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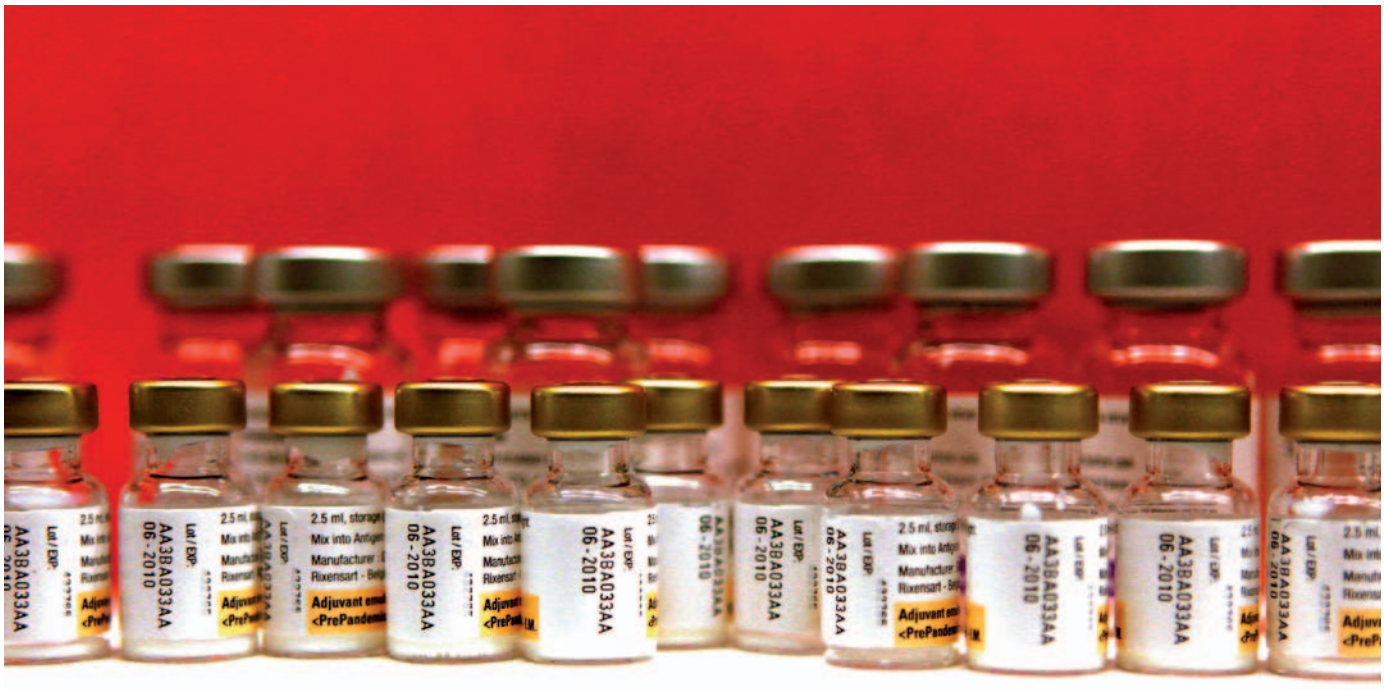

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Vaccinate for the next H2N2 pandemic now

An old influenza strain still circulating in birds and swine could easily jump back to humans now that immunity to it has dropped, warn **Gary J. Nabel** and his colleagues.

The emergence of a new strain of H1N1 influenza virus in 2009 took the world by surprise. The public-health community had assumed that a pandemic strain would arise from a major genetic reshuffling if RNA from a seasonal strain recombined with RNA from a virus that had never circulated in humans before.

As it turned out, the virus bore a remarkable resemblance to one that had already caused a pandemic — 90 years earlier. The major surface protein from the 2009 H1N1 was strikingly similar to the same type of protein from the 1918 H1N1 Spanish flu virus[1–4], which killed about 50 million people worldwide. Indeed, last year, researchers discovered that antibodies able to prevent the 1918 strain from entering cells in mice had the same effect on the 2009 H1N1[1–3].

Although the 1918 virus has long since evolved into widely divergent seasonal strains, a version with a very similar surface protein has circulated in pigs for nearly a century. It was therefore poised to cross back into humans and cause a new pandemic when broad protective human immunity had waned.

This unexpected source of the 2009 H1N1 pandemic is a cautionary tale for the public-health community. Another subtype of influenza, H2N2, looms as a public health threat[5–7], and could re-emerge in a similar way. Governments, regulatory agencies and industry should develop a pre-emptive vaccination programme for H2N2.

Like the 1918 virus, H2N2 influenza has already demonstrated its ability to cause a pandemic. From 1957 until 1968, an H2N2 strain caused between 1 million and 4 million deaths worldwide. Also like the 1918 strain, H2N2 viruses have not circulated in humans for several decades, but continue to do so among birds and swine[8]. The ▶

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oldest human H2N2 strains are closely related to avian strains, suggesting that the 1957 pandemic arose from birds. In fact, the H2N2 subtype mutates relatively slowly: in most bird and human strains, the surface proteins are 92% or more identical.

To examine levels of immunity to this class of virus, between 2003 and 2007, we tested for antibodies against H2N2 strains in the blood of a small cohort of 90 people in the United States. Ideally, this assay should be repeated in several thousand individuals, but our study suggests that people under the age of 50 have little or no immunity, and resistance dramatically increases for those older than 50 (see 'Vulnerability of youth'). This was also the case for the 2009 H1N1.

The low mutation rate for H2N2, and evidence of waning human immunity, make it likely that an H2N2 pandemic could arise from animals[5–7]. What steps can be taken to prevent its re-emergence?

EXISTING VACCINE

The genetic similarity of the circulating H2N2 strains and the fact that antibodies effective for one strain can work for others suggest that vaccines previously used for an H2N2 virus are likely to protect people against future pandemics[5,6,9]. Indeed, the vaccine licensed in 1957, and administered until the late 1960s, can protect mice against currently circulating animal H2N2 strains[5,9].

"An influenza pandemic is likely to cost far more and create a much greater health burden than a well-planned pre-emptive programme."

However, the manufacturing process for vaccines is unpredictable and costly, making it difficult to conduct a reactive but timely response. For example, by the time vaccines against the 2009 H1N1 virus were made available in most industrialized countries, the outbreak was past its peak. The result of this delay was an estimated 1 million extra infections, stressed health systems and tens of millions of unused vaccine doses[10].

For H2N2 — for which a safe vaccine that is likely to be effective is already available — a pre-emptive vaccination strategy[10] is far preferable, in our view. There are several ways to proceed.

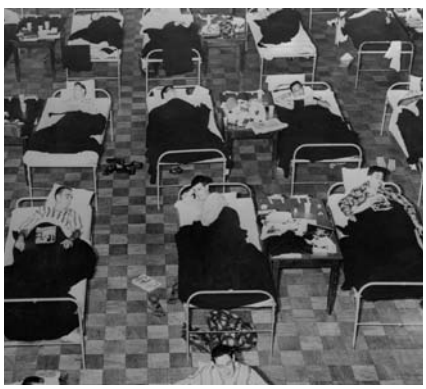
One approach would be to manufacture the vaccine licensed in 1957 and immunize enough of the world's population to provide 'herd immunity' to the rest. This could be achieved by a 'one-time' campaign to immunize most of the adult population worldwide — for example, as part of standard seasonal flu vaccinations — accompanied by an ongoing programme to administer the vaccine to children. Currently, immunizing 10 million people in the United States costs just US$250 million or less.

Another approach is to stockpile the vaccine so supplies are ready in the event of an outbreak. This would allow health practitioners to deploy the vaccine faster than they could if there was no preemptive strategy in place. This is likely to be more expensive and less effective than routine vaccination. The inevitable delay in distributing the vaccine would allow the virus to spread, kill more people and potentially mutate to the point of being able to evade people's immune systems. Maintaining large amounts of quality-controlled vaccine could also cost tens to hundreds of millions of dollars each year in the United States alone, because its limited shelf life means that it would need to be replenished.

A third possibility is to make 'master lots' of the H2N2 vaccine and ramp up production as soon as signs of an outbreak occur. Although this approach may be cheaper, it is less likely to be effective than either of the above. The 2009 epidemic demonstrated that it takes time to distinguish a serious outbreak from ordinary seasonal fluctuations and to identify the agent responsible.

Some argue that it is impossible to justify politically the cost of developing a pre-pandemic H2N2 vaccine. They cite the impediments to distributing vaccines internationally (including regulatory hurdles); the degree of public distrust of vaccines, particularly in Europe and the United States; and the finite public-health resources available. However, another major influenza pandemic is likely to cost far more and create a much greater health burden than a well-planned pre-emptive programme. The US Centers for Disease Control and Prevention estimates that a pandemic outbreak costs the United States between $71 billion and $167 billion.

Sceptics also raise concerns over whether it makes sense to expose individuals to vaccines for pathogens that are not currently in circulation. Fortunately, the previously licensed H2N2 vaccine has a proven safety and efficacy record. The virus that does emerge might have evolved to the point of being able to evade human immunity to this vaccine, but the H2 surface protein's high degree of conservation suggests that this is unlikely.



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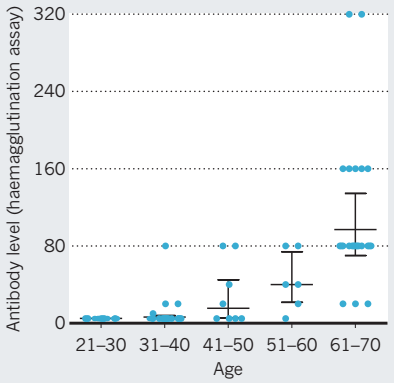
From 1957 to 1968, H2N2 influenza killed more than 1 million people.

VULNERABILITY OF YOUTH

Vaccination against H2N2 ended in the late 1960s, so people younger than 50 have little immunity to the virus (mean antibody counts shown with 95% confidence intervals).



With the knowledge and technologies available today, the efficacy of an H2N2 vaccine could markedly improve, and its cost may decrease in the coming years. A first step towards a pre-emptive vaccine would be to re-examine the safety and efficacy of the existing H2N2 vaccine in animal models and in phase I and II clinical trials. These studies would allow researchers and public-health officials to determine what dose is needed, and establish who to immunize and when.

Our understanding of influenza-virus biology should allow us to prepare for and even mitigate future pandemics. A deliberate and thoughtful strategy for H2N2 vaccination will save lives and spare the world a major public-health crisis. ■

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The views expressed are those of the authors and do not represent the policy of the National Institutes of Health or the US Department of Health and Human Services.

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