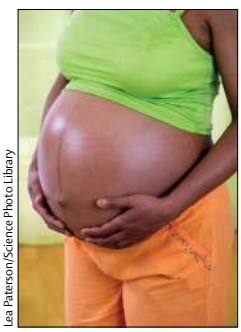
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against infectious diseases during the first months of life. This strategy could potentially provide additional benefit by preventing infectious causes of preterm births and stillbirths, and by protecting pregnant women.

The effectiveness of maternal immunisation has been shown by the Maternal and Neonatal Tetanus Elimination programme,[5] which has reduced the burden of neonatal tetanus in low-income and middle-income countries. Additionally, increasing evidence shows the safety and efficacy of vaccines against influenza and pertussis for the protection of pregnant women and their infants.[6,7] The success of these programmes has stimulated the development of new vaccines for maternal immunisation against group B streptococcus and respiratory syncytial virus, among others. A respiratory syncytial virus vaccine has been advanced to phase 3 clinical trials (ClinicalTrials.gov NCT02624947) in pregnant women and could represent the first vaccine explicitly approved for use in pregnant women to protect newborn babies. This novel development shows that maternal immunisation is gaining recognition as an important strategy that could combat neonatal morbidity and mortality.

However, further research is needed regarding the underlying mechanisms of maternal immunisation. The development of safe and efficacious vaccines for use during pregnancy requires an improved understanding of the unique immunobiology of pregnancy, and of the fetus and neonate, as described in the first paper of this Series by Arnaud Marchant and colleagues.[8] Subsequently, this knowledge could be used to optimise vaccine formulations, timing, and dosing of immunisation during pregnancy and for diverse populations.

Marchant and colleagues' paper[8] outlines the process by which a broad community of experts and stakeholders collaborated to identify the important knowledge gaps in immunobiology that are most relevant for the advancement of maternal immunisation. The subsequent papers identify knowledge gaps most important for pertussis and influenza,[9] and discuss group B streptococcus and respiratory syncytial virus vaccine development for maternal immunisation.[10] Together, these papers provide a timely landscape review that serves to inform the design and development of safe and effective vaccines for use in pregnancy to potentially reduce global infant mortality. Maternal immunisation vaccine development and implementation programmes could be further strengthened by the inclusion of future research that is geared towards closing such knowledge gaps.

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Zika enhancement: a reality check

The recent Zika virus epidemic in Brazil was associated with microcephaly and fetal malformation. Severe cases of CNS malformation in northeastern Brazil have raised questions about why infection in pregnant women was apparently more severe in this region. We wonder whether antibody-dependent enhancement (ADE) of infection might have contributed to the high incidence of congenital Zika syndrome.

Two populations of dengue virus antibodies, monotypic and multitypic, participate in dengue virus intrinsic and extrinsic ADE.[1] The polyclonal antibodies induced after a single dengue virus infection enhance a second dengue

virus infection and are associated with more than 90% of cases in southeast Asian children who are admitted to hospital.[2] Antibodies raised by two or more dengue virus infections, transferred via the placenta, enhance disease during an infant's first encounter with dengue virus, contributing 5% of total hospital admissions in southeast Asia.[3] By contrast, antibodies from a mother with a single dengue virus infection have not been shown to enhance disease in infants during a breakthrough dengue virus infection.[4] West Nile virus and yellow fever virus infections that are followed by dengue virus infections have also not resulted in enhanced disease.[2] However, in Thai children, antibodies induced by infection or vaccination with Japanese encephalitis virus did modify a subsequent dengue virus infection that ranged from asymptomatic to a mild illness.[5]

Zika was initially associated only with mild disease in Asia, where Zika virus and dengue virus co-circulated.[6] In 2007, on the Yap Islands in the western Pacific, there was an outbreak of a mild Zika virus febrile exanthem. Then on Tahiti, in 2013–14, Zika virus infection was implicated as a cause of Guillain-Barré Syndrome (GBS).[6] Although most of these cases had evidence of previous dengue virus infection, the dengue infection rate in GBS cases did not differ from controls without GBS who were matched for age and sex.[6] The interval between Zika virus infection and onset of GBS is remarkably short (a median of 6 days).

Why has Zika virus pathogenicity expanded, and is it possible that ADE by dengue virus antibodies is a contributing factor? Polyclonal and monoclonal dengue antibodies can neutralise and enhance Zika virus infection in vitro.[7,8] Monoclonal antibodies to the dengue virus fusion loop epitope can cause ADE of Zika virus in Fc-receptor bearing K-562 human myelogenous leukaemia cells and the U-937 human monocytic cell line.[7,8] Dengue virus monoclonal antibodies directed at a conformational quaternary epitope bounded by two dengue virus envelope protein monomers were able to neutralise Zika virus at a picomolar concentration.[8]

During natural infections, do dengue virus antibodies retard or enhance human Zika virus infections? Secondary-type dengue virus antibody responses correlate significantly with case incidence at the severe end of the dengue disease spectrum (relative risk 15·3, 95% CI 2·0–56·0, p<0·0001).[9] To establish causality, similar epidemiological evidence associating previous dengue infections with the occurrence of GBS that follows a Zika virus infection has been studied. The dengue antibody-mediated pathogenic process might be complicated, since there are four different dengue viruses, each of which might affect subsequent Zika virus infections differently. For example, infections with dengue virus 1 then dengue virus 2, or dengue virus 1 then dengue virus 3 resulted in a more severe clinical outcome than infections in other infection sequences.[10] The interval between dengue virus and Zika virus infections might have a bidirectional effect. For example, sequential dengue virus infections at short intervals might suppress the severity of Zika virus disease; however, as the interval widens (2–20 years), Zika clinical disease might become more severe.[11,12] Zika virus disease severity could be controlled by how many previous dengue virus infections have occurred. This hypothesis is based on the observation that a single previous dengue virus infection might enhance the next dengue virus infection, whereas two or more lifetime dengue virus infections protect against a subsequent infection.[2] Finally, there is concern that dengue virus vaccines might raise antibodies that enhance Zika virus infections.

In-vitro studies have already shown that dengue antibodies can facilitate Zika virus infection[8] and Zika virus antibodies can facilitate dengue infection.[13] It remains to be shown whether dengue antibodies can cause ADE of Zika virus infection and disease severity in vivo. Experimental studies will need to dissect the mechanisms underlying neuronal damage of the fetus in vivo and whether different anti-dengue antibodies will differentially affect disease severity.

In northeast Brazil, dengue seropositivity is high but is not homogenous in the population.[14] It is not known whether cases of congenital Zika syndrome occurred preferentially in women with previous dengue infection or whether cases cluster in regions with greater dengue seropositivity. Additionally, the situation might be much more complex because of the presence of yellow fever vaccination in the area. A spatial analysis study[15] showed that the risk of congenital Zika syndrome in northeast Brazil clustered in regions where yellow fever vaccination rates were the lowest. Epidemiological evidence correlating sequential dengue virus–Zika virus infections in individuals with different Zika virus clinical syndromes compared with matched controls should be sought expeditiously. Dengue virus ADE of Zika virus infections, if real, will have profound implications for the design, testing, and delivery of Zika virus and dengue virus vaccines.

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Improving communication about viral hepatitis in Africa

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Viral hepatitis is the seventh leading cause of death worldwide.[1] By 2030, WHO's elimination strategy[2] seeks to reduce mortality from chronic infection with hepatitis B and C viruses by 65%. To achieve this goal, it is essential to scale up antiviral treatment programmes in low-income and middle-income countries, where most deaths due to hepatitis occur. These programmes must identify, engage, and retain infected populations. Yet, only with a genuine understanding of viral hepatitis can people living with these infections fully commit to a treatment programme. WHO published new guidelines for testing for hepatitis B and C viruses in February, 2017;[3] however, the guidelines make little mention of communicating with these populations about chronic viral hepatitis. Our anthropological research investigating local understanding of hepatitis B in sub-Saharan Africa (The Gambia,[4] Côte d'Ivoire,[5,6] Burkina Faso,[7,8] Central African Republic,[7] and Madagascar[9]) highlighted communication challenges between health-care workers and local populations.

Knowledge of hepatitis is slim to non-existent in sub-Saharan African populations, although the prevalence of chronic hepatitis B virus infection exceeds 8% in that region.[4] Less than 1% of The Gambia's general population has heard of hepatitis B, although most are familiar with HIV/AIDS and malaria.[4] Our findings in Burkina Faso, Côte d'Ivoire, and Madagascar suggested a similar lack of recognition of hepatitis B in these countries.[5,6,8] Nevertheless, a small, knowledgeable lay public in these three countries use the illness category hepatitis, which they associate with wide-ranging causes and symptoms.[7]

That the African lay public is unfamiliar with hepatitis B might be related to the complex natural history of chronic infection.[10] Most infected people remain asymptomatic for decades, without recognising their chronic carriage unless they undergo blood donation screening or develop decompensated cirrhosis or hepatocellular carcinoma.[8,11]

Nevertheless, some sub-Saharan African populations appear to recognise and name symptoms associated with end-stage liver disease. In the Central African Republic, Bangui people use the terms *lé ti mafuta* (palm oil eyes) or *fièvre jaune* (yellow fever) to evoke jaundice, whereas Djula and Mooré speakers in Burkina Faso and Mandinka speakers in The Gambia use diagnostic categories that describe ascites symptoms: *founoubana* (swelling sickness), *kapouga* (mature millet panicle), and *konofa jankaroo* (full stomach sickness).[7,8] In Madagascar, some also speak of *angorigosy* or *tazo-vony* (big fever), suggesting acute hepatitis symptoms.

Although these local terms capture vividly the signs and symptoms of liver disease, they might have alternative