A BRIEF HISTORY OF THE HUMAN VIRAL CHALLENGE (HVC) MODEL.

AN EXAMPLE OF THE CONTROLLED HUMAN INFECTION MODEL (CHIM)

This text is adapted from Lambkin-Williams et al. 2018, the original manuscript is open source and available here along with the citation details.

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Since Sir Edward Jenner performed the first documented HVC study with smallpox on the 14th of May 1796 the usefulness of such studies has been apparent. More than a century later, Sir Christopher Andrews returned from the US in 1931 he had observed the use of chimpanzees in the study of influenza. The funding for similar work in the UK was insufficient, and therefore Sir Christopher enrolled students from St Bartholomew's Hospital in London. He explained the next best thing would be a "Bart's" student as "they were cheaper than chimpanzees". Over 100 students immediately enrolled, but continued their studies and were not isolated in the same way the chimpanzees had been in the USA. Unfortunately, the investigators believed that the symptoms observed may not have been due to the challenge virus, but other respiratory infections acquired in the community, thus confounding the studies. A year later, the UK's Medical Research Council (MRC) terminated the work.

After the conclusion of World War II, the withdrawal of the US troops from the UK left the American Red Cross 'Harvard Hospital' Field Unit on Salisbury plain. The hospital became the Common Cold Unit (CCU) led by Dr David Tyrell, from 1946, volunteers were inoculated by instilling small quantities of the virus into their noses. The CCU housed healthy volunteers in relative isolation from other people, thereby reducing the risk of contact with community-acquired sources of infection or from them passing on the virus to members of the public. The unit was eventually closed in 1989; during four decades of research, it attracted over 20,000 volunteers. Its research contributed to a better understanding of respiratory viruses, viral lifecycle, pathogenesis, possible vaccines as well as the first licensed anti-influenza compound amantadine.

The use of healthy volunteers in the HVC model provided, and still offers, a unique opportunity to describe the viral lifecycle. Investigators know with certainty the time of infection, nasal virus shedding can be measured, symptoms recorded prospectively, and participants are selected with low pre-existing immunity to the challenge virus to ensure a statistically significant infection rate with a small number of volunteers. Thus, such studies can maximise the safety and efficacy data obtained while minimising the risk to study volunteers and limited research funding.

Although serum IgG, for influenza virus, was traditionally measured via the HAI assay, as the entry criteria for volunteers into studies, micro neutralisation assays are used for RSV and HRV. Other work does suggest screening for antibodies to the NA influenza surface protein should be considered or T-cell responses to internal proteins.

After the closure of the CCU experimental infection studies continued in the USA using small motels and hotels were replacing the huts on Salisbury Plain. These studies contributed to the significant development of the new NA inhibitors during the 1990s, including the inhaled drug zanamivir and the orally available drug oseltamivir.

Studies however also continued in the UK, specifically the University of Southampton who performed important work in atopic volunteers, demonstrating they had more severe colds when experimentally challenged with rhinovirus, than non-atopic controls.

The experimental A/Texas H1N1 influenza virus that was used successfully during the 1990s was implicated in the development of myocarditis in an experimentally infected subject, although a causal link was never demonstrated. However, this incident halted work in the USA for a substantial period. This work has now resumed at the NIH and other facilities.

Most, if not all, challenge viruses are manufactured according to the principles of Good Manufacturing Practice (GMP). Although controlled nasal inoculation differs from naturally occurring infection – in which exposure to variable quantities of the virus may occur at various mucosal sites – the developed HVC model used in challenge studies mimics natural disease as far as possible.

Several groups now conduct the HVC model, some have more experience than others, but the increasing acceptance of the model in the drug development pathway is improving the decision-making process as a new investigational product, whether it be an antiviral, vaccine, monoclonal antibody or immunomodulator moves along the development process.

DECLARATION;

The author of this article Dr Rob Lambkin-Williams has previously worked with multiple groups; this information is in the public domain. He previously held multiple roles at the CRO hVIVO Services Ltd.