A universal influenza vaccine – are we almost there?

Seasonal influenza has a significant health care and economic impact and pandemic influenza is believed to have the potential to result in a global catastrophe. Regardless of developments with antivirals, vaccination remains the most effective option for limiting the impact of both seasonal and pandemic influenza.

Current inactivated virus vaccines, while useful against seasonal influenza, have serious deficiencies. They induce immunity that is largely dependent on circulating antibody directed to the exposed highly variable head of the major surface protein the haemagglutinin (HA) and, to a lesser extent a second surface protein the neuraminidase (NA). Ongoing antigenic changes in these molecules (‘antigenic drift’) require vaccine reformulation and administration on essentially an annual basis with the potential for vaccine mismatch. These vaccines have reduced effectiveness in older adults, a major risk group, possibly due to immunosenescence. Vaccine production has a lead time of 4–6 months and global production capacity is limited, which restricts the ability to respond to antigenic drift changes and to the emergence of a pandemic.

Living vaccines, adjuvants such as the squalene-based oil in water formulations MF59 and AS03, and new delivery systems including intradermal injectors, all of which are currently licensed, broaden and strengthen the immune response and may reduce the effect of antigenic drift, and of immunosenescence. In addition, new vaccine production approaches, which do not rely on embryonated chicken eggs, the vaccine substrate used for over 60 years, may help to reduce response times and global production capacity is limited, which restricts the ability to respond to antigenic drift changes and to the emergence of a pandemic.

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target that has been the subject of extensive study is the highly conserved 24 amino acid ectodomain (M2e) of the third influenza A virus, which is used as a vaccine candidate.

While earlier monoclonal antibody studies indicated that there are neutralising epitopes shared widely by influenza A viruses, only recently have these emerged as serious vaccine candidates.

Antibodies to epitopes within the stem of the HA interfered with the critical membrane fusion process that occurs during infection. The 16 influenza A subtypes fall into two phylogenetically distinct groups and monoclonal antibodies raised in one of the studies inhibit only Group 1 viruses, which contains 10 of the subtypes, including H1, H2 and H5, but not the H3 subtype that is frequently responsible for epidemic mortality. Another study involved polyclonal antibody raised to HA molecules engineered to lack the highly immunogenic globular head and the results of the limited cross-protection studies suggested a similar restriction to Group 1 viruses.

Differences between the HA stem region of Group 1 and Group 2 viruses include a potential glycosylation site that may mask the relevant epitope and it has been suggested that this may explain the reason that antibodies are HA group-specific. Nevertheless, it has recently been reported that antibodies raised to an H3 (Group 2) stem peptide also demonstrated some protection against H1 (Group 1) viruses in mice.

However, as yet it seems that no target has been identified which could be claimed unequivocally to both cover all subtypes and provide solid protection against infection. For those candidate vaccines that do go forward in clinical trial there will be substantial hurdles. One will be how to ethically demonstrate that a universal vaccine may be feasible but much remains to be done.

The most practical prospect in the immediate future may be to develop improved more broadly protective vaccines by combining proposed universal targets with strain-specific antigens and improved methods of delivery.

### References


### Biography

A virologist with over 40 years’ experience working with influenza, Alan’s career includes responsibility for developing influenza vaccine production processes and his role as Deputy Director and operational head of the WHO Collaborating Centre for Reference and Research on influenza, Melbourne, from its designation in 1992 until his retirement in September 2005. Since retirement he has maintained an active role as a consultant, to the government and WHO, as Chairman of the Australian Influenza Specialist Group (ISG) and as Editor in Chief of a new international journal Influenza and Other Respiratory Viruses. Alan was awarded an AOM and an Honorary Doctorate of Medicine for his public health contributions on influenza.