observer-blind, randomised, placebo-controlled trial to evaluate the efficacy, immunogenicity, and safety of a *C difficile* vaccine candidate (containing toxoids A and B) in preventing symptomatic *C difficile* infection (primary outcome). Participants were eligible if they were aged 50 years or older and were at an increased risk of *C difficile* infection, which was defined as those who had at least two hospital stays (each ≥24 h in duration) and had received systemic antibiotics in the previous 12 months, or those who were anticipating being admitted to hospital for 72 h or more for elective surgery within 60 days of enrolment. Although the vaccine candidate elicited an immune response (a higher response against TcdA than against TcdB) up to day 60, clinical futility in the prevention of *C difficile* infection was observed. At the first planned interim analysis, 34 *C difficile* infections occurred over 11 697 person-years at risk in the *C difficile* vaccine candidate group (0·29 infections per 100 person-years [95% CI 0·20–0·41]) and 16 infections occurred over 5789 person-years at risk in the placebo group (0·28 infections per 100 person-years [0·16–0·45]), indicating a vaccine efficacy of –5·2% (95% CI –104·1 to 43·5). No safety concerns were reported.[8]

It is indeed disheartening to see these results. There are plausible explanations for the observed absence of vaccine efficacy. In the MODIFY trials,[5] actoxumab (anti-TcdA IgG) was not found to protect against recurrent *C difficile* infection, but bezlotoxumab (anti-TcdB IgG) was shown to be protective. In the study by de Bruyn and colleagues,[8] a higher anti-TcdA response than anti-TcdB response was observed.[8] Unsurprisingly, the overall incidence of *C difficile* infection was low. Although the study included patients with risk factors for infection, the cadence and timing of these risk factors might not put a person at high risk of *C difficile* infection. For instance, the risk of *C difficile* infection after receiving systemic antibiotics is highest within the first 3 months of exposure.[9] Including patients beyond 3 months of antibiotic exposure would draw the primary differences

in the primary outcome towards the null hypothesis in both groups.

Future studies of primary *C difficile* infection prevention should include patients at the highest risk of *C difficile* infection, including those who are aged 50 years and older, have received antibiotics within 3 months of enrolment, and have at least one comorbidity (such as chronic kidney disease or diabetes), to enable a bigger effect size of the primary outcome. Including patients who fulfil all of these risk criteria would enable us to see a meaningful difference from the placebo with a relatively smaller sample size compared with the study by de Bruyn and colleagues.[8]

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Group B streptococcus vaccines: one step further

In *The Lancet Infectious Diseases*, Judith Absalon and colleagues[1] report on a phase 1/2 clinical trial evaluating the safety, tolerability, and immunogenicity of a vaccine composed of capsular polysaccharide

conjugated to cross-reactive material 197 (CRM_{197}) and directed against six capsular polysaccharide serotypes of group B streptococcus (GBS). These serotypes (Ia, Ib, II, III, IV, and V) account for the vast majority of isolates

causing invasive GBS disease worldwide—in neonates as well as in adults.[2-4] The authors report that three different doses of this hexavalent vaccine formulated with or without aluminium phosphate as its adjuvant were safe and well tolerated in healthy, non-pregnant, adult volunteers. The vaccine elicited a robust immune response for at least 6 months.

It is a good point in time to report some success with a GBS vaccine. In the era of COVID-19 and the worldwide anticipation of a severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccine, it might appear as if vaccine development works as in the proverb that states that where there's a will, there's a way. For GBS vaccines, progress has been very difficult. In the 1980s, pioneers Carol Baker and Dennis Kasper started to investigate polysaccharide-based GBS vaccines. In 1988, they showed that maternal immunisation against GBS is feasible, but immunogenicity of GBS polysaccharide-based vaccines was weak.[5] In 1996, a phase 1 trial with conjugate vaccines prepared with GBS type-specific capsular polysaccharide coupled to protein antigens induced stronger immune responses than capsular polysaccharide alone.[6] Although more than 20 years have elapsed since then, unfortunately no GBS vaccine has been licensed. In the meantime, pneumococcal, meningococcal, and *Haemophilus influenzae* type b conjugate vaccines have all been licensed. Several phase 1 and 2 studies of GBS vaccines have been done, including that by Absalon and colleagues.[1] The results often are very encouraging—as in this study—but the next steps that are urgently needed, including studies in pregnant women, analysing the passive antibody transfer to the neonate, and subsequently assessing protection against disease, are often not taken.

There is an urgent need for a global strategy to protect the most vulnerable population—neonates and young infants up to age 3 months—against this sometimes devastating disease, which can cause neonatal GBS sepsis and meningitis, and which is an unresolved challenge, especially in low-income countries. GBS is estimated to cause more than 300 000 cases of neonatal disease annually, resulting in roughly 90 000 infant deaths worldwide.[7] GBS is also associated with maternal sepsis, stillbirths and preterm births, and severe neurological impairment among patients who survive neonatal meningitis. Intrapartum antibiotic prophylaxis has substantially

reduced the incidence of early onset GBS disease in high-income countries that have implemented this strategy; however, this strategy is not feasible in many low-income and middle-income countries. Moreover, intrapartum antibiotic prophylaxis will not protect against late-onset GBS disease, which in most cases is transmitted postnatally. By contrast, a vaccine given to pregnant women to stimulate passive transplacental transfer of protective antibodies has the potential to reduce maternal disease, adverse pregnancy outcomes, and newborn early onset and late-onset disease. Maternal IgG is actively transported across the placenta, providing passive immunity. Of course, the risks and benefits of maternal vaccination must always be carefully weighed and analysed, and protection of the mother and the fetus must be prioritised.

The next step would then be doing efficacy studies, which for a GBS vaccine candidate is a difficult task. It would require large numbers of immunised mothers because of the low incidence of neonatal GBS disease. It has therefore been proposed that alternative options to vaccine licensure should be explored. Recent studies suggest that maternal capsular antibody thresholds could be used as immunological correlates of protection. Thus, a regulatory approved correlate of protection and safety evaluation in mothers, fetuses, and infants are needed.[8,9] After the vaccine is licensed, phase 4 studies would then have to follow to evaluate vaccine effectiveness.

Beyond conjugate vaccines, which have some limitations, surface proteins, as candidate vaccines with or without being coupled to the capsular polysaccharide, might broaden protection against invasive GBS disease. However, the immunogenic potential of pilus island and other GBS surface proteins, which has been shown in animal-model studies, could not be confirmed by association analysis of maternal antibody concentration and invasive GBS disease in infants.[10] Therefore, the study by Absalon and colleagues is particularly important and encouraging. The hexavalent conjugate vaccine covers the majority of invasive serotypes worldwide. Serotype replacement should be kept in mind as a potential problem, but should not hamper further steps. In these days of the SARS-CoV-2 pandemic, when awareness of the paramount importance of vaccine development is as high as ever, the time has come to initiate the required studies designed to prove immunogenicity of
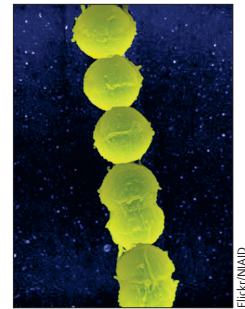
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a hexavalent vaccine in pregnant women, diaplacental transfer of antibodies, and protection of neonates from disease, disability, or death.

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Is it time to reconsider measles, mumps, and rubella immunisation strategies?

Since the late 1990s, measles has continued to be a public health problem, and so WHO launched a global plan for measles and congenital rubella elimination in 1997. Despite the relevant efforts, the goals of elimination have not yet been achieved, and the deadline to reach them has been postponed many times. Moreover, even in areas where high immunisation coverage has been registered, epidemics of measles have occurred in the past 10 years worldwide.[1–4] What can be done to eliminate this disease?

Increased immunisation coverage in children and susceptible individuals continues to be the most important way to reach the elimination objectives. However, it is now evident that vaccination uptake should be encouraged in any suitable way. For example, some countries have adopted effective mandatory vaccination, in order to increase coverage.[5]

In addition, it is also necessary to better understand potential problems of immunogenicity (primary vaccine failure) and the waning protection over time (secondary vaccine failure) of the measles-mumps-rubella (MMR) vaccine.

In *The Lancet Infectious Diseases*, Julie Schenk and colleagues[6] did an accurate meta-analysis, which is—to our knowledge—the first of its kind, on the overall data related to the immunogenicity and antibody persistence after immunisation with trivalent MMR vaccines. Their results show that antibody levels are high (>91%) soon after immunisation, but they decline over time. These data could be very useful for the future assessment of MMR immunisation strategies and their effectiveness. Thus, continuing to vaccinate is imperative, but we must keep in mind that primary and secondary vaccine failure can sometimes occur.

As reported by the authors, their results are also valuable to build more truthful mathematical models representing transmission of infectious diseases. These models will allow us to identify the most relevant susceptible groups in society and, consequently, the most suitable vaccination strategies to achieve the elimination of measles. However, it will also be crucial to recognise that the circulation of wild-type viruses decreases and natural boosters disappear when universal immunisation is implemented. The reduction of natural boosters could have a further relevant impact on the rate of waning of immunity. This issue in particular must be included in any future consideration of strategies for the prevention of measles.

The authors analysed humoral immunity only, which is a proxy in the estimation of protection, and could