based on mRNA expression signatures, which are now being evaluated for prediction of active tuberculosis.[12]

In conclusion, the second-generation IGRAs represent two promising new twigs on the IGRA branch, with a high sensitivity in a selected population in the UK. They merit further study in various settings to assess their diagnostic potential for latent, incipient, active tuberculosis, or all.

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Enhancing immune responses to oral vaccines: still an enigma

See **Articles** page 203

In *The Lancet Infectious Diseases*, James A Church and colleagues[1] report the results of a systematic review and meta-analysis of studies on attempts to enhance the immune responses to oral vaccines, especially infants given oral polio vaccine (OPV) and oral rotavirus vaccine. The suboptimal immune responses to these oral vaccines in Africa and Asia has long been recognised, and it would seem there should be a reasonable explanation and a simple intervention that could improve effectiveness. This review, however, concludes that there are no simple solutions that could be applied generally for oral vaccines.

OPV was highly successful in eliminating polio from North America and it was assumed that the vaccine would have a similar outcome in low-income countries. Unfortunately, this was not the case in India and other low-income countries.[2] More doses of vaccine were required to achieve similar response rates to those in North America, and cases of polio continued to occur even in areas of high OPV coverage.

Similarly, rotavirus vaccines, which were highly efficacious in North and South America,[3,4] showed lower efficacy in Africa[5] and Asia.[6] Now that the vaccines are used routinely, their effectiveness is confirmed, but at a lower rate in lower-income countries.[7] Clearly, even with the lower efficacy, these vaccines provide a major public health benefit because the disease burden is so high; however, if there was a way to improve immunogenicity, these vaccines would be even more powerful.

Many reasonable theories have been suggested as to why children in low-income countries have a weaker response to oral vaccines than do those in high-income countries.[8] The most common suggestions relate to interference by maternal antibody in serum or breast milk, intestinal parasitic infestations, micronutrient (especially zinc or vitamin A) or macronutrient malnutrition, concurrent enterovirus infection, and intestinal mucosal enteropathy. Considering the young age at immunisation, some of these explanations seem more likely than others. For example, parasitic infestations, micronutrient deficiencies, or even enteropathy would seem to be uncommon at this young age. Nevertheless, considering these potential mechanisms, controlled clinical trials have attempted to improve the immune responses to these vaccines. In short, Church and colleagues found that there was no general strategy that seems to substantially improve the serological responses to these oral vaccines. Of those tested, some would have been difficult to implement, such as avoiding breastfeeding for a few

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.

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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