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Yearly influenza vaccinations: a double-edged sword?

Rogier Bodewes DVM [a], Joost HCM Kreijtz PhD [a], Dr Guus F Rimmelzwaan PhD [a]

Summary

Yearly vaccination against seasonal influenza viruses is recommended for certain individuals at high risk of complications associated with influenza. It has been recommended in some countries, including the USA, that all children aged 6—59 months are vaccinated against seasonal influenza. However, it has been shown—mainly in animals—that infection with influenza A viruses can induce protective immunity to influenza A viruses of other unrelated subtypes. This so-called heterosubtypic immunity does not provide full protection, but can limit virus replication and reduce morbidity and mortality of the host. This type of immunity might be relevant to human beings when a new subtype of influenza A virus is introduced into the population, such as the new influenza A H1N1 virus responsible for the present influenza pandemic and the highly pathogenic avian influenza H5N1 viruses that are causing an ever increasing number of human infections with high mortality rates. Preventing infection with seasonal influenza viruses by vaccination might prevent the induction of heterosubtypic immunity to pandemic strains, which might be a disadvantage to immunologically naive people—eg, infants.

Introduction

Influenza A viruses are a major cause of respiratory disease in human beings. Seasonal epidemics of influenza are caused by human influenza A viruses of the H3N2 and H1N1 subtypes and influenza B viruses. The attack rate of these viruses is about 5—10%, and every year 300 000—500 000 people die of influenza worldwide.[1] Particularly patients with underlying diseases, such as cardiovascular or pulmonary disease, and elderly people have a high risk of influenza-related complications and might develop severe disease or die. Therefore, yearly influenza vaccination is recommended for these people.[2]

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Yearly vaccination is necessary because of the substantial antigenic drift of influenza viruses that necessitates the update of vaccines every year. The antigenic drift is driven by selective pressure mediated by antibodies induced by natural infection or vaccination. The vaccination of healthy children aged 6—59 months against seasonal influenza has been recommended in several countries, including the USA and some European countries, because the disease is an important cause of illness and admission to hospital in this age group.[2] Although annual vaccination against seasonal influenza is beneficial for all patients at high risk, including children,[3—7] vaccination of the 6—59 month age group every year against seasonal influenza might have a downside that has not been given much thought.

Because yearly vaccination against seasonal influenza is effectively preventing infection, it might also prevent the induction of immune responses that would otherwise have been induced. Immune responses induced after infection confer protective immunity against alternative subtypes of influenza A viruses in animals—so-called heterosubtypic immunity.

This consideration is especially relevant in light of the present pandemic caused by the influenza A H1N1 subtype and the pandemic threat caused by avian influenza viruses of the H5N1, H7N7, and H9N2 subtypes.[8—11]

Since young children are immunologically naive to influenza viruses, vaccination of this age group every year might prevent the induction of heterosubtypic immunity, leaving infants more susceptible to pandemic strains of influenza. We recently confirmed this in mice.[12]

Pandemic threats

Influenza viruses of the H1N1 subtype that emerged in Mexico in April, 2009, have spread all over the world. Since their emergence, more than 300 000 cases have been reported, of which at least 3917 led to death.[11] In response to the efficient transmission of the virus between people, WHO raised the pandemic alert level to phase six on June 11, 2009.

By contrast with the efficient spread of the new H1N1 virus, only a few clusters of probable transmission between people of the highly pathogenic avian influenza (HPAI) A H5N1 have been reported since the first human cases in 1997. However, more than 440 people with H5N1 infection have been reported to WHO, of which 59% have died.[9, 13, 14] Because so far these avian viruses are not efficiently transmitted between people, WHO has set the pandemic alert level for them at phase three.[15, 16] However, because of the continuous spread of HPAI A H5N1 viruses among domestic birds and the ever-increasing number of human cases, a pandemic caused by these viruses is still feared.[9, 17]

Other influenza A viruses that can infect human beings are of the H7N7 and H9N2 subtypes.[8, 10, 18] All of these avian viruses are potential sources of a pandemic, since antibodies against these viruses are not present in the human population. Whatever the subtype of the new pandemic strain, pre-existing immunity against human seasonal influenza A viruses might provide some protection through heterosubtypic immunity.

Heterosubtypic immunity against influenza A

In animals, previous infection with an influenza A virus can induce heterosubtypic immunity to infection with an influenza A virus of an unrelated subtype.[19] Infection with influenza A H3N2 or A H9N2 provide substantial protection against infection with H5N1-subtype HPAI viruses.[20], [21] Infection-induced heterosubtypic immunity is long-lasting (18 months) in ferrets, which are the gold-standard model of human influenza virus infection.[22] Heterosubtypic immunity is not dependent on antibodies against haemagglutinin and neuraminidase; therefore sterilising immunity cannot be expected. However, although infection with a heterologous subtype is not prevented, the clinical course of infection is attenuated and the mortality rate reduced.[23–25] The immunological basis for heterosubtypic immunity has been the topic of numerous studies.[26–34] Experiments in animals have shown that CD4 T cells, CD8 T cells, local mucosal antibodies, and B cells all contribute to heterosubtypic immunity. Cell-mediated immune responses directed at conserved internal proteins of influenza A virus are believed to play an important part.[19], [23] Indeed, cytotoxic-T-cell responses in people directed at human influenza A viruses show substantial cross-reactivity with HPAI A H5N1 viruses.[35–37]

Consequently, also in people in the absence of antibodies specific for the virus used for experimental infection, the presence of cross-reactive cytotoxic T cells inversely relates to the amount of viral shedding.[38] Thus, cross-reactive T-cell responses induced after previous infection might provided some protection against new subtypes of influenza A viruses.[36,38–40] Infection with influenza A viruses might induce heterosubtypic immunity in people, since individuals that were infected with an influenza A H1N1 virus before 1957 were less likely to develop influenza during the H2N2 pandemic of 1957.[41] In this respect, the disproportional age distribution of severe human H5N1 cases and the high incidence of laboratory-confirmed new H1N1 cases among children is of interest and at present a matter of debate.[42–44] Younger individuals are particularly at risk, and although other confounding factors cannot be excluded, it is tempting to speculate that young people have been infected with seasonal influenza viruses less frequently and therefore have not developed protective heterosubtypic immune responses against infection with the new influenza A H1N1 virus and the HPAI A H5N1 viruses.

Vaccination against seasonal influenza

Influenza vaccination is recommended for elderly people, immunocompromised people, and other high-risk groups, because H3N2 and H1N1 subtypes of seasonal influenza A viruses and influenza B viruses cause yearly epidemics, mainly among these high risk groups, associated with excess morbidity and mortality. Furthermore, children are at high risk of complications and admissions to hospital secondary to influenza,[45], [46] and several countries already recommend vaccination of healthy children.[2], [47] Inactivated influenza vaccines are used most frequently, including subunit preparations that contain haemagglutinin and neuraminidase. Furthermore, the use of adjuvants is thought to further increase vaccine effectiveness in young children.[48] Vaccination every year against epidemic influenza is effective in children, both clinically and in terms of cost, since it decreases the burden of disease and the number of children admitted to hospital because of infection with influenza A viruses.[3–7]

Thus, vaccination of infants against seasonal influenza is beneficial. However, there is a potential downside to yearly seasonal influenza vaccination that has not been given much thought. In theory, effective vaccination of children against seasonal influenza A viruses might prevent the induction of heterosubtypic immunity otherwise induced after productive, in most cases, self-limiting infection of the upper respiratory tract. This interference with the

induction of heterosubtypic immunity might not be important under normal circumstances, but in context of the pandemic threat caused by HPAI A H5N1 and the pandemic outbreak of new influenza A H1N1 viruses, the presence or absence of heterosubtypic immunity might affect the clinical outcome of infection with the new pandemic strain. Consequently, we hypothesised that effective vaccination against seasonal influenza interferes with the development of protective immunity against a lethal infection with an influenza virus of a new subtype (eg, H5N1).

Vaccination and interference with immunity

As mentioned, influenza pandemics are caused by the introduction of influenza A viruses with haemagglutinins and neuraminidases that are antigenically distinct from the circulating human seasonal influenza A viruses. Therefore antibodies directed against the seasonal influenza viruses are unable to recognise and neutralise the new strains, allowing them to replicate to higher titres causing high transmission and attack rates. In these circumstances, the presence of heterosubtypic immunity might tip the balance in favour of the host and provide some level of protection against these new pandemic strains. The induction of T cells that are cross reactive after infection with seasonal influenza viruses might contribute to protection against the pandemic strains and attenuate the clinical outcome of infection.

Since infants are immunologically naive to influenza viruses,[49] yearly vaccination of this age group against seasonal influenza might prevent the induction of heterosubtypic immunity, leaving this group more susceptible to pandemic strains than are children that have been infected with seasonal strains. Most of the seasonal influenza vaccines used until now are inactivated influenza vaccines that provide protection against the homologous seasonal strains but fail to induce immune responses that are cross protective against strains of alternative subtypes. This poor cross-protective potential relates to the inefficient CD8-T-cell responses induced by these vaccines.[50], [51] We recently mapped the effect of vaccination against a seasonal influenza virus A H3N2 strain on the induction of heterosubtypic immunity against a potentially pandemic HPAI A H5N1 virus in mice.[12]

Mice were vaccinated twice with a H3N2 subunit antigen preparation with alum as an adjuvant. The use of an adjuvant was necessary because vaccination with subunit alone only induced detectable antibody responses in a small proportion of mice and would not provide a useful model for successful vaccination against seasonal influenza. The vaccine, derived from the vaccine strain X31, induced antibodies against H3N2-strain A/Hong Kong/2/68 and fully protected against challenge infection with this virus. Subsequently, these mice and those with productive infection with influenza virus A/Hong Kong/2/68 (H3N2) were infected with a lethal dose of influenza virus A/Indonesia/5/05 (H5N1). Strikingly, the mice that were protected from infection with the seasonal A H3N2 strain developed severe disease and died as a consequence of the A H5N1 infection, whereas those that were not vaccinated became less ill and did not die (table). The lack of clinical protection in the H3N2-vaccinated mice against infection with A H5N1 virus was related to the lack of control of virus replication in the lungs normally seen in mice previously infected with the influenza A H3N2 virus. The disease was similar to that in fully naive mice infected with the A H5N1 strain and was characterised as a severe necrotising bronchointerstitial pneumonia. Vaccination against the A H3N2 strain prevented not only the efficient induction of virus-specific CD8-T-cell responses after infection with influenza A/Hong Kong/2/68, but also the formation of inducible bronchus associated lymphoid tissue. Both the induction of CD8-T-cell responses that were cross reactive and the

formation of inducible bronchus associated lymphoid tissue most likely contributed to the heterosubtypic immunity seen after A H3N2 virus infection in non-vaccinated mice.[12, 52]

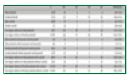

Table **Table image**

Interference with induction of heterosubtypic immunity by vaccination against seasonal influenza

Conclusions

Although yearly vaccination against seasonal influenza is beneficial for infants that are immunologically naive to influenza viruses, it might have some unwanted long-term effects. As we showed in mice, effective vaccination against seasonal influenza might prevent the induction of heterosubtypic immunity against potentially pandemic strains. This issue has been given little thought and the general recommendation to vaccinate all healthy children between 6 months and 59 months of age should perhaps be re-evaluated in view of the pandemic threat caused by HPAI H5N1 viruses and the pandemic caused by the recently emerged A H1N1 viruses. We therefore feel that in children living in areas where HPAI H5N1 viruses are endemic the absence of heterosubtypic immunity is undesirable because it could increase the risk of a more severe clinical outcome after infection with these viruses.

Young children might also benefit from heterosubtypic immunity to the influenza A H1N1 viruses that have caused the first pandemic of the 21st century. The decision to vaccinate this vulnerable age group every year against seasonal influenza with inactivated influenza vaccines should be given careful thought in view of the present pandemic threats. Although in mice the presence of heterosubtypic immunity can mean the difference between life and death, more research is needed to define the risk for higher susceptibility to pandemic viruses by yearly vaccination against seasonal influenza. Only then can there be an assessment of the relative increase in seasonal influenza disease burden, resulting from not vaccinating, compared with the relative decrease in pandemic influenza disease burden.

There are seasonal influenza vaccines in use that do induce heterosubtypic immunity.[53] For example, live-attenuated vaccines induce virus-specific CD8-T-cell responses by contrast with the frequently used subunit, split virion, or whole inactivated virus vaccines and therefore might confer some degree of protection against heterosubtypic influenza virus strains.[51, 54] Indeed, in animals, live-attenuated vaccines induce broad protective immune responses.[55–57]

Seroepidemiological studies are needed to show when infants first become infected with influenza viruses. Perhaps before that age the use of live-attenuated vaccines would be preferred, inducing cell-mediated immune responses that are cross reactive.

In addition, new generations of influenza vaccines, like viral-vector vaccines, might be attractive alternatives because they can also induce CD8-T-cell responses that are virus specific and directed to conserved viral proteins like the matrix protein and the nucleoprotein, in addition to antibodies directed against the haemagglutinin of seasonal influenza virus strains.[58–62] Examples of vector vaccine production platforms are the recombinant

replication-deficient adenoviruses and poxviruses and the Newcastle disease virus vector, which efficiently induce protective immunity against influenza viruses.[63–67] Another conserved viral protein is the M2 protein that can induce cross-reactive antibodies. Using M2-based candidate vaccines, protective immunity could be induced against influenza A viruses of various subtypes.[68, 69] These vaccine candidates might not only provide protection against seasonal influenza viruses but also against future pandemic strains.

More research is needed to find out if heterosubtypic immunity contributes to protection against infection with pandemic strains in people and if yearly vaccination against seasonal influenza prevents the induction of heterosubtypic immunity.

The present influenza pandemic caused by new A H1N1 viruses might provide a unique opportunity to investigate heterosubtypic immunity and would allow randomised-prospective studies. Close monitoring of admissions to hospital and mortality rates among infants that have received annual influenza vaccination since birth and comparison with unvaccinated age-matched children might provide information on the potential downside of yearly influenza vaccination.

The development and use of vaccines that can induce broad protective immunity might be a solution for these potential problems and we think this is a priority.[53, 54]

Contributors

All authors contributed equally to the preparation of this paper.

Conflicts of interest

RB and JHCMK declare that they have no conflicts of interest. GFR is a consultant to Viroclinics BV.

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a Department of Virology, Erasmus Medical Center, Rotterdam, The Netherlands

Correspondence to: Dr Guus F Rimmelzwaan, Department of Virology, Erasmus Medical Center, PO Box 2040, 3000 CA Rotterdam, Netherlands