hours, but if the strategies had been effective, at least they would have provided insight into the causes of the suboptimal immune responses.

Although there appears to be no simple intervention, there have been ways to mitigate the problem. Because trivalent OPV does not protect every infant, two changes to polio vaccine programmes have been made.[9] First, OPV was changed from a trivalent to a bivalent vaccine by eliminating type 2 from the vaccine. Second, at least one dose of injected polio vaccine is to be given during infancy. Interestingly, despite suboptimal responses to OPV, infants respond well to injected polio vaccine[1] and the bivalent vaccine appears to be more immunogenic than the trivalent vaccine that was used previously. Because serotype 2 virus has been eradicated, a vaccine for this type is no longer needed. These changes were important, not only to protect individual children, but also because they are crucial for polio's eradication.

One strategy being considered for rotavirus is a supplemental dose of vaccine at age 9 months.[10] In many places, the peak incidence of rotavirus diarrhoea is between 9 and 18 months, and this later dose could increase protection during this high-risk period. When first studied, a late dose was not considered because of concern over intussusception, but the current vaccines have a low intussusception risk, which is probably even lower in previously immunised children.

As with polio, there could be a role for an injectable rotavirus vaccine, which, either alone or in conjunction with oral vaccine, could improve protection.[11] An injectable vaccine was not originally developed because it was thought that an oral vaccine would better stimulate intestinal immunity. However, rotavirus diarrhoea is mainly a disease of young children, and since natural infections stimulate immunity, it is possible that only short-term protection is needed and could be accomplished with an injectable vaccine.

Finally, if new strategies are identified, they will still have to be practical to be included in routine immunisation programmes. A delayed dosing for rotavirus vaccine did seem to improve immune response, but this approach needs to be balanced against the potential of not immunising some infants who drop out early. Similarly, a 9-month oral rotavirus dose and an injectable rotavirus vaccine seem promising, but the logistical challenges and costs for these will need to be investigated.

David A Sack
Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA
dsack1@jhu.edu

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A new tuberculosis vaccine: breakthrough, challenges, and a call for collaboration

Tuberculosis is the deadliest infectious disease in human history, and remains the leading cause of death from a single infectious agent globally. WHO estimates that tuberculosis caused illness in 10 million people and claimed 1·6 million lives in 2017 alone.[1,2] Currently, tuberculosis is responsible for a quarter of annual deaths

due to antimicrobial resistance, and remains the primary cause of death among people with HIV.[1,3] Overcoming the disease's destructive potential will require a mix of incremental progress and giant leaps forward. The End TB Strategy, developed by WHO in 2014, set out ambitious goals and milestones to end the epidemic by reducing incidence by 80% and mortality by 90% by 2030, relative to 2015, in the context of the Sustainable Development Goals. Research and innovation comprise one of the three essential pillars for the attainment of these goals.[4] In particular, a new tuberculosis vaccine that is safe, affordable, and more effective than BCG in providing protection against all forms of tuberculosis in adolescents and adults is crucial for rapidly reducing the incidence of tuberculosis.[4,5]

Despite this need, the tuberculosis vaccine pipeline has remained quite stagnant during the past decades, mainly because of severe under-funding. Between 2011 and 2015, only 25% of the projected tuberculosis vaccine research and development investment needs were met.[6] Today, the BCG vaccine developed in 1921 remains the only WHO-prequalified vaccine against tuberculosis. However, although BCG remains effective in protecting infants and young children from severe forms of tuberculosis disease, it does not adequately protect adolescents and adults, who account for the majority of tuberculosis transmission. Several obstacles have hindered progress in tuberculosis vaccine research. These obstacles include the lack of market incentives to invest in a disease that disproportionately affects poor people in low-income and middle-income countries; the absence of reliable biomarkers that can be used as prospective signatures of tuberculosis risk or as correlates of protection;[7] and a lack of mechanisms to reduce the inherent uncertainties of vaccine development—it is unclear whether animal models predict protection in humans, and large sample sizes are needed to demonstrate vaccine efficacy during the later stages of tuberculosis vaccine development. Altogether, these factors are important disincentives for researchers and study sponsors.[8]

A phase 2b trial conducted in Kenya, South Africa, and Zambia,[9] and published in 2018, showed that M72/AS01$_E$, an experimental tuberculosis vaccine developed by GlaxoSmithKline and Aeras, was significantly protective against tuberculosis disease. Two doses of M72/AS01$_E$, administered 1 month apart to HIV-negative adults with evidence of latent *Mycobacterium tuberculosis* infection, provided 54% protection (90% CI 13·9–75·4; 95% CI 2·9–78·2; p=0·04) against pulmonary tuberculosis, over about 2 years of follow-up. The study, still blinded at an individual level, showed no concerning imbalance in the occurrence of serious adverse events, with more local and influenza-like general reactogenicity, including some grade 3 reactions, reported in the vaccinated group.[9] These findings constitute important progress and provide unprecedented opportunity to advance the field of tuberculosis vaccine development towards potential public health effects. Moreover, the study shows that a proof-of-concept human trial on the prevention of pulmonary tuberculosis in adults, the most relevant clinical outcome when considering public health need,[10] is possible.

Future research will need to consider additional questions to realise the full potential of this candidate vaccine. Final clinical study data analyses are expected in 2019, and immunological investigations are also awaited, which might allow for a better understanding of protective immune mechanisms against tuberculosis.[11] If positive results are confirmed, the vaccine should be rapidly progressed to a well designed phase 3 programme supported by a long-term vaccine-development strategy, possibly including post-licensure evaluations, with a clear vision of health-systems requirements for access and use, where needed.[10]

The M72/AS01$_E$ trial[9] included only people with evidence of tuberculosis infection at the time of the first vaccination, in countries with a high tuberculosis burden in Africa. Public health need warrants similar evaluation in people without previous exposure to tuberculosis and across various geographical settings. Re-evaluating this vaccine with regard to preventing relapse or re-infection in individuals previously treated for tuberculosis should be considered, with heightened pharmacovigilance in anticipation of stronger reactogenicity among these individuals.[12] The role of this candidate vaccine to protect children, older people, and those at increased risk of developing tuberculosis disease (such as people living with HIV, people with diabetes, household contacts of tuberculosis patients,[13] and people who inject drugs) should be considered, as should the duration of protection and requirement for booster doses. Different vaccination strategies

might need to be considered to address regional heterogeneities in the epidemiology and transmission of tuberculosis.[14] Although wide population coverage might be justified in settings with intense transmission, risk-targeted strategies might be more suited in other settings. Health-economic modelling and a comprehensive evaluation of the public value of the candidate vaccine should support and guide responsible investments towards vaccine availability.

In conclusion, a promising new vaccine against tuberculosis seems to be on the horizon. Transforming this research success into a tool for global health will require long-standing and continuous efforts from governments, funders, industries, civil society, advocacy groups, health-care practitioners, and international agencies. Early planning is required, and WHO has called for concerted efforts and a wide mobilisation of resources and know-hows. There is no better time to echo the need for solidarity than now, with bold commitments on tuberculosis research and development endorsed by all UN member states during the first UN high-level meeting on ending tuberculosis, and supported by partners in public health.[15] The imperative to achieve the Sustainable Development Goals and End TB targets demands that we use the existing political momentum to increase and sustain support for tuberculosis vaccine research. Ongoing research and evaluation of other tuberculosis vaccine candidates must also continue. We should collectively consider ways to shorten the time to availability of effective vaccines and to mobilise resources to ensure future equitable access and affordability.

*Johan Vekemans, Nebiat Gebreselassie, Matteo Zignol, Martin Friede, Tereza Kasaeva, Soumya Swaminathan
Immunization, Vaccines and Biologicals (JV, MF), and Global Tuberculosis Programme (NG, MZ, TK), World Health Organization, 1211 Geneva, Switzerland
vekemansj@who.int

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Drugs and vaccines in the 21st century for neglected diseases

Neglected diseases are a diverse group of infectious conditions prevalent in tropical and subtropical areas, and affect billions of people worldwide, disproportionately among the poorest populations and those living in remote, rural areas or conflict zones, almost exclusively in the developing world. Neglected diseases include malaria, tuberculosis, diarrhoeal diseases, and the 20 neglected tropical diseases defined by WHO. As major public health problems, these diseases are a focus of the WHO Sustainable Development Goals programme, which aims to end the epidemics of tuberculosis, malaria, and neglected tropical diseases by 2030. Other commitments—including the WHO Roadmap on neglected tropical diseases and the 2012 London Declaration on Neglected Tropical Diseases—have established action plans to control, eliminate, or eradicate ten diseases by 2020. A central focus of these agreements is the development of novel therapeutic agents. By incorporating cutting-edge science and technology, drug research and development for neglected diseases have progressed considerably.