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In shadow of COVID-19, TB vaccine research enters new era

In less than a year, scientists were able to develop several efficacious vaccines against COVID-19.

Almost 140 years after the discovery of *Mycobacterium tuberculosis,* there is only one licensed vaccine against tuberculosis: the bacille Calmette-Guérin (BCG) vaccine, which has modest benefits, noted *Infectious Disease News* Editorial Board Member **David L. Cohn, MD,** physician at Denver Public Health and professor of medicine in the division of infectious diseases at the University of Colorado School of Medicine.

Tereza Kasaeva, MD, PhD, seen here visiting a lab in Nigeria, said a new effective TB vaccine would "herald a new era in efforts to end TB."

Source: WHO

"TB vaccine research has progressed significantly over the past several years, if one considers there is now a greater understanding of the immune response to *Mycobacterium tuberculosis,* identification of specific immunogenic TB antigens, and changes in strategies and target populations," Cohn said.

"In contrast, many consider TB vaccine development as sluggish and underfunded in comparison to many other infectious diseases, when the only licensed vaccine against the leading infectious disease cause of mortality of adults in the world is 100 years old," he said.

To bring renewed attention to TB and help reinvigorate efforts to create a vaccine, the United Nations held a high-level meeting in 2018 to discuss TB and make a new commitment to ending it. Since then, efforts have lagged and progress has stalled, according to experts, and WHO said that to meet End TB Strategy targets, a new vaccine is needed.

Infectious Disease News spoke with Cohn and other experts about efforts to end TB and develop an effective vaccine.

According to **Tereza Kasaeva, MD, PhD,** director of the WHO Global TB Programme, global TB targets set in the U.N.'s sustainable development goals and the End TB Strategy call for reductions in TB disease burden — disease incidence, number of TB deaths and that zero of TB-affected households face catastrophic costs.

"The political declaration reaffirmed these targets and set new targets for TB treatment, TB preventive treatment and funding," Kasaeva told *Infectious Disease News.*

Some of the targets of the End TB Strategy are an 80% reduction in TB incidence by 2030 and a 90% reduction in the number of TB deaths by 2030 compared with 2015.

According to Kasaeva, TB kills close to 4,000 people each day and around 1.4 million people annually. It is the leading killer of people with HIV and a major contributor of antimicrobial resistance-related deaths. The most recent data from WHO showed that more than 10 million people were infected with TB worldwide in 2019, including 5.6 million men, 3.2 million women and 1.2 million children. Among those infected, 8.2% were living with HIV.

"This preventable and curable disease places an enormous human and societal toll on those affected, their families and communities," Kasaeva said.

Commitments made by heads of state and other leaders at the 2018 U.N. meeting offered hope for ending the death and suffering of millions worldwide who are struggling with TB, Kasaeva said.

According to this year's global TB report from WHO, around 63 million people have been saved from TB since 2000 and there was a 9% reduction in TB incidence between 2015 and 2019, with a 14% drop in deaths in the same period. Milestones for 2020 included a 20% reduction in TB incidence and a 35% reduction in deaths. According to the report, Europe was on track to hit these targets and Africa has made significant gains, but global progress toward the milestones has lagged.

The WHO report also demonstrated that more people than ever before received life-saving treatment for TB in 2019, which the authors said is largely due to improved detection and diagnosis. Globally, WHO reported that 14.1 million people were treated for TB in 2018 and 2019, which is more than a third of the way to the 5-year target of 40 million.

Unfortunately, the report showed that progress in expanding access to TB preventive treatment has been slow — particularly among contacts of patients with TB — with approximately 6.3 million people starting TB preventive treatment in 2018-2019. This is about one-fifth of the way to the 5-year target of 30 million.

The report also showed that funding remains a major issue in the fight against TB. Despite this, there have been intensified efforts to drive the development of affordable and accessible rapid point-of-care tests, as well as new, safer and more effective treatments and vaccines.

'A lot of good science'

According to **Mike Frick, MPH,** co-director of the research and policy think tank Treatment Action Group's TB program, TB vaccine research is beginning to pick up.


Mike Frick

"For a few years I've been telling fellow activists and policymakers that it's time to start paying closer attention to TB vaccine development." Frick told *Infectious Disease News.* "It's an exciting moment, one full of potential, with several successful phase 2 studies recently completed and preparations underway for phase 3 trials."

According to Frick and Kasaeva, the most watched candidate is M72/AS01$_E$ (GlaxoSmithKline), a subunit vaccine that includes the same adjuvant used in GSK's zoster vaccine, Shingrix. M72/AS01$_E$ was shown to be 50% efficacious (95% CI, 12.1%-71.2%) in protecting against developing bacteriologically confirmed TB disease in more than 3,000 HIV-negative adults with latent TB infection after around 3 years of follow-up, according to the results of a phase 2b trial. This would meet WHO's preference that a TB vaccine demonstrate 50% or greater efficacy in preventing confirmed pulmonary TB.

After a final analysis of the trial was published in *The New England Journal of Medicine* last year, **Barry R. Bloom, PhD,** an endowed professor of public health at the Harvard T.H. Chan School of Public Health, told *Infectious Disease News* that, even at just 50% efficacy, the vaccine could save many lives if it worked as well in different populations and uninfected individuals as it did in the trial, which took place in Kenya, South Africa and Zambia.

"This is the first vaccine that has ever shown protection in previously *M. tuberculosis*-infected individuals and so offers the potential for protection of vast numbers of people in endemic countries," Bloom said.

Frick and Kasaeva said there are plans by the Gates Medical Research Institute to enter the vaccine candidate in a phase 3 trial.

"Once it begins, it will easily be the largest and most expensive TB vaccine trial in decades," Frick said.

Another candidate in the pipeline is DAR-901, an inactivated whole cell vaccine that is entering late-stage development, said **C. Fordham von Reyn, MD,** a professor of medicine at the Geisel School of Medicine at Dartmouth College and principal investigator of the DAR-901 trials.

"DAR-901 is the updated version of SRL 172, which is the only vaccine in development to have completed a phase 3 trial," von Reyn told *Infectious Disease News.*

According to von Reyn, during the phase 3 trial, the vaccine was shown to be 39% efficacious in preventing TB disease in people living with HIV in Tanzania. These findings held true among participants with or without previous TB infection, he said. The newer DAR-901 was shown to be safe and immunogenic in a phase 1 trial at Dartmouth. A phase 2b trial was recently completed in Tanzanian adolescents and the vaccine was shown to be safe.


C. Fordham von Reyn

Although DAR-901 did not reduce the risk for new TB in the Tanzania trial, those who were infected showed an immune response that investigators believe may be the basis for protection against subsequent TB disease.

"The next step will be a phase 3 trial," von Reyn said.

Frick listed other promising candidates, including VPM1002, a recombinant version of the BCG vaccine that is in late-stage development and is also being tested against SARS-CoV-2. Two candidates, MTBVAC and H56:IC31, are entering phase 2 trials. Additionally, the Gates Medical Research Institute is studying an approach in which adolescents are revaccinated with BCG.

Frick said it is worth keeping an eye on candidates in the pipeline that are in the early stages of development.

"Over the next few years, we will likely see novel candidates enter clinical development," he said.

One such candidate is a TB vaccine based on cytomegalovirus. Frick explained that work is also underway to develop TB vaccines based on messenger RNA — the construct used for several COVID-19 vaccine candidates that demonstrated high efficacy in phase 3 trials. Scientists are also developing ways to deliver TB vaccines by aerosol, and building off the success of clinical trials by using samples collected and stored from clinical studies to discover biomarkers, he said.

"In short, there is a lot of good science happening," Frick said.

However, Frick also expressed concerns over the future of TB research and the vaccine pipeline.

"The TB vaccine field will need to grapple with some big questions in the coming years," Frick said. "One involves thinking through where TB vaccines sit within the broader agenda for TB prevention."

An example of Frick's concern centers around WHO's new guidance recommending short-course TB preventive therapy for more people at risk for TB. He wonders: Is it ethical to conduct a TB vaccine study without offering TB preventive therapy to trial participants? Do TB vaccines need to be studied alongside and together with preventive therapy?

According to Tereza Kasaeva, MD, PhD, director of the WHO Global TB Programme, tuberculosis kills close to 4,000 people each day.

Source: WHO

Additionally, the field also needs to consider ways to increase the inclusion of special populations in TB vaccine trials, he said — namely children, people living with HIV and other groups vulnerable to TB.

These concerns are secondary to funding issues, which Frick cited as the biggest weakness of the pipeline. Data from the Treatment Action Group demonstrated that from 2005 to 2019, the world spent a combined $1.4 billion on TB vaccine research.

"TB vaccine development is seriously underfunded relative to its potential to help end the TB epidemic," he said. "By way of comparison, this amount is less than the $1.5 billion contract the U.S. government signed with Moderna for the clinical testing and commercial scale manufacturing of its COVID-19 vaccine candidate. In other words, what the U.S. government gave a single COVID-19 vaccine developer exceeds all the money spent on TB vaccine research, for the entire field, over the last 15 years."

David L. Cohn

According to WHO's TB report, funding for TB prevention, diagnosis, treatment and care in 2020 reached $6.5 billion, representing only half of the $13 billion target agreed on by world leaders at the U.N. meeting.

Based on these funding shortfalls and where candidates stand in the pipeline, Cohn believes it will likely be several more years before there is a new safe and effective TB vaccine that would be approved in most countries.

Making matters worse, public health measures to contain the COVID-19 pandemic have interrupted clinical trials and delayed the planning stages of new studies, according to Kasaeva.

Who benefits?

Having a new effective TB vaccine would "herald a new era in efforts to end TB," Kasaeva said.

"It would mean that less medication is needed to treat TB disease and infection because the TB burden and transmission will diminish wherever the vaccine coverage would be high enough," she said.

Kasaeva noted that vaccines that work in different ways to prevent initial infection (pre-exposure) or to prevent progression to disease (post-exposure) would probably be necessary.

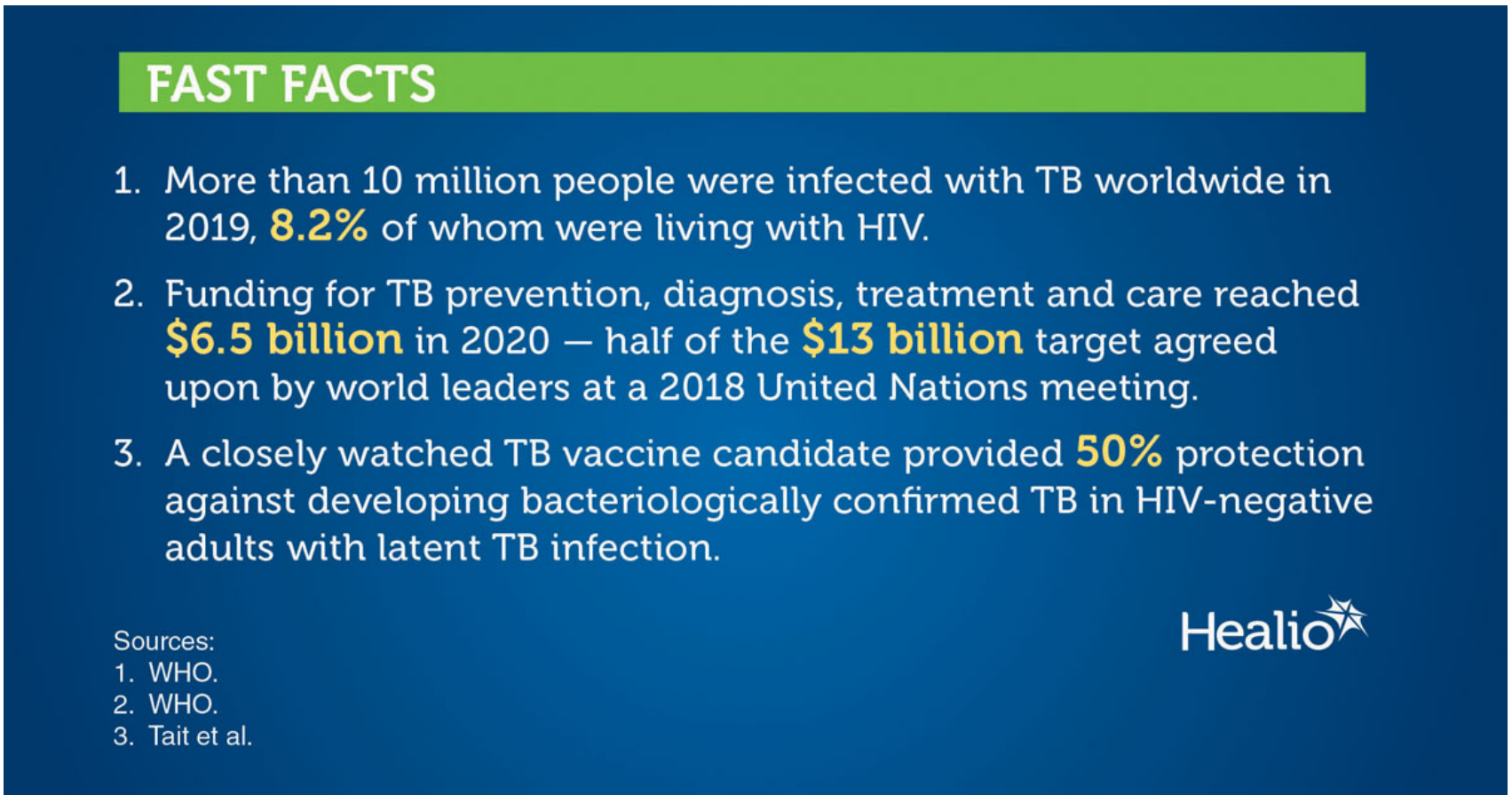
"An immunizing vaccine that can be used widely would speed up the decline in TB incidence and mortality to the rate needed to achieve the End TB Strategy targets," she said.

Experts agreed that having effective TB vaccines would reduce the number of people impoverished by the costs of TB prevention, and curb the development of drug resistance by reducing the use of antibiotics.

Kasaeva said "the most vulnerable populations and the countries with highest TB burden will see most benefit" from an effective TB vaccine, numerically speaking.

"A vaccine would also make it more likely to achieve TB elimination in countries with a lower TB burden," she said.

Cohn said the more than 150 countries currently using the BCG vaccine in the first year of life would benefit most from a new vaccine, especially where resources are limited and there is a high incidence of TB. The



vaccine is not generally recommended in the U.S.

"In developed nations with adequate TB control programs and access to care, a new TB vaccine would have limited impact over current diagnostic and treatment modalities," he said.

While the world waits for another vaccine, experts said there is other work to be done.

"In the interim, countries need to continue to expand efforts to prevent and treat TB," Kasaeva said. "Finding people with active TB and keeping them on appropriate treatment will be key."

She said BCG vaccination can protect newborns, and the expanded use of TB preventive treatment among people at risk is also important.

To achieve WHO targets in the absence of a vaccine, Cohn said the world will need "improved case detection for diagnosis, effective treatment with better and shorter regimens for both drug-sensitive and drug-resistant TB, and broader implementation of TB preventive treatment."

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