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Strengthening Global Health Security by Developing Capacities to Deploy Medical Countermeasures Internationally

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In 2014, the United States in partnership with international organizations and nearly 30 partner countries launched the Global Health Security Agenda (GHSA) to accelerate progress to improve prevention, detection, and response capabilities for infectious disease outbreaks that can cause public health emergencies. Objective 9 of the GHSA calls for improved global access to medical countermeasures and establishes as a target the development of national policy frameworks for sending and receiving medical countermeasures from and to international partners during public health emergencies. The term *medical countermeasures* refers to vaccines, antimicrobials, therapeutics, and diagnostics that address the public health and medical consequences of chemical, biological, radiological, and nuclear events; pandemic influenza; and emerging infectious diseases. They are stockpiled by a few countries to protect their own populations and by international organizations, such as the World Health Organization (WHO), for the international community, typically for recipients with limited resources. However, as observed during the 2009 H1N1 influenza pandemic, legal, regulatory, logistical, and funding barriers slowed the ability of WHO and countries to quickly deploy or receive vaccine. Had the 2009 H1N1 influenza pandemic been more severe, the world would have been ill prepared to cope with the global demand for rapid access to medical countermeasures. This article summarizes the US government efforts to develop a national framework to deploy medical countermeasures internationally and a number of engagements to develop regional and international mechanisms, thus increasing global capacity to respond to public health emergencies.

In an increasingly interconnected world, naturally occurring emerging or reemerging infectious diseases such as novel influenzas, or deliberately used or accidentally released chemical, biological, radiological, or nuclear (CBRN) agents, have the potential to spread rapidly and affect populations across international borders, substantially affecting global health security. Medical countermeasures, including pharmaceutical interventions such as vaccines, antimicrobials, antidotes, and antitoxins, as well as nonpharmaceutical interventions such as ventilators, diagnostics, personal protective equipment, and patient decontamination supplies, are critical to prevent, mitigate, or treat the adverse health effects of a public health emergency. The ability to have access to and be able to rapidly deploy

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medical countermeasures in response to a disease outbreak that can cause or has caused an emergency is a fundamental tool for detecting and tracking the outbreak, preventing the spread of disease by using preventive vaccination, and/or mitigating disease effects and saving lives if therapeutics are available.

Medical countermeasures are key components of the US plans to contain or slow outbreaks or otherwise mitigate the medical and public health consequences of these threats, whether they originate within or outside of US borders.[1] The Public Health Service Act provides the authority for the Secretary of the US Department of Health and Human Services (HHS), in coordination with the Secretary of the Department of Homeland Security (DHS), to maintain medical countermeasures in the US Strategic National Stockpile (SNS) "to provide for the emergency health security of the United States."[2] However, many countries and international organizations lack similar legislative mandates and, because of the multiple challenges faced in developing, acquiring, and maintaining sustainable programs for medical countermeasures for CBRN threats, pandemic influenza, and other emerging infectious diseases, there are very limited supplies available worldwide, which limits the global capacity to respond to public health emergencies. Because of this limited supply and the fact that many of these medical countermeasures are not commercially available, the United States, a few other countries, and international organizations that have acquisition programs and stockpiles have been requested to deploy medical countermeasures internationally to assist partner countries in containing a disease or mitigating the public health consequences of an event. A typical example was the large-scale international deployment of antivirals and vaccine during the 2009 H1N1 influenza pandemic, which evidenced the lack of global access to medical countermeasures and, due to multiple legal, regulatory, and logistical challenges, showed the limited capacity of WHO and donors to rapidly deploy vaccine to areas where assistance was needed.[3]

The threat of future pandemics and other international public health emergencies has not diminished. In the past 2 years alone, multiple cases of the highly pathogenic avian influenza H5N1 have been detected in Southeast Asia, and North America has recently seen the first imported case. In the period between 2012 and 2014, multiple countries around the world, including the United States, had imported cases of the Middle East respiratory syndrome coronavirus (MERS-CoV).[4] In 2013, the world also witnessed the emergence of avian influenza A (H7N9), and in 2014, both the polio outbreak and the outbreak of Ebola virus disease in western Africa have been declared public health emergencies of international concern (PHEIC) by WHO in accordance with the International Health Regulations (2005) [IHR(2005)].[5-7] The lack of approved medical countermeasures, the limited amount of products available, and the impaired capabilities to quickly deploy them to contain the spread of these diseases and to treat ill people have proven to be one of the global challenges of the present time. These are just examples of disease threats to global health security and a reminder to the global community of the need to work together to develop capacities to respond to public health emergencies, including improving availability and access to medical countermeasures, and subsequently developing the capability to deploy them to places where they are needed.

Recognizing the challenges of today's interconnected world, the United States, in partnership with other nations, international organizations, and public and private stakeholders, launched the Global Health Security Agenda (GHSA)[8] in February 2014. GHSA seeks to accelerate progress toward a world safe and secure from infectious disease threats and to promote global health security as an international security priority by focusing on *preventing* and reducing the likelihood of outbreaks, whether natural, accidental, or intentional; *detecting* threats early to save lives; and rapidly and effectively *responding* to public health emergencies that require multisectoral, international coordination and communication.

GHSA has 9 main objectives to prioritize coordinated action and specific, measurable steps focused on these 3 areas.[9] Under the response area, objective 9 calls for international cooperation in several areas including improving global access to medical countermeasures. As part of that effort, one of the targets is the development of national policy frameworks for sending and receiving medical countermeasures from and to international partners during public health emergencies. Based on the challenges observed during the 2009 H1N1 influenza pandemic vaccine deployment, this article describes some of the US government's efforts on this matter, as well as its engagement with international partners to address existing barriers and to develop frameworks to share medical countermeasures internationally to strengthen global health security.

Deployment of Medical Countermeasures in the 2009 H1N1 Influenza Pandemic

In a matter of weeks, and in some cases days, after the outbreak of the 2009 H1N1 influenza pandemic was first identified, the US government received requests for antiviral drugs from 14 countries and for vaccine from 17 countries—in most cases even before the vaccine was manufactured.[10] To contribute to global response efforts, the US government provided nearly a million doses of antivirals at the beginning of the pandemic to other countries directly or through the Pan American Health Organization (PAHO). At the onset of the 2009 H1N1 influenza pandemic, WHO deployed more than 3 million courses of antivirals to 72 countries in the span of 3 weeks directly from a manufacturer and nearly half a million additional courses to 20 countries from a WHO warehouse within 1

week. The success of this rapid deployment of antivirals was due in part to extensive pandemic preparedness planning by the WHO team in charge of the antiviral stockpile and by many other countries. In addition, the antivirals were preregistered or approved for use in most recipient countries by their national regulatory authorities, which facilitated rapid import processes.[11]

In addition to the antiviral donation, and in collaboration with donor countries, the US government pledged up to 25 million doses, or 10% of its available 2009 H1N1 influenza vaccine supply, to the WHO to support countries that would not otherwise have access to the vaccine.[3,12,13] It took nearly a year from April 2009, when the 2009 H1N1 influenza was first detected in North America, for the US government to deploy the first 5 million doses of vaccine internationally in March 2010. Based on WHO requests, which were in turn based on global demand during the course of the pandemic, the US deployed nearly 17 million doses of vaccine internationally by October 2010, more than a year after the outbreak detection.[3]

The US government donation was part of a larger effort coordinated by WHO to deploy 78 million doses of 2009 H1N1 influenza vaccine provided by donor countries and manufacturers through the WHO Pandemic Influenza A (H1N1) Vaccine Deployment Initiative. While this was supposed to be a rapid emergency deployment of medical countermeasures, it took more than a year to complete following the declaration of the 2009 H1N1 influenza pandemic as a public health emergency of international concern in June 2009. This complex process yielded a number of lessons regarding the international deployment of medical countermeasures. These included the need for preexisting international arrangements for mutual assistance, development of intersectoral plans with a domestic and international interface for global response, creation of emergency use regulatory mechanisms for countries to deploy and receive products that are unapproved by their national regulatory authorities, and strengthening of the logistics for transporting medical countermeasures across borders.[3,13]

Legal, Regulatory, Logistical, and Funding Issues

Over the past decade, the US government has received more than 20 requests for medical countermeasures for CBRN threats from the SNS in addition to those received during the 2009 H1N1 influenza pandemic. The response to each of these requests has uncovered multiple issues and challenges, and, as a result, the US government has dedicated efforts to analyzing and addressing them and exploring common solutions. Together with the lessons from the deployment of 2009 H1N1 influenza vaccine, these issues can be summarized in several categories.

National Legal Authorities

Legal authorities that govern the procurement, stockpiling, and use of medical countermeasures may have conditions that foster or constrain a country's ability to share medical countermeasures with foreign governments or international organizations. As stated above, under the Public Health Service Act, medical countermeasures in the US SNS are maintained "to provide for the emergency health security of the United States."[2] In the United States, appropriations acts, under which the US Congress provides funding to HHS for public health emergency response, also may contain requirements regarding the use of medical countermeasures that must be considered when procuring and deploying countermeasures using these funds. For instance, supplemental appropriations provided to HHS by Congress to respond to the 2009 H1N1 influenza outbreak included funds that were used to acquire and deploy pandemic influenza medical countermeasures under provisions of that act.

In order to develop policy recommendations to respond to international requests for medical countermeasures that are consistent with existing US legal and funding authorities, HHS has created the International Sharing of Medical Countermeasures Working Group (ISMPG). The ISMPG is chaired by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR) and the Centers for Disease Control and Prevention (CDC) and includes members from across HHS and several US government departments and agencies. In addition to the requests and deployments during the 2009 H1N1 influenza pandemic, the ISMPG has received and considered more than 20 requests for medical countermeasures from the SNS from foreign countries (ranging from low and middle to high income) as well as from international organizations, either to respond to emergencies or to prepare for them. Other countries and international organizations may choose to create similar dedicated groups to understand the relevant domestic and international laws and policies and to develop mechanisms to deploy or receive international assistance with medical countermeasures as part of their preparedness plans to respond to emergencies.

Legal Terms and Conditions

A country or organization donating or providing medical countermeasures internationally may require that the recipient country or organization accept certain terms and conditions related to the countries' responsibilities and liability risks. Liability protections may be of particular interest to donors in instances where the medical countermeasures are not approved by the national regulatory authorities in the providing and/or recipient countries. For example, some medical countermeasures in the SNS are not approved by the US Food and Drug Administration (FDA) under standard procedures for approval of pharmaceuticals.

Thus, they can be used in the United States only under Emergency Use Authorization (EUA) or Investigational New Drug (IND) protocols.[14,15] Additionally, liability protections for use of these countermeasures may be based in domestic law. For example, the US Public Readiness and Emergency Preparedness (PREP) Act authorizes the HHS Secretary to issue a declaration that provides immunity from liability under US law to manufacturers, distributors, program planners, and qualified persons involved in the administration and use of specified medical countermeasures, including those used under EUA or IND protocols.[16]

Developing legal terms and conditions among donors, recipients, and WHO was a significant issue during the international deployment of 2009 H1N1 influenza vaccine. According to the WHO after-action report, "The regulatory and liability issues were noted to be complex and some countries did not have the resources to adequately interpret them and put in place measures to implement the necessary systems."[3] Negotiating complex legal terms and conditions, including liability protections in the midst of a public health event that requires immediate action (eg, containing a disease outbreak or avoiding the spread of a threat agent), can delay or jeopardize an international response, resulting in a significant impact on global health security.[3] Potential donor and recipient countries and organizations may want to explore in advance what domestic terms and conditions they would require to rapidly deploy and/or receive medical countermeasures, taking into consideration their existing laws and policies. Additionally, for any mutual assistance process to succeed, they may consider pursuing bilateral or multilateral engagements to discuss joint preparedness plans that include the legal terms and conditions that would be required to deploy medical countermeasures internationally during an emergency.

National Regulatory Authority Approvals

Recipient countries need to ensure that requirements put in place by their national regulatory authorities are met in order for medical countermeasures to be imported, distributed, or administered in their countries during an emergency. However, these medical countermeasures may not be approved for routine use in the country of origin or the donor country and may not be previously prequalified via the WHO Prequalification of Medicines Program, which provides universal standards and evaluates the "quality, safety, and efficacy" of medical products and manufacturers to ensure that donated products can be deployed rapidly to recipient countries.[17]

As previously mentioned, some medical countermeasures that are acquired by HHS and maintained in the SNS are not currently approved by the FDA or may not be approved for certain uses at this time. For example, medical countermeasures can be used under EUA if the totality of the evidence makes it reasonable to believe (1) that the product may be effective in diagnosing, treating, or preventing a serious or life-threatening disease or condition; (2) that known and potential benefits of the product outweigh its known and potential risks; and (3) that no adequate, approved alternative to the product is available.[14] Similarly, potential recipient countries may consider developing or strengthening processes to authorize the emergency use of medical countermeasures in their own country or to allow for fast-tracking or waiving standard regulatory requirements at the time of the emergency response within legal and ethical boundaries. Additionally, according to their domestic threat and risk assessments, they may consider pursuing preliminary regulatory authorization of certain medical countermeasures that could be imported in a public health response, including those available in the market or stockpiled by certain countries.

As evidenced during the deployment of 2009 H1N1 influenza vaccine, 75% of national regulatory authorities depended on the WHO prequalification process to issue waivers or approve medical countermeasures for import and use in their countries.[3] This lengthy process, combined with the unique regulatory processes in each recipient country to allow for import and distribution of the vaccine, resulted in significant delays in the international deployment of 2009 H1N1 influenza vaccine. The WHO prequalification process requires that the manufacturer in at least 1 country license the product, but it is not designed to apply to medical countermeasures that have not been approved for routine use in their countries of origin. Specifically, the WHO prequalification process cannot be applied for any medical countermeasure used under EUA in the United States or similar mechanisms in other countries. This may present a significant problem in future responses to CBRN incidents in which the only medical countermeasures available are unapproved in the country of origin and can only be used under special regulatory provisions. If a significant number of countries rely on WHO prequalification in order to accept medical countermeasures and no international mechanisms exist to prequalify unapproved products, recipient countries may be unable to import and distribute critical medical countermeasures to aid in response to events. A priority for the international community moving forward should be to foster WHO efforts to establish a new process for rapid regulatory approval of new or existing unapproved products to be used during emergencies or to determine how the current WHO prequalification process could be adapted to aid in the rapid international deployment and use of medical countermeasures during a public health emergency.

Import and Export Regulations

To rapidly mobilize assets internationally, it is essential that donors and recipients understand relevant export and import guidelines or regulations. In the United States, export controls and nonproliferation activities that can affect the

ability to deploy or receive medical countermeasures are regulated by a number of federal agencies, including the US Departments of State, Commerce, Homeland Security, Treasury, Defense, and Energy. For example, the US International Trafficking in Arms Regulations is a set of guidelines under the Arms Export Control Act[18] that governs the import and export of information or technology that may have military or defense applications. These regulations may affect the deployment of some assets, such as autoinjectors or other medical devices, that may be classified as technology with military applications.[19] The Commerce Control List, which falls under the Export Administration Regulations, may pose export restrictions on deploying certain medical countermeasures to certain recipient nations—for example, those with embargos or that are designated as terrorist states.[20]

Both potential donor and recipient countries must engage appropriate cross-sectoral partners to conduct a review and understand relevant import and export control regulations to determine which may facilitate, restrict, or impede the sharing of medical countermeasures internationally. Countries may consider engaging with relevant customs and border authorities to develop mechanisms to expedite export and import of medical countermeasures rapidly during a public health emergency.

Logistics

Even when addressing legal, regulatory, funding, and import/export issues, the logistics of moving medical countermeasures across international borders is highly complex. WHO has published specific *Guidelines on the International Packaging and Shipping of Vaccines,*[21] which addresses issues such as temperature monitoring and vaccine arrival reports. Individual donor and recipient countries and/or freight forwarders may have different standards or guidelines that they must adhere to, as seen during the 2009 H1N1 influenza vaccine deployment. Vaccine and transportation-related documentation, procedures, and points of transfer of custody of shipments also had to be determined in the midst of the response, which was extremely time-consuming in a massive deployment operation with multiple players including several donor countries, manufacturers, WHO, different carriers or freight forwarders, airlines, customs permits and certifications, and vaccination teams.

Another logistical challenge was securing commercial flights with sufficient cargo space to accommodate large containers, as well as import restrictions on the amount of vaccine permitted in each shipment. Insurance for the cargo and responsibility for it also generated delays, since not all donors or recipients were familiar with the International Commercial Terms (Incoterms) that govern cargo security (eg, insurance) among other international trade issues.[22] Long shipping distances also presented challenges in maintaining cold-chain, with some vaccine having to be repacked at various airports during transport. Monitoring and maintaining cold-chain capacity in recipient countries and ensuring the proper distribution plans to target populations in recipient countries also presented a significant issue.[3] The language of dossiers or instructions also presented challenges, as instructions for handling and administration of medical countermeasures needed to be adequate for the recipient country.

Manufacturers, donor countries, and freight forwarders should be familiar with, and able to rapidly produce when necessary, the specific shipping documentation that must accompany international shipments of medical countermeasures. Recipient countries may consider maintaining awareness of and communicating to donors or freight forwarders any additional unique or specific documentation requirements relating to the import of the medical countermeasures. In acute emergency responses to a deadly pathogen, it is possible that some of these requirements could be waived to expedite transportation. However, another issue that can make logistics complex is that there may not be enough transportation capabilities to mobilize medical countermeasures, as airlines may limit or cancel flights to disease areas—as we are seeing, for example, with the current Ebola outbreak.[23] Moreover, countries may issue travel warnings and take precautionary measures, including not deploying personnel critical to transporting, distributing, and administering medical countermeasures to patients. The ability to rapidly transport and distribute medical countermeasures during a public health emergency can be facilitated and potentially expedited by preestablishing operational frameworks or concepts of operation that outline the logistics of how medical countermeasures can be deployed, received, and administered, taking into account all the issues discussed above.

Funding

Developing, acquiring, and stockpiling medical countermeasures is typically a complex, time-consuming, and costly process for the country or institution carrying out these activities. Donors or providers of products may seek to recover their cost if the products are deployed internationally in order to offset their investments and potentially replenish their stockpiles. Additionally, it must be determined how the cost of the deployment of medical countermeasures—including but not limited to the costs of shipping, storage, cold-chain requirements, and potentially ancillary supplies—may need to be funded. Additional funding will likely be required to support distribution and administration in recipient countries. To the best of our knowledge, there is currently no specific funding set aside for the deployment of emergency medical countermeasures internationally, nor are there sufficient mechanisms to rapidly transfer funding internationally to WHO or among countries to support public health emergency responses.

On a global scale, during the 2009 H1N1 influenza pandemic response, "funding to support national deployment

efforts was inflexible and could not always be provided to countries quickly enough."[3] In 2011, the 130th session of the WHO executive board included a report by the secretariat on establishing a contingency fund for outbreaks.[24] WHO has since issued donor flash appeals to obtain support for outbreak responses to H7N9, MERS-CoV, and Ebola virus disease, though not specifically for medical countermeasures. Although this mechanism is established under the WHO Emergency Response Framework, it is unlikely that mobilization of resources through this process can happen fast enough when funds are required immediately to contain an outbreak that can become a public health emergency of international concern.[25] Similarly, the US government does not currently have specific funding dedicated for the replenishment of stockpiles after international deployment nor to cover transport costs for major international deployments of medical countermeasures. In the event of a large-scale or acute emergency response, HHS may request supplemental appropriations from the US Congress specifically for that emergency or may consider reprograming funds. However, these processes can be time consuming and certainly slow down the provision of international assistance.

Identifying who will provide funding and bear responsibility for supporting donors' stockpile replenishment, transportation, and distribution and administration in recipient countries is a critical preparedness need. Similar to the efforts under the WHO Pandemic Influenza Preparedness (PIP) framework,[26] countries, manufacturers, and international organizations may decide to work to identify, develop, and strengthen funding mechanisms for international nonflu medical countermeasure deployment on a global scale.

International Collaborations

The Global Health Security Agenda presents a unique opportunity for the international community to commit to lay a framework for cooperation during a response to public health emergencies. This commitment builds on the IHR (2005), which calls for international collaboration for the "detection and assessment of, and response to" public health emergencies of international concern.[6] In order to develop the capacity to respond rapidly and effectively to CBRN threats to global health security, it is critical that the international community address the challenges identified during previous international deployments of medical countermeasures and strengthen legal, regulatory, and logistical capacities through bilateral, regional, and international collaborations and arrangements.

The US government is collaborating with international partners to improve global access to medical countermeasures during health emergencies through several bilateral, regional, and multilateral initiatives, including collaborating to develop new products, discussing how to create expedited regulatory pathways that can allow a product to be used rapidly in countries that need it, exploring alternatives to stockpiling, and accelerating frameworks for rapid international deployment. An example of these efforts is the 2011 Beyond the Border (BTB) initiative, which is a bilateral endeavor launched by President Barack Obama and Canadian Prime Minister Stephen Harper in February 2011. BTB articulates a shared approach to cross-border security in which both countries work together to address threats at and away from their borders.[27] The health security objective of the BTB work plan focuses on enhancing collective preparedness and response capacity for health security threats, including supporting the ability to share mutual public health and medical assistance across the US-Canada border by establishing a bilateral framework for the deployment of medical countermeasures. Similarly, the North American Plan for Animal and Pandemic Influenza (NAPAPI), a trilateral effort among the United States, Canada, and Mexico, focuses on strengthening the ability of all 3 countries to jointly prepare and respond to pandemic threats. NAPAPI calls for the sharing of pandemic influenza medical countermeasures in the human and animal health sectors in North America during a pandemic event.[28]

The Global Health Security Initiative (GHSI) is a ministerial-level collaboration among Canada, France, Germany, Italy, Japan, Mexico, the United Kingdom, the United States, the European Commission, and WHO to strengthen health preparedness and response for CBRN threats and pandemic influenza. As reflected in the 2007 GHSI ministerial communique, GHSI members "considered the need to develop a sustainable global infrastructure [for medical countermeasures] that would allow us to work together to counteract the health consequences of natural or man-made threats."[29] In the 2013 GHSI ministerial communique, the heads of the health sector of these countries and organizations recognized the "significant progress [of GHSI members and WHO] towards building an operational framework for the international deployment of medical countermeasures which contemplates the legal, regulatory, and logistical issues to be considered during such a deployment."[30] For the first time, policymakers, regulatory and legal experts, and logisticians have come together to explore mechanisms to address the issues encountered during the 2009 H1N1 influenza vaccine deployment. These discussions are intended to assist WHO to establish a mechanism to accept medical countermeasures from donor countries or manufacturers and to deploy them to countries where assistance is needed to respond to a public health or medical emergency. This issue has also been examined during the 2013 Biological Weapons Convention (BWC) meeting of experts, and the BWC has provided a forum for the continued development of these partnerships to address the identified barriers to the international sharing of assistance.[31]

While ensuring the ability to deploy medical countermeasures across international borders is a key component of global health security, there will likely be situations where

there are not sufficient medical countermeasures available to meet the needs of the global population. The current Ebola outbreak is a clear example of this. Although some experimental treatments and vaccines exist at various degrees of development and in limited quantities, it is challenging to ramp up production, conduct clinical trials, and distribute the scarce resources in a fair and equitable manner.[32] This situation has raised many of the legal, regulatory, and logistical issues discussed here. It has also led to discussions of the ethics associated with using medical countermeasures that have never been tested in humans and, given the extremely limited amount of medicine available, if used, who should receive them.[33] To address these potential shortages in access and availability of products as well as transportation and administration capabilities, existing and new international collaborations should be leveraged to explore opportunities for pursuing joint international efforts.

Thus, the US government is working with international partners to develop a sustainable global infrastructure for medical countermeasures including contributing to international stockpiles such as the WHO Smallpox Vaccine Emergency Stockpile,[34] pursuing international collaborations on research and development, and expanding manufacturing capacity through programs like the WHO-led Global Action Plan for Influenza Vaccines (GAP program). The GAP program focuses on increased manufacturing and access to both seasonal and pandemic influenza vaccines.[35] Similarly, other regional efforts have been launched. Among them, the European Commission has developed a joint procurement strategy for the purchase and stockpiling of medical countermeasures to increase access to these supplies among its member states.[36] And in 2013, the Association of Southeast Asian Nations (ASEAN) also announced a joint stockpile for flu countermeasures under the Japanese International Cooperation System (JICS).[37]

In a recent publication about the lessons learned from the 2009 H1N1 influenza pandemic, the author states that "the most serious operational shortcoming, however, was the failure to distribute enough influenza vaccine in a timely way."[38] Addressing this critical global preparedness gap, identified as such in the GHSA, can only be accomplished through a concerted and sustained commitment from the highest level of leadership in WHO and member states.

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