costs are considered relatively low and integrating it into an already existing system will further reduce costs. However, developing the system from scratch requires some investment.

To maintain the effect, CDSS needs to be used and updated on a continuous basis.

Option 3. Using audit and feedback to improve prescribing behaviour

Option three includes the following observations.

- Using audit and feedback directed to prescribers can be effective in improving prescribing behaviour; mostly, however, the effect was moderate or minimal.
- It was found that audit and feedback can have a positive impact on AMS if clinicians are compared with their peers.
- Individualised feedback can be more effective than general feedback measures, which include practice-based feedback, educational sessions and educational mailings.
- We did not find any cost effectiveness data for primary health care but implementing AMS programmes in the hospital setting may be cost-effective. However, comprehensive cost-effectiveness data remain relatively scarce.
- Feedback alone was only moderately effective, whereas combining it with goal setting and action planning was associated with significantly enhanced effectiveness.
- Many of the interventions evaluated in the reviews were multifaceted and therefore, in most studies, the effects of different intervention components could not be distinguished. Audit and feedback were combined in most studies with the dissemination of guidelines and education of physicians.
- The most effective interventions took place within AMS programmes and were combined with clinical decision support or with audit and feedback.
- While many interventions were conducted at multiple sites, few were replicated or provided long-term results after the initial research team was no longer present.

Overall, the evidence suggests that the three policy options complement each other and combining them together under an AMS programme could be the most effective course of action.

While the policy options described in this evidence brief for policy are primarily focused at the level of PHCP, it is also known that awareness-raising and educational programmes aimed at patients will help to reduce patients’ demand to use antibiotics. This could form part of a general AMS programme.
About barriers to and opportunities for implementation, we found that, as a prerequisite, it is necessary to have clinical guidelines about antibiotic prescribing and use. These are missing in Estonia. Moreover, AMR itself needs more recognition and prioritization in the country, to ensure appropriate resource allocation to prevent AMR and promote appropriate prescribing of antibiotics. On the positive side we found that, as there already are several systems in place allowing incorporation of AMR and antibiotics use-related measures, there is no need to start from scratch. More specifically we found the following.

Regarding **policy option 1** (strengthening postgraduate education and continuing the education of primary care clinicians about appropriate use of antibiotics and AMR), there are no AMS programs for outpatient settings in Estonia and no updated national guidelines on antibiotic prescribing, which would form a solid basis for providing education. Education is hindered also by time constraints, especially if the training of health care workers (HCW) takes place away from the workplace. Language barrier plays a role for some Russian-speaking HCW, as most of the training materials are in Estonian or English. Counterstrategies would include organizing workplace-based trainings and online trainings; providing protected time for physicians to engage in educational and training activities, as opposed to offering them as add-ons after working hours; and providing training materials in Russian as well.

Regarding the implementation of **policy option 2** (providing clinical decision support to PHCP for the prudent use of antibiotics), the Estonian Health Insurance Fund (EHIF) recently developed a CDSS for PHCP (in Estonian: *Eesti Haigekassa otsustustugi*). Information on the prudent use of antibiotics could be added to the system. However, a prerequisite for this – up-to-date national antibiotic treatment guidelines – is missing.

Finally, concerning **policy option 3** (using audit and feedback to improve prescribing behaviour), clinical audits have been organized in Estonia since 2002 by the EHIF. Evaluators are persons appointed by professional associations. Individual feedback is provided to the audited institutions. The process also includes reassessment. However, audit and feedback should only cover the areas where best practice is widely agreed. There are no updated national guidelines on antibiotic prescription. Also, success depends on the delivery method of feedback to prescribers and needs good communication with practitioners.
AMR is a major public health problem that can be accelerated by the non-prudent use of antibiotics. In Estonia, one must have a physician prescription to get access to antibiotics that limits access and therefore misuse. Most antibiotics in Estonia are used in outpatient care, accounting for about 87% of the total consumption of antibiotics in 2019 (1). While European Surveillance of Antimicrobial Consumption Network and European Antimicrobial Resistance Surveillance Network (3) data show that antibiotic use and resistance to key bacteria in Estonia is low, the consumption of broad-spectrum antibiotics, including those falling into WHO Watch category (4) – which are those that have higher resistance potential and should be used as essential first or second choice empiric treatment options for a limited number of specific infectious syndromes – is rising in Estonia. Furthermore, the ECDC quality indicators for antibiotic consumption in the community reveal that the ratio of consumption of broad-spectrum to that of narrow-spectrum penicillins, cephalosporins and macrolides in Estonia (17.27) notably exceeded that of the Nordic countries (Finland 0.48, Sweden 0.24 and Denmark 0.60) (2). Overall, there are indications that the current AMR situation in the human health sector might be evolving to pose serious threats in the country. The problem stems from a number of factors, including antibiotic prescribing patterns among Estonian doctors, pressure from patients to prescribe antibiotics, and current health care system arrangements, which may not promote appropriate prescription of antibiotics.

Global antibiotic consumption in humans increased by 65% between 2000 and 2015. If nothing changes to alter these trajectories, antibiotic consumption is projected to increase worldwide by 200% between 2015 and 2030. Per capita antibiotic consumption in low- and middle-income countries is lower than in high-income countries, despite a higher infectious disease burden; however, consumption rates are rapidly converging. These trends reflect both better access to antibiotics for those who need them and increases in inappropriate antibiotic use. (5).

In 2015, to combat the global emergence of AMR, the need for an effective One Health approach – including human, animal and environmental health – was recognized by the World Health Assembly, the decision-making body of WHO (6). Member States were urged to develop national action plans to ensure the continuity of successful treatment and prevention of infectious diseases with effective and safe medicines, used in a responsible way.
In 2017, the One Health Action Plan against AMR was published by the European Commission (EC) (7). To follow up on and assist Estonia in developing and implementing its national strategies and policies against AMR, a joint visit to Estonia was made by the ECDC and the EC’s Directorate-General for Health and Food (DG SANTE) in 2019. In Estonia, informal collaboration on AMR between relevant competent authorities and stakeholders had already started and a veterinary AMR action plan for 2019–2023 was in place, but the corresponding human health and environmental plans were still due and the overarching national One Health AMR action plan was not yet finalized. Although the One Health approach requires collective management of antimicrobial misuse in humans and animals, most AMR in humans arises from human antibiotic use (7). The human health, environmental health and One Health AMR action plans were due in 2020, but their development was delayed due to the COVID-19 pandemic. Nevertheless, they are planned and therefore this issue is not addressed in the current evidence brief for policy. The authors’ review and synthesis of evidence (the process for how the research evidence was mobilized is described in Box 3) therefore concentrates on issues and possible interventions related to the human health care sector, including the problem of antibiotic misuse in human medicine, especially at the primary health care level.

Box 3. Mobilizing research evidence about the problem

The available evidence about the problem was sought from a range of published research and grey literature.

Relevant published literature was sought using PubMed and Health System Evidence. Articles were identified by searching each database for systematic reviews and meta-analysis with topic-related keywords in the title or abstract. The keywords included “antibiot*”, “antimicrobe”, “antibacter*”, “stewardship”, “intervention”, “program”, “strategy”, “practice”, “regulat*”, “guideline”, “policy”, “polic*”, and a filter of “primary care” was used. A total of 166 articles were found from PubMed and 43 from Health System Evidence.

Grey literature was sought by reviewing the websites of a number of national and international organizations, such as the Health Board of Estonia, Ministry of Social Affairs of Estonia, AMR project RITA in Estonia, Organisation for Economic Co-operation and Development, European Centre for Disease Prevention and Control, and WHO.

Priority was given to research evidence that was published more recently and to high quality studies.

Regarding the human health aspects of AMR in Estonia, the following conclusions (among others) were made by ECDC (8).

1) According to various European surveillance networks, antibiotic consumption in the human health sector in Estonia is low.
2) Compared to other European countries, the situation in Estonia is characterised by a low level of AMR in key bacteria.

3) Although there is a low level of AMR in key bacteria obtained from human clinical isolates, there are hints that the current AMR situation in the human health sector might be evolving, with hospital outbreaks of resistant bacteria, growing numbers of patients with extended-spectrum beta-lactamase-producing Enterobacteriaceae and an increasing number of isolation-days in some hospitals.

4) The relatively limited size of the problem of AMR has led to underestimating the potential consequences that AMR could have in the future, and possibly to de-prioritizing the necessary measures to safeguard the health care system from AMR threats.

In 2019, at the time of the ECDC and DG SANTE joint country visit, a three-year strategic research and development project, funded through an Estonian Research Council grant, was in progress in Estonia. The project focused on the emergence of AMR in Estonia and aimed to determine the main pathways of spread and identify knowledge gaps. (9).

One of the studies in this project compared outpatient use of antibiotics, quality indicators for antibiotic consumption in the community, and AMR in Estonia with its neighbouring countries of Latvia, Finland and Sweden plus Denmark (10). The study revealed that, in Estonia, the consumption of broad-spectrum antibiotics (e.g. penicillins combined with beta-lactamase inhibitors, and cephalosporins) had increased from 2008 to 2018, with the consumption of the combination of amoxicillin and clavulanic acid exceeding that of amoxicillin in 2018 (1.9 vs 1.6 defined daily doses (DDD) per 1000 inhabitants per day). Also, the consumption of cephalosporins had increased over time. While the total antibiotic consumption in Estonia (10.2 DDD per 1000 inhabitants per day) was similar to that of Finland (13.2), Sweden (10.8), Latvia (11.4) and Denmark (13.7), the consumption of penicillins in Estonia (as well as in Latvia and Finland) was much lower compared to Sweden and Denmark. In addition, the highest consumption of macrolides in all these countries is in Estonia. The study also showed that, in Estonia, AMR is low and did not change significantly from 2011 to 2018. This finding does not justify the increase in the use of broad-spectrum antibiotics, which, if continued, might lead to AMR problems in the future. (10).

Also, according to the ECDC quality indicators for antibiotic consumption in the community, in 2019 the ratio of the consumption of broad-spectrum to that of narrow-spectrum penicillins, cephalosporins and macrolides in Estonia (17.27) notably exceeded that of the Nordic countries (Finland 0.48, Sweden 0.24 and Denmark 0.60) (See Table 1) (2).

In 2019, WHO developed the Access, Watch, Reserve (AWaRe) classification of antibiotics. The “Access” group includes antibiotics that have activity against a wide range of commonly encountered susceptible pathogens while also showing lower resistance potential than antibiotics in the other groups. These are recommended as essential first or second choice empiric treatment options for infectious syndromes and are listed as individual medicines.
on the Model Lists of Essential Medicines to improve access and promote appropriate use. The “Watch” category represents the antibiotics which have higher resistance potential and are thus recommended as first or second choice treatments only for a specific, limited number of indications to prevent the emergence of AMR. The “Reserve” group includes antibiotics and antibiotic classes that should be reserved for the treatment of confirmed or suspected infections due to multi-drug-resistant organisms and should be treated as last resort options. To optimize antibiotic use and reduce AMR, advice was given about which essential antibiotics to use for common infections and which to preserve for the most serious conditions. A target was set that at least 60% of antibiotic consumption at the country level should be from medicines in the Access Group. [4].

Several antibiotics that seem to be overused in Estonia, such as cephalosporins and macrolides, fall into the WHO Watch category, recommended as first or second choice treatments only for a specific, limited number of indications to prevent the emergence of AMR. [4].

### Consequences of inaction

Overuse of antibiotics, especially the use of a broad-spectrum antibiotic in cases when the species of bacteria causing the disease is known and not resistant to a narrow-spectrum antibiotic, is like using a sledgehammer to crack a nut. It will not give a better result than a narrow-spectrum antibiotic, and yet enables the bacteria to develop a defense mechanism, namely resistance to that antibiotic. The next time, even in cases where the use of this broad-spectrum antibiotic would be justified, it may no longer work, as the bacteria, already familiar with it, have had time to develop resistance to it. This causes problems on an individual level but also for society as a whole as the resistant pathogens spread from person to person and can also pass on the resistance genes to other bacteria. Over time, as resistance spreads and the last-line antibiotics are no longer effective, treatment options will be limited, and in many cases, it will be impossible to treat infected patients. Without effective antibiotics, even currently common and easily treated infections will become life-threatening and treatments such as surgical procedures and chemotherapy will not be possible.

### Table 1. Quality indicators for antibiotic consumption in the community (primary care sector) in Estonia and other selected (neighbouring) countries*

<table>
<thead>
<tr>
<th>Country</th>
<th>Consumption in DDD per 1000 inhabitants and per day</th>
<th>Relative consumption as percentage of total consumption of antibacterials for systemic use</th>
<th>Ratio of consumption (broad-/narrow-spectrum)</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anti-bacterials for systemic use (J01_DID)</td>
<td>Penicillins (J01C_DID)</td>
<td>Cephalosporins (J01D_DID)</td>
<td>Macrolides and similar (J01F_DID)</td>
</tr>
<tr>
<td>Estonia</td>
<td>10.24</td>
<td>3.75</td>
<td>1.19</td>
<td>2.33</td>
</tr>
<tr>
<td>Latvia</td>
<td>12.02</td>
<td>4.64</td>
<td>0.62</td>
<td>2.13</td>
</tr>
<tr>
<td>Finland</td>
<td>12.56</td>
<td>4.33</td>
<td>1.78</td>
<td>0.63</td>
</tr>
<tr>
<td>Sweden</td>
<td>10.33</td>
<td>5.48</td>
<td>0.06</td>
<td>0.52</td>
</tr>
<tr>
<td>Denmark</td>
<td>13.44</td>
<td>8.93</td>
<td>0.03</td>
<td>1.43</td>
</tr>
</tbody>
</table>

*a* Please see Annex 1 for the definitions of the indicators presented in this table. Green refers to the most favourable 25% of values and red to the least favourable 25% of values for the indicator (considering all the European countries that provided the data).

*b* Denominator for relative consumption.

**Source:** Quality indicators for antibiotic consumption in the community (primary care sector) in Europe 2019 [2]
AMR has a significant detrimental effect on health – each year, AMR is responsible for about 33 000 deaths (comparable to 100 medium-sized airplanes full of passengers) in EU and European Economic Area (EEA) countries and costs about 1.1 billion euros to their health care systems (11). The health burden of infections due to bacteria with AMR in the EU/EEA population is comparable to that of influenza, tuberculosis and HIV/AIDS combined. In addition to loss of life, more than 670 000 infections due to bacteria with AMR occur every year in the EU/EEA and the trend is increasing (11). The severity of resistant infections is often greater than that of treatment-susceptible infections, and this can be intensified by the delayed start of effective treatment. Moreover, treatment for resistant strains is often more costly. Treating resistant strains also carries a higher risk of complication and a greater chance that patients will require hospital treatment and longer hospital stays. This all comes at significant cost to patients (including non-monetary costs), the health care system and the wider economy.

A higher than normal level of administration of antibiotics during current COVID-19 times is also expected and, considering the scarcity of data so far, it is likely that the number, type and amounts of antibiotics used are currently undocumented and thus underestimated (12). It is feared that current errors or excesses could accelerate the advent of the next global public health crisis caused by resistance of a large variety of microorganisms to a spectrum of drugs (12). Empirical evidence from family doctors in Estonia also indicates an increase in the use of antibiotics after the emergence of SARS-CoV-2. This is related to patients’ demand for antibiotics but also due to the lack of physical visits during high COVID-19 infection levels where patient consultations were done by phone or electronically.

The situation is more alarming as not many new antibiotics are coming to the market and the antibiotics pipeline at pharmaceutical companies is running dry. While there were 18 big companies actively investing into antibiotics research and development in 1990, only six companies were still active in this field in 2016 (11).

**Underlying causes of the problem**

There are several factors which contribute to the overuse of broad-spectrum antibiotics in Estonia.

Regarding governance arrangements, there are no up-to-date national level guidelines on the use of antibiotics in outpatient care. Such guidelines can standardize quality of care, including the prescribing decisions of physicians within primary care (13). They have also been used for addressing AMR (14). The most recent national guideline for diagnostics and management of common infectious diseases in outpatient care dates back to 2005 (15). There is a guideline developed by the Estonian Society for Infectious Diseases with the support of...
a pharmaceutical company, but other professional societies have not been involved in the development process and this has not been approved by the EHIF or the Estonian Society of Family Doctors. Also, in Estonia there is a low awareness of classification of antibiotics in terms of AMR potential, similar to the WHO AWaRe classification of antibiotics, in Estonia’s Essential Medicines List (4).

There are no AMS programmes for outpatient settings, including no systems for monitoring of antibiotic prescribing and systematic feedback to health care providers (HCP) working in primary care regarding their prescription of antibiotics.

It should be pointed out that a prescription-only antibiotic policy is well-established in Estonia and patients cannot buy antibiotics over the counter. Only physicians can prescribe systemic antibiotics, with the exception of nitrofurantoin and fluconazole, which can be also prescribed by nurses and midwives (16). Pharmacists cannot prescribe antibiotics in Estonia.

Only a small number of narrow-spectrum antibiotics are currently available in Estonia and this is mostly due to the fact that the market is small (Estonia’s population is 1.3 million inhabitants) and demand has been limited (17). In neighbouring Scandinavian countries, there are a number of narrow-spectrum antibiotics used, such as pivmecillin for urinary tract infections (UTIs) and flucloxacillin for skin and soft tissue infections, which are currently not available in Estonia (18). Physician interactions with pharmaceutical industry representatives are currently limited in Estonia, but such interactions in the past (about 10 years ago, when the marketing of pharmaceuticals was less regulated) may have contributed to physicians’ preferences to use broad-spectrum antibiotics.

Regarding financial arrangements, there are currently no incentives, such as pay-for-performance systems (i.e. monetary incentives to support optimal antibiotic prescribing and to reduce inappropriate prescribing for physicians) (19).

For patients there is no financial gain associated with optimal antibiotic use as the out-of-pocket costs are about the same for Access and Watch group antibiotics. There are generally similar drug prices and discount rates for both groups of antibiotics. However, being on sick leave is associated with financial loss as the sickness benefit is 70% of the wage (20). Thus, patients can be motivated to use antibiotics rather than to be on sick leave, which may increase the pressure on physicians to prescribe them.

Diagnostic tests are valuable in promoting judicious antibiotic use. For example, a test that will diagnose a viral illness will deter the use of antibiotics. Diagnostic tests also help change broad empiric treatment to target narrow-spectrum antibiotics. However, due to current legislation, the diagnostic tests are covered by the EHIF, but there is an upper limit for the expenditures of each family doctor’s centre for diagnostic tests, and if this limit has been exceeded, the extra costs have to be from other budget lines of the centre, such
as from wages. Additionally, extra factors, such as waiting times for or the interpretation of results, add to the workload of family doctors compared to limiting their work to only prescribing antibiotics.

Also, there are no up-to-date guidelines on rapid and/or point-of-care diagnostics for defined patient groups to complement clinical assessment; current guidelines were developed in 2005 (15).

In general, family doctors' centres are equipped with some rapid diagnostic tools, such as Strep A test and C-reactive protein measurement, and X-ray and biochemistry results are usually available within 24 hours. The services are paid by the EHIF, but there is an upper limit for payments and costs exceeding the limit must be covered at the expense of other cost items, such as wages.

Regarding delivery arrangements, there is a good electronic prescribing database in Estonia, however, PHCP do not receive feedback about antibiotic prescribing rates, peer comparisons or guidance compliance. The electronic decision support system used by PHCP in their clinical work in Estonia does not include supportive information about optimal antibiotic prescribing. Additionally, the information about AMR patterns in Estonia is not easily accessible for PHCP.

There is low awareness about AMR among HCP, the general public and at the government level. The relatively limited size of the problem of AMR in the country has led HCP to underestimate the potential consequences that AMR could have in the future (8). The overall level of the general population’s knowledge on the use of antibiotics is below the EU average, although knowledge has increased over time (21). About a quarter of the adult population in Estonia expect that antibiotics are effective in managing colds (21).

There are regional differences in prescribing antibiotics (18). Also, there might exist regional differences in HCP and general public awareness about AMR, especially in Russian-speaking regions, as the availability of information may be limited for them. To our best knowledge there are no studies directly addressing this aspect. As a rule, patients are not involved in decision-making related to antibiotic choice (e.g. between narrow-spectrum vs broad-spectrum) in Estonia.

An additional problem is low influenza vaccine rates in Estonia – this has been less than 10% and may contribute to increased antibiotic use in flu seasons (22).
THREE OPTIONS FOR ADDRESSING THE PROBLEM

Many options could be selected to address the problem of non-prudent use of antibiotics, especially broad-spectrum antibiotics, which potentially accelerates the development of AMR. This evidence brief for policy focuses on primary health care and how to improve antibiotics prescribing in ambulatory settings, given that about 85% of antibiotics use occurs in this setting in Estonia compared to about 15% in the hospital setting (23).

To promote discussion about the pros and cons of potentially viable options, three have been selected for more in-depth review:

1) strengthening post-graduate education and continuing the education of primary care clinicians about the appropriate use of antibiotics and AMR;
2) providing clinical decision support to PHCP for the prudent use of antibiotics; and
3) using audit and feedback to improve prescribing behaviour.

The focus in this section is on what is known about these options. In Box 4 the method for how the evidence was collected and assessed is prescribed. In the next section the focus turns to the barriers to adopting and implementing these options and to possible implementation strategies to address the barriers. Each option proposed contributes to more appropriate use of antibiotics in primary health care settings; while each can be implemented independently, combined implementation as part of a wider AMS programme would likely have a greater impact.

Box 4. Mobilizing research evidence about options for addressing the problem

An additional PubMed search was made in relation to each of the three policy options.

For option 1, strengthening post-graduate education and continuing the education of primary care clinicians about the appropriate use of antibiotics and AMR, 24 articles were found, five of which were considered relevant and included in the analysis.

For option 2, providing clinical decision support to PHCP for the prudent use of antibiotics, six systematic reviews and meta-analyses were retrieved, but none of them were applicable. Thus, an additional search for individual studies was done and 254 articles were retrieved, six of which were considered relevant and included in the analysis.

For option 3, using audit and feedback to improve prescribing behaviour, 98 articles were found, six of which were considered relevant and included in the analysis.
The review authors’ key findings were extracted from the identified reviews. Each review was also assessed in terms of its quality (AMSTAR 2 or GARADE rating), local applicability (proportion of studies that were conducted in the country), equity considerations (proportion of studies that deal explicitly with prioritized groups) and the review’s degree of focus on the issue. The overall evidence about the options was then summarized and relevant caveats were introduced about the review authors’ key findings based on the quality, local applicability, equity, and issue applicability assessments.

Attention was given to whether reviews contained no studies despite an exhaustive search (that is, they were “empty” reviews) and whether reviews concluded that there was uncertainty about the option based on the identified studies. Being aware of what is not known can be as important as being aware of what is known. When faced with an empty review, or with uncertainty or concerns about the reviews’ quality, local applicability of the reviews’ findings, or a lack of attention to equity considerations, primary research could be commissioned or an option could be pursued and a monitoring and evaluation plan designed as part of its implementation. When faced with a review that was published many years ago, an update of the review could be commissioned if time allowed.

No additional research evidence was sought beyond what was included in the systematic reviews, except for the option on providing decision clinical support. Those interested in pursuing a particular option may want to search for a more detailed description of the option or for additional research evidence about the option.

**Option 1. Strengthening post-graduate education and continuing the education of primary care clinicians about the appropriate use of antibiotics and AMR**

Improving awareness and understanding of antibiotic resistance and promoting expert-driven behavioural change, through effective communication, education and training, is critical to tackling the issues of AMR (24). Therefore, effective educational efforts targeted at antibiotic prescribers are certainly required. Different educational activities can be used, such as educational materials, formal continuing medical education (CME) activities, outreach visits, small discussion groups, and online courses. Educational activities that are more interactive, use more methods, involve multiple exposures, are longer, and are focused on outcomes that are considered important by physicians have led to more positive outcomes (25).

In primary care in Estonia, antibiotics for both adults and children are prescribed by family doctors with one minor exception: nitrofurantoin and fluconazole can also be prescribed
by nurses and midwives. Patients cannot buy antibiotics without prescription. Therefore, family doctors have a critical role in the choice of antibiotics.

In Estonia, family doctors are actively participating in various educational activities. For recertification, family doctors should meet minimum continuous professional development requirements, including educational activities for at least 300 hours every five years. Recertification of health care professionals is voluntary in Estonia. However, there are monetary incentives for family doctors to be recertified (26). More than 80% of family doctors have undergone the recertification process. Educational activities arranged or sponsored by the pharmaceutical industry are not taken into account in the recertification process (27).

A summary of key findings from research on option 1 is provided in Table 2. A more detailed description of the evidence presented in Table 2 is provided in Annex 2.

### Table 2. Summary of key findings from systematic reviews relevant to option 1, strengthening post-graduate education and continuing the education of primary care clinicians about the appropriate use of antibiotics and AMR

<table>
<thead>
<tr>
<th>Category of finding</th>
<th>Key findings</th>
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<tr>
<td><strong>Benefits</strong></td>
<td>Four systematic reviews have found that educational interventions directed to prescribers, mostly within AMS programs, are effective in reducing inappropriate antibiotic prescriptions (14, 28-30). Most studies reported reduced overall prescribing of antibiotics in respiratory tract infections (14, 28, 30, 31).</td>
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<td>In two of the systematic reviews, the educational interventions took place within AMS programmes, and most provider education interventions were multifaceted, including seminars and workshops about current guidelines, educational outreach visits, small discussion groups, practice-based learning, and communication skills training (14, 28). However, there is no evidence on the relative effectiveness of these interventions.</td>
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<td>In a third systematic review, out of 47 studies conducted in primary care, the vast majority (n=43) reported significant post-intervention improvements, with follow-up periods ranging from two months to 24 months (30). Some of the randomized controlled trials (RCTs) included in this systematic review specifically reported reduced broad-spectrum antibiotic prescribing after interventions where the clinician education was combined with clinical decision support or with audit and feedback (32, 33). Clinician education coupled with audit and feedback decreased broad-spectrum antibiotic prescribing from 26.8% to 14.3% (absolute difference, 12.5%) among intervention practices (32). The intervention delivered by specially trained general practitioners resulted in significant decreases of macrolides and tetracyclines prescriptions – the intervention consisted of two</td>
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<tr>
<td>(contd) Benefits</td>
<td>visits to a primary health care center: the first presenting the national clinical guidelines for antibiotic use and recent research evidence on acute respiratory tract infections, and the second based on feedback reports on each general practitioner’s antibiotic prescribing profile from the preceding year (33). One systematic review found that digital educational interventions, which included personal digital assistants, text messages, and online courses, resulted in increased professional knowledge and reduced antibiotic prescribing compared to traditional education; it concluded that digital education on antibiotic management is complementary to traditional educational sessions (31).</td>
</tr>
<tr>
<td>Potential harms</td>
<td>We did not find any studies that evaluated untoward or adverse effects of the educational interventions of clinicians for patients. We expect the potential theoretical risk to be low. For clinicians, there will be opportunity costs (that is, the time and money that could be spent elsewhere instead of on education), but we did not find any studies addressing this. We have no data to expect that the benefit/harms ratio of educational interventions is negative.</td>
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<tr>
<td>Resource use, costs and/or cost-effectiveness</td>
<td>The cost-effectiveness of educational programmes is difficult to estimate as there are many different forms of educational intervention and, moreover, educational interventions are typically combined with other interventions. We did not find any study that analyzed the cost-effectiveness of educational interventions directed to reduce prescribing of broad-spectrum antibiotics or in terms of reduced AMR. A few studies have analyzed the effectiveness of the intervention in terms of the cost of the educational intervention versus the cost of reducing antibiotic use (30, 31); digital education is found to be cost-effective in this respect (31). Internet-based training in communication skills is a cost-effective intervention to reduce antibiotic prescribing for respiratory tract infections in primary care if the cost of AMR is accounted for (34, 35).</td>
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| Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option was pursued) | We found:  
  — few data on the effectiveness of educational interventions to reduce, specifically, the prescribing of broad-spectrum antibiotics (30);  
  — a lack of data about the cost-effectiveness of educational interventions compared with other interventions to improve antibiotic prescription practices;  
  — little evidence to support the use of educational interventions as a stand-alone intervention (14, 28-31); |
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| (contd) Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option was pursued) | — little evidence that educational interventions can reduce inappropriate antibiotic prescriptions in cases other than respiratory infections (14, 29, 30); and  
— little evidence of the persistence of prescribing behaviour change as the follow-up periods in most studies ranged from a few months to a year (30). The findings of the studies may not be directly generalizable due to the differences in health care systems and CME practices. |
| Key elements of the policy option if it was tried elsewhere                        | Interventions which took place within AMS programmes, and which were combined with clinical decision support or with audit and feedback, were most effective (14, 28, 30). |
| Stakeholders’ views and experiences                                                | According to a qualitative synthesis of data, the educational interventions of prescribers should: support a larger AMS programme intervention; use interactive techniques for application, such as role playing; include feedback and/or periodic reinforcement; and focus on a single topic per session (28). |

**Option 2. Providing clinical decision support to PHCP for the prudent use of antibiotics**

Support to clinical decisions can be provided through a system or tool that integrates available clinical, patient, and reference information to assist evidence-based decision-making in the flow of patient care (for example, incorporating clinical guidelines and local resistance data). The system helps providers by taking over some routine tasks, warning of potential problems, and/or providing suggestions for providers and patients to consider. Regarding antibiotics, such a system could support their prudent use. Prudent in this context means both prescribing antibiotics only for bacterial infections (that is, reducing overuse of antibiotics) and targeting the alleged pathogen with the most appropriate antibiotic (that is, a narrow-spectrum antibiotic, if applicable).

In Estonia, antibiotics are available with prescription only, and most prescriptions are provided by family doctors. The EHIF has recently introduced a clinical decision support system that has been integrated into the software of Estonian family doctors, and offers patient management recommendations based on the clinical history of the particular patient. However, currently in Estonia there are no up-to-date guidelines on the use of
antimicrobials (including antibiotics) in outpatient care, and local bacterial susceptibility/antibiotic resistance data, that would enable building an antibiotic prescription component into this system, are not collected.

No systematic reviews and meta-analyses were found that would specifically study the use of CDSSs to reduce the use of broad-spectrum antibiotics in primary care settings. The key findings are from single studies. A summary of key findings from research on option 2 is provided in Table 3. A more detailed description of the evidence presented in Table 3 is provided in the summary of systematic reviews in Annex 3.1 and summary of single studies in Annex 3.2.

Table 3. Summary of key findings from studies relevant to option 2, providing clinical decision support to PHCP for the prudent use of antibiotics

<table>
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<th>Category of finding</th>
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<tr>
<td>Benefits</td>
<td>Three single studies demonstrated that CDSSs in primary care practices have been effective in reducing the use of broad-spectrum antibiotics for the most common infectious diseases, such as acute respiratory infections (ARIs) and UTI, and large reductions in rates of prescription in different classes of antibiotics were observed (36–38). In the studies, CDSS was often combined with other interventions, such as education of HCP (39) and/or the community (40). While in one study, the overall use of antibiotics decreased (40), in another a decrease in the ratio of consumption of broad- to narrow-spectrum antibiotics was observed (39). While several studies reported the effect of CDSS to be sustainable (36, 39, 41), it had to be used continuously (41).</td>
</tr>
<tr>
<td>Potential harms</td>
<td>No studies showing adverse effects of CDSS for patients were found. We expect the potential theoretical risk to be low. However, the authors of one study noted that, when in CDSS the use of antibiotics is restricted for certain conditions (for example, a common cold) and yet allowed for others (for example, sinusitis), HCP may change how they classify patients with a certain set of symptoms (37). We found no data to suggest that the benefit/harms ratio of CDSS is negative.</td>
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<tr>
<td>Resource use, costs and/or cost-effectiveness</td>
<td>The implementation costs of CDSS were considered relatively low when combined with existing systems. One large cluster-RCT, assessing the effectiveness and return on investment of a multifaceted intervention aimed at improving antibiotic prescribing for ARIs in primary care, has been conducted (39). The study demonstrated that, when</td>
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<td>(contd) Resource use, costs and/or cost-effectiveness</td>
<td>designing an intervention based on gaps in knowledge and attitudes previously shown to be linked to inappropriate prescribing of antibiotics, the resources would be used more effectively (39). It has also been demonstrated that integrating a decision support system into other existing systems in an institution or organization makes the system less costly (37). We did not identify any studies analyzing the cost-effectiveness of CDSS in reducing the use of broad-spectrum antibiotics.</td>
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<tr>
<td>Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)</td>
<td>CDSS was often combined with other approaches (most often education, but also monitoring and feedback), limiting the ability to isolate the independent effect of CDSS (36-40). The uptake of the intervention varied: it was considered high in some studies (36, 37), yet limited in one (38). Two studies did not include a concurrent control group, thus there is no way of ensuring that the observed changes in antibiotics prescribing were not due to secular trends (36, 41). While some studies also demonstrated that the general use of antibiotics for inappropriate indications was reduced (37, 39, 40), it was not achieved in others (36). There might also be some generalizability issues, as some studies were conducted for a small group of volunteer practices (36, 37), while others only focused on certain infections and their treatment – most often ARIs (36, 37, 39, 40) or UTI (38). It is also possible that an intervention may lead to so-called gaming practices if providers shift their diagnoses to justify prescribing antibiotics. However, this was not the case in one study, which explicitly considered this phenomenon (37).</td>
</tr>
<tr>
<td>Key elements of the policy option if it was tried elsewhere</td>
<td>CDSS is usually utilized as part of a more complex intervention, combined with either or both of the other two options described in this policy brief. It has been demonstrated that the most effective interventions took place within an AMS program, when combining education, CDSS, and some form of monitoring (audit) and feedback (14, 28, 30). It has also been demonstrated that automatically provided CDSSs, in contrast to those that have to be actively initiated by the health care provider, are more likely to increase the appropriateness of antibiotic treatment (42).</td>
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Option 3. Using audit and feedback to improve prescribing behaviour

The majority of antibiotics prescribed to patients originate in outpatient settings. In making prescribing decisions, primary care providers often have a lack of awareness of AMR and a lack of understanding of the seriousness of AMR. There is evidence that a multifaceted strategy involving audit and feedback can reduce inappropriate behaviour in ordering tests as well as improve appropriate treatment of asthma patients in primary care (43).

Audit and feedback involve reviewing a clinician’s antibiotic prescribing behaviour and providing feedback to help the clinician adjust his/her performance. The use of audit and feedback for outpatient AMS has been largely studied in primary care clinics (33, 44).

A summary of key findings from research on option 3 is provided in Table 4. A more detailed description of the evidence presented in Table 4 is provided in Annex 4.

Table 4. Summary of key findings from systematic reviews and primary studies relevant to option 3, using audit and feedback to improve prescribing behaviour

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<td>Benefits</td>
<td>Six systematic reviews found that using audit and feedback directed to prescribers can be effective in improving prescribing behaviour (14, 45–49). Mostly, the effect was moderate, reaching a 15-20% improvement. In one review, significant decreases in antibiotic prescribing were reported, but the risk of bias was high in all included studies (14).</td>
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In all these systematic reviews, audit and feedback took place within AMS programmes. Different studies provided feedback in different forms: graphical individualized audit and feedback either by pharmacists or an opinion leader, educational feedback on previous prescribing in a more generalised way (group prescribing data), written feedback for behaviour plus academic detailing (outreach visit from the research coordinator), or postal feedback alone. A systematic review studying the effect of interventions on optimizing the prescription of antibiotics in dental care found the strongest effects among studies conducted in the outpatient setting \(^{(48)}\). Audit, feedback, education, local consensus and the dissemination of guidelines were the elements most often used and combined in the studies. The Scottish cluster RCT testing an audit and feedback intervention was able to reduce the number of prescriptions for antibiotics. Two of the studies provided in the United Kingdom of Great Britain and Northern Ireland in general dental care and outpatient settings reported significant reductions of the inappropriate prescription of antibiotics of about 50% before intervention to roughly 30% after the intervention, which entailed educational material by post and an academic detailing visit by a trained pharmacist \(^{(50, 51)}\). Marked reductions in the inappropriate prescription of antibiotics were also seen in large studies within the primary dental care setting \(^{(48)}\).

It was found that audit and feedback can have a positive impact on AMS if clinicians are compared with their peers. In a cluster randomized trial (CRT), comparing clinicians with top performers (those who seldom prescribe antibiotics inappropriately) decreased inappropriate prescriptions from 20% to 4%. Also, antibiotic use decreased among providers who received a letter from England’s chief medical officer saying they were prescribing more antibiotics than did 80% of local practices \(^{(45)}\). Individualized feedback can be more effective than more general reports. Two trials of individualized feedback reported significant decreases compared to more general feedback, such as an educational mailing or feedback for practice groups as a whole, and one reported a significant decrease compared to usual care \(^{(14)}\). Interventions aimed at increasing the prescribing of certain recommended first-line antibiotics for specific infections were more likely to produce substantial changes in prescribing than those interventions targeting overall inappropriate antibiotic use \(^{(46)}\).

Another systematic review showed that the combination of clinician education and audit and feedback can decrease antibiotic prescribing overall and broad-spectrum prescribing in particular. While audit and feedback alone resulted in no or only small changes in prescribing, a study in Finland demonstrated that

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<td>(contd) Benefits</td>
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<td>(contd) Benefits</td>
<td>audit and feedback in combination with the publication of a warning against the use of macrolides for group A streptococcal infections produced a sustained reduction in macrolide use (46). One systematic review found that feedback alone could be only moderately effective, whereas combining it with goal setting and action planning was associated with significantly enhanced effectiveness of the audit and feedback intervention (49). The meta-analysis in hospital settings supports the use of restrictive interventions, such as the freedom of prescribers to select some antibiotics, which appeared to have a larger effect than persuasive methods, such as advising physicians about how to prescribe or giving them feedback about how they were prescribed (47).</td>
</tr>
<tr>
<td>Potential harms</td>
<td>Harms associated with AMS efforts, including the additional utilization of health care services and adverse events due to under-treatment, are rarely reported. For patient outcomes, where reported, there were few differences between intervention and control or from pre- to post-intervention in return clinic visits, hospitalizations, adverse events, late antibiotic prescribing, or patient satisfaction. Overall, the quality improvement interventions did not adversely impact patient outcomes (14). For health care organizers or practice administrators, there will be opportunity costs, namely that the time and money could be spent elsewhere beyond audit and feedback. None of the included studies addressed this aspect.</td>
</tr>
<tr>
<td>Resource use, costs and/or cost-effectiveness</td>
<td>The reporting of costs is limited and typically includes only drug costs rather than costs associated with implementation of the intervention and a cost-benefit analysis. Resources required for programme implementation were often not reported. Only some studies reported programme costs covering administration costs, seminar preparation and seminar delivery. One study showed, in the cost-effectiveness analysis, that a postal prescribing feedback service would cost 88 euros per percentage change in prescribing practice compared with 778 euros for an individual prescriber adviser service. (14). A significant decrease (p=0.004) in drug costs was reported following introduction of an individualized feedback programme in another study. There was a non-significant increase in drug costs in the comparator group – where minimal intervention was applied (52). Implementing AMS programmes in the hospital setting may be cost-effective (53). However, comprehensive cost-effectiveness data remain relatively scant, underlining the need for more prospective clinical and epidemiological studies to incorporate robust economic analyses into clinical decisions.</td>
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</table>
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)

Audit and feedback may not be sustainable if an intervention is removed. In one RCT, after the termination of audit and feedback, the prescribing of broad-spectrum antibiotics returned to a level above baseline, suggesting that the intervention must be sustained. In a follow-up qualitative study, some clinicians expressed skepticism and discounted the reports. Furthermore, in a recent RCT of high-prescribing physicians across Switzerland, receiving letters and an online log-in code with information about antibiotic prescribing did not impact antibiotic prescribing over two years. Only 11% of physicians in the intervention group viewed their prescribing data. Similarly, a CRT of an audit and feedback dashboard led to no difference in antibiotic prescribing for ARI visits, but only 28% of intervention group physicians used the dashboard. These clinicians had a lower ARI antibiotic prescribing rate (42% versus 50%) (45).

In one systematic review, clinician education with audit and feedback was less effective than clinician education alone (14). However, many potential confounders in the studies were identified and authors noted that the overall quality of the studies was fair. In another review, a high risk of bias was found across all studies (48).

Many of the interventions evaluated in the reviews were multifaceted and therefore, in most studies, the effects of different intervention components could not be distinguished. Audit and feedback were combined in most studies with dissemination of guidelines and education of the physicians.

While only a few studies were replicated or provided long-term results, it is unclear how long the improvements would persist after intervention. Also, there is a lack of studies looking for improvements in clinically meaningful outcomes, such as patient and microbial outcomes, in addition to the usual prescribing outcomes.

Interventions which took place within AMS programmes and were combined with clinical decision support or educational activities were most effective (14, 46).

General practitioners thought that management of ARI is complex. AMS interventions were viewed as opportunities to reflect on prescribing patterns (through personal and local feedback), opportunities for learning (particularly discussions with peers creating a uniform practice), facilitators of more patient-centred care (through opportunities to educate patients and a better understanding of patient wishes), and ways to possibly reduce workload.
(contd) Stakeholders’ views and experiences

<table>
<thead>
<tr>
<th>Category of finding</th>
<th>Key findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>(contd) Stakeholders’ views and experiences</td>
<td>(although there were concerns about the possibility of additional costs and longer consultation times) (14). Key components associated with the success of the intervention in significantly reducing antibiotics prescription were listed as: the comfort of practitioners discussing prescribing practices with peers within their continuing medical education group; provider willingness to reflect on baseline reports of their prescribing practice; and the use of tutors who were general practitioner colleagues and who had a high level of enthusiasm and dedication (14).</td>
</tr>
</tbody>
</table>
IMPLEMENTATION CONSIDERATIONS

Even though the policy options that are examined in this evidence brief for policy are effective in principle, it is necessary to consider barriers to implementation in practice. This requires consideration of the local context of Estonia – including its health care system, cultural context and political institutions.

Up-to-date clinical guidelines about antibiotic prescription and use are prerequisites for a successful policy strategy in this area. These are missing in Estonia, and their development needs to be treated as a high-priority policy issue. AMR itself needs more recognition and prioritization in Estonia in order to ensure appropriate resource allocation to prevent AMR and promote appropriate prescribing of antibiotics. On the positive side we found that there are already multiple existing activities in place in Estonia that are helpful in terms of implementing the recommendations from this evidence brief into practice, and with many of them there is no need to start from scratch. Another high-level opportunity is the potential inclusion of the policy options within the human health AMR action plan which is being developed in Estonia.

There are also a number of implementation considerations that are specific to the three options set out in this report, which are detailed in this section. This section utilized the information from the systematic reviews on the problem and policy options, but as implementation was mostly not covered in these studies, the chapter relies on the knowledge and expertise of the study group, which is validated through local stakeholder consultations.

**Option 1. Strengthening post-graduate education and continuing the education of primary care clinicians about the appropriate use of antibiotics and AMR**

There are potential barriers to the implementation of option 1 at three levels. At the professional level, time constraints hinder educational activities, especially if the training takes place away from the workplace. A language barrier may also play a role for some Russian-speaking HCW, as most of the training materials are currently in Estonian or English. At the organizational level, HCW training on AMR and antibiotic choice is not currently treated as a priority by professional societies, as it does not directly affect the treatment outcomes of a particular patient at a given time. At the system level, there are no AMS programmes in the outpatient setting and no updated national guidelines on antibiotic
prescription, which would form a solid basis for providing education. Overall, education about AMR is not seen as a priority that needs resource allocation.

There are several enablers which can support the implementation of proposed interventions. In Estonia, for PHCP, workplace-based training and online training are held for other topics, and these platforms can be used to develop an AMR education programme. AMS programmes are already implemented in hospital settings in Estonia, and knowledge and experience from these can be used and built on to introduce AMS programmes into primary care settings as well. In Estonia, there is a well-established framework and longstanding cooperation between the University of Tartu and the EHIF for developing evidence-based clinical guidelines (54).

Table 5. Potential barriers to implement policy option 1, strengthening post-graduate education and continuing the education of primary care clinicians about the appropriate use of antibiotics and AMR

<table>
<thead>
<tr>
<th>Level</th>
<th>Barriers</th>
<th>Counterstrategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional</td>
<td>Time constraints, especially if the training takes place away from the workplace</td>
<td>Workplace-based training, online training</td>
</tr>
<tr>
<td></td>
<td>Language barrier for some Russian-speaking HCW, as most of the training materials are in Estonian or English</td>
<td>Provide protected time for physicians to engage in educational and training activities (as opposed to offering them as adds-on after working hours activities)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Provide training materials in Russian as well</td>
</tr>
<tr>
<td>Organization</td>
<td>Difficulties finding substitute clinicians if the training takes place away from the workplace</td>
<td>Workplace-based training, online training</td>
</tr>
<tr>
<td></td>
<td>Covering the costs of HCW training on AMR and antibiotic choice is not currently treated as a priority for organizations as it does not directly affect the treatment outcomes of a particular patient at a given time.</td>
<td>Provide financial support for the development and implementation of training on AMR by the state</td>
</tr>
</tbody>
</table>
Table 5. (contd)

<table>
<thead>
<tr>
<th>Level</th>
<th>Barriers</th>
<th>Counterstrategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>System</td>
<td>AMR not being seen as a priority</td>
<td>Public statements from the governmental agencies and key health and health professional organizations that AMR is a major public health problem that needs to be prioritized and resources allocated to avoid further deterioration</td>
</tr>
<tr>
<td></td>
<td>No AMS programmes for outpatient settings</td>
<td>Conducting campaigns directed to HCP and the general public to raise awareness on AMR</td>
</tr>
<tr>
<td></td>
<td>No updated national guidelines on antibiotic prescription as a basis for education – developing and periodically updating national guidelines to support rational antibiotic use is labor-intensive, requiring institutional and budgetary support.</td>
<td>Implementing AMS programmes that include education for PHCP in addition to the development of guidelines</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Supporting development and launching guidelines on antibiotic treatment by the state</td>
</tr>
</tbody>
</table>

**Option 2. Providing clinical decision support to PHCP for the prudent use of antibiotics**

Clinical decision support to PHCP for the prudent use of antibiotics can be added to the already existing system in Estonia, developed by the EHIF.

However, the implementation of option 2 could be hindered by the lack of awareness about excessive usage of broad-spectrum antibiotics in primary health care and AMR implications, and thus it may not be considered as a priority, by both the system (starting from the Ministry of Social Affairs) and health professionals (including PHCP). To overcome this obstacle, policy-makers should be briefed on both the problem and the most promising option(s) to overcome it. For professionals, option 2 should be combined with education on antibiotic usage through the system already in place in primary care. And, as an important prerequisite to option 2, national antibiotic treatment guidelines for PHCP should be developed. In Estonia, there is a well-established framework and good cooperation between the University of Tartu and the EHIF for developing evidence-based
clinical guidelines according to the internationally renowned Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach (54). The development of guidelines on antibiotic treatment of the most common infections in primary care should be prioritized by the state (the Ministry of Social Affairs and the EHIF), and appropriate funding provided. In addition, local data on bacterial susceptibility/antibiotic resistance would complement the CDSS.

Table 6. Potential barriers with counterstrategies to implementing policy option 2, providing clinical decision support to PHCP for the prudent use of antibiotics

<table>
<thead>
<tr>
<th>Level</th>
<th>Barriers</th>
<th>Counterstrategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional</td>
<td>Limited uptake of CDSS due to lack of understanding of the possible harms caused by broad- versus narrow-spectrum antibiotics, thus making CDSS seem irrelevant and unnecessary. Disagreement with current antibiotic prescribing guidelines (underlying the CDSS) and thus some hesitance in following the CDSS suggestions. Feeling restricted rather than supported or guided, as CDSS allows less independence in clinical decision-making. Concern about missing a more serious diagnosis. When not getting feedback on performance, losing interest in CDSS and decreasing its use over time.</td>
<td>Taking the following measures to ensure the uptake of and sustained use of CDSS – combining CDSS with other interventions, such as: → educating PHCP on AMR and prudent use of narrow- versus broad-spectrum antibiotics; → monitoring/auditing the use of antibiotics by PHCP; and → contextualizing feedback to HCP (i.e. comparing their personal prescribing data to local antibiotic treatment guidelines, and the prescribing patterns of colleagues). The above activities could be coordinated by the EHIF. Integrating support on prescribing antibiotics into the existing CDSS for PHCP in Estonia, developed by E HIF. Defining the main gaps in PHCP knowledge and attitudes towards AMR and prescribing antibiotics and designing the support system to address these gaps. A study could be initiated by the Ministry of Social Affairs and/or EHIF in cooperation with the Estonian Family Medicine Association.</td>
</tr>
</tbody>
</table>
### Table 6. (contd)

<table>
<thead>
<tr>
<th>Level</th>
<th>Barriers</th>
<th>Counterstrategies</th>
</tr>
</thead>
</table>
| **Organization** | The existing CDSS for PHCP in Estonia is not integrated into all the software programmes used by Estonian family doctors. | EHIF adding information on prudent prescribing of antibiotics into the already existing CDSS for PHCP  
Software developers making CDSS available in all computer programmes used by Estonian family doctors – currently it is available in two of three programmes.  
Software developers and/or institution/organization administration ensuring appropriate IT support to family doctors using the CDSS |
| **System** | No interest in (i.e. awareness and understanding) of AMR and prudent use of antibiotics (narrow- versus broad-spectrum antibiotics), and thus no central support to the option  
Up-to-date clinical guidelines are a prerequisite for CDSS. | Briefing decision-makers (starting from the Ministry of Social Affairs) on the threat of AMR and the solution (or at least one of the solutions, such as CDSS), and keeping them updated, either by regular meetings and/or a website on the topic  
Developing a key speaker for the topic (and policy option)  
Obtaining the highest level (e.g. political, starting with the Minister of Health and Labour) acknowledgement of the problem and support to the solution, so that providers (and their organizations) would feel central support for developing and implementing the option  
Conducting a national CDSS rapid cost-effectiveness analysis – this could be conducted by the health technology assessment unit at the University of Tartu.  
Prioritizing the development of national antibiotic treatment guidelines for primary care providers (by the Ministry of Social Affairs and EHIF) and ensuring appropriate funding clinical guideline development (from EHIF) |
Option 3. Using audit and feedback to improve prescribing behaviour

In Estonia, clinical audits have been organized by the EHIF since 2002. During an audit, patient treatment and treatment outcomes are assessed against specific criteria which are agreed by an expert group. The standards and criteria are usually based on treatment guidelines. The results of the audit are presented at a feedback event and follow-up is planned based on the audit recommendations. Summaries of the audit are available for the public.

Audit and feedback in improving antibiotic prescribing behaviour can be added into the already existing system developed by the EHIF. Such a strategy would guarantee the necessary financial and administrative support.

An important prerequisite for audit and feedback is the availability of national antibiotic treatment guidelines for primary care providers. Another prerequisite is availability of data. In Estonia, routinely collected electronic health care data (e.g. number of claims for treatment and number of prescriptions) are available at the level of the individual family doctor. One way in which current practice in antibiotic prescriptions may be improved is through the provision of individualized feedback on antibiotic prescribing to family doctors. The use of administrative datasets presents limitations as well as strengths. It is much less costly and less time-consuming compared to traditional methods of clinical audits, which use the patient’s records and sometimes require so-called content analysis. On the other hand, physicians often make individual choices based on the specificity of the patient’s problem or background data that cannot be estimated from routinely collected data. Therefore, even if routinely collected administrative data are used in audit, practitioners appreciate: an open and comfortable atmosphere for discussing prescribing practices, preferably with their peers; and the possibility to reflect on baseline reports of their prescribing. Studies show that doctors value the opportunity to clarify their rationale and considerations for decision-making (55).

<table>
<thead>
<tr>
<th>Level</th>
<th>Barriers</th>
<th>Counterstrategies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Professional</td>
<td>The intervention may cause distress because it is perceived as a threat to the usual clinical practice or institution.</td>
<td>Feedback should be individualized, non-punitive and actionable, so that the health professional receiving the feedback understands how to improve his/her practice.</td>
</tr>
</tbody>
</table>
### Table 7. (contd)

<table>
<thead>
<tr>
<th>Level</th>
<th>Barriers</th>
<th>Counterstrategies</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Organization</strong></td>
<td>Lack of clear guidelines for some conditions</td>
<td>Start from areas where best practice is clear and widely agreed, and focus on just a few primary indicators</td>
</tr>
<tr>
<td><strong>System</strong></td>
<td>Interventions are perceived as too costly or too time-consuming to fit into usual practice, and can be very labor-intensive. Interventions may require information technology support and/or the purchase of computerized surveillance systems. Success depends on the delivery method of feedback to prescribers; need good communication with practitioners</td>
<td>Availability of electronic patient record systems and routinely collected data In Estonia, there is a centralized audit body (EHIF) who manages the database and provides financial support in analysing data and designing and disseminating feedback. The provision of adequate support to programmes for audit and feedback (financial and human resources) Training of feedback providers about appropriate and provider-centred feedback methods Use of tutors who are other family doctors and who have a high level of enthusiasm and dedication</td>
</tr>
</tbody>
</table>
REFERENCES


16. Ravimite väljakirjutamise ja apteekidest väljastamise tingimused ja kord ning retsepti vorm [Conditions and procedure for prescribing and dispensing medicines from pharmacies and the form of the prescription]. Sotsiaalministri määrus 18.02.2005 nr 30. RT I, 06.01.2021, 15.


The following table provides definitions for the indicators presented in Table 1 in the main text of the evidence brief for policy.

**ANNEX 1. Quality indicators for antibiotic consumption in the community (primary care sector) in Estonia and other selected (neighbouring) countries, 2019 (2)**

<table>
<thead>
<tr>
<th>Quality indicators</th>
<th>Consumption</th>
<th>Relative consumption</th>
<th>Broad/narrow</th>
<th>Seasonal variation</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consumption</strong></td>
<td></td>
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</tr>
<tr>
<td>J01</td>
<td>J01_DID</td>
<td>Consumption of antibacterials for systemic use (J01) expressed in DDD per 1000 inhabitants and per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J01C</td>
<td>J01C_DID</td>
<td>Consumption of penicillins (J01C) expressed in DDD per 1000 inhabitants and per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J01D</td>
<td>J01D_DID</td>
<td>Consumption of cephalosporins (J01D) expressed in DDD per 1000 inhabitants and per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J01F</td>
<td>J01F_DID</td>
<td>Consumption of macrolides, lincosamides and streptogramins (J01F) expressed in DDD per 1000 inhabitants and per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J01M</td>
<td>J01M_DID</td>
<td>Consumption of quinolones (J01M) expressed in DDD per 1000 inhabitants and per day</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Relative consumption</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J01CE</td>
<td>J01CE_%</td>
<td>Consumption of beta-lactamase sensitive penicillins (J01CE) expressed as percentage of the total consumption of antibacterials for systemic use (J01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J01CR</td>
<td>J01CR_%</td>
<td>Consumption of combination of penicillins, including beta-lactamase inhibitor (J01CR), expressed as percentage of the total consumption of antibacterials for systemic use (J01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>J01MA</td>
<td>J01MA_%</td>
<td>Consumption of fluoroquinolones (J01MA) expressed as percentage of the total consumption of antibacterials for systemic use (J01)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Broad/narrow</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>J01</td>
<td>J01_B/N</td>
<td>Ratio of the consumption of broad-spectrum (J01(CR+DC+DD+(F-FA01))) to the consumption of narrow-spectrum penicillins, cephalosporins and macrolides (J01(CE+DB+FA01))</td>
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</tr>
<tr>
<td><strong>Seasonal variation</strong></td>
<td></td>
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</tbody>
</table>
| J01                | J01_SV      | Seasonal variation of the total antibiotic consumption (J01) Seasonal variation: Overuse in the winter quarters (January–March and October–December) compared with the summer quarters (April–June and July–September) of a one-year period starting in July and ending the next calendar year in June, expressed as percentage: \[
\frac{\text{DDD per 1000 inhabitants and per day (winter quarters) - DDD per 1000 inhabitants and per day (summer quarters)}}{\text{DDD per 1000 inhabitants and per day (summer quarters)}} \times 100
\]
| J01M               | J01M_SV     | Seasonal variation of quinolone consumption (J01M) |
The revised instrument, AMSTAR 2, retains 10 of the original domains, has 16 items in total (compared with 11 in the original), has simpler response categories than the original AMSTAR, includes a more comprehensive user guide, and has an overall rating based on weaknesses in critical domains. AMSTAR 2 is not intended to generate an overall score. A low rating based on AMSTAR 2 does not mean that the review should be discarded; it means merely that less confidence can be placed in its findings and that the review needs to be examined closely to identify its limitations.

The last two columns convey information about the utility of the review in terms of local applicability, equity, and issue applicability. The sixth column notes the proportion of studies that were conducted in Estonia. The final column indicates the review’s issue applicability in terms of whether or not it was addressed at the primary health care level or in outpatient settings.

All of the information provided in the annex tables was taken into account by the evidence brief for policy’s authors in compiling tables 2–4 in the main text of the evidence brief for policy.

### ANNEX 2. Systematic reviews relevant to option 1, strengthening post-graduate education and continuing the education of clinicians about the appropriate use of antibiotics and AMR

<table>
<thead>
<tr>
<th>Reference and option element</th>
<th>Focus of systematic review</th>
<th>Key findings</th>
<th>Time of last search</th>
<th>AMSTAR 2 (quality) rating</th>
<th>Proportion of studies that were conducted in Estonia</th>
<th>Proportion of studies included in the review that deal explicitly with health care professionals working in outpatient setting/primary care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satterfield J, Miesner AR,</td>
<td>Systematic review with</td>
<td>Educational interventions appear to be an integral</td>
<td>July 2019</td>
<td>low</td>
<td>None</td>
<td>18 out of 31 (58%)</td>
</tr>
<tr>
<td>Percival KM.</td>
<td>qualitative synthesis to</td>
<td>component of other interventions of AMS programmes;</td>
<td></td>
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<td></td>
<td>outline the methods and</td>
<td>however, there is a paucity of evidence to support</td>
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<tr>
<td></td>
<td>impact of many types of</td>
<td>use as a stand-alone intervention outside of regional</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>practical educational</td>
<td>public health interventions.</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>interventions on AMS</td>
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<td></td>
<td>outcomes in inpatient</td>
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<td></td>
<td>and outpatient settings</td>
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</tr>
<tr>
<td>Kyaw BM, Tudor Car L,</td>
<td>Summary of evidence on</td>
<td>Findings from studies deploying mobile or online</td>
<td>September 2018</td>
<td>moderate</td>
<td>None</td>
<td>8 out of 8 (100%)</td>
</tr>
<tr>
<td>van Galen LS, van Agtmael</td>
<td>the effectiveness of</td>
<td>modalities of digital education on antibiotic</td>
<td></td>
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<tr>
<td>MA, Costelloe CE, Ajuebor</td>
<td>digital education of</td>
<td>management were complementary and found to be more</td>
<td></td>
<td></td>
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<tr>
<td>O, et al.</td>
<td>antibiotic management</td>
<td>cost-effective than traditional education in</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>compared to traditional</td>
<td>improving clinical practice and postintervention</td>
<td></td>
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<tr>
<td></td>
<td>education for improving</td>
<td>knowledge, particularly in post-registration settings.</td>
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<tr>
<td></td>
<td>health care professionals’</td>
<td>There is a lack of evidence on the effectiveness of</td>
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<tr>
<td></td>
<td>knowledge, skills,</td>
<td>other digital education modalities, such as virtual</td>
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<tr>
<td></td>
<td>attitudes, and clinical</td>
<td>reality or serious games. Future studies should also</td>
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<tr>
<td></td>
<td>practice</td>
<td>include health care professionals working in settings</td>
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<td></td>
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<td>other than primary care and low- and middle-income</td>
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<td>countries.</td>
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</tr>
</tbody>
</table>
### Reference and option element

<table>
<thead>
<tr>
<th>Focus of systematic review</th>
<th>Key findings</th>
<th>Time of last search</th>
<th>AMSTAR 2 (quality) rating</th>
<th>Proportion of studies that were conducted in Estonia</th>
<th>Proportion of studies included in the review that deal explicitly with health care professionals working in outpatient setting/primary care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systematic review of interventions to reduce inappropriate use of antibiotics for ARIs</td>
<td>The moderate-strength evidence of reduced antibiotic prescribing and low-strength evidence of no adverse consequences was found for combined patient/clinician education (7% reduction, no change in complications/satisfaction).</td>
<td>January 2018</td>
<td>moderate</td>
<td>None</td>
<td>7 out of 95 (7%)</td>
</tr>
<tr>
<td>Evaluation of the effect of outpatient AMS programmes on prescribing, patients, microbial outcomes, and costs</td>
<td>Low- to moderate-strength evidence suggests that AMS programmes in outpatient settings improve antimicrobial prescribing without adversely affecting patient outcomes. Effectiveness depends on programme type. Most studies were not designed to measure patient or resistance outcomes. Data regarding sustainability and scalability of interventions are limited.</td>
<td>November 2013</td>
<td>moderate</td>
<td>None</td>
<td>13 out of 16 (81%)</td>
</tr>
<tr>
<td>Systematic review of educational programmes aimed at improving antibiotic prescribing by physicians and/or antibiotic dispensing by pharmacists, in both primary care and hospital settings</td>
<td>The studies included in the systematic review (a total of 78 studies) differed widely in design but mostly reported positive results. Outcomes measured in the reviewed studies were adherence to guidelines, total of antibiotics prescribed, or both, attitudes and behaviour related to antibiotic prescribing and quality of pharmacy practice related to antibiotics. The results show that antibiotic use could be improved by educational multifaceted interventions.</td>
<td>December 2011</td>
<td>low</td>
<td>None</td>
<td>46 out of 78 (59%)</td>
</tr>
</tbody>
</table>

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McDonagh MS, Peterson K, Winthrop K, Cantor A, Lazur BH, Buckley DI.


### ANNEX 3.1. Summary of systematic reviews relevant to option 2, providing clinical decision support to PHCP for the prudent use of antibiotics

<table>
<thead>
<tr>
<th>Reference and option element</th>
<th>Focus of systematic review</th>
<th>Key findings</th>
<th>Time of last search</th>
<th>AMSTAR 2 (quality) rating</th>
<th>Proportion of studies that were conducted in Estonia</th>
<th>Proportion of studies included in the review that deal explicitly with primary health care or outpatient settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Holstiege J, Mathes T, Pieper D.</td>
<td>Systematic review of RCTs and CRTs on the effectiveness of computer-aided CDSSs in improving antibiotic prescribing in primary care</td>
<td>Five of the seven trials showed that CDSS had a statistically significant slight to moderate effect on increasing the appropriateness of antibiotic treatment compared to no intervention. In the remaining two trials the difference between the study groups was not statistically significant.</td>
<td>November 2013</td>
<td>moderate</td>
<td>None</td>
<td>7 out of 7 (100%)</td>
</tr>
</tbody>
</table>

As no systematic reviews were retrieved that look at the effect of the intervention on prescribing broad-versus narrow-spectrum antibiotics, the same search strategy was performed without limiting the study design to systematic reviews and meta-analyses, and individual studies (presented in Annex 1.2) were used as evidence for option 2 in this evidence brief.

### ANNEX 3.2. Summary of individual studies relevant to option 2, providing clinical decision support to PHCP for the prudent use of antibiotics

<table>
<thead>
<tr>
<th>Reference and option element</th>
<th>Focus of study</th>
<th>Key findings</th>
<th>GRADE study quality rating</th>
<th>Study location</th>
</tr>
</thead>
<tbody>
<tr>
<td>Litvin CB, Ornstein SM, Wessell AM, Nemeth LS, Nietert PJ.</td>
<td>Use of an electronic health record clinical decision support tool to improve antibiotic prescribing for acute respiratory infections: the ABX-TRIP study. J Gen Intern Med. 2013; 28(6):810-6. Epub 2012 Nov 2.</td>
<td>Use of broad-spectrum antibiotics for ARIs encounters improved significantly — the estimated 27 months change in adults was -16.30% (95% CI -24.81% to -7.79%), and in children -16.30% (95% CI -23.29 % to -9.31%). The effect was sustained for 27 months.</td>
<td>High</td>
<td>Nine primary care practices in PPRNet, a practice-based research network, whose members use a common electronic health record (EHR) Charleston, South Carolina, USA</td>
</tr>
</tbody>
</table>

**CDSS**

Intervention also included some education and feedback
### Reference and option element
### Focus of study
### Key findings
### GRADE study quality rating
### Study location

<table>
<thead>
<tr>
<th>Reference and option element</th>
<th>Focus of study</th>
<th>Key findings</th>
<th>GRADE study quality rating</th>
<th>Study location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Eudaley ST, Mihm AE, Higdon R, Jeter J, Chamberlin SM.</strong> Development and implementation of a clinical decision support tool for treatment of uncomplicated UTI in a family medicine resident clinic. J Am Pharm Assoc. 2019; 59(4):579-85.</td>
<td>An observational study to develop and implement a CDS tool into the EHR of the study clinic to optimize antimicrobial prescribing for uncomplicated UTI</td>
<td>The rate of guideline-directed therapy was 85% (n = 23) with use of the CDS tool compared to 53% (n = 36) without the tool (OR = 4.34; 95% CI 1.148-12.73; p = 0.005). Overall fluoroquinolone use decreased from 42% to 15% after tool implementation (OR = 0.25; 95% CI 0.13-0.5; p = 0.001). Also, trimethoprim/sulfamethoxazole use decreased by 20% (OR = 0.21; 95% CI 0.45-0.955; p = 0.003); nitrofurantoin for cystitis increased by 31% (OR = 3.83; 95% CI 1.32-11.1; p = 0.01), and guideline-directed duration of therapy increased by 32% (OR = 4.34; 95% CI 1.48-12.73; p = 0.005).</td>
<td>Low</td>
<td>University-affiliated family medicine resident clinic Knoxville, Tennessee, USA</td>
</tr>
<tr>
<td><strong>Figueiras A, López-Vázquez P, Gonzalez-Gonzalez C, Vázquez-Lago JM, Piñeiro-Lamas M, López-Durán A, et al.</strong> Impact of a multifaceted intervention to improve antibiotic prescribing: a pragmatic cluster-randomised controlled trial. Antimicrob Resist Infect Control. 2020;9(1):195.</td>
<td>A cluster-randomised controlled trial to assess the effectiveness and return on investment (ROI) of a multifaceted intervention aimed at improving antibiotic prescribing for ARIs in primary care</td>
<td>The ratio of consumption of broad to narrow-spectrum penicillins, cephalosporins, and macrolides was -8.97% (95% CI -13.99% to -4.14%). The adjusted effect (change from baseline in percentage) on overall antibiotic prescribing attributable to the intervention was -4.2% (95% CI -5.3% to -3.2%). There were statistically significant improvements in 7 out of the 10 indicators (measured), with changes of: -4.23% (95% CI -5.26% to -3.21%) in total DID prescribed; -6.51% (95% CI -7.92% to -5.22%) in the use of penicillins; -3.89% (95% CI -6.18% to -1.65%) in the use of cephalosporins; and -3.45% (95% CI -5.23% to -1.70%) in the use of macrolides, lincosamides, and streptogramins. The cost of the intervention was €87 per physician. Direct savings per physician attributable to the reduction in antibiotic prescriptions was €311 for the NHS and €573 for patient contributions, with an ROI of €2.57 and €5.59, respectively.</td>
<td>High</td>
<td>Physicians at primary care health centres operated by the Spanish National Health Service Galicia, Spain</td>
</tr>
<tr>
<td><strong>Gifford J, Vaeth E, Richards K, Siddiqui T, Gill C, Wilson L, et al.</strong> Decision support during electronic prescription to stem antibiotic overuse for acute respiratory infections: a long-term, quasi-experimental study. BMC Infect Dis. 2017; 17(1):528.</td>
<td>An observational study to evaluate the long-term effectiveness of a CDSS interposed at the time of electronic (e-)prescriptions for selected antibiotics in outpatients with an initial visit for ARI</td>
<td>CDSS exposure was associated with guideline concordance. For azithromycin, the CDSS remained in place for the entire 8-year study period, and there was no significant difference in guideline concordance between the pre-withdrawal period (49/69 or 71.0%) and the post-withdrawal period (32/61 or 52.5%). There was also no significant difference in concordance for the other control group, 'All Other Antibiotics', between the pre-withdrawal period (44/268 or 16.4%) and the post-withdrawal period (62/478 or 13.0%). For gatifloxacin for which CDSS was not implemented for the 4.5-year post-withdrawal (of CDSS) period, guideline concordance decreased from 88.6% (39 of 44 visits) during the pre-withdrawal period to 51.3% (59 of 115 visits) post-withdrawal (p = 0.002). The corresponding adjusted odds of concordance compared to 'All Other Antibiotics' visits decreased from 24.4 (95% CI 9.0-66.3) pre-withdrawal to 5.5 (95% CI 3.5-8.8) post-withdrawal (p = 0.008).</td>
<td>Very low</td>
<td>Veterans Affairs Maryland Health Care System Baltimore, Maryland, USA</td>
</tr>
</tbody>
</table>
### Annex 3.2. (contd)

<table>
<thead>
<tr>
<th>Reference and option element</th>
<th>Focus of study</th>
<th>Key findings</th>
<th>GRADE study quality rating</th>
<th>Study location</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mainous AG 3rd, Lambourne CA, Nietert PJ.</strong>&lt;br&gt;Impact of a clinical decision support system on antibiotic prescribing for acute respiratory infections in primary care: quasi-experimental trial. J Am Med Inform Assoc. 2013; 20:317–24. CDSS</td>
<td>A quasi-experimental study assessing the effect of a CDSS integrated into an EHR on antibiotic prescribing for ARIs in primary care</td>
<td>In adult patients, prescribing of antibiotics in ARI episodes where antibiotics are inappropriate declined more (0.6%) among intervention practices than in control practices (+4.2%)(p = 0.03). However, among adults, the CDSS intervention improved prescribing of broad-spectrum antibiotics, with a decline of 16.6% among intervention practices versus an increase of 1.1% in control practices (p&lt;0.0001). A similar effect on broad-spectrum antibiotic prescribing was found in pediatric patients with a decline of 19.7% among intervention practices versus an increase of 0.9% in control practices (p&lt;0.0001).</td>
<td>Low</td>
<td>Practice Partner Research Network using the same EHR 9 states, USA</td>
</tr>
<tr>
<td><strong>Samore MH, Bateman K, Alder SC, Hannah E, Donnelly S, Stoddard GJ, et al.</strong>&lt;br&gt;Clinical decision support and appropriateness of antimicrobial prescribing: a randomized trial. JAMA. 2005; 294(18):2305–14.</td>
<td>A CRT to measure the added value of CDSS when coupled with a community intervention to reduce inappropriate prescribing of antimicrobial drugs for ARIs</td>
<td>In CDSS communities, rates of prescribing of antimicrobials belonging to the macrolide class decreased by 12% (p = 0.002) during the first intervention year and by 28% (p&lt;0.001) during the second intervention year but remained stable in the other communities. In total, 83% of the macrolide prescriptions were for azithromycin. Prescriptions of other drug classes – cephalosporins and penicillins – declined by 6% and 7%, respectively, in the CDSS communities in 2003 compared with 2001; yet neither change reached statistical significance. In the multinomial model, the reduction in odds of prescribing macrolides relative to penicillins was 50% in CDSS communities (p = 0.001). This corresponded with a decreased market share for macrolides in CDSS communities from 28% to 17% and increased market share for penicillins from 53% to 63%. In contrast, the odds of macrolide use relative to penicillins increased by 12% in community intervention communities (p = 0.22), corresponding with a stable market share of penicillins (52%–51%) and a slight increase for macrolides (22%–25%). The fraction of antimicrobial agents represented by cephalosporins did not change significantly in either group of communities.</td>
<td>Moderate</td>
<td>12 rural communities Utah and Idaho, USA</td>
</tr>
</tbody>
</table>
Annex 4. Summary of systematic reviews relevant to option 3, using audit and feedback to improve prescribing behaviour

<table>
<thead>
<tr>
<th>Option element</th>
<th>Focus of systematic review</th>
<th>Key findings</th>
<th>Time of last search</th>
<th>AMSTAR 2 (quality) rating</th>
<th>Proportion of studies that were conducted in Estonia</th>
<th>Proportion of studies included in the review that deal explicitly with primary health care or outpatient settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keller SC, Tamma PD, Cosgrove SE, Miller MA, Sateia H, Szymczak J, et al.</td>
<td>Ambulatory Antibiotic Stewardship through a Human Factors Engineering Approach: A Systematic Review. J Am Board Fam Med. 2018 May-Jun;31(3):417-430. doi: 10.3122/jabfm.2018.03.170225. PMID: 29743225 Free PMC article.</td>
<td>Human factors engineering is the ‘scientific discipline concerned with understanding interactions among humans and other elements of a system.’ Ambulatory settings were examined, and 42 quantitative studies and 17 qualitative studies met inclusion criteria. Effective interventions focused on tools and technology (e.g. clinical decision support and point-of-care testing), the person (e.g. clinician education), organization (e.g. audit and feedback and academic detailing), tasks (e.g. delayed antibiotic prescribing), the environment (e.g. commitment posters), and the external environment (e.g. media campaigns). Findings are more applicable to ARIs, the focus of most studies, as we were unable to identify many high-quality studies that implemented AMS for other conditions (e.g. UTI and cellulitis). A human-factors engineering approach suggests that investigating the role of the clinic’s processes or physical layout or external pressures’ role in antibiotic prescribing may be a promising way to improve ambulatory AMS. Audit and feedback and academic detailing had a positive impact on AMS. Regarding audit and feedback interventions, the following were found: audit and feedback interventions, where clinicians are compared with others, have had success. In a Canadian CRT where clinicians were mailed educational information or prescribing feedback, the feedback group was more likely to use first-line antibiotic prescriptions. In a CRT, comparing clinicians with top performers (those who seldom prescribe antibiotics inappropriately) decreased inappropriate prescriptions from 20% to 4%. In an RCT, antibiotic use decreased among providers who received a letter from England’s chief medical officer saying they were prescribing more antibiotics than 80% of local practices. An RCT found that the combination of clinician education and audit and feedback decreased antibiotic prescribing overall and broad-spectrum prescribing in particular. However, audit and feedback may not be universally successful. In the above RCT, after the termination of audit and feedback, prescribing of broad-spectrum antibiotics returned to a level above baseline. In a follow-up qualitative study, some clinicians expressed skepticism and discounted the reports. Furthermore, in a recent RCT of high-prescribing physicians across Switzerland, receiving letters and an online log-in code with information about antibiotic prescribing did not impact antibiotic prescribing over two years. Only 11% of physicians in the intervention group viewed their prescribing data. Similarly, a CRT of an audit and feedback dashboard led to no difference in antibiotic prescribing for ARI visits, but only 28% of intervention group physicians used the dashboard. These clinicians had a lower ARI antibiotic prescribing rate (42% versus 50%).</td>
<td>Databases were searched through November 7, 2016</td>
<td>Not rated</td>
<td>None of the included studies looked at Estonia</td>
<td>All of the studies looked into ambulatory care settings but not all were about audit and feedback or wide spectrum AB prescribing.</td>
</tr>
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</table>
### Annexes

<table>
<thead>
<tr>
<th>Option element</th>
<th>Focus of systematic review</th>
<th>Key findings</th>
<th>Time of last search</th>
<th>AMSTAR 2 (quality) rating</th>
<th>Proportion of studies that were conducted in Estonia</th>
<th>Proportion of studies included in the review that deal explicitly with primary health care or outpatient settings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnold SR, Straus SE.</td>
<td>Interventions to improve antibiotic prescribing practices in ambulatory care. Cochrane Database Syst Rev. 2005 Oct 19:2005(4):CD003539. doi: 10.1002/14651858.CD003539.pub2. PMID: 16235325 Free PMC article. Review.</td>
<td>Interventions to improve antibiotic prescribing practices in ambulatory care Use of printed educational materials or audit and feedback alone resulted in no or only small changes in prescribing. The exception was a study documenting a sustained reduction in macrolide use in Finland following the publication of a warning against their use for group A streptococcal infections. Interactive educational meetings appeared to be more effective than didactic lectures. Educational outreach visits and physician reminders produced mixed results. Patient-based interventions, particularly the use of delayed prescriptions for infections for which antibiotics were not immediately indicated, effectively reduced antibiotic use by patients and did not result in excess morbidity. Multi-faceted interventions combining physician, patient and public education in a variety of venues and formats were the most successful in reducing antibiotic prescribing for inappropriate indications. Only one of four studies demonstrated a sustained reduction in the incidence of antibiotic-resistant bacteria associated with the intervention. No single intervention can be recommended for all behaviours in any setting. Multi-faceted interventions where educational interventions occur on many levels may be successfully applied to communities after addressing local barriers to change.</td>
<td>1966–2002</td>
<td>Not rated</td>
<td>None</td>
<td>Ambulatory care</td>
</tr>
<tr>
<td>Davey P, Brown E, Charani E, Fenelon L, Gould IM, Holmes A, et al.</td>
<td>Interventions to improve antibiotic prescribing practices for hospital inpatients. Cochrane Database Syst Rev. 2013 Apr 30;4(4):CD003543. doi: 10.1002/14651858.CD003543.pub3. PMID: 23633313 Updated. Review.</td>
<td>Interventions to improve antibiotic prescribing practices for hospital inpatients The results show that interventions to reduce excessive antibiotic prescribing to hospital inpatients can reduce AMR or hospital-acquired infections. Interventions to increase effective prescribing can improve clinical outcome. The main comparison was between persuasive and restrictive methods. Persuasive methods advised physicians about how to prescribe or gave them feedback about how they prescribed. Restrictive methods put a limit on how they were prescribed; for example, physicians had to have approval from an infection specialist in order to prescribe an antibiotic. The meta-analysis supports the use of restrictive interventions when the need is urgent but suggests that persuasive and restrictive interventions are equally effective after six months. Overall, the 89 studies showed that the methods improved prescribing. In addition, 21 studies showed that the methods decreased the number of infections in hospitals. The restrictive methods appeared to have a larger effect than persuasive methods</td>
<td>1980–2009</td>
<td>Not rated</td>
<td>None</td>
<td>Hospital inpatients</td>
</tr>
<tr>
<td>Option element</td>
<td>Focus of systematic review</td>
<td>Key findings</td>
<td>Time of last search</td>
<td>AMSTAR 2 (quality) rating</td>
<td>Proportion of studies that were conducted in Estonia</td>
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<tr>
<td><strong>Davey P, Peden C, Charani E, Marwick C, Michie S.</strong>&lt;br&gt;Time for action- Improving the design and reporting of behaviour change interventions for antimicrobial stewardship in hospitals: Early findings from a systematic review. Int J Antimicrob Agents. 2015 Mar;45(3):203-12. doi: 10.1016/j.ijantimicag.2014.11.014. Epub 2015 Jan 7. PMID: 25630430 Review.</td>
<td>Improving the design and reporting of behaviour change interventions for AMS in hospitals – behaviour change techniques taxonomy</td>
<td>There is a strong evidence base regarding behaviour change techniques in other contexts that should be applied to AMS now if we are to further our understanding of what works, for whom, why and in what contexts. For example, there is good evidence to support inclusion of feedback and action planning in interventions to change human behaviour in general and the behaviour of health care professionals in particular. Feedback alone was only moderately effective, whereas combining it with goal setting and action planning was associated with significantly enhanced effectiveness of the audit and feedback intervention.</td>
<td>Up to December 2012</td>
<td>Not rated</td>
<td>None</td>
<td>Hospital settings</td>
</tr>
<tr>
<td><strong>Drekonja DM, Filice GA, Greer N, Olson A, MacDonald R, Rutks I, et al.</strong>&lt;br&gt;Antimicrobial stewardship in outpatient settings: a systematic review. Control Hosp Epidemiol. 2015 Feb;36(2):142-52. doi: 10.1017/ice.2014.41. PMID: 25632996.</td>
<td>To synthesize the evidence about the effectiveness of AMS programmes implemented in outpatient settings to optimize the use of antimicrobial agents</td>
<td>Authors identified 50 trials meeting eligibility criteria that were not included into the previous systematic review. Provider and/or patient education, guideline implementation, delayed prescribing, communication skills training, decision support, and laboratory testing interventions were generally associated with significant reductions in antimicrobial use. Results were less conclusive for provider feedback, formulary restriction, and financial incentives due to either mixed results across studies or few studies of the intervention type. Although differences in the intervention group compared to the control group were observed in both the number of antibiotic prescriptions and the reduction in broad-spectrum antibiotics, the strength of the evidence is considered low because of high-risk bias.</td>
<td>January 2000 – Nov 2013</td>
<td>Not rated</td>
<td>None of the studies provided in Estonia</td>
<td>Ambulatory care, mostly in primary care</td>
</tr>
</tbody>
</table>
### Option element

<table>
<thead>
<tr>
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<th>Proportion of studies included in the review that deal explicitly with primary health care or outpatient settings</th>
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</thead>
</table>
| Löffler C, Böhmer F.  
The effect of interventions aiming to optimise the prescription of antibiotics in dental care: A systematic review. PLoS One. 2017 Nov 14;12(11):e0188061. doi: 10.1371/journal.pone.0188061. eCollection 2017. PMID: 29136646. | Investigated: (1) which type of interventions aiming to optimize prescription of antibiotics exists in dentistry; (2) the effect of these interventions; and (3) the specific strengths and limitations of the studies reporting on these interventions. | Nine studies met these inclusion criteria. Five studies reported on the prescription of antibiotics in primary dental care and four studies focused on outpatient dental care. Interventions used in primary dental care included a combination of audit, feedback, education, local consensus, dissemination of guidelines and/or academic detailing. All studies successfully reduced the number of antibiotics prescribed and/or increased the accuracy of the prescription. Interventions most strongly associated with reducing the number of prescriptions for antibiotics include the establishment of internal guidelines and educational feedback on previous acts of prescribing antibiotics. The combination of audit, education, local consensus and dissemination of guidelines showed less pronounced but still high levels of reductions. However, most studies were confounded by a high-risk bias. | Up to June 2016 | Not rated | None | Primary dental care |
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