in neighbouring endemic areas. However, substantial work remains to be done to harmonise and validate collected data. Currently, a major concern is the interpretation of molecular data because of the high diversity of the K13 gene: except for four mutations (C580Y, R539T, R543I, and Y493H), no clinical or in-vitro data have been associated with the other K13 mutant alleles.[1,3] We believe that the scientific community working on artemisinin resistance should now create a consortium around a K13 reference centre that could take over the management and data validation, the harmonisation of molecular biology techniques, the provision of control samples, and the organisation of a quality assurance system, to recommend the best therapeutic options—a prerequisite to move effectively toward malaria elimination.

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Rotavirus vaccines roll-out in resource-deprived regions

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Rotaviruses cause 30–50% of severe diarrhoea cases in children younger than 5 years, leading to about 450 000 deaths every year.[1] Infections during the first months of life are protective against symptomatic reinfections later on, setting the stage for vaccine development.[2,3] The existence of four major genotypes—G1[P8], G2[P4], G3[P8], and G4[P8]—created a great challenge because in-vitro studies suggested that antibodies to a specific type neutralised only that type, raising the question of whether it would be necessary for a vaccine to include all common genotypes.

During the 1990s the first licensed vaccine, Rotashield (Wyeth Laboratories, Collegeville, PA, USA), which contained an attenuated simian and three simian–human reassortant strains of the virus, showed that 70–90% of cases of severe rotavirus disease could potentially be prevented in lower-middle-income and high-income countries with vaccination.[4] However, intestinal intussusception was induced in about one in 11 000 children who received the vaccine, leading to its withdrawal and posing a large challenge for new candidate vaccines because future trials needed to include 60 000 children to reasonably assure safety.[5,6] Post-licensure studies of the second-generation vaccines Rotarix (GlaxoSmithKline, Brentford, UK), which contains a single human attenuated strain, and RotaTeq (Merck, Kenilworth, NJ, USA) based on five human-bovine reassortant strains, suggest an acceptable class effect risk for intestinal intussusception of somewhere between one in 20 000 and one in 100 000 individuals.[7] Importantly, both vaccines showed high efficacy (more than 80%) against severe rotavirus disease in prelicensure studies[5,6] and against several predominating genotypes. As trials were progressively done in various regions worldwide, it became clear that protective efficacy for both vaccines was lower in resource-deprived countries than in high-income countries[8] and that efficacy might not be the same among serotypes and genotypes, especially against G2[P4].[5,9]

First licensed in 2006, these vaccines have been progressively introduced worldwide and dozens of effectiveness trials, done mostly in high or middle-high income countries, have confirmed efficacy rates reported in prelicensure trials. A major unanswered question is how effective these vaccines will be in real-world scenarios in the poorest regions of the world (where diarrhoea mortality is at its highest) and in the presence of varied circulating types. Children might be infected in their first months of life in these regions (where a first infection is not as protective as in higher-income regions) such that children develop several severe episodes of rotavirus disease throughout their first years.[3,10] Vaccine effectiveness could be substantially lower in these regions, and, thus, meticulous prospective studies are essential for policy decisions and for the potential design and assessment of new vaccine strategies.

In *The Lancet Infectious Diseases*, Naor Bar-Zeev and colleagues[11] report results of the second effectiveness study to be done in Africa (Blantyre, Malawi). In the first study, Michelle Groome and colleagues[12] showed 57% (95% CI 40–68) effectiveness against rotavirus diarrhoea that required a minimum of overnight hospital admission in children in South Africa younger than 2 years who were vaccinated at 6 and 14 weeks of life. Bar-Zeev and colleagues[11] report 64% (24–83) effectiveness for reduction of emergency room visits (compared with rotavirus test-negative controls) for rotavirus in children younger than 5 years (94% of samples tested from children younger than 2 years) using an accelerated 6 and 10 week of age schedule with the monovalent human rotavirus vaccine. Early effect was documented with roughly 10% reductions every year in rotavirus detection rates in infants during their first and second years of age, and an overall rate reduction of near 15% after 2 years for all children younger than 5 years. Genotype G2[P4] was the most commonly detected (25% of samples tested), but the vaccine had a lower non-significant effectiveness point estimate of 53% (95% CI –28 to 83) for G2[P4] than it did for G1[P8] (82%, 42–95), strongly suggesting lower effectiveness against this genotype.

That data for vaccine effectiveness in Malawi are similar to, if not better than, those for other efficacy trials is good news and findings can probably be extrapolated to regions with similar socioeconomic conditions. Differential serotype and genotype effectiveness will have to be continuously monitored and the search for even better vaccines and strategies must continue. Although, the natural history of rotavirus infection and disease in low-resource regions[10] suggests that oral vaccines that mimic protection conferred by natural infections might have reached their maximum effectiveness, this figure is still substantial and vaccines could potentially prevent nearly 300 000 deaths of infants and children every year.

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Tuberculosis-associated immune reconstitution inflammatory syndrome: a manifestation of adaptive or innate immunity?

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In *The Lancet Infectious Diseases,* Shruthi Ravimohan and colleagues[1] investigate whether immunological profiles before and after antiretroviral therapy (ART) can distinguish patients co-infected with HIV and tuberculosis who develop tuberculosis-associated immune reconstitution inflammatory syndrome (IRIS) from those who do not develop this disorder and those who have early mortality. The investigators noted decreased pre-ART concentrations of several pro-inflammatory cytokines in patients with tuberculosis-associated IRIS (eg, interleukin [IL]-6 adjusted odds ratio [OR] per 1 $\log_{10}$ increase 0·40 [95% CI 0·18–0·89]), which resurged during the disease. After ART initiation, the most prominent changes in patients with tuberculosis-associated IRIS were reported for cytokines related to innate immunity (eg, IL-6: adjusted OR 1·7 [95% CI 1·2–2·5] and tumour necrosis factor [TNFα: 1·5 [1·0–2·2]), whereas recovery of the CD4 T-cell compartment was similar to that shown in control participants who survived without a diagnosis of tuberculosis-associated IRIS.

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These findings seem to challenge the fundamental role of T cells in patients with tuberculosis-associated IRIS. Findings from early key reports pointed towards an overproduction of inflammatory T-helper-1 cytokines, such as interferon-γ, as being the driving force behind tuberculosis-associated IRIS.[2] Lately, however, increasing evidence is emerging implicating the innate immune system in this syndrome.

Why is it that so many studies of tuberculosis-associated IRIS report different or even conflicting observations? In truth, tuberculosis-associated IRIS is a disease with many faces. Even when guidelines proposed by the International Network For The Study of HIV-Associated IRIS are used,[3] patients diagnosed with tuberculosis-associated IRIS still present with symptoms that widely vary in type, severity, and timing.[4] As such, the clinical picture of this disease might not be uniform across different studies, which could lead to observations becoming just as heterogeneous as the disease itself. For example, Ravimohan and colleagues now show the importance of the study of tuberculosis-associated IRIS during the actual IRIS event, when the inflammatory process is peaking. The increase in IL-6 concentrations between baseline and 4 weeks of ART in patients with tuberculosis-associated IRIS was much more pronounced