

Addressing Antimicrobial Resistance through Negotiation of a Pandemic Instrument

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A pandemic instrument will be most effective if it is comprehensive and responds to the full range of cross-border infectious disease threats that can lead to pandemics.

Photo: Ralph (Ravi) Kayden.

Key Points

1. Antimicrobial resistance (AMR) should be addressed when negotiating the World Health Organization's new pandemic instrument in order to comprehensively tackle both primary natural sources of pandemics and not just zoonotic threats that resemble the COVID-19 pandemic.
2. The efforts needed to address AMR and zoonoses overlap significantly, which means negotiations that have initially been focused on zoonotic threats just require small adjustments to also tackle the silent pandemic of AMR for greater impact.
3. Dual-purpose provisions could synergistically promote a) equitable access to medical countermeasures, b) globally integrated One Health surveillance and monitoring systems, and c) increased technical and laboratory capacity in low- and middle-income countries.
4. A comprehensive pandemic instrument can also include provisions to safeguard the effectiveness of antimicrobial medicines, as such efforts would especially benefit from strengthened global governance and would additionally help manage the spread and/or severity of future zoonotic pandemics.

Executive Summary

The COVID-19 pandemic has led governments to re-examine current global health security arrangements and create an intergovernmental negotiating body through the World Health Organization (WHO) to consider how they can more effectively prevent, prepare for, and respond to future pandemics. To date, countries have taken a narrow approach in their discussions, focusing on emerging zoonotic infections, like COVID-19, that are transferred from animals to humans. This narrow approach could severely limit the world's ability to address future pandemics as zoonoses represent only one of the two most likely natural sources of pandemics. A comprehensive pandemic instrument would also need to address antimicrobial resistance (AMR), the natural process through which pathogens become resistant to the antimicrobial medicines that were invented to treat them. AMR has been recognized by WHO as one of the top ten global health threats facing humanity and is estimated to have caused over 1.27 million deaths in 2019.

If the opportunity to address AMR in a pandemic instrument is not seized now, the next pandemic could be caused not by novel pathogens that have transferred from animals to humans but from existing pathogens that have become resistant to antimicrobial medicines. In addition to being a substantial global health threat in its own right, the diminishing effectiveness of antimicrobials poses a threat during zoonotic pandemics: for example, the treatment for many zoonoses relies on antimicrobials to reduce the severity of, and death from, secondary bacterial infections.

There are significant overlaps between the strategies required to address zoonoses and AMR. Dual-purpose provisions within a pandemic instrument could synergistically work to comprehensively prevent, prepare for, and respond to both threats. For instance, access to medical countermeasures, such as antimicrobials, diagnostics, personal protective equipment, and vaccines, is vital for controlling the spread of infectious diseases, including zoonoses and AMR. Achieving this access will require strategies to finance countermeasures' invention, development, and validation through research, as well as their regulatory approval, manufacturing, and distribution. A pandemic instrument could designate antimicrobials, diagnostics, personal protective equipment, and vaccines as 'global public goods' and create or adopt trusted mechanisms for expediting their development, ensuring their availability when needed, and financing their efficient procurement and equitable distribution.

Similarly, a globally integrated One Health surveillance and monitoring system is key to identifying and supporting pandemic responses. Like zoonoses, some new antimicrobial-resistant strains of bacteria arise at the human-animal-environment interface. Surveillance is needed for early detection and notification of potential zoonoses and antimicrobial-resistant pathogens in animals, tracking emerging variants of zoonoses and the spread of resistant pathogens among humans to identify population transmission patterns, and sharing of information at domestic and global levels to coordinate global pandemic responses. A pandemic instrument could mandate the implementation of minimum One Health surveillance and monitoring capacities that go beyond sector-specific monitoring of established infectious disease threats to include capacity for monitoring the emergence of potential zoonoses and resistant pathogens in humans, animals and the environment. This could be supported by an additional mandate for the development of standardized protocols on data reporting and knowledge sharing systems for potential zoonoses and AMR.

Furthermore, increased technical capacity and laboratory infrastructure is needed for truly global One Health surveillance and monitoring of infectious diseases, including zoonoses and AMR. While many wealthier countries may already be able to fully participate in a global surveillance system, many low- and middle-income countries (LMICs) face human resources shortages and fewer clinical laboratories and diagnostic facilities to conduct laboratory testing for emerging pathogens and antimicrobial-resistant organisms. A pandemic instrument could promote financial support for LMICs to meet minimum One Health surveillance and monitoring capacities and mandate the universal implementation of joint external evaluations of both surveillance and laboratory capacities.

Safeguarding the long-term effectiveness of antimicrobial medicines will require a regulatory framework promoting global stewardship. Embedding this one AMR-specific element in a pandemic instrument is useful because it could help resolve the global collective action problems that currently disincentivize countries from investing in antimicrobial stewardship at socially optimal levels. Global coordination to sustain the effectiveness of life-saving antimicrobials can also help manage the spread and/or severity of future pandemic threats, including through the treatment of secondary bacterial infections often associated with zoonotic pandemics. A comprehensive pandemic instrument could mandate the development or use of a regulatory framework governing which antimicrobials should be accessed, watched, and reserved in health care (i.e., WHO's AWaRe framework) and which critically important antimicrobials should be limited to human use.

The articulated goal of a pandemic instrument is to develop a comprehensive framework to prevent, prepare for, and respond to future global pandemics. Solely addressing zoonoses will not adequately prepare the world for both primary natural sources of future pandemic threats, which includes AMR. The good news is that, given the substantial overlap between AMR and zoonoses, many dual-purpose provisions could be designed to simultaneously address zoonotic and AMR pandemics. A comprehensive pandemic instrument of this type offers the opportunity to address core challenges across pandemic threats and promote the stewardship of antimicrobials that is unlikely to be implemented at socially optimal levels without global coordination.

Addressing Antimicrobial Resistance through Negotiation of a Pandemic Instrument

Introduction

The COVID-19 pandemic has laid bare shortcomings of current global health security arrangements, presenting an opportunity to re-examine and strengthen global governance to better protect people and societies from infectious diseases. The robust global coordination needed to prevent, prepare for, and respond to future global health security threats are at least partly dependent on future revisions to international instruments.¹ As a new World Health Organization (WHO) intergovernmental negotiating body (INB) prepares to draft and negotiate an instrument for pandemic prevention, preparedness, and response,² it is important to critically consider the full range of substantive issues that should be addressed in a potential pandemic instrument to ensure adequate global readiness for the next pandemic – whether it looks like COVID-19 or a different kind of pandemic threat, like antimicrobial resistance (AMR).

Indeed, to date, discussions of a pandemic instrument have taken a narrow approach, focusing attention on the need for better surveillance and monitoring of emerging *zoonotic* infections, like COVID-19, that are transferred from animals to humans.^{1,3} Taking a narrow approach can severely limit the world's ability to prevent, prepare for, and respond to the full range of future global pandemic threats. Zoonoses are not the only natural source of pandemics. If governments want to be adequately prepared for the next pandemic, the COVID-19 pandemic cannot be the only point of reference.⁴

At the very least, a future pandemic instrument should also address AMR — the natural process by which pathogens become resistant to the antimicrobial medicines intended to treat them¹ — which WHO has recognized as one of the top ten global health threats facing humanity. AMR was responsible for over 1.27 million deaths in 2019⁵ and could result in substantial direct and indirect economic damage akin to the annual costs of the global financial crises that began in 2008⁶ (see Panel 1). If the opportunity to address AMR in a pandemic instrument is not seized, the next pandemic could be caused not by novel pathogens that have transferred from animals to humans but from existing pathogens that have become resistant to antimicrobial medicines. Even if the next pandemic starts from cross-species transmission, the treatment for many zoonoses relies on antimicrobials to reduce severity of, and death from, infections and to treat secondary infections. For instance, the majority of deaths during the 1918 Influenza pandemic likely resulted from secondary bacterial pneumonia caused by common upper respiratory tract infections.⁷ Had antibiotics been available in 1918, countless lives could have been saved. Similarly, antibiotics have been critical to treating secondary bacterial infections in COVID-19 patients.^{8–11} As rising drug resistance continues to threaten the effectiveness of antimicrobials, the negotiation of a pandemic instrument represents an unprecedented opportunity to strengthen access, conservation, and innovation of antimicrobials as part of a comprehensive global response to pandemic threats.



AMR is one of the **top 10 global public health threats** facing humanity.



AMR was responsible for **1.27 million deaths in 2019** and was associated with an estimated 4.95 million deaths.



Despite the need to decrease the use of antimicrobials, use in livestock is predicted to **increase 67% by 2030.**



AMR is projected to cause **GDP shortfalls of up to 3.4 trillion annually** by 2030.

Panel 1: Consequences of unabated AMR for human health, animal health, and the global economy.^{12–15}

Fortunately, there is not only a strong rationale for including provisions to address the “silent pandemic” of AMR in a pandemic instrument, but this work can be done synergistically with proposed provisions to address zoonotic pandemics. Indeed, the strategies needed to support global mechanisms to prevent, prepare for, and respond to zoonoses and AMR overlap significantly (see Panel 2).¹ This means that most of the provisions needed to address AMR in a pandemic instrument would already exist or would only need to be slightly adjusted to address any unique facets of AMR. Also, any adjustments could be focused and minor since many efforts to address AMR more specifically can be developed after negotiation of the main pandemic instrument if (but only if) AMR is defined within the scope of the pandemic instrument. These small adjustments would enhance global readiness for the next pandemic beyond what is currently being contemplated.

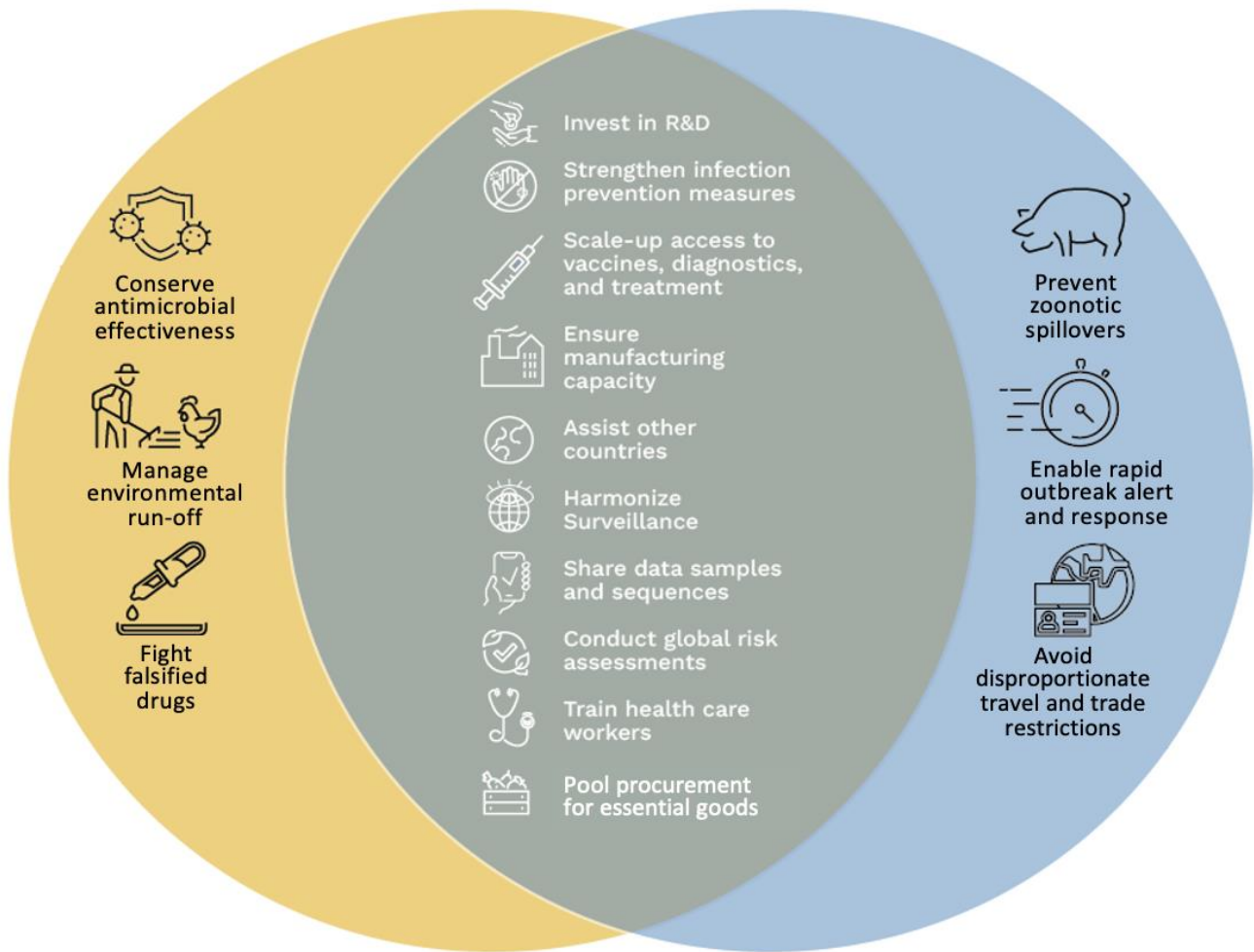
This policy brief explains how governments can practically and efficiently address AMR through negotiation of a pandemic instrument. By illustrating the clear link between efforts to address zoonoses and AMR, this policy brief makes the case that including AMR in pandemic instrument negotiations makes the most effective use of limited time and resources to ensure our best opportunity for global pandemic readiness for the future. Six illustrative examples of how AMR can be addressed in the text of a pandemic instrument are highlighted in Panel 3.

Zoonoses and AMR Have Overlapping Needs Which Can Be Addressed Simultaneously in a Pandemic Instrument for Greater Impact

Most of the policy responses required to address zoonotic pandemics overlap with what is needed for AMR (see Panel 2). This section identifies some of these overlaps and discusses the adjustments needed to make the overall global policy response work for both zoonoses and AMR.

Actions needed to address AMR

Actions needed to address zoonoses



Panel 2: Overlap in strategies needed address AMR and zoonoses.¹

1) Zoonoses and AMR both require access to medical countermeasures and would each benefit from provisions in a pandemic instrument that supports their development and distribution

Medical countermeasures, such as antimicrobials, diagnostics, personal protective equipment, and vaccines, are vital for controlling the spread of infectious diseases, including zoonoses and AMR.^{16–18} The extent to which they can be effective however hinges on access to them, which in turn depends on their invention, development, and validation through research, as well as their regulatory approval, manufacturing, and distribution.

A pandemic instrument could designate antimicrobials, diagnostics, personal protective equipment, and vaccines as ‘global public goods’ and create or adopt trusted mechanisms for expediting their development, ensuring their availability when needed, and funding their efficient procurement and equitable distribution. For example, a pandemic instrument could harmonize

emergency regulatory approval processes and support the development of regional manufacturing hubs to produce these specific goods. In addition, through a financing mechanism or otherwise, a pandemic instrument could expand financial support for the Coalition for Epidemic Preparedness Innovations (CEPI), Combating Antibiotic-Resistant Bacteria Biopharmaceutical Accelerator (CARB-X), Global Antibiotic Research and Development Partnership (GARDP), and a permanent Access to Pandemic Tools Accelerator (like ACT-A).¹⁹ Some of these trusted mechanisms have been central to the rapid development of the COVID-19 vaccine and the global coordination of their distribution, albeit not at the ideal speed or scale to achieve equitable access.²⁰ Instead of re-inventing the wheel, pandemic instrument negotiators could leverage these mechanisms by officially incorporating them as part of the global pandemic response strategy and scale up financial support for them to ensure medical countermeasures are available and equitably distributed as needed in future global pandemics.

The similarities in the kind of financing strategies needed for these two pandemic threats further supports the development of strategies that simultaneously tackle both. For example, one of the prominent mechanisms proposed to finance antimicrobial research and development (R&D) is the delinked subscription model.^{21,22} This model would see governments paying an annual subscription fee for access to new antimicrobial medicines. This is similar to COVAX, an advanced market commitment and procurement mechanism used to finance the rapid scaling up of COVID-19 vaccine manufacturing,²³ which required governments to pay in advance for access to future vaccines. Further, excess R&D or manufacturing capacity that might be created in anticipation of future pandemics could be efficiently used during inter-pandemic periods to develop or make global public goods related to AMR.

2) Zoonoses and AMR both require globally integrated One Health surveillance and monitoring systems and would each benefit from provisions in a pandemic instrument that supports the expansion and integration of these systems

One Health approaches to the surveillance and monitoring of infectious diseases, including zoonoses and AMR, are fundamental to effective global pandemic responses.²⁴ Like zoonoses, some new antimicrobial-resistant strains of bacteria arise at the human-animal-environment interface, especially in food and agricultural systems where antimicrobials are used in intensified agricultural practices.²⁵⁻²⁸ Surveillance is therefore needed for early detection and notification of potential zoonoses and antimicrobial-resistant pathogens in animals, tracking emerging variants of zoonoses and the spread of resistant pathogens among humans to identify population transmission patterns, and sharing of information with researchers and policymakers at the domestic and global levels to coordinate global pandemic responses.^{29,30} In order for a One Health approach to surveillance and monitoring to be effective, it must be globally integrated to facilitate the transfer of knowledge and data on new infections to activate public health responses, guide decision-making at the domestic and global level, and inform R&D efforts towards new global public goods.²⁴ The absence of these requirements has manifested as a major barrier to action on global infectious disease threats, including COVID-19.^{25,29,30}

A pandemic instrument could mandate the implementation of minimum One Health surveillance and monitoring capacities and develop international benchmarks for measurement of these capacities. These international benchmarks could include a risk assessment and management

methodology that guides governments in identifying, assessing, and managing risks within their countries and sub-national jurisdictions. These surveillance capacities should go beyond sector-specific monitoring of established infectious disease threats to include capacity for monitoring the emergence of potential zoonoses and resistant pathogens in humans, animals and the environment. Additionally, a pandemic instrument could mandate the development of standardized protocols on data reporting and knowledge sharing systems for potential zoonoses and AMR, including creating a mechanism for subsequent One Health regulation-making wherein an entity is created to develop technical standards related to One Health issues, including AMR. Modelled on the FAO/WHO CODEX Alimentarius, which makes non-binding regulations affecting food, agriculture, and trade,³¹ a new One Health regulatory entity could standardize evidence-based rules to create robust preventative measures in relation to zoonotic and AMR surveillance and monitoring practices and develop or endorse customary rules regarding the sharing of research, data, and technology for these threats at the global level.

3) Zoonoses and AMR both require increased technical and laboratory capacity and would each benefit from provisions in a pandemic instrument that enables greater international cooperation and financing for capacity development

All countries need trained personnel and lab infrastructure, including physical space and equipment, to undertake One Health surveillance and monitoring for infectious diseases, including zoonoses and AMR.²⁴ While many wealthier countries should already be able to fully participate in a globally integrated One Health surveillance and monitoring system, many low- and middle-income countries (LMICs) face more barriers and constraints.³² For instance, human resources shortages have created a technical capacity gap. This manifests in the limited availability of highly qualified technical staff, such as laboratory technicians, epidemiologists, and data managers to steward surveillance systems in LMICs and enable international data sharing.³³ There are also fewer clinical laboratories and diagnostic facilities in many LMICs to conduct laboratory testing for antimicrobial-resistant organisms and other infectious pathogens, exacerbating the barriers to participating in a globally integrated surveillance and monitoring system.^{24,32,33}

To address these challenges, a pandemic instrument could promote technical assistance and knowledge sharing among countries and encourage financial support for LMICs to meet minimum One Health surveillance and monitoring capacities. All governments would also benefit from the inclusion of a mechanism for developing and sharing international best practices on laboratory testing, with support provided to LMICs to build capacity for newer technologies such as genomic sequencing and wastewater surveillance. In addition, a pandemic instrument could mandate the implementation of joint external evaluations of both surveillance and laboratory capacities as well as support to prioritize limited lab capacities during times of emergencies. These provisions are necessary to retain and increase technical capacity in LMICs in order to scale up surveillance and monitoring and enable full participation in the globally integrated One Health surveillance and monitoring system needed for both zoonoses and AMR.

The Effectiveness of Antimicrobials Can Also Be Safeguarded in a Pandemic Instrument with Additional Benefits for Zoonotic Pandemics

AMR can develop even when antimicrobials are correctly prescribed.²⁷ As such, focused action is needed to promote antimicrobial stewardship and to protect the effectiveness of existing antimicrobial medicines.^{1,34,35} Taking action within a pandemic instrument to safeguard antimicrobials serves two purposes: first, it reduces the threat posed by AMR, and second, it preserves an essential resource for responding to future pandemic threats, as the treatment for many zoonoses relies on antimicrobials to reduce severity and death from secondary bacterial infections. Given the transnational nature of AMR, the stewardship of antimicrobials must be addressed at the global level to avoid disincentivizing investment in stewardship and encourage implementation at socially optimal levels. A comprehensive pandemic instrument could mandate the development or use of a regulatory framework governing the use of antimicrobials in a sustainable, acceptable, fair, and effective manner. This regulatory framework could govern which antimicrobials should be accessed, watched, and reserved in health care (i.e., WHO's AWaRe framework)³⁶ and which critically important antimicrobials should be limited to human use. The existing AWaRE framework could be enshrined in a pandemic instrument so that the rules governing the conservation of antimicrobials are globally harmonized. Continued antimicrobial effectiveness is likely to be important for reducing the spread and/or severity of future pandemics, which means that antimicrobial stewardship efforts should ideally be addressed in a comprehensive pandemic instrument.

Panel 3: Illustrative examples for how AMR can be addressed within the text of a pandemic instrument

1. Designate antimicrobials, diagnostics, personal protective equipment, and vaccines as 'global public goods' and create or adopt mechanisms for expediting their development, ensuring their availability when needed, and funding their efficient procurement and equitable distribution.
2. Mandate Member States to implement minimum One Health surveillance and monitoring capacities based on agreed-upon international benchmarks.
3. Mandate the development of standardized protocols on data reporting and knowledge sharing systems for potential zoonoses and AMR, including mandating the development of a mechanism for One Health regulation-making wherein an entity is created to develop technical standards related to One Health issues, including AMR.
4. Require Member States to undertake efforts to increase technical and laboratory capacity in LMICs, such as expanding genomic sequencing capacities and wastewater surveillance.
5. Create mechanisms for the development and sharing of international best practices for laboratories and the implementation of joint external evaluations of lab capacities.
6. Mandate the development or use of a regulatory framework governing the use of antimicrobials in a sustainable, acceptable, fair, and effective manner, including which antimicrobials should be accessed, watched, and reserved in health care (i.e., WHO's AWaRe framework) and which critically important antimicrobials should be limited to human use.

Conclusion

The articulated goal of a pandemic instrument is to ensure that there is a comprehensive framework to prevent, prepare for, and respond to future global pandemics. Solely addressing zoonoses and neglecting the silent pandemic of AMR would be an overly narrow approach that will not adequately prepare the world for both primary natural sources of future pandemic threats. The good news is that not many changes would be needed to achieve this goal (see Panel 3, above). At the very least, AMR should be defined as within the scope of the pandemic instrument. Even better would be to make the small adjustments needed to ensure efforts targeting zoonoses simultaneously target AMR sources of pandemics, converting what would otherwise be a zoonotic pandemic instrument into a comprehensive pandemic instrument. If one AMR-specific provision can be included in a pandemic instrument, it should focus on promoting antimicrobial stewardship, as such efforts are needed to sustain the effectiveness of existing antimicrobials and are unlikely to be implemented at socially optimal levels without coordinated global action such as through an international agreement like the pandemic instrument.

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About the Global Strategy Lab

The Global Strategy Lab is a bi-campus interdisciplinary research lab that brings cutting-edge science and scholarship to bear on how global institutions, instruments and initiatives are designed to better address the most pressing global challenges. Directed by Professor Steven J. Hoffman and based at York University and the University of Ottawa, we advise governments and public health organizations on how to design laws, policies and institutions that make the world a healthier place for everyone. The Lab's work on antimicrobial resistance is supported by the Wellcome Trust [222422/Z/21/Z].



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