**Identifying AWaRe Indicators for appropriate antibiotic use: a narrative review.**

# Elisa FUNICIELLO1(†)\*, Giulia LORENZETTI1(†), Aislinn COOK1,2, Jan GOELEN1, Catrin E MOORE1, Stephen M. CAMPBELL3,4, Brian GODMAN4,5,, Deborah TONG6, Benedikt HUTTNER7, Pem CHUKI8, Michael SHARLAND 1

1. Centre for Neonatal and Paediatric Infection, St. George’s University of London, London SW17 0RE, UK
2. Health Economics Research Centre, Nuffield Department of Population Health, University of Oxford, Oxford OX1 2JD, UK
3. School of Health Sciences, University of Manchester, Manchester M13 9PL, UK
4. School of Pharmacy, Sefako Makgatho Health Sciences University, Ga-Rankuwa, Pretoria 0208, South Africa
5. Strathclyde Institute of Pharmacy and Biomedical Sciences, Strathclyde University, Glasgow G4 0RE, UK
6. Department of Surveillance, Prevention and Control, Division of Antimicrobial Resistance, World Health Organization, Avenue Appia 20, 1211, Geneva, Switzerland
7. Department of Health Products Policy and Standards, World Health Organization, Avenue Appia 20, 1211, Geneva, Switzerland
8. Antimicrobial Stewardship Unit, Jigme Dorji Wangchuck National Referral Hospital, Thimphu, Bhutan

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# (†)These authors contributed equally to this work and share the first authorship

# \*Corresponding author. E-mail: elisa.funiciello@unito.com

**RUNNING TITLE:** AWaRe Indicators for appropriate antibiotic use

# Synopsis

**Introduction.** Quality indicators (QIs) are widely used tools for antibiotic stewardship programmes (ASPs). The AWaRe (Access, Watch, Reserve) system has been developed by the WHO to classify antibiotics based on their spectrum of activity and potential selection of antibiotic resistance. This review aimed to identify existing indicators for optimal antibiotic use to inform the development of future AWaRe QIs.

**Methods.** A literature search was performed in PubMed. We included articles describing QIs for hospital and primary healthcare antibiotic use. We extracted information about (1) the type of infection; (2) setting; (3) target for quality assessment; and (4) methodology used for the development. We then identified the indicators that reflected the guidance provided in the AWaRe system.

**Results**. A total of 773 indicators for antibiotic use were identified. The management of health services and/or workers, the consumption of antibiotics, and antibiotic prescribing/dispensing were the principal targets for quality assessment. There was a similar distribution of indicators across primary and secondary care. For infection-specific indicators, about 50% focused on respiratory tract infections. Only a few QIs included information on review treatment or microbiological investigations. Although only 8 (1%) indicators directly cited the AWaRe system in the wording of the indicators, 445 (57.6%) indicators reflected the guidance provided in the AWaRe book.

**Conclusions.** A high number of indicators for appropriate antibiotic use have been developed. However, few are currently based directly on the WHO AWaRe system. There is a clear need to develop globally applicable AWaRe based indicators that can be integrated into ASPs.

# Background

Antimicrobial resistance (AMR) poses a significant global threat to public health1. The inappropriate use of antibiotics both in terms of choice and volume is an important driver behind this health emergency and reducing inappropriate use is important in tackling AMR 2. Consequently, monitoring consumption and appropriateness of antibiotic use is a priority as highlighted in the Global Action Plan (GAP) on AMR (**Table 1**) 3,4. Towards this, the World Health Organization (WHO) established the AWaRe (Access-Watch-Reserve) system in2017 as an antimicrobial stewardship tool, in which antibiotics are classified into four groups (Access, Watch, Reserve and Not Recommended) based on their spectrum of activity and potential selection for resistance 5. The WHO AWaRe antibiotic book (AWaRe book) was published in 2022 6, guiding the diagnosis and treatment of the 34 most common infections in primary health care and hospitals, in alignment with the recommendations for antibiotics included in the WHO Model List of Essential Medicines and Essential Medicines 7,8.

Quality indicators (QIs) have been developed for different healthcare areas, including antibiotic prescribing 9, and are able to reflect the degree to which an antibiotic is clinically indicated and appropriate. Quantity metrics (QMs) are quantifiable measures used to assess the performance, effectiveness, and overall quality of a process, service, or system such as reflecting the volume of antibiotic use but focus primarily on quantity rather than the direct quality of care or single measurable elements of care 10. QIs focus on discrete single issues or processes as measurable elements of care that provide an indication of the *quality of care* as a standardized, evidence-based measure of health care quality using routinely available data to measure and track clinical performance and outcomes. QIs generally have an associated target or achieved ‘standard’ giving an indication of good or poor quality, which can be used to show and track differences and changes in quality 11. It is important that indicators adhere to essential measurement attributes to ensure clearly defined, objective, evidence based, measurable, reliable, valid and feasible quality assessment 11–15 that mean that they are likely to be valid and feasible across varying localities and countries 16. QIs are crucial components of antimicrobial stewardship programs. These quality assessment tools are essential for improving quality of care and for indicating the extent to which a healthcare system meets the needs of patients, they enhance treatment outcomes, while reducing the selection of antibiotic resistance and limiting the costs of healthcare and treatment regimens 1,3,4.

The recent publication of the AWaRe book provides an opportunity for developing a common set of agreed AWaRe QIs across sectors and countries in combination with indicators published in existing literature. To refine the scope of potential future AWaRe QIs, we performed a narrative review of existing indicators.

This review aimed to identify published QIs evaluating the appropriateness of antibiotic use in hospital and primary healthcare settings. As a secondary objective, we evaluated the proportion of current indicators that were based directly on or reflected the guidance of the AWaRe system.

# Methods

Search strategy

We searched the MEDLINE database using PubMed for articles describing QIs for hospital and primary health care antibiotic use published from 01 January 1996 up to 01 March 2023. The search strategy is shown in Supplementary **Figure S1**. The reference lists of all included articles were screened manually for additional relevant papers.  A manual search of the grey literature was also conducted together with websites (in English) from 26 national and international infectious disease societies and public health organisations (**Table S1**). Two reviewers (G.L. and E.F.) screened these websites using ‘indicator or metric’ with or without ‘antibiotics or antimicrobials’ as search terms.

Screening process and data collection.

Articles published in English focusing on systemic (oral or intravenous [IV]) antibiotic use describing QIs were included. We included all populations; adults and/or children attending community and/or hospital healthcare facilities in high-, low- and middle-income countries (HIC and LMICs). Articles on the use of antiviral, antifungal, antiparasitic, or antituberculosis drugs were excluded.

Titles, abstracts, and articles were reviewed by a single investigator (G.L.). Two investigators (G.L. and E.F.) extracted data using a standardised form and eliminated duplicates and indicators not focused on antibiotics. Data on relevant indicators were collected and classified as ‘Clinical’ (e.g. choice of antibiotic or performance of diagnostic tests such as ‘Outpatients with an acute tonsillitis/pharyngitis and positive group A streptococcal diagnostic test should be treated with antibiotics’), 'Organisational' (e.g. recording of data, premises/facilities management such as ‘Prophylactic antibiotics should be added to a pre-operative checklist’), and 'Workforce' (i.e. focused on health workers, e.g. ‘Each member of the OPAT team is responsible for personal continuing professional development relating to best clinical practice’) indicators. This classification was carried out by a team of 7 members (M.S., C.E.M., S.M.C., A.C., E.F., G.L., J.G.) with additional expertise in infectious diseases epidemiology, healthcare, public health, and antimicrobial stewardship. The final set of indicators was divided into five subgroups based on setting: ‘Hospital facility’, ‘Primary Health Care’, ‘Both Hospital and Primary Health Care’, ‘Outpatient parenteral antibiotic therapy', and ‘General indicators’. General indicators were defined as those not specific to any particular disease and/or setting (e.g. ‘Antibiotics should not be prescribed for (most) viral infections or self-limiting bacterial infections’ 17). To describe and compare the identified indicators, information on the type of infection, and the target for quality assessment were analysed. Among the latter we identified five categories: i). antibiotic prescribing/dispensing (i.e. indicators focusing on the decision to prescribe antibiotics and/or the choice, dose, review, and duration of antibiotic therapy), ii). consumption of antibiotics/prescription rate, iii). diagnostic process (i.e. indicators focusing on laboratory, microbiological or radiological assessment), iv). management (i.e. indicators focusing on the organisation of health services, health workers, and staff tasks/workforce), v). outcomes (e.g. pneumonia mortality rate).

Indicators that were specifically based on the AWaRe system (i.e. indicators in which the AWaRe classification or the AWaRe book were cited) and indicators that reflected the contents and treatment recommendations of the AWaRe book were included. Indicators were defined as “non-AWaRe indicators” if they were focused on topics not explicitly taken into account by the AWaRe system such as national/regional/local policies (e.g. ‘The local guidelines should correspond to the national guideline but should be adapted based on local resistance patterns’), other settings (e.g. outpatient parenteral antibiotic therapy), specific clinical diseases (e.g. otitis externa), laboratory tests (e.g. therapeutic drug monitoring) and/or specific therapies (e.g. topical preparations).

**Results**

Search results and study characteristics

The literature search of MEDLINE identified 1271 studies. After Title/Abstract screening, 58 potentially relevant studies were selected for full-text screening. Of these, 13 were excluded as no indicators assessed the quality of care (n=3) or concerned antibiotic use (n=5) or the development of indicators (n=5). We added 2 studies and 14 websites after screening the reference list of all included articles and the principal infectious disease societies and public health organisations' websites (**Table S1**). The selection process resulted in a total of 61 studies and guidelines fulfilling the criteria for synthesis in this review **(Figure 1)** 4,13,17–22 23–28 29–36 37–42 43–48 49–55 56–63 64 65 66 67 68 69 70 71 72 73 74 75. **Table 2** provides an overview of all papers included in this review.

Selection and analysis of indicators

A total of 1104 indicators for antibiotic prescribing were identified, from which 264 duplicates (23.9%) and 67 irrelevant indicators (6.1%) were excluded: 27 were concerned with elements unrelated to the use of antibiotics (e.g. ‘Use of hand disinfectants in ICU setting’), 26 with venous/urinary catheter placement and management, 9 with drugs other than antibiotics, 3 with laboratory and microbiological tests, and 2 were performance indicators.
**Figure 2** provides a flow diagram summary of the indicator selection process. Among the final set of indicators, 282/773 indicators (36.5%) referred to a specific type of infection, of which 135/282 (47.9%) were related to respiratory tract infections (RTIs), 55/282 (19.5%) to bloodstream infections, and 46/282 (16.3%) to urinary tract infections. (**Figure 3**).
177/773 indicators (22.9%) were related to hospital facilities, 137/773 (17.7%) to primary health care, 44/773 (5.7%) to both hospital and primary health care, 60/773 (7.8%) to outpatient parenteral antibiotic therapy, and 355/773 (45.9%) were general indicators. Regarding the target for quality assessment, 206/773 indicators (26.6%) focused on antibiotic prescribing/dispensing (e.g. ‘Proportion of patients with no relevant comorbidities presenting with acute bronchitis that should be prescribed oral antibiotics’), 163/773 (21.1%) on the consumption of antibiotics/prescription rate (e.g. ‘Antimicrobial prescribing rates for men and non-pregnant women with asymptomatic bacteriuria’), 67/773 (8.7%) on the diagnostic process (e.g. ‘Number of patients with acute tonsillitis/pharyngitis treated with antibiotics with negative StrepA test’), 33/773 (4.3%) on the outcome (e.g. ‘Community Acquired Pneumonia Admission Rate’), and 304/773 (39.3%) on the management (e.g. ‘Indication for antimicrobial use documented in the patient notes’), (**Table 3**).

Among the antibiotic prescribing indicators (n=206), 93 concerned the type of antibiotic, 54 the duration of therapy, 45 the timing of administration, 45 the route of administration, 26 therapy revision (i.e. reduction of the spectrum and/or switching from IV to oral therapy), 23 the decision to prescribe antibiotics and 5 the dose. 25/67 indicators (37.3%) focused on the diagnostic process related to microbiological investigations.

Only 8/773 indicators (1%) directly cited the AWaRe system in the wording of the indicator (**Table S2**). However, 445/773 indicators (57.6%) reflecting the contents and treatment recommendations of the AWaRe book were identified **(Table S3)**. In total, 320/773 indicators (41.4%) were defined as “non-AWaRe indicators” because they focused on: national/regional/local policies (203, 63.4%), settings (60, 18.8%), or infectious diseases (21, 6.6%) not included in the AWaRe book, patients with special conditions (19, 5.9%), laboratory tests (15, 4.7%) or therapies (2, 0.6%) not included in the AWaRe book **(Table S4)**. The detailed list of indicators included in our review is available in the Supplementary Appendix as **Table S2-S4.**

Reported method of indicator development

The majority of studies documented in **Table 2** utilized a consensus methodology for the formulation of indicators. Most studies (n=23), used a RAND/UCLA Appropriateness Method 76, 7 studies used a Delphi Technique procedure 77,78, 11 studies developed QIs through other consensus methods with a description of how consensus was obtained (e.g. multidisciplinary team agreement) 79, 6 studies did not describe the consensus method used.

**Discussion**

Principal findings

We identified 773 indicators for appropriate antibiotic use of which only 1% were directly and 57.6% were indirectly related to the AWaRe system. Around 50% of infection-based indicators focused on RTIs, while for some serious infections (e.g. osteoarticular and abdominal infections) no indicators were identified. There was a similar distribution of indicators across primary and secondary care, with a high percentage of general indicators (45.9%) which can be used independently of the setting. Most of the indicators not included in the AWaRe book relate to the management of health services, health workers, and/or staff tasks, contrasting with those directly or indirectly related to the AWaRe system, which mostly focused on the consumption of antibiotics (frequency and/or volume of antibiotic use without reference to the indication) and antibiotic prescribing/dispensing. Among the latter, only 26 indicators included information on therapy review. 8.7% of indicators focused on the diagnostic process, and among them, 37.3% were based on the results of microbiological investigations.

Comparison with the previous literature

Improving the quality of care and reducing avoidable harm requires reliable, valid, and comparable data 10.Quality assessment leads to a steady improvement in antibiotic prescribing, allowing institutions to track their progress towards targets over time and to compare with other health facilities 80–87. In accordance with the literature 30,63,88, our review highlighted the increasing number of QIs for appropriate antibiotic use developed in recent decades, with considerable emphasis on RTIs. This finding could be due to the high prevalence of patients with RTIs and the relatively high percentage of antibiotic prescriptions for this condition both in primary and secondary care, despite the predominantly viral nature of RTIs 89–91. In recent years, the high rate of inappropriate antibiotic prescriptions in this patient category has resulted in RTIs becoming the focus of antimicrobial stewardship programmes (ASPs), especially in primary care in LMICs 92.Skin/soft tissue and intra-abdominal infections are also among the main indications for prescribing antibiotics in hospitals and ambulatory care 89, despite the almost total absence of indicators for these types of infections 84,88 .

To optimise antibiotic use, several aspects of care must be considered. A multi-faceted strategy based on the development of national/local guidelines, the allocation of adequate resources, and the creation of an experienced and competent team are key to responsible antibiotic use13,36,72,93,94. Indicators focused on antibiotic prescribing and/or dispensing remain a fundamental tool to monitor appropriate antibiotic use. Among these, the review of therapy, closely linked to the performance of microbiological investigations, is a crucial aspect of the appropriate use of antibiotics. As highlighted by national guidelines 77, differences in local resistance patterns and antibiotic availability (or lack of availability) may prevent the use of the same class of antibiotics as empirical therapy worldwide. Nevertheless, switching from IV to oral therapy at an appropriate time and using pathogen-directed therapy as soon as possible are associated with a reduction in the length of hospital stay95 and antibiotic use 96,97.

In our review, not surprisingly we identified only a few indicators directly citing the relatively new AWaRe system. In 2019, the monitoring and evaluation framework for the GAP on AMR provided a core set of indicators measurable by countries, including the use of the AWaRe system in monitoring national antibiotic consumption (**Table 1**) 4. To date, no indicators that prioritise the quality, rather than the volume, of antibiotic use in alignment with the AWaRe book contents have been developed.

Bias and limitations

This study has clear limitations. A formal systematic review was not conducted, and only English language publications were included, so some studies may have been missed. Secondly, only the MEDLINE database was searched, a limitation which was mitigated by screening the reference lists of all included articles and exploring the grey literature by including relevant websites.

Next steps

Many countries are now implementing national action plans (NAPs) on AMR although at different stages of implementation 13,98,99, with the optimisation of antibiotic use a key priority. Generating standardised, quality assured, globally comparable data is essential to the continuous improvement of ASPs and NAPs. QIs for antibiotic prescribing allow data to be collected on both the consumption and the quality of antibiotic care. The AWaRe book provides essential educational elements that include the clinical diagnosis and treatment of the most frequent infections in health care and is a key instrument for ASPs 100. The introduction of disease-specific QIs based on the AWaRe system and book, both in therapeutic and diagnostic terms, could provide discrete and measurableelements of quality that could be used globally and be comparable between countries84.Designed with the overarching goal of reducing the inappropriate use of antibiotics, the AWaRe book champions a targeted risk-based approach, advocating for 'no antibiotic care' when appropriate. At the core of its recommendations lies the emphasis on the appropriate use of the Access group antibiotics. Following the principles of the AWaRe system and stratifying total antimicrobial use (AMU) by the AWaRe groups, allows overall monitoring of national and global progress towards a country-level target of at least 60% of total antibiotic consumption being Access group antibiotics, as outlined in the WHO 13th General Programme of Work 101.

The small number of existing indicators related directly to the AWaRe system/book identified in this review suggests the next step is to develop new AWaRe QIs as essential tools to improve future antibiotic use.

Consensus techniques are fundamental and effective tools for quality improvement, enabling the evaluation and enhancement of different aspects of care where evidence is contested or not used appropriately. Most of the studies included in this review (50%) used the RAND/UCLA Appropriateness Method to develop new indicators. The Delphi Technique and RAND/UCLA Appropriateness Method are both widely used for the formulation of indicators, but the latter has been described as the only systematic method of combining expert opinion and evidence 12, resulting in widespread use 17,30,37,39,46,50,63 and it is important to adhere to optimal use and reporting of feedback in a Delphi Technique 78.

With this purpose, a Delphi Technique has been conducted with panellists across WHO regions and both Higher Income and Lower- and Middle-Income countries to assess the appropriateness and feasibility in local settings of indicators based on the findings of this review. This will be followed by a formal RAND/UCLA Appropriateness Method with leading international experts to assess the clarity, appropriateness, and feasibility of all the QIs globally, in all countries. Because indicators identified using a narrative literature review do not assess validity and the outcome of a consensus technique such as a Delphi Technique or RAND/UCLA Appropriateness Method provides only face validity 11, future research activities will then seek to validate and test the indicators using an indicator testing protocol including content validity, reliability and feasibility to underpin their potential purpose applied at both the local context and at a global level for quality assessment and improvement based on the WHO AWaRe system 14,102 .

**Conclusions**

# Being able to measure the quality of antibiotic prescribing is an essential prerequisite to promoting the appropriate use of antibiotics, reducing unnecessary prescribing, and mitigating antibiotic resistance. Despite the global awareness of the urgency of this issue and the efforts made so far, our review revealed the lack of discrete and dedicated quality indicators based on the WHO AWaRe system. These findings highlight the need to develop and test indicators based directly on the AWaRe system focused on their feasible integration and implementation into both local and national antimicrobial stewardship programmes.

# Acknowledgments

# All authors contributed to the conceptualisation, writing, and revision of this article.

# Funding

# Support for this study was provided by the Wellcome Trust funded ADILA project (Antibiotic Data to Inform Local Action) Grant number [222051/Z/20/Z].

# Transparency declarations

# All other authors: none to declare.

# Supplementary data

# Tables S1-S4 are available as Supplementary data at JAC Online.

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**Tables
Table 1.** Indicators from the Monitoring and Evaluation of the Global Action Plan on Antimicrobial Resistance relevant to humans4.

|  |
| --- |
| OUTCOME 4: Optimized use of antimicrobials in human and animal health |
| **Measurement** | **Indicator name** | **Source of data at the global level** |
| 4.1 Use of antimicrobials in humans | 1. Total human consumption of antibiotics for systemic use (Anatomical Therapeutic Chemical classification code J01) in Defined Daily Doses per 1000 population (or inhabitants) per day
2. Proportion of Access antibiotics for systemic use, relative to total antibiotic consumption in Defined Daily Doses
3. Relative proportion of AWaRe (Access, Watch and REserve) antibiotics for paediatric formulations
4. Percentage of adult and paediatric hospital patients receiving an antibiotic according to AWaRe categories
 | Global Antimicrobial Resistance and Use Surveillance System (GLASS)Cross-sectional point prevalence survey |
| 4.2 Access to antibiotics | Percentage of health facilities that have a core set of relevant antibiotics available and affordable on a sustainable basis | Sustainable Development Goal (SDG) indicator 3.b.3, with Access antibiotics disaggregated |
| 4.3 Appropriate use of antimicrobials | Percentage of inpatient surgical procedures with appropriate timing and duration of surgical antibiotic prophylaxis | Point prevalence surveys |
| 4.7 Optimized AMU and regulation | Legislation or regulation that requires antimicrobials for human use to be dispensed only with a prescription from an authorized health worker | Tracking AMR country self-assessment survey (TrACSS) |

**Table 2**. Overview of studies reporting quality indicators (QIs) for appropriate antibiotic use.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| First author, year | Consensus methods | Evidence base | Stakeholder involvement | Focus / Population (when specified) | No. of indicators | Application (when specified) |
| Hospital care |
| Afriyie, 2019 18 | NA | Indicators based on the GPPSS and other studies | NA | NA | 5 | International |
| Berenholtz, 2007 19 | Modified Nominal Group Technique | Literature review (MEDLINE via PubMed) | National (Dutch) multidisciplinary panel from multiple hospitals | Sepsis Care in Intensive Care Unit(Adults - age > 16 years) | 6 | NA |
| Bramesfeld, 2015 20 | Modified RAND/UCLA Appropriateness Method | Systematic literature review (EMBASE) + additional international databases | National (Germany) multidisciplinary panel of 13 experts + 2 representatives of federal patient organisations | Prevention and management of central venous catheter-relatedbloodstream infections (Adults + Children) | 32 | National (Germany) |
| Buyle, 2013 21 | Non-Delphi method(three-step procedure - described) | Literature review | Multidisciplinary panel of 13 international experts from 4 European countries | Antimicrobial stewardship programmes evaluation | 58 (minimal set of 10 key structure indicators) | Europe |
| Coll, 2012 22 | Non-Delphi method (multidisciplinary team agreement) | Literature review, national guidelines, local policy | Multidisciplinary team in one UK hospital | Inpatient setting | 30 | National (UK) |
| Farida, 2015 23 | Two-round Delphi procedure | National guidelines + indicators by Schouten et al 2005 24 | National (Indonesia) multidisciplinary panel of 18 experts from multiple hospitals | Community-acquired pneumonia care in hospitalised patients | 6 | Middle-income developing countries (Indonesia) |
| Schouten, 2005 24 | Four-step RAND-modified Delphi procedure | Systematic literature review (PubMed) + national and international guidelines | Multidisciplinary panel of 11 experts | CAP and acute exacerbation of chronic bronchitis or chronic obstructive pulmonary disease care in hospitalized adults | 15 | NA |
| Harvey, 2023 25 | Four-step Delphi procedure | Literature review, individual hospital policies, expert advice | National (UK) multidisciplinary panel of experts | Antimicrobial Intravenous-to-OralSwitch (IVOS) Criteria in hospital setting (Adults) | 12 | National (UK) |
| Hermanides, 2008 26 | Three-step RAND-modified Delphi procedure | National guideline for treatment of complicated UTI in adults | National (Dutch) multidisciplinary panel of 13 experts from multiple hospitals | Complicated urinary tract infection care in the hospital setting(Adults) | 13 | NA |
| Kallen, 2018 27 | Four-round modified-RAND Delphi procedure | Systematic literature review (MEDLINE) + international guideline search | National (Dutch) multidisciplinary panel of 15 experts from multiple hospitals | Intensive Care Unit(Adults) | 5 | NA |
| Kim, 2021 28 | Four-step RAND-modified Delphi procedure | Systematic literature review (PubMed, EMBASE, Cochrane) | National (Korea) multidisciplinary panel of 25 experts from multiple hospitals | Inpatients, Prophylaxis(Adults + Children) | 8 | National (Korea) |
| Li, 2017 29 | Three-round Delphi procedure | Literature search (PubMed, EMBASE, Cochrane), China Biology Medicine disc (CBM), National guidelines | National (China) multidisciplinary panel of 22 experts from multiple hospitals | CAP care in hospitals and clinics(Children) | 21 | National (China) |
| Monnier, 2018 (DRIVE-AB) 30 | Four-step RAND-modified Delphi procedure | Systematic literature review (MEDLINE) + web site search | Multidisciplinary panel of 51 international experts from 15 countries | Inpatient setting (including ICU), Surgical Prophylaxis(Adults + Children) | 51 | International |
| Morris, 2012 31 | RAND-modified Delphi procedure | Literature review | Multidisciplinary panel of 10 international experts from Canada and USA | Antimicrobial stewardship programmes evaluation | 5 | International |
| Oduyebo, 2018 32 | NA | Indicators based on other studies | NA | Inpatient setting (including ICU), Surgical Prophylaxis(Adults) | 3 | International |
| Okoth, 2019 33 | NA | Indicators based on other studies | NA | Indicators based on other studies | 6 | International |
| Pollack, 2016 34 | RAND/UCLA -modified Delphi procedure | Literature review, list of indicators by Davey et al,guidelines in the European Union andUSA | Multidisciplinary panel of 20 international experts | Antimicrobial stewardship programmes evaluation | 33 | USA and EU |
| Pulcini, 2008 35 | Non-Delphi method (team agreement) | Literature review focused on guidelines | Panel of 3 infectious diseases experts | Assessment ofinpatient empirical antibiotic prescriptions | 5 | NA |
| Pulcini, 2019 36 | Three-step Modified Delphi procedure | Literature review (MEDLINE) + web site search | Multidisciplinary panel of 15 international experts (13 countries in 6 continents) | Antimicrobial stewardship programmes evaluation | 7 core elements + 29 related checklist items | International |
| Schoffelen, 2021 37 | RAND-modified Delphi procedure | DRIVE-AB outpatients and inpatients QIs | Multidisciplinary panel of 13 international experts from 7 countries | Emergency Department(Adults) | 22 | International |
| Science, 2016 38 | Modified Delphi procedure | Literature review | National (Canada) multidisciplinary panel of 38 experts from multiple paediatric hospitals | Paediatric Antimicrobial stewardship programmes evaluation in Canada(Children) | 4 | International |
| Stanić Benić, 2018 (DRIVE-AB) 39 | Four-step RAND-modified Delphi procedure | Systematic literature review (MEDLINE) + web site search | Multidisciplinary panel of 23 international stakeholders | Inpatient setting | 12 | International |
| Skosana, 2021 40 | NA | Indicators based on other studies | NA | Inpatient setting (including ICU), Surgical Prophylaxis(Adults) | 3 | International |
| ten Oever, 2019 41 | RAND-modified Delphi procedure | Systematic literature review (MEDLINE, EMBASE) | Multidisciplinary panel of 30 international experts | Management of*Staphylococcus aureus* bacteraemia in hospitalized patients(Adults) | 15 | NA |
| Thern, 2014 42 | Three-step RAND/UCLA-modified Delphi procedure | Extensive literature review, national guidelines | National (Germany) multidisciplinary panel of experts from multiple hospitals | Hospital Antimicrobial Stewardship and Infection management in the inpatient setting | 42 | National (Germany) |
| van den Bosch, 2014 43 | Five-step RAND-modified Delphi procedure | National guideline for antimicrobial use in hospitalized patients with sepsis | National (Dutch) multidisciplinary panel of 14 experts from multiple hospitals | Sepsis care in patients hospitalized in general medical ward or ICU(Adults) | 5 | National (Netherlands) |
| van den Bosch, 2015 44 | Four-step RAND-modified Delphi procedure | Literature review (PubMed, EMBASE) | Multidisciplinary panel of 17 international experts from 6 European countries | Inpatient setting, excluding ICU(Adults) | 11 | International |
| Vera, 2014 45 | NA | Literature review and guidelines by Spanish working group of Infectious Diseases | NA | Critically ill patients admitted to ICU | 10 | NA |
| Ambulatory care |
| Adriaenssens, 2011 (ESAC-Net) 46 | RAND/UCLA Appropriateness Method, 2 rounds of scoring | Workshop of experts from different research groups and projects, guidelines | Multidisciplinary panel of international experts from 24 European countries and Israel | Outpatient setting(Adults + Children) | 21 | Europe |
| Bateman, 1996 47 | Non-Delphi method(team agreement) | National guidelines | Panel of 8 UK general practitioners | General Practice | 1 | National (UK) |
| Berrevoets, 2020 48 | Four-step RAND-modified Delphi procedure | Systematic literature review (MEDLINE via PubMed, EMBASE, Cochrane) | Multidisciplinary panel of 19 international experts | OPAT (Adults) | 33 (12 prioritized) | International |
| Campbell, 2000 49 | Two-round Delphi procedure | Previous studies,prescribing analysis and cost (PACT) data | Multidisciplinary panel (health authority medical andpharmaceutical advisers) | General Practice | 4 | National (UK) |
| Coenen, 2007 (ESAC-Net) 50 | RAND/UCLA appropriateness method, two rounds of scoring | Workshop of experts, ESAC data on antibiotic consumption | Multidisciplinary panel of 22 international experts from 12 European countries | Outpatient setting(Adults) | 12 | Europe |
| Cottrell, 2020 (rhinosinusitis) 51 | RAND/UCLA appropriateness method | Literature review, international guidelines | Multidisciplinary panel of 9 experts | Diagnosis and management ofpatients with Acute bacterial rhinosinusitis(Adults) | 2 | International |
| Cottrell, 2020 (tonsillitis) 52 | RAND/UCLA appropriateness method | Literature review, international guidelines | National (Canada) multidisciplinary panel of 11 experts | Diagnosis and management ofPaediatric patients with tonsillitis(Children) | 5 | NA |
| de Bie, 2016 53 | Non-Delphi method(team agreement) | Expert consensus | NA | Outpatient setting(Children) | 2 | Europe |
| Fernández Urrusuno, 2008 54 | Non-Delphi method (multidisciplinary team agreement) | National guidelines, local resistance patterns, expert consensus | Multidisciplinary panel of experts | General Practice prescribing patterns of RTIs and UTIs | 5 | National (Spain) |
| Giesen, 2007 55 | Non-Delphi method(three-step procedure - described) | National clinical guidelines for general practice | Panel of 6 Dutch general practitioners | Out-of-hours general practice in the Netherlands(Adults + Children) | 6 | National (Netherlands) |
| Hansen, 2010 56 | Modified 2-round Delphi procedure | Literature review, workshop of experts, national guidelines | Multidisciplinary panel of 27 international experts from 13 countries | RTIs in General Practice(Adults + Children) | 41 | International |
| Hussein, 2017 57 | RAND/UCLA-Appropriateness Method | Systematic literature review (MEDLINE, EMBASE, Cochrane), clinical guidelines | National (Germany) multidisciplinary panel of 11 dental experts (dentists, oral and maxillofacial surgeons) | Systemic antibiotics in dentistry(Adults + Children) | 15 | National (Germany) |
| Korom 2017 58 | Non-Delphi method (multidisciplinary team agreement over three rounds of meetings) | Literature review, Kenyan Ministry of Health guidelines | National (Kenia) multidisciplinary panel of experts | Management of UTIs in ambulatory setting | 1 | National (Kenia) |
| Le Maréchal, 2018 (DRIVE-AB) 17 | RAND-modified Delphi procedure | Systematic literature review (MEDLINE via PubMed) + web site search | Multidisciplinary panel of 25 international experts from 14 countries | Outpatient setting including OPAT(Adults + Children) | 32 (12 OPAT) | International (High-, middle, low-income settings) |
| Pulcini, 2013 59 | NA | Literature review + international guidelines | National (France) multidisciplinary panel of 3 experts | General Practice (Adults - age ≥16 years) | 6 | National (France) |
| Saust, 2017 60 | RAND/UCLA Appropriateness Method | National and international guidelines for management of RTIs | National (Denmark) multidisciplinary panel of 9 experts | General Practice (Adults + Children) | 50 | National (Denmark) |
| Smith, 2018 61 | Expert elicitations (2) and anonymous online prescriber survey | Literature review,National guidelines | Multidisciplinary panel of 9 experts | General Practice (Adults + Children) | 12 | National (UK) |
| van Roosmalen, 2007 62 | Non-Delphi method (multidisciplinary team agreement after iteratedconsensus rating procedure – not described) | National clinical guidelines by the Dutch College of General practitioners | NA | General practice (Adults + Children) | 7 | National (Netherlands) |
| Versporten, 2018 (DRIVE-AB) 63 | RAND-modified Delphi procedure | Systematic literature review (MEDLINE) + web site search | Multidisciplinary panel of 23 international experts from 4 continents | Outpatient setting(Adults) | 6 | International |

NA = Not Available; GPPS = Global Point Prevalence Survey; UK = United Kingdom; UTIs = Urinary Tract Infections; CAP = Community-acquired Pneumonia; ICU = Intensive Care Unit; USA = United States of America; OPAT = Outpatient Parenteral Antimicrobial Therapy; RTIs = Respiratory Tract Infections.

**Table 3.** The final set of indicators related to the to the classification, setting and target for quality assessment.

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | AWaRe indicators(N = 8) |  Indicators reflecting the AWaRe system/book (N = 445) |  Indicators not related to the AWaRe system/book(N = 320) | Total(N=773) |
| Classification N (%): Clinical Organisational Workforce | 7 (87.5)1 (12.5)0 (0) | 388 (87.2)55 (12.4)2 (0.4) | 49 (15.3)267 (83.4)4 (1.3) | 444 (57.4)323 (41.8)6 (0.8) |
| Setting N (%): Hospital facility Primary health care Both OPAT General | 0 (0)0 (0)0 (0)0 (0)8 (100) | 110 (24.8)118 (26.5)34 (7.6)0 (0)183 (41.1) | 67 (20.9)19 (5.9)10 (3.1)60 (18.7)164 (51.4) | 177 (22.9)136 (17.6)45 (5.8)60 (7.8)355 (45.9) |
| Target for quality assessment N (%): Antibiotic prescribing/dispensing Consumption/prescription rate Diagnostic process Outcome Management | 0 (0)7 (87.5)0 (0)0 (0)1 (12.5) | 180 (40.4)156 (35.1)63 (14.2)25 (5.6)21 (4.7) | 26 (8.1)0 (0)4 (1.3)8 (2.5)282 (88.1) | 206 (26.6)163 (21.1)67 (8.7)33 (4.3)304 (39.3) |

OPAT = outpatient parenteral antibiotic therapy

**Figures**

**Figure 1.** Flow diagram summary of the papers selection process.

Articles included in the review
N = 45

Records identified from PUBMED
N = 1271

Records excluded after title/abstract screening
N = 1213

Articles read in full-text
N = 58

Articles excluded

N = 13

N = 3 did not use QIs to assess the quality of care

N = 5 not on antibiotic use

N = 5 no development of QIs

Articles added after:

- reference screening N = 2

- website search N = 14

Total N of studies included in the review

N = 61

**Figure 2**. Flow diagram summary of the indicators selection process.

Total indicators
N = 1104

Excluded (not antibiotic related)
N = 67

Final set of indicators
N = 773

Duplicates
N = 264

Workforce indicators
N = 6

Clinical indicators
N = 444

Organisational indicators
N = 323

Non AWaRe

N = 267

Non AWaRe

N = 49

Non AWaRe

N = 4

AWaRe
N = 1
Indirectly
AWaRe
N = 55

Indirectly
AWaRe
N = 2

AWaRe
N = 7
Indirectly
AWaRe
N = 388

AWaRe indicators
N = 453

Non AWaRe indicators
N = 320

Policy N = 203
Setting N = 60
Disease N = 21
Patients with special conditions N = 19
Laboratory test N = 15
Therapy N = 2

**Figure 3.** Indicators related to a specific type of infection.

**Total N = 282**

RTIs = Respiratory Tract Infections; UTIs = Urinary Tract Infections; Other = Two or more different types of infection