Pennsylvania Consortium for Antimicrobial Stewardship

A Collaborative Approach to Antibiotic Stewardship in Pennsylvania

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Editor's Note: For a valuable update on recent progress in Multidrug-Resistant Bacterial Infections in U.S. Hospitalized Patients 2013-2017, see the encouraging article with that title by Jernigan and co-workers in the **April 2, 2020** issue of the *New England Journal of Medicine*:

N Engl J Med 2020; 382:1309-1319; https://www.nejm.org/doi/full/10.1056/NEJMoa1914433. Equally worthwhile is the accompanying editorial by Fang and Schooley: Antimicrobial Resistance – The Glass Is Half Full:

N Engl J Med 2020; 382:1363-1365; https://www.nejm.org/doi/full/10.1056/NEJMe2002375

BACKGROUND

Antimicrobial resistance (AMR) is an urgent threat to public health and modern medical therapy. Globally, an estimated 700,000 people die each year from antimicrobial-resistant infections. Without action, the number is expected to reach 10 million by 2050, with a cumulative cost of $100 trillion.[1]

In the United States alone, approximately 2.8 million people are infected with antibiotic-resistant bacteria each year, resulting in 35,000 deaths.[2] The associated financial burden is estimated to raise annual healthcare costs as much as $20 billion, plus $35 billion in productivity losses.[3]

Although the problem has multiple causes, inappropriate clinical use of antimicrobials facilitates the emergence and spread of resistant pathogens. In the United States, approximately 258 million prescriptions for oral antibiotics were written in 2017, equivalent to eight prescriptions for every 10 Americans.

In Pennsylvania, an estimated 852 prescriptions per 1,000 residents were dispensed in 2017, which puts our state close to the national average. (Fig. 1) Many of these prescriptions are not needed. For example, when antibiotics are prescribed in emergency care settings, approximately 30%, or 47 million prescriptions, are deemed unnecessary.[3]

In addition to antibiotics used for clinical medicine, 8,361,740 kilograms (92,000 tons) of antibiotics were given to food animals in 2016. These drugs include broad-spectrum antibiotics, such as macrolides and cephalosporins. Macrolides were used in meat producing animals such as swine (337,295 kg.), cattle (194,811 kg,), chickens (20,718 kg.) and other animals.[4] (Fig. 2)

Though the high level of antibiotic use in meat-producing animals is declining in response to efforts by the Food and Drug Administration to ensure judicious use, it is likely that excessive prior use will continue to influence the persistence of antibiotic-resistant bacteria, such as *Campylobacter and Salmonella*. [5]

DEVELOPMENT OF ANTIBIOTICS AND THE RISE OF DRUG RESISTANCE

As is well known, the antibacterial action of the first antibiotic, penicillin, was discovered by Alexander Fleming in 1928, but he never purified it or tested it against bacterial infections in animals or humans. Those studies were done in the 1930s by Howard Florey and Ernst Chain at Oxford, resulting in the first clinical use in 1941.[6] Penicillin was released for public use in 1943. With World War II raging in Europe, there was pressure to mass produce penicillin for the military, and supplies were severely limited. (Fig. 3)

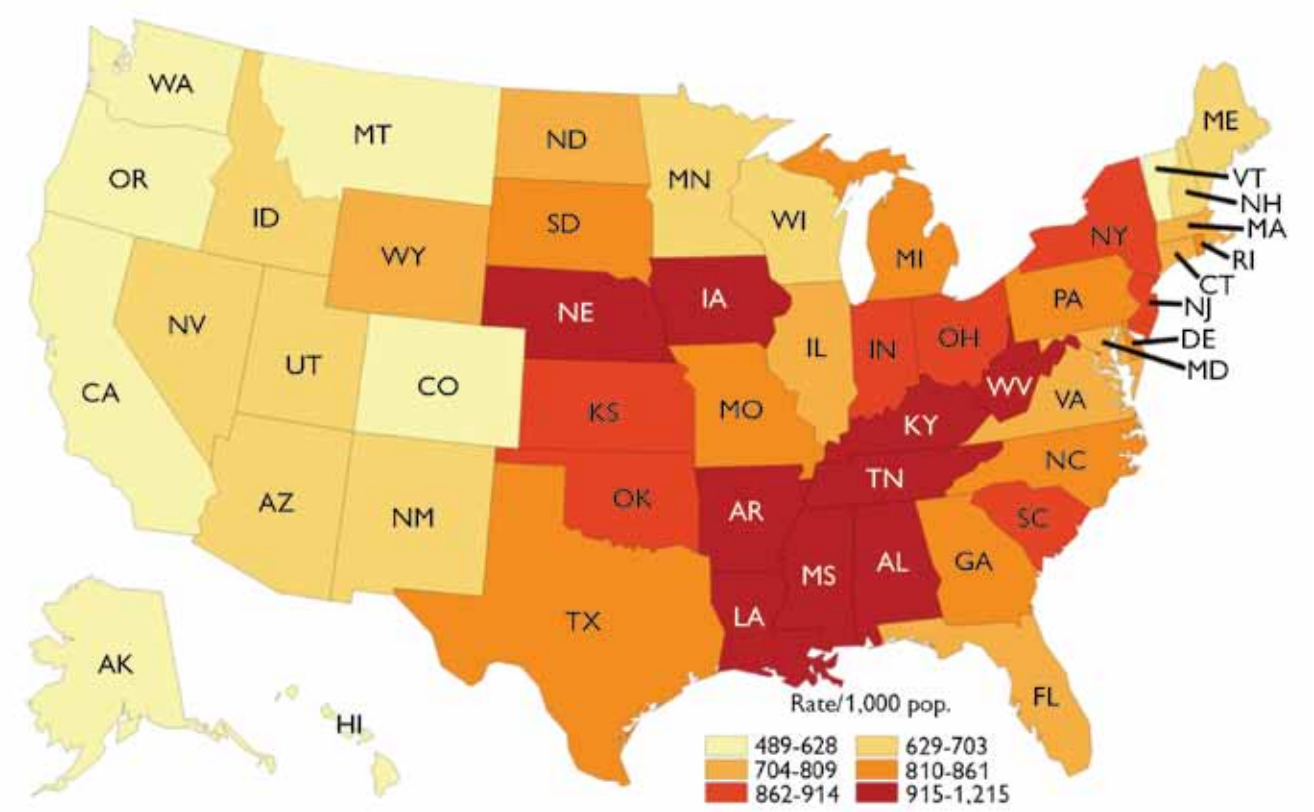

Fig. 1. Antibiotic prescriptions per 1,000 population by state (2017 data).

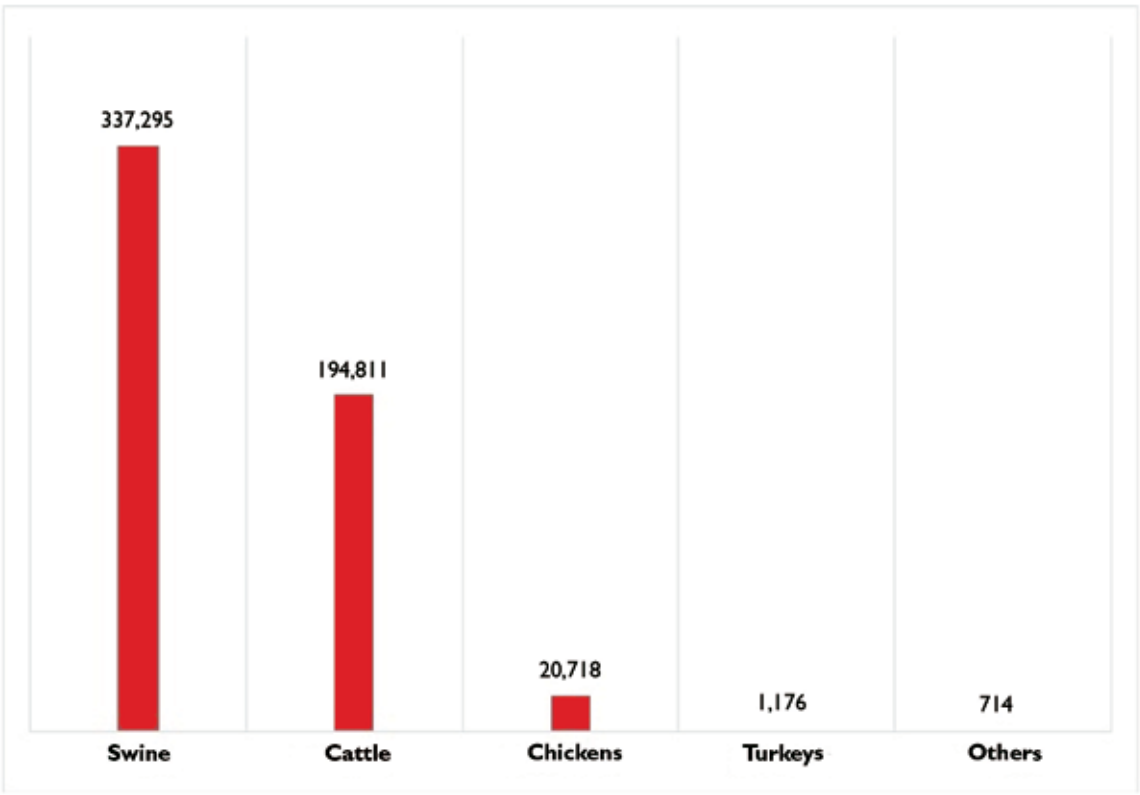

Fig. 2. Macrolides used in food animals (kg of active ingredient) in United States (2016 data)..

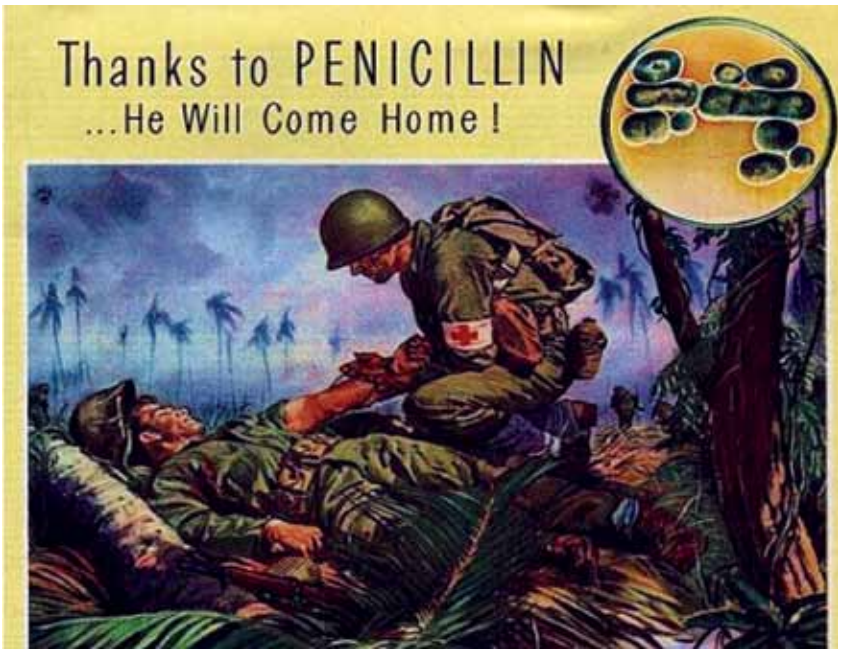

Fig. 3. World War II spurred the mass production of penicillin. This advertisement for penicillin production was in the Aug. 14, 1944, edition of *Life* magazine.

And yet, from the beginning, the miracle of penicillin was at risk. Alexander Fleming predicted the consequences of antimicrobial resistance during his 1945 Nobel Lecture, stating: "Then there is the danger that the ignorant man may easily underdose himself and by exposing his microbes to non-lethal quantities of the drug make them resistant." [7]

In 1967, the penicillin-resistant *Streptococcus pneumoniae* was identified.[8] (Fig. 4) The first U.S. case of infection due to *E.coli* harboring the plasmid-borne colistin resistance gene, *mcr-1*, occurred in Pennsylvania in April 2016, when a 49-year-old female visited a clinic with symptoms of a urinary tract infection.[9]

The use of antibiotics in animals is also a major concern. According to the CDC, up to 75% of new and emerging infectious diseases in people are spread by animals,[8] which can become infected themselves, or act as carriers of bacteria like *Salmonella* and pass them to humans. A 2019 outbreak in humans of multi-drug resistant *Salmonella* was caused by pig ear pet treats for dogs.[10] This outbreak affected 154 people (19% of whom were children) in 34 states, including eight cases in Pennsylvania. *Salmonella* infections have also been linked to ground beef (13 cases, one death), backyard poultry (1,134 cases, two deaths), and pets, such as turtles (26 cases) and hedgehogs (54 cases). [11]

ANTIMICROBIAL STEWARDSHIP AND PREVENTION OF DRUG RESISTANCE

Antimicrobial stewardship is a coordinated effort to promote the appropriate use of antimicrobials, improve patient outcomes, reduce resistance, and decrease the spread of infections caused by multi-drug resistant organisms.[12] The idea of antimicrobial stewardship was first presented in 1996 by McGowan and Gerding, two physicians at Emory University School of Medicine.[13] They noted the connection between antimicrobial use and resistance, and highlighted the urgent need for preventive and collective measures against antimicrobial resistance.

While this was the first published stance for stewardship, the concerns regarding injudicious prescribing practices and resistance had been discussed in medicine for decades. As early as 1968, it was reported that 50% of antimicrobial use was either unnecessary or inappropriate.[14] At the Children's Hospital in Winnipeg, Canada, during the 1970s, approximately 200 courses of antibiotic therapy were evaluated for drug selection, dosage, and necessity of use. Errors in therapy were found in 30% of medical orders and 63% of surgical orders, with the most frequent error being unnecessary treatment.[15]

The use of antibiotics in farm animals is also a concern. While reports have shown a 33% decrease in domestic sales and distribution of antibiotics for use in livestock from 2016 through 2017, there are still improvements to be made. The beef and pork industries are high utilizers of these medications, accounting for 2 million kilograms in sales in 2017.[16] Fortunately, as of 2017, use of antibiotics to promote growth or improve feed efficiency is forbidden in the United States.[17] In addition, the vast majority of antibiotics used in animal water and feed now require veterinary oversight

and can no longer be purchased over the counter.[18]

Since resistant bacteria can spread in multiple ways, including individuals, communities, agriculture, health care facilities, and the environment, a One Health approach to antibiotic stewardship that looks beyond only human medicine was developed.[19] One Health is a collaborative approach that recognizes the interconnection between people, animals, plants, and their shared environment, with the goal of achieving optimal health outcomes.[19] While the concept is not new, originating with Dr. Rudolf Virchow in the 19th century, the notion has received increased attention in recent years. The U.S. Senate recognized One Health as an important issue by passing a bipartisan resolution to designate January 2020 as National One Health Awareness Month.[20] Sen. Barbara Feinstein stated that "by using the 'One Health' approach, global health problems including antibiotic resistance and the spread of infectious diseases can be more easily addressed…Our resolution will hopefully draw attention to the need for holistic approaches to addressing human health that take into account changes in environmental and animal health. With diminishing resources and a growing human population, fighting problems with a 'One Health' approach must be encouraged now more than ever."

PENNSYLVANIA CONSORTIUM FOR ANTIMICROBIAL STEWARDSHIP'S RESPONSE (PCAS)

In 2015, collaborators with aligned interests formed the Pennsylvania Consortium for Antimicrobial Stewardship (PCAS). PCAS is a unified response to the emergence and spread of resistant bacteria through a One Health approach. We aim to

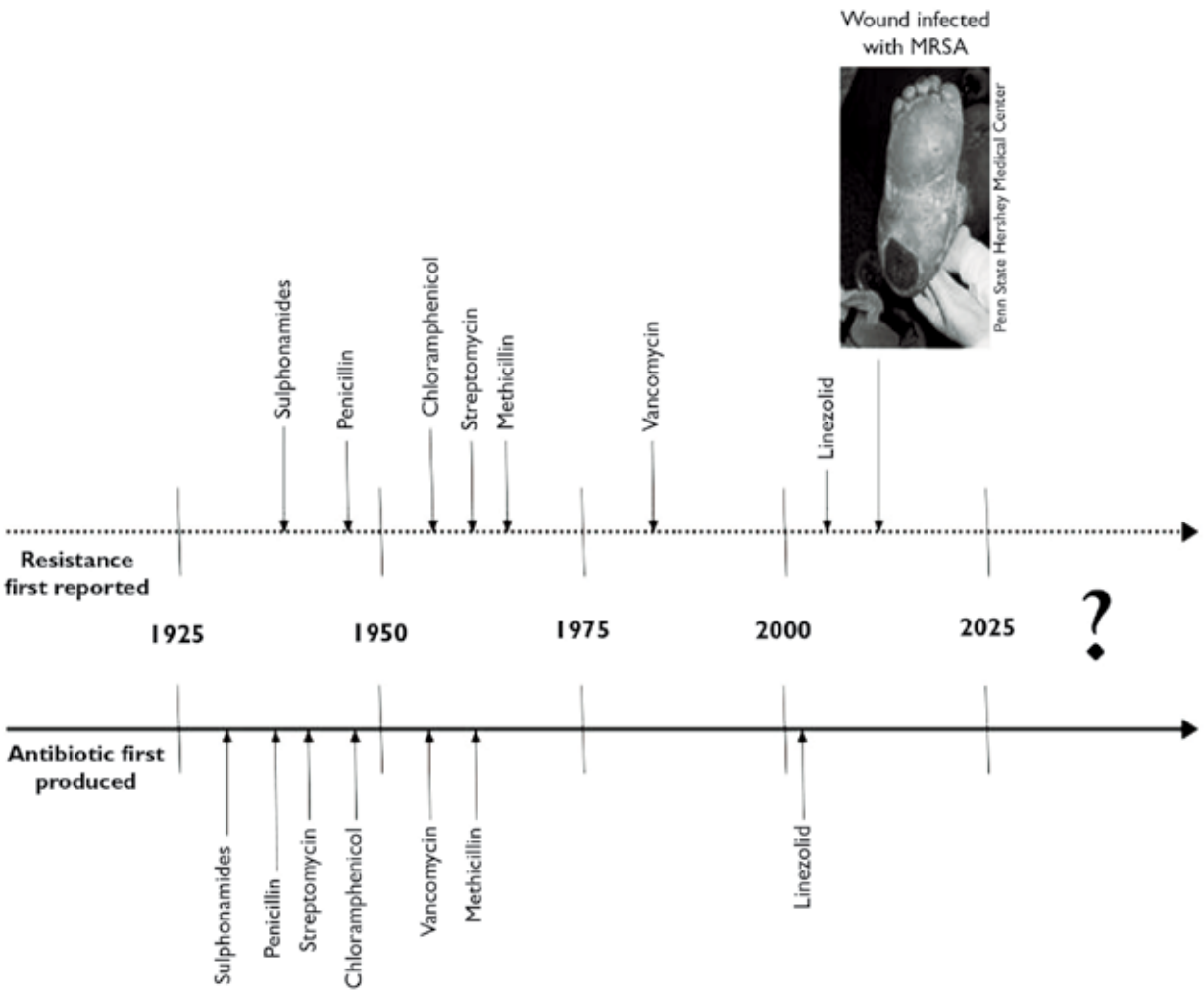

Fig. 4. Timeline depicting the introduction of antibiotics and detection of resistance.

strengthen antimicrobial stewardship through multidisciplinary One Health collaborations that recognize interdependence of humans, animals, and the environment. Collaborations are focused on four objectives:

1) integrated surveillance for antimicrobial resistant pathogens;

2) use of rapid and innovative diagnostic tests for identification and characterization of infections;

3) promotion of evidence-based guidelines for antibiotic use;

4) development of partnerships with stakeholders. (Table 1)

Prior to the formation of PCAS, the group members collaborated under the CDC programs Get Smart and Be Antibiotic Aware through the Pennsylvania Department of Health.

Over the past five years, PCAS has monitored and characterized antimicrobial resistant pathogens of human and animal origin in collaboration with federal partners. Interdisciplinary teams secured research support to assess use of antibiotics for pediatric acute otitis media (AOM) and investigated behavioral factors that influence the prescription of antimicrobial drugs and consumers' attitudes towards antibiotic use in food animals. PCAS has supported public health observance of annual Antibiotics Awareness Week by hosting events in Allegheny County, Penn State Hershey, and State College. PCAS contributed to an innovative children's art and student video competition held annually in Pennsylvania. In addition, PCAS has disseminated findings under each objective in various modalities, including publications and presentations at state and national conferences.

The pediatric initiative aims to reduce unnecessary antibiotic use, give provider-based feedback on antibiotics, and address parents' expectations for antibiotics. A debut document was issued by a multidisciplinary advisory group on best practices when implementing sick-child exclusion policies, and was titled the "Sick-Child Exclusion Policy Advisory Group Report Summary: Practical Considerations in Implementing of Model Sick-Child Exclusion Policy in Childcare Settings." [21] This initiative also included research into watchful waiting for cases of pediatric otitis media. Penn State researchers and PCAS collaborators applied communication theories to understand how caregivers utilize physician-provided watchful waiting advice[22] and act as stewards outside of the clinic.[23] Glo-GermTM and hand hygiene demonstrations at childcare facilities and preschools allowed PCAS to educate staff and children on proper hygiene techniques, as well as to disseminate information, such as the "Sick-Child Exclusion Policy Advisory Report."

PCAS INITIATIVES

a. The pharmacy initiative engages pharmacists and student pharmacists in antimicrobial stewardship. This initiative includes an annual workshop for second

Table 1. Pennsylvania Consortium for Antimicrobial Stewardship Goals

√ Strengthen integrated surveillance efforts to characterize the emergence and spread of resistant infections, as well as policies, attitudes, and behaviors related to emergence and spread (e.g., prescriptions, and vaccination).
√ Implement programs, guidelines, and reporting policies that advance antibiotic stewardship among health providers, veterinarians, agricultural members, and the public in Pennsylvania based on the most accurate and current evidence from the social and life sciences: • Increase people's understanding of the biological and behavioral mechanisms that increase antibiotic resistance. • Promote prevention activities that prevent the spread of infections, such as vaccination, hygiene and sanitation. • Decrease demand and prescriptions for unnecessary antibiotic.
√ Advance the development and use of rapid and innovative diagnostic tests for identifying and characterizing an infection's cause (e.g., viral, bacterial).
√ Promote collaboration among stakeholders, including state and federal agencies, academic institutions, physicians, health plans, medical centers, and public health organizations, who share the goal of reducing antimicrobial resistance.

year pharmacy students at the University of Pittsburgh and prepares students to educate clients on appropriate use of antibiotics as part of their community pharmacy practice outreach rotation.

b. The long-term care (LTC) initiative seeks to increase awareness of antibiotic overuse in LTC facilities and monitor antibiotic use and infection control practices, as well as to disseminate guidelines to facilities. PCAS has assisted in two workshops for long-term care facility staff on prescribing practices in conjunction with PCAS collaborations at the Allegheny County Health Department.

c. The animal husbandry/food systems initiative engages microbiologists and social scientists to understand how practices in animal husbandry shape the emergence and spread of antibiotic resistant germs that influence human health. Conversely, it is human decisions that can place pressure on the animal husbandry system to treat animals; consumer purchasing is an important part of the system.

d. PCAS works to spread the antibiotic stewardship message through multiple events and avenues. The CDC started an annual antibiotic awareness week in 2008. They provided materials to agencies, nonprofit organizations, and for-profit companies to educate the public about antibiotic resistance and antibiotic stewardship. PCAS sponsored its first events to promote antibiotic stewardship at academic institutions, hospitals, and child care centers in PA in 2015. During those events, Dr. Rachel Levine, Pennsylvania's Physician General, read a proclamation created by Gov. Tom Wolf, recognizing Nov. 16-22 as Get Smart Week in Pennsylvania. Annual Antibiotic Awareness Week events have continued at Penn State University, University of Pittsburgh, and Penn State Health Milton S. Hershey Medical Center.

e. Marketing of PCAS messages has engaged the community and providers through a website to disseminate guidelines and training materials as well as via social media to share short messages on resistance, stewardship, and upcoming PCAS-related events. In addition, a monthly newsletter reached 6,000 licensed childcare facilities and other stakeholders between September 2013 and December 2018. Newsletter topics included articles on winter pathogens, watchful waiting, breastfeeding, and vaccinations.

f. To engage a younger audience, an art and video competition was developed for youth in Pennsylvania. The art competition for children under 12 years of age encourages kids to use their imagination to create a project with a theme of hand washing, vaccinations, or using antibiotics appropriately. Youth in grades 7-12 were given the prompt to create a video on how to avoid illness from a bacterial or viral infection, which could include hand hygiene, immunizations, proper antibiotic use, and promoting ways to prevent the spread of microbes.

PCAS is fortunate to have dedicated members volunteering their time from academic institutions, clinical settings, and the Department of Health. Consortium members include epidemiologists, pharmacists, communication scientists, infectious disease physicians, pediatricians, childcare directors, microbiologists, and a space scientist (Table 2, next page). PCAS members have expressed their ongoing commitment to the mission. Activities are organized by the PCAS coordinator, Tabitha Reefer, MBA, MPH, and led by a core team (NM, RS, NH).

As with any volunteer-based organization, PCAS encounters challenges to advancing its mission. These include lack of dedicated staff, and lack of consistent funding. Challenges also include logistics in organizing seminars for diverse audiences (e.g. physicians, pharmacists, and veterinarians), geographic distances between members, and scarce resources for interventions and studies.

CONCLUSION

Antimicrobial resistance is a major public health threat that will persist without collaborative efforts from stakeholders across disciplines. To enhance collaboration and dissemination of information, PCAS is launching a new website: https://pennsylvaniacas.wixsite.com/pcas. Here, the public, practitioners, and researchers will be able to access information on antimicrobial resistance and stewardship. Inquires to join this effort can be made to PCAS via email at PAantimicrobialstewardship@gmail.com.

ACKNOWLEDGEMENTS

The authors extend their thanks to the other contributors:

- Nkuchia M. M'ikanatha, DrPH, MPH, Surveillance Epidemiologist, Pennsylvania Department of Health
- Sameh W. Boktor, MD, MPH, Epidemiologist, Pennsylvania Department of Health
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Table 2. **Pennsylvania Consortium for Antimicrobial Stewardship: Members' institutions and expertise ***

INSTITUTION	TYPE	EXPERTISE
Penn State College of Medicine	Academic medical center	Physician, pediatrics, breast feeding and antimicrobial stewardship research
University of Pittsburgh School of Pharmacy	Pharmacy training institution	Pharmacist, infectious disease, education inpatient antibiotic management
MIT/Harvard	Research/higher education	Engineering, research in extraterrestrial genomes and biomedical instruments
Allegheny County Health Department	Local government public health	Applied epidemiology, outbreak investigation, antimicrobial stewardship for all settings
Pennsylvania Department of Health	State government public health	Influenza surveillance, antimicrobial resistance monitoring, infectious disease genomics, antimicrobial stewardship and One Health
U.S. Department of Housing and Urban Development	Federal government housing	Microbiology, plant ecology, antimicrobial resistance research
Geneia	Health insurance	Health education, training
University of Pennsylvania Perelman School of Medicine	Academic medical center	Specialized infections disease treatment, research in antimicrobial stewardship long-care
Pennsylvania State University Department of Communication Arts and Sciences	Academic research, higher education	Quantitative social influence research, modeling, One Health
Children's Hospital of Pittsburgh	Academic medical center	Pediatric infectious diseases, transplant infection, antimicrobial stewardship
Pennsylvania State University College of Agriculture Sciences	Academic research, higher education	Microbiology, genomics research, virulence genes, CRISPR
Pennsylvania State University Health Services	Academic research, higher education	Communicable diseases treatment and management

* Sources: Nicole Hackman, MD; Bonnie Falcione, PharmD, BCPS-AQ ID; Christopher Carr, ScD; Kristen Mertz, MD, MPH; Jennifer Fiddner, MPH; Molly Nance, MPH; Nkuchia M'ikanatha, DrPH, MPH; Sameh Boktor, MD, MPH; Xin Yin, MPH; David Hewitt, PhD; Lindsay Vogt, MPH; Jennifer Han, MD, MSCE; Rachel Smith, PhD; Erina MacGeorge, PhD; Michael Green, MD, MPH; Edward Dudley, PhD; Shelley Haffner, RNC

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