

## White Paper: Bridging the gap between surveillance data and antimicrobial stewardship in the outpatient sector—practical guidance from the JPIAMR ARCH and COMBACTE-MAGNET EPI-Net networks

Fabiana Arieti<sup>1</sup>†, Siri Göpel<sup>2,3</sup>†, Marcella Sibani <sup>1\*</sup>, Elena Carrara<sup>1</sup>, Maria Diletta Pezzani<sup>1</sup>, Rita Murri<sup>4</sup>, Nico T. Mutters<sup>5</sup>, Lorena Lòpez-Cerero<sup>6</sup>, Andreas Voss<sup>7</sup>, Roberto Cauda<sup>4</sup> and Evelina Tacconelli<sup>1,2,3</sup> on behalf of the ARCH working group‡

<sup>1</sup>Infectious Diseases Section, Department of Diagnostics and Public Health, University of Verona, Verona, Italy; <sup>2</sup>Infectious Diseases, Department of Internal Medicine I, Tübingen University Hospital, Tübingen, Germany; <sup>3</sup>German Centre for Infection Research (DZIF), Clinical Research Unit for healthcare associated infections, Tübingen, Germany; <sup>4</sup>Institute of Infectious Diseases, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; <sup>5</sup>Institute of Hygiene and Public Health, Bonn University Hospital, Bonn, Germany; <sup>6</sup>Microbiology and Infectious Diseases Unit, University Hospital Virgen Macarena, Sevilla, Spain; <sup>7</sup>Department of Clinical Microbiology and Infectious Diseases, Canisius-Wilhelmina Hospital, Nijmegen, The Netherlands

\*Corresponding author. E-mail: marcella.sibani@univr.it

†Equally contributing first authors.

‡Members are listed in the Acknowledgements section.

**Background:** The outpatient setting is a key scenario for the implementation of antimicrobial stewardship (AMS) activities, considering that overconsumption of antibiotics occurs mainly outside hospitals. This publication is the result of a joint initiative by the JPIAMR ARCH and COMBACTE-MAGNET EPI-Net networks, which is aimed at formulating a set of target actions for linking surveillance data with AMS activities in the outpatient setting.

**Methods:** A scoping review of the literature was carried out in three research areas: AMS leadership and accountability; antimicrobial usage and AMS; antimicrobial resistance and AMS. Consensus on the actions was reached through a RAND-modified Delphi process involving over 40 experts in infectious diseases, clinical microbiology, AMS, veterinary medicine or public health, from 18 low-, middle- and high-income countries.

**Results:** Evidence was retrieved from 38 documents, and an initial 25 target actions were proposed, differentiating between essential or desirable targets according to clinical relevance, feasibility and applicability to settings and resources. In the first consultation round, preliminary agreement was reached for all targets. Further to a second review, 6 statements were re-considered and 3 were deleted, leading to a final list of 22 target actions in the form of a practical checklist.

**Conclusions:** This White Paper is a pragmatic and flexible tool to guide the development of calibrated surveillance-based AMS interventions specific to the outpatient setting, which is characterized by substantial inter- and intra-country variability in the organization of healthcare structures, maintaining a global perspective and taking into account the feasibility of the target actions in low-resource settings.

### Introduction

Antimicrobial stewardship (AMS) in the outpatient setting is a critical aspect within a global scenario of the continuous increase in antimicrobial resistance (AMR) and overconsumption of antibiotics, which mainly occurs (approximately 80%–90%) outside hospitals.<sup>1–3</sup> Hence, it is impossible to hypothesize any AMS intervention

in the outpatient setting without the ability to adequately track antimicrobial use (AMU) and AMR. This process can be done in several ways, from single prescribing units to large territorial areas, and should be able to guarantee feedback to individual prescribers and allow benchmarking with regional and national data. Due to

the relevance of these data, many efforts have been undertaken at the international level (WHO, ESAC ECDC, Canadian Antimicrobial Resistance Surveillance System, Japanese Antimicrobial Consumption Surveillance) to standardize reporting. However, the heterogeneity of metrics for AMU surveillance, especially for the outpatient setting, makes it difficult to formulate clear recommendations on which metric should be preferred.<sup>4</sup>

While many AMS interventions focus on reducing consumption, it is important to point out that in many settings the AMS programme is developed to reduce AMR. In the outpatient setting, a number of initiatives (i.e. educational tools and awareness campaigns) have been proved to be successful in enhancing appropriateness of prescriptions. However, although good examples of bottom-up AMS initiatives integrated into outpatient daily clinical practice are increasingly being described,<sup>5</sup> high-quality evidence data showing the impact of such initiatives on microbiological outcomes are still limited, mainly because of scarce and heterogeneous reporting of data.<sup>6</sup> Indeed, when it comes to the other pillar of AMS interventions (i.e. monitoring AMR), the outpatient setting is even more challenging because most therapeutic decisions are made empirically. Microbiological data, when available, are difficult to interpret and are rarely representative of the general population.

Despite the availability of guidelines for implementation and management of AMS programmes in the community (CDC Core Elements and Field Guide, SHEA MITIGATE for Emergency Department and Urgent Care, Joint Commission Antimicrobial Stewardship Ambulatory Care), practical recommendations on how prescribers should relate to local microbiological and consumption data to improve prescriptions are rarely discussed. Undoubtedly, in a context where each country has its own legislation regulating both antibiotic policies and outpatient entities, it is difficult to issue widely applicable recommendations. The outpatient setting can be an elusive concept to outline and several definitions are found in the literature (Table 1); additionally, its organization has been continuously and rapidly changing in recent decades, even in low- and middle- income countries (LMICs).<sup>7,8</sup>

For the purposes of this research paper, JPIAMR ARCH and COMBACTE-MAGNET EPI-Net<sup>9,10</sup> have harmonized efforts to

outline a structured approach that provides a set of actions to facilitate antibiotic policy interventions and drive the link between surveillance data on AMR and antibiotic consumption and implementation of AMS activities.

The international expert panel has produced a series of White Papers focused on four different settings: hospital; outpatient; long-term care facilities (LTCFs); and veterinary. The research questions that constitute the evidence base for the recommendations focused on three main areas: (i) leadership commitment, accountability and AMS team; (ii) AMU and AMS; and (iii) AMR and AMS. The final list of target actions summarizes the epidemiological, microbiological and antimicrobial data that are essential for antibiotic prescribing and policy. The entire process was underpinned by a strong focus on the feasibility of the actions and the One Health approach. This paper focuses on the outpatient setting, namely any care service provided to patients who are not admitted to a hospital or LTCF, ranging from immediate treatment for an acute and often serious illness (e.g. emergency outpatient clinics) to outpatient specialty clinics and primary health care facilities that provide preventive and curative services (Table 1). The intended audience of this White Paper is healthcare professionals and leaders working in outpatient clinics in high-income countries who are willing to establish or implement an effective AMS programme; however, specific references to LMICs are also provided whenever feasible and relevant. The checklists produced are available for download on the ARCH website,<sup>9</sup> and can be used as practical tools by health professionals and policymakers to establish and/or monitor stewardship activities. Dissemination will be ensured by the networks involved in the JPIAMR ARCH project that are listed in Table 1 of the first paper in this series.<sup>11</sup>

## Methods

Using a One Health approach, the present project was conceived to develop expert consensus based on evaluation of the available literature and guidance documents on AMS and surveillance. This was followed by the development of a first draft of targets and a RAND-modified Delphi process for the definitive validation of targets (protocol available at the ARCH website).<sup>9</sup> The entire process is described in the first paper of this series, which focuses on the hospital setting.<sup>11</sup> Briefly, the process involved the following: development of key research questions (listed in Table 3 of the first White Paper of this series) deriving from a systematic review previously developed to provide guidance on the AMR surveillance modalities that are best suited to driving stewardship interventions in hospitals (EPI-Net COACH project);<sup>12</sup> a narrative review of the available evidence; the production of a first draft of targets provided to the experts in a web-based survey in which agreement was expressed on a nine-point Likert scale; a 2 day face-to-face meeting held at the end of October 2019. For the literature search, relevant publications in English, published in the last 10 years, were screened with a step-wise approach: first, guidance (from scientific societies, international and national authorities) and documents included in the EU-JAMRAI repository<sup>13</sup> were assessed, and then the search was carried out using MEDLINE (National Library of Medicine, Bethesda, MD, USA) with a combination of the following terms: antimicrobial, consumption, outpatient, antimicrobial drug resistance and surveillance.

Next, during the face-to-face meeting, the experts were presented with a summary of the evidence, discussed the results of the online survey and finalized the list of targets. Recommendations, state of the art, and original approaches were evaluated by focusing on feasibility and adaptability to different economic and healthcare contexts to compile a list of 'essential' and 'desirable' targets. Targets were recognized as 'essential' when widely

**Table 1.** Definitions of outpatient settings

Reference	Definition
59	An outpatient is a person who goes to a healthcare facility and who leaves the facility within 3 h of the start of consultation. An outpatient is not formally admitted to a facility.
60	Care provided in facilities where patients do not remain overnight (e.g. hospital-based outpatient clinics, non-hospital-based clinics and physician offices, urgent care centres, ambulatory surgical centres etc.).
61 <sup>a</sup>	Any care service provided to patients who are not admitted as inpatients to a hospital.

<sup>a</sup>For the purposes of this document, we considered this broad definition of outpatient setting; however, most of the evidence found in the literature review was related to GP clinics, family physician clinics and paediatric clinics.

practicable if not already broadly accomplished, and 'desirable' in the case of limited feasibility or resource constraints. Topics for which more evidence was required in order to draw up recommendations were defined as priority topics for future research. A total of 40 experts from 18 countries and 30 networks developed the protocol, contributed to reaching a consensus and approved the final list of indications (see first paper in this series).

## Results

A total of 38 documents were included for the appraisal,<sup>2,6,14-49</sup> covering all regions worldwide; however, the majority (32, 84%) were from Europe, North America or the East Asia and Pacific regions. Most of the evidence was retrieved from guidelines, systematic reviews, practical guides or tools, studies and surveillance reports, mostly encompassing adult and paediatric settings. A limited number of expert opinion and study protocol documents were also included.

Evidence for the leadership commitment, accountability and AMS team research area was retrieved from 10 guidelines, 3 systematic reviews and 1 study protocol, while evidence relative to AMU and AMS was obtained from 8 guideline documents, 6 reviews, 13 study articles or reports, 3 practical tools and 1 expert opinion. No guidelines specifically addressing AMR and AMS were identified, and evidence for this topic was retrieved from eight documents, including reviews, studies, a few practical tools and expert opinion.

Preliminary statements for the three areas of research (leadership commitment, accountability and AMS team; AMU and AMS; and AMR and AMS) were established. Twenty experts rated the initial statements through an online survey and agreement was reached for all of them; however, during the face-to-face meeting (October 2019) some aspects were discussed further: 6 statements were re-considered and re-phrased and 3 were deleted, leading to a list of 22 target actions that were approved in their final version by the entire panel. Tables 2-4, respectively, list the

recommended targets for the three areas of research. Due to lack of evidence or expert agreement, it was not possible to formulate targets on one research question for AMU and AMS and on three research questions for AMR and AMS, highlighting the gaps in the literature and expanding the list of research priorities (Table 5).

## Discussion

### **Leadership commitment, accountability and antimicrobial stewardship team**

The outpatient setting is characterized by consistent inter- and intra-country variability in the organization of healthcare structures, which reflects the complexity in the design of AMS programmes. Nevertheless, it is crucial to identify a clear leader (or leaders) to guide the AMS team and activities.<sup>19,50</sup> In large administrative settings such as outpatient clinics, an organizational structure following the 'hub and spoke' model can be considered. For example, in the case of an outpatient service linked to a hospital, resources such as the microbiology laboratory, pharmacy, IT structure and guidance by infectious disease specialists can be used to drive AMS activities, while in low-income countries existing programmes such as those for HIV, malaria and tuberculosis can be integrated with AMS to save resources. By contrast, in the case of smaller prescribing units such as single GPs, dentists or other specialties, a clear AMS leader should be identified for each unit. The working group highlighted the crucial role of several different professionals within the outpatient setting. GPs are necessarily the pivots of most AMS activities in this setting; however, depending on the resources and specific characteristics, leading roles can be assigned to other physicians, a physician's assistant, an advanced practice registered nurse or a pharmacist. The inclusion of a district pharmacist can be a key element to deliver messages to patients and physicians,<sup>21,51</sup> especially, but not only, in low-resource settings and in countries with a high proportion of unprescribed

**Table 2.** Leadership commitment, accountability and antimicrobial stewardship team in the outpatient setting

#### **Participants in the antimicrobial stewardship team**

##### 1.1. Essential

The AMS team should be multidisciplinary. Core members should include leaders with experience in AMS and surveillance, a representative of pharmacies in the local district and a representative of general practitioners.

##### 1.2. Desirable

Include additional figures in the core group according to the setting, resources and type of intervention (i.e. other specialists from target wards, infection control nurses and IT experts).

#### **Institutional support for the organization and management of antimicrobial stewardship programmes: legal framework**

##### 1.3. Essential

Regulate and promote AMS activities at every level of healthcare organization with well-defined roles, responsibilities and a clear governance structure.

#### **Institutional support for the organization and management of antimicrobial stewardship programmes: staffing personnel**

##### 1.4. Essential

Include dedicated time and specific salary support for AMS activities as part of AMS programmes.

##### 1.5. Essential

Allocate full-time equivalents according to national requirements for the different settings and level of intervention, where available.

**Table 3.** Antimicrobial usage and antimicrobial stewardship in the outpatient setting**Which antibiotics should be monitored?**

## 2.1. Essential

Include as minimum requirements of monitoring:

- overall consumption of antibiotics
- IV and oral antibiotics used in high volumes or according to the local ranking (5–10 most used agents)
- antimicrobials included in the Watch and Reserve categories WHO Essential Drug List AWARE index
- antibiotics used for treating infections caused by locally clinically relevant resistant pathogens as defined by the AMS team

## 2.2. Desirable

Monitor the total consumption of systemic antimicrobials (ATC J01 class), both IV and oral formulations, as overall aggregated data and as sub-classes or individual agents.

## 2.3. Desirable

Stratify data by prescribing medical specialty (i.e. general practitioner, paediatrician, dentist) to allow for benchmarking. Target indications/syndromes for which antibiotics should be monitored:

- Respiratory tract infection (RTI), including upper and lower RTI
- Urinary tract infection
- Diarrhoea (depending on local epidemiology and relevance)
- Sexually transmitted diseases
- Skin and soft tissue infections

**Which metrics should be employed?**

## 2.4. Essential

For national/regional surveillance, monitor DDDs per 1000 inhabitants per day and number of prescriptions per 1000 inhabitants per year

## 2.5. Essential

For surveillance at the prescriber level, monitor number of prescriptions either per 100 patients/year or 100 patient contacts/year

## 2.6. Desirable

For national/regional surveillance, monitor number of prescriptions per 100 physician contacts/year

## 2.7. Desirable

For surveillance at the prescriber level, monitor DDD per 100 patients per year

## 2.8. Desirable

Further metrics should be based on logistics and the types of Antimicrobial Stewardship interventions that will be implemented; for interventions targeting over-prescription for specific diagnoses, monitor prescription rate for specific diagnoses [prescription/indication/prescriber/year (month)].

**Report delivery**

## 2.9. Essential

Make local aggregated data available for physician networks and specific prescribing units. Stratification by specialty or indication should be done whenever possible.

## 2.10. Desirable

If consumption data broken down by single prescriber activity (i.e. number of DDDs or prescriptions attributable to each individual general practitioner or other prescribers) are available, deliver them to the specific prescribing units, making them available to prescribers and caregivers, but also to administration. Perform further aggregation by specialty or stratification by indication whenever possible.

**Which time interval should be used for reporting?**

## 2.11. Essential

Provide antimicrobial consumption data on a regular basis, at least annually.

## 2.12. Desirable

The data should be aggregated at least quarterly to allow for describing seasonal variation in trends in high-usage indications of respiratory infections.

antibiotic sales where pharmacies and other private drug stores represent the primary access points for antimicrobials.<sup>52</sup> Other potential partners, especially in the case of smaller administrative

units, can be local healthcare departments, health insurance companies, healthcare professional societies, local microbiology laboratories and LTCFs. In LMICs, the integration of AMS efforts into

**Table 4.** Antimicrobial resistance and antimicrobial stewardship in the outpatient setting**Which resistant pathogens should be targeted?**

## 3.1. Essential

Identify and monitor most predominant resistance patterns among urinary tract cultures.

**How should resistance be monitored?**

## 3.2. Desirable

All samples (obtained inside and outside the hospital) should be clearly categorized in healthcare-associated or community-acquired samples to allow for risk stratification and direct empirical therapy in outpatient and hospital settings.

**What time interval should be used for reporting antimicrobial resistance surveillance data?**

## 3.3. Essential

Provide resistance surveillance data at least yearly, reporting only data for which 30 or more isolates are available.

**Should the report be delivered to healthcare professionals other than the antimicrobial stewardship team?**

## 3.4. Essential

Deliver a report to prescribing units, making them available to prescribers and caregivers, but also to administration.

## 3.5. Desirable

Deliver a report to prescribers with a commentary; consider highlighting specific data that might require re-evaluation of therapeutic guidelines.

well-established structures for surveillance and treatment of communicable diseases such as HIV, malaria and tuberculosis was identified by the panel as a strategy to use in the implementation of AMS activities.

In terms of institutional support through a legal framework, the available literature mostly focuses on the relevance of the commitment of public health authorities in promoting AMS and communicating with patients and healthcare professionals, identifying AMS coordinators at a local level and including AMS-related duties within job descriptions.<sup>19,22,25,50</sup> Some countries, for example, have implemented financial incentives for primary care providers. Pay-for-performance systems are implemented within the UK's National Health Service, the national health service in France and the healthcare system in the USA.

**Antimicrobial usage and antimicrobial stewardship**

The available guidance on AMS in the outpatient setting suggests monitoring prescriptions for conditions typically associated with a high rate of inappropriate prescribing without indicating specific pharmaceutical categories. Currently, most high-income countries and an increasing number of LMICs have data flows from reimbursement or sales records that can provide data to national or international surveillance systems. Periodic reports or electronic tools allow open consultation of these surveillance data at the country or regional level,<sup>27,31</sup> with the additional possibility of tracking consumption of systemic antibiotics (ATC J01) in distinct hospitals and communities. In some cases, the data can be also broken down to J01 subgroups or to single agents and presented as absolute consumption of single classes or as the ratio of broad-spectrum antibiotics to total consumption. Antimicrobials other than antibiotics (e.g. antimycobacterials, antiparasitics) may also be available in some cases.

The AWARE index, introduced by the WHO, appears to be a promising globally oriented approach for data stratification and evaluation of performance.<sup>53,54</sup> Most national action plans, as well

as the WHO 'adopt AWaRe' initiative, establish goals in terms of desirable shifts in consumption (i.e. reduction or increase in consumption of specific agents, classes or other defined categories). Considering the intrinsic need for benchmarking and improvements in tracking, the targets proposed by the expert panel are intended to promote alignment between local and referral AMU data. Tracking consumption at the ATC J01 subclass or agent level represents the most desirable option, but its feasibility is restricted to well-structured contexts such as hospital outpatient clinics or countries where primary care services are organized on a local basis and include a centralized pharmacy service that is able to maintain a complete and updated data flow. Consistent with other human settings, for the outpatient setting the experts proposed a less demanding, bundle approach as an essential target, which requires monitoring, beyond overall consumption, of the most frequently prescribed agents, including those in the Watch and Reserve categories of the WHO AWaRe index and other antibiotics specifically indicated by the AMS team, considering local epidemiology (Table 3). The introduction of monitoring of IV antibiotics (Table 3, target 2.1) finds its rationale in the growing implementation of services for IV administration without hospital stay through community-based management, such as outpatient parenteral antimicrobial therapy (OPAT). For surveillance purposes, consumption in the community setting is reported as DDDs per 100 or 1000 inhabitants. A previous consensus effort, aiming to develop a set of quantitative AMS metrics to be employed in outpatients, highlighted the need to combine more than one metric to overcome intrinsic pitfalls and optimize interpretation.<sup>39</sup> Considering different AMS organizations and levels of intervention, the expert panel provides distinct stepwise approaches (Table 3, targets 2.4–2.8). Where a centralized pharmacy service is in place, DDD-based metrics are easy to obtain and can be routinely calculated for monitoring of consumption, handling costs and reimbursements; in this context, obtaining the number of prescriptions requires additional work and dedicated resources. When initiatives for AMS

**Table 5.** Research priorities

---

- **Develop standardized and reliable surveillance definitions and outcome data**

Rationale

While criteria to discriminate hospital- from community-acquired infections exist, microbiological samples submitted from outpatient settings may not reflect the true origin of infections. Resistance rate in the community could be overestimated when overrepresentation of samples from patients with specific risk factors (e.g. exposure to healthcare facilities such as day service practices, indwelling device carriers, recurrent infections, etc.) occurs. Standardized definitions allowing unambiguous views of the most probable setting of infection acquisition, further patient-based stratification criteria (e.g. age, gender, specific risk factor) and the establishment of the minimum number of isolates necessary to provide consistent data, would help in collecting more reliable surveillance data to inform prescribing practice and empirical therapy.

---

- **Appraise and establish new strategies for AMU surveillance in community**

Rationale

As current metrics and formats for AMU monitoring were developed for surveillance not directly considering AMS goals and strategy, the most effective methods for antimicrobial consumption data collection in the community setting still have to be identified, especially in regard to its correlation with antimicrobial resistance trends. The feasibility/reliability of point prevalence surveys (PPSs) of antibiotic use in the community setting have been poorly explored until now.

The assessment of self-medication and over-the-counter dispensing at national, regional and local levels (through PPSs or other suitable methodologies) would not only provide essential data to correctly estimate actual antimicrobial consumption, but would also guide policymakers in establishing antimicrobial dispensing regulations.

---

- **Generate evidence to understand the role of vaccination in AMS**

Rationale

Many AMR regulatory documents and AMS guidance point out vaccination as a promising strategy to limit AMR. Even though the rationale of this endorsement appears clear, limited studies have analysed antimicrobial consumption and resistance trend variations as direct effects of vaccination campaigns or the association between vaccination coverage and antimicrobial usage and resistance rate. More evidence is needed on the effect of vaccines on antibiotic use and resistance. Solid statistical tools and adequate study designs to assess such a link should be evaluated and implemented.

---

efforts come from small prescribing units, simple databases can record the number of prescriptions over time. As a further step, the panel encourages data stratification based on prescriber speciality, and suggests the tracking of prescriptions (overall volumes as well as relative consumption of specific antimicrobial agents/classes) tackling high-priority conditions, such as those for which antibiotics are overprescribed (e.g. acute bronchitis, viral pharyngitis) or are likely to be ineffective due to increasing resistance rates [e.g. urinary tract infections (UTIs) and sexually transmitted diseases]. Although this approach requires detailed recording of prescribing indications that is rarely in place, its implementation would allow meaningful benchmarking and data tracking improvements.

The data collected should be regularly disseminated to administrators and prescribers (Table 3 targets 2.9–2.12). The aforementioned stratification should be employed to tailor reports, which should also consider the specific intervention to be implemented and goals to be pursued. Regional or local, aggregated, population-based data should be provided to increase awareness of prescribers and administrators regarding the distance from best practice and progress made over time, as well as to promote shared efforts within the same area and across the continuum of care (e.g. referral hospitals and surrounding LTCFs). The importance of complementing data dissemination with structured educational activities to foster understanding and enhancing desirable prescribing practice is further stressed by the panel.

Detailed data for single prescribing units (small prescriber groups, ambulatory care) or individual prescribers allow peer

comparisons of performance, an approach that has been demonstrated to be highly effective in outpatient AMS.<sup>55,56</sup> To provide meaningful and close-to-practice data, annual reporting is suggested. Quarterly aggregated data and corresponding reporting, when volume of use is large enough to provide reliable data, has the potential to reveal seasonal trends that warrant further investigation or specific countermeasures.

Self-medication and over-the-counter distribution were also acknowledged by the members of the panel as issues that can have an important impact on AMR, especially (but not only) in LMICs where policies regulating the sale of antimicrobials, including the requirement of a prescription for human use, are not in place.<sup>57,58</sup> Estimating the amount of this dispensing route was deemed to be of value. However, considering that local and national healthcare authorities are responsible for this rather than single practitioners or a local AMS team acting in small prescribing units, after discussion the target was deleted from the list and outlined as a topic for future research (Table 5).

### **Antimicrobial resistance and antimicrobial stewardship**

With regard to AMR surveillance, evidence on specific pathogens to be targeted in the outpatient setting is limited. The majority of guidance documents suggest the tracking of antibiotic resistance trends among ‘common outpatient pathogens’, community-associated *Clostridioides difficile* infections and infection rates with ‘multidrug-resistant organisms’ without specifying which pathogens.<sup>22,38,47,48</sup> This limitation is mainly related to the fact that, in

the outpatient context, microbiological analysis of various specimens to determine pathogens and related susceptibilities is often impractical. Some review documents focus on the most common infections, such as respiratory tract infections (RTIs) and UTIs. Consequently, the most relevant pathogens are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae* and Enterobacteriaceae.<sup>4,7</sup> Acknowledging the difficulties associated with sample collection, the panel considered that monitoring RTI resistance in outpatients is not feasible, as only a few samples are normally submitted for microbiological analysis. Accordingly, it was decided to focus on syndromes displaying a greater burden of resistance, suggesting that resistance be monitored only for UTIs (Table 4, target 3.1). Nevertheless, the importance of categorizing all samples (obtained both in and out of hospital) in healthcare-associated or community-acquired settings to allow risk stratification and direct empirical therapy in outpatient and hospital settings was underlined. Further stratifications by gender, age and risk factors were discussed, but they were not included in the final targets due to lack of feasibility and reliability.

On AMR reporting, the expert panel agreed on the fact that the report should be delivered to all prescribing units and healthcare authorities. It should be made available to administration, prescribers, caregivers and nurses of all units. The expert panel further stressed the importance not only of passively delivering a report, but also of linking dissemination of surveillance data with structured educational activities to improve understanding and drive clinical practice. However, considering possible resource constraints, this was held to be desirable and not essential (target 3.5). It was also suggested that an English version of the report be included to foster the sharing of information between countries. Moreover, as previously advocated,<sup>58</sup> the panel highlighted the fact that educational efforts should target not only physicians, but also undergraduate students. In this context, the undergraduate curriculum could be expanded to allow teaching of the principles of microbiology, infectious diseases and clinical pharmacology with emphasis on AMR and prudent prescribing.

The available literature did not allow the development of detailed indications on a few important questions related to AMU reporting and AMR monitoring and reporting in the outpatient setting. The research question initially formulated for topic 2, 'Which criteria should be used to define a ranking for antibiotic use?', and the research questions of topic 3, 'Should non-clinical samples (e.g. screening) be monitored?', 'Should specific thresholds be established for driving AMS recommendations for empirical therapy?' and 'Which stratification should be used to drive selective reporting of antibiograms?', should therefore be considered priorities for future research. Three main research priorities including inputs for policymakers are summarized in Table 5. Lastly, the panel discussed the importance of expanding a similar list of consensus targets for tuberculosis and other pathogens (fungi and viruses) in the future.

## Conclusions

The 22 targets developed herein were conceptualized as a list of pragmatic and broadly applicable actions to guide development of an AMS programme in the outpatient setting. Despite the intrinsic limitations given by the subjective nature of expert opinion

methodology, one strength of this work is that the target actions have been proposed by a broad panel of professionals, encompassing human and veterinary medicine in a One Health approach. Another strength of this work is the categorization of the target actions as essential (considered as the minimum requirements) and desirable (actions to be considered for the further and optimal implementation of an AMS plan), taking into account low-resource settings, including those characterized by lack of qualified personnel and laboratory infrastructure due to budget constraints.

## Acknowledgements

We are very grateful to Ruth Joanna Davis for her support in the management of the project, and to Michaela Hardiman and Nadine Conzelmann for their administrative support.

## Members of the ARCH working group

Ayola Akim Adegnikia, Centre de Recherches Médicales de Lambaréné (CERMEL), Lambaréné, Gabon, and Institut für Tropenmedizin and German Center for Infection Research, partner site Tübingen, Universitätsklinikum, Wilhelmstraße, Tübingen, Germany; Fabiana Arieti, Infectious Diseases Section, Department of Diagnostics and Public Health, University of Verona, Verona, Italy; Nithya Babu Rajendran, Infectious Diseases, Department of Internal Medicine I, Tübingen University Hospital, Tübingen, Germany, and German Centre for Infection Research (DZIF), Clinical Research Unit for healthcare associated infections, Tübingen, Germany; Julia Bielicki, Pediatric Infectious Diseases, University Children's Hospital Basel, Basel, Switzerland, and Pediatric Infectious Disease Research Group, Institute for Infection and Immunity, St George's University of London, London, UK; Steffen Borrmann, Centre de Recherches Médicales de Lambaréné (CERMEL), Lambaréné, Gabon, and Institut für Tropenmedizin and German Center for Infection Research, partner site Tübingen, Universitätsklinikum, Wilhelmstraße, Tübingen, Germany; Elena Carrara, Infectious Diseases Section, Department of Diagnostics and Public Health, University of Verona, Verona, Italy; Roberto Cauda, Institute of Infectious Diseases, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; Monica Compri, Infectious Diseases Section, Department of Diagnostics and Public Health, University of Verona, Verona, Italy; Giulia De Angelis, Dipartimento di Scienze Biotechnologiche di base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Rome, Italy; Raquel Duro, Unit for the Prevention and Control of Infection and Antimicrobial Resistance, Centro Hospitalar Universitário de São João, Oporto, Portugal; Isabel Frost, Centre for Disease Dynamics, Economics & Policy, New Delhi, India; Faculty of Medicine, Department of Infectious Disease, Imperial College, London, UK; Liliana Galia, Infectious Diseases Section, Department of Diagnostics and Public Health, University of Verona, Verona, Italy; Petra Gastmeier, German Centre for Infection Research Association (DZIF), Braunschweig, Germany, and Institute for Hygiene and Environmental Medicine, Charité – Universitätsmedizin Berlin, Germany, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health; Christian Giske, Department of Clinical Microbiology, Karolinska University Hospital, Stockholm, Sweden; Department of Laboratory Medicine, Karolinska University Hospital, Stockholm, Sweden; Siri Göpel, Infectious Diseases, Department of Internal Medicine I, Tübingen University Hospital, Tübingen, Germany, and German Centre for Infection Research (DZIF), Clinical Research Unit for healthcare associated infections, Tübingen, Germany; Herman Goossens, Department of Medical Microbiology, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium; Gunnar Kahlmeter, Department of Clinical Microbiology, Växjö Central Hospital, Växjö, Sweden; Souha S. Kanj,

Division of Infectious Diseases, Department of Internal medicine, and Infection Control and Prevention Program, and Antimicrobial Stewardship Program, American University of Beirut Medical Center, Beirut, Lebanon; Tomislav Kostyanev, Department of Medical Microbiology, Vaccine & Infectious Disease Institute, University of Antwerp, Antwerp, Belgium; Leonard Leibovici, Medicine E, Rabin Medical Center, Beilinson Hospital, Petah Tikva, Israel, and Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel; Jean-Christophe Lucet, Infection Control Unit, Bichat-Claude Bernard Hospital, AP-HP, Paris, France; IAME, UMR 1137, DeSCID team, Université Paris Diderot, Sorbonne Paris Cité, Paris, France; Lorena López-Cerero, Microbiology and Infectious Diseases Unit, University Hospital Virgen Macarena, Sevilla, Spain; Rodolphe Mader, University of Lyon, French Agency for Food, Environmental and Occupational Health and Safety (ANSES), Laboratory of Lyon, Antimicrobial Resistance and Bacterial Virulence Unit, Lyon, France; Fulvia Mazzaferri, Infectious Diseases Section, Department of Diagnostics and Public Health, University of Verona, Verona, Italy; Elena Mazzolini, Department of Epidemiology, Istituto Zooprofilattico Sperimentale delle Venezie, Legnaro, Padua, Italy; Marc Mendelson, Division of Infectious Diseases and HIV Medicine, Department of Medicine, University of Cape Town, Cape Town, South Africa; Rita Murri, Institute of Infectious Diseases, Fondazione Policlinico Universitario A. Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy; Nico T. Mutters, Institute of Hygiene and Public Health, Bonn University Hospital, Bonn, Germany; Mical Paul, Diseases Institute, Rambam Health Care Campus, Ruth and Bruce Rappaport Faculty of Medicine, Technion - Israel Institute of Technology, Haifa, Israel; Maria Diletta Pezzani, Infectious Diseases Section, Department of Diagnostics and Public Health, University of Verona, Verona, Italy; Elisabeth Presterl, European Committee on Infection Control, Basel, Switzerland, and Department of Infection Control and Hospital Epidemiology, Medical University of Vienna, Vienna, Austria; Hanna Renk, University Children's Hospital Tübingen, Department of Paediatric Cardiology, Pulmology and Intensive Care Medicine, Tübingen, Germany; Oana Sandulescu, Department of Infectious Diseases I, Faculty of Medicine, Carol Davila University of Medicine and Pharmacy, Bucharest, National Institute for Infectious Diseases 'Prof. Dr Matei Balș' Bucharest, Romania; Le Huu Song, Vietnamese German Center for Medical Research, Hanoi, Vietnam, and 108 Military Central Hospital, Hanoi, Vietnam; Maurizio Sanguinetti, Dipartimento di Scienze Biotechnologiche di base, Cliniche Intensivologiche e Perioperatorie, Università Cattolica del Sacro Cuore, Rome, Italy, and Dipartimento di Scienze di Laboratorio e Infettivologiche, Fondazione Policlinico Universitario A. Gemelli IRCCS, Rome, Italy; Remco Schrijver, VetEffect, Bilthoven, The Netherlands; Luigia Scudeller, Scientific Direction of IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano, Milano, Italy; Mike Sharland, Paediatric Infectious Diseases Research Group, Institute for Infection and Immunity, St George's University of London, London, UK; Marcella Sibani, Infectious Diseases Section, Department of Diagnostics and Public Health, University of Verona, Verona, Italy; Evelina Tacconelli, Infectious Diseases Section, Department of Diagnostics and Public Health, University of Verona, Verona, Italy, and Infectious Diseases, Department of Internal Medicine I, Tübingen University Hospital, Tübingen, Germany, and German Centre for Infection Research (DZIF), Clinical Research Unit for healthcare associated infections, Tübingen, Germany; Didem Torumkuney, International Federation of Pharmaceutical Manufacturers and Associations (IFPMA), Geneva, Switzerland; Thirumalaisamy P. Velavan, Institute of Tropical Medicine, Universitätsklinikum Tübingen, Germany, and Vietnamese German Center for Medical Research, Hanoi, Vietnam, and Faculty of Medicine, Duy Tan University, Da Nang, Vietnam; Andreas Voss, Department of Medical Microbiology, Radboud University Medical Centre, Nijmegen, The Netherlands.

## Funding

This research project has received funding from the Innovative Medicines Initiative Joint Undertaking under grant agreement No. 115737, resources of which are composed of financial contribution from the European Union Seventh Framework Programme (FP7/2007-2013) and European Federation of Pharmaceutical Industries and Associations (EFPIA) companies in-kind contribution, and the German Federal Ministry of Education and Research (BMBF) (Project ID 01KI1830) under the Joint Programme Initiative on Antimicrobial Resistance (JPIAMR) 2018 call.

## Transparency declarations

The authors have none to declare. Patrick Moore of Adriatic Health Communications provided medical writing services for the editing and proofing of this paper. This article forms part of a Supplement.

## References

- 1 Ashiru-Oredope D, Hopkins S. Antimicrobial stewardship: English Surveillance Programme for Antimicrobial Utilization and Resistance (ESPAUR). *J Antimicrob Chemother* 2013; **68**: 2421-3.
- 2 Suda KJ, Hicks LA, Roberts RM *et al*. Antibiotic expenditures by medication, class, and healthcare setting in the United States, 2010-2015. *Clin Infect Dis* 2018; **66**: 185-90.
- 3 English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018-2019. [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/843129/English\\_Surveillance\\_Programme\\_for\\_Antimicrobial\\_Utilisation\\_and\\_Resistance\\_2019.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/843129/English_Surveillance_Programme_for_Antimicrobial_Utilisation_and_Resistance_2019.pdf).
- 4 Morris AM, Calderwood MS, Fridkin SK *et al*. Research needs in antibiotic stewardship. *Infect Control Hosp Epidemiol* 2019; **40**: 1334-43.
- 5 Rodriguez-Bano J, Perez-Moreno MA, Penalva G *et al*. Outcomes of the PIRASOA programme, an antimicrobial stewardship programme implemented in hospitals of the Public Health System of Andalusia, Spain: an ecological study of time-trend analysis. *Clin Microbiol Infect* 2020; **26**: 358-65.
- 6 Drekonja DM, Filice GA, Greer N *et al*. Antimicrobial stewardship in outpatient settings: a systematic review. *Infect Control Hosp Epidemiol* 2015; **36**: 142-52.
- 7 Berman P. Organization of ambulatory care provision: a critical determinant of health system performance in developing countries. *Bull World Health Organ* 2000; **78**: 791-802.
- 8 Cox JA, Vlieghe E, Mendelson M *et al*. Antibiotic stewardship in low- and middle-income countries: the same but different? *Clin Microbiol Infect* 2017; **23**: 812-8.
- 9 JPIAMR ARCH. <https://archnet-surveillance.eu/>.
- 10 COMBACTE-MAGNET EPI-Net. <https://www.epi-net.eu>.
- 11 Pezzani MD, Carrara E, Sibani M *et al*. White Paper: Bridging the gap between human and animal surveillance data, antibiotic policy and stewardship in the hospital sector—practical guidance from the JPIAMR ARCH and COMBACTE-MAGNET EPI-Net networks. *J Antimicrob Chemother* 2020; **75** Suppl 2: ii20-ii32.
- 12 Pezzani MD, Mazzaferri F, Compri M *et al*. Linking antimicrobial resistance surveillance to antibiotic policy in healthcare settings: the COMBACTE-Magnet EPI-Net COACH project. *J Antimicrob Chemother* 2020; **75** Suppl 2: ii2-ii19.
- 13 European Joint Action Antimicrobial Resistance and Healthcare-Associated Infections. *Deliverable 7.1 (Rev 01) Website with Evaluated Tools and Information, Guidelines, Tools and Implementation Methods for Antibiotic Stewardship*. <https://ec.europa.eu/research/participants/documents/downloadPublic?documentIds=080166e5bed42157&appId=PPGMS>

- 14** Australian Commission on Safety and Quality in Health Care. *Antimicrobial Stewardship in Australian Health Care*. <https://www.safetyandquality.gov.au/sites/default/files/migrated/AMSAH-Book-WEB-COMPLETE.pdf>.
- 15** EU Guidelines for the Prudent Use of Antimicrobials in Human Health. <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52017XC0701%2801%29>
- 16** European Centre for Disease Prevention and Control. *Proposal for EU Guidelines on the Prudent Use of Antimicrobials in Humans*. <https://www.ecdc.europa.eu/sites/default/files/media/en/publications/Publications/EU-guide-lines-prudent-use-antimicrobials.pdf>.
- 17** Bielicki J, Lundin R, Patel S et al. Antimicrobial stewardship for neonates and children: a global approach. *Pediatr Infect Dis J* 2015; **34**: 311–13.
- 18** Health: Republic of South Africa. *Guidelines on Implementation of the Antimicrobial Strategy in South Africa: One Health Approach & Governance*. [http://nahf.co.za/wp-content/uploads/Antimicrobial-Stewardship-Guidelines-Governance\\_June2017.pdf](http://nahf.co.za/wp-content/uploads/Antimicrobial-Stewardship-Guidelines-Governance_June2017.pdf).
- 19** Sanchez GV, Fleming-Dutra KE, Roberts RM et al. Core elements of outpatient antibiotic stewardship. *MMWR Recomm Rep* 2016; **65**: 1–12.
- 20** Kilgore JT, Smith MJ. Outpatient pediatric antibiotic use: a systematic review. *Curr Infect Dis Rep* 2019; **21**: 14.
- 21** Saha SK, Hawes L, Mazza D. Effectiveness of interventions involving pharmacists on antibiotic prescribing by general practitioners: a systematic review and meta-analysis. *J Antimicrob Chemother* 2019; **74**: 1173–81.
- 22** Centers for Disease Control and Prevention. *A Field Guide to Antibiotic Stewardship in Outpatient Settings*. [https://qioprogram.org/sites/default/files/editors/141/C310\\_Field\\_Guide\\_20180730\\_FNL.pdf](https://qioprogram.org/sites/default/files/editors/141/C310_Field_Guide_20180730_FNL.pdf).
- 23** Ministry of Health Malaysia. *Protocol on Antimicrobial Stewardship Program in Healthcare Facilities*. <https://www.pharmacy.gov.my/v2/en/documents/protocol-antimicrobial-stewardship-program-healthcare-facilities.html>.
- 24** Colliers A, Coenen S, Philips H et al. Optimising the quality of antibiotic prescribing in out-of-hours primary care in Belgium: a study protocol for an action research project. *BMJ Open* 2017; **7**: e017522.
- 25** Zetts RM, Stoesz A, Smith BA et al. Outpatient antibiotic use and the need for increased antibiotic stewardship efforts. *Pediatrics* 2018; **141**: e20174124.
- 26** Nathwani D; British Society for Antimicrobial Chemotherapy. *Antimicrobial Stewardship from Principle to Practice*. 2018. <http://www.bsac.org.uk/antimicrobialstewardshipebook/BSAC-AntimicrobialStewardship-FromPrinciplestoPractice-eBook.pdf>.
- 27** The Center for Disease Dynamics, Economics & Policy. *The State of the World's Antibiotics*. [https://cddep.org/wp-content/uploads/2017/06/swa\\_edits\\_9.16.pdf](https://cddep.org/wp-content/uploads/2017/06/swa_edits_9.16.pdf).
- 28** European Surveillance of Antimicrobial Consumption Network. *Antimicrobial Consumption—Annual Epidemiological Report*. <https://www.ecdc.europa.eu/sites/default/files/documents/antimicrobial-consumption-annual-epidemiological-report-2017.pdf>.
- 29** Johnson AP, Muller-Pebody B, Budd E et al. Improving feedback of surveillance data on antimicrobial consumption, resistance and stewardship in England: putting the data at your fingertips. *J Antimicrob Chemother* 2017; **72**: 953–6.
- 30** Antimicrobial Use and Resistance in Australia. *Third Australian Report on Antimicrobial Use and Resistance in Human Health*. <https://www.safetyandquality.gov.au/sites/default/files/2019-06/AURA-2019-Report.pdf>.
- 31** Schweickert B, Feig M, Schneider M et al. Antibiotic consumption in Germany: first data of a newly implemented web-based tool for local and national surveillance. *J Antimicrob Chemother* 2018; **73**: 3505–15.
- 32** Sharland M, Pulcini C, Harbarth S et al. Classifying antibiotics in the WHO Essential Medicines List for optimal use—be AWARe. *Lancet Infect Dis* 2018; **18**: 18–20.
- 33** Frost HM, Knepper BC, Shihadeh KC et al. A novel approach to evaluate antibiotic utilization across the spectrum of inpatient and ambulatory care and implications for prioritization of antibiotic stewardship efforts. *Clin Infect Dis* 2020; 1675–82.
- 34** Yadav K, Meeker D, Mistry RD et al. A multifaceted intervention improves prescribing for acute respiratory infection for adults and children in emergency department and urgent care settings. *Acad Emerg Med* 2019; **26**: 719–31.
- 35** Germanos GJ, Trautner BW, Zoorob RJ et al. No clinical benefit to treating male urinary tract infection longer than seven days: an outpatient database study. *Open Forum Infect Dis* 2019; **6**: ofz216.
- 36** Guzik J, Patel G, Kothari P et al. Antibiotic prescribing for acute respiratory infections in New York City: a model for collaboration. *Infect Control Hosp Epidemiol* 2018; **39**: 1360–6.
- 37** Jaggi P, Wang L, Gleeson S et al. Outpatient antimicrobial stewardship targets for treatment of skin and soft-tissue infections. *Infect Control Hosp Epidemiol* 2018; **39**: 936–40.
- 38** Klepser ME, Dobson EL, Pogue JM et al. A call to action for outpatient antibiotic stewardship. *J Am Pharm Assoc (2003)* 2017; **57**: 457–63.
- 39** Versporten A, Gyssens IC, Pulcini C et al. Metrics to assess the quantity of antibiotic use in the outpatient setting: a systematic review followed by an international multidisciplinary consensus procedure. *J Antimicrob Chemother* 2018; **73**: vi59–66.
- 40** World Health Organization. *Monitoring Global Progress on Addressing Antimicrobial Resistance: Analysis Report of the Second Round of Results of AMR Country Self-Assessment Survey*. <https://apps.who.int/iris/handle/10665/273128>.
- 41** Zweigner J, Meyer E, Gastmeier P et al. Rate of antibiotic prescriptions in German outpatient care - are the guidelines followed or are they still exceeded? *GMS Hyg Infect Control* 2018; **13**: Doc04.
- 42** Howard P, Huttner B, Beovic B et al. ESGAP inventory of target indicators assessing antibiotic prescriptions: a cross-sectional survey. *J Antimicrob Chemother* 2017; **72**: 2910–14.
- 43** Wang S, Pulcini C, Rabaud C et al. Inventory of antibiotic stewardship programs in general practice in France and abroad. *Med Mal Infect* 2015; **45**: 111–23.
- 44** Hallit S, Zahreddine L, Saleh N et al. Practice of parents and pharmacists regarding antibiotics use in pediatrics: a 2017 cross-sectional study in Lebanese community pharmacies. *J Eval Clin Pract* 2020; **26**: 181–9.
- 45** Anderson M, Clift C, Schulze K et al. *European Observatory Policy Briefs*. Copenhagen, Denmark: WHO, 2019.
- 46** Organisation for Economic Co-operation and Development. *Evidence Synthesis Summary: Interventions to Address Antimicrobial Use*. <https://www.canada.ca/content/dam/phac-aspc/documents/services/publications/drugs-health-products/interventions-address-antimicrobial-use/technical-report-interventions-eng.pdf>.
- 47** Garau J, Nicolau DP, Wullt B et al. Antibiotic stewardship challenges in the management of community-acquired infections for prevention of escalating antibiotic resistance. *J Glob Antimicrob Resist* 2014; **2**: 245–53.
- 48** Williams PCM, Isaacs D, Berkley JA. Antimicrobial resistance among children in sub-Saharan Africa. *Lancet Infect Dis* 2018; **18**: e33–44.
- 49** Bosso JA, Sieg A, Mauldin PD. Comparison of hospitalwide and custom antibiograms for clinical isolates of *Pseudomonas aeruginosa*. *Hosp Pharm* 2013; **48**: 295–301.
- 50** Australian Commission on Safety and Quality in Health Care. *Antimicrobial Stewardship in Australian Health Care*. 2018. <https://www.safetyandquality.gov.au/our-work/antimicrobial-stewardship/antimicrobial-stewardship-australian-health-care-2018>.
- 51** Essack S, Bell J, Shephard A. Community pharmacists—leaders for antibiotic stewardship in respiratory tract infection. *J Clin Pharm Ther* 2018; **43**: 302–7.

- 52** Mendelson M, Rottingen JA, Gopinathan U *et al*. Maximising access to achieve appropriate human antimicrobial use in low-income and middle-income countries. *Lancet* 2016; **387**: 188–98.
- 53** World Health Organization. *Adopt AWaRe: Handle Antibiotics with Care*. 2019. <https://adoptaware.org>.
- 54** Sharland M, Gandra S, Huttner B *et al*. Encouraging AWaRe-ness and discouraging inappropriate antibiotic use—the new 2019 Essential Medicines List becomes a global antibiotic stewardship tool. *Lancet Infect Dis* 2019; **19**: 1278–80.
- 55** Linder JA, Meeker D, Fox CR *et al*. Effects of behavioral interventions on inappropriate antibiotic prescribing in primary care 12 months after stopping interventions. *JAMA* 2017; **318**: 1391–2.
- 56** Hallsworth M, Chadborn T, Sallis A *et al*. Provision of social norm feedback to high prescribers of antibiotics in general practice: a pragmatic national randomised controlled trial. *Lancet* 2016; **387**: 1743–52.
- 57** Pereira JQ, Silva MT, Galvao TF. Use of antibiotics by adults: a population-based cross-sectional study. *Sao Paulo Med J* 2018; **136**: 407–13.
- 58** Pulcini C, Gyssens IC. How to educate prescribers in antimicrobial stewardship practices. *Virulence* 2013; **4**: 192–202.
- 59** World Health Organization. *Guidelines on Hand Hygiene in Health Care*. Geneva: World Health Organization. 2009.
- 60** Centers for Disease Control and Prevention. *Guide to Infection Prevention for Outpatient Settings: Minimum Expectations for Safe Care*. <https://www.cdc.gov/infectioncontrol/pdf/outpatient/guide.pdf>.
- 61** World Health Organization. *Hand Hygiene in Outpatient and Home-Based Care and Long-Term Care Facilities: A Guide to the Application of the WHO Multimodal Hand Hygiene Improvement Strategy and the “My Five Moments for Hand Hygiene” Approach*. [https://apps.who.int/iris/bitstream/handle/10665/78060/1/9789241503372\\_eng.pdf?ua=1](https://apps.who.int/iris/bitstream/handle/10665/78060/1/9789241503372_eng.pdf?ua=1).