Expert Review of Vaccines

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Severe acute respiratory syndrome (SARS) may be controlled in future outbreaks thanks to efforts of a research group from the Netherlands, China, Germany and Singapore. Their work has been published in the July issue of the journal *Public Library of Science Medicine*.

The 2003 SARS epidemic claimed more than 700 lives in Asia, Europe and North America. Since then, SARS has been under control thanks to successful patient quarantine, however, isolated cases in Asia, which are associated with live animal trade emerge occasionally. Neutralizing antibodies play a crucial role in preventing SARS coronavirus (SARS-CoV) spread and symptom development. Approaches toward SARS prophylaxis include vaccination using inactivated SARS-CoV, as well as passive immunization using anti-SARS-CoV antibodies.

Jan ter Meulen and colleagues have combined two human monoclonal antibodies (mAbs) against the infective agent, SARS-CoV, in this passive immune prophylaxis. The first mAb, CR3014, neutralizes SARS-CoV and effectively prevents the disease in infected ferrets. This mAb binds to amino acids 318–510 of the glycoprotein spike (GPS) of SARS-CoV. However, a single mutation in this region of the GPS resulted in failure of CR3014 to neutralize SARS-CoV, as well as an escape virus variant with revived infective ability.

Therefore, the researchers screened an antibody library to find the second mAb, CR3022, which binds to the same region of GPS as CR3014 and inhibits the mutant SARS-CoV effectively. No escape variants could be generated further from this mutant SARS-CoV. Furthermore, CR3022 does not compete with CR3014 in binding to GPS.

The combination of two noncompeting human mAbs inactivates SARS-CoV successfully and prevents its immune escape by mutation. Furthermore, synergy between CR3014 and CR3022 may allow a lower total antibody dose while remaining protective against SARS-CoV infection.

Passive immunization has proven successful in controlling hepatitis A outbreaks and varicella-zoster virus infection. Scientists hope to see this prophylaxis work for SARS as well.

New routine immunization with pneumococcal vaccine in the UK

In July of this year, the UK's Chief Medical Office, Sir Liam Donaldson, announced a new childhood vaccination program, which includes the pneumococcal vaccine, to start on the 4th of September this year.

"Every child starting their routine immunizations at 2 months of age will be offered the (pneumococcal) vaccine. We will also run a catch-up campaign, which will mean that every child aged up to 2 years of age will also be offered the vaccination from September until early next year," he said.

Currently, routine vaccines for children in the UK include: diphtheria/tetanus/acellular pertusis (DTaP), inactivated poliovirus (IPV), *Haemophilus influenzae* type b (Hib), meningitis C (MenC) and measles/mumps/rubella (MMR) vaccines. The new routine immunization is:

- At 2 months of age: DTaP/IPV/Hib and the pneumococcal vaccine (DTaP/IPV/Hib is given as a single injection);
- At 3 months of age: DTaP/IPV/Hib and MenC;
- At 4 months of age: DTaP/IPV/Hib, MenC and the pneumococcal vaccine;
- At 12 months of age: Hib/MenC (single injection);
- At 13 months of age: MMR and the pneumococcal vaccine.

More information for parents and healthcare staff can be found on the website (www.immunisation.nhs.uk).

Besides being a common cause of pediatric otitis media, pneumococcal infection can lead to severe diseases, including meningitis and pneumonia. Vaccination will save lives, prevent disease and lessen the burden on medical care.

India develops successful avian influenza vaccine

The Indian Council of Agricultural Research (ICAR) announced its new successful avian6 influenza vaccine development in July of this year at the 77th Annual General Meeting of the ICAR Society (New Delhi, India). The vaccine aims to protect poultry from avian influenza.

This effort should allow India to produce poultry influenza vaccines domestically and vaccine import may soon be unnecessary. The Indian poultry industry was hit by the avian influenza outbreak in February this year, resulting in the culling of hundreds of thousands of birds. However, no cases of avian influenza have been reported in humans.

ICAR is India's leading agricultural research organization and its High Security Animal Disease Laboratory in Bhopal is the only place in India to carry out experiments with the H5N1 avian influenza virus. "Since the disease has got recurring possibility, further research

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would focus on developing another type of vaccine," said Mangala Rai, Director General of ICAR.

Novel adjuvant boosts immune responses to HPV vaccine

GlaxoSmithKline (GSK)'s vaccine against human papillomavirus (HPV), Cervarix™, might provide competition for its rival, Gardasil™ (Merck & Co.), thanks to a novel adjuvant system, it was revealed in the July issue of *Vaccine*.

Aluminum salt is normally added to human vaccine formulations as an adjuvant to enhance the immune response. Sandra Giannini and colleagues at GSK (Belgium) and MedImmune Inc. (MD, USA) have found a new adjuvant system, AS04, which boosts antibody production, as well as memory B-cell immunity in mice, monkeys and humans in response to Cervarix, compared with aluminum salt adjuvant.

AS04 contains 3-*O*-desacyl-4'-monophosphoryl lipid (MPL)A absorbed onto aluminum salt. The research team demonstrated that MPL can activate the innate immune response as assessed by cytokine production. Total anti-HPV antibody production was enhanced up to eight-times compared with aluminum salt only and the effect persisted for at least 3.5 years. Furthermore, the group also showed a fivefold increase in the HPV-specific memory B-cell response that is responsible for fast and effective antibody production upon contact with HPV.

Cervarix's competitor Gardasil (Merck) was approved by the US FDA in May of this year and is available commercially. GSK has tackled the competition by confirming the advantage of its AS04 adjuvant system in inducing long-lasting and high-quality immune responses against HPV, the most common cause of cervical cancer. Cervarix protects against HPV types 16 and 18, which together are responsible for approximately 70% of cervical cancer cases. The vaccine is under FDA consideration for approval. A Phase III clinical trial is underway, involving 30,000 women worldwide.

A step closer to mass production of influenza vaccine

Last month, Michigan State University (MSU) (MI, USA) revealed its new cell culture-based technology that could enable faster and cheaper influenza vaccine production.

Currently, avian influenza vaccines are made from viruses grown in chicken embryos. Every 11-day-old fertilized egg can only provide enough viruses for one or two vaccine doses. Each egg can only be used to grow one virus strain, while an influenza vaccine dose typically contains three different virus strains. Although purified viruses are included in vaccine formulations, a person with egg allergy should not receive vaccines made from chicken embryos.

While researching Marek's disease (a common disease that causes huge losses in the poultry industry), Paul Coussens, a MSU professor, and colleagues have incidentally found a cell line that could harbor several influenza viruses, including avian, swine, equine and human. The new cell line and methodology have been adopted by HepaLife Technologies Inc. (Canada), which plans to produce a cell culture-based influenza vaccine 'as quickly as possible'. "There's no time to waste. Sooner or later, the avian flu virus will be in North America. It's not if, it's when," said Harmel Rayat, President of HepaLife.

Growing viruses in cell culture can speed up vaccine production dramatically, as well as lower the cost. "We'll also be able to produce much more vaccine in a smaller space, and the virus that is grown is more pure," added Coussens. Cell culture has been used widely to produce many other vaccines, such as for hepatitis A virus and rabies.

Review on meningitis C vaccine

In the July issue of the *Cochrane Database Systematic Reviews*, Lucieni Conterno and colleagues have concluded that MenC may help to protect infants and small children and reduce the number of meningococcal meningitis cases in the USA.

This polysaccharide-conjugated vaccine against meningococcal serogroup C has been used widely in the UK, Canada and Spain for vaccination of children and susceptible populations. The vaccine, however, has not been approved by the FDA.

Meningococcal disease, caused by *Neiserria meningitidis*, is the leading cause of bacterial meningitis and sepsis in the USA with approximately 3000 cases per year. The mortality rate is 13% and is higher in infants than in teenagers and adults, owing to the immature immune system of infants.

The FDA-approved vaccine for meningitis in the USA is MCV-4 (Menactra™), which is also a polysaccharide-conjugated vaccine containing four types of meningitis, including serogroup C. This vaccine is administered to children aged 11–12 years or older, but unfortunately does not work well in infants and small children.

The authors have analyzed 17 randomized clinical studies and their review strongly suggests that MenC is safe and clinically effective in all age groups. Therefore, MenC could be more advantageous than MCV4 in protecting US infants and toddlers from meningococcal infections.

"This review can improve the confidence of using MenC vaccine, based on good evidence about immunogenicity and indirect evidence of clinical efficacy," said Conterno.

"There is, however, no FDA-approved conjugated vaccine in the USA that contains antigen against serogroup C alone," added Julia McMillan, a member of the American Academy of Pediatrics. This is clearly a barrier between available vaccines and the potential beneficial.