

Evidence brief for policy

EVIPNet Europe

Number 3

Antibiotic prescribing in long-term care facilities
for the elderly



Evidence-informed Policy Network (EVIPNet) Europe



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ABSTRACT

The Ministry of Health of Slovenia commissioned this evidence brief for policy, to be published under the aegis of the WHO European Evidence-informed Policy Network, to develop evidence-informed options for the country to consider in tackling the problem of prescribing broad-spectrum antibiotics to elderly people in long-term care facilities. Such treatment is taking place without proper diagnosis of infection and microbiological testing, and without indication, choice, dose or duration of therapy, thus representing the key driving factor for antimicrobial resistance. The work was carried out within the framework of the Biennial Collaborative Agreement between the Ministry of Health and WHO, involving high-level national policy institutions and national experts, and supported by the technical experts of WHO Regional Office for Europe. The Slovene National Institute for Public Health convened a working group comprising representatives from the clinical field, pharmacology, public health and health care management. The 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: surveillance, monitoring and audit/feedback on antibiotic consumption and antimicrobial resistance in long-term care facilities; development and implementation of guidelines and clinical pathways for diagnosing and treating infections; and continuous medical education for health care professionals and provision of health information to residents of long-term care facilities and their relatives /visitors.

KEYWORDS

Drug Prescriptions
Drug Resistance, Microbial
Long-Term Care
Anti-Bacterial Agents - therapeutic use
Homes for the Aged
Aged

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LIST OF ABBREVIATIONS

AB	antibiotic
ACE	angiotensin converting enzyme
ACSQHC	Australian Commission on Safety and Quality in Health Care
AMDA	Society for Post-Acute and Long-Term Care Medicine
AMR	antimicrobial resistance
AMSTAR	a measurement tool to assess reviews
APIC	Association for Professionals in Infection Control and Epidemiology
ARB	angiotensin receptor blockers
ASP	antimicrobial stewardship programme
CI	confidence interval
CCNC	Canadian Cochrane Network and Centre
CDC	Centres for Disease Prevention and Control
CME	continuous medical education
CYP	cytochrome P450 (protein/enzyme)
DDD	defined daily dose
DOTs	days of therapy
EARS-Net	European Antimicrobial Resistance Surveillance Network
EBP	evidence brief for policy
ECDC	European Centre for Disease Prevention and Control
ESAC-Net	European Surveillance of Antimicrobial Consumption Network
ESBL	extended-spectrum beta-lactamase
ESCMID	European Society of Clinical Microbiology and Infectious Diseases
EVIPNet	Evidence-informed Policy Network
GP	general practitioner
HAI	health care-associated infection

HIIS	Health Insurance Institute of Slovenia
ICM	Intersectoral Coordinating Mechanism
IDSA	Infectious Diseases Society of America
IEA	International Epidemiological Association
IMI	Institute for Microbiology and Immunology
ISID	International Society for Infectious Diseases
IT	information technology
LTCF	long-term care facility
MDR	multidrug-resistant
MRSA	methicillin-resistant <i>Staphylococcus aureus</i>
NICE	National Institute for Health and Care Excellence
NIJZ	National Institute of Public Health
NLZOH	National Laboratory of Health, Environment, and Food
PIDS	Pediatric Infectious Diseases Society
PPD	Program in Policy Decision-Making
RTI	respiratory tract infection
SHEA	Society for Healthcare Epidemiology of America
SKUOPZ	Slovenian National Antimicrobial Susceptibility Testing Committee
SSTI	skin and soft tissue infection
UTI	urinary tract infection
WHO	World Health Organization

KEY MESSAGES

What is the problem?

Residents of long-term care facilities (LTCFs) are often prescribed broad-spectrum antibiotics (ABs) without proper diagnosis of infection and microbiological testing. On average, between 25% and 75% of AB prescriptions in LTCFs for the elderly are inappropriate in terms of their indication, choice, dose or duration of therapy, representing the key driving factor for antimicrobial resistance (AMR) among LTCF residents. In addition, infections in LTCF residents are often caused by resistant microorganisms that compromise the efficacy of AB treatment and increase morbidity and mortality in the fragile LTCF population. High prevalence of drug-resistant infections leads to increased use of broad-spectrum ABs, further aggravating the problem of AMR.

What do we know about the three viable options to address the problem?

- **Option 1. Surveillance, monitoring and audit/feedback on AB consumption and AMR in LTCFs.**
 - Development of a system for proper surveillance, which includes monitoring of AB consumption and AMR, is an essential component of any successful antimicrobial stewardship programme (ASP) as it helps identify and quantify the problems.
 - The surveillance data are needed to assess the effectiveness of specific ASP interventions, for benchmarking and observation of trends, and to develop institution-specific guidelines.
 - Surveillance as a part of a good ASP has been well documented for hospitals; there are, however, few data on surveillance in LTCFs.
 - Audit and feedback strategies are a necessary component of ASPs.
- **Option 2. Development and implementation of guidelines and clinical pathways for diagnosing and treating infections.**
 - Guidelines for prudent use of ABs in LTCFs should be comprehensive and should include diagnostic criteria for common infections, and recommendations on appropriate diagnostic tests and empirical AB treatment, with instructions on de-escalation and duration of treatment. End-of-life situations should also be addressed by the guidelines.
 - Guidelines should focus on the types of infection that are most common in LTCF settings: urinary tract infections (UTIs), respiratory tract infections (RTIs), and skin and soft tissue infections (SSTIs).
 - Guidelines for AB prescribing in LTCFs should be contextualized and implemented after broad consensus within professional societies.

- **Option 3. Continuous medical education (CME) for health care professionals and provision of health information to LTCF residents and their relatives/families/visitors.**
 - CME increases health care professionals' knowledge and influences physicians' behaviour and patient outcomes.
 - Education as one of the ASP interventions has been recommended in the Infectious Diseases Society of America (IDSA) guidelines and by the AMDA – the Society for Post-Acute and Long-Term Care Medicine in the United States. Education, together with other interventions, is a crucial part of guidelines implementation.
 - Education should be provided for all health care workers.
 - In addition to the CME of health care professionals, health information on the optimal use of ABs should be shared with LTCF residents and their relatives and visitors on a regular basis, using standardized procedures to ensure optimal collaboration and satisfaction.

What implementation considerations need to be borne in mind?

Awareness of AMR is increasing worldwide. Experiences with ASPs are already being observed in hospitals and outpatient facilities, along with several examples in LTCFs that may facilitate the introduction of ASPs in LTCFs in Slovenia.

The main barriers to delivering a functional and effective ASP are the lack of personnel and/or funding; other competing initiatives that are afforded higher priority by the management; lack of commitment from leadership at LTCFs; opposition from physicians/prescribers; lack of information technology (IT) support; limited resources (including personnel) at LTCFs to conduct data analysis and tracking, or to share information and feedback; along with limited ability to obtain, upload and/or update surveillance data.

To overcome the barriers to implementing an ASP it was suggested to: increase the awareness and commitment of managers and other stakeholders; allocate enough funding to staffing and resources; develop local guidelines; and introduce e-prescribing or electronic systems that mandate the AB indication and duration of treatment, in compliance with guidelines.

EXECUTIVE SUMMARY

Both in Slovenia and worldwide, a growing number of elderly people reside in LTCFs. Existing research has shown that LTCF residents are often prescribed broad-spectrum ABs without proper indication, infection diagnosis or microbiological tests. The choice of AB, dose and duration of therapy are often inappropriate, and this kind of inappropriate AB use is a key driving factor for AMR in LTCFs.

According to two European point-prevalence studies on health care-associated infections (HAIs) in European LTCFs (HALT-1 and HALT-2) conducted in 2010 and 2013, the average prevalence of antimicrobial use in European LTCFs was 4.3% and 4.4%, respectively. The prevalence of AB use in Slovene LTCFs, according to a study conducted in 2017, was 2.3%. Despite relatively low AB use in Slovene LTCFs, the spectrum of AB use is problematic and related to an increase in AMR. In most cases, the residents in Slovene LTCFs received co-amoxiclav and fluoroquinolones, which are broad-spectrum ABs with strong AMR selection potential. The use of microbiological tests was extremely low, and approximately one fifth of the LTCF residents who received ABs were colonized with a multidrug-resistant (MDR) microorganism.

Consequences of inappropriately prescribed ABs, which account for 25–75% of ABs prescribed in LTCFs, range from increased costs and a higher possibility of drug interactions to undesirable effects/adverse drug events (promotion of AMR, and infection caused by *Clostridium difficile*). These consequences lead to higher morbidity and mortality, as well as increasing health care costs.

Various surfaces of the body are covered by normal bacterial flora (colonization) – for example the skin, or the bowel – and are exposed to the environment, resulting in possible transfer of bacteria that can cause infection under certain conditions. Frequent AB therapy, alongside other factors, leads to development of AMR in the bacteria colonizing the body. Other factors for acquisition and promotion of resistant bacteria in LTCFs include living in an enclosed environment, with limited mobility; repeated interactions between residents, staff and visitors; and frequent contact with hospital environments. High resistance rates consequently compromise the efficacy of AB treatment, increasing morbidity and mortality in the LTCF population. High prevalence of AMR leads to increased use of broad-spectrum ABs, which further aggravates the problem.

Studies show that LTCFs are a unique setting in terms of AB use and that several factors influence AB prescribing in such environments. Uncertainties can arise in diagnosing infections in elderly patients because typical signs and symptoms of infections are often absent or blunted in the elderly. Furthermore, physicians often rely on nursing staff to provide information on residents' symptoms and status. Colonization (i.e. presence of bacteria without signs and symptoms of infection) can be mistaken for infection and treated with ABs. Use of diagnostic tools in LTCFs is often limited or unavailable, particularly microbiological tests; this can lead to diagnostic uncertainty and consequently to unnecessary AB prescribing. All these factors need to be addressed when tackling inappropriate AB use in LTCFs.

This evidence brief for policy (EBP) was produced to support Slovene policy-makers and other decision-makers in formulating evidence-informed policies, strategies and interventions. The background to it is described in Box 1.

Box 1. Background to the EBP

This EBP mobilizes both global and local research evidence about AB prescribing in LTCFs, outlining three options for addressing the problem, and providing key implementation considerations. Whenever possible, the EBP summarizes research evidence drawn from systematic reviews of the research literature and occasionally from individual research studies. 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. The EBP does not contain recommendations.

The preparation of the EBP involved five steps.

1. A working group was convened, comprising representatives from the University Medical Centre Ljubljana, the Faculty of Medicine of the University of Ljubljana, and the National Institute of Public Health (NIJZ).
2. The terms of reference for the EBP were drafted and refined, focusing on framing the problem and drafting three viable options for addressing it.
3. Relevant research on the problem, options, and implementation considerations were identified, selected, appraised and synthesized.
4. The EBP was drafted in such a way as to present the evidence concisely and in accessible language. The evidence brief for policy advocates formulating recommendations for policy.
5. The brief was finalized after input from several reviewers.

The EBP was prepared to inform a policy dialogue at which 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.

Box 2: Mobilizing research evidence about the problem

Research evidence about the problem was sought from a range of published and “grey” research literature sources (Annex 1). Published literature that provided a comparative dimension to an understanding of the problem was sought, using three health services research “hedgies” in MedLine; namely, those for appropriateness, processes, and outcomes of care (which increase the chances of identifying administrative database studies and community surveys). Published literature that provided insights into alternative ways of framing the problem was sought, using a fourth hedge in MedLine; namely, one for qualitative research. Grey literature was also sought, by reviewing the websites of several national and international organizations, including the European Observatory on Health Systems & Policies, Health Evidence Network, Health Policy Monitor, Organisation for Economic Co-operation and Development, World Bank, and WHO (details provided in the later section on options for addressing the problem).

The first step was mobilizing research evidence about the problems associated with AB prescribing in LTCFs (see Box 2). Through literature research, three key options were identified for improving the use of ABs in LTCFs. The research provided 12 systematic reviews, 8 narrative reviews, 10 position papers with recommendations, 14 studies and 2 letters containing personal views. The three options were supported by the data found in the research; however, it should be noted that these data mostly reflect the hospital environment.

The options selected (surveillance, monitoring and audit/feedback; guidelines; and education) are cornerstones of any efficacious ASP, are supported by the results of the research conducted, and address the problems of AB prescribing and AMR.

Surveillance, monitoring and audit/feedback are essential parts of an ASP that help to identify the problem and determine the efficacy of specific individual interventions or a bundle of interventions. They recommend the following actions.

- » Monitoring AB consumption helps identify problematic areas and determines the efficacy of a specific intervention (or interventions). It also tracks the efficacy of ASPs over time.
- » Monitoring AMR with cumulative antibiograms provides insight into local susceptibility and helps guide local AB prescribing.
- » Monitoring infections and colonization with MDR bacteria is also important from the viewpoint of developing guidelines, and it helps to determine the effect of the implemented interventions.
- » Monitoring *C. difficile* infections, as a serious adverse event resulting from AB therapy, is essential.
- » Audit and feedback strategies are a necessary component of ASPs and are associated with lower levels of systemic AB prescribing. They are helpful in improving prescribing patterns and habits.

Implementation of guidelines has been proven to be one of the most successful ASP strategies. Guidelines for prudent use of ABs in LTCFs should be comprehensive and include certain key recommendations.

- » Diagnostic criteria are needed to initiate AB therapy. Since ABs are often inappropriately prescribed in LTCFs, it is recommended that any guidelines trying to improve AB prescribing must include diagnostic criteria that need to be fulfilled in order to start AB treatment.
- » Empirical AB therapy for most common infections (UTIs, RTIs, SSTIs) should form part of any recommendations for ASPs in LTCFs, tailored to local resistance data.
- » An important element of good AB prescribing is evaluation or reassessment of the treatment 2–3 days after its initiation. Post-prescribing review and de-escalation interventions have had a significant impact on AB prescribing in hospitals.
- » Guidelines should also be developed for LTCF residents in end-of life-situations, for whom only comfort measures are provided.
- » To be relevant and accepted, guidelines should be developed and implemented in consensus with representatives of health care professionals (or their associations) that provide care in LTCFs. Implementation can be driven by mandatory regulatory measures relating to antimicrobial stewardship, since LTCFs are regulated by law and are required to meet national standards. Special attention should be paid to encouraging the implementation of guidelines through education.

CME and providing **health information** are also important factors in successful ASP strategies.

- » CME increases health care professionals' knowledge and influences their behaviour, as well as patient outcomes. CME has the greatest effect when health care professionals search for answers to questions that arise directly from the clinical practice setting, rather than at an arbitrary time designated for CME. The use of learning portfolios and information provision can be integrated with self-directed CME to help foster a lifelong learning approach. Education is a crucial part of ensuring guidelines are appropriately implemented, and is recommended by several medical associations (including in the IDSA guidelines and by the ADMA in the United States) as one of the key ASP interventions.
- » Continuity of skills and competences relating to AB prescribing in LTCF settings should be assured via a system of CME credits, required for the licensing of physicians and nurses through the relevant professional regulatory boards.
- » In addition to receiving CME themselves, health care professionals should provide health information to LTCF residents and their relatives and visitors on a regular basis, using standardized procedures to ensure optimal collaboration and satisfaction.

Implementation of an ASP imposes additional financial constraints and places an additional workload on the personnel involved. Lack of good data – specific to LTCFs, both to guide the development of local guidelines and taking into consideration local AMR patterns – is a location-specific barrier to implementation. Lack of knowledge on the importance of an ASP also weakens preparedness for implementation, and there is a lack of IT capacity at national level in Slovenia to support surveillance, monitoring and audit/feedback.

Key facilitators to delivering a functional and effective ASP are: increasing the awareness and commitment of managers at LTCFs, along with other stakeholders, by allocating sufficient resources for personnel, education and materials; developing local guidelines; and introducing e-prescribing or electronic systems. It is also important to provide sufficient personnel at LTCFs to conduct data analysis and tracking, share information and feedback, and to obtain, upload and/or update surveillance data. Implementation of an ASP can be driven by mandatory regulatory measures relating to antimicrobial stewardship, since LTCFs are regulated by law and are required to meet national standards. Some processes are already in place that address to a certain extent the problem of AB prescribing and AMR, and these could be used as a basis from which to improve.

THE PROBLEM

How the problem came to light

Two European Centre for Disease Prevention and Control (ECDC) studies on antimicrobial prescribing in LTCFs that included a few Slovene facilities, along with the recent nationwide study, revealed that AB use in Slovene LTCFs is lower than in many other European countries; however, more detailed analysis highlighted the poor quality of AB prescribing in these facilities (ECDC, 2014a, 2014b). Despite low AB use, many residents in Slovene LTCFs are colonized with MDR microorganisms (Stepan et al. [in press]). Other important factors included the ageing of the population in Slovenia, the increasing number of elderly people residing in LTCFs, and the high prevalence of antimicrobial use among the elderly. The recent reorganization and inclusion of long-term care under the auspices of the Ministry of Health provided a window of opportunity to try to increase implementation of the relevant interventions. A meeting of public health medicine and infectious diseases specialists, general practitioners (GPs) and Ministry of Health officials was held to discuss the Evidence-informed Policy Network (EVIPNet) approach to preparing the EBP on the introduction of ASPs in Slovene LTCFs. The group received support from the WHO Country Office in Slovenia as well as the WHO Regional Office for Europe (both the Secretariat of EVIPNet Europe at the Division of Information, Evidence, Research, and Innovation, and the Control of AMR Programme at the Division of Health Emergencies and Communicable Diseases). The national working group was formed to prepare the EBP on AB prescribing/stewardship in LTCFs for the elderly in Slovenia.

The Intersectoral Coordinating Mechanism (ICM) for AMR at the Slovene Ministry of Health was designated to serve as the steering committee for developing this EBP. In the first phase of the work, stakeholder mapping was conducted to identify and to develop a good understanding of the most important policy-makers (both elected officials and civil servants), stakeholders (including managers from service provider organizations and representatives of professional associations), and researchers involved in AMR work in Slovenia. Due to the selection of the topic for the EBP, the mapping was focused on AMR in LTCFs, and in particular on AB prescribing.

The relevant stakeholders were identified and invited to participate in the EBP preparation working group as key informants. The decision to include the participants in the group was based on their personal preferences, but also their current involvement in AMR activities.

Extent of the problem

Global results show that ABs are prescribed to many LTCF residents, and several studies have shown that they are often inappropriately prescribed, which has many untoward consequences for the LTCF residents and the elderly population. About 20% of the European population with functional limitations aged over 65 years live in LTCFs; about 30% receive formal care at home and the remaining 50% of elderly individuals rely on informal care or receive no care at all.

In the coming decades, the population with functional limitations is projected to increase by about 120% and the number of people receiving formal care in institutions will rise by about 130% on average (ECB, 2006; Giannakouris, 2008; Onder et al., 2012; Pickard et al., 2008). In 2017, 19.1% of the general population in Slovenia was aged over 65 years (SURs, 2018), and by the end of 2060, the number of people in this age group is predicted to reach 33.4% (Vernon, 2011). A clear consequence of the growing ageing population is increased residency in LTCFs for the elderly (Knickman & Snell, 2002).

In Slovenia, there are 98 LTCFs, with more than 20 000 elderly people residing in them (1% of the population). The Slovene LTCFs are rather large; in the ECDC point-prevalence survey of infections in LTCFs (HALT-2) the mean size of an LTCF was 80 beds (ECDC, 2014b). The average number of elderly residents per LTCF in Slovenia is 200 and the largest LTCF has more than 800 residents.

An enclosed environment of this sort promotes frequent interactions among LTCF residents, family, caretakers and other staff (Kotnik Kevorkijan, Skok & Saletinger, 2015). This can lead to higher infection rates among the vulnerable LTCF residents, with associated chronic diseases and immune function issues (Chesley, 2014). Frequent contact of LTCF residents with the health care environment and the difficulties associated with performing infection control measures in a home-like environment (as is the case in LTCFs) contribute to high colonization rates and infections with resistant microorganisms. In some cases bacteria are only present on the surfaces of the body (colonization), while in other cases the same bacteria may cause infection. Often patients who are only colonized are treated unnecessarily, which is another facet of the problem, contributing to the development of AMR (Montoya, Cassone & Mody, 2016; Dyar et al., 2014).

Owing to limited mobility, often unavailable or distant access to laboratory and/or microbiology services and specialist health care, GPs often decide to prescribe ABs only empirically and without any microbiological diagnostics. This is particularly frequent in the case of UTIs, with the intention to avoid prolongation and/or complications associated with any infection (Murray et al., 2014; McClean et al., 2012). Another major problem is the recognition of infections and clear diagnosis, as clinical symptoms are often absent or nonspecific among elderly patients (Fleming-Dutra et al., 2016; Faulkner, Cox & Williamson, 2005).

In fact, AB use in the elderly population in Slovenia is much higher than in other adult age groups (Čižman et al., 2016). In general, outpatient AB use represents around 90% of total AB use, with more than half of these prescriptions being either unnecessary or inappropriate (Dyar et al., 2016). The two European point-prevalence studies on HAIs in European LTCFs (HALT-1 and HALT-2) were conducted in 2010 and 2013 and Slovenia provided a representative sample of LTCFs in the HALT-1 study (ECDC, 2014a). The prevalence of AB use in Slovene LTCFs found in the HALT-1 study was 2.3% (range: 0.5–4.1%). The nationwide study performed in 2016 also showed similar AB prescribing rates, with a prevalence of 2.4% (range: 0.0–7.6%). Despite relatively low AB use in Slovene LTCFs, the spectrum of AB use is problematic, resulting in an increase in AMR. In most cases, the residents in Slovene LTCFs received co-amoxiclav and fluoroquinolones, which are broad-spectrum ABs with strong AMR selection potential. The use of microbiology tests was extremely low, and approximately one fifth of the LTCF residents who received ABs were colonized with MDR microorganisms (Stepan et al. [in press]).

Estimates from other international studies showed that 25–75% of AB prescriptions in LTCFs are inappropriate in terms of their indication, choice of AB, dose or duration of therapy, and therefore unnecessarily potentiate the problem of AMR among LTCF residents (Beckett, Harbarth & Huttner, 2015; Van Buul et al., 2012; Flokas et al., 2017). Hence, it is crucial to map and analyse AB prescribing practices in Slovene LTCFs.

Consequences of AB prescribing in LTCFs for the elderly

AB therapy has several consequences, spanning from health effects to socioeconomic issues, for individuals as well as at the population level. The following subsections describe some of the consequences of unnecessary AB prescribing in LTCFs.

Drug interactions

LTCF residents usually have high prevalence of polypharmacy, which can lead to higher incidence of drug interactions and therapeutic duplications. Studies have identified significant potential for drug interactions in most institutionalized geriatric patients and the risk for interactions in this population is more prominent, since they can have several risk factors (e.g. a decrease in overall hepatic metabolic function through the cytochrome P450 (CYP) enzyme system, along with impaired renal function) (Alves-Conceição et al., 2017).

Some drugs, including ABs such as macrolides, are potent inhibitors of CYP3A4, responsible for the metabolism of many drugs (e.g. statins). Inhibition of CYP3A4 by macrolides can elevate the blood levels of certain drugs and cause severe consequences (e.g. rhabdomyolysis in combined macrolide and statin therapy), as was shown in one Canadian study (Patel et al., 2013). Bleeding can occur through the enhanced effect of the anticoagulant warfarin caused by antimicrobials, and antimicrobials can interact with sulfonylureas, causing hypoglycaemia (Jacobs, 2006; Schelleman et al., 2010). Trimethoprim/sulfamethoxazole was associated in older patients with several risk factors (impaired renal function and poor general health, in therapy with multiple potassium-increasing drugs, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) or spironolactone), leading to an increased likelihood of sudden death (Koronkowsky, Eisenhower & Marcum, 2016).

These consequences lead to higher morbidity and mortality and can be cause for hospitalization (Pea, 2015).

Undesirable effects/adverse drug events

In a report from the year 1999, LTCFs in the United States were identified as the most common site for adverse drug events, with more than 800 000 estimated prescription-related errors occurring annually (Rotjanapan, Dosa & Thomas, 2011). The extensive use of antimicrobials not only results in higher risk of adverse drug reactions, but also promotes AMR and *C. difficile* infection (Drinka et al., 2013; Malani et al., 2016). One of the reasons for high prevalence of *C. difficile* infection in LTCF residents is inappropriate antimicrobial use; other reasons include

low adherence to infection control interventions, ribotype distribution, and patient transfer from or within hospitals (Krishna et al., 2017). LTCF residents receiving ABs are eight times more likely to develop *C. difficile* infection, which can lead to hospitalization in 16% of the patients and a mortality rate of 23% within 30 days after hospital admission (Rotjanapan, Dosa & Thomas, 2011; Pawar et al., 2012). Antimicrobials can also have deleterious effects on various organs (e.g. kidneys) in elderly patients, which can cause organ failure (e.g. acute renal failure or deterioration of chronic kidney failure) (Pea, 2015).

AMR

ABs exert selective pressure on bacteria, which in turn is the main driver behind the development of various mechanisms of AMR. Colonization with MDR bacteria in LTCF residents was associated with many potentially modifiable risk factors, including recent AB use (Flokas et al., 2017). LTCF residents who had received antimicrobials had 2.4 times higher chance of colonization with *Enterobacteriaceae*, producing extended-spectrum beta-lactamases (ESBL-producing *Enterobacteriaceae*), and 3.1 times higher chance of colonization with methicillin-resistant *Staphylococcus aureus* (MRSA) (Ludden et al., 2015a). These facts were confirmed by several other studies. In a Slovene study, AMR of bacteria from clinical samples was higher in the age group over 64 years, in comparison to age group under 15 years, in certain cases (*Staphylococcus aureus*, *Enterococcus faecalis*, *Enterococcus faecium*, *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Haemophilus influenzae*) (Pirš et al., 2017).

Among LTCF residents and community-dwelling elderly, outbreaks of infections and colonization with MDR bacteria are reported (Giannella et al., 2016; Beckett, Harbarth & Huttner, 2015). Colonization serves as a reservoir for the spread of MDR bacteria in LTCFs and in the acute-care setting (Crnich et al., 2015; Fleming, Browne & Byrne, 2013; Ludden, et al., 2015b; Beckett, Harbarth & Huttner, 2015). In a recent nationwide point-prevalence survey in Slovene LTCFs, 5% and 16% of residents receiving ABs were colonized by MRSA and ESBL-producing Gram-negative bacteria, respectively (Stepan et al. [in press]).

AMR increases both the subsequent risk of fatal outcomes and health care costs (Drinka et al., 2013).

Costs

Annually, 50–80% of LTCF residents are prescribed at least one course of ABs (Dyar, Pagani & Pulcini, 2015; Van Buul et al., 2012). They are most frequently prescribed for RTIs, UTIs and SSTIs (ECDC, 2011; ECDC, 2014b). According to some studies, inappropriate AB prescriptions account for 25–75% of all AB prescriptions in LTCFs (Fleming et al., 2015; Stuart et al., 2012). Taking into consideration these two factors (high prescribing rate and high level of inappropriate AB prescribing), it is clear that the cost of AB prescribing could be significantly lowered.

Factors that influence AB prescribing in LTCFs for the elderly

Several factors were identified that influence AB prescribing in LTCFs (Table 1). These factors are diverse and include: clinical situation, diagnostics, LTCF characteristics, physicians' knowledge

Table 1. Factors influencing AB prescribing in LTCFs**Clinical situation**

A patient's clinical presentation is a vital factor influencing AB prescribing. Physicians decide to prescribe or not to prescribe an AB based on the patient's current and past medical history and clinical examination (Van Buul et al., 2014b). However, uncertainties around diagnosing infections in elderly patients can arise, particularly in cases in which history cannot be obtained owing to the patient's cognitive decline, hearing or speech difficulties and/or impaired mobility. Also, typical signs and symptoms of infections are often absent or blunted in elderly patients, and vague systemic symptoms (such as low-grade fever, confusion or weakness) can predominate (Dyar et al., 2014). Furthermore, colonization (presence of bacteria without signs and symptoms of infection) can be mistaken for infection and treated with ABs unnecessarily (Loeb et al., 2001a; Walker et al., 2000).

Diagnostics

Diagnostic tools are often limited/unavailable in LTCFs, particularly microbiological tests, which can lead to diagnostic uncertainty and consequently to inappropriate AB prescribing. Lack of on-site diagnostic resources leads to logistical problems that deter many physicians from performing diagnostic tests. Cultures are often not performed because of difficulties in obtaining quality urine samples or sputum (Fleming et al., 2015). Furthermore, physicians sometimes opt against aggressive diagnostics because it can cause discomfort to frail, elderly patients (Van Buul et al., 2014b). Finally, diagnostics mean additional treatment costs. Most Slovene elderly are covered by health insurance, based on the payments made during their working life. Physicians working in LTCFs receive per-capita payments for their services. Diagnostics are included in the per-capita payment, so the physicians frequently opt for empirical treatment, without carrying out expensive and complicated diagnostics (Van Buul et al., 2014b; Tratnik-Volasko, 2012).

LCTF characteristics

There are wide variations in the providers of medical care across different countries. In Slovenia, a primary care physician or GP regularly visits LTCFs (usually three times per week) and ensures continuity of care. When a doctor is needed out of hours (at night or weekends) a physician from the emergency department is called to check on a patient. Emergency department doctors are usually not familiar with LTCF residents. They rely on nursing staff to provide the information on resident's symptoms and status. They also have limited access to the patient's medical documentation and are not familiar with the expectations of the resident and family/caretaker's expectations; they are therefore more likely to readily prescribe ABs. Similar observations were also reported elsewhere (Van Buul et al., 2014b; Dyar et al., 2014; Fleming et al., 2015).

Table 1. (Contd)

Physicians' knowledge and perceived risks

Inappropriate AB prescribing can stem from unfamiliarity with guidelines and local resistance data (Fleming et al., 2015). Perceived risks can also play a role in the decision-making process and can lead to defensive prescribing. Side-effects and AMR are considered as risks of AB treatment and can sometimes deter a physician from prescribing an AB. Perceived risks of not treating are usually connected with situations of diagnostic uncertainty, which is when physicians are more prone to prescribing ABs. Thus, physicians could either not prescribe or overprescribe ABs, depending on their knowledge, information available to them, and the perceived risks (Van Buul et al., 2014b).

Influence of others

Nursing personnel play an important role in AB prescribing. On-call physicians, who are rarely familiar with LCTF residents, rely on nurses' assessment of symptoms and changes in clinical status, even though nurses are not trained to diagnose infections (Dyar et al., 2014). Studies show that nurse pressure can lead to increased AB prescribing (Fleming et al., 2015). Nurses can influence AB prescribing directly, by expressing a request for AB treatment, or indirectly, by performing diagnostics tests (most commonly a urine dipstick test) when they notice changes in urine appearance or odour (Walker et al., 2000).

Expectations of patients and their families/caretakers are usually considered by physicians, when deciding on AB treatment (Van Buul et al., 2014b; Fleming et al., 2015). On the other hand, physicians can also influence their colleagues through giving advice and by setting an example with their own prescribing practices (Van Buul et al., 2014b).

Influence of the environment

Socio-geographic factors can play a role in AB prescribing. AB practices vary in different countries, which can be attributed to different local resistance patterns, but also to cultural differences. According to some studies, physicians in the United States prescribe ABs more readily than those in Canada and Europe, in part because of the fear of litigation from the patient's family/caretakers in case of complications (Fleming et al., 2015; Loeb et al., 2004). Prescribing ABs at the end of life is also a controversial topic, and approaches can vary. In the Netherlands, physicians are more likely to withhold ABs in this scenario, compared to physicians in the United States, for example (Mehr et al., 2003).

AB prescribing in LTCFs is usually empirical, so guidelines are important for AB prescribers on the treatment of infections in LTCFs, tailored to local susceptibility data; however, very few guidelines exist specifically for this setting (Dyar et al., 2014).

and perceived risks, and the influence of others and the environment (Table 1). Studies on the topic include two reviews of literature (Dyar et al., 2014; Fleming et al., 2015), two focus group discussions/structured interviews (Van Buul et al., 2014b; Walker et al., 2000), two prospective observational cohort studies (Loeb et al., 2001b; Mehr et al., 2003) and a compendium of reports and discussions on the discrimination of elderly people in Slovenia (Tratnik-Volasko, 2012) (see the later section on equity-related observations about the problem).

Equity-related observations about the problem

The National Council of the Republic of Slovenia discussed the discrimination of elderly in terms of poverty, access to health care and social services, and other aspects of life in comparison with younger generations. This growing problem has been also recognized in other European countries. Special attention is needed to recognize and assess the inequalities that exist, and to start acting in order to ameliorate the problem. Elderly individuals represent a sensitive group regarding the availability of specialist health care, as they frequently depend on relatives or others for transportation and help with preventive services and treatment cooperation. However, most of the elderly in Slovenia are insured and have access to all levels of health care (Tratnik-Volasko, 2012).

A growing number of elderly people reside in LTCFs, where nursing care is provided, either with or without the assistance of medical staff and availability of psychosocial or rehabilitation services. An enclosed environment – with residents with limited mobility and repeated interactions between residents, staff, and visitors – provides the requisite elements for acquiring and spreading infections among the elderly, which in turn influences empirical AB use in the LTCF setting (Murray et al., 2014; McClean et al., 2012; Rainwater-Lovett, Chun & Lessler, 2014). Addressing the problem of AB prescribing and AMR in LTCFs will help to reduce inequities in elderly, but controlling AMR may also be beneficial in turn for other population groups.

THREE OPTIONS FOR ADDRESSING THE PROBLEM

Antimicrobial stewardship, by means of implementing an ASP, is seen to be one of the most effective ways to reduce AMR. The term antimicrobial stewardship is quite open and encompasses a variety of interventions that have at their core the aim of preserving a valuable resource. The interventions can roughly be divided into: (i) enabling interventions (such as educational activities, recommendations, audit and feedback); (ii) restrictive interventions (e.g. selective reporting of susceptibilities and closed formulary restrictions on AB use); and (iii) structural interventions (e.g. introduction of rapid microbial testing, measurement of inflammatory markers, and transition to computerized patient records and order forms) (Davey et al., 2017). ASP interventions are often implemented in combination and are therefore not very comparable across the literature. Implementation decisions are also related to the level of the health care system to which they apply, availability of suitable personnel (a team approach), and the broader health system context (in terms of funding, sustainability of the interventions and overall feasibility).

Most of the studies regarding ASPs have been carried out either in hospitals or at the primary care level (Davey et al., 2017; Drekonja et al., 2015; Schuts et al., 2016). LTCFs are a unique and understudied setting in terms of ASPs. Despite the lack of research into ASPs in LTCFs and the poor quality of data (Fleming, Browne & Byrne, 2013), recommendations that exist on ASPs in LTCFs (mainly based on expert opinion and data from studies performed in hospitals) include advice to introduce ASP strategies that have proved to be effective elsewhere, in order to use ABs more critically (Barlam et al., 2016a; Dyar et al., 2014; Jump et al., 2017; McElligott et al., 2017; Nicolle, 2014).

Several options could be selected to address the problem of AB prescribing in LTCFs. After reviewing the literature on ASPs in LTCFs and in hospitals, three options were put forward that were more prominent and most widely supported by the literature. These options are also recommended in the existing guidelines for ASP in LTCFs and hospitals in Slovenia.

The pros and cons of potentially viable options were assessed by the EBP working group and the ICM for AMR at the ministerial level (at the Slovene Ministry of Health), whereby the national multidisciplinary/multisectoral coordinating group (for human, animal and environmental health) facilitates and coordinates ASP priorities and guidelines among the key negotiating partners (Ministry of Health, the Health Insurance Institute of Slovenia (HIIS), the NIJZ, the National Laboratory of Health, Environment, and Food (NLZOH), and the Institute for Microbiology and Immunology (IMI)), for more in-depth review. The options selected are:

- » surveillance, monitoring and audit/feedback of AB consumption and AMR;
- » development and implementation of guidelines and clinical pathways for diagnosing and treating infections; and
- » CME for health care professionals and providing health information for the LTCF residents, caretakers, families and visitors.

Through literature research (see Box 3 for details), the three key options to improve AB use in LTCFs were identified.

Box 3: Mobilizing research evidence about options for addressing the problem

The available research evidence about options for addressing the problem was sought primarily from a continuously updated database containing more than 500 systematic reviews of delivery, financial, and governance arrangements within health systems (the Program in Policy Decision-Making (PPD)/Canadian Cochrane Network and Centre (CCNC) database. Furthermore, a systematic search of the peer-reviewed literature (PubMed and Scopus) and a comprehensive grey literature search were conducted, including the Google search engine and websites from the ministries of health, health care services, institutes of public health, the ECDC, WHO and scientific bodies in the field (including the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the International Society for Infectious Diseases (ISID) and the International Epidemiological Association (IEA)).

Titles and abstracts of the retrieved manuscripts were initially assessed, and non-relevant documents were ultimately excluded. For manuscripts from grey literature, executive summaries, tables of contents/tables and documents (whichever was available) were screened. The full text of the potentially eligible manuscripts was then obtained and assessed for relevance or duplication by all authors. Disagreements were resolved by review and consensus with all the co-authors. A total of 25 systematic reviews and 27 individual studies were retrieved and used in this EBP. The reviews were identified by first searching the database for reviews containing topic-related keywords in the title and/or abstract. The keywords included [antibiotic; antimicrobial; antibacterial; prescribing; prescribe; prescribed; prescription; use; administration; administering; administer; nursing home; long-term care facility for elderly; residential elderly home; residential aged care facility]. Additional reviews were identified by searching the database for reviews addressing features of the options that were not identified using topic-related keywords.

The review authors' key findings were extracted from the identified reviews. Each review was also assessed in terms of its quality (rated according to A Measurement Tool to Assess Reviews (AMSTAR)), local applicability (proportion of studies that were conducted in the country), equity considerations (proportion of studies that deal explicitly with prioritized groups) and the degree of focus on the issue (issue applicability to the Slovenian case). The overall evidence about the options was then summarized and relevant caveats introduced about the review authors' key findings, based on the quality, local applicability, equity, and issue applicability assessments.

Attention was paid to whether reviews contained no studies, despite an exhaustive search (i.e., 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 updating of the review could be commissioned if time allowed.

No additional research evidence was sought beyond what was included in the systematic reviews. Those interested in pursuing an option might want to search for a more detailed description of the option or for additional research evidence about it.

A summary of the systematic scientific and grey literature search and review of AB prescribing in LTCFs is presented in Annex 1.

Option 1. Surveillance, monitoring and audit/feedback

The focus in this section is on what is known about these selected options. In the next section, the focus turns to the barriers to adopting and implementing these three options and to possible implementation strategies to address the barriers.

Overview and context

Surveillance and monitoring quantify a problem and determine a baseline; in this case they are beneficial in helping to identify and quantify the problems of AB consumption and AMR. Implementing an ASP helps to determine the effectiveness of specific interventions.

Surveillance as a part of an ASP that functions well has been clearly documented for hospitals and there are several examples of experiences with ASPs in LTCFs (Kidd et al., 2016; Lim, Stuart & Kong, 2015; McElligott et al., 2017; National Centre for Antimicrobial Stewardship & ACSQHC, 2016; NCAS, 2018; Stuart et al., 2012).

Monitoring AB consumption and AMR has been recommended as a part of ASPs in LTCFs by the Association for Professionals in Infection Control and Epidemiology (APIC) and by the Society for Healthcare Epidemiology of America (SHEA) (Smith et al., 2008). The CDC guidelines for managing MDR bacteria also advise LTCFs to review antimicrobial consumption and resistance (CDC, 2006 (update 2017)). In Slovenia, surveillance of AB consumption is conducted as part of the European Surveillance of Antimicrobial Consumption Network (ESAC-Net) (ECDC, 2018b); surveillance of AMR is carried out as part of the European Antimicrobial Resistance Surveillance Network (EARS-Net) (ECDC, 2018a); and the national monitoring of AMR is accomplished by the Slovenian National Antimicrobial Susceptibility Testing Committee (SKUOPZ). Slovenia performs national point-prevalence studies on HAI prevalence and AB prescribing in acute-care hospitals, based on the ECDC protocol.

Specific recommendations on how to launch surveillance systems were found in the reviewed literature (Central Asian and Eastern European Surveillance of Antimicrobial Resistance (CAESAR); Global Antimicrobial Resistance Surveillance System (GLASS)) (WHO Regional Office for Europe, 2015; WHO, 2015). The implementation process for setting up ASPs in LTCFs was suggested in one review (covering issues such as leadership commitment, accountability, drug expertise, suggested actions, tracking, reporting, and education), and implementing surveillance was part of this process (McElligott et al., 2017).

Results of the literature review

The following systematic reviews and other publications/studies were found in the literature search and review (see the tables in Annex 2 for details, including the quality rating):

- five systematic reviews (Ivers et al., 2012; Fleming, Browne & Byrne, 2013; Drekonja et al., 2014b; Drekonja et al., 2015; Dik et al., 2015a);
- five reviews/narrative reviews (Dyar et al., 2014; Lim, Kong & Stuart, 2014; Nicolle, 2014; Crnich et al., 2015; McElligott et al., 2017);

- six recommendations/position papers (Smith et al., 2008; Nicolle et al., 2000; CDC, 2014; Barlam et al., 2016a; Jump et al., 2017; CDC, 2015);
- nine studies (Gugkaeva & Franson, 2012; McClean et al., 2012; Mylotte et al., 2013; Fleming et al., 2014b; Furuno et al., 2014; Doernberg, Dudas & Trivedi, 2015; Jump et al., 2015; Morrill et al., 2016; Campbell et al., 2017);
- two letters/personal views (Malani et al., 2016; Tacconelli et al., 2018).

Most of the studies regarding surveillance in ASPs were performed either in hospitals or at the primary health care level. The lack of studies regarding ASPs in LTCFs resulted in a scarcity of (systematic) reviews, recommendations and position papers. As such, hospital/primary care-level data will be used to advise on ASPs in LTCFs. The following sections outline in detail various aspects of surveillance and monitoring that are integral to successful ASPs.

Monitoring AB consumption

Recommendations of the Infection Advisory Committee at the AMDA in the United States for developing ASPs in LTCFs include developing and maintaining a system for monitoring AB consumption (Jump et al., 2017). The system should include periodic reviews of AB prescriptions in terms of indication, dose and duration. At least annually, AB use should be reviewed at facility level (and at the level of individual prescribers, if problematic) to identify misuse or overuse of ABs in total or within specific groups of ABs. Feedback on facilities' AB consumption should be provided to physicians, nursing staff, administration personnel and allied health care professionals (Jump et al., 2017). There are several metrics that capture AB use, such as days of therapy (DOTs), defined daily dose (DDD), and the start and end dates of each course of ABs. Ideally, an information professional and a pharmacist should work together to collect and analyse the relevant data (Jump et al., 2017). Whenever possible, patient-level data on AB consumption should be linked with surveillance data on infections caused by resistant microorganisms (Nicolle et al., 2000). The preferred type of monitoring of AB consumption in the SHEA/IDSA/Pediatric Infectious Diseases Society (PIDS) guidelines – bearing in mind that these are not LTCF specific – is DOTs, since there are more or important limitations associated with some of the other monitoring methods (such as DDD) (Barlam et al., 2016a).

Monitoring AMR and *C. difficile* infections

LTCFs should also develop and maintain a system to monitor AMR. At least annually, data on infections and colonization with resistant microorganisms connected with AB use (e.g. MRSA, ESBL, carbapenem-resistant Gram-negative bacilli) and infection with *C. difficile* should be reviewed (Drekonja et al., 2014a; Jump et al., 2017). Feedback regarding resistance data should be provided to all staff members of LTCFs (Jump et al., 2017). One narrative review suggests monitoring using point-prevalence studies or tracking resistance rates (e.g. number of events per month/resident days per month x 1000). The latter method allows a more accurate assessment of the impact of interventions (Crnich et al., 2015). One paper (not specifically focused on LTCFs) suggests coupling resistance monitoring with local-level, hospital-level and community-level resistance data (Tacconelli et al., 2018).

Cumulative antibiograms for a specific LTCF can be prepared from clinical samples sent to the microbiology laboratory (Crnich et al., 2015). They give insight into local susceptibility patterns and are helpful in choosing the most appropriate empirical AB therapy. The usefulness of antibiograms is well recognized in acute-care facilities, but their role in ASPs in LTCFs remains largely unknown (McElligott et al., 2017). However, since they can unmask differences in local susceptibility, they are an important tool for preparing optimized treatment recommendations and guidelines (Barlam et al., 2016a). A cross-sectional pre-test/post-test study, which evaluated the effect of the antibiogram on appropriate AB prescribing, found an increase in appropriate AB prescribing from 32% to 45%; however, the increase was not statistically significant (Furuno et al., 2014). According to the IDSA/SHEA/PIDS guidelines published in 2016, the evidence pointing to the development of stratified antibiograms is of low quality and the recommendation is weak (Barlam et al., 2016a).

Narrative reviews and position papers recommend developing tools to monitor AMR and *C. difficile* infections. Although the data supporting this measure (applicable to LTCFs) are insufficient, the notion of monitoring AMR and *C. difficile* infections is incorporated into some of the guidelines.

Audit with feedback

Audit and feedback strategies are a necessary component of ASPs; carrying out regular analysis is associated with lower systemic AB use (Dyar et al., 2014). Systematic reviews showed that prospective audits providing feedback to prescribers about their prescribing patterns have proved helpful in changing behaviour. Their effect seems to be greater when materials are provided as well to encourage a change in prescribing habits (such as guidelines), and/or when feedback is delivered by a supervisor or senior colleague, or when it is delivered more than once (Ivers et al., 2012; Fleming, Browne & Byrne, 2013). In a pharmacist-led prospective intervention, inappropriate AB treatment was reduced by 50% (Gugkaeva & Franson, 2012); a prospective audit with feedback on treatment of UTIs led to a reduction in AB prescribing for UTIs and other infections (Doernberg, Dudas & Trivedi, 2015). Two prospective studies on audit with feedback performed in a hospital setting demonstrated a trend towards decreasing broad-spectrum antimicrobial use, antimicrobial costs, and adverse drug events (Morrill et al., 2016; Campbell et al., 2017). One of the components of ASPs recommended by the AMDA is to ensure feedback at least annually on AB use and resistance data, with recommendations on facility-specific AB use practices (Jump et al., 2017). The combination of education with audit and feedback allows targeted physician feedback and therefore has an even more beneficial effect on improving physicians' prescribing habits (Doernberg, Dudas & Trivedi, 2015).

A systematic review on audit and feedback as a part of an outpatient ASP found mixed findings for prescribing outcomes and potential improved costs (Drekonja et al., 2014b). The same author published a systematic review on the effects of audit and feedback as a part of an inpatient ASP, which showed a decrease in the use of targeted antimicrobials and in excessive AB use, as well as improved (shorter) duration of therapy (Drekonja et al., 2015).

As described, audit and feedback can be used as a method to assess the quality of antimicrobial prescribing, but also to assess an individual patient, as a part of the ASP, supporting the

implementation of guidelines, and as an individualized form of education on AB prescribing. These concepts are explored further in the forthcoming sections on option 2 and option 3.

In Slovenia, recent partial data are available on colonization with MDR bacteria in LTCFs, along with data on AB consumption that are age specific; however, the data do not reflect the true picture of AB use in LTCFs (Stepan et al. [in press]). Also, national data are available on AMR patterns for certain bacteria isolated from clinical samples (Kolman et al., 2017). The current surveillance system could be upgraded by implementing the features described above. It could be made more facility-specific, to provide more detailed insight and serve as a starting point for targeted interventions.

A summary of key findings from systematic reviews and other studies and publications relevant to Option 1 is provided in Table 2.

Table 2. Summary of key findings from systematic reviews and other studies/publications relevant to Option 1: Surveillance and monitoring.

CATEGORY OF FINDING	KEY FINDINGS
Benefits	<ul style="list-style-type: none"> — Primary study: Unit-specific and/or physician-specific mean AB use and cost indicators have broad application for monitoring AB prescribing in LTCFs (Mylotte & Neff, 2003). — Recommendation/position paper: In acute-care settings, ASPs show efficacy in improving patient outcomes, reducing <i>C. difficile</i> infections and decreasing the prevalence of MDR bacteria (Jump et al., 2017). — Point-prevalence studies: Audits and feedback have little to moderate influence on professional practice and health care outcomes (McClellan et al., 2012). — Review/narrative review: Audit and feedback strategies are necessary components of ASPs and medication reviews that were conducted regularly were associated with lower systemic AB use in Northern Irish residential homes (Dyar et al., 2014).
Potential harms	<ul style="list-style-type: none"> — A systematic review found no possible harms associated with implementing ASPs in outpatient settings; however, there was limited reporting of return clinic visits, hospitalizations, and adverse events (including mortality) (Drekonja et al., 2014b).
Resource use, costs and/or cost-effectiveness	<ul style="list-style-type: none"> — No data specific to surveillance and monitoring are available on resource use, costs or cost-effectiveness.

Table 2. (Contd)

CATEGORY OF FINDING	KEY FINDINGS
<p>Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)</p>	<ul style="list-style-type: none"> — Review/narrative review: Further studies are needed to evaluate the effects of ASPs on facility and resident outcomes, including health care costs, as well as rates of infections caused by <i>C. difficile</i> and MDR bacteria (Crnich et al., 2015). — Review/narrative review: A combination of interventions targeted at different phases of the AB prescribing process requires more studies (Crnich et al., 2015). — Review/narrative review: Since several distinct activities are usually implemented simultaneously, the efficacy and relative importance of any single programme component is unknown. Some improvement in antimicrobial use is usually evident following the introduction of stewardship interventions (Nicolle, 2014). — Systematic review: Further studies are needed to evaluate economic benefit of ASPs (Dik et al., 2015b). — No data exist on the economic impact of ASPs in LTCFs. — No data exist on the value of cumulative antibiograms in LTCFs.
<p>Key elements of the policy option if it was tried elsewhere</p>	<ul style="list-style-type: none"> — Review/narrative review: LTCFs should take measures to monitor <i>C. difficile</i> infections and discuss the development of facility-specific antibiograms (Crnich et al., 2015). — Review/narrative review: AB use in LTCFs should be monitored in some manner (e.g. DDDs, DOTs) (Crnich et al., 2015). — Review/narrative review: IDSA guidelines recommend monitoring antimicrobial use and local antimicrobial susceptibility, with feedback to relevant authorities (Lim, Kong & Stuart, 2014).
<p>Stakeholders' views and experiences</p>	<ul style="list-style-type: none"> — No stakeholders' views or experiences were discussed in the systematic reviews.

Option 2. Development and implementation of guidelines and clinical pathways for diagnosing and treating infections

Overview and context

Implementing clinical guidelines for treating infections has been proven as one of the most successful ASP strategies (Davey et al., 2017; Schuts et al., 2016). There are currently no guidelines on AB prescribing in LTCFs in Slovenia. However, recommendations have been developed by professional societies on AB treatment of infections in hospitals and in the community that are widely accepted by health care workers (Čižman & Beović, 2013; Quiba, 2017). These recommendations could be adapted to the LTCF setting, with recommendations on empirical treatment tailored to AMR data among the elderly (Pirš et al., 2017).

Results of the literature review

The following systematic reviews and other publications/studies were found in the literature search and review (see the tables in Annex 2 for details, including the quality rating):

- five systematic reviews (Davey et al., 2017; Drekonja et al., 2015; Fleming, Browne & Byrne, 2013; Fleming et al., 2015; Schuts et al., 2016);
- five narrative reviews (Crnich et al., 2015; Dyar et al., 2014; McElligott et al., 2017; Morrill et al., 2016; Nicolle, 2014);
- three recommendations/position papers (Barlam et al., 2016a; Jump et al., 2017; Nicolle et al., 2000), five studies (Daneman et al., 2011; Mehr et al., 2003; Rotjanapan, Dosa & Thomas, 2011; Trautner et al., 2013; Zabarsky, Sethi & Donskey, 2008); and
- recommendations on palliative care by the Slovene National Medical Ethics Committee (Grosek, Grošelj & Oražem, 2015).

Guidelines for prudent use of ABs in LTCFs should be comprehensive and include: diagnostic criteria for common infections; and recommendations on appropriate diagnostic tests and empirical AB treatment, with instructions on de-escalation and duration of treatment (Jump et al., 2017). Guidelines should focus on infections that are most common in the LTCF setting: UTIs, RTIs and SSTIs (Dyar et al., 2014).

As multiple antimicrobial stewardship strategies are often implemented simultaneously, it can be hard to evaluate the effect of a single intervention. As a part of a multifaceted intervention, implementing guidelines can be an effective strategy in an LTCF setting. One systematic review of four randomized controlled trials conducted in LTCFs showed a modest and variable effect of a multifaceted intervention, in terms of success and sustainability (Fleming, Browne & Byrne, 2013). Interventions in all four studies included treatment algorithms or guidelines on AB prescribing, among other approaches, which included prescribing feedback and educational sessions for physicians and nurses. In two studies, inappropriate AB use was reduced significantly; in the other two, the reduction was not significant. It was also noted that the intervention had to be repeated at regular intervals to sustain its effect (Fleming, Browne & Byrne, 2013).

Diagnostic criteria for initiating AB therapy

Since initiation of AB treatment in LTCFs is often inappropriate – because ABs are prescribed for colonization (that is, presence of bacteria without signs and symptoms of infection, like asymptomatic bacteriuria), including for colonization of open wounds and for viral infections – it is recommended that any guidelines trying to improve AB prescribing must include diagnostic criteria that need to be fulfilled in order to trigger AB treatment (Jump et al., 2017). They should include the presence of certain clinical signs and symptoms, alongside microbiological investigations that need to be performed (Nicolle, 2014).

One of the most important targets to be addressed by guidelines for AB prescribing in LTCFs is the treatment of asymptomatic bacteriuria (i.e. presence of bacteria in urine, without signs and symptoms of infection), which was emphasized in the systematic and narrative reviews (Fleming, Browne & Byrne, 2013; Fleming et al., 2015; Crnich et al., 2015; Morrill et al., 2016) and recommendations/position papers (Dyar et al., 2014; Jump et al., 2017; Nicolle, 2014). Guidelines that targeted over-testing of urine samples and recommended testing urine only in LTCF residents with fever and/or localizing UTI symptoms succeeded in reducing the number of urine cultures ordered and the treatment of asymptomatic bacteriuria. Thus, one study found that treatment of asymptomatic bacteriuria reduced from 52% to 10% following the implementation of the intervention (Trautner et al., 2013). Another study showed a reduction in: urine cultures (1.5 (post-intervention) versus 3.7 (baseline) cultures per 1000 resident days); treatment of asymptomatic bacteriuria (0.6 (post-intervention) versus 1.7 (baseline) courses per 1000 resident days); and overall days of AB therapy (117 (post-intervention) versus 168 (baseline) days per 1000 resident days) (Zabarsky, Sethi & Donskey, 2008).

Empirical AB therapy

A systematic review on ASPs in hospitals found that prescribing empirical AB therapy according to guidelines is associated with reduced mortality in 31/37 studies (Schuts et al., 2016). The relative risk reduction across all studies was 35% (relative risk ratio 0.65; 95% confidence interval (CI) 0.54–0.80, $p < 0.0001$). Data about the effect of adherence to guidelines regarding empirical AB therapy in LTCFs are scarce. Nevertheless, empirical AB therapy for the most common types of infection (UTIs, RTIs, SSTIs), tailored to local resistance data, is recommended for ASPs in LTCFs (Nicolle, 2014).

Reassessment of AB therapy

An important element of good AB prescribing is evaluation/reassessment of the treatment 2–3 days after its initiation. At this time, one should consider whether the patient still needs AB therapy and whether the empirical AB therapy is appropriate based on clinical status and results of diagnostic tests (Dyar et al., 2014). The prescriber can choose to stop the AB course, continue with the empirical therapy or de-escalate to an AB with a narrow spectrum. The option to switch from intravenous to oral therapy should also be considered, along with the duration;

treatment should be as short as possible. In this way, the benefits of ABs can be maximized, while the adverse effects can be minimized (Crnich et al., 2015). Such a review/assessment may be performed by the prescriber themselves or by an external antimicrobial stewardship team, as part of a prospective audit with feedback (see Option 1). Post-prescription review and de-escalation interventions have had a significant impact on AB prescribing in hospitals and have been associated with reduced mortality. However, such interventions remain inadequately studied in LTCFs (Crnich et al., 2015; Schuts et al., 2016).

Prescribers in LTCFs rarely switch to ABs with narrow spectrum and most prescriptions exceed the recommended duration of treatment (Daneman et al., 2011; Rotjanapan, Dosa & Thomas, 2011). As reassessment was shown to be effective in the hospital environment, it should also be addressed in the guidelines, although the available evidence suggests such an approach is not currently being employed in LTCFs (Rotjanapan, Dosa & Thomas, 2011).

End-of-life situations

Guidelines should also be developed for LTCF residents for whom only comfort measures are provided (Nicolle et al., 2000). Studies show that AB treatment preferences at the end of life vary between countries (Mehr et al., 2003). Guidelines should be adapted to the context of Slovenia, according to the recommendations for palliative care and end-of-life decisions by the National Medical Ethics Committee (Grošek, Grošelj & Oražem, 2015).

Implementation of guidelines

To be relevant and accepted, guidelines should be developed and implemented in consensus with representatives of health care professionals (or their associations) providing care in LTCFs (Fleming, Browne & Byrne, 2013; Nicolle, 2014). Since this requires enough administrative and financial support, health committees, programme managers and policy-makers should be included in the process. Implementation can be driven by mandatory regulatory measures relating to antimicrobial stewardship since LTCFs are regulated by law and are required to meet national standards (Dyar et al., 2014).

Special attention should be paid to the implementation of guidelines through education (see Option 3).

A summary of the key findings from systematic/narrative reviews and other studies and publications relevant to Option 2 is provided in Table 3.

Table 3. Summary of key findings from systematic/narrative reviews and recommendation/position papers relevant to Option 2: Development and implementation of guidelines and clinical pathways for diagnosing and treating infection

CATEGORY OF FINDING	KEY FINDINGS
Benefits	<ul style="list-style-type: none"> – Structured review: Providing guidelines leads to a decrease in inappropriate AB prescribing (Fleming, Browne & Byrne, 2013). – Systematic review: Prescribing according to guidelines (empirical AB therapy, de-escalation of therapy) is associated with reduced mortality (Schuts et al., 2016). – Systematic review: implementing an ASP in outpatient settings decreases prescribing costs and increases use of narrow spectrum antimicrobials (Drekonja et al., 2015). – Systematic review: Guidelines for diagnosis and/or management decrease uncertainty in AB prescribing (Fleming et al., 2015).
Potential harms	<ul style="list-style-type: none"> – No harms were identified in the systematic reviews.
Resource use, costs and/or cost-effectiveness	<ul style="list-style-type: none"> – Systematic review: According to observational studies performed in hospitals, adherence to guidelines in terms of empirical treatment is associated with reduced costs (Schuts et al., 2016). – Systematic review: Observational studies performed in hospitals show savings where AB therapy is de-escalated compared to unmodified therapy (Schuts et al., 2016).
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)	<ul style="list-style-type: none"> – Structured review: The effect of introducing guidelines is usually not sustained and interventions should thus be repeated at regular intervals (Fleming, Browne & Byrne, 2013). – Structured review: Most of the interventions are multifaceted, making specific recommendations about key components difficult (Fleming, Browne & Byrne, 2013).
Key elements of the policy option if it was tried elsewhere	<ul style="list-style-type: none"> – Narrative review: Guidelines should focus on the most common infections in the LTCF setting: UTIs, RTIs and SSTIs (Dyar et al., 2014).

Table 3. (Contd)

CATEGORY OF FINDING	KEY FINDINGS
<i>Key elements of the policy option if it was tried elsewhere (contd)</i>	<ul style="list-style-type: none"> — Recommendations: Guidelines should include diagnostic criteria for common infections, instructions on appropriate diagnostic tests and empirical AB treatment, including on de-escalation and (as short as possible) duration of treatment (Jump et al., 2017) — Position paper: Guidelines should address end-of-life situations (Nicolle et al., 2000). — Narrative review: Development and implementation should be carried out in consensus with representatives of health care professionals/physicians. Sufficient administrative and financial support should be provided. Implementation can be driven by mandatory regulatory measures (Dyar et al., 2014).
Stakeholders' views and experiences	<ul style="list-style-type: none"> — No stakeholders' views and experiences were discussed in the systematic reviews assessed.

Option 3. CME and providing health information

Overview and context

CME opportunities for health care professionals play an important role in increasing knowledge on judicious AB prescribing and AMR, and enhancing skills and competences for managing common infections. CME helps physicians to: prescribe ABs appropriately and ensure their correct use; improve collaboration at the point of care; and change behaviours (Mazmanian, 2009; Zeiger, 2005).

Health care workers need to provide adequate health information to patients and their relatives and/or caretakers to assure patient cooperation and satisfaction, to decrease the burden of infections, and to prevent poor clinical outcomes (Rainwater-Lowett, Chun & Lessler, 2014).

Results of the literature review

The following systematic reviews and other publications/studies were found in the literature search and review (see the tables in Annex 2 for details, including the quality rating):

- seven reviews/systematic reviews (Arnold & Strauss, 2005; Davey et al., 2013; Drekonja et al., 2015; Filice et al., 2015; Fleming et al., 2014a; McDonagh et al., 2016; Ranji et al., 2008);

- three narrative reviews (Crnich et al., 2015; Dyar et al., 2016; Van der Velden et al., 2012);
- eight recommendations/position papers (Barlam et al., 2016b; Fleming et al., 2015; Gillespie et al., 2013; Heath et al., 2016; Jump et al., 2015; Zeiger, 2005; CDC, 2015).

Most of the studies about CME on AB prescribing and AMR have been performed either in hospitals or at the primary care level. Despite the lack of studies regarding CME in LTCFs, and the poor quality of the data available (Crnich et al., 2015), CME is recommended for implementing antimicrobial stewardship strategies in the LTCF setting, to ensure judicious use of ABs in such facilities (Crnich et al., 2015; Gillespie et al., 2013; Heath et al., 2016; Jump et al., 2015). More emphasis should be put on front-line nursing staff, as they present the greatest opportunity to affect stewardship and patient care in LTCFs, but often lack confidence to challenge prescribers (Kullar et al., 2018).

General benefits of CME and providing the health information

CME increases physicians' knowledge on patient care, enhancing both clinical and communication skills, as well as having an impact on physician behaviour and patient outcomes. That said, it needs to target multiple individuals and be delivered via several modalities to ensure maximum effectiveness, including in-service training sessions, newsletters, pocket guides, posters and brochures (Mazmanian, 2009; Naughton et al., 2001; Van der Velden et al., 2012; Zeiger, 2005). Two reviews concluded that multifaceted interventions, whereby educational interventions occur on many levels and combine physician- and patient-targeted elements, are even more effective. This type of intervention should be the approach used to resolve AB-related problems after addressing local barriers to change (Arnold & Straus, 2005; Gross & Pujat, 2001). CME also increases the likelihood that the guidelines will be well implemented into clinical practice (Lim, Kong & Stuart, 2014). Furthermore, CME has the biggest impact when physicians search for answers to questions that arise directly from the clinical practice, instead of that which occurs at an arbitrary time designated for CME (Van Buul et al., 2014a). The use of learning portfolios and information provision (e.g. through clinical/medical librarians) can be integrated with self-directed CME to help foster a lifelong learning approach, locating and providing high quality, patient-specific information to physicians at the point of care (Zeiger, 2005).

Implementation

CME should be implemented by the professional organizations/bodies that are also responsible for developing and providing the educational material for health care workers and LTCF residents, families and caretakers. Overall, education using active clinician participation demonstrated a trend toward greater effectiveness than passive education techniques (Ranji et al., 2008). In Slovenia, CME credits are needed to ensure the licensing of physicians and nurses. In order to sustain CME on AB prescribing, each year every health care professional should undergo a certain number of hours of CME that is pre-agreed by the respective competent authority for specialty board certification. This, together with the national AMR action plan, forms part of the national One Health strategy for AMR control that is under development by the ICM for AMR at the Slovene Ministry of Health and is due to be approved in 2018.

The proposed CME strategies are to:

- establish small groups of physicians and nurses at the LTCFs and regional level that would help to build a professional educational network at the local level, including LTCF management;
- share guidelines/clinical pathways for AB treatment management and advanced care plans relating to diagnosis and laboratory testing;
- provide education organized by professional bodies (i.e. professional societies in the fields of medicine, pharmacy, nursing);
- involve stakeholders, including the ICM for AMR (Slovene Ministry of Health), the NIJZ, NLZOH, HIIS, and medical schools, to guide and sustain the knowledge about AB practices in LTCFs (Dyar et al., 2016; Arnold & Strauss, 2005; Drekonja et al., 2015; McDonagh et al., 2016; Van der Velden et al., 2012; CDC, 2015; Crnich et al., 2015; Jump et al., 2015; Zeiger, 2005).

Providing health information on AB practices in LCTFs should include organizing regular educational training sessions (workshops/seminars, for example, on clinical situations and the initiation and outcome of treatment, clinical pathways and guidelines, algorithms/indications for appropriate testing, audit of and feedback on baseline AB prescribing patterns, adherence to treatment recommendations, local AB resistance patterns, de-escalation interventions, consultant reviews, physician reminders, and electronic decision support for health care professionals). Additionally, information should be provided to LTCF residents and their relatives about the benefits and risks of AB therapy, including hygiene matters, through dissemination of written and electronic educational materials, such as leaflets or brochures and videos, and by using other modern communication tools for campaigns (websites and forums, social media platforms, etc.). Time constraints and miscommunication between physicians and patients about expectations for consultations are thought to lead physicians to prescribe against their better judgement (Pettursson, 2005). Education of LCTF residents and their families – when combined with staff education and interventions to enhance interdisciplinary communication – has proven to reduce AB use in LTCFs (Zimmerman et al., 2014).

All these approaches can: (i) support the improvement of health care professionals' AB prescribing behaviour; (ii) promote prudent AB prescribing in LTCFs; and (iii) encourage antimicrobial stewardship in order to enable the health care system to be modified as necessary by the key informants (Dyar et al., 2016; Arnold & Strauss, 2005; Drekonja et al., 2015; McDonagh et al., 2016; Van der Velden et al., 2012; CDC, 2015; Crnich et al., 2015).

ASPs should focus on prescription durations and target the determinants of prescriber behaviours in order to improve AB prescribing in LCTFs (Fleming & Byrne, 2014).

Currently, all professional associations in Slovenia organize regular educational events on antimicrobial prescribing and stewardship. In addition, the Slovenian Society of Antimicrobial Chemotherapy organizes targeted postgraduate courses on AB prescribing, encompassing specifically also AB prescribing among the elderly in LTCFs.

A summary of key findings from systematic reviews relevant to Option 3 is provided in Table 4.

Table 4. Summary of key findings from systematic reviews relevant to Option 3: Continuous medical education and providing health information.

CATEGORY OF FINDING	KEY FINDINGS
<p>Benefits</p>	<ul style="list-style-type: none"> – Narrative review: Physician education is important in optimizing AB use (Van der Velden et al., 2012). – Position paper/survey: Education of patients about appropriate AB use and better understanding of patient wishes improve the quality of AB prescribing (CDC, 2015; Jump et al., 2015). – Systematic review: Guidelines for diagnosis and/or management improve AB prescribing (Drekonja et al., 2015).
<p>Potential harms</p>	<ul style="list-style-type: none"> – Systematic review: Undertreatment is the result of poor adaptation of guidelines, relocation of resources, and/or increased costs (Drekonja et al., 2015).
<p>Resource use, costs and/or cost-effectiveness</p>	<ul style="list-style-type: none"> – Intervention population study: Having pharmacy staff as part of the team improves AB prescribing (Fleming et al., 2015; Gillespie et al., 2013). – Intervention population study: Nurses are pivotal to improving ASPs, particularly in the LTCF setting (Gillespie et al., 2013; Heath et al., 2016). – Systematic review: Reducing workload/patient numbers may improve AB prescribing but may add costs and prolong consultation times (Drekonja et al., 2015). – Population study: AB costs should be measured based on prescriptions or AB administration, instead of purchasing data (Barlam et al., 2016).
<p>Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued)</p>	<ul style="list-style-type: none"> – Systematic reviews: The effectiveness of an intervention on AB prescribing depends on the physician’s prescribing behaviour/preference and the barriers to change in the community (Arnold & Strauss, 2005; Drekonja et al., 2015). – Systematic review: Physicians are faced with patient expectations and with patient and provider lack of awareness of AMR, as well as lack of understanding of the seriousness of AMR, leading to AB overprescribing (Drekonja et al., 2015).

Table 4. (Contd)

CATEGORY OF FINDING	KEY FINDINGS
<i>Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued) (contd)</i>	<ul style="list-style-type: none"> — Systematic review: Physicians recognize the potential value of guidelines but are not always trusting of the information contained in the guidelines and the relevance to their patients (Drekonja et al., 2015). — Systematic review: Few studies report patient satisfaction with their care (Drekonja et al., 2015). — Systematic review: Most interventions are multifaceted, making specific recommendations about key components difficult (Drekonja et al., 2015).
Key elements of the policy option if it was tried elsewhere	<ul style="list-style-type: none"> — Systematic review: It is important to educate physicians and prevent the misuse/overuse of ABs in cases of viral infection (for which ABs are of no value) or where there is no infection; as well as the excessive use of broad-spectrum ABs in place of narrow-spectrum ABs; and to reduce the duration of AB use for conditions such as acute otitis media, to improve AB prescribing in ambulatory settings (Arnold & Strauss, 2005). — (Systematic) reviews: No single intervention can be recommended for all behaviours in any setting for any outcome (Arnold & Strauss, 2005; Drekonja et al., 2015; McDonagh et al., 2016; Ranji et al., 2008). — Systematic review: Active clinician education strategies showed a trend toward greater effectiveness than passive strategies (Ranji et al., 2008). — Systematic review: Multifaceted interventions, whereby educational interventions occur on many levels, can be successfully applied to communities after addressing local barriers to change (Arnold & Strauss, 2005). — Systematic review: Experience with withholding antimicrobials, external pressure to reduce AB prescribing, and potential conflicts with patients all play an important role in AB prescribing and AMR (Drekonja et al., 2015). — Systematic review: Interventions should focus on changing physicians' behaviour rather than simply providing information (Drekonja et al., 2015).

Table 4. (Contd)

CATEGORY OF FINDING	KEY FINDINGS
<p><i>Key elements of the policy option if it was tried elsewhere (contd)</i></p>	<ul style="list-style-type: none"> – Systematic review: Communication with patients, health professionals, parents, educators, and day-care providers emphasizes the benefits and risks of AB use (Drekonja et al., 2015). – Systematic review: Information provided should be clear, consistent, and positive (e.g. on bacterial versus viral infections, and treatment of symptoms) (Drekonja et al., 2015). – Systematic review: A multimedia and multicultural approach is recommended, with focus groups to help refine the educational materials, spokespersons to deliver the messages, and academic detailing for health care providers (Drekonja et al., 2015). – Systematic review: Leadership is important (ideally with peers as local champions, instructors, and/or discussion leaders), along with use of a team approach (with input from health care professionals at all levels), patient education materials (ideally linked with provider materials on the same topic), provider reminders, user-friendly interfaces, and evidence-based materials to reduce overall AB use and improve AB prescribing (Drekonja et al., 2015). – Systematic review: The best evidence supports the use of specific education interventions for patients/parents and clinicians and electronic decision support to reduce overall AB prescribing and improve AB prescribing for acute RTIs (McDonagh et al., 2016). – Systematic review: Strategies using active clinician education and targeting the management of all acute RTIs (rather than single conditions in single age groups) yield larger reductions in community-level AB use (Ranji et al., 2008). – Narrative review: Interventions aiming to decrease overall AB prescribing are more frequently effective than interventions aiming to increase first-choice prescription (Van der Velden et al., 2012). – Retrospective cohort study: ASPs should focus on prescription durations and target the determinants of prescriber behaviour to improve AB prescribing in LTCFs (Fleming & Byrne, 2014).

Table 4. (Contd)

CATEGORY OF FINDING	KEY FINDINGS
<i>Key elements of the policy option if it was tried elsewhere (contd)</i>	<ul style="list-style-type: none"> — Population study: ASPs should develop and implement facility-specific clinical practice guidelines for common infectious diseases in order to improve AB use (Barlam et al., 2016).
Stakeholders' views and experiences	<ul style="list-style-type: none"> — Systematic review: Planning and stakeholder support improve antimicrobial use (Drekonja et al., 2015). — Position paper: Changing health care professionals' attitudes and behaviour, and modifying the health care system, are important factors for improving AB prescribing (Dyar et al., 2016). — Systematic review: Stakeholder involvement in developing the intervention improves antimicrobial use (Drekonja et al., 2015).

Equity-related observations about the three options

The following potential equity issues were identified:

- the needs of people with physical and sensory disabilities;
- the needs of people with impaired cognitive function or impaired mobility (NICE, 2012; NICE, 2013; NICE, 2015).

The populations in LTCFs for the elderly are complex, with a range of long-term physical or mental health conditions. The aim of the proposed options is to develop generic recommendations to benefit all elderly people in LTCFs.

Good communication is essential between health and social care practitioners and the elderly population in LTCFs (and their families). Treatment, care and support, and the information provided about them, should be both age and culturally appropriate. These elements should also be accessible to people with additional needs, such as physical, sensory or learning disabilities, and to people who do not speak or read Slovene. Health and social care providers should aim to implement the proposed options in their local context, taking into account their duties to have due regard to the needs of the elderly and to provide high-quality services, reducing health inequalities and fostering satisfaction with health services among the Slovene population, across various health care settings (Wensing et al., 2002). Moreover, health literacy (i.e., general perceived ability to acquire, evaluate and act on health information) may be a preventive mechanism to use ABs more critically. Health illiteracy, particularly among patients of

low socioeconomic status, as well as the elderly, still plays a major role in when and how to use ABs, especially for acute upper RTIs (O'Sullivan et al., 2016). Hence, interventions should target competencies such as knowledge and health literacy, especially among vulnerable populations in the primary health care setting (Salm et al., 2018). While those aged over 80 years usually show decreased levels of health knowledge and health literacy, yet increased need for ABs, younger cohorts of older adults often show good knowledge and health literacy. Interventions should specifically balance the need for ABs with clear age-tailored communication strategies in cases when AB therapy is clearly inappropriate (Sørensen et al., 2015).

When older people in care homes lack capacity, decisions made on their behalf should be made in line with the legal framework and code of practice and ethics.

Option 1

Surveillance and monitoring of AB consumption and AMR are associated with additional costs, so there could be differences between LTCFs in terms of public versus private ownership. Although Slovenia is a small country with a well-developed network of microbiology laboratories, LTCFs in urban areas have easier access to the laboratories in comparison to those in more rural areas. Such inequities and their consequences could also arise from the different economic statuses of LTCFs. Access to educated staff could also be problematic in more rural areas.

Option 2

National guidelines and clinical pathways for diagnosing and treating infections with ABs in LTCFs could be easily distributed via modern means of communication (i.e. digital technology). Implementing new guidelines, however, also requires education of both physicians and nursing staff, which could prove to be more problematic financially. This applies in particular to privately owned LTCFs, which are more profit-oriented, versus publicly owned LTCFs. Including more laboratory and microbiology testing in the guidelines could result in additional costs for the facilities, whereby privately owned LTCFs could decide not to follow the guidelines. Staff in LTCFs in rural areas may also find it harder to adhere to guidelines, because of the logistical problems associated with laboratory and microbiology testing, which can be harder to access.

Option 3

CME largely depends on health system constraints, in terms of the budget/resources of the individual facility; these may be unevenly distributed in rural versus urban settings and in the private versus public health sectors (Basu et al., 2012). Providing health information for LTCF residents and their families has proven to have beneficial effect on the health status of the elderly population in residential settings (Gaugler, 2005). However, accessibility of health information to LTCF residents and families with lower socioeconomic status may be hampered owing to logistical barriers, such as unstable schedules, lack of transport and/or child care, and lack of access to modern technology/telecommunications. For example, lower-income households with elderly individuals receiving lower pensions can visit their relatives less often and receive less information about their health status and health care in LTCFs, compared to their wealthier counterparts.

Implementation considerations

Processes that are already in place (described within the sections on the three individual options) can be upgraded to improve each modality. Well-developed primary health care in all LTCFs in Slovenia is a good platform for further improvements. As the education system of some health care workers is organized and regulated, this can be a good starting point for disseminating information and providing new knowledge. However, this must be supported by the health care regulators. Also, some of the monitoring and surveillance modalities are already in place but need further development to fulfil the specific needs of LTCFs. Guidelines for AB treatment of infectious diseases also exist; however, they could be made more specific to the LTCF setting (Kullar et al., 2018; Meeker et al., 2016).

Facilitators and enablers

One of the most prominent facilitators is sufficient knowledge and awareness about the growing importance of AMR among different stakeholders, including leadership within LTCFs and among society more generally (Lim, Stuart & Kong, 2015; National Centre for Antimicrobial Stewardship & ACSQHC, 2016). Along with availability of data specific to ASP implementation in LTCFs, a sufficient number of educated and motivated experts, and no time constraints, these elements would further facilitate the development of guidelines and clinical pathways, and their implementation in the field (Kullar et al., 2018). Restrictive measures like guidelines have the potential (if followed) to improve the current patterns of AB prescribing in Slovene LTCFs.

Awareness of the consequences of inappropriate AB prescribing among physicians and LTCF residents also facilitates optimal prescribing practices. Availability of the relevant IT infrastructure at national and local/regional levels, to support surveillance and monitoring, is important for data collection, comparison and analysis. CME targeting problems specific to LTCFs and for those directly providing health care in LTCFs should be widely available. The development of guidelines, clinical pathways and national initiatives for improvement in the field would not impose a significant workload on health care providers if their number is sufficient to share the contribution.

The potential barriers to implementing the three options are presented in Table 5.

Table 5. Potential barriers to implementing the three options

LEVELS	OPTION 1: SURVEILLANCE AND MONITORING
A) RECIPIENTS OF CARE/FAMILIES	
<p>Knowledge and skills</p>	<ul style="list-style-type: none"> ○ Obtaining a good sample for microbiological examination is sometimes difficult in LTCF settings and there is a lack of microbiological data to guide AB therapy (Lim, Kong & Stuart, 2014). ○ The low number of isolates from clinical samples precludes the frequent development of facility-specific antibiograms (Jump et al., 2017).
<p>Attitudes regarding programme acceptability, appropriateness and credibility</p>	<ul style="list-style-type: none"> ○ Recipients of care sometimes do not understand the importance of the programmes and refuse to participate (Personal opinion of the working group).
<p>Motivation to change or adopt new behaviour</p>	<ul style="list-style-type: none"> ○ Recipients of care sometimes do not understand the importance of the programmes and refuse to participate (Personal opinion of the working group).
B) PROVIDERS OF CARE	
<p>Knowledge and skills</p>	<ul style="list-style-type: none"> ○ Lack of knowledge, evidence and experience are notable barriers to implementing an ASP (Jump et al., 2017, Malani et al., 2013; Dyar et al., 2014). ○ Lack of familiarity or experience can be a problem, along with lack of awareness or insight (Drekonja et al., 2015).

OPTION 2: DEVELOPMENT AND IMPLEMENTATION OF GUIDELINES

- There is a lack of knowledge regarding treatment of infections and AMR (Van Buul et al., 2014b).

- Patient non-cooperation is a problem, associated with expectations about AB treatment (Van Buul et al., 2014b).

- Recipients of care sometimes do not understand the importance of the programmes and refuse to participate (Personal opinion of the working group).

- There is a lack of knowledge, evidence and experience (Jump et al., 2017; Dyar et al., 2014).

OPTION 3: CME AND PROVIDING HEALTH INFORMATION

- There is insufficient knowledge (health illiteracy) (O’Sullivan et al., 2016; Salm et al., 2018; Schouten, Berrevoets & Hulscher, 2017).

- Patient non-cooperation can be a barrier (Schouten, Berrevoets & Hulscher, 2017).

- There is a lack of personnel and/or heavy workload of the personnel that provide education (Schouten, Berrevoets & Hulscher, 2017).
- There are insufficient patient preferences, with health care guideline recommendations (Schouten, Berrevoets & Hulscher, 2017).

- A lack of knowledge/skills exists on developing and implementing behavioural change programmes (Meeker et al., 2016).

Table 5. (Contd)

LEVELS	OPTION 1: SURVEILLANCE AND MONITORING
B) PROVIDERS OF CARE (CONTD)	
<p>Attitudes regarding programme acceptability, appropriateness, and credibility</p>	<ul style="list-style-type: none"> ○ Financial constraints, lack of personnel, and inadequate knowledge and time can cause negative attitudes towards monitoring and surveillance (Personal opinion of the working group).
<p>Motivation to change or adopt new behaviour</p>	<ul style="list-style-type: none"> ○ There are not enough resources and/or legislative support to include and motivate a sufficient number of doctors, nurses and pharmacists to raise antimicrobial stewardship as a priority item for patient care and quality improvement (Fleming et al., 2014a).
C) OTHER STAKEHOLDERS (OTHER HEALTH CARE PROVIDERS, COMMUNITY HEALTH COMMITTEE, COMMUNITY LEADERS, PROGRAMME MANAGERS, DONORS, POLICY-MAKERS AND OPINION LEADERS)	
<p>Knowledge and skills</p>	<ul style="list-style-type: none"> ○ More research is needed on implementing ASP interventions in environments with limited quality improvement resources (e.g. LTCFs) (Crnich et al., 2015).

OPTION 2: DEVELOPMENT AND IMPLEMENTATION OF GUIDELINES

- Conflicting guidelines exist, along with no locally adapted guidelines (Schouten, Berrevoets & Hulscher, 2017).
- Problems include: lack of agreement with the guidelines, including their applicability to patients; lack of confidence in the guideline developers; disagreement about interpreting the evidence; no positive expectations regarding outcomes; and the inertia of existing practices/habits/routines (Drekonja et al., 2015).

- Barriers to guideline adherence include the inertia of existing practices, volume of information, lack of positive expectations regarding the outcome, and lack of: agreement, familiarity, accessibility of guidelines, self-sufficiency, motivation (Schouten, Berrevoets & Hulscher, 2017).

- Lack of knowledge is problematic (Schouten, Berrevoets & Hulscher, 2017).

OPTION 3: CME AND PROVIDING HEALTH INFORMATION

- Conflicting guidelines (or those that are not facility-specific), along with organizational constraints, can present barriers (Schouten, Berrevoets & Hulscher, 2017).
- There is a lack of motivation and/or the inertia of existing practices/habits/routines (Schouten, Berrevoets & Hulscher, 2017).

- There is a lack of motivation/the inertia of existing practices/habits/routines (Schouten, Berrevoets & Hulscher, 2017).
- Lack of time and resources is a problem (Schouten, Berrevoets & Hulscher, 2017).
- Barriers include: lack of knowledge and familiarity with the guidelines; the time needed to stay informed; accessibility of guidelines; lack of agreement and self-sufficiency; no positive expectations regarding outcomes; lack of motivation/the inertia of existing practices/habits/routines (Schouten, Berrevoets & Hulscher, 2017).

- There is a lack of time and resources for health information provision (Schouten, Berrevoets & Hulscher, 2017).

Table 5. (Contd)

LEVELS	OPTION 1: SURVEILLANCE AND MONITORING
C) OTHER STAKEHOLDERS (OTHER HEALTH CARE PROVIDERS, COMMUNITY HEALTH COMMITTEE, COMMUNITY LEADERS, PROGRAMME MANAGERS, DONORS, POLICY-MAKERS AND OPINION LEADERS) (CONTD)	
<p>Attitudes regarding programme acceptability, appropriateness, and credibility</p>	<ul style="list-style-type: none"> ○ Different stakeholders are indifferent towards the benefits of the monitoring and surveillance modalities of ASPs (Personal opinion of the working group).
<p>Motivation to change or adopt new behaviour</p>	
D) HEALTH SYSTEM CONSTRAINTS	
<p>Accessibility of care, Financial resources, Human resources, Education system, Clinical supervision, Internal communication, External communication, Allocation of authority, Accountability, Management and or leadership, Information systems, Facilities, Patient flow processes, Procurement and distribution systems, Incentives, Bureaucracy, Relationship with norms and standards.</p>	<ul style="list-style-type: none"> ○ An important barrier to the improvement of antimicrobial stewardship is the lack of physical presence of providers in LTCFs (Crnich et al., 2015). ○ Lack of governance structures is a problem, along with inadequate national specific LTCF guidelines or policies, and a lack of awareness (Lim, Kong & Stuart, 2014). ○ Infrastructure (mainly IT) can place considerable constraints on the implementation of monitoring and surveillance (Personal opinion of the working group).

OPTION 2: DEVELOPMENT AND IMPLEMENTATION OF GUIDELINES

- Stakeholders do not recognize the importance of ASPs (and guidelines as an essential part of these programmes) in LTCFs (Personal opinion of the working group).

- There is a perceived increase in malpractice liability (Schouten, Berrevoets & Hulscher, 2017).

- Lack of time, personnel, and reimbursement are barriers (Schouten, Berrevoets & Hulscher, 2017).
- There is no availability of on-site diagnostics (Crnich et al., 2015).
- Decisions on AB treatment are made by off-site providers (Crnich et al., 2015).
- There is suboptimal intersectoral/multisectoral collaboration (Schouten, Berrevoets & Hulscher, 2017).
- Unclear (or conflicting) guidelines exist (Drekonja et al., 2015).
- There are no infection control units/specialized personnel who monitor the work of physicians and follow up on their adherence to guidelines/clinical pathways (Meeker et al., 2016).

OPTION 3: CME AND PROVIDING HEALTH INFORMATION

- Organizational constraints represent a barrier (suboptimal intersectoral/multisectoral collaboration, lack of reimbursement, perceived increase in malpractice liability (Schouten, Berrevoets & Hulscher, 2017).

- There are no positive expectations regarding outcomes, and the inertia of existing practices/habits/routines are a problem (Schouten, Berrevoets & Hulscher, 2017).

- Lack of awareness, the volume of information, and inefficient information channels are motivational barriers (Schouten, Berrevoets & Hulscher, 2017).

- Lack of reimbursement is a problem (Schouten, Berrevoets & Hulscher, 2017).

Table 5. (Contd)

LEVELS	OPTION 1: SURVEILLANCE AND MONITORING
E) SOCIAL AND POLITICAL CONSTRAINTS	
<p>Ideology, Short-term thinking, Contracts, Legislation or regulations, Donor policies, Influential people, Corruption, Political stability.</p>	<ul style="list-style-type: none"> ○ Social and political constraints are a barrier, along with poor support for surveillance at national level, and legal misunderstanding concerning data protection (Personal opinion of the working group).

**OPTION 2:
DEVELOPMENT AND IMPLEMENTATION
OF GUIDELINES**

- There is no clear vision for elderly care for the coming decades (Personal opinion of the group).
- The political nomenclature engages in only short-term thinking, only addressing popular issues to gain political points and refusing to embark on complex problems requiring time, dedication, funds and a broad consensus across the whole political spectrum (Personal opinion of the working group).
- Legislation is rigid (not flexible), discouraging public initiatives/motivation and stakeholder initiatives (Schouten, Berrevoets & Hulscher, 2017).

**OPTION 3:
CME AND PROVIDING HEALTH INFORMATION**

- Rigid/non-flexible legislation is a barrier, discouraging of public initiatives/motivation and stakeholder initiatives (Schouten, Berrevoets & Hulscher, 2017; Struwe, 2008).

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Annex 1. Summary of systematic scientific and grey literature search and review of AB prescribing in LTCFs

A systematic scientific and grey literature search and review of AB prescribing in LTCFs following two independent strategies

1. Systematic search of the peer-reviewed literature (PubMed and Scopus) was conducted. References from the retrieved articles were reviewed for potential additional articles. Slovene, English, French, Spanish, and German language restrictions were applied. An example of the search strategy designed for the peer-reviewed literature for AB prescribing in nursing homes or long-term care facilities for elderly is (“Antibiotic*” OR “antimicrobial*” OR “antibacterial” OR “antibacterial”) AND (“prescribing” OR “prescribe” OR “prescribed” OR “prescription” OR “use” OR “administration” OR “administering” OR “administer”) AND (“nursing home*” OR “long-term care facility*” for elderly” OR “residential elderly home*” OR “residential aged care facility*”).
2. A comprehensive grey literature search was performed and included Google search engine and websites of the ministries of health, health care services, institutes of public health, European Centre for Disease Prevention and Control (ECDC), WHO and various scientific societies in the field (including the European Society of Clinical Microbiology and Infectious Diseases (ESCMID), the International Society for Infectious Diseases [ISID] and the International Epidemiological Association [IEA]). The time-period was 1 September to 17 November 2017.
3. Titles and abstracts of the retrieved manuscripts were initially assessed, and non-relevant documents were ultimately excluded. Manuscripts from grey literature, executive summaries, tables of contents/tables and documents (whichever was available) were screened. The full text of the potentially eligible manuscripts was then obtained and assessed by all authors for relevance or duplication. Disagreements were resolved by review and consensus with all co-authors. A total of 25 systematic reviews and 27 individual studies were retrieved and used in this EBP.

Annex 2. Summary of systematic reviews relevant to the three options for addressing the problem

The following tables provide detailed information about the systematic reviews identified for each option. Each row in a table corresponds to a systematic review. The focus of the review is described in the second column. Key findings from the review that relate to the option are listed in the third column, while the fourth column presents a rating of the overall quality of the review.

The quality of each review has been assessed using A Measurement Tool to Assess Reviews (AMSTAR), which rates overall quality on a scale of 0 to 11, where 11/11 represents a review of the highest quality. It is important to note that AMSTAR was developed to assess reviews focused on clinical interventions, so not all criteria apply to systematic reviews pertaining to delivery, financial, or governance arrangements within health systems. Where the denominator is not 11, an aspect of the tool was considered not relevant by those rating it. In comparing ratings, it is therefore important to keep both parts of the score (i.e., the numerator and denominator) in mind. For example, a review that scores 8/8 is generally of comparable quality to a review scoring 11/11; both ratings are considered “high scores”. A high score signals that readers of the review can have a high level of confidence in its findings. A low score, on the other hand, does not mean that the review should be discarded, merely that less confidence can be placed in its findings and that the review needs to be examined closely to identify its limitations (Lewin et al., 2009).¹

The last three columns convey information about the utility of the review in terms of local applicability, equity, and issue applicability (to the Slovene case). The fifth column notes the proportion of studies that were conducted in Slovenia, Europe or the European Union.

All the information provided in the tables in Annex 2 was considered by the authors of the evidence brief for policy (EBP) in compiling Tables 1–4 in the main body of the brief (and therefore the References list for the main report also contains the sources for the Annex tables).

1 Lewin S, Oxman AD, Lavis JN, Fretheim A (2009). SUPPORT Tools for evidence-informed health Policymaking (STP): 8. Deciding how much confidence to place in a systematic review. *Health Res Policy Syst.* 7(Suppl 1):8 (<https://health-policy-systems.biomedcentral.com/articles/10.1186/1478-4505-7-S1-S8>).

Table A2.1. Summary of systematic reviews relevant to Option 1 – Surveillance and monitoring

Option element (and reference)	Focus of systematic review	Key findings	AMSTAR checklist (quality) rating	Proportion of studies that were conducted in Europe
Benefits (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Antimicrobial stewardship programme (ASP) in outpatient settings decreases prescribing costs and increases use of narrow-spectrum antimicrobials	8/11	27 out of 50 articles included were European
Potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Systematic review found no possible harms of implementing ASPs in outpatient settings; however, there was limited reporting of return clinic visits, hospitalizations, and adverse events (including mortality)	8/11	27 out of 50 articles included were European
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued (Crnich et al., 2015)	Optimizing AB stewardship in nursing homes: a narrative review and recommendations for improvement	Underlying frailty of most LTCF residents causes a high level of risk aversion in care providers	7/11	Among 14 ASP intervention studies included, 3 were conducted in Europe
Uncertainty regarding benefits and potential harms (Crnich et al., 2015)	Optimizing AB stewardship in nursing homes: a narrative review and recommendations for improvement	Further studies are needed to evaluate the effects of ASP on facility and resident outcomes, including health care costs, as well as rates of infections caused by <i>Clostridium difficile</i> and multidrug-resistant (MDR) bacteria	7/11	Among 14 ASP intervention studies included, 3 were conducted in Europe
Uncertainty regarding benefits and potential harms (Crnich et al., 2015)	Optimizing AB stewardship in nursing homes: a narrative review and recommendations for improvement	A combination of interventions targeted at different phases of the AB prescribing process requires more studies	7/11	Among 14 ASP intervention studies included, 3 were conducted in Europe
Uncertainty regarding benefits and potential harms (Nicolle, 2014)	Antimicrobial stewardship in LTCFs: what is effective?	Since several distinct activities are usually implemented simultaneously, the efficacy and relative importance of any single programme component is unknown At least some improvement in antimicrobial use is usually shown following the introduction of stewardship interventions	5/11	Among 9 studies, 2 were conducted in Europe

Table A2.1. (Contd)

Option element (and reference)	Focus of systematic review	Key findings	AMSTAR checklist (quality) rating	Proportion of studies that were conducted in Europe
Uncertainty regarding benefits and potential harms (Dik et al., 2015a)	Financial evaluations of ASPs – a systematic review	Further studies are needed to evaluate the economic benefit of ASPs	5/11	Among 99 studies, 28 were carried out in Europe
Key elements of the policy option if it was tried elsewhere (Crnich et al., 2015)	Nursing homes: a narrative review and recommendations for improvement	LTCFs should take measures to monitor <i>C. difficile</i> infections and discuss the development of facility-specific antibiograms	7/11	Among 14 studies included, 3 were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Crnich et al., 2015)	Nursing homes: a narrative review and recommendations for improvement	AB use in LTCFs should be monitored in some manner (e.g. defined daily doses (DDDs), days on therapy (DOTs))	7/11	Among 14 studies included, 1 was conducted in the United Kingdom; the rest in the United States
Key elements of the policy option if it was tried elsewhere (Lim, Kong & Stuart, 2014)	Reducing inappropriate AB prescribing in the residential care setting: current perspectives	Infectious Diseases Society of America (IDSA) guidelines recommend monitoring of antimicrobial use and local antimicrobial susceptibility, with feed-back to relevant authorities	2/11	Not clear
Key elements of the policy option if it was tried elsewhere (Lim, Kong & Stuart, 2014)	Reducing inappropriate AB prescribing in the residential care setting: current perspectives	A survey from Nebraska in the United States revealed that more than half of participating LTCFs have established ASPs, some of which with high-intensity interventions, such as pre-authorization and audit/feedback	2/11	Not clear
Key elements of the policy option if it was tried elsewhere (Dyar, Pagani & Pulcini, 2015)	Strategies and challenges of antimicrobial stewardship in LTCFs	Audit and feedback strategies are necessary components of ASPs and regularly conducted medication reviews were associated with lower systemic AB prescribing in Northern Irish residential homes	5/11	Among 12 intervention studies on improving AB prescribing, 3 were performed in Europe

Table A2.2. Systematic and narrative reviews relevant to Option 2 – Development and implementation of guidelines

Option element (and reference)	Focus of systematic review	Key findings	AMSTAR checklist (quality) rating	Proportion of studies that were conducted in Europe
Review and recommendations for optimizing ASPs in LTCFs (Crnich et al., 2015)	Optimizing AB stewardship in nursing homes: a narrative review and recommendations for improvement	<p>Development and implementation should be carried out with consensus from representatives of health care professionals, and with enough administrative and financial support provided</p> <p>Implementation can be driven by mandatory regulatory measure</p> <p>The AB prescribing process in LTCFs is complex and differs from the prescribing process in hospital settings</p> <p>Improvements in the quality of AB prescribing in LTCFs have been achieved through a variety of AB stewardship interventions</p> <p>Implementing and sustaining AB stewardship in LTCFs requires organizational commitment and a strategy based on goal-setting, measuring processes and outcomes, and continuous quality improvement</p>	7/10	14 studies were included, of which 3 in Europe
Estimate the effectiveness and safety of interventions to improve AB prescribing to hospital inpatients (Davey et al., 2013)	Assessment of the effectiveness and safety of ASP interventions	<p>The duration of treatment decreased when inpatients were treated according to AB policies</p> <p>The risk of death was similar between interventional and control groups</p> <p>ASP interventions reduced length of stay in hospital</p>	10/11	221 studies were included, 87 of which were conducted in Europe
Evaluate the effect of outpatient ASPs on prescribing, patient, microbial outcomes, and costs (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Outpatient ASP interventions of all types (provider and/or patient education, provider feedback, guidelines, delayed prescribing, communication skills training, restriction, decision support, financial incentives, laboratory testing) were associated with favourable changes in antimicrobial prescribing	8/11	50 studies were included, 24 of which were conducted in Europe

Table A2.2. (Contd)

Option element (and reference)	Focus of systematic review	Key findings	AMSTAR checklist (quality) rating	Proportion of studies that were conducted in Europe
<p><i>Evaluate the effect of outpatient ASPs on prescribing, patient, microbial outcomes, and costs (Drekonja et al., 2015) (contd)</i></p>		<p>Changes in prescribing did not adversely affect patient outcomes or costs</p> <p>Studies of outpatient ASPs predominantly involved respiratory tract infections (RTIs).</p> <p>Only the associations between prescribing outcomes and communication skills training and laboratory testing were supported by medium-strength evidence; strength of evidence was low for other associations</p>		
<p>Strategies and challenges of antimicrobial stewardship in LTCFs (Dyar et al., 2014)</p>	<p>Review of interventional studies that aimed to improve AB prescribing in LTCFs and practical recommendations to help guide the development and implementation of ASPs in LTCFs</p>	<p>Interventional studies (mainly multifaceted educational interventions) that aimed to improve AB prescribing in LTCFs did predominantly show improvement in AB use</p>	<p>5/11</p>	<p>12 intervention studies were included, 3 of which were conducted in Europe</p>
<p>Collect the results of interventions intended to improve AB prescribing in LTCFs and determine the key components for a successful intervention (Fleming, Browne & Byrne, 2013).</p>	<p>The effect of interventions to reduce potentially inappropriate AB prescribing in LTCFs: a systematic review of randomized controlled trials</p>	<p>Interventions in the LTCFs involving local consensus procedures, educational strategies, and locally developed guidelines may improve the quality of AB prescribing, but the quality of evidence is low</p>	<p>8/10</p>	<p>4 studies were included, 1 of which was conducted in Europe</p>
<p>Factors influencing AB prescribing (Fleming, Browne & Byrne, 2013)</p>	<p>Synthesize findings of studies investigating factors influencing AB prescribing in LTCFs: a meta-synthesis of qualitative research</p>	<p>LTCF context, social factors, variability in knowledge and prescribing practices, and AMR all have an important impact on AB prescribing in this setting</p> <p>ASP strategies must emphasize the importance of knowledge of guidelines and AMR, and the strategies must be specifically designed for implementation in the LTCF setting</p>	<p>6/10</p>	<p>8 studies were included, 2 of which were conducted in Europe</p>

Table A2.2. (Contd)

Option element (and reference)	Focus of systematic review	Key findings	AMSTAR checklist (quality) rating	Proportion of studies that were conducted in Europe
Identify the need for and the barriers to ASPs in LTCFs, and identify studies related to ASP in LTCFs (Morrill et al., 2016)	Antimicrobial stewardship in LTCFs: a call to action	<p>The quality of evidence was weak, the results were mixed, and the interventions varied greatly, as did study definitions and outcome measures</p> <p>Several studies suggest that multifaceted educational interventions may be effective in increasing appropriate AB use in LTCFs</p>	7/10	14 studies were included, of which 3 were performed in Europe
Review current evidence on effectiveness of ASPs in LTCFs; summarize potential effective approaches; and identify issues which must be addressed to support effective ASPs in LTCFs (Nicolle, 2014).	Antimicrobial stewardship in LCTFs: what is effective?	<p>Comprehensive programmes addressing all infections were reported to have improved AB use for at least some outcomes</p> <p>Targeted programmes for treatment of pneumonia were minimally effective</p> <p>Programmes focusing on specific aspects of treatment of urinary tract infections (UTIs) were reported to be effective</p>	5/11	9 studies were included, of which 2 were performed in Europe
Assess of effects of ASP objectives on clinical outcomes, adverse effects, costs, and bacterial resistance rates (Schuts et al., 2016).	Current evidence on hospital antimicrobial stewardship objectives: a systematic review and meta-analysis	<p>Empirical therapy according to the guidelines was associated with reduced mortality, reduced length of stay in hospital, and cost reductions</p> <p>De-escalation of therapy based on culture was associated with reduced mortality</p> <p>Switching from intravenous to oral AB therapy did not influence mortality; it reduced costs and length of stay in hospital</p> <p>Discontinuation of empirical treatment based on no evidence of infection did not influence mortality; it was associated with reduced costs and had beneficial effects on resistance rates</p> <p>Bedside consultation was associated with reduced mortality</p>	10/11	145 studies were included, of which 64 were performed in Europe

Table A2.3. Summary of systematic reviews relevant to Option 3 – Continuous medical education (CME) and providing health information

Option element (and reference)	Focus of systematic review	Key findings	AMSTAR checklist (quality) rating	Proportion of studies that were conducted in Europe
Benefits (Van der Velden et al., 2012)	Effectiveness of physician-targeted interventions to improve AB use for RTIs	Physician education is important in optimizing AB (AB) use	8/11	The review comprised 58 studies describing a total of 87 interventions aiming to optimize AB prescribing; however, no list of authors was included in the main manuscript
Benefits (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	ASPs improve the quality of AB prescribing and reduce misuse and overuse of ABs	8/11	50 articles were included; 28 studies were conducted in Europe
Benefits (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Guidelines for diagnosis and/or management decrease uncertainty in AB prescribing	8/11	50 articles were included; 28 studies were conducted in Europe
Potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	The effectiveness of an intervention on AB prescribing depends on the physician's prescribing behaviour/preference and the barriers to change in the community	8/11	50 articles were included; 28 studies were conducted in Europe
Potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Physicians are faced with patient expectations, patient and provider lack of awareness of AMR, and lack of understanding of the seriousness of the issue of AMR	8/11	50 articles were included; 28 studies were conducted in Europe
Potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Physicians recognize the potential value of guidelines but are not always trusting of the information contained in the guidelines and the relevance to their patients	8/11	50 articles were included; 28 studies were conducted in Europe

Table A2.3. (Contd)

Option element (and reference)	Focus of systematic review	Key findings	AMSTAR checklist (quality) rating	Proportion of studies that were conducted in Europe
Potential harms (Crnich et al., 2015)	Optimizing AB stewardship in nursing homes: a narrative review and recommendations for improvement	Adoption of ASPs that promote judicious use of ABs is slower in nursing homes than in hospital and clinic settings, with formidable challenges to their effective implementation	7/11	Among 14 ASP intervention studies included, 3 were conducted in Europe
Potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Undertreatment is an issue, due to poor adaptation of guidelines, relocation of resources, and increased costs	8/11	50 articles were included; 28 studies were conducted in Europe
Resource use, costs and/or cost-effectiveness (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Planning and stakeholder support improve antimicrobial use	8/11	50 articles were included; 28 studies were conducted in Europe
Resource use, costs and/or cost-effectiveness (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Timing the intervention to coincide with peak infection season results in higher quality AB prescribing	8/11	50 articles were included; 28 studies were conducted in Europe
Resource use, costs and/or cost-effectiveness (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Reduced workload may improve AB prescribing but may add costs and prolong consultation times	8/11	50 articles were included; 28 studies were conducted in Europe
Uncertainty regarding benefits and potential harms (so monitoring and evaluation could be warranted if the option were pursued) (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Continuous quality improvement approaches might provide more valuable information than randomized trials	8/11	50 articles were included; 28 studies were conducted in Europe
Uncertainty regarding benefits and potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Harms associated with ASPs efforts are rarely reported, including additional utilization of health care services, and adverse events due to undertreatment.	8/11	50 articles were included; 28 studies were conducted in Europe

Table A2.3. (Contd)

Option element (and reference)	Focus of systematic review	Key findings	AMSTAR checklist (quality) rating	Proportion of studies that were conducted in Europe
Uncertainty regarding benefits and potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Few studies report patient satisfaction with care	8/11	50 articles were included; 28 studies were conducted in Europe
Uncertainty regarding benefits and potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Reporting of costs is limited and typically includes only drug costs, rather than costs associated with implementing the intervention and cost-benefit analyses	8/11	50 articles were included; 28 studies were conducted in Europe
Uncertainty regarding benefits and potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Most of the interventions are multifaceted, making specific recommendations about key components difficult	8/11	50 articles were included; 28 studies were conducted in Europe
Uncertainty regarding benefits and potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	There is uncertainty because no systematic reviews were identified about studies that reported microbial outcomes	8/11	50 articles were included; 28 studies were conducted in Europe
Uncertainty regarding benefits and potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	There is uncertainty because no systematic reviews were identified about resources required for programme implementation	8/11	50 articles were included; 28 studies were conducted in Europe
Uncertainty regarding benefits and potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Little information is available about ASPs in outpatient settings other than primary care or for patient conditions other than RTIs	8/11	50 articles were included; 28 studies were conducted in Europe
Uncertainty regarding benefits and potential harms (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Conclusions about the long-term effects of interventions are not yet possible	8/11	50 articles were included; 28 studies were conducted in Europe

Table A2.3. (Contd)

Option element (and reference)	Focus of systematic review	Key findings	AMSTAR checklist (quality) rating	Proportion of studies that were conducted in Europe
Uncertainty regarding benefits and potential harms (McDonagh et al., 2016)	Improving AB prescribing for uncomplicated acute RTIs	A few studies that attempted to assess appropriate prescribing have important limitations and there is a lack of consistency in outcome definition and ascertainment methods across studies	10/11	The review included 133 studies, including 88 randomized controlled trials; 55% of studies were conducted in Europe
Uncertainty regarding benefits and potential harms (McDonagh et al., 2016)	Improving AB prescribing for uncomplicated acute RTIs	Actual use of ABs was reported in too few studies to assess separately from prescribing	10/11	The review included 133 studies, including 88 randomized controlled trials; 55% of studies were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Arnold & Strauss, 2005)	Interventions to improve AB prescribing practices in ambulatory care	It is important to educate physicians to prevent the misuse/overuse of ABs for viral infections (for which they are of no value), or where there is no infection, and regarding the excessive use of broad-spectrum ABs in place of narrow-spectrum ABs, and the duration of use of ABs for conditions such as acute otitis media to improve AB prescribing in ambulatory settings	7/11	39 studies were examined, of which 13 were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	No single intervention can be recommended for all behaviours in any setting for any outcome	8/11	50 articles were included; 28 studies were conducted in Europe
Key elements of the policy option if it was tried elsewhere (McDonagh et al., 2016)	Improving AB prescribing for uncomplicated acute RTIs	No single intervention can be recommended for all behaviours in any setting for any outcome	10/11	The review included 133 studies, including 88 randomized controlled trials; 55% of studies were performed in Europe

Table A2.3. (Contd)

Option element (and reference)	Focus of systematic review	Key findings	AMSTAR checklist (quality) rating	Proportion of studies that were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Ranji et al., 2008)	Interventions to reduce unnecessary AB prescribing: a systematic review and quantitative analysis	No single intervention can be recommended for all behaviours in any setting for any outcome	10/11	43 studies reporting 55 separate trials were included; 14 studies were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Ranji et al., 2008)	Interventions to reduce unnecessary AB prescribing: a systematic review and quantitative analysis	Active clinician education strategies tended to be more effective than passive strategies	10/11	43 studies reporting 55 separate trials were included; 14 studies were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Arnold & Strauss, 2005)	Interventions to improve AB prescribing practices in ambulatory care	Multifaceted interventions where educational interventions occur on many levels can be successfully applied to communities after addressing local barriers to change	7/11	39 studies were examined, of which 13 studies were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	AMR, experience with withholding antimicrobials, external pressure to reduce ABP, and potential conflicts with patients play important role in AB prescribing	8/11	50 articles were included in the review; 28 studies were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Interventions should focus on changing behaviour, rather than simply providing medical information	8/11	50 articles were included in the review; 28 studies were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Communication with patients, health professionals, parents, educators, and day-care providers emphasizes the benefits and risks of AB use	8/11	50 articles were included in the review; 28 studies were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	The information should be clear, consistent, and positive (e.g. on bacterial versus viral infections, and the treatment of symptoms)	8/11	50 articles were included in the review; 28 studies were conducted in Europe

Table A2.3. (Contd)

Option element (and reference)	Focus of systematic review	Key findings	AMSTAR checklist (quality) rating	Proportion of studies that were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	A multi-media and multicultural approach is recommended, with focus groups to help refine the educational materials, use of spokespersons to deliver the messages, and academic detailing for health care providers	8/11	50 articles were included in the review; 28 studies were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Leadership is important (ideally with peers as local champions, instructors, and/or discussion leaders) along with use of a team approach (with input from health care professionals at all levels), patient education materials (ideally linked with provider materials on the same topic), provider reminders, user-friendly interfaces, and evidence-based materials to reduce overall AB use and improve AB prescribing	8/11	50 articles were included in the review; 28 studies were conducted in Europe
Key elements of the policy option if it was tried elsewhere (McDonagh et al., 2016)	Improving AB prescribing for uncomplicated acute RTIs	The best evidence supports the use of specific education interventions for patients/parents and clinicians, as well as electronic decision support to reduce overall AB use and improve AB prescribing for acute RTIs	10/11	The review included 133 studies, including 88 randomized controlled trials; 55% of studies were performed in Europe
Key elements of the policy option if it was tried elsewhere (Ranji, et al., 2008)	Interventions to reduce unnecessary AB prescribing: a systematic review and quantitative analysis	Strategies using active clinician education and targeting management of all acute RTIs (rather than single conditions in single age groups) yield larger reductions in community-level AB use	9/11	A total of 43 studies were included, reporting results for 55 separate trials; most studies were performed in the United States (17 studies) or Europe (12 studies)

Table A2.3. (Contd)

Option element (and reference)	Focus of systematic review	Key findings	AMSTAR checklist (quality) rating	Proportion of studies that were conducted in Europe
Key elements of the policy option if it was tried elsewhere (Van der Velden et al., 2012)	Effectiveness of physician-targeted interventions to improve AB use for RTIs	Interventions aiming to decrease overall AB prescribing are more frequently effective than interventions aiming to increase first-choice prescription	8/11	The review comprised 58 studies describing a total of 87 interventions aiming to optimize AB prescribing. However, no list of authors was included in the main manuscript
Stakeholders' views and experiences (Dyar et al., 2016)	How can we improve AB prescribing in primary care?	Changing health care professionals' attitudes and behaviour and modifying the health care system is important for improving AB prescribing practices	5/11	Among 12 intervention studies on improving AB prescribing, 3 were performed in Europe
Stakeholders' views and experiences (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Stakeholder involvement in developing the interventions improves antimicrobial use	8/11	50 articles were included in the review; 28 studies were conducted in Europe
Stakeholders' views and experiences (Drekonja et al., 2015)	Antimicrobial stewardship in outpatient settings: a systematic review	Planning and stakeholder support improve antimicrobial use	8/11	50 articles were included in the review; 28 studies were conducted in Europe

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