11 Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. *N Engl J Med* 2014; **371:** 2155–66.

12 Kalesan B, Pilgrim T, Heinimann K, et al. Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction. *Eur Heart J* 2012; **33:** 977–87.

Implementation of the malaria candidate vaccine RTS,S/AS01

Tony Karumba/Stringer

Published **Online** November 5, 2015 http://dx.doi.org/10.1016/S0140-6736(15)00807-7

See **Articles** page 367

As vaccine manufacturers tackle increasingly intractable pathogens, vaccines will be developed that show efficacy, but that are less efficacious than established vaccines. Consequently, regulatory and public health authorities will be faced with difficult decisions about whether such vaccines should be recommended for implementation and, if so, under what circumstances. The RTS,S/AS01 malaria candidate vaccine provides an important example of such a challenge.

After a long period of development,[1,2] a large phase 3 trial[3] of RTS,S/AS01 in children aged 5–17 months at first vaccination showed a vaccine efficacy of 28·3% (95% CI 23·3–32·9%) against clinical malaria in children who received three doses, and of 36·3% (31·8–40·5%) in those given a fourth dose, during 48 months of follow-up. The vaccine also provided significant protection against severe malaria and hospital admissions in the group of children who received a fourth dose.[3] An average of 1774 cases (95% CI 1387–2186) of clinical malaria were averted per 1000 children vaccinated in the four-dose group. An unexplained increase in incidence of meningitis was identified as a safety signal. Efficacy was lower in infants who received their first dose of vaccine aged 6–12 weeks than in children aged 5–17 months. Could this vaccine with restricted efficacy still have a useful role in malaria control? In *The Lancet,* Melissa Penny and colleagues[4] provide some important new information that suggests that it could.

Four modelling groups have worked together to estimate the potential impact of RTS,S/AS01 on malaria cases and deaths. Overall, the models gave similar results. On the basis of assumptions of 72% coverage with a four-dose schedule, a 15 year follow-up period (needed to account for any age shift in malaria incidence), and a vaccine price of US$2–10 per dose, the models predicted that in the areas where the parasite prevalence in children aged 2–10 years ($Pf PR_{2-10}$; a widely used measure of the intensity of malaria transmission) lies between 10% and 65%, RTS,S/AS01 would prevent 116 480 (range 31 450–160 410) cases of clinical malaria and 484 (190–860) deaths per 100 000 fully vaccinated children. At $5 a dose, the cost per disability-adjusted life-year (DALY) averted in areas with a $Pf PR_{2-10}$ of 10% or more would be less than $100, an amount comparable to that of other malaria control measures.[3] As recognised by the investigators, the study includes several unproven assumptions. The most important of these is the assumption that RTS,S/AS01 will have a significant impact on mortality, a key factor for decision makers and for calculation of DALYs; this assumption is not yet supported by empirical data. However, the quality of care provided to children in trials of RTS,S/AS01 was exemplary and, in the phase 3 trial, mortality was very low in all study groups.[5] Trials of seasonal malaria chemoprevention also failed to show a statistically significant impact on mortality,[6] but this intervention is having a major impact when deployed on a large scale. By contrast, trials of insecticide-treated nets did show an impact on mortality,[7] but these studies were done at the community level, with less intensive follow-up of individual participants. The assumption that RTS,S/AS01 will have a significant impact on mortality if deployed in high transmission areas is a reasonable one.

The European Medicines Agency reviewed the efficacy and safety of RTS,S/AS01 and, under article 58, gave a positive opinion on its use in both the younger and older age groups included in the phase 3 trial.[8] By contrast, WHO's Strategic Advisory Group of Experts on Immunization and Malaria Policy Advisory Committee only recommended use of the vaccine in children in the older age group.[9] They also recommended that several pilot studies should be undertaken before widespread deployment of the vaccine. The objective of these pilot projects would be to assess whether routine immunisation programmes can deliver the four-dose schedule effectively, whether the vaccine prevents deaths, and whether the safety signals detected in the phase 3 trial were just chance findings. To abandon RTS,S/AS01 at this point would be a major setback in the endeavour to develop a malaria vaccine, in addition to vaccines against other infections present mainly in low-income countries, and a discouragement to major pharmaceutical companies and public–private partnerships to engage in these activities. Therefore, these pilot programmes must move forward quickly, should be large enough to evaluate

an impact on mortality, and will need to be followed up as soon as possible with more widespread deployment of the vaccine in appropriate epidemiological situations if they show that the vaccine can be delivered, is effective, and is safe. RTS,S/AS01 should not be regarded as a replacement for other control measures, but rather as an additional method to be used in areas where malaria is proving difficult to control despite high levels of coverage with established control measures, and possibly in other specific circumstances, such as elimination programmes and control of malaria in areas where transmission is very seasonal.

Brian Greenwood, Ogobara K Doumbo
Faculty of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK (BG); and Malaria Research and Training Centre, University of Bamako, Bamako, Mali (OKD)
brian.greenwood@lshtm.ac.uk

BG declares that the London School of Hygiene & Tropical Medicine has received a grant from PATH to support work on the evaluation of RTS,S/AS01 candidate malaria vaccine in Ghana. OKD declares that the Malaria Research and Training Centre, Bamako, receives support from the National Institute for Allergy and Infectious Diseases, National Institutes of Health, for trials of malaria vaccine candidates in Mali.

1 Cohen J, Nuessenzweig V, Nussenzweig R, Vekemans J, Leach A. From the circumsporozoite protein to the RTS,S/AS candidate vaccine. *Hum Vaccin* 2010; **6:** 90–96.
2 Casares S, Brumeanu TD, Richie TL. The RTS,S malaria vaccine. *Vaccine* 2010; **28:** 4880–94.
3 RTS,S Clinical Trials Partnership. Efficacy and safety of the RTS,S/AS01 malaria vaccine with or without a booster dose in infants and children in Africa: final results of a phase 3, individually randomised, controlled trial. *Lancet* 2015; **386:** 31–45.
4 Penny MA, Veity R, Bever CA, et al. Public health impact and cost-effectiveness of the RTS,S/AS01 malaria vaccine candidate: a systematic comparison of predictions from four mathematical models. *Lancet* 2015; published online Nov 5. http://dx.doi.org/10.1016/S0140-6736(15)00725-4.
5 Hamel MJ, Oneko M, Williamson J, et al. A marked reduction in mortality among participants in a clinical trial that removed barriers to care and implemented national case management guidelines. 63rd Annual Meeting of the American Society of Tropical Medicine and Hygiene; New Orleans, LA; Nov 2–6, 2014. 631 (abstr).
6 Wilson AL, IPTc Taskforce. A systematic review and meta-analysis of the efficacy and safety of intermittent preventive treatment of malaria in children (IPTc). *PLoS One* 2011: **6:** e16976
7 Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. *Cochrane Database Syst Rev* 2004; **2:** CD000363
8 European Medicines Agency (EMA). First malaria vaccine receives positive scientific opinion from EMA. July 24, 2015. http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2015/07/news_detail_002376.jsp&mid=WC0b01ac058004d5c1 (Oct 30, 2015).
9 WHO. Pilot implementation of first malaria vaccine recommended by WHO advisory groups. Oct 23, 2015. http://www.who.int/mediacentre/news/releases/2015/sage/en/ (accessed Oct 30, 2015).

Refugees: towards better access to health-care services

See **Editorial** page 312

The migration crisis is one of the most pressing global challenges, as worldwide displacement is now at the highest level ever recorded. Latest global estimates by the UN Commissioner for Refugees (UNHCR) show that 59·5 million people are forcibly displaced as a result of persecution, conflict, generalised violence, or human rights violations.[1] The estimated refugee population reached an unprecedented 19·6 million individuals worldwide in 2015—half of them being children—and the number is steadily increasing, with Syria as the leading country of origin of refugees.[1,2] A lengthy drought preceded the Syrian crisis that led to a large movement of people into cities and contributed to instability; recent evidence suggests that risks of such droughts in the region are more than doubled as a result of climate change.[3]

More than a million refugees and migrants arrived in the European Union in 2015.[4] The growing influx of vulnerable populations poses many challenges to host countries, not least with regard to preparedness and resilience of health systems and access to health-care services. Furthermore, increasing numbers of refugees are likely in future as a result of a complex combination of driving forces, such as faltering and unequal economic growth, population increases, conflicts, and environmental change. The need to develop more effective approaches that respond to the health needs of displaced populations and address the root causes of displacement is therefore imperative.

A refugee is someone who "owing to a well-founded fear of being persecuted for reasons of race, religion, nationality, membership of a particular social group or political opinion, is outside the country of his nationality, and is unable to, or owing to such fear, is unwilling to avail himself of the protection of that country".[5] Refugees experience conditions of vulnerability, marginalisation, and poverty, in addition to the high stress of displacement, which seriously affect the health of these populations, including women, children, and older people.

Evidence suggests that refugees often have acute mental health problems and trauma symptoms, notably depression and post-traumatic stress disorder (PTSD), related to organised violence, torture, human