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Towards a global definition of responsible antibiotic use: results of an international multidisciplinary consensus procedure

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Background: Conducted as part of the Driving Reinvestment in Research and Development and Responsible Antibiotic Use (DRIVE-AB) project, this study aimed to identify key elements for a global definition of responsible antibiotic use based on diverse stakeholder input.

Methods: A three-step RAND-modified Delphi method was applied. First, a systematic review of antibiotic stewardship literature and relevant organization web sites identified definitions and synonyms of responsible use. Identified elements of definitions were presented by questionnaire to a multidisciplinary international stakeholder panel for appraisal of their relevance. Finally, questionnaire results were discussed in a consensus meeting.

Results: The systematic review and the web site search identified 17 synonyms (e.g. *appropriate*, *correct*) and 22 potential elements to include in a definition of responsible use. Elements were grouped into patient-level (e.g. *Indication*, *Documentation*) or societal-level elements (e.g. *Education*, *Future Effectiveness*). Forty-eight stakeholders with diverse backgrounds [medical community, public health, patients, antibiotic research and development (R&D), regulators, governments] from 18 countries across all continents participated in the questionnaire. Based on relevance scores, 21 elements were retained, 9 were rephrased and 1 was added. Together, the 22 elements and associated best-practice descriptions comprise an exhaustive list of elements to be considered when defining responsible use.

Conclusions: Combination of concepts from the literature and stakeholder opinion led to an international multidisciplinary consensus on a global definition of responsible antibiotic use. The widely diverging perspectives of stakeholders providing input should ensure the comprehensiveness and relevance of the definition for both individual patients and society. An aspirational goal would be to address all elements.

Introduction

The human impact of antimicrobial resistance is increasing worldwide with more and more antimicrobials losing their power to cure infections. At the same time, the pipelines for new antibiotics are running dry.[1,2] A steep growth of initiatives aiming at improving antimicrobial use and tackling antimicrobial resistance indicates that the 'tipping point'[3] on this major global health threat may have been reached. Examples of such international initiatives include the WHO's Global Action Plan on Antimicrobial Resistance and the Transatlantic Taskforce on Antimicrobial Resistance.[4,5] Altogether, these initiatives contributed to a worldwide call to address antimicrobial resistance, reaching the agenda of the United Nations General Assembly as a major global health priority in September 2016.[6]

While all use of antimicrobial drugs contributes to the development of resistance, major forces driving the increasing resistance include inappropriate infection prevention and inappropriate use.[1,7] Inappropriate use is also known to drive increased costs of care, morbidity and mortality.[8–10] In order to define inappropriate use, a clear understanding of what appropriate, correct or responsible use entails is crucial. The definition of rational use of drugs, as per the WHO, states that patients receive medications appropriate to their clinical needs, in doses that meet their own individual

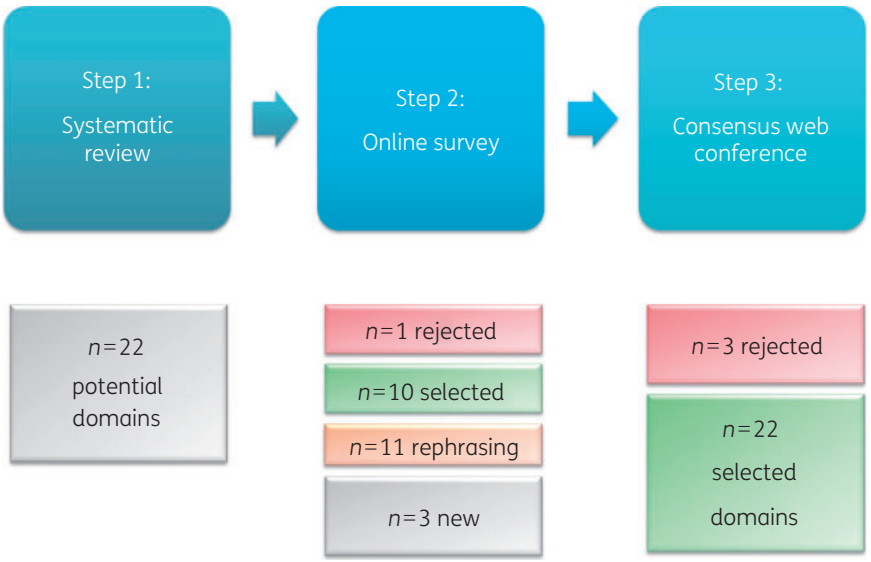

Figure 1. The number of elements of the definition of responsible use resulting from each step of the RAND-modified Delphi method.

requirements for an adequate period of time, and at the lowest cost to them and their community.[11] More recently, the WHO introduced the concept of responsible use of medicines, implying that the activities, capabilities and existing resources of health system stakeholders should be aligned to ensure patients receive the right medicines at the right time, use them appropriately, and benefit from them.[12]

However, antimicrobials are one-of-a-kind drugs as they are the only drugs that do not directly and exclusively affect the patient. Indeed, antimicrobials target the biology of microorganisms, both pathogens and commensals, carried by the patient, which can also be shared with a larger human or animal community. Antimicrobial therapy should therefore consider factors related to these microorganisms and the societal ramifications of antibiotic use in addition to patient and drug-related characteristics. The 'pyramid of infectious diseases' illustrates the many interplays between the bug, the drug and the patient.[13] These interactions are the basis of the complexity of antimicrobial prescription and use but are not explicitly addressed in the WHO definition of rational drug use.

Activities aiming at reducing the undesired consequences of inappropriate use have been undertaken since the early 1970s.[14] In the mid-1990s, the term 'antimicrobial stewardship' was introduced, describing a collection of strategies, policies, guidelines or tools that could improve antimicrobial prescribing with the aim of decreasing antimicrobial resistance and use.[15,16] Stewardship addresses *how* improved antimicrobial use should be achieved. A definition of responsible antibiotic use would provide clear goals of *what* should be improved and should thereby steer stewardship activities.

While the medical community, including the antibiotic prescribers, is crucial in assessing responsible antibiotic use, they are not the only stakeholders concerned by the global antibiotic resistance health threat. Great expectations are arising for public health organizations, developers and producers of antibiotics to help solve the issue. Increased political attention is leading to the involvement of policy makers and governments. It is therefore important that all these different cross-disciplinary perspectives should be accounted for in any attempt to define responsible antibiotic use.

This study was conducted within the Driving Reinvestment in Research and Development and Responsible Antibiotic Use (DRIVE-AB) project focusing on human antibiotic use.[17,18] The aim of this study was to develop a consensus-driven definition of responsible antibiotic use considering different perspectives, including those of the medical community, public health, patients, antibiotic developers, regulators and governments. The definition should account for diverse socioeconomic settings, thereby ensuring a global scope.

Materials and methods

A three-step RAND-modified Delphi method[19] was applied to reach consensus on a global definition of responsible antibiotic use (Figure 1). The consensus procedure combined the individual opinions of four groups of stakeholders.

Step 1 – Literature and web site search

A systematic review was performed in the MEDLINE database (since 1966) to identify elements of and definitions of responsible antibiotic use and its synonyms in the scientific literature. Articles were screened in title and abstract with the following search strategy: 'antibiotic stewardship' OR 'antimicrobial stewardship' OR 'antibiotic policies' OR 'antibiotic policy'. In the context of antibiotic use, *policy* is a synonym and a predecessor of the term *stewardship*, a term coined in the mid-1990s.[15,16] The search was performed on 25 March 2015. Two researchers (A. A. M. and M. E. H.) independently screened papers discussing general principles of antibiotic stewardship within a random sample of 25% of the found literature. After reaching consensus on this 25% sample, one researcher (M. E. H.) continued the selection process of the remaining literature. Exclusion criteria were papers: not written in English, not discussing antibiotics, not describing general principles of antibiotic stewardship and not containing statements on responsible antibiotic use or its synonyms. Papers were also excluded for which the full-text version was not accessible from one of the following libraries: Radboud University Medical Center, University of Rijeka, University of Antwerp, University of Genève, University of Leuven, University of

Lorraine and Google Scholar®. A complementary search was performed on web sites of relevant (inter)national organizations and institutions active in the field of antibiotic stewardship and/or public health. Organizations, institutions and their web sites were identified using lists provided in four publications on antibiotic stewardship and antibiotic research and development (R&D) activities.[18,20–22] Ultimately, an exhaustive search of references of included web pages was done. The searches were restricted to web sites in English. Relevant sections of the web sites were searched by one researcher (A. A. M.) using the search terms 'antibiotic' and 'use'.

The data extraction of synonyms and definitions of responsible antibiotic use was performed by one researcher (A. A. M.). For the papers included in the systematic review, the extraction process was repeated by the same researcher 1 month later for 10% of the references. No discrepancies were found, thus ensuring comprehensiveness of the data and intra-rater reproducibility. The data extraction from web sites was performed by the same researcher twice in order to ensure the comprehensiveness of the data. The extracted data were compiled and definition components were clustered into different non-overlapping logical elements (e.g. *Microbiologic Diagnostics, Indication)*, each of which appeared distinctly relevant to defining responsible use. The categorization into elements was done by one researcher (A. A. M.) and then validated by a second researcher (I. C. G.). Discrepancies were discussed until consensus was reached. For each potential element, an explanatory phrase describing the goal for responsible use was proposed by combining different phrasings extracted from the literature. The phrasing was done in consensus between three authors (A. A. M., I. C. G. and M. E. H.). The explanatory phrases for each element were formulated to complete the sentence 'Responsible antibiotic use includes . . .' (e.g. Responsible use includes *using microbiology diagnostic tools to provide diagnostic testing.*). Finally, the wording of the element names and corresponding explanatory phrases was reviewed by two native English speakers and experts in the field of antibiotic stewardship, one from the UK and one from the USA. Preliminary results of the systematic review were discussed at a 'train-the-trainer event' in collaboration with the BSAC during the 26th European Congress of Clinical Microbiology and Infectious Diseases. Senior members of the European medical antibiotic stewardship community were asked for feedback.[23]

Step 2 – Online questionnaire

The consensus procedure took place from July until September 2016. Seventy-four international stakeholders were invited by e-mail to participate. Reminders were sent 4 and 2 weeks before the closing of the questionnaire. Stakeholders were invited based either on demonstrated experience and expertise on the topic of antibiotic use and/or stewardship, e.g. relevant publications, or involvement in national stewardship activities, or on different perspectives on antibiotic use, e.g. having a prominent role within a relevant organization, institute, society or company. Stakeholders from the extended international network of academic and European Federation of Pharmaceutical Industries and Associations (EFPIA) partners of the DRIVE-AB project were solicited.

Individuals amongst four different stakeholder groups, aiming at representing all parties involved with antibiotic use, were identified: medical community ($n = 18$); public health and patients ($n = 18$); antibiotic R&D ($n = 21$); payers, policy makers, governments and regulators ($n = 17$). The invited stakeholders originated from 20 countries across all continents.

A web-based questionnaire on responsible antibiotic use was designed in SurveyMonkey®. Together with the invitation e-mail, stakeholders were sent a document providing the scientific references from the systematic review for each of the identified elements. The stakeholders were asked to appraise the relevance of each element to be included in the definition of responsible antibiotic use. The relevance was graded using a nine-point Likert scale (1 = clearly not relevant, 9 = clearly relevant). Relevance scores were calculated for each element following the RAND agreement criteria.[19] Median scores were analysed across the four stakeholder groups. If the element had a median of 8 or 9 and >70% of the stakeholders scored in the upper tertile (i.e. 7, 8 or 9), the element was selected. If the element had a median <8 or <70% of the stakeholders scored in the upper tertile, the element was rejected.

Stakeholders could comment on the elements as well as make suggestions for new elements. If comments referred to the clarity of the element and/or wording of its explanatory phrase, these elements were labelled for discussion. Newly proposed elements that did not present any overlap with other elements were selected.

Step 3 – Consensus meeting

The first 20 stakeholders that filled in the questionnaire were asked for their availability to take part in a consensus meeting after the summer of 2016. The aim was to have balanced numbers of participants across the four stakeholders groups. The meeting was held on 28 September 2016 using a web conferencing interface. During the meeting, the stakeholders discussed elements labelled for discussion and newly proposed elements. For the elements labelled for discussion, the researchers prepared a new wording proposal based on the comments made by the stakeholders in the questionnaire. These comments were categorized for each stakeholder group and shown during the consensus meeting to expedite the discussions. Typically, modifications to the new wording proposal were made until agreement was reached. An audio recording of the meeting was made and used to make sure no relevant suggestions were missed.

Results

Step 1 – Literature and web site search

The systematic literature search identified 1700 articles of which 343 were considered eligible for full-text screening. After exclusion and inclusion criteria were applied, 161 articles (10%) were included and data extraction was performed. The flowchart of the systematic review is shown in Figure S1 (available as Supplementary data at *JAC* Online). The web sites of 50 institutions and organizations were identified and searched for definitions. Fifteen web sites (30%) were ultimately included for data extraction (Table S1).

The systematic review and the complementary web site search led to the identification of 17 synonyms of responsible antibiotic use: *adequate*, *appropriate*, *better*, *correct*, *effective*, *focused*, *improved*, *judicious*, *optimal*, *optimized*, *proper*, *proportionate*, *prudent*, *rational*, *right*, *safe*, *thoughtful*. Furthermore, this first step led to the identification of 22 potential elements of responsible antibiotic use for appraisal by the stakeholders (Figure 1; Table 1).

Delegates from 19 EU countries attended the train-the-trainer event. During discussions at this event it was acknowledged that the balance between the elements *Patient Outcome*, *Resistance* and *Future Effectiveness* of the antibiotic drug implied important ethical considerations, which should be made visible. As a result, *Ethics: Making the balance between Patient Outcome, Future Effectiveness and Resistance based on ethical considerations* was added as an aspect of importance to the definition of responsible antibiotic use as shown in the infographic (Figure 2) and Table 2.

Step 2 – Online questionnaire

In the online questionnaire, a multidisciplinary panel of 50 stakeholders (response rate 68%) from 18 countries across all continents appraised the relevance of the 22 potential elements of responsible antibiotic use. The online questionnaire is shown in

Table 1. Results of the consensus procedure on the elements of responsible antibiotic use.

Final no.	Element name	References	Result after the online survey	Result after the consensus meeting	Element description
1	**Microbiological Diagnostics**	41–61	Labelled for rephrasing	Rephrased and selected	*Using high quality available microbiology laboratory facilities to provide routine diagnostic testing.* Rephrased: **Using microbiology diagnostic tools to provide diagnostic testing.**
2	**Indication**	29,46–50,52,53,55,57,59–96	Labelled for rephrasing	Rephrased and selected	*Restricting antibiotic use to prevent or cure suspected or microbiologically proven bacterial infections.* Rephrased: **Using antibiotics only to prevent or cure infections for which antibiotic treatment provides a proven benefit.**
3	**Antibacterial Activity**	29,41–43,45,46,48,50,52–55,59,64,66, 67,69–71,75,76,79,80,85,87,89, 93,94,97–152	Labelled for rephrasing	Rephrased and selected	*Rationally selecting antibiotics based on their antibacterial activity.* Rephrased: **Selecting antibiotics based on their antibacterial activity.**
4	**Antibacterial Spectrum**	29,41–43,45,47–51,56,58,67,69,74,76,78, 79,86,94,105,123,127,139,143, 153–156	Selected	–	**Selecting antibiotics based on their antibacterial spectrum (as narrow as possible).**
5	**Dosing, PK/PD, Interval**	Dosing 16,29,41–43,45–49,51–54,59,60,64–71, 73–76,78–80,85–87,89,94–99,101,102, 104–107,109–111,113,115–117,119,120, 123–125,128–138,140,142–152,157–159 PK/PD 42,45,50,51,76,88,143,154–156,160 Interval 47,60,76,87,95,126	Labelled for rephrasing	Rephrased and selected	*Dosing and dosing frequency of the antibiotic regimen based on clear PK/PD principles (ensuring sufficient free concentrations of antibiotic at the site of infection).* Rephrased: **Dose and dosing frequency of the antibiotic regimen based on available knowledge on PK/PD (ensuring sufficient free concentrations of antibiotic at the site of infection).**
6	**Duration**	16,29,41–43,45–55,59,60,64–67,69–71, 73–76,78–80,85–89,91,94–99,101,102, 104–107,109–111,113,115–121,124–138, 140,142–151,155,156,158,159,161	Labelled for rephrasing	Rephrased and selected	*Using the shortest possible duration of the antibiotic regimen.* Rephrased: **Using the shortest possible evidence-based duration of the antibiotic regimen.**
7	**Route**	29,41,43,46,48,51–54,64,66,68,70, 74–76,79,80,86,93,97,98,101,102, 104,105,109,111,113,115–117,120, 123–125,127,128,132,139,140,143, 144,146–150,152,162	Labelled for rephrasing	Rephrased and Selected	*Selecting the proper route (parenteral or oral) based on antibiotic and patient characteristics.* Rephrased: **Selecting the proper route (e.g. parenteral or oral) based on antibiotic, severity or type of infection and patient characteristics.**
8	**Timing**	29,49,52,66,68,71,74,78,83,89,94, 121,123,124,126,127,142,153,156	Labelled for rephrasing	Selected	**Administering antibiotics in a timely manner.**
9	**Interactions**	45,76,159	Selected	–	**Selecting antibiotics taking into account possible interactions with other medication(s).**
10	**Toxicity**	20,29,41,45,48–50,52–55,59,60,62,73, 75,76,83,85,86,93,97,99,101,106, 109,115,116,118,119,122,123,125, 126,128,131,133,134,136–138,141, 148,149,151–154,159,160,162–180	Selected	–	**Selecting the antibiotic with the least toxicity possible.**

11	**Unintended Consequences**	20,29,41,48,49,53,55,66,68,69,71, 73,75,76,85,89,91,94,99,103,110, 114,117,119,123,125–127,132–134,136, 138,140,141,143,144,146,147,149, 151–153,160,163,164,168,172,173, 177,179–189	Selected	–	**Selecting the antibiotic with the lowest risk of secondary infections such as *C. difficile* diarrhoea.**
12	**Documentation**	41,47,49,88	Selected	–	**Fully documenting the antibiotic regimen including indication in the medical record.**
13	**Patient Compliance**	47,50,60,154	Selected	–	**Ensuring patient compliance with the antibiotic prescription.**
14	**Patient Outcome**	20,29,41,42,45,47,48,50,52–54,57, 59,62,66,71–74,77,79,83,85,89,91, 93,97,98,101,106,107,109,110, 114–116,118,119,122,123,125,126,128, 129,131–134,136–138,140,142–144, 146–151,153,154,156,158,162,164–170, 172–185,187–199	Labelled for rephrasing	Rephrased and selected	*Optimizing outcome (reduced morbidity, mortality and length of hospital stay) following the treatment or prevention of bacterial infections.* Rephrased: **Optimizing patient outcome (reduced morbidity, mortality and length of hospital stay) by treating or preventing bacterial infections.**
15	**Access-Availability**	57,60,61,200	Selected	–	**Ensuring access and routine availability of quality antibiotics.**
–	Costs	20,41,45,47,50,52–54,57,60,66,69, 71,85,89,97,110,112,115,117,118, 126,133,134,141–143,148–150,153–155, 158,162–170,175,179–181,188,189, 191–193,195,201	Rejected	–	*Using the most cost-effective antibiotic regimen.*
16	**Resistance**	16,29,41,42,44,45,48–50,53–55,57,59, 60,62,66,69,71,73,75,76,81,83,85, 89,91,97,99,101,103,106,109,110, 112,114,115,117,120,123,125–127, 131–134,136–138,140–142,144–151,153, 160,163–174,176,178–195,197–200,202,203	Labelled for rephrasing	Selected	**Limiting the emergence of antibiotic resistance.**
17	**Future Effectiveness**	41,49,53,57,62,93,103,105,120,128, 134,193,200,204–207	Selected	–	**Conserving the effectiveness of antibiotics for the future.**
18	**Resistance Surveillance**	48,50,57,60,61,86,94,103,105,123, 130,134,139,189,208,209	Labelled for rephrasing	Rephrased and selected	*Using resistance surveillance data for empirical prescribing.* Rephrased: **Using local antibiotic resistance surveillance data for guidelines on empirical antibiotic prescribing.**
19	**Evidence-based Guidelines**	Evidence 47,98,159,191,209–211 Guidelines 41,47,49,50,52,60,66,70,71,76,91, 103,155,189,208,212,213	Selected	-	*Ensuring the availability and use of local (or national) evidence-based treatment guidelines.* Rephrased: **Ensuring educational programmes on antibiotic use from an early stage for the public and all relevant professionals, including trainees in healthcare curricula.**
20	**Expertise and Resources**	49,60,70,123,139	Selected	–	**Using available infectious disease expertise and resources.**

Continued

Table 1. *Continued*

Final no.	Element name	References	Result after the online survey	Result after the consensus meeting	Element description
21	**Education**	29,60–62,77,91,93,95,98,103,123, 160,161,208	Labelled for rephrasing	Rephrased and selected	*Ensuring educational programmes on antibiotic use for all relevant professionals and the public.* Rephrased: **Ensuring educational programmes on antibiotic use from an early stage for the public and all relevant professionals, including trainees in healthcare curricula.**
22	**Waste Disposal**	Proposed in the online survey	-	Rephrased and selected	*Disposing waste antibiotics to prevent selection in the environment.* Rephrased: **Safely disposing of unused antibiotics and waste products containing antibiotics to prevent selection in the environment.**
-	Alternatives	Proposed in the online survey	-	Rejected*	*Considering alternatives for antibiotics to prevent infections (e.g. vaccines, hygiene, infection control).*
-	Multidisciplinarity	Proposed in the online survey	-	Rejected	*Stimulating collaboration between different types of healthcare professionals (e.g. nurses, doctors, pharmacists).*

Element 1-14: patient level elements; elements 15-22: societal elements.
*Indicates rejected as an element of responsible antibiotic use but added to the figure as an additional aspect.

Figure S2. These 50 stakeholders were distributed as follows: 13 belonged to the medical community group including professional societies, hospital pharmacists, infectious disease physicians, clinical microbiologists and a nurse; 12 belonged to the public health and patients group including the WHO, Médecins Sans Frontières, national public health institutes and ethicists; 13 belonged to antibiotic R&D organizations including small and medium enterprises, pharmaceutical companies and economists; and 12 were payers, policy makers, governments and regulators including the European Centre for Disease Prevention and Control, the Centers for Disease Control and Prevention, the US Food and Drug Administration, European Medicines Agency, governments and a national health insurance advisor. The answers of two stakeholders were incomplete; as a result 48 answers were used for data analysis. A detailed list of all the stakeholders and their affiliations is shown in Table S2.

The results of the questionnaire are shown in Table 1. Based on relevance scores, 21 elements to be included in the definition of responsible use were selected and one element, *Costs: Using the most cost-effective antibiotic regimen*, was rejected. Comments provided by stakeholders to explain their low relevance scores for this element included e.g. 'Ceftriaxone has been a major driver of inappropriate use due to cost' and 'Cost-efficiency is not a great criterion for being responsible'.

Ten elements were selected without suggestions for rephrasing: *Access-Availability*, *Antibacterial Spectrum*, *Documentation*, *Evidence-based Guidelines*, *Expertise and Resources*, *Future Effectiveness*, *Interactions*, *Patient Compliance*, *Toxicity* and *Unintended Consequences*.

Among the 21 selected elements, 11 were labelled for rephrasing of the explanatory text based on comments made by stakeholders: *Antibacterial Activity*, *Dosing-PK/PD-Interval*, *Duration*, *Education*, *Indication*, *Microbiological Diagnostics*, *Patient Outcome*, *Route*, *Resistance*, *Resistance Surveillance* and *Timing*. Three new potential elements were suggested: *Waste Disposal*, *Alternatives* and *Multidisciplinarity*.

Step 3 – Consensus meeting

Ten stakeholders discussed the 11 elements labelled for rephrasing as well as the 3 newly suggested elements. The stakeholders represented all groups: medical community ($n = 3$); public health and patients ($n = 3$); antibiotic R&D ($n = 1$); payers, policy makers, governments and regulators ($n = 3$). The details of the consensus procedure including the final selection and rejection as well as the rephrasing of the elements are shown in Table 1. Nine elements were rephrased and two remained unchanged (*Resistance*, *Timing*). The newly suggested element *Waste Disposal* was rephrased to *Safely disposing of unused antibiotics and waste products containing antibiotics to prevent selection in the environment* and selected. The other two suggested elements, *Multidisciplinarity* and *Alternatives*, were rejected as these were not found to be defining elements of responsible antibiotic use. *Multidisciplinarity: Stimulating collaboration between different types of healthcare professionals (e.g. nurses, doctors, pharmacists)* was rejected as it was argued that the opposite, antibiotic stewardship performed without any multidisciplinary aspect, could not be considered bad clinical practice. *Alternatives: considering alternatives for antibiotics to prevent infections (e.g. vaccines, hygiene,*

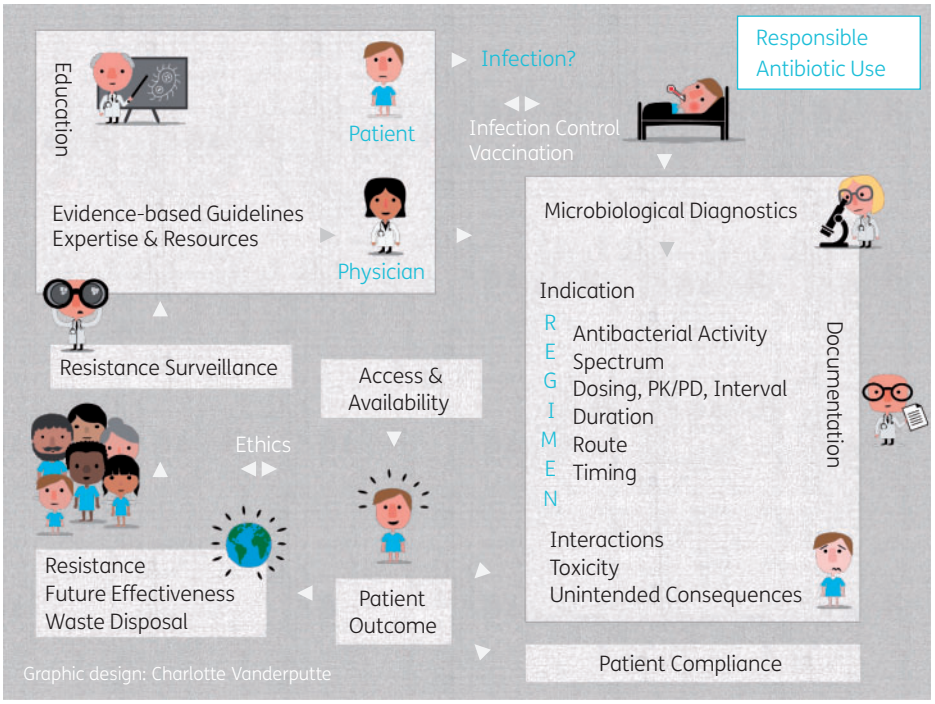

Figure 2. The final 22 elements included in the definition of responsible antibiotic use. The elements of responsible antibiotic use are shown in black text; two additions, suggested during stakeholder consultations, were inserted into the infographic on responsible antibiotic use: *Ethics* and alternatives (*Infection Control, Vaccination*) were considered of important value without directly defining responsible use. On the right: patient-level elements; on the left: societal elements.

infection control) was recognized as extremely important for reducing the number of infections and thereby reducing antibiotic resistance; however, it also did not directly contribute to defining responsible use. Therefore, *Infection Control* and *Vaccination* were added to the infographic as additional aspects of importance related to the definition of responsible antibiotic use (Figure 2). The final 22 elements of responsible use resulting from the Delphi procedure are shown in Table 2 and illustrated in Figure 2. Fourteen elements were patient-level elements that related to aspects of responsible use of antibiotics: *Antibacterial Activity*, *Antibacterial Spectrum*, *Documentation*, *Dosing-PK/PD-Interval*, *Duration Indication*, *Interactions, Microbiological Diagnostics*, *Patient Compliance*, *Patient Outcome*, *Route*, *Timing*, *Toxicity* and *Unintended Consequences.* Eight elements were considered societal-level as relating to responsible antibiotic use in a broader societal context: *Access-Availability*, *Education*, *Evidence-based Guidelines*, *Expertise and Resources*, *Future Effectiveness*, *Resistance*, *Resistance Surveillance* and *Waste Disposal.*

Discussion

In this study a list of 22 key elements and their associated best-practice descriptions were developed that, taken together, need to be included in the definition of responsible antibiotic use. This exhaustive list was the result of a systematic review followed by an international and multidisciplinary consensus. Fourteen elements corresponded to patient-level and 8 to societal-level elements. Patient-level elements reflect individual care parameters whereas societal-level elements typically affect large populations. At present, all the identified elements should be considered relevant and an aspirational goal would be to address them when using antibiotics.

Two additions, suggested during stakeholder consultations, were inserted in the infographic of responsible antibiotic use: *Ethics* and *Alternatives* were considered of important value without directly defining responsible use. The ethical dimensions of the balance between present and future patients have been addressed previously by others.[24,25] In a recent perspective on responsible use, Dyar *et al.*[26] also highlight two relevant dimensions of 'responsible': the responsible individual practices and the societal implications of being responsible. Regarding alternatives to antibiotics, the importance of infection control in parallel to stewardship activities has been highlighted by, among others, the Infectious Diseases Society of America and the Society for Healthcare Epidemiology of America.[20,27] In addition, vaccines are effective against bacterial diseases and therefore reduce the need for antibiotic usage.[28]

The global scope of the definition was emphasized by considering both its comprehensiveness and its worldwide relevance. Socio-economic, cultural or care-setting specific factors as well as feasibility or practical implications were not considered in this study, so that the resulting elements would be relevant to any setting worldwide. The elements of responsible antibiotic use should be considered as a consensus-derived set of principles of what responsible antibiotic use should entail. From these elements, generic quality and quantity measures can be developed, for both current and newly developed antibiotic drugs in the future. Finally, the definition constitutes a valuable educational tool for use in different healthcare curricula, including undergraduate education.[29]

Table 2. The final 22 elements of the definition of responsible antibiotic use and their explanatory phrase

Element	Explanatory phrase
Microbiological Diagnostics	Using microbiology diagnostic tools to provide diagnostic testing.
Indication	Using antibiotics only to prevent or cure infections for which antibiotic treatment provides a proven benefit.
Antibacterial Activity	Selecting antibiotics based on their antibacterial activity.
Antibacterial Spectrum	Selecting antibiotics based on their antibacterial spectrum (as narrow as possible).
Dosing, PK/PD, Interval	Dose and dosing frequency of the antibiotic regimen based on available knowledge on PK/PD (ensuring sufficient free concentrations of antibiotic at the site of infection).
Duration	Using the shortest possible evidence-based duration of the antibiotic regimen.
Route	Selecting the proper route (e.g. parenteral or oral) based on antibiotic, severity or type of infection and patient characteristics.
Timing	Administering antibiotics in a timely manner.
Interactions	Selecting antibiotics taking into account possible interactions with other medication(s).
Toxicity	Selecting the antibiotic with the least toxicity possible.
Unintended Consequences	Selecting the antibiotic with the lowest risk of secondary infections such as *C. difficile* diarrhoea.
Documentation	Fully documenting the antibiotic regimen including indication in the medical record.
Patient Compliance	Ensuring patient compliance with the antibiotic prescription.
Patient Outcome	Optimizing patient outcome (reduced morbidity, mortality and length of hospital stay) by treating or preventing bacterial infections.
Access-Availability	Ensuring access and routine availability of quality antibiotics.
Resistance	Limiting the emergence of antibiotic resistance.
Future Effectiveness	Conserving the effectiveness of antibiotics for the future.
Resistance Surveillance	Using local antibiotic resistance surveillance data for guidelines on empirical antibiotic prescribing.
Evidence-based Guidelines	Ensuring the availability and use of local (or national) evidence-based treatment guidelines.
Expertise and Resources	Using available infectious disease expertise and resources.
Education	Ensuring educational programmes on antibiotic use from an early stage for the public and all relevant professionals, including trainees in health care curricula.
Waste Disposal	Safely disposing of unused antibiotics and waste products containing antibiotics to prevent selection in the environment.

Until now, such a consensus-driven definition of responsible antibiotic use was lacking within the infectious disease and antibiotic stewardship community. The limitations of the WHO definition of rational use were previously addressed in the introduction of this manuscript. A strength of this work is the use of a systematic and stepwise method combining both concepts from the literature and stakeholder opinion. An additional innovative aspect is that the perspectives of a wide range of stakeholders involved with antibiotics were accounted for. This approach contrasts, however, with previous research efforts, which have mainly involved medical and public health communities. Previously, scientists have called for a multi-stakeholder approach including the producers and regulators of antibiotics, without any concrete success to date.[30,31]

The adjective 'responsible' was the terminology used in the Innovative Medicines Initiative (IMI) call, and therefore it was a logical continuation for use in the DRIVE-AB project. In our study, 17 synonyms of responsible antibiotic use were identified. This diversity in vocabulary is also illustrated by the fact that currently the WHO opts for 'rational' and 'appropriate'[7], while the ECDC uses the term 'prudent'[32] and the CDC 'appropriate'.[33] According to the authors, the identified synonyms should be considered as interchangeable as long as all the 22 elements are being considered.

A limitation of this work is the focus on human medicine only. As human health, animal health and the environment are closely interrelated, a One Health approach is of paramount importance. Antibiotic resistance has been recognized as the quintessential One Health issue, illustrating its principles better than any other public health threat.[34] In the global definition of responsible use, the element *Waste Disposal* of human antibiotics addresses the environment. Over the last 20 years, the importance of *Safely disposing of unused antibiotics and waste products containing antibiotics to prevent selection in the environment* has been demonstrated by several studies reporting pollution with antibiotics in effluents of drug manufacturers, which is driving antibiotic selection pressure in the environment.[35] Another limitation is that the veterinary sector was not addressed in any of the elements of the definition. However, the principles illustrated by the human elements of responsible antibiotic use are equally pertinent for animal health. Aspects relating to applicability or implementation in clinical practice were not included in this definition. While this contributes to the simplicity required for the global scope, including the coverage of low-income settings, and could be considered a strength, this should also be addressed as a flaw. A methodological limitation of this study is the use of a single literature database (MEDLINE) for the systematic review. However, both the complementary web site search and the opportunity given to the stakeholders to propose new elements should have ensured that no relevant element was missed. Another limitation is that the screening of the literature and websites and the data extraction process were performed by a single researcher. However,

measures to address intra-rater bias included a second data extraction process for a proportion of the articles and for all the web sites, and inter-rater bias was reduced by performing the screening of a proportion of the articles in duplicate. Finally, language subtleties might have been missed or might have contributed to a lack of understanding of the elements, as the researchers as well as some of the stakeholders were non-native English speakers.

In conclusion, a global list of elements key to the definition of responsible antibiotic use was developed considering the perspectives of a wide range of stakeholders involved with antibiotics. DRIVE-AB identified measures for assessing the quality and quantity of antibiotic use.[36–39] Together, these tools will be proposed as a global standard of responsible use for old and new antibiotics. Indeed, the ultimate goal of the DRIVE-AB initiative is to reconcile the long-term conservation of antibiotics through responsible use and incentives for novel antibiotic development.[40]

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Author contributions

A. A. M. performed the literature and web site searches, the data extraction, sent the questionnaire, collected and analysed the data and drafted the wording of the elements and the manuscript. M. E. H., I. C. G. and B. I. E. co-designed the study. M. E. H. performed the screening for the systematic review and provided methodological support. I. C. G. validated the classifications of the definitions into the elements. B. I. E. piloted the questionnaire. All authors have critically reviewed and approved the final manuscript.

Supplementary data

Figures S1 and S2 and Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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