Selection of Challenge Agent is Key to Vaccine Development

Influenza viruses are commonly used in human challenge studies. Both the viruses and the disease they cause are well understood, and the induced illness is short-lasting. There are established cGMP manufacturing processes for both H1N1 and H3N2 strains of influenza A, and such agents may be used to simulate high-incidence community-acquired respiratory diseases. As subjects are infected in a controlled manner, the risk of serious adverse events is substantially lower than with community-acquired infections.

These two strains have been responsible for multiple pandemics in the past 100 years or so, having both emerged as a known threat in the late 19th century. Whenever a new serotype spreads in the population for the first time, the fatality rate is much higher than in subsequent incidents as the virus attenuates over time, and the population generates antibodies conferring immunity to subsequent infection. The 1918 H1N1 pandemic, for example, had a fatality rate of 2%, in contrast to just 0.03% in the 2009 H1N1 pandemic.

The reduced fatality rate, allied to the overall clinical characteristics of these two strains, make them the ideal choice for challenge trials, whether influenza-specific, or more general upper respiratory tract infection studies. Both viruses have drifted over time to become less pathogenic, and can be grown in eggs or cell lines. Controlled inoculation will lead to an 80–90% infection rate; whereas the infection rate within the community for a normal seasonal epidemic is typically 5–10%.

The two strains produce broadly similar signs and symptoms. These include an elevated temperature of 39–40°C, allied to headache, lethargy, sore throat and aching limbs. Further symptoms may develop, including a runny nose, cough, even nosebleeds and bloodshot eyes in extreme cases. Unusually, diarrhoea and vomiting can occur, although this is more common with influenza B strains. Up to half of all influenza infections remain asymptomatic.

Pandemic-causing strains may involve changes in antigenicity and other expressed proteins, and are more associated with cytokine cascade and extreme illness, even mortality. Post-infection problems, such as pulmonary haemorrhaging, are more likely in such instances. However, strains selected for human challenge trials are unlikely to cause either extreme or dangerous symptoms. They have been circulating for sufficiently long that those parts of their genome that cause cytokine cascades have mutated and been truncated.

H1N1 or H3N2?

The mean ages of infection are almost a decade older with H1N1, and it generally causes a less severe infection than seasonal H3N2. The latter strains typically produce leucopenia, a higher fever, and raised levels of C-reactive protein and other inflammatory biomarkers. The higher likelihood of hospitalisation in H3N2-prevalent years is a problem when allied to the younger average age of H3N2 infection, as it is precisely these younger people, with stronger immune systems, who are most likely to be adversely affected during an influenza pandemic.

H3N2 causes more hospitalisations, and a H3N2-prevalent flu season has a significantly higher death rate than one where the predominant strain is H1N1.

This might imply that choosing H1N1 for a challenge trial is preferable, however this is not necessarily the case. It is easier to detect and measure changes from baseline when symptoms are more severe, and thus, using H3N2 may make it easier to estimate the treatment's effectiveness.

Another difference is the decreasing ability of circulating H3 strains to agglutinate. In contrast, H1 strains will still agglutinate in vitro. Vaccine failure is more common with H3, and thus, challenge trials with H3N2 may give a better insight into how virus drift and shift may operate. But the overall higher stability of the H1N1 antigenic structure means it is likely to retain its relevance as a challenge agent, despite its downsides.

Why Run a Challenge Study?

It is becoming increasingly difficult to gain FDA approval for a disease-preventing vaccine or an anti-infective drug purely on the basis of biomarker studies. Proof of real-world efficacy (or 'effectiveness') is required. While this can be achieved in studies in the community, in practice, such trials are extremely costly to run, as the low rates of infection mean the necessary patient pool is enormous. A challenge trial's higher infection rate reduces the number of subjects required.

Even if the levels of a biomarker, such as viral shedding, are greatly changed, a drug will be of little therapeutic value if it has only a minimal impact on the course of the disease. A challenge trial will give an indication of how effectively the vaccine is preventing infection, or the drug is improving the symptoms of the disease.

The most common circulating H3N2 serotype in Europe during 2014–2015 was the A/Switzerland/2013 H3N2. Having access to this strain for challenge trials would allow real-world-applicable results on the effectiveness of a vaccine or drug to be assessed and thus be advantageous to flu research, which is why a related strain is currently finishing its development and validation at SGS.

Adrian Wildfare

Adrian has 30 years' experience in communicable diseases.
He obtained his Fellowship in Medical Microbiology in 1990 and a Masters in Parasitology in 1998. He is the author / co-author of numerous papers with many of the UK's leading infectious disease experts and KoLs in tuberculosis, HIV, and influenza.
He trained at the Wolfson Institute and LSHTM before moving on to lead teams within various institutions."

Email: adrian.wildfire@sgs.com