**Current Topics**

**ASM MICROBE 2016**

Gates Foundation: "Catalytic Philanthropy" Seeking "Global Health Equity"

**Jeffrey L. Fox**

“People are willing to have standing armies for war. We need to do something similar for public health,” says Bill Gates, cofounder of the Bill & Melinda Gates Foundation in Seattle, Wash., and former head of Microsoft. He spoke during the opening keynote session, “A Conversation with Bill Gates: Bringing the Frontiers of Science to the Front Lines of Development,” convened at the 2016 ASM Microbe Meeting, held in Boston, Mass., in June.

The Gates Foundation is providing resources for health surveillance and health care delivery in several parts of the world, particularly Africa and Asia, while also supporting a broad array of public health efforts throughout much of the developing world. Although some of this effort is directed to chronic diseases, much of it aims at several key infectious diseases, notably polio and agents such as norovirus that cause diarrheal disease, particularly among children.

In terms of his top four health-related challenges to address in Africa, where needs are great, Gates ranks nutrition and three specific infectious diseases—HIV, malaria, and tuberculosis (TB)—as having high priority. “I hope that we will have approaches for those four in the next 20 years,” he says. Another priority is to fill the infectious disease diagnostic gap in Africa, where the tendency is to “treat all fevers as malaria,” he adds.

Despite these avowed priorities, a major focus for the Gates Foundation during the past few years continues to be polio eradication—a campaign that other organizations launched in 1988 and which now seems close to meeting that goal. “In the last few years, it’s gone well, and we’re now down to two countries with polio, Pakistan and Afghanistan,” Gates says. However, ridding the world of the “last 1% is very hard.”

Aside from technical challenges, polio vaccine workers have had to cope with attacks from terrorist groups, including the Taliban, as well as fears in some quarters that the polio vaccine somehow might be dangerous for children. Nonetheless, the goal of eradication seems within reach.

That focused goal is part of a larger, far more ambitious aim of attaining “global health equity,” Gates says. However, he is quick to say that this larger goal requires far more resources than the Gates Foundation can provide directly. Thus, the strategy for meeting this larger goal depends on “catalytic philanthropy”—leveraging the foundation’s resources to set important and far-broader programs in motion. This approach entails working with international and national public health entities, including the World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) in Atlanta, Ga. They, too, face resource shortfalls as they cooperate to meet these and other challenges. For example, he notes, “There is a huge gap between what WHO is funded to do and what is expected.”

Catalytic philanthropy inevitably requires “tradeoffs” when trying to leverage resources, he says. Under this regimen, if a particular product or strategy being developed “can’t save a life for $1,000, it’s not effective” in the eyes of the foundation. The vaccine-based polio eradication program meets
such criteria and, as an important bonus, has strengthened health delivery systems in dozens of developing countries—thus bringing the more ambitious goal of health equity a bit closer.

Jeffrey L. Fox is the Microbe Current Topics and Features Editor.

ASM MICROBE 2016
Host-Targeted TB Therapies of Limited Efficacy So Far

Shannon Weiman

*Mycobacterium tuberculosis* (Mtbc) is notoriously difficult to eradicate even with combinations of antibiotics, leading researchers to pursue alternate strategies, including one aimed at bolstering host defenses against this pathogen. “Our inability to effectively treat all infected individuals necessitates a deeper understanding of the host-pathogen interface to facilitate new approaches,” says Amy Barczak of the Ragon Institute and Massachusetts General Hospital in Boston, Mass. She was one of several experts who participated in the symposium “Aiming at Non-Conventional Approaches to TB Therapies,” held at the 2016 ASM Microbe Conference in Boston last June.

Mtbc exploits innate immunity to its advantage, according to Jeffery Cox of the University of California, Berkeley. Inside host macrophage cells, the pathogen ejects its DNA from phagosomes into the cytosol, where it is misidentified as viral DNA, tricking the host cell into mounting misdirected antiviral responses that favor Mtbc survival. Specifically, various immune modulators, including OasL1 (2′-5′-oligoadenylate synthase-like protein 1), which controls type-1 interferon (IFN) production, are degraded. “We suspect that this primarily antiviral pathway has been co-opted by bacterial pathogens, perhaps primarily to elicit type-1 IFNs,” he says, adding that blocking OasL1 ubiquitinylation might shift host immunity back toward antibacterial responses.

Mtbc also exploits host cytokine signaling, further helping it survive within phagosomes, according to Priscille Brodin of the Institut Pasteur de Lille, France. She is investigating a mechanism by which phagocytosis of Mtbc triggers cytokine signaling pathways that ultimately block phagosome acidification. Cancer drugs that target these pathways may thwart Mtbc’s survival strategy, promoting phagosome maturation to kill internalized Mtbc.

Meanwhile, although a cyclic-di-AMP-dependent cytosolic surveillance mechanism detects Mtbc second messengers and activates antibacterial autophagy defenses, Mtbc encodes a phosphodiesterase that degrades cyclic-di-AMP, allowing it to fly under the radar, according to William Bishai of John Hopkins University in Baltimore, Md. Phosphodiesterase inhibitors, including drugs widely used to treat erectile dysfunction, might give the upper hand back to the immune system, he points out.

Other drugs that promote autophagy defenses and benefit the host include the antidepressant fluoxetine and the cancer drug gefitinib, according to Barczak. “Fluoxetine induces autophagy and enhances production of tumor necrosis factors,” he says, adding that blocking drug efflux may allow the drugs to stay in the cells longer.

MINITOPIC
Microbiology Policy Bulletin Board

Recent developments involving microbiology and related science policy matters include:

- Following the G7 Summit Conference earlier this year, World Bank officials said they were helping to launch a Pandemic Emergency Financing facility, which will “create a new market for pandemic risk insurance, and ensure that resources get to the right place at the right time to the sites of outbreaks,” said World Bank Group President Jim Yong Kim last May.
- Although new cases are decreasing, a yellow fever outbreak in Angola is “not yet under control” and is “challenging the ongoing mass vaccination campaign,” said World Health Organization (WHO) officials last June, and it threatens to spread to China. Separate, smaller yellow fever outbreaks are ongoing in Uganda and the Democratic Republic of Congo, they said.
- U.S. Food and Drug Administration (FDA) officials in June approved Vaxchora, a vaccine for preventing cholera caused by serogroup O1 in adults 18 through 64 years. Vaxchora, which is being produced by PaxVax Bermuda Ltd., in Hamilton, Bermuda, is based on a live, weakened strain of *Vibrio cholerae*.
- FDA in May finalized a new food safety rule under the FDA Food Safety Modernization Act that requires companies in the United States and abroad to take steps to prevent intentional adulteration of the food supply.
- In June, FDA approved use of the Procleix Zika virus blood screening assay on the Procleix Panther system under the agency’s investigational new drug protocol. The test was developed by Hologic of Marlborough, Mass., and Grifols of Emeryville, Calif. Earlier, the agency authorized the emergency use of the Altona Diagnostics RealStar® Zika Virus RT-PCR Kit U.S. for detecting RNA from Zika virus in serum or urine and, separately, the Zika Virus RNA Qualitative RT-PCR test from Focus Diagnostics, Inc., of Cypress, Calif.
- Gene-drive modified organisms “are not ready to be released into the environment and require more research in laboratories and highly controlled field trials,” according to a report released last June from the National Academies of Sciences, Engineering, and Medicine in Washington, D.C. Details are available at http://national-academies.org.