of A H7N9 viruses in China is probably the result of the primary host being terrestrial poultry; any shift towards waterfowl hosts would be a worrying change. Irrespective, the spread of the virus through provinces such as Guangxi, which have extensive water bodies, increases the chance of waterfowl exposure. But how much of the above is speculation and how much is likely to be true? Herein lies the biggest unknown in the A H7N9 story.

There is a very unsatisfactory understanding of the true prevalence of the virus in the various avian sectors in China. Although other effects could be at play, a change in the epidemiology of the virus in poultry—even at the provincial level—is the most parsimonious explanation for the features of the fifth epidemic and needs to be further explored. Pandemic warning fatigue, costs, and economic implications are real hurdles for implementing extensive and longitudinal surveillance in poultry and waterfowl, but its importance cannot be overstated.

The other unknown that could not be fully addressed by Wang and colleagues was the emergence of the highly pathogenic A H7N9 viruses in late 2016. Some H5 and H7 viruses can transition to the highly pathogenic form by accumulation of amino acids in the haemagglutinin protein. This transition is accompanied by a marked increase in viral virulence for chickens, whereas its effect on mammals is less clear. Before the emergence of the A H7N9 viruses, and driven largely by highly pathogenic A H5N1 experiences, a defendable position was that highly pathogenic viruses were likely to cause more human disease than their low pathogenic counterparts. The equivalent mortality rates—albeit with the many inaccuracies of measuring true mortality—of the highly pathogenic A H5N1 and low pathogenic A H7N9 viruses in human beings has forced us to question this assumption. The initial evidence suggests that human disease with low pathogenic and highly pathogenic forms of A H7N9 are not markedly different,[4] but the full effect is yet to be established. Wang and colleagues[3] are to be congratulated for their rapid data collation and analyses; continuing this work is of crucial importance for global public health.

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Stopping emerging influenza viruses at their origin


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During the past 100 years, two of four influenza virus pandemics originated in Asia. Additionally, many of the emerging influenza viruses that are deemed to have pandemic potential, including H5N1, H5N6, H6N1, H7N9, and H10N8, have crossed the species barrier from animals to human beings in Asia.[1–6] One reason for this might be the extensive interface between human beings, domestic poultry, and wild waterfowl, which is generated by the high human population density, the high density of domestic poultry, and ample opportunities for domestic birds to be exposed to wild waterfowl in some regions of Asia. This environment provides avian influenza viruses with the opportunity to evolve, reassort, and, ultimately, infect human beings. Although zoonotic infections might have high case-fatality rates, it is unlikely that a fully avian virus will cause the next pandemic. However, a higher number of zoonotic infections results in a higher chance of co-infection of human beings with avian and seasonal human viruses. Reassortants resulting from these co-infections might have substantial pandemic potential. In a study in *The Lancet Infectious Diseases,* Punnee Pitisuttithum and colleagues[7] describe a major step forward towards better pandemic preparedness in low-income and middle-income countries.

Efforts to create vaccines against avian influenza viruses of concern have mainly focused on H5 and H7 viruses. These vaccines are considered to be poorly

immunogenic in human beings, particularly if the traditional correlate of protection, the haemagglutination-inhibition titre, is used.[8] One way to overcome this poor immunogenicity is to use heterologous prime–boost vaccine regimens, in which a prime is given in the form of a live-attenuated influenza virus vaccine (LAIV) and a boost is given as an inactivated influenza virus vaccine (IIV). In a landmark paper in 2014,[9] the immune response to H5 haemagglutinin was shown to be boosted when an IIV is given after LAIV even in the absence of a strong primary response to the LAIV component. The immunity induced by the heterologous prime–boost regimen proved to be very robust and broad, spanning several clades of H5N1 viruses, and clearly outperforming the standard vaccine regimen of giving IIV twice in a short interval. These findings have sparked hope that a heterologous prime–boost vaccination regimen could become an effective tool to protect from emerging influenza viruses.[9]

Major efforts are under way to establish capacity to produce influenza virus vaccine in low-income and middle-income countries.[10] Such capacity would enable the local production of vaccines in response to a novel influenza pandemic or might even help to prevent pandemics by containing local outbreaks. Punnee Pitisuttithum and colleagues[7] report the results of a clinical trial that tested an H5 LAIV–IIV vaccination regimen in Thailand. This trial was made possible by a collaboration between Mahidol University, which did the trial, the Governmental Pharmaceutical Organization of Thailand, which locally produced the LAIV, the Institute of Experimental Medicine in St Petersburg, Russia, which provided the LAIV seed virus,[11] WHO, and several other partners including the US Biomedical Advanced Research and Development Authority, which provided funding through WHO. Although the LAIV donor strain and the H5 haemagglutinin of the vaccine were different from the ones used in the 2014 US study,[7,9] the results and conclusions are the same: vaccination with an H5 LAIV followed by an H5 IIV induces robust and broad antibody responses against H5N1 viruses.

The outcome of this study proves that it is feasible to transfer this highly valuable vaccine concept to low-income and middle-income country settings. The study also raises several questions: how will this vaccine strategy be tested in phase 2 and 3 clinical trials? The LAIV was administered to vaccinees in an isolation unit to prevent reassortment of the LAIV strain with circulating human influenza viruses. A reassortment event could lead to a new virus perfectly adapted to human beings, but carrying an H5 haemagglutinin to which human beings are naive. Will all LAIV vaccinations have to be done in isolation units in future trials? Is that feasible? And what is the risk of reassortment? Are there technologies that could reduce the risk involved with this approach? How will the vaccine be used in the field once approved? Would it make sense, and would it be ethical, to prime, or even fully vaccinate, local health-care personnel, public safety personnel, and essential community personnel in anticipation of an H5 pandemic? Could priming (or even full vaccination) of the local at-risk population, including individuals in close contact with poultry, help to reduce the risk of a novel pandemic? Although there are many open questions, it is clear that the LAIV–IIV prime–boost approach could become a powerful tool to enhance global pandemic preparedness against H5N1 and other influenza virus strains of concern.

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My research group is working on the design of influenza virus vaccines and my institution has patent applications on influenza virus vaccines pending.

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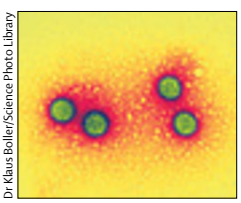
Parenteral protein-based rotavirus vaccine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Vaccination is the best method for the prevention of the severe diarrhoeal disease and estimated 215 000 deaths that occur annually due to rotavirus infection.[1] The first rotavirus vaccine, Rotashield, reached the US market in 1998 but was withdrawn after less than a year following concerns about its association with intussusception.[2] It took nearly another decade to develop two second-generation vaccines, Rotarix and RotaTeq, both of which are highly efficacious and have a lower risk of intussusception than their predecessor.[3,4]

The Rotarix and RotaTeq vaccines are currently used in national immunisation programmes of over 80 countries and subnationally or in the private sector of many others. Their use has led to impressive reductions in incidence of severe rotavirus diarrhoea by more than 80% in high-income and 50% in low-income settings.[5] Increasingly, evidence shows reductions in diarrhoea-associated mortality of 31% in infants younger than 1 year and 42% in children younger than 5 years in countries with low child mortality.[6] Other vaccines have been or will soon be developed, including the Lanzhou Lamb vaccine (China), Rotavin-MI (Vietnam), Rotavac (India), UK bovine strain-based reassortant vaccine (USA, India, and Brazil), and neonatal strain RV3BB (Australia). Clinical trials of these products in India, Ghana, and Niger suggest similar efficacy to Rotarix and RotaTeq in low-income settings.[7–9] All these vaccines are live human-attenuated or animal–human reassortants administered orally. Like other live oral vaccines such as oral polio, cholera, and typhoid, they are less immunogenic and efficacious in children in low-income settings, probably because of a combination of factors that underpins the infant's immune response, including maternal antibodies, chronic enteropathy, the microbiota, and interference from other infections. Additionally, a low-level risk for intussusception (in the range of one to seven cases per 100 000 vaccinated infants) has been observed for Rotarix and RotaTeq;[10] this finding might be due to a class effect of replicating rotavirus vaccines.

In this context, Michelle Groome and colleagues[11] report the first phase 1/2 study of a novel parenteral rotavirus vaccine for use in infants. The vaccine includes a truncated VP8 subunit protein of the human Wa strain (VP7 serotype 1 and VP4 serotype 8) and a tetanus toxoid P2 protein. Infants were randomly assigned to receive 10, 30, or 60 µg of vaccine with aluminium hydroxide or a saline placebo, coadministered with routine vaccines at ages 6, 10, and 14 weeks. Frequency and severity of adverse events were similar between groups. Adjusted and unadjusted IgG seroresponses against VP8 strains were 98–100%; unadjusted IgA seroresponses were in the range of 58–81% against the P8 protein, but only 9–27% when whole lysate was used. Adjusted neutralising antibody responses were over 80% for P8 strains, 30–50% for P4 strains and 17–23% for P6 strains.

Using similar methodology to that used to assess polio vaccines,[12] infants received the human attenuated Rotarix vaccine after the last parenteral vaccine dose, and vaccine virus excretion at day 5, 7, and 9 after the first dose was measured by stool ELISA.[11] Encouragingly, vaccine shedding (any positive sample) was 57% (95% CI 23–76%) lower in vaccinated children (30 µg and 60 µg dose groups combined) than in the children who received placebo. Taking these results together, the authors conclude that the vaccine is immunogenic, and that reduced Rotarix vaccine virus shedding suggests intestinal immunity, which might be a proxy for vaccine efficacy. The authors also acknowledge the absence of significant heterotypic immunity, indicating that studies with vaccines with different P serotypes are needed.

The study is the first phase 2 human trial of an inactivated rotavirus vaccine, and shows the potential of such a strategy, as well as the challenges it faces. First, a non-replicating vaccine approach could possibly