Antimicrobial Resistance: formulation of the response in the global health context

Resistência a Antimicrobianos: a formulação da resposta no âmbito da saúde global

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ABSTRACT Antimicrobial Resistance (AMR) has proved to be a major public health problem at the global level. This paper examined the formulation of the response to AMR negotiated through the World Health Organization (WHO) by its Member States. Related WHO reports and resolutions from 1998 to 2019 were analysed. The findings indicate that, from 2014 on, more robust conditions were established for approval of a Global Action Plan on AMR, encompassing the concept of One Health and involving other international entities (FAO, OIE, WTO and Unep). Content analysis and various analytical frameworks, considering two economic sectors (the livestock and pharmaceutical industries), proved relevant to illustrating the complexity of the issue, reinforcing its global importance and acknowledging the extent of antibiotic use in animals and the gaps in technological innovation. As the WHO is not only an important agent for mobilizing the response to AMR at the global level, but – despite a context of de-funding – has guaranteed a budget for action in this area, it is concluded that the public health perspective should prevail in the response to AMR.

KEYWORDS Global health. Drug resistance, microbial. One Health. Livestock industry. Orphan drug production.

RESUMO *A Resistência a Antimicrobianos (AMR) tem se revelado como um dos maiores problemas para a saúde pública no nível global. O objetivo deste artigo foi analisar a formulação da resposta à AMR negociada no âmbito da Organização Mundial da Saúde (OMS) por seus Estados-Membros. Foram analisados os relatórios e resoluções produzidos na Assembleia Mundial da Saúde no período de 1998 a 2019. Os achados indicam que, a partir de 2014, foram estabelecidas condições de possibilidade para a aprovação do Plano de Ação Global em AMR de forma mais robusta, abrangendo o conceito de Saúde Única e envolvendo outras instâncias internacionais (FAO, OIE, OMC e PNUMA). A análise dos conteúdos e o uso de diferentes referenciais analíticos, considerando dois setores econômicos – agropecuária e indústria farmacêutica –, mostraram-se relevantes para ilustrar a complexidade da temática, reforçando sua relevância global, reconhecendo a dimensão do uso de antibióticos em animais e as lacunas em inovação tecnológica. Como a OMS, além de ser um importante agente mobilizador para a resposta à AMR no nível global, tem garantido orçamento para ações nessa área mesmo em um contexto de desfinanciamento, conclui-se que a perspectiva da saúde pública deve prevalecer na resposta à AMR.*

PALAVRAS-CHAVE *Saúde global. Resistência microbiana a medicamentos. Saúde Única. Indústria agropecuária. Produção de droga sem interesse comercial.*

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Introduction

Antimicrobial Resistance (AMR) is currently considered to be a major global public health problem. It is estimated that approximately four million people acquire health care-related infections annually in the European Union (EU) and that some 37,000 die as a result of resistant infections acquired in hospital environments. Most (67.6%) of these deaths are caused by multi-antibiotic-resistant bacteria[1].

The World Health Organization (WHO) describes AMR as the ability of microorganisms (bacteria, fungi, viruses, and parasites) to change when exposed to antimicrobial drugs and to resist such drugs, leaving them ineffective[2]. Often, however, the term is exemplified by the case of antibiotics used in bacterial infections.

AMR occurs as a result of the natural interaction among microorganisms in the environment[3], but its increasing incidence may result from a series factors, such as high consumption and improper use of antimicrobial drugs; populations' lack of information; overuse of antimicrobial drugs in agriculture and livestock production; and environmental pollution caused by discharge of pharmaceutical waste into soil or water. The problem is aggravated by a lack or insufficiency of regulation; a lack of oversight of antimicrobial drug consumption by government institutions; and a lack of innovative antimicrobial drugs as a result of low investment in Research and Development (R&D)[4-9].

Improper and excessive use of antimicrobial drugs in agriculture and livestock contributes to increasing incidence of AMR in humans. These medicine are used in the livestock industry to treat and prevent infections, as well as to promote animal growth, bringing selective pressure to bear on microorganisms to become resistant. Transmission to humans can occur directly, by contact, or indirectly, on consuming food products and from pollution caused by agricultural biological waste[7].

Despite the seriousness of AMR, few new antibiotics have been developed in the past 40 years. Traditional market incentives have not been – and are unlikely to be – able to bridge this gap in innovation, especially in a context where use of these medicines is being restricted[10].

At the international level, in 2015, the WHO Member States adopted the Global Action Plan on Antimicrobial Resistance (Resolution WHA68.7) at the World Health Assembly (WHA)[11]. This plan was based on the One Health concept, which assumes that human, animal and environmental health are interrelated and proposes that different fields of knowledge integrate with each other to address health problems[12,13].

Given the complexity and multi-causality of AMR, responses to it involve regulatory networks at various stages in the chain of antimicrobial drug production, use and trade, with implications for various economic sectors, such as the livestock and pharmaceutical industries. Considering the multiple dimensions of the response required by AMR, as well as the different actors in society and the economy directly involved and affected, this paper examines the formulation of the AMR response negotiated at the WHO by its Member States. Its working assumption is that the fronts on which it is considered important to take action to tackle AMR have broadened over the years, posing the need to involve other multilateral bodies and actors.

Methodology

This study falls within the policy analysis field, because it acknowledges the role of proposal formulation in a multilateral arena such as the WHO. The WHO belongs to the United Nations (UN) system and is characteristically member-driven, that is, directed

by the decisions of its Member States. By negotiating and approving resolutions in the WHA, the Member States mandate the work of the WHO and agree on country guidelines on the various issues negotiated[14]. Although the resolutions approved in the WHA are not binding, they do have the potential to guide policies, plans and programmes at the national level.

The reports and resolutions approved are important sources for examining the main arguments agreed among the countries on the subject of AMR. In this study, these arguments are themselves considered to constitute formulations of responses to AMR, which can in turn influence the formulation of national-level responses. In addition to reports and resolutions, this study examined other documents (*chart 1*), such as WHO budgets, spanning the 22-year period from 1998 to 2019.

Chart 1. List of documents examined

Year	Documents
1998	Report A51/9[15] Resolution WHA51.17[16] Financial Report and Audited Financial Statements for the period 1998-1999[17]
2001	Global Strategy for Containment of Antimicrobial Resistance - WHO/CDS/CSR/DRS/2001.2[18] Financial Report and Audited Financial Statements for the period 2000-2001[19]
2005	Report A58/14[20] Resolution WHA58.27[21] Financial Report and Audited Financial Statements for the period 2002-2003[22] Performance assessment report: Programme budget 2004-2005[23]
2014	Report A67/39[24] Resolution WHA67.25[25] Global Action Plan (draft) A67/39 Add.9[26] Performance assessment report: Programme budget 2006-2007[27] Performance assessment report: Programme budget 2008-2009[28] Performance assessment report: Programme budget 2010-2011[29] Performance assessment report: Programme budget 2012-2013[30] Performance assessment report: Programme budget 2014-2015[31]
2015	Report A68/19; A68/20[32] Resolution WHA68.7[33] Global Action Plan (draft) A68/20 and A68/20 Add.1[11]
2016	Report A69/24[34] Global Action Plan – Stewardship Framework – Report by the Secretariat A69/24 Add.1[35] High-Level Meeting of the General Assembly on Antimicrobial Resistance (ONU)[36] WHO Results Report: Programme budget 2016-2017[37]
2017	Report A70/12[38] Guidelines on use of medically important antimicrobials in food-producing animals[39]
2018	Memorandum of Understanding between FAO/OIE/WHO/Unep[40] WHO Results Report: Programme budget 2018-2019[41]
2019	Follow-up to the high-level meetings of the United Nations General Assembly on health-related issues[42] Resolution and decisions of the Seventy-second World Health Assembly. Antimicrobial resistance[43] Report to the Secretary-General of the United Nations: 'No time to wait: Securing the future from drug-resistant infections'[44]

Source: The authors. Documents available at: https://www.who.int/.

The study used a triangulation among multiple theoretical frames of reference, including the policy cycle concept proposed by Howlett & Ramesh (2009) (as in Mattos et al.)[45], involving five distinct phases: agenda setting, policy formulation, decision process, policy implementation and policy evaluation. Although related to national-level policymaking, some of these phases – formulation and implementation – can be of use in analysing the role of international processes and, subsequently, their influence on policy formulation at the national level. Accordingly, this study is considered to be an endeavour to recognise the international dimension in national-level public policymaking.

The global health governance proposal described by Frenk & Moon[46] is considered in analysing the architecture established in the process conducted at the WHO on the issue in question. The analysis of the institutional dimension offered by Sell[47] also proved relevant to appraising issues of global governance (*chart 2*).

Chart 2. The institutional dimension as proposed by Sell and the global health functions as proposed by Frenk & Moon

Institutional Dimension
Scope of multilateral institutions (political arenas) that establish binding and non-binding laws, declarations and resolutions with regard to global health[47].

Global Health System
Comprising a group of actors whose aim is to improve global health by setting rules at the international level. Works on the assumption that no country alone is able to tackle the health threats to its population. Accordingly, it is believed that strategies need to be developed at the international level[46].

Governance
The manner in which the global health system is managed. Comprises formal and informal mechanisms used by government and non-governmental actors to coordinate strategies in multilateral forums to respond to risks to the world population[46].

Function	Description	Tool
Mobilising global solidarity[46]	Commitment by the global community to protecting the rights of minority groups. The aim is to reduce inequalities in the distribution of health problems among nations[46]	Financial and technical support, professional capacity-building and humanitarian assistance[46]
Management of externalities across countries[46]	Some situations that occur in one country may produce effects in others. This function proposes to prevent or mitigate adverse effects on global health[46]	Epidemiological surveillance and information sharing and coordination for preparation and response[46]
Production of global public goods[46]	Information shared by the global community[46]	Tools for international standardisation and guidelines on best practices, e.g., International Classification of Diseases and List of Essential Drugs[46]
Stewardship[46]	Responsible for guiding the whole global health system strategically, meaning that the other essential functions mentioned depend on it in order to function properly[46]	Sub-functions Convening to negotiation and consensus building; priority setting; specifying managerial rules; assessing actors and their actions; and advocating for health causes in other political arenas that can influence decisions taken in the global health arena[46]

Source: The authors, based on Frenk& Moon[46] and Sell[47].

The document analysis, based on the proposal by Minayo et al.[48], at first considered three categories (general aspects of AMR, pharmaceutical innovation and agriculture and livestock). After reading the documents, the categories were reorganised, making the results easier to interpret and synthesise. These were: formulation of the response to AMR; the new formulation of the response to AMR and developments from it; and global health system governance and functions applied to the case of AMR.

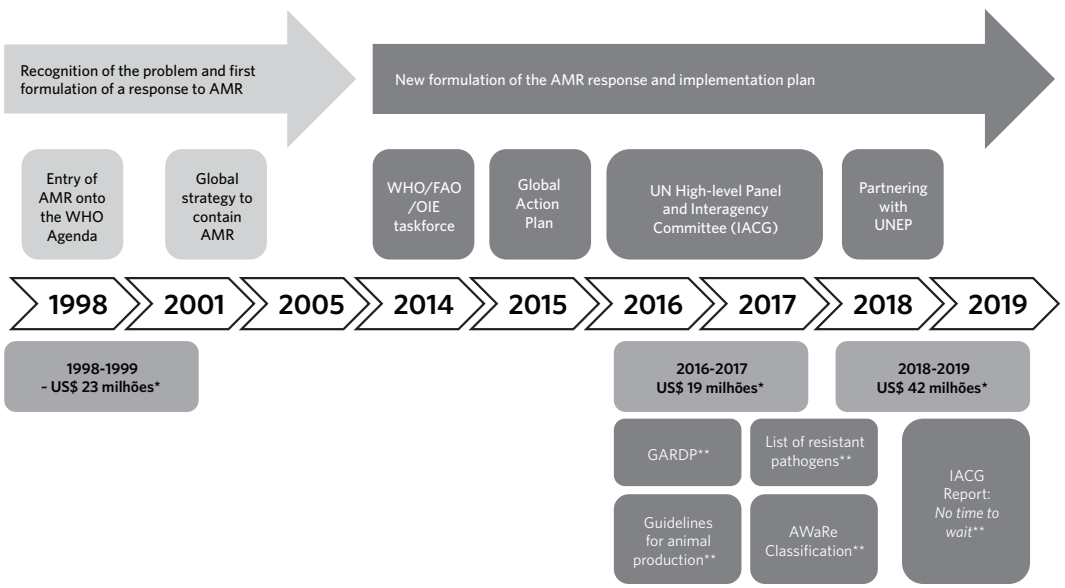
As the analysis was based on documents that were the outcome of negotiations, the study is recognised to be limited as regards any possibility of identifying tensions among countries on sensitive aspects of the subject over the course of the negotiating process. The 'formulation process' was considered to be the development, over time, of content included in the AMR response, as well as the involvement of other multilateral institutions.

Results and discussion

Formulation of the response to tackle AMR

The period from 1998 to 2013 was identified to be when the response to AMR was formulated in the WHO: when the issue was acknowledged to be a public health problem and discussions were held on the action to be taken to deal with the problem. It was possible to organise this period into the three distinct phases described below (*figure 1*).

Figure 1. Timeline of AMR response formulation



Source: the authors, from document analysis.

*Biennial budget.

**International-level response.

World Health Organization (WHO), World Animal Health Organization (OIE), United Nations Food and Agriculture Organization (FAO), United Nations Organization (UN), United Nations Environment Programme (Unep). Global Antibiotic Research and Development Partnership (GARDP), List of antibiotics by level of resistance (AWare Classification).

Period from 1998 to 2001: the problem recognition and first formulation of the response to AMR

AMR appeared on the WHO agenda for the first time in 1998, when discussion of a Report[15] resulted in the approval of Resolution WHA51.17[16]. In the two-year period 1998-1999, the organisation approved a specific budget of about US$23 million for this issue[17].

That Resolution mentioned that using antimicrobial drugs in humans or animals, whatever the amount or purpose, fostered selective pressure on bacteria to become resistant to such medicines, which favours the spread of AMR[16]. Responsibility for the problem was acknowledged to lie with both human and veterinary medicine, because medicines are also used in animal production and agriculture[15]. It was recommended that governments develop strategies to reduce antibiotic consumption in humans and in animal production[15,16].

One possible reason why the subject entered onto the WHO agenda in 1998 was that, in that year, the European Union (EU) had embarked on a process of reviewing of its community rules on the use of antibiotics in animal production[49]. Castanon[49] reported that Sweden was the first European country to ban the use of antibiotic growth promoters, and its entry into the EU in 1995 brought the issue into the bloc's discussions. Also in 1995, Germany and Denmark banned certain therapeutic classes of antibiotic for animal use, further helping to raise the issue within the EU. In the late 1990s, EU rules were altered to tighten restrictions on the use of antibiotics as animal growth promoters[49].

As regards innovation, the Resolution asserted that antimicrobial drug-resistant infections are made harder to treat by the lack of effective agents for some cases and by the prohibitive prices of new generation antimicrobial drugs[15]. Many countries were unable to afford innovative medicines, while existing antimicrobial drugs were being prescribed irrationally. The solutions proposed included strengthening patent laws. That Resolution made no provision for recommendations to countries as regards the innovation gap. It merely recommended that the WHO collaborate in knowledge sharing among the public sector, academia and industry, and encourage promotion of R&D in the area[17].

In 2001, the WHO published the Global Strategy for Containment of Antimicrobial Resistance (WHO/CDS/CSR/DRS/2001.2)[18], proposing a series of interventions to retard the emergence and reduce the dissemination of microorganisms resistant to antimicrobial drugs.

With regard to animal production, the document addressed the relation between the food production system and the spread of AMR. World population growth had driven mounting demand for foods from animal sources and, in order to meet that need, animal production had shifted to an intensive model, thus creating an environment favourable to the spread of infectious diseases among animals. This, in turn, led to antibiotics' being used to treat and prevent diseases and also to promote animal growth[18].

The WHO recognised the relationship between antibiotic use in animal production and AMR in humans in the light of evidence that antibiotic-resistant bacterial strains had appeared in humans after antibiotics were introduced into production of foods from animal sources. France, Germany, Ireland, the Netherlands, Russia and other countries had reported that certain strains had become less susceptible to antibiotics after their use was permitted in animal production[18].

Recognising that AMR is a complex, multifactor problem, the 2001 document[18] outlined an inter-sector strategy resting on collaboration among various sectors of society (doctors, veterinary doctors, pharmacists and other health professionals, agricultural and livestock producers, the pharmaceutical industry, civil society, governments and other interested parties)[18]. That document also proposed legislation

to control the consumption of antibiotics in animal production; for instance, making veterinary prescription mandatory for the dispensing of antibiotics[18].

Regarding technological innovation, the 2001 document repeated that the risk of there being no effective therapies in coming years resulted from a gap to innovate in antimicrobial drugs. The gap was justified by the lengthy, expensive R&D activities involved and by the fact that restrictions on the use of new medicines, indicated as the therapeutic option of last resort, could have adverse impact on sales. The document acknowledged that firms should recover their R&D expenditures and gain profit from the product. Accordingly, new antimicrobial drugs and vaccines should be developed in order to avert the future impact of resistance, but that incentives were necessary for private R&D in this field[18].

The Global Strategy of 2001[18] warned of the existence of biases in cost-effectiveness studies, which favoured new antimicrobial agents, because older ones unprotected by patents were not attractive, and that studies of the cost or clinical impact of AMR were lacking. Added to this, access to new medicines was unequal, because it was limited in less-developed countries, and solutions were required for resource-limited settings. Greater interaction among industry, government and academia was cited as one possible solution in this context[18].

It proposed that international research and cooperation networks be set up to work on harmonizing regulatory requirements, and specifically mentioned interaction with industry through innovative incentives for investment in antimicrobial drug R&D. The suggestions mentioned included a regulatory fast track or application of a policy similar to that in place for orphan diseases; time-limited exclusivity; and appropriate patent protection. Action to combat AMR should be taken at the global level, framed by the concept of "global public goods for health"[18], and coordinated in such a way as to avoid duplicating efforts. It was also suggested to establish an international database of funding sources for research in the field, thus creating a single gateway for projects, developing new programmes and strengthening existing ones[18].

PERIOD FROM 2002 TO 2005: LITTLE DISCUSSION ON THE ISSUE

Between 2002 and 2004, the topic of AMR was not addressed at the WHA, probably in view of the 2001 Global Strategy and the expectation that Member States would be drawing up their own action plans. In 2005, AMR was mentioned again at the WHA, but matters relating to antibiotic use in agriculture and livestock production were not discussed[20,21].

On innovation, Report A58/14[20] once again stressed the high prices of antimicrobial drugs when launched onto the market and proposed solutions to the problem, such as prices being lowered by the industry and using generic alternatives. Nonetheless, Resolution WHA58.27[21] of the same year contained no action in this respect.

The mention of competition with generic medicines to address high prices marked a shift from solutions put forward in previous documents, which had pointed to reinforcing the intellectual property system. That shift in orientation is likely to have reflected the process – underway in the WHO as well – on the subject of public health, innovation and intellectual property, triggered chiefly by the approval in 2003 of Resolution WHA56.27[50], which set up the Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH)[50].

PERIOD FROM 2006 TO 2013: LITTLE VISIBILITY FOR AMR ON THE WORLD HEALTH ASSEMBLY AGENDA

Few documents on the subject of AMR were found to have been issued in the WHO from 2006 to 2013. Meanwhile, between 2003 and

2012, the subject of public health, innovation and intellectual property gained prominence in the wake of developments from the 2006 CIPIH report[51] and approval in 2008 of the Global Strategy and Plan of Action on Public Health, Innovation and Intellectual Property[52] and the 2012 report of the Consultative Expert Working Group on R&D: Financing and Coordination (CEWG)[53,54]. The latter sought proposals of new funding sources and innovative funding mechanisms to encourage R&D to meet health needs that affected developing countries disproportionately.

In the eight years during which the issue of AMR was not addressed explicitly at WHA meetings, advances were observed in implementation of a global strategy for AMR, such as the development of integrated epidemiological surveillance systems on the African continent and in Latin American countries and the implementation of strategies to address the problem in regions including the Eastern Mediterranean, Southeast Asia, the EU and the Western Pacific[50].

Although the Plan of Action on AMR approved in 2001 was in place, the WHO considered it not to have been widely accepted by countries[50]. In 2014, of the 92 Member States present, only 29 had developed national strategies, 20% of them developing countries. Accordingly, in 2013, the WHO Director-General set up a strategic and technical consultative committee on AMR, which met for the first time that same year and concluded that it was necessary to renew and expand the global strategy to contain AMR[50,51].

Reformulation of the AMR response and related developments

PERIOD FROM 2014 TO 2019: FORMULATION OF THE AMR RESPONSE AND AN IMPLEMETATION PLAN.

In 2014, AMR returned to the WHO agenda in more robust form and with a view to engaging other global actors. Report A67/39[24] and Resolution WHA67.25[25] were approved

Two changes proposed in 2014 stand out in relation to the plan approved in 2001. The first was the adoption of the One Health concept as a guiding principle for formulation of a global plan of action on AMR. The WHO regarded the concept as allowing a coherent, comprehensive and integrated approach at the global, regional and national levels, involving different actors and sectors, such as human and veterinary medicine, agriculture, environment and consumers.

The second change was the establishment of a Global Task Force on Antimicrobial Resistance based on tripartite collaboration among the United Nations Food and Agriculture Organization (FAO), the World Animal Health Organization (OIE) and the WHO[24,25].

In that context, the WHO Director-General called for a Global Plan to be drawn up to assist the Assembly with its decisions and assure that all countries, especially developing countries, were able to respond to AMR[24,25]. That document was then drafted in collaboration among the three organisations mentioned earlier.

The draft approved in 2014[26] outlined the priority areas for AMR response action, with quantifiable targets and goals and implementation plans specifying roles and responsibilities of the actors involved. It also provided for indicators to enable progress to be monitored, measured and replicated.

The 2014 Report (A67/39)[24] broadened its view of the innovation problem to include the lack of innovation in diagnostics. The report mentioned the insufficiency of investment in R&D for AMR-related technologies, whether preventive (vaccines), treatment-related (antimicrobial drugs) or diagnostic. It stressed the need for incentives for innovation in the field, associated with sustainable new models to support R&D in the long term and recommended

that the WHO partner with industry. That year's Resolution (WHA67.25)[25] cited limited development of new antimicrobial agents, and mentioned the CEWG Report and the R&D Observatory. It recommended that countries encourage new collaborative and financing models for innovation. The need to finance R&D and Innovation (RD&I) in this field was mentioned both in recommendations to the countries and in the WHO mandate[25].

This gap in technological innovation is a central item in discussions of AMR. Beginning in 2003, the issue of public health, innovation and intellectual property began to gain prominence in the WHO, and arguments and actions relating to this public health issue can be seen as included into documents issued from 2014 onwards.

In 2015, the 68th WHA reaffirmed the importance of the tripartite collaboration (WHO/FAO/OIE) and mentioned the institutions' common interest in tackling AMR[32]. That year the Tripartite developed a new Global Action Plan on AMR[11] and a meeting was convened with the Secretary-General to hold a high-level meeting on AMR in 2016[33].

The Resolution approved that same year (WHA68.7) requested all Member States to adapt the Global Action Plan on AMR to their national priorities. It also stipulated that, by the 70th WHA, in 2017, all country plans should be aligned with the WHO plan[11] and with the standards and guidelines laid down by other international bodies, such as the *Codex Alimentarius* Commission, FAO and OIE[33].

In 2016, the WHO published Report A70/12[35], as well as a Global Framework for Development and Stewardship to Combat Antimicrobial Resistance, produced jointly by the WHO, FAO and OIE. The Framework pointed to the need to support the development, control, distribution and appropriate use of new antimicrobial drugs, diagnostic tools, vaccines and other interventions, with a view to promoting affordable access to existing and new antimicrobial medicines and diagnostic tools, taking into account the needs of all countries and in line with the Global Action Plan on Antimicrobial Resistance[35].

In 2016, AMR became an issue beyond the health arena with the UN's approval of the Political Declaration of the High-Level Meeting of the General Assembly on Antimicrobial Resistance. The document reaffirmed that the Global Plan of Action on AMR should be drawn up by the WHO in collaboration with the FAO, OIE and UN, and represent the commitment of Heads of State and Government to developing a multi-sector action plan in line with the One Health concept[36].

That document mentioned that AMR posed a challenge to attainment of the Sustainable Development Goals set in Agenda 2030. It also instituted the Interagency Coordination Group (IACG) on AMR. The Group was co-chaired by the WHO and the UN Secretariat, with the participation of other institutions of the UN system, international organisations, civil society and private sector representatives and experts in a number of AMR-related fields. Its main aim was to produce a report to assist decision-making on AMR at the 73rd WHA[36]. In 2019, the Group published the report 'No time to wait: securing the future from drug-resistant infections'[44].

Unlike previous years, in 2016 and 2017 no Resolution was approved on AMR at the WHA, because the Global Plan of Action on AMR had been approved in 2015. In 2018, the Tripartite signed a collaboration agreement with the United Nations Environment Programme (UNEP) (*figure 1*) to tackle AMR at a multi-sector (human-animal-environment) interface[40].

At each WHA after 2015, countries were updated as to the status of Member States' adoption of the Global Action Plan. In 2017, 67 countries had developed their plans to address the problem[38]; by 2019, 117 countries

had done so. However, only half of these – among them Brazil – had set up a multisector committee with representatives of various fields[13]. The number of countries still developing their plans remained at 62 from 2017[38] to 2019[42].

At the 2019 WHA, the countries reaffirmed their commitment to continue increasing their efforts to adopt the Global Plan of Action on AMR at the national level[43]. The Resolution addressed the question of the rational use of antibiotics in humans and animals, and mentioned the clinical guidelines for using antibiotics that are important to human health[43] (the 'AWaRE' Classification). As regards RD&I, it was agreed that the countries would support voluntary technology transfer to prevent and control AMR[43].

Other initiatives led by the WHO during this period included setting up the Global Antibiotic Research and Development Partnership (GARDP) in 2016, publication of a list of resistant pathogens and approval of guidelines and best practices for animal production in 2017 (*figure 1 and chart 3*).

The WHO approved specific budgets for AMR for the two-year periods 2016-2017 and 2018-2019 of US$19 million and US$42 million, respectively. What is striking is that the budget for 2018-2019 is roughly double those approved for 2016-2017 and 1998-1999 (about US$23 million). That fact indicates that, despite the structural crisis in WHO funding[58], funds were earmarked for AMR. It also points to greater breadth and commitment in the 2015 plan as compared with 2001.

Global health system governance and functions applied to the case of AMR

Drawing on the concept of Global Governance for Health[46], the document analysis in this study found that the WHO recognised AMR as a global health problem, because no country alone could contain its advance, which overrides national borders and involves diverse sectors of society[18].

It is evident that, over the whole course of formulation of the Global Plan of Action on AMR at the WHO, the issue of international cooperation to support developing countries and least-developed countries (LDCs) to formulate their plans to tackle AMR. Inequality among Member States was recognised as an important issue and, for that reason, international cooperation served as a tool for supporting LDCs by developing epidemiological surveillance laboratories and programmes and training personnel[11,18].

Both the 2001 Global Strategy[18] and the 2015 Global Action Plan[18] reinforced the importance of epidemiological surveillance as one of the structural components of the response to AMR. It was recommended that each Member State develop a national system to monitor antibiotic consumption in humans and animals and the incidence of AMR. Also as regards epidemiological surveillance, the platform of the Global Antimicrobial Resistance Surveillance System (Glass) was inaugurated in 2015. This initiative was designed to collect and analyse country-level information on AMR so as to produce evidence to guide national, regional and global action to tackle AMR. By 2019, 105 countries claimed to have their own surveillance systems; 67 shared their findings and 48 input crude data to the GLASS initiative[42].

The Global Plan of Action on AMR, as well as the guidelines and initiatives on antibiotic use in agriculture and livestock, and research, development and innovation in new antimicrobial drugs (*chart 3*), are all regarded as examples of 'global public goods'[46] in the AMR context.

Chart 3. Examples of 'global public goods'[55] in the AMR field

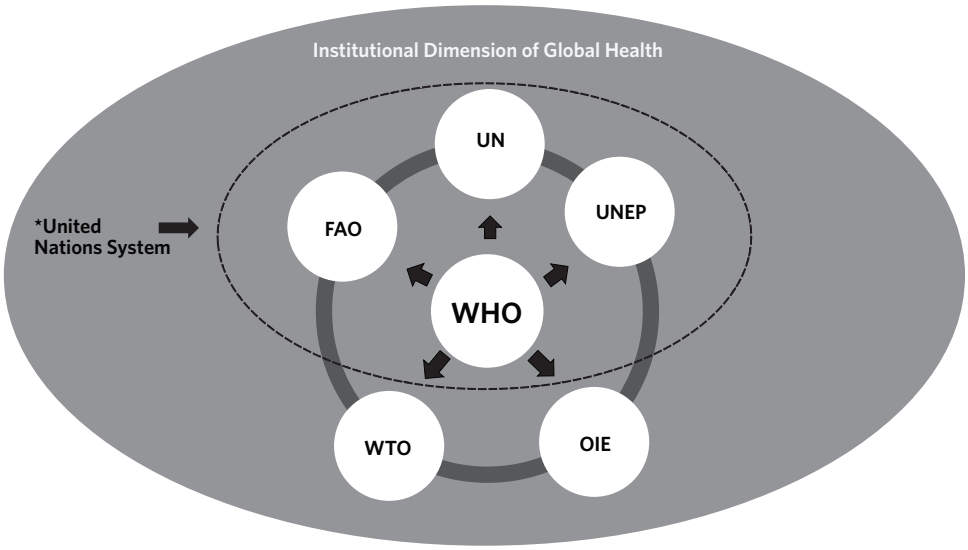
Initiatives taken at the global level to tackle the lack of research and development in new antibiotics	
Initiative	**Description**
Global Antibiotic Research and Development Partnership (GARDP)	Partnership between the WHO and the Drugs for Neglected Diseases Initiative (DNDi), to develop new therapeutic classes of antibiotics[55].
List of resistant pathogens	List of resistant pathogens with priority for R&D of new antibiotics. Classifies resistant pathogens by threat risk to global health, so as to guide the process of R&D into new therapeutic classes of antibiotics[56].
'AWaRE' Classification of antibiotics	The WHO has developed a data base containing 180 classes of antibiotics classified, by level of resistance, into 'Access', 'Watch' and 'Reserve' groups[57]. The data base is a tool to guide countries in monitoring antibiotic use[57].
Initiatives taken within the WHO to reduce consumption of antibiotics in animal production **WHO Guidelines on use, in animal production, of important antibiotics for human health[39]**	
Guidelines	**Best practices**
Reduce use of all classes of antibiotics important to human health in animal production[39]	New antibiotics developed for human use should be considered critically important to human health[39].
Antibiotics important to human health should not be used to promote animal growth[39]	Drugs that are important to human health and are not used in animal production should not be used for that purpose in the future[39].
Antibiotics important to human health should not be used in animal production to prevent undiagnosed infectious diseases[39].	
Antibiotics classified as critically important (high priority) to human medicine should not be used to treat animals[39]. (Conditional recommendation*)	
Antibiotics critically important to human medicine should not be used to control the spread of diseases in animal production[39]. (Conditional recommendation*)	

Source: the authors, based on DNDi[55] and WHO[39,56,57].

*In this document, the WHO endorsed this recommendation as conditional due to the poor quality of the available scientific evidence.

Global health is thus the outcome of the policymaking process in a diversity of institutional spaces[46]. Considering the concept of institutional dimension proposed by Sell[47], the document analysis found that a number of multilateral institutions participated in the process of formulating the plan to tackle AMR, including the WHO, FAO, OIE, UN, World Trade Organization (WTO) and later the UNEP (*figure 2*). This gives greater grounds for claiming that development of the AMR response plan was the outcome of meshing among organisations with different perspectives.

Figure 2. Diagram of the institutional dimension of global health in the case of AMR



Source: the authors, on the theoretical basis proposed by Sell[47].

*The United Nations System comprises specialised agencies and institutional programmes.

United Nations Environment Programme (Unep), United Nations Food and Agriculture Organization (FAO), United Nations Organization (UN), World Health Organization (WHO), World Trade Organization (WTO), World Animal Health Organization (OIE).

Illustrating that interrelationship, it can be seen that three of the four sub-functions of Stewardship were applied there[46]: cross-sector health advocacy; negotiation and consensus building; and setting rules to manage the dimensions of health across sectors.

The Resolution of the 68th WHA states that the WHO partnered with the UN in order to join forces in search of efficient mechanisms with which to implement the Global Action Plan for all nations, considering the needs of developing countries[33]. With regard to AMR, the WHO was found to have collaborated with other multilateral organisations so as to further the interests of global health in other institutions that were not responsible for health-related issues, but which could influence the global health field.

As regards negotiating and consensus building on the use of antibiotics in agriculture and livestock, no mention was found of any ban on the use antibiotics as growth promoters in animal production, probably because this was an issue of tension and dissent among countries. At the national level, some countries took different positions on the issue on the basis of various arguments. EU countries banned growth promoters as of 2006[59] and recently (2018)[60] restricted the preventive use of antibiotics in animal production[60]. Meanwhile, some developing countries, such as Brazil, permit the use of growth promoters[8,13].

The 2014 Resolution mentions that the partnership among the WHO, FAO and OIE was set up to manage conflicts of interest, with a view to support the drafting Global Action Plan on AMR[25].

On the option between 'banning' or 'not banning' the use of growth promoters, the IACG reached a compromise in which it recommended that certain antibiotics classified as critically important to human health should

gradually be phased out[44] of animal use. The report considered that initiative to be a first step towards the rational use of antibiotics in animal production[44]. Accordingly, the establishment of the FAO/WHO/OIE taskforce is believed to have been fundamental in building consensus on the use of antibiotics for promoting growth.

In addition to consensus building, the actors are considering settting new rules or instruments to manage AMR-related issues. The 2016 Report mentioned the legal status of the standards, guidelines and codes of practice of the *Codex Alimentarius* and OIE enjoyed under WTO agreements[34].

The Stewardship sub-function 'setting rules to manage the dimensions of health across sectors' is exemplified in the IACG report by the process still under way among countries with regard to adopting binding and non-binding instruments for measures on AMR[44].

Conclusions

This study examined the formulation of the response to AMR in the WHO. The findings indicate that, although the issue has been on the agenda since 1998, and a plan to address AMR was approved in 2001, few advances can be seen as regards adoption by WHO Member States. In 2014, when the One Health concept was endorsed, conditions were created for adhesion by other international institutions (FAO, OIE and WTO) and for approval of the Global Plan of Action on AMR.

Given the complexity and comprehensiveness of the factors relating to AMR, it was to be expected that design of a global response to the problem would be immersed in that complexity, particularly because not only do public health needs affect sensitive economic sectors – the agriculture and livestock and pharmaceutical industries – but they also reinforce asymmetries among countries. In that light, it was fundamental to triangulate among multiple analytical frames of reference so as to permit a broader understanding of the study object, underscoring its global importance and recognising the dimension of antibiotic use in animals and the gap in technological innovation.

Besides being an important mobilising agent for the response to AMR at the global level, the WHO has also assured a budget for actions on this issue even in a context of defunding. It is thus concluded that the public health perspective should prevail in the response to AMR. It remains to be analysed how far-reaching will be national-level adoption of the proposals approved multilaterally to curtail the spread of AMR and, at the same time, assure that therapeutic options involving existing and new antimicrobial drugs continue to be available to those who need them.

Collaborators

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