

# Influenza vaccine – for whom?

Having had influenza can reduce the risk of serious illness from infection by a different strain of influenza virus. Health personnel and healthy employees who are vaccinated regularly, in part to protect vulnerable patients and elderly people, may themselves be susceptible to a serious course of influenza illness.

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«Don't play tough,» the *Aftenposten* daily wrote on 2 January 2009 (1), with reference to a representative of the Norwegian Institute of Public Health, to encourage people in risk groups and their immediate contacts to take that year's influenza vaccine instead of going through the illness. At the time, less than half of those who belonged to the risk groups in 2005/06 had been vaccinated (2).

The Norwegian Institute of Public Health recommends that people belonging to certain risk groups be vaccinated against influenza each year. This applies to those who are 65 years or older, residents in sheltered housing and nursing homes, pregnant women in the second and third trimester, and children and adults with certain chronic and/or serious diseases, morbid obesity or reduced resistance to infection. In addition, household contacts of patients with severe immunosuppression should consider being vaccinated, and vaccination is recommended for health personnel who have contact with patients, and for pig farmers (3).

Vaccinating health personnel who are in frequent contact with patients can prevent the illness from spreading to vulnerable groups (4) – in the same way as shown by «the Japanese experiment», in which the excess mortality from pneumonia and influenza-like diseases among the elderly was strongly reduced during those years when schoolchildren were vaccinated against influenza on a regular basis (5). A large-scale study, however, could not prove any significant effects of such vaccination of health personnel on the prevalence of influenza or hospitalisation/death due to respiratory illness in patients in nursing homes and residents in sheltered housing who were 60 years or older (6). Neither has it proven cost-effective to vaccinate healthy, adult employees to reduce sickness absence (7).

In Norway, we have hitherto used non-

replicating, or inactivated, influenza vaccines that mainly consist of the outer parts of the virus – as split virus or as purified antigen. These surface proteins – haemagglutinin (H) and neuraminidase (N) – are constantly mutating. Even though these changes are relatively small from one year to the next, they are nevertheless so important that a new vaccine needs to be manufactured every year. At irregular intervals a complete mutation of the surface parts occurs, and the infection then spreads rapidly as a pandemic.

When the swine flu broke out in 2009, many months passed before pandemic vaccines were ready for use, and the seasonal vaccine remained the only alternative in many countries. In the aftermath, questions were raised as to whether vaccines against the seasonal influenza of that year or previous years nevertheless had a certain effect on the new virus (8, 9) – or whether the use of the seasonal vaccine could have harmful effects (10). In this article, we discuss the possibility that an infection with an influenza virus may give rise to cellular immunity to conserved, internal parts of the virus that are not constantly mutating, and that such immunity can protect against new strains of the influenza virus.

## Humoral and cellular immunity

In general, the effect of vaccines has been regarded as a result of circulating antibodies. With regard to influenza, this has been so unambiguous that a certain serum concentration of antibodies to one sub-type of haemagglutinin is used as a measure of the protection offered against viruses of the same subtype.

A bold trial in which 63 volunteers were infected with an influenza A(H1N1) virus confirmed that such antibodies from previous years could neutralise the virus in those exposed. In addition, it was shown that cytotoxic T-cells could eliminate or render viruses inactive in test persons, even if they had *not* previously developed subtype-specific antibodies or been exposed to infection by an H1N1 virus (11).

Since many of these test persons developed influenza symptoms shortly after

becoming infected, it was assumed that such cellular cross-protective immunity did not necessarily provide protection against infection, although the course of illness would be less severe, or that possibly the infection would remain at a sub-clinical stage (11). This negative correlation between the degree of seriousness of clinical influenza symptoms and the level of CD8-positive T-cell activity has later been proven (12).

## What have we learned from the pandemics?

During the Spanish flu in 1918, deaths primarily occurred among young people, while those aged over 50 years were less exposed, relatively speaking (13). In addition, it is notable that a change occurred in the mortality from influenza and pneumonia – mortality rose from the age of ten until the late twenties, and then fell abruptly with age in those over thirty. It is tempting, therefore, to see this sudden change in light of the so-called Russian pandemic in 1889–90, i.e. 28–29 years earlier. It is unlikely, however, that any protective effect in those who were born in 1889 or earlier, and who may have been infected in 1889, can be ascribed to antibodies against haemagglutinin, since the preceding pandemic had most likely been caused by a type A influenza virus of the subtype H3 (the N is unknown), while the Spanish flu was caused by a virus of the subtype H1N1 (14).

Observations from Cleveland during the Asian flu in the autumn of 1957 showed that the adults in a family were better protected than the children, and that this tendency was reinforced if they had had influenza in recent years (15). In previous years – since the Spanish flu in 1918 – influenza viruses of the subtype H1N1 had circulated in the population, while the Asian flu was caused by an H2N2 virus. Again, the protective effect could thus not be ascribed to antibodies against these surface proteins.

During the swine flu pandemic in 2009, the young and the middle-aged were struck hardest (16). Recent estimates indicate that on a global basis, deaths from the disease are counted in six-digit figures, and that



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80 % of these deaths occurred in people younger than 65 (17). One reason why the oldest people fared best could be cross-reactive immunity against non-pandemic A(H1N1) viruses that were in circulation in the periods 1918–57 and 1977–2009; this has also been suggested as an explanation of why the pandemic took a milder course than expected (18).

Several studies are now indicating that contracting a seasonal influenza caused by subtypes other than A(H1N1) can stimulate cellular immunity against conserved antigens in both the bird flu virus (A(H5N1) (19) and the swine flu virus (20–22). Older people have thus over many years had the opportunity to develop such cross-reactive immunity against completely new strains of the virus (23).

#### **Vaccination against seasonal influenza**

Already in 2009, it was indicated that children who had been regularly vaccinated

against seasonal influenza could be prevented from developing natural immunity and thus be more susceptible to a serious course of illness in later pandemics (24). The same research group recently reported that healthy children who had not been vaccinated developed a significantly greater increase in their virus-specific T-cell response than children suffering from cystic fibrosis, who had been vaccinated annually (25).

In Canada, it appeared that those who had been vaccinated against seasonal influenza as part of a general population programme in the year prior to the swine flu ran an increased risk of contracting it, and also had the pandemic virus confirmed by laboratory analyses (26, 27). Similar findings have recently been reported from Japan, where schoolchildren who had been vaccinated against influenza during the preceding season had an increased risk of contracting influenza-like diseases during the ongoing pandemic (28).

In Norway, as in the rest of the world, the elderly constitute the largest risk group for common seasonal influenza, and have significantly higher mortality if affected (29). Unfortunately, these individuals react poorly to vaccination, and the extent to which better vaccines can reduce the high mortality rate among this age group is being discussed (30). A «live» attenuated influenza vaccine for intranasal use is no solution, since it is not approved for use in persons over 49 years (31). Moreover, it is not approved for use by pregnant women, which renders it less useful for fertile women in the health and care professions.

Until we have more effective and safe vaccines targeting a broad spectrum of influenza strains, there is reason to benefit from the experience from previous pandemics and inform healthy adolescents and adults about the advantages of contracting the influenza of the coming autumn and winter seasons. Concerns have recently been expressed, saying that a population

group that has been completely protected against seasonal influenza through regular vaccination may be left without a cross-reactive T-cell immunity to influenza (23).

To avoid an increased risk of serious illness in health personnel during a later pandemic, we should reconsider whether these should remain on the list (3) of those who are recommended to be vaccinated annually, and rather focus on intensified vaccination of the risk groups. It has also been proven that other measures for the prevention of infections, for example providing a pneumococcal vaccine along with the influenza vaccine to the elderly, can prevent cardiac infarction as well as stroke (32). In this manner, a large vocational group can be relieved of an increased risk of serious illness in the case of a later pandemic.

*The viewpoints presented in this article are those of the authors, and do not necessarily reflect the views held by the Norwegian Institute of Public Health.*

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