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Enhancing US-Japan Cooperation to Combat Antimicrobial Resistance

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The Global Health Security Agenda (GHSA) is aimed at preventing, detecting, and responding to infectious disease threats. To move toward these goals, the United States has committed to partner with at least 30 countries around the world. One of the objectives of the GHSA includes "[p]reventing the emergence and spread of antimicrobial drug resistant organisms." Antimicrobial resistance (AMR) has become a growing global health security problem, with inappropriate use of antimicrobial medications in humans and animals and a lack of new antimicrobial medications contributing to this problem. While AMR is a growing global concern, working on it regionally can make this multifaceted problem more manageable. The United States and Japan, both world leaders in the life sciences, are close allies that have established cooperative programs in medical research and global health that can be used to work on combating AMR and advance the GHSA. Although the United States and Japan have cooperated on health issues in the past, their cooperation on the growing problem of AMR has been limited. Their existing networks, cooperative programs, and close relationships can and should be used to work on combating this expanding problem.

The Global Health Security Agenda (GHSA), an effort involving multiple US departments and agencies as well as other nations and international organizations, is aimed at preventing, detecting, and responding to infectious disease threats.[1,2] To help achieve these goals, the United States has committed to work with at least 30 partner countries over the next 5 years.[2] Japan has been a US partner in medical science research for nearly half a century—since 1965[3]—and has joined the dozens of countries committed to working toward goals of the GHSA.[4] The United States and Japan are close allies and leaders in the life sciences field. One of the objectives of the GHSA is "[p]reventing the emergence and spread of antimicrobial drug resistant organisms and emerging zoonotic diseases and strengthening international regulatory frameworks governing food safety."[1] While the United States and Japan have collaborated on various health and medical issues in the past, they have had limited cooperation on the growing global health problem of antimicrobial resistance (AMR). Through existing cooperative medical and health programs and collaborations between counterpart agencies, the United States and Japan can partner to make a substantial impact on combating AMR in the Asia-Pacific region, which would contribute greatly to advancing the GHSA.

Global statistics for AMR, including antibiotic resistance, as a whole are lacking, but the World Health Organization (WHO) estimates that there were about 450,000 new cases of multidrug-resistant tuberculosis worldwide in 2012, and resistance to earlier generation antimalarial medications is widespread in most countries where malaria is endemic.[5] A 2014 WHO report found high global rates of antibiotic resistance in all WHO regions, major gaps in surveillance, and a lack of methodology standards, data sharing, and coordination.[6] This report examined antibacterial drug resistance for 7 bacteria of international concern. Resistance to these drugs was found in Japan and the United States for

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many of these selected bacteria, to varying degrees,[6] but comparison of resistance data between countries is limited by differences in methodology and sample sizes. The US Centers for Disease Control and Prevention (CDC) has called antibiotic resistance "one of the world's most pressing health problems."[7] CDC estimates that, each year in the United States, at least 2 million people become ill from antibiotic-resistant infections and at least 23,000 people die because of these infections.[8]

In the United States, antibiotic-resistant infections are estimated to cost up to $55 billion annually (up to $20 billion in excess direct healthcare costs and as much as $35 billion in lost productivity costs)[8] and are responsible for 8 million additional hospital days annually.[9] While this is a relatively low economic burden compared with societal costs of other diseases like cardiovascular disease ($380 billion) and cancer ($185 billion), the estimates for antibiotic resistance do not consider the worst case scenario: a world without effective antimicrobial drugs.[10]

In April 2014, WHO's Assistant Director-General for Health Security wrote, "A post-antibiotic era—in which common infections and minor injuries can kill—far from being an apocalyptic fantasy, is instead a very real possibility for the 21st century."[6(pIX)] In addition to treating infectious diseases, antimicrobials are used prophylactically before surgeries[11] and as adjuvant therapy in cancer treatment.[12] Antibiotics are routinely used as prophylaxis with hip replacement surgeries, where infection rates are about 0.5% to 2%. It has been estimated that without effective antimicrobials, that number could rise to 40% to 50%, with about 30% of those infections resulting in death.[10]

The last novel class of antibiotics was discovered in 1987.[13] This gap in discoveries, combined with the decreasing efficacy of current medications, has led to a dire need for new antibiotics. There is little financial incentive for pharmaceutical companies to develop these drugs because of the nature of their use: They are typically used for short courses of therapy, whereas cancer drugs[14] or drugs for chronic diseases are more profitable.[15]

Several factors have contributed to antimicrobial resistance, including inappropriate use of these drugs in humans and animals and a lack of public understanding about appropriate use of these medicines. In the United States, up to 50% of antibiotics prescribed for people are not necessary or are not prescribed for optimal efficacy.[8] Unsuitable use of these drugs is partly attributed to inappropriate prescribing by physicians and a lack of specific and timely diagnostic tests. Consumption of suboptimal doses[16] of these medications or counterfeit drugs containing subtherapeutic doses also contributes to the development of AMR.[17]

In the United States and Japan, prescribing of antibiotics is driven in part by patient expectations.[18] However, there is a lack of understanding in countries around the world, including in Asia, the United States, and the European Union (EU), about how antibiotics should be used.[19] In a 2009 survey of people 20 to 69 years old, only 37.5% of respondents in Japan, 42.7% of respondents in the US, and 44.7% of respondents in the UK correctly answered "false" to the following question: "Antibacterial medicine [*sic*] suppress the proliferation of viruses as well as bacteria."[20(p5)]

Antimicrobials are commonly used in agriculture[21] and aquaculture.[22] It is estimated that up to 70% of antimicrobial drug use in the United States is for livestock and is nontherapeutic.[21] Evidence indicates that antimicrobial-resistant bacteria can spread from animals to humans.[23] New US Food and Drug Administration (FDA) guidance on antimicrobial use for food-producing animals was released in 2013 in an effort to curb this use,[24] and the animal pharmaceutical industry is currently phasing in changes,[25] but critics argue that more steps are needed to limit this drug use.[26]

Shared Concern

Both the United States and Japan have recognized AMR and global health as issues of concern, as evidenced by their domestic surveillance systems and global health initiatives. Some hospitals in both countries have implemented antimicrobial stewardship programs,[27-29] but there is still much work to do to develop better and more widespread practices.[8,30]

United States

The CDC monitors antimicrobial resistance through a tracking platform comprised of multiple networks, including the National Antimicrobial Resistance Monitoring System for Enteric Bacteria (NARMS) and the Emerging Infections Program (EIP), among others. The FDA and the US Department of Agriculture (USDA) also contribute to antimicrobial surveillance through NARMS. Through the tracking platform, the United States monitors antimicrobial resistance in humans (including community- and healthcare-associated AMR), retail meats, and food-producing animals.[8]

The US fiscal year (FY) 2015 budget includes funding requests for extant and new AMR initiatives across several government agencies. The budget request would more than double CDC funding for antibiotic resistance work.[31] The CDC budget request includes an increase of $30 million for its Detect and Protect Against Antibiotic Resistance initiative, to enhance surveillance and domestic laboratory capacity.[32] The USDA budget request includes $25 million for a new public-private innovation institute that will focus on research to address information gaps in mitigating AMR.[33] To expand global health security activities, the CDC budget request includes an increase of $45 million.[34] The United States is also the world's largest donor to the Global Fund to Fight AIDS, Tuberculosis and Malaria, an organization created to combat these infectious diseases,[35] which all have drug-resistant forms.[6]

The continued high priority of addressing antibiotic resistance is further underscored by its inclusion in the

Obama administration's science and technology priorities for the FY2016 budget.[36] Furthermore, a dedicated budget guidance document for FY2016 on priorities for combating antibiotic resistance and AMR was sent to multiple US departments and agencies. One of the priorities listed in the guidance is "Improve International Collaboration and Capacities for Prevention, Surveillance, and Antimicrobial Research and Development."[37(p4)]

Japan

Japan Nosocomial Infections Surveillance (JANIS), organized by the Ministry of Health, Labour and Welfare (MHLW), monitors nosocomial infections and antimicrobial-resistant bacterial infections in Japanese medical settings.[38] Through the Japanese Veterinary Antimicrobial Resistance Monitoring System (JVARM), the National Veterinary Assay Laboratory (NVAL) of the Ministry of Agriculture, Forestry and Fisheries (MAFF) monitors the quantities of antimicrobials used in animals and antimicrobial resistance in food-producing animals.[39]

Japan, like the United States, has a strong commitment to the Global Fund and recently announced an $800 million contribution.[35] Another organization with a similar disease focus, the Global Health Innovative Technology (GHIT) Fund, is a Japan-led initiative focused on research and development.[40] Japan's Ministry of Foreign Affairs (MOFA) and MHLW committed approximately $60 million combined to this partnership.[41]

US-EU Cooperation

The United States and the European Union cooperated to develop recommendations for collaborations through the Transatlantic Taskforce on Antimicrobial Resistance (TATFAR). Members of TATFAR identified 17 recommendations in 3 areas that could benefit from enhanced cooperation: "Appropriate therapeutic use of antimicrobial drugs in human and veterinary medicine,"[42(p5)] "Prevention of drug resistant infections,"[42(p7)] and "Strategies to improve the pipeline of new antibacterial drugs for use in human medicine."[42(p9)]

TATFAR has provided a structured program for promoting specific outcomes, and lessons learned from this work can be used in collaborations with other countries. TATFAR recently gained dedicated staff to facilitate intergovernmental work (personal communication, CDC official, February 18, 2014), and a review of the recommendations resulted in changes to some of the collaborative areas.[43] Through the TATFAR experience, it was learned that an assessment at an earlier stage in the work would have been beneficial. For example, an assessment 6 months into the project to determine which goals are practical enough to move forward with would be useful for similar future collaborative efforts (personal communication, CDC official, February 18, 2014). TATFAR is an extant program that could be used to advance work on the GHSA regionally, as well as through sharing of outcomes with countries around the globe, and by providing a model for initiating similar programs in other regions.

US-Japan Cooperation

Allies for decades, the US and Japanese governments have described their alliance as "the cornerstone of peace, security, and stability in the Asia-Pacific region."[44] The United States and Japan cooperate on security and defense and are strong trading partners.[45] They have also committed to work together on global challenges, through cooperation on humanitarian assistance and disaster relief and development assistance, and they have a shared focus on global health.[46]

In addition to bilateral partnerships, the United States and Japan cooperate on a wide variety of issues along with other Asia-Pacific nations through Asia-Pacific Economic Cooperation (APEC), a forum that aims to support economic growth and prosperity in this region.[47] These areas of cooperation have included health, agriculture, and energy.[48]

US-Japan Medical and Health Cooperation

The United States and Japan currently cooperate on medical research and global health through various programs, some of which could be used to combat AMR. The governments cooperate bilaterally on medical research through the US-Japan Cooperative Medical Sciences Program (CMSP)[3] and the US-Japan Framework Initiative for a Safe and Secure Society.[49] The CMSP is funded by the US National Institutes of Health (NIH) and Department of State, and the Japanese MOFA, MHLW, and Ministry of Education, Culture, Sports, Science and Technology (MEXT).[3]

In 2014, the CMSP held its 16th International Conference on Emerging Infectious Diseases in the Pacific Rim. The focus changes with each conference, and this year's choice, Antimicrobial Drug Resistance in Bacterial and Parasitic Diseases,[50] indicates the recognition of this problem for the Asia-Pacific region. To combat AMR, this program could be further used to initiate and foster more collaboration on research on various microorganisms to develop new medicines, vaccines, and diagnostic methods.

The GHIT Fund is a Japanese-led initiative that was established as a partnership among Japan's MOFA and MHLW, 5 of Japan's leading pharmaceutical companies, and the US-based nonprofit Bill & Melinda Gates Foundation. This collaboration is working to combat infectious diseases prevalent in developing countries, including HIV/AIDS, tuberculosis, malaria, and neglected tropical diseases (NTDs), through development of new medicines, vaccines, and diagnostic tools.[40,51] These development goals are in line with what is needed to combat AMR.

In addition to bilateral partnerships, the United States works with Japan through the e-ASIA Joint Research

Program (JRP), which promotes collaboration among science and technology researchers through multilateral team projects in areas such as infectious diseases and advanced interdisciplinary research toward innovation. Participating countries provide matching funding for collaborative projects.[52,53] This program was initiated in 2012 by the Japan Science and Technology Agency (JST) and is additionally supported by MEXT.[54] Like the previously described research collaborations, this program could be used to work toward developing new medical tools to combat AMR.

The US-Japan Partnership for Global Health is another collaborative effort, involving Japan's MOFA, the Japan International Cooperation Agency (JICA), and the US Agency for International Development (USAID), in which the governments work on mutual global health priorities.[55] Through field-based partnerships in Senegal, Ghana, and Bangladesh, the United States and Japan have cooperated on a variety of issues including nutrition, newborn and child health, health system strengthening, and infectious diseases (personal communication, USAID official, March 11, 2014). To fight AMR, cooperation could be expanded to include increased surveillance of drug-resistant HIV/AIDS, malaria, and tuberculosis infections. Additionally, the partnership could be used to do valuable work to minimize gaps in antibacterial resistance surveillance, through current country collaborations.

The Case for US-Japan Cooperation on AMR

The United States and Japan are among the world's leaders in the pharmaceutical industry and the first and second largest pharmaceutical markets in the world, respectively.[56] The US, the EU, and Japan lead the industry in innovation, both in industry-financed R&D investment and in patents.[57] The importance of these 3 global players in this industry is underscored by the fact that their regulatory bodies and pharmaceutical research–based industries comprise the governing body of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). This organization aims to increase international harmonization of technical requirements for pharmaceutical product registration and improve efficiency in the development of high-quality medications.[58] The US cooperates with the EU on AMR through TATFAR, and this conversation would benefit from greater inclusion of Japan. Considering Japan's status as an important piece of the global pharmaceutical industry, greater cooperation between the United States and Japan would be mutually beneficial. Through the US-Japan health and medical partnerships discussed previously, AMR has been addressed in various scientific research areas,[3,50] but it has not yet been addressed at a more holistic level through cooperative government initiatives similar to TATFAR—that is, through discussions of the overall problem and ways to effectively address needs specific to the region. The strong US-Japan relationship and current medical and health cooperative programs provide established networks and important opportunities for these nations to work collaboratively on combating AMR. Collaborating on development of new antimicrobial medications and diagnostic tools and finding ways to incentivize this development would capitalize on each country's resources.

Developed countries like the United States and Japan have growing populations of elderly people,[59,60] which may contribute to an increase in hospital-acquired resistant infections,[16] furthering the need for effective antimicrobials and improved antimicrobial stewardship. Additionally, with their high level of technical expertise, the United States and Japan can work together in other parts of the Asia-Pacific region, particularly with low- and middle-income countries, to help them raise their level of preparedness and mitigate infectious disease threats. Working together lessens the burden for the United States and Japan separately and strengthens the global defense against infectious diseases. USAID and JICA have a shared focus on global health, which can present opportunities for cooperative engagement on combating AMR.

While multiple programs exist that would facilitate US-Japan collaboration on combating AMR, this cooperation has been limited. As with work on many other issues, funding limitations are a challenge to expanding cooperation (personal communication, NIAID official, January 21, 2014). However, AMR is a rising priority. The FY2015 US budget includes funding increase requests for AMR work domestically and internationally,[31,34] and its high priority is described in the previously mentioned FY2016 budget guidance.[37] It has also been included in 2014 programs involving the United States and Japan, including the GHSA and the previously described Emerging Infectious Diseases conference focused on AMR. In addition, the United States has committed to rebalance efforts toward Asia,[61] and the FY2015 US budget prioritizes the Asia-Pacific region, including requests for resources to strengthen regional cooperation and promote regional security.[31] This increased focus on AMR and US interest in the Asia-Pacific region can foster an environment for increasing US-Japan and regional collaborative efforts to combat AMR. The previously described US-Japan collaborative research and global health programs present opportunities to work productively on various AMR issues.

Proposed Policy Recommendations

Transpacific Taskforce on Antimicrobial Resistance

Although AMR is a global health issue, addressing the problem regionally can be a more efficient way to tackle this enormous and multifaceted problem. Development of a

Transpacific Taskforce on Antimicrobial Resistance, modeled after and using lessons learned from TATFAR, would be a useful step in fighting AMR and working toward achieving goals in the GHSA. Although some of the outcomes from TATFAR may be applied to countries outside the US and the EU, issues that are specific to the Asia-Pacific region should be examined cooperatively between countries of this region to better determine causes of the problems and to tailor appropriate responses. The United States and Japan could lead this effort through an initiative similar to TATFAR, to work on issues including AMR surveillance, antimicrobial stewardship, and improving the pipeline of new antimicrobial medications. The cooperative US-Japan programs already in place could be used to develop such a program. Government officials from the US Department of Health and Human Services (HHS), CDC, FDA, NIH/National Institute of Allergy and Infectious Diseases (NIH/NIAID), the Department of Defense, USAID, and USDA; the Japanese MAFF, MEXT, MHLW, JICA, JST, and Pharmaceuticals and Medical Devices Agency (PMDA); and industry and nonprofit sector representatives could work together to determine appropriate recommendations for cooperation based on mutual interests and available resources. Additionally, other countries in the Asia-Pacific region should be considered as potential partners for a transpacific taskforce to address this problem for the region. Eventually, TATFAR and the analogous transpacific committee could be joined to facilitate broader cooperation.

Existing programs can be used to provide supporting networks with valuable expertise to help set up the taskforce. The previously mentioned e-ASIA JRP, with an interest in infectious diseases and involvement of many Asia-Pacific government health agencies,[52] could provide a network of officials with the necessary expertise. Additionally, APEC has several groups in place that could provide expertise for the taskforce. These include the working groups on health, agricultural technical cooperation, and policy partnership on science, technology, and innovation.[62] In addition to providing expertise, e-ASIA JRP and APEC programs can provide further opportunities for cooperation on combating AMR through current activities.

Improving Antimicrobial Stewardship

One potential area of US-Japan cooperation is improving antimicrobial stewardship. This involves developing better practices for prescribing antimicrobial drugs for people and for use in food-producing animals, as well as raising awareness of how to minimize AMR. Better surveillance of antimicrobial-resistant infections is also needed to gain a more comprehensive understanding of the problem. As partners working together in other countries, the United States and Japan could cooperate with less well-resourced nations to work on these stewardship issues. For example, the United States and Japan can help these countries with capacity building through initiatives to support diagnostic testing such as training laboratory staff. The CDC, USAID, JICA, and MHLW could cooperate on these programs, and work could be done through the US-Japan Partnership for Global Health.

Opportunity in Agriculture for Improved Antimicrobial Stewardship

Japan is one of the US's largest importers of beef and pork.[63] Cows and pigs in the United States are routinely given antibiotics for nontherapeutic use.[21,64] Japan's resistance to opening its agricultural markets to imports has been an obstacle in negotiations for the Trans-Pacific Partnership (TPP), an Asia-Pacific trade agreement.[65] Among TPP nations, there are different regulations on antimicrobial use in animal production. For example, New Zealand has stricter regulations on the use of antibiotics for growth promotion than does the United States.[66] If TPP negotiations are concluded, this will likely facilitate increased trade of livestock products between TPP nations, potentially making antimicrobial resistance more widespread. The desire to form the TPP presents an opportunity for these countries to work together on harmonizing agriculture practices to minimize antimicrobial use, which will be beneficial for the region. The FDA, USDA, and MAFF could work with other countries in the region on this issue.

Incentivizing Development

New antimicrobial drugs and better and less expensive diagnostic tests to determine the cause of infections are needed to combat AMR. Scientific collaborations between US and Japanese scientists through the CMSP, as well as work through the GHIT Fund and e-ASIA JRP, can provide valuable opportunities to work on development of these tools. Additionally, government funding specifically for new antimicrobials would provide incentives for research and development. A recent example of this type of incentive is a public-private partnership between the US Biomedical Advanced Research and Development Authority (BARDA) and the healthcare company GlaxoSmithKline, in which BARDA will provide the company up to $200 million for development of new antibiotics.[67] The US and Japanese governments could cooperate through HHS and MHLW to pool funds to provide resources for development of new antimicrobials and improved diagnostic tests. These governments can also cooperate to provide other incentives for these innovations, like guaranteed markets[68] and innovation inducement prizes.[69]

To obtain drug approvals in global markets, pharmaceutical companies are required to submit applications to

regulatory authorities in various countries, which can entail different scientific requirements.[70] A decrease in burden for antimicrobial drug approval could provide incentives for companies to develop these medicines. For example, the time spent until approval can be shortened through streamlining clinical trial and drug approval processes.[71] Additionally, parallel scientific advice and parallel application submission[72] with multiple countries' regulatory authorities can help companies seeking approval in global markets. These are some areas on which the United States and Japan can cooperate, through discussions among FDA, NIH, PMDA, and MHLW and work with other countries.

Infectious Diseases of Mutual Interest

While AMR is a global health security issue, certain diseases are of particular mutual interest to the United States and Japan, such as HIV/AIDS, tuberculosis, and malaria. Their contributions to combating these diseases through the differently focused work of the GHIT Fund and the Global Fund to Fight AIDS, Tuberculosis and Malaria are complemented by other cooperative programs. For example, through the President's Malaria Initiative (PMI), the United States is working with JICA in Burma/Myanmar to strengthen entomologic capacity (personal communication, USAID official, March 11, 2014). A major concern in the Greater Mekong subregion is the development and spread of resistance to the artemisinin antimalarial drugs.[73] To combat this, the United States and Japan can expand cooperation in this region by working together on issues such as improving quality of malaria diagnosis and treatment, antimalarial drug resistance surveillance, and antimalarial drug quality monitoring.[73] These activities could be carried out through PMI and the US-Japan Partnership for Global Health, with cooperation among CDC, USAID, MHLW, and JICA.

Another microorganism of concern to both the United States and Japan is drug-resistant *Neisseria gonorrhoeae*, the bacterium that causes the sexually transmitted disease gonorrhea. In 2013, CDC listed drug-resistant *N. gonorrhoeae* as an urgent threat, which is the most serious category of threat levels.[8] Drug-resistant gonococcal strains have been reported in Japan prior to reports from other countries,[6,74] and it has been theorized that these strains, which are resistant to first-line antimicrobial therapies, have spread internationally from Japan.[74] However, it should be noted that most gonococcal disease occurs in countries with fewer resources.[6] While new antibiotics are needed to minimize this disease threat, working together to enhance surveillance and raise awareness of safer sex practices and current recommended treatment regimens are other areas of potential US-Japan cooperation that can help achieve this goal. This could be accomplished through CDC and MHLW collaborations.

Conclusion

AMR has become a global health security problem, in part because of a lack of vigilance against the threat of ever-evolving microorganisms. This problem has gained global awareness, but much work is still needed to mitigate the loss of efficacy of antimicrobial medications and develop new treatments and diagnostic tools. The United States and Japan together—with their strengths in the life sciences, established programs for medical and health cooperation, strong trading partnership of agricultural products, and close relationships—can and should work together on combating AMR. Their collaborations and networks hold great potential to minimize AMR, particularly for the Asia-Pacific region, and can be valuable to advancing the Global Health Security Agenda.

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