Influenza vaccination: revision of the indication

Gezondheidsraad **President**
Health Council of the Netherlands

To the Minister of Health, Welfare and Sport

Subject : Presentation of advisory report *Influenza vaccination: revision of the indication*
Your reference : POG/ZP 2.498.210
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Dear Minister,

Having consulted the Standing Committee on Immunology and Infectious Diseases and the Standing Committee on Medicine, I hereby submit the advisory report entitled *Influenza vaccination: revision of the indication*. In this advisory report, a specially appointed committee, chaired by myself, determined which target groups are eligible for vaccination against influenza as part of the National Influenza Prevention Programme.

The seven criteria for the inclusion of vaccinations in the National Vaccination Programme (NVP), which were drawn up by the National Vaccination Programme Review Committee, served as a guideline. They are equally applicable in the case of influenza vaccination. Accordingly, the scientific findings were routinely tested against these criteria. Where important data were missing, the Health Council contracted the Julius Center for Health Sciences and Primary Care of the University Medical Center, Utrecht to conduct supplementary research. The research in question dealt with morbidity and mortality resulting from influenza in healthy individuals aged 50 to 65, and in children. The Committee took this supplementary data into account when making its assessment.
The Committee concluded that most of the current target groups can be retained. Given the current level of knowledge, the only group for which vaccination is no longer recommended are patients with furunculosis. At the same time, the Committee recommends expanding the range of target groups to include healthy adults in the 60 to 65 age group, healthcare personnel who are in direct contact with patients, and family members of those who would be at very serious risk if they were to contract influenza.

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The Committee also identified measures for maintaining vaccination coverage in the Netherlands (which, it is worth noting, is already high relative to other countries) or even improving it still further.

It has also made recommendations for further research. This is because, in assessing the current level of knowledge, the Committee identified a number of gaps. This involves knowledge related to specific target groups, such as the effect of influenza vaccination in children from six months to two years of age, as well as knowledge concerning more general effects, for example the effect of vaccinating children on the circulation of the influenza virus within the population as a whole. In view of the anticipated growth in our knowledge of this and other fields, the Health Council of the Netherlands plans to review the situation again in a few years' time.

Yours sincerely,

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No. 2007/09E, The Hague, March 8, 2007

The Health Council of the Netherlands, established in 1902, is an independent scientific advisory body. Its remit is “to advise the government and Parliament on the current level of knowledge with respect to public health issues...” (Section 22, Health Act).

The Health Council receives most requests for advice from the Ministers of Health, Welfare & Sport, Housing, Spatial Planning & the Environment, Social Affairs & Employment, and Agriculture, Nature & Food Quality. The Council can publish advisory reports on its own initiative. It usually does this in order to ask attention for developments or trends that are thought to be relevant to government policy.

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INAHTA

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Contents

Executive summary

Influenza vaccination: who should be vaccinated and who should not?

Influenza is caused by the influenza virus. Because the virus is constantly changing, people do not build up life-long resistance, as frequently happens with other infectious diseases. This explains why there are annual epidemics. Healthy individuals are usually well able to withstand an infection, but for people in the risk groups, influenza can lead to serious illness and even death (for example as a result of pneumonia, diabetes dysregulation or aggravation of lung and heart disease).

There has consequently been a specific policy for a longer period of time whereby people who are at risk for developing complications in connection with influenza are offered influenza vaccination. In 1997, an infrastructure was established for this very purpose: the National Influenza Prevention Programme (NPG). Owing to the changes that influenza viruses undergo, vaccination needs to be repeated annually and the vaccine has to be continually modified.

A recurring question in this connection is which sections of the population should be offered influenza vaccination. New research data may, for example, reveal that vaccination of a particular group is insufficiently effective, or that other target groups who were not previously eligible for vaccination may actually be the ones who stand to derive major health benefits. The choice of target groups is therefore reviewed on a regular basis. With this in mind, the Minister of

Health, Welfare and Sport requested the Health Council to consider which risk groups should be eligible for influenza vaccination in the years to come. The Minister also wished to know how it might be possible to maintain – or even further increase – the level of vaccination coverage within the target groups, which is already high.

So that it can advise the Minister, the Health Council has applied the seven vaccination criteria that were formulated in its advisory report *The future of the National Immunisation Programme (RVP): Towards a programme for all age groups*. These criteria were drawn up in order to make decisions on inclusion of vaccinations under the RVP. They can, however, equally well be applied when choosing target groups for the National Influenza Prevention Programme.

Majority of the current target groups to be retained

For the large majority of the current target groups, the beneficial effect of influenza vaccination remains undisputed. For this section of the population, vaccination serves to prevent significant damage to health, or at least to substantially reduce any damage that does occur. Furthermore, it is cost-effective to offer vaccination as part of a national programme. Thus the earlier recommendation that influenza vaccination should be offered to these groups still stands.

This applies to the following groups: people aged 65 years and over, patients with abnormalities or a dysfunction of the airways and lungs, patients with chronic cardiac dysfunction, patients with diabetes mellitus, patients with chronic renal insufficiency, patients who have recently undergone bone marrow transplantation, people with HIV infection, children aged between 6 months and 18 years who receive long-term salicylate therapy, people with mental retardation in residential institutions, people with reduced resistance to infection (e.g. because of cirrhosis, (functional) asplenia, autoimmune diseases, chemotherapy and immunosuppressive medication), and residents of nursing homes who do not fall into one of these categories.

The main topic of discussion was whether children with asthma should still be offered influenza vaccination. Earlier publications pointed to increased mortality as a result of influenza in this group and suggested that vaccination had a beneficial effect which could be measured by a reduction in respiratory infections and visits to the general practitioner (GP). However, recently published Dutch research has not corroborated these results. Nevertheless, the possibility that influenza vaccination may have a beneficial effect in this risk group cannot be dismissed at this moment in time. A decision to stop offering vaccination to

this group can only be made once further research has shed more light on this issue.

One target group has, however, been dropped from the programme. Up until now, vaccination against influenza has been recommended in the Netherlands for patients with furunculosis and for members of their family. However, it is unclear from the scientific data whether furunculosis patients are at greater risk of complications after influenza. Nor do we know how effective influenza vaccination is in this group.

Four new target groups to be added

Healthy people aged 60 to 65 years

Up until now it has been recommended that people over 65 years of age should be vaccinated against influenza. A study performed especially for this advisory report has now revealed that episodes of influenza can also lead to more GP visits, hospital admissions and higher mortality rates in healthy younger people. This is especially evident in the 60-65 year age group. Therefore it is recommended that this age group should also be offered influenza vaccination in the future.

Healthcare personnel in institutions

Although in theory healthcare personnel who work in healthcare institutions are actually no more burdened by influenza than people in other occupations, they may transmit the disease to patients. This is particularly important for people whose daily work brings them into contact with patients who are at high risk of complications from influenza. Vaccination reduces the risk of these complications. Healthcare personnel have a special responsibility in this respect. Consequently, it is recommended that healthcare personnel in hospitals, care homes and nursing homes should in the future be included among the target groups for vaccination.

Other healthcare personnel

Other healthcare personnel also regularly have intensive contact with patients at high risk of complications from influenza (home care workers and general practitioners, for example) and they too bear a special responsibility. In practice, it is actually difficult to draw the line between those professionals who are eligible

for vaccination and those who are not. Consequently, a general recommendation has been made that healthcare personnel who in daily practise come into direct contact with patients should be vaccinated against influenza.

Family members of very high-risk individuals

Family members can be a source of infection for people who are at high risk when developing influenza. There are, however, no data available at present that prompt the Committee to recommend the vaccination of family members of people from all risk groups. The Committee nevertheless considers it prudent to recommend vaccination for family members of patients who are at particularly high risk. Examples are: patients with serious abnormalities of or a dysfunction of the airways and lungs, patients with severe liver or kidney failure, and patients whose immune system is compromised (e.g. as a result of HIV infection, chemotherapy or treatment with other drugs that suppress the immune system).

Other possible target groups not (yet) included

In other countries, influenza vaccination is offered to pregnant women. The scientific literature does not indicate, however, that healthy pregnant women are at higher risk when developing influenza. Moreover, they are rarely admitted to hospital during the influenza season, and mortality from influenza does not occur in this group. Thus there is no reason to add healthy pregnant women to the target groups for influenza vaccination.

Another target group for whom influenza vaccination has been considered are children. Research has been conducted especially for this advisory report into morbidity and mortality in children in the Netherlands as a result of influenza. Although the results do not show any additional mortality, they do reveal an extra disease burden in the form of more hospital admissions and GP visits.

The increased morbidity mainly applies to children aged between 0 and 6 months. However, influenza vaccines have not been registered for and tested in children from this age group and this group has consequently been ruled out. Vaccination of pregnant women could well be an alternative means of protecting newborn babies. There is, however, no scientific evidence that maternal vaccination is an effective means of achieving this goal and this is therefore not recommended.

Influenza also results in higher morbidity in children aged between 6 months and 2 years. However, the efficacy of the influenza vaccine has not been demonstrated in this age group. Although vaccination is effective in healthy children

over 2 years of age, influenza does not cause additional serious morbidity or mortality in this group and hence there is no reason at present to include them among the target groups for influenza vaccination.

A further possible target group consists of people who have intensive contact with the general public through their work (lecturers, for example). Based on the available scientific literature, however, there is no reason to assume that these individuals would be at increased risk of influenza, complications or mortality in the event that they should fall ill. Nor are they more likely to transmit influenza to people for whom this would pose a serious threat. There is consequently no reason to offer vaccination to people in these occupations.

It has also been considered whether people with addictions to alcohol and drugs ought to be eligible for influenza vaccination. The Committee has found no evidence to suggest that these individuals might have low immunity and it therefore has no reason to assume that these groups are at increased risk of developing complications or even dying as a result of influenza. The committee therefore does not recommend to add them to the target groups for influenza vaccination either. They may, however, be eligible for vaccination for other reasons (e.g. because of cirrhosis or HIV infection). Healthcare providers need to be alert, since this group is often less familiar with regular care.

It has also been considered whether occupational groups who have intensive contact with poultry – such as poultry farmers and veterinarians – would benefit from yearly influenza vaccination. However, in the absence of an avian influenza epidemic, there is no reason to vaccinate them. If avian influenza were to break out, there would be a risk that genetic material might be exchanged between different strains of the virus, giving rise to the possibility that a new virus strain might emerge which is highly infectious for humans. Such a new strain might then lead to a pandemic (an epidemic on a global scale). In case of an outbreak of avian influenza, there may therefore be grounds for vaccinating professional groups who have intensive contact with poultry. This is a decision that the Minister of Health, Welfare and Sport would have to make at the time.

Boosting effectiveness through proper education

Many Dutch people who are eligible for an influenza vaccination do actually receive one in practice. Vaccination coverage is high. Nevertheless, not everyone has been reached as yet. For example, some people are unaware that they belong to a target group. Proper, well-targeted education can help to rectify this situation. Information about the risks of influenza and the mild side effects of vaccination may help to further boost vaccination coverage. Furthermore, the role of

GPs is crucial in ensuring acceptance of vaccination. Their central role must therefore be maintained. Vaccination of healthcare personnel is best performed in the workplace, and this may possibly be a task for the occupational health services.

Further research

In assessing the current level of knowledge, the Committee has identified a number of gaps. It recommends that research be conducted in order to reduce these gaps. More specifically, focussed research is needed into the effectiveness of influenza vaccination in children aged between 6 months and 2 years and the effectiveness of influenza vaccination in children with asthma. Furthermore, general research is recommended into the possible indirect effects of influenza vaccination in healthy children (as a result of reduced transmission), research into the long-term effects that annual influenza vaccination at an early age may have on the clinical course of influenza later in life, and continuation and intensification of research aimed at improving the effectiveness of influenza vaccines.

Chapter 1

Introduction

1.1 Background

For quite some time, the Netherlands has pursued a targeted policy with regard to providing and administering influenza vaccinations. Influenza is the infection caused by the influenza virus. Strictly speaking, the vaccination targets the virus rather than the disease, but 'influenza vaccination' has become the established term. Influenza vaccinations are currently provided for those at high risk of complications, should they catch influenza (such as patients with a chronic disorder of cardiac function or lung function).

From 1997 onwards, this policy took shape as the National Influenza Prevention Programme (Nationaal Programma Griepppreventie, NPG). This is a separate vaccination programme for influenza which, like the National Vaccination Programme (Rijksvaccinatieprogramma, RVP), is financed by the government. The coordination of the NPG was previously organised by the Health Care Insurance Board (College voor zorgverzekeringen, CVZ). With effect from 1 January 2006, that task was transferred to the National Institute of Public Health and the Environment (Rijksinstituut voor Volksgezondheid en Milieu, RIVM).

In 2003, the CVZ published the results of the PRISMA study, an investigation into the programme's cost effectiveness and efficiency.[1] The main conclusion was that the NPG was a successful prevention programme, with major beneficial health effects. To a large extent, it even produces cost savings. Accordingly, the

CVZ recommended that the NPG be continued. Nevertheless, the CVZ did raise the issue of whether certain target groups should be added to the programme, and whether others should be removed from it.

For instance, the vaccination of healthy individuals in the 50 to 65 age group might prove to be cost effective, while it may not make sense to include those at high risk who are below the age of 18. Against the background of these results, the CVZ advised the Minister of Health, Welfare and Sport (VWS) to consult the Health Council about granting eligibility for influenza vaccination to some target groups and withdrawing it from others.

Other bodies have also considered the issue of which target groups to include in the influenza vaccination. One example is the World Health Organisation (WHO), which for several years has recommended that healthcare personnel be vaccinated against influenza.[2] Many countries have since adopted this recommendation, but not the Netherlands.[3]

There are also details of people's experiences in other countries. There, groups are vaccinated that are not currently eligible for vaccination in the Netherlands, such as pregnant women, the family contacts of individuals in high-risk groups, and (in the United States) children from six months to five years of age.[3,4] On the other hand, influenza vaccination was for many years recommended for patients with furunculosis and for contacts within their family, while no other country made this recommendation.

These considerations constituted sufficient reason for the Minister of Health, Welfare and Sport to ask the Health Council of the Netherlands to produce an advisory report concerning possible amendments to the list of groups currently eligible to receive the influenza vaccination. The Minister also enquired about the best way to provide this vaccination. The full text of the request for advice can be found in Annex A. In order to respond to the request for advice, the President of the Health Council installed the Influenza Vaccination: Revision of the Indication Committee. Details of the make-up of the Committee are set out in Annex B.

1.2 Question posed

The Health Council has been making recommendations about influenza vaccination since 1975. From 1981 to 1998 it published annual reports on this topic. The most recent report ('Vaccination against influenza, 1998-1999 season') cites a number of target groups for influenza vaccination:[5]

Influenza vaccination was *urgently* recommended for:
- patients with abnormalities and function disorders of the airways and lungs
- patients with a chronic disorder of cardiac function
- patients with diabetes mellitus
- patients with chronic renal insufficiency
- patients with furunculosis, members of their family, and contacts of a comparable nature.

Influenza vaccination was recommended for:
- patients who have recently undergone a bone marrow transplant
- individuals who are infected with HIV
- children and adolescents from six months to eighteen years of age who use salicylates for a prolonged period
- mentally handicapped individuals living in intramural facilities
- individuals aged 65 and above (following a long period of consultation, this group was added to the target groups for influenza vaccination in 1994).

Influenza vaccination could be considered for:
- individuals with reduced resistance to infections (as a result of cirrhosis of the liver and asplenia, for example)
- those resident in nursing homes who are not covered by the above-mentioned categories.

When assessing the target groups, the present Committee based its approach on this advisory report. The associated requests for advice were couched as follows:

a Which target groups should be offered an influenza vaccination?
   - Should the current groups be expanded to include individuals in the 50 to 65 age group, pregnant women, children, healthcare personnel, professions that involve intensive contacts with the public, professions that involve intensive contacts with poultry, individuals with family contacts in a high-risk group, drug addicts, and people with alcohol addiction?
   - Should high-risk individuals below the age of 18, as well as patients with furunculosis and members of their family, be removed from the current target groups?

b What approach is needed to ensure that vaccination coverage in the recommended target groups is as broad as possible?
   - What form should the associated public information campaign take?
   - How should people be invited to attend for vaccination?
   - Should they receive the vaccine free of charge?

- Who is best suited to administer the vaccine?

1.3 Method

The CVZ report entitled: 'The National Influenza Prevention Programme: the success of influenza vaccination' is one of the documents on which the literature study was based.[1] Other important factors were the standard used by the Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG): 'Influenza and Influenza Vaccination', the guideline used by the Dutch Association of Nursing Home Physicians (Beroepsvereniging van Verpleeghuisartsen en Sociaal Geriaters, NVVA): 'Influenza prevention in nursing homes and residential care homes'. There was also the recommendation of the Advisory Committee on Immunization Practices *(ACIP):* 'Prevention and Control of Influenza', which serves as a guideline for influenza vaccination in the United States.[4,6,7]

In addition, the available systematic reviews and other recent literature (made accessible via PUBMED and The Cochrane Collaboration) were used for each target group (or potential target group). The Committee has also consulted various experts (see Annex C), and has submitted questions to the Scientific Panel on Vaccines and Immunisation of the European Centre for Disease prevention and Control (ECDC).

In addition, the Health Council has contracted the Julius Center for Health Sciences and Primary Care of the University Medical Center Utrecht (hereafter referred to as the Julius Center) to conduct research into the morbidity and mortality resulting from influenza in healthy individuals aged 50 to 65, and in children (a summary of this study is given in Annex E). Subsequent to this, a cost-effectiveness analysis of influenza vaccination in healthy individuals aged 50 to 65 was also carried out (a summary of this is contained in Annex F). The Committee made use of both of these studies while conducting its assessment.

1.4 Structure of the advisory report

In the second chapter, the Committee has included a summary of the present situation in the area of influenza and influenza vaccination. Chapter 3 contains details of the criteria to be used in establishing the target groups. These criteria are then applied to each target group individually. That results in a conclusion regarding which groups are eligible for the influenza vaccination, and which are not. In chapter 4, the Committee then addresses the issue of how to ensure that vaccination coverage in the recommended target groups is as broad as possible.

In the final chapter, the Committee discusses its conclusions and recommendations.

Chapter 2

The current situation

This chapter gives details of the Dutch situation in the area of influenza vaccination. In doing so, it examines the effects of infection, and of various properties of the vaccines in question. The resources used included the new Influenza Pandemic standard, which was developed by the Dutch College of General Practitioners (NHG).[8]

The effects of infection

Virus

The influenza virus is a single-stranded RNA virus with a protein coat. The virus is a member of the orthomyxovirus family. Three types of influenza virus have been identified: A, B and C. It is only types A and B that cause the familiar influenza epidemics. Influenza viruses are classified into subtypes, on the basis of variations in the two surface proteins hemagglutinin (H) and neuraminidase (N). A given strain of virus expresses one type of hemagglutinin and one type of neuraminidase. Sixteen hemagglutinin subtypes (H1-H16) and nine neuraminidase subtypes (N1-N9) have been identified in influenza A-type viruses.[9,10] All of these subtypes occur in migratory birds and in waterfowl (avian influenza), often without causing disease symptoms. Only those virus strains with hemagglutinin subtypes H1, H2 and H3, and neuraminidase subtypes N1 and N2 have been

shown to be capable of efficient human-to-human transmission. Influenza B has only one hemagglutinin and neuraminidase subtype.

Epidemics

In the course of an infection, virus particles develop which have slight variations in their hemagglutinin and neuraminidase. These therefore differ from the original virus strain. This mechanism, which is referred to as antigenic drift, results in virus strains against which previously developed resistance is no longer effective. Those variants to which the lowest levels of antibodies circulate in the general population have the greatest chance to spread further. They are also capable of re-infecting those who have already suffered a bout of influenza.

Antigenic drift causes the influenza epidemics that return every year, or thereabouts. It is also the reason why vaccination must be carried out each year, using a modified vaccine. Individuals who have previously been infected by an influenza virus generally enjoy some degree of protection against a subsequent infection with a changed strain. This so-called cross-protection most often concerns the H-subtype. The degree of difference in the changed surface proteins determines the epidemic potential of the virus.

Healthy individuals are usually well able to withstand an infection, but for people in the risk groups, influenza can lead to serious illness (for example as a result of complications such as pneumonia, deregulation of diabetes or aggravation of chest and heart conditions). That then requires a visit to the GP and, in some cases, admission to hospital. Influenza can even lead to death. In the 1990s, it was found that in the Netherlands about 2000 people die each year as a result of influenza.[11] The research carried out for the purpose of this advisory report also revealed an excessive burden of disease and mortality resulting from influenza, especially in individuals aged 65 and above (see Annex E).

Vaccination is the best way to reduce the risk of contracting influenza. The composition of the vaccine is changed each year, on the basis of the virus strains that are expected to circulate in the population. As long as the composition of the infecting strain does not differ too much from that of the strains use to create the vaccine, then vaccination will generally provide protection against influenza.

Pandemics

Pandemics are much rarer than epidemics. They are epidemics on a global scale, caused by a virus with a highly modified antigenic composition. Past pandemics have all been caused by type A influenza viruses.

The basis for influenza pandemics is antigenic shift.[9] This produces an entirely new virus, with a hemagglutinin that humans have never before encountered, and possibly a previously unknown neuraminidase too. A pandemic can only develop if the new virus is easily transmitted from one individual to another. This situation can arise through direct, gradual mutations (gradual adaptation). Another possibility is that influenza viruses circulating among birds can exchange genes with influenza viruses that are found in humans. This can result in the creation of a new virus that is highly infectious to humans (a reassortant). Pigs or other mammals can also be involved, as intermediate hosts.

This process results in such a major change in the antigenic structure of the virus that any immunity acquired during previous influenza epidemics is ineffective (or virtually so) against the new virus. Furthermore, the present influenza vaccine, which is used to contain annual epidemics, offers insufficient protection against this new subtype. The new virus will then be able to spread throughout the world, creating a pandemic.

2.1 Vaccines

Composition

A range of influenza vaccines are registered in the Netherlands. These are all based on inactivated virus particles derived from two types of influenza A and one type of influenza B. Each year, the exact composition of the vaccines is attuned to the most recent epidemiological data. This procedure is carried out in accordance with the guidelines of the WHO, after which the European Medicines Agency (EMEA) determines whether this recommendation is consistent with the specific situation as it pertains in Europe.

Administration

Administration is by means of an intramuscular or subcutaneous injection (the injection site for adults and older children is the upper arm, whereas the thigh is used in the case of young children). Vaccination consists of a single dose of 0.5 ml. In the case of children who have not previously been vaccinated against influenza, a second dose is administered after a period of at least four weeks.

No vaccines have been registered for use in infants below the age of six months. Contra-indications for influenza vaccination are an acute infectious disease and/or fever at the time of vaccination. Nor can the vaccine be administered to individ-

uals who are hypersensitive to eggs or to chicken proteins, or to one of the other components of the vaccine.

Effectiveness

The effectiveness of an influenza vaccine depends on its efficacy, and on the age and immune competence (the ability to respond to the administration of the vaccine) of the recipient. Another factor is the degree of correspondence (matching) between the circulating strains and those used to prepare the vaccine.

Another important aspect is the intensity of viral activity from one influenza season to another.

Research also reveals differences in terms of effectiveness which, on further consideration, may correspond to differences in the yardstick used. The yardsticks used in the course of research into the effectiveness of influenza vaccination are:

- the prevention of serologically or virologically confirmed influenza (efficacy)
- the prevention of clinical influenza: disease that is confirmed on the basis of symptoms, such as:
  - influenza-like illnesses
  - upper respiratory tract infections
  - acute respiratory tract infections
- the prevention of complications caused by influenza, such as:
  - mortality
  - pneumonia
  - cardiovascular diseases (such as a myocardial infarction)
  - middle-ear inflammation
- production of antibodies:
  - the levels of antibody produced in response to the vaccine serotypes (seroprotection)
  - the levels of antibodies produced in responses to an influenza virus circulating in the population (seroconversion)
- use of healthcare facilities and absenteeism, such as:
  - hospital admissions
  - visits to GPs
  - absence due to illness.

The details of studies into the effectiveness of influenza vaccination are discussed in chapter 3. This includes an indication of which of the above yardsticks was used in each case.

Cost effectiveness

A cost-effectiveness analysis (CEA) is used to estimate the costs incurred per prevented case of disease or per year of life gained. A cost-utility analysis (CUA) goes a step further. Here, the effects on health are corrected for quality of life and expressed as Quality Adjusted Life Years (or QALYs).

This makes it possible, in theory, to compare the cost-utility ratios between different interventions, even if these are not analogous.

The principle commonly applied to preventive interventions in the Netherlands is that one year of life gained or one QALY should cost no more than € 20,000. The Council for Public Health and Health Care (Raad voor de Volksgezondheid en Zorg) has proposed an upper limit of € 80,000 per QALY for collectively financed care.[12]

It should be noted that determining QALYs is no simple matter. Sometimes by no means all of the data to be entered into the model is available. For instance, there is sometimes no epidemiological data pertaining to the Dutch situation, or too little is known about the risk of transmitting an infectious disease, the duration of the infectious period, or the importance of various transmission routes. In addition, the question of how disease states should be rated in terms of loss of quality of life is sometimes a difficult one to answer.

It is occasionally possible to adapt the model to such information as is available. If, for example, no information is available concerning the quality of life, then the number of prevented infections or years of life gained often form a good alternative. It is often possible to obtain a clear picture by means of a thorough analysis of the available data.

In this way it is possible to assess various types of investment to determine which one produces the most health gains. For a more detailed explanation of cost-effectiveness analyses and cost-utility analyses see the advisory report entitled ‘The future of the national immunisation programme: towards a programme for all age-groups’ [De toekomst van het Rijksvaccinatieprogramma: naar een programma voor alle leeftijden], which was produced by the National Vaccination Programme Review Committee.[13] However, it is important to be aware of the fact that the various assumptions made will impose certain limitations on cost-utility analyses.

This advisory report, and the publications cited, focus purely on the cost effectiveness of the direct protection afforded by influenza vaccination to vaccinated individuals. The effects of indirect protection, which arise by virtue of the fact that the vaccinated individuals reduce the degree of exposure to influenza experienced by their friends and family, were not taken into consideration.

Duration of protection

A protective quantity of antibodies is usually produced within two to three weeks after vaccination (haemagglutination inhibition titer 40).[14] The vaccine is generally assumed to provide protection for a period of approximately six months to a year.

Adverse effects

The most common adverse effects are localised (i.e. at the injection site), mild and transient in nature. Other adverse effects are seldom seen. There is no evidence to suggest that the current vaccine is associated with an increased risk of Guillain-Barré syndrome. Previously observed incidents were related to another influenza vaccine, one that was used in the past.[15] A full description of all possible adverse effects can be found in the instructions for use of the influenza vaccines in question.

Developments

A considerable research effort is being made to further improve influenza vaccines based on inactivated virus, and to optimize the production process. This includes research into the use of additives (adjuvants) that can be used to bring about a better immune response. In addition, a cell-culture production technique is under development. This could replace the traditional method, which involves the use of hen's eggs. The first two influenza vaccines manufactured using cell culture techniques have already been registered in the Netherlands (but not yet in the rest of the European Union).

In the United States, aside from influenza vaccines based on inactivated virus, a live attenuated influenza vaccine is now available for use in healthy individuals aged from 5 to 49. This new vaccine is administered by means of a nose spray. This vaccine has not yet been registered in Europe. Accordingly, it is not being used here.

Chapter 3

Establishing target groups

In this chapter, the Committee first addresses the criteria that it used when assessing the target groups for whom influenza vaccination is advisable. This is followed by a discussion of the various target groups.

3.1 Assessment method

Seven criteria

When establishing the target groups for influenza vaccination, the Committee used the seven criteria formulated by the Health Council's National Vaccination Programme Review Committee. The details have also been published in scientific literature.[16] A detailed description of this assessment framework for public vaccination programmes can be found in the advisory report entitled 'The future of the national immunisation programme: towards a programme for all age-groups' (*De toekomst van het Rijksvaccinatieprogramma: naar een programma voor alle leeftijden*), that is scheduled for publication at about the same time as this advisory report.[13] The Health Council has used an assessment framework of this kind in other advisory reports on the topic of vaccination, such as the report on the vaccination of infants against pneumococci.[17]

The criteria are formulated in such a way that they can be used as a guideline for a well-founded decision about whether a specific vaccination for a given target group deserves a place in the public vaccination programme.

Accordingly, they can also be used when establishing the target groups for influenza vaccination within the National Influenza Prevention Programme (NPG). This involves a step by step consideration of the following points:

Seriousness and extent of the disease burden

1 The infectious disease causes considerable disease burden within the population:
   - the infectious disease is serious for individuals, and
   - the infectious disease affects or has the potential to affect a large number of people.

Effectiveness of the vaccination

2 Vaccination may be expected to considerably reduce the disease burden within the population:
   - the vaccine is effective for the prevention of disease or the reduction of symptoms
   - the necessary vaccination rate is attainable (if eradication or the creation of herd immunity is sought)

3 Any adverse reactions associated with vaccination are not sufficient to substantially diminish the public health benefit.

Acceptability of the vaccination

4 The inconvenience or discomfort that an individual may be expected to experience in connection with his/her personal vaccination is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

5 The inconvenience or discomfort that an individual may be expected to experience in connection with the vaccination programme as a whole is not disproportionate in relation to the health benefit for the individual concerned and the population as a whole.

Efficiency of the vaccination

6 The ratio between the cost of vaccination and the associated health benefit compares favourably to the cost-benefit ratio associated with other means of reducing the relevant disease burden.

Priority of the vaccination

7 The provision of vaccination may be expected to serve an urgent or potentially urgent public health need.

Use in this advisory report

How are the criteria for public vaccination programmes used in the assessment in this advisory report? The first important factor is the risk posed by influenza to the target group in question (criterion 1). This means that, within the target group, there must be an extra burden of disease as a result of influenza, in the form of serious disease or death. Secondly, the extent to which the vaccine is effective and safe carries considerable weight (criteria 2 and 3). Accordingly, it must be shown that influenza vaccination reduces the burden of disease safely and effectively. Thirdly there is the issue of cost effectiveness (criterion 6). While the Committee does take this into consideration, its remit means that it will ultimately have no part in deciding this issue. Finally, the Committee took into consideration the discomfort experienced by individuals as a result of their individual influenza vaccination (criterion 4) and the urgency of the public health interest (criterion 7) in reaching its judgement.

The assessment based on these criteria is summarised in an extensive table (Annex D). The results are set out below, in each case accompanied by the major considerations involved.

3.2 Assessment of vaccination in current target groups

With regard to a number of target groups for whom influenza vaccination was already recommended, the situation remains unchanged. The Committee's view is that they meet the criteria for public vaccination programmes. Accordingly, for these target groups, the Committee upholds the recommendation that they should be offered an influenza vaccination. This applies to the following groups:[5]

1 Patients with abnormalities and function disorders of the airways and lungs
2 Patients with a chronic disorder of cardiac function
3 Patients with diabetes mellitus
4 Patients with chronic renal insufficiency
5 Patients who have recently undergone a bone marrow transplant
6 Individuals who are infected with HIV
7 Children and adolescents from six months to eighteen years of age who use salicylates for a prolonged period
8 Mentally handicapped individuals living in intramural facilities
9 Individuals aged 65 and above
10 Individuals with reduced resistance to infections (for instance as a result of cirrhosis of the liver, asplenia (including functional asplenia), autoimmune diseases, and treatment involving chemotherapy)

11 Those resident in nursing homes who are not covered by these categories.

3.3 Assessment of vaccination in healthy individuals in the 50 to 65 age group

Importance in terms of public health

At present, neither in the Netherlands nor elsewhere, have any details been published of studies into the morbidity and mortality resulting from influenza in healthy individuals aged 50 to 65. In order to better understand the burden of disease and mortality resulting from influenza, the Health Council has contracted the Julius Center to investigate the problem. The following is a brief summary of the results of this study (a more detailed summary can be found in Annex E).

Given the lack of any national data that could be used to establish a direct link between influenza and various complications, the decision was taken to conduct an excess study. This provides a basis for making estimates. In this connection, the incidence of influenza measured via sentinel practices is related to mortality, hospital admissions, and visits to GPs in the Netherlands. By comparing the influenza season with the immediately adjacent periods (the peri-influenza season) and the summer, it is possible to make statements concerning the observed extra mortality, hospital admissions, and visits to GPs.

In this way, it was estimated that for all individuals in the 50 to 65 age group (both healthy individuals and those with an increased risk) periods in which the influenza virus is active coincide with extra mortality of 3.8 to 7.6 per 100,000 individuals per winter, relative to the peri-influenza season and the base period in the summer respectively. This is equivalent to 117 to 233 deaths per annum in the Netherlands.

When this was divided up into 5-year age groups, it emerged that the total extra mortality in the winter is mainly restricted to individuals aged from 60 to 65. In this group, the estimated total extra mortality per winter amounted to 7.7 to 16 deaths per 100,000 individuals, relative to the peri-influenza season and the base period in the summer respectively. In the 50 to 54 and 55 to 59 age groups, this estimated total extra mortality per winter was 2.7 to 4.5 and 1.9 to 4.7 deaths per 100,000 individuals respectively.

With regard to these mortality figures, it should be pointed out that (based on the data sources) no distinction can be made between healthy individuals and those with an increased risk.

In addition, for the 55 to 59 age group, total extra mortality per winter relative to the base period in the peri-influenza season was not statistically significant.

Furthermore, the data cannot automatically be causally interpreted, and the possibility of effects caused by interfering variables cannot be excluded. The smaller the observed differences in mortality, the more heavily these uncertainties weigh. Accordingly, the Committee attaches less value to the results obtained for individuals below 60 years of age than to those for the 60 to 65 age group. From the age of 60 onwards, there is a clear increase in the observed over-mortality.

In addition, it was estimated that – for healthy 50 to 65-year olds – the influenza periods coincided with an excess of hospital admissions (averaging between 17.7 and 38.0 per 100,000 individuals per winter) and visits to GPs (averaging between 632 and 1259 per 100,000 individuals per winter). The excess hospital admissions per individual category, classified by diagnosis at discharge, is not always statistically significant. The total excess hospital admissions per 100,000 individuals is statistically significant, however, and this increases with age (for the 60 to 65-year olds, this is between 26.1 and 66.2 per 100,000 individuals per winter).

With this data too, it is important to remember that the existence of a causal relationship has not been demonstrated and that the effects of interfering variables cannot be excluded.

Effectiveness and safety

No research has been carried out into the effectiveness of influenza vaccination in healthy individuals aged 50 to 65. However, data is available on the effectiveness of influenza vaccination in all healthy adults below the age of 65. A systematic review published in 2004 revealed that healthy adults below the age of 65 exhibited a 67 percent reduction in serologically confirmed influenza.[18] In the various studies on which this review was based, the reduction in question ranged from 50 to 90 percent. The reduction is dependent on a variety of factors, including the match between the circulating virus strain and the strains used to prepare the vaccine, and the influenza activity in the seasons concerned.[19,20] In terms of clinical influenza, these studies indicate an approximately 30 percent reduction of influenza-like illness and a 10 to 25 percent reduction in all upper respiratory tract infections.[19-21]

On the basis of the available data, it is unclear whether influenza vaccination also results in a reduction of complications and in the use of healthcare facilities (death, hospital admissions, visits to GPs). No research was conducted into a potential reduction in mortality, nor was it demonstrated that vaccination leads to a reduced number of hospital admissions.[18]

This may be related to the limited frequency of death and hospital admissions in the entire group of 18 to 65-year-olds.[19] Some of the available studies do indicate a reduction in absence due to illness, however.[20,21]

The adverse effects of influenza vaccination in healthy adults below the age of 65 consist primarily of pain and redness around the injection site. These symptoms were about twice as frequent in vaccinated subjects as in individuals who were given a placebo. A local adverse effect of this kind occurred in 59 percent of vaccinated subjects. No separate systematic adverse effects of influenza vaccination were found.[18]

Cost effectiveness

The PRISMA study that was carried out for the purposes of the CVZ report included a cost-effectiveness analysis (which only included direct costs, such as the purchase of the vaccine). This analysis revealed that influenza vaccination in healthy individuals aged 50 to 65 could be cost effective.[1] This is supported by a cost-effectiveness analysis published in Great Britain (which, aside from direct costs, also included indirect costs such as absence due to illness), with regard to healthy individuals in the 50 to 65 age group.[22]

On the basis of the study conducted by the Julius Center into disease and mortality resulting from influenza, a cost-effectiveness analysis was also carried out (see Annex F). This shows that the cost of influenza vaccination for all individuals aged from 50 to 65 is estimated at € 28,019 per year of life gained, if the peri-influenza season is taken as the base period. If the summer is used as the reference period, then the cost is € 9,421 per year of life gained. The costs associated with loss of productivity have been included.

When this was divided up into 5-year age groups, this cost-effectiveness analysis also showed that the costs per year of life gained were lowest in the 60 to 65 age range. If the peri-influenza season is taken as the reference period, then this is estimated at € 15,810 per year of life gained (including the costs of lost productivity), as against € 79,247, € 44,558 and € 37,632 per year of life gained for individuals in the 45 to 49, 50 to 54 and 55 to 59 age groups. If the summer is used as the reference period, then the cost for the 60 to 65 age group is € 4,314 per year of life gained, as against € 25,044, € 19,036 and € 11,151 for the 45 to 49, 50 to 54 and 55 to 59 age groups respectively.

In summary, it can be stated that the cost of influenza vaccination for individuals in the 60 to 65 age group will not exceed € 20,000 per year of life gained (including the costs of lost productivity), and that vaccination will very probably be cost effective. However, the Committee notes that the same restrictions and

uncertainties apply here as in the previously discussed excess study, on which these calculations are based.

Other cost-effectiveness analyses focus on all healthy adults below the age of 65. For this group as a whole, the conclusion is that vaccination is cost-effective and possibly even produces cost savings, based on both the direct costs and the indirect costs.[23-27] Furthermore, some of these analyses show that influenza vaccination is cheaper than antiviral therapy.[23-25,27]

Verdict on vaccination

To date, the effectiveness of influenza vaccination for healthy individuals in the 50 to 65 age group has not been separately investigated in sound clinical studies. In the entire group of healthy adults below the age of 65 (which, of course, also includes the 50 to 65 age group) the effectiveness of influenza vaccination in terms of catching influenza has been demonstrated.

A study carried out by the Julius Center (at the Health Council's instruction) into disease burden and mortality resulting from influenza, showed that for healthy individuals in the 50 to 65 age group, influenza periods coincided with an excess of visits to GPs, hospital admissions and mortality. The extra mortality mainly occurs in the 60 to 65 age group. The figure for excess hospital admissions per 100,000 individuals is also highest in that group.

Allowing for the restrictions and uncertainties that are associated with studies of this type, the Committee considers the findings for the 60 and above age group to be particularly relevant. On the basis of the subsequent cost-effectiveness analysis and in accordance with currently applicable standards, influenza vaccination for individuals in the 60 to 65 age group seems likely to be cost effective. The Committee takes the view that this is sufficient grounds for including healthy 60 to 65-year-olds in the target groups for vaccination against influenza.

3.4 Assessment of vaccination in pregnant women

Importance in terms of public health

Research has shown that it is rare for pregnant women to be admitted to hospital during the influenza season. There were no cases whatsoever of mortality caused by influenza.[28] Nor did influenza during pregnancy result in an increased risk of pregnancy complications in healthy women.[29,30] However, it has been shown that pregnant women suffering from a disorder that heightens the risk of complications caused by influenza (such as asthma) do have an increased risk of hospital

admission during the influenza season, in comparison to healthy pregnant women [29,31]

Effectiveness and safety

Research into the effectiveness of influenza vaccination in pregnant women shows that there is no difference between vaccinated and unvaccinated healthy pregnant women in terms of the chance that they will visit their GP in connection with an influenza-like illness.[28]

Furthermore, two American studies found no data to suggest that influenza vaccination during pregnancy was associated with additional adverse effects, pregnancy complications, or congenital defects. These two studies used study populations of 3707 and 252 pregnant women respectively. However, larger study populations need to be used before it can be definitely concluded that it is safe to administer influenza vaccinations to pregnant women.[28,32]

Cost effectiveness

There is no study data pertaining to the cost effectiveness of influenza vaccination in healthy pregnant women.

Verdict on vaccination

It appears that healthy pregnant women are not associated with an extra burden of disease as a result of influenza. In addition, the effectiveness of influenza vaccination in this group has not been demonstrated. Thus the Committee sees no reason to add healthy pregnant women to the target groups for influenza vaccination.

Pregnant women who make up part of a high-risk group for which vaccination is recommended will, of course, be eligible for an offer of vaccination on that basis. For them, the recommendation that they receive an influenza vaccination stands. It is reassuring to note that there is no evidence to indicate that influenza vaccination during pregnancy carries an increased risk of congenital defects or of pregnancy complications.

The Committee has also considered whether it might be useful to offer influenza vaccination to pregnant women, in order to protect their newborn children. The Committee examines this in more detail in the following section.

3.5 Assessment of vaccination in children

3.5.1 Infants below the age of six months

Influenza vaccines have not been registered or tested in infants below the age of six months. Accordingly, this group is not eligible for vaccination. Another option is to protect them by vaccinating people who regularly come into contact with them. Their most important contact within the family is often the mother, so it might be an option to offer vaccination to pregnant women as a means of protecting their future baby. It is also conceivable that vaccination of the mother during pregnancy could provide extra protection for her newborn child in the form of antibodies transferred via the placenta. Accordingly, this option is also considered here.

Importance in terms of public health

It has been shown that, during the influenza season, infants below the age of six months have an increased risk of being admitted to hospital.[33]

Effectiveness and safety

Studies have shown that the vaccination of pregnant women has no beneficial effect in terms of the risk of newborn children having to be seen by a doctor or admitted to hospital in connection with influenza or pneumonia.[28]

Two American studies found no data to suggest that influenza vaccination during pregnancy was associated with additional adverse effects, pregnancy complications, or congenital defects (see also section 3.4).[28,32]

Cost effectiveness

There are no cost-effectiveness studies on influenza vaccination in healthy pregnant women.

Verdict on vaccination

Infants below the age of six months are associated with extra disease as a result of influenza. Yet this group cannot be directly vaccinated against influenza. There is currently no scientific evidence that vaccination of the mother is an

effective means of reducing the number of infections or of diminishing the effects of influenza in infants below the age of six months.

For this reason, the Committee has decided against recommending that healthy pregnant women should be offered an influenza vaccination for the purpose of protecting infants below the age of six months.

3.5.2 *Children aged from six months to two years*

Importance in terms of public health

American studies have shown that, in periods when the influenza virus is in circulation, there is an increase in the number of hospital admissions of children up to the age of two.[33,34] No increase in mortality resulting from influenza was found.

Given the lack of any Dutch data on the burden of disease as a result of influenza among children, the Health Council has also contracted the Julius Center to investigate influenza related disease and mortality among children (see Annex E). This research has shown that there is no extra mortality among children below the age of two during periods of influenza. Nevertheless, the periods of influenza did coincide with excess hospital admissions among this group (on average, between 79 and 271 per 100,000 individuals per winter) and visits to GPs (on average, between 520 and 6578 per 100,000 individuals per winter). This means that, in a period of approximately eight weeks each year, the influenza virus could be responsible for between 312 and 1072 hospital admissions among children up to the age of two.

The excess hospital admissions specifically related to lower respiratory tract infections have been shown to largely involve infants up to the age of six months (between 26 and 429 hospital admissions per winter). It is worth noting that, compared to the influenza virus, respiratory syncytial virus in children up to the age of two appeared to be responsible for at least four times the number of admissions in relation to lower respiratory tract infections (the respective figures are between 13 and 143 admissions and from 488 to 608 admissions per 100,000 individuals per winter). It should be pointed out that this data is also subject to the above-mentioned limitations, which are inherent to research of this type.

The conclusion is that, in children of up to two years of age, the periods in which the influenza virus circulates do not coincide with excessive disease and mortality, but that they probably do coincide with extra hospital admissions and visits to GPs. The majority of such cases involved infants up to the age of six months.

Effectiveness and safety

Many questions still remain to be answered concerning the effectiveness of influenza vaccination in children aged from six months to two years. The studies into serologically or virologically confirmed influenza include very little data on such young children. This is because the study populations are very small. These studies found indications of a possible reduction in confirmed influenza as a result of influenza vaccination, yet these results are generally not statistically significant.[35,36]

As yet, therefore, there is no evidence that influenza vaccination results in a reduction of serologically or virologically confirmed influenza. No data whatsoever are given concerning the effectiveness of the influenza vaccine in clinical influenza, nor was it demonstrated that vaccination leads to a reduction in hospital admissions.[36]

The Scientific Panel on Vaccines and Immunisation of the European Centre for Disease prevention and Control (ECDC) has confirmed that, as yet, there is no clear scientific evidence to support the effectiveness of influenza vaccination in children aged from six months to two years.[37]

Furthermore, there has only been a limited amount of research into the possible adverse effects of influenza vaccination in children aged from six months to two years. The limited amount of data available does indicate that there are mild adverse effects (such as local reactions and fever).[38,39]

Cost effectiveness

No cost-effectiveness studies have been carried out in the Netherlands on influenza vaccination in children aged from six months to two years. Cost-effectiveness studies carried out in larger age-groups in other countries may not be applicable, as the effectiveness of influenza vaccination in children below the age of two has not been established.[36]

Verdict on vaccination

Published studies on this topic indicate that there is no extra mortality in healthy children below the age of two, although there may well be an extra burden of disease. The excess hospital admissions and visits to GPs found by the Julius Center, however, relates mainly to infants up to the age of six months. The influenza vaccination has not been not registered for individuals in this age group, so vaccinating them is not an option. While a vaccine is available for children aged

from six months to two years, its effectiveness has not been demonstrated. The Committee therefore recommends that this group should not be vaccinated.

Nevertheless, it does recommend that research be carried out into the effectiveness of influenza vaccination in such children. If the results of such research supported it, consideration might then be given to the possibility of adding these children to the target groups for influenza vaccination.

3.5.3 *Children aged two and above*

Importance in terms of public health

American studies have shown that, in periods when the influenza virus is in circulation, there is only a limited increase in the number of hospital admissions for children aged two and above. In addition, these studies found no increase in mortality resulting from influenza in this age group.[33,34] The study conducted by the Julius Center into disease burden and mortality resulting from influenza in children also showed that there was no clear extra burden of disease as a result of influenza in children aged two and above.

Effectiveness and safety

In this age group, vaccination leads to a 58 to 72 percent reduction in serologically or virologically confirmed influenza.[36,40] With regard to clinical influenza, a 28 to 59 percent reduction in influenza-like illness was found.[36,40]

In this group it was also unclear whether, with regard to complications caused by influenza, vaccination leads to a reduced number of hospital admissions or deaths. Nevertheless, cohort studies have found that vaccinating these children results in less absenteeism from school, reduced prescription of antibiotics and, for their carers, less absenteeism from work.[36,41]

Cost effectiveness

From cost-effectiveness studies that have been carried out in other countries, it has been concluded that if the direct costs (e.g. the purchase of the vaccine) and indirect costs (e.g. absenteeism from work by parents or carers) are included in the calculations, influenza vaccination in children (defined in the first study as children below the age of eighteen[42] and in the second study as children below the age of five[43]) would very probably produce cost savings. However, there is no

data available for the Netherlands. These are certainly important, given the differences in care and social insurance.

Verdict on vaccination

In children above the age of two, influenza vaccination is certainly effective, but not required, as influenza in this group no longer leads to serious disease or death. On this basis, the Committee currently sees no reason to add healthy children over two years of age to the target groups for influenza vaccination.

3.6 Assessment of vaccination in asthma sufferers up to the age of 18

In the present situation, vaccination is recommended for individuals up to the age of 18 who make up part of an at-risk group. This includes children suffering from asthma, cystic fibrosis, diabetes mellitus, congenital cardiac defects, and asplenia (including functional asplenia). The Committee takes the view that this group should continue to be offered influenza vaccination. Given the debate that has arisen concerning the effectiveness of influenza vaccination in countering asthma-related symptoms or complications in children suffering from asthma, this target group is discussed separately here.

Importance in terms of public health

Observational studies carried out in the United States show that the influenza season coincides with an increase in hospital admissions, visits to GPs, and prescriptions of antibiotics in children below fifteen years of age with an increased risk (most of whom are asthma sufferers).[44] However, there is no data concerning the burden of disease in the Netherlands.

Effectiveness and safety

In a randomised study of children suffering from asthma, which was carried out in the Netherlands, vaccinated children exhibited no reduction in the number or severity of asthma attacks relative to non-vaccinated children.[45] However, the vaccinated children did experience a better quality of life during the bout of influenza.[46]

There are a number of points to be made with regard to this first randomised study. For instance, in one of the two seasons studied the incidence of influenza

was very low. In addition, the virus strains and the observed effect throughout the seasons studied differed, which may have influenced the results.

Nor was the GP's diagnosis of asthma confirmed. These points have resulted in a debate concerning the conclusions that can be drawn from this study.[47]

Another Dutch observational study, which was carried out in 2002, revealed a reduction in acute lower respiratory tract infections among vaccinated juvenile asthma sufferers below the age of six.[48] In children above the age of six, however, no such reduction was found.[48] The CVZ report stated that there was a 41 percent reduction in respiratory tract infections in all children under the age of 18 with an increased risk.[1] The study carried out for this CVZ report also found a 43 percent reduction in visits to GPs in children below the age of 18 with an increased risk.[49]

In the past, it was thought that administering influenza vaccinations to asthma sufferers might aggravate their symptoms.[50] Since then, various studies have demonstrated that this is not the case. The administration of influenza vaccinations to this group can therefore be seen as safe.[50,51]

Cost effectiveness

The cost-effectiveness studies in the CVZ report gave an average of € 2,574 per prevented GP treatment.[1] This study only addressed the direct costs, not the indirect costs. However, beyond addressing the occurrence of complications in the primary health care system, this study does not permit conclusions to be drawn about possible deaths or hospital admissions, as the number of children examined was too small. Nevertheless, cost-effectiveness studies carried out in other countries (in which indirect costs were included) did show that vaccination can result in cost savings.[52,53]

Verdict on vaccination

Various observational studies into influenza vaccination in juvenile asthma sufferers found evidence for an extra burden of disease as a result of influenza. They also found that vaccination had a beneficial effect on yardsticks such as respiratory tract infections and visits to GPs.[1,48,49,54] However, these results were not confirmed by the only randomised study of which the Committee is aware.[45]

Taking all of the available data into account, it is the Committee's view that the possibility that influenza vaccination may have a beneficial effect for asthma sufferers up to the age of 18 cannot be dismissed at this moment in time. Additional and more convincing evidence would be required before the current offer of influenza vaccination to this at-risk group could be suspended.

For this reason, the Committee upholds the recommendation that juvenile asthma sufferers should be offered influenza vaccination. The Committee also recommends that further research be carried out into the effectiveness of influenza vaccination in juvenile asthma sufferers.

The Committee adds that it can imagine that the indication for influenza vaccination (such as asthma) could be reconsidered at regular intervals in each individual patient.

3.7 Assessment of vaccination in patients with furunculosis and members of their family

Furunculosis or Recurrent Boils is the repeated appearance of boils, which are generally caused by a *Staphylococcus aureus* infection. In the Netherlands, influenza vaccination for patients with furunculosis and for members of their family (or contacts of a comparable nature) has been recommended for quite some time. Nevertheless, the Committee is again judging vaccination of this target group, since there are doubts concerning the scientific basis that underpins the current recommendation. In other countries, this group of patients is not vaccinated. One difficulty, in practical terms, is that it is difficult to identify this group.

Importance in terms of public health

The scientific basis for previous recommendations concerning influenza vaccination for patients with furunculosis consists of two publications dating from the 1950s. These included various case reports and a selected case series, consisting of furunculosis patients (or a member of their family) who developed a post-influenza secondary pneumonia, caused by *Staphylococcus aureus*.[55,56]

In the Committee's view, however, these publications do not support the view that furunculosis patients are at greater risk of post-influenza secondary staphylococcal pneumonia.

Effectiveness and safety

There is no data concerning the effectiveness of influenza vaccination in this group.

Cost effectiveness

Nor is anything known about its cost effectiveness.

Verdict on vaccination

The Committee takes the view that the risk of furunculosis patients and members of their families developing post-influenza secondary staphylococcal pneumonia is probably slight. In addition, nothing is known about the effectiveness of influenza vaccination in this group. Nor does the Committee feel that there is any point in identifying *Staphylococcus aureus* carriers (even if it were feasible to do so), especially as so few of them will actually be suffering from furunculosis.

Accordingly, the Committee feels that there are substantial grounds for no longer including this group in the influenza vaccination programme. However, the Committee would urge therapists to be alert to the possibility of bacterial superinfections by *Staphylococcus aureus* in furunculosis patients.

3.8 Assessment of vaccination in healthcare personnel

Importance in terms of public health

Data from the available scientific literature shows that, in the performance of their duties, healthcare personnel are not at increased risk of acquiring an influenza infection. Furthermore, since healthcare personnel are generally among the healthy members of the population, this group would not be expected to experience excessive levels of death or disease following infection. However, this does not apply to the patients in their care. If the latter make up part of an at-risk group, then transmission of the virus from carer to patient will indeed result in an increased risk of serious disease or death.

Effectiveness and safety

The vaccination of healthcare personnel has two possible effects, the effect on the healthcare personnel themselves and the indirect effect – in terms of morbidity and mortality – on their patients.

Two randomised studies carried out in Britain investigated the indirect effectiveness of influenza vaccination on healthcare personnel in nursing homes and residential care homes.[57,58] An increase in vaccination coverage among such personnel led to an approximately 40 percent reduction in deaths among their

patients. However, in these studies, the reduction of influenza-like illness among patients was not statistically significant.

On this basis, the authors of a recent systematic review concluded that vaccinating healthcare personnel against influenza does have an indirect effect on morbidity and mortality among patients.[59]

A 2006 Cochrane review concluded, however, that there is no credible evidence for such indirect protection, as the results relating to influenza-like illness are not statistically significant.[60] Nevertheless, it was concluded that administering influenza vaccinations to the elderly residents of nursing homes and residential care homes reduces complications, and that giving influenza vaccinations to healthy adults reduces the number of influenza cases among them.[18,61] Accordingly, the authors quite understand why it is that healthcare personnel who care for the elderly opt to have influenza vaccinations. It is recommended that the effect of this measure should be investigated by means of well designed studies.

Very recently, following the publication of these reviews, a third randomised study was published in Britain.[62] This study focused on the 2003-2004 influenza season. It found that higher vaccination coverage among nursing home personnel was associated with specific effects among their patients. These involved a reduction in mortality, in influenza-like illness, in hospital admissions associated with influenza-like illness, and in visits to GPs associated with influenza-like illness. So it seems that there is evidence of indirect protection after all.

The conclusion reached in the above-mentioned 2006 systematic review concerning protection of the healthcare personnel themselves is based on three randomised studies.[59] The first is an American study in which the vaccination of healthcare personnel led to a reduction of 88 percent in serologically confirmed influenza.[20] The second study found no reduction in the incidence of influenza-like illness, but there was a poor match between the vaccines and the circulating virus strain.[63] The third study, which investigated the personnel of two children's hospitals, revealed a limited reduction in the average number of days' absence due to illness as a result of respiratory infections.[64]

Therefore, all things considered, the various studies provide only limited insights into the clinical effectiveness of influenza vaccination among healthcare personnel. However, as part of the assessment of vaccination among healthcare personnel, the Committee has included the previously discussed data on influenza vaccination in healthy adults. It assumes that the effectiveness of vaccination among healthcare personnel will not differ from that seen among other healthy adults.

Cost effectiveness

The previously discussed systematic review, conducted in 2006, concluded that the vaccination of healthcare personnel is cost effective, and that it probably even results in cost savings.[59]

Verdict on vaccination

Healthcare personnel themselves exhibit no clearly increased burden of disease as a result of influenza. The Committee anticipates the effectiveness of vaccination in this group to be comparable with that seen in healthy adults. It also expects the vaccination of healthcare personnel to result in a reduced burden of disease among patients. The Committee takes the view that this is not restricted to patients in nursing homes and residential care homes, but that it also applies to patients in hospitals.

The Committee believes that healthcare personnel who have regular, intensive contact with patients with an increased risk have a special responsibility in this regard. It is also important to note here that the vaccination of patients themselves does not provide full protection. For these reasons, the Committee feels that it is justifiable to add healthcare personnel in hospitals, residential care homes and nursing homes to the target groups for influenza vaccination. One additional concern is the need to safeguard the continuity of adequate care for such patients. After all, the vaccination of healthcare personnel can also lead to a reduction in absence due to illness.

The Committee feels that this special responsibility also extends to other healthcare personnel (such as GPs and home care workers), especially where such personnel are in direct contact with patients who are at very high risk of serious morbidity and mortality resulting from influenza. The Committee anticipates, however, that it would be difficult to draw sharp distinctions between various types of patient contacts in practice. Accordingly, it feels that the general vaccination of a well-defined target group of personnel would be more feasible in organisational terms than selective vaccination, and that it would result in more extensive vaccination coverage. For this reason, the Committee recommends that healthcare personnel who, in the course of their work in the cure or care sector, have direct contact with patients, should be vaccinated against influenza.

3.9 Assessment of vaccination in the family members of individuals in an at-risk group

Importance in terms of public health

In theory, those in at-risk groups will already be vaccinated against influenza. Nevertheless, the possibility of vaccinating members of their family might be worthy of consideration, in order to provide these at-risk individuals with extra protection. However, the Committee has been unable to find any information in the scientific literature that specifically relates to the risk posed by influenza in family members to those who are at increased risk of developing complications or even of dying as a result of influenza.

Nor is there any data relating to the option of protecting them from influenza by vaccinating the members of their family. Nevertheless, a demographic statistical study that was carried out in 2004 did unearth evidence for the transmission of influenza within families.[65]

Effectiveness and safety

With regard to the effectiveness and safety of influenza vaccination, beyond the data on healthy adults there is no supplementary data specifically pertaining to individuals with family contacts in an at-risk group.

Cost effectiveness

Nothing is known about its cost effectiveness.

Verdict on vaccination

Due to the lack of data, the Committee is not in favour of vaccinating all those individuals who have family contact with people in an at-risk group. The Committee is well able to imagine that individuals with family contacts who are at very high risk of serious morbidity and mortality resulting from influenza will arrange to be vaccinated as a matter of course. On the basis of previously discussed data (the demonstrated serological and clinical effectiveness of vaccination in healthy adults and the reduction in transmission achieved by vaccinating healthcare personnel in nursing homes and residential care homes), the Committee expects that very high-risk individuals will, by this means, be less exposed to

influenza, even if they themselves have already been vaccinated. While it is impossible to provide a comprehensive list of all very high-risk individuals, the following do fall into this category:

- patients with serious abnormalities and dysfunctions of the cardiac function or lung function who, despite their medication, are at great risk of decompensation of this cardiac function or lung function
- patients with severe liver or kidney failure
- patients whose immune system is compromised (e.g. as a result of HIV infection, chemotherapy or treatment with drugs that suppress the immune system).

These groups include individuals of all ages. With regard to individual patients who do not fall within any of the categories cited here, it is the responsibility of the attending physician to assess the requirement to vaccinate the patient's family contacts.

3.10 Assessment of vaccination in professions that involve intensive contacts with the population

Importance in terms of public health

The available scientific literature contains no data to show that healthy individuals who, in the performance of their duties, have intensive contacts with other individuals (e.g. teachers) are at increased risk of acquiring an influenza infection or of serious morbidity or mortality resulting from influenza. Nor are there any studies to show whether those in professions that involve intensive contacts with the population have an increased risk of infecting individuals who make up part of an at-risk group.

Effectiveness and safety

The anticipated effectiveness of influenza vaccination in this target group is the same as that in healthy adults.

Cost effectiveness

Furthermore, its cost effectiveness is expected to be the same as that in healthy adults.

Verdict on vaccination

Based on the available scientific literature, there is no reason to assume that those in professions that involve intensive contacts with the population are at increased risk of influenza or of serious morbidity or mortality resulting from influenza. Nor does the Committee have any reason to assume that this group has an increased risk of infecting individuals who make up part of an at-risk group. On this basis, the Committee sees no grounds for adding this group to the target groups for influenza vaccination.

3.11 Assessment of vaccination in professions that involve intensive contacts with poultry

The Committee has a special reason for addressing the issue of professions that involve intensive contacts with poultry (poultry farmers, veterinarians) here. In the past few years – as recently as February 2007 in the United Kingdom – influenza virus (avian influenza or 'bird flu') infections in poultry have caused major problems on poultry farms. As yet, there have been few reports of human infections with the virus strains responsible for these outbreaks. Simultaneous infection with 'human' influenza and avian influenza carries the risk that the infecting viral strains will exchange genetic information. This could result in the creation of a new strain of virus that is highly infectious in humans.

Importance in terms of public health

There is no scientific literature available indicating that healthy individuals who, in the performance of their duties, have numerous intensive contacts with poultry are at increased risk of acquiring an influenza infection or of serious morbidity or mortality as a result. Yet there may be an increased risk of coming into contact with avian influenza (bird flu). However, the influenza vaccine is ineffective against this disease.

Effectiveness and safety

The effectiveness and safety of influenza vaccination in healthy individuals who, in the performance of their duties, have numerous intensive contacts with poultry is generally expected to be the same as that in healthy adults.

Cost effectiveness

The cost effectiveness of influenza vaccination in this group is also generally expected to be the same as that for vaccination in healthy adults.

Verdict on vaccination

In the absence of an avian influenza epidemic, the Committee sees no reason for switching to annual vaccination for healthy individuals who, in the performance of their duties, have numerous intensive contacts with poultry. However, this would not apply in the event of an outbreak of avian influenza. There would then be a risk that genetic material might be exchanged between different strains of the virus, giving rise to the possibility that a new virus strain might emerge which is highly infectious in humans. Such an event might well create the need to vaccinate veterinary personnel and poultry farmers. The committee sees this decision as one the Minister would have to make at the time, if necessary on the basis of advice from the Outbreak Management Team (OMT).

3.12 Assessment of vaccination in drug addicts

Importance in terms of public health

Drug addicts may have an underlying affliction, whereby extra morbidity or mortality resulting from influenza can be expected (caused by HIV infection, for example). On this basis, they already constitute a target group for influenza vaccination. Where this is not the case, then the addict in question is not considered to be immune compromised. In addition, no study data is available for this group concerning the occurrence of extra morbidity or mortality resulting from influenza. All things considered, there is no reason to expect extra health impairment in this group.

Effectiveness and safety

There is no data specifically concerning the effectiveness of influenza vaccination in drug addicts. However, there are no reasons for assuming that the effectiveness of influenza vaccination in drug addicts will be clearly different from that in healthy adults.

Cost effectiveness

Nothing is known about its cost effectiveness.

Verdict on vaccination

The Committee has found no evidence to suggest that drug addicts might have reduced immunity. Thus the Committee sees no reason to assume that this group is at increased risk of serious morbidity or mortality resulting from influenza. On this basis, therefore, the Committee sees no reason why drug addicts should be added to the target groups for influenza vaccination.

If, on the basis of an underlying affliction, a drug addict already falls within one of the target groups for influenza vaccination (resulting from an HIV infection, for example), then that does of course constitute sufficient reason for an influenza vaccination. Extra alertness to this situation is justified, since this group is often less familiar with regular care.

3.13 Assessment of vaccination in people with alcohol addiction

Importance in terms of public health

People with alcohol addiction may have an underlying affliction, whereby extra morbidity or mortality resulting from influenza can be expected (caused by cirrhosis of the liver, for example). For this reason, they already constitute a target group for influenza vaccination. If this is not the case then there is no expectation of serious morbidity or mortality resulting from influenza. While mild disorders of the immune system have been found in people with alcohol addiction, this group cannot be classified as immune compromised. Furthermore, none of the study data available for this group indicates the occurrence of extra morbidity or mortality resulting from influenza. Accordingly, there is no reason to expect it in this group.

Effectiveness and safety

There is no reason to assume that the effectiveness of influenza vaccination in people with alcohol addiction will be clearly different from that in healthy adults.

Cost effectiveness

Nothing is known about its cost effectiveness.

Verdict on vaccination

People with alcohol addiction are, in theory, not considered to be immune compromised. Thus the Committee sees no reason to assume that this group is at increased risk of serious morbidity or mortality resulting from influenza. On this basis, the Committee sees no reason why people with alcohol addiction should be added to the target groups for influenza vaccination.

If, on the basis of an underlying affliction, someone with an alcohol addiction already falls within one of the target groups for influenza vaccination (due to cirrhosis of the liver, for example), then they would of course be eligible for an influenza vaccination.

3.14 Additional considerations

When assessing the requirement for influenza vaccination, it is necessary to address two extra points that did not appear among the criteria listed in section 3.1. The first of these involves the question of the extent to which the vaccination of a given target group helps to reduce the circulation of the virus within that target group, or within the population as a whole. The second question concerns the extent to which routine vaccination contributes to preparations for a pandemic. In evaluating this issue, the Committee adheres to the principle that the criteria set out in section 3.1 should first be met.

Reduction of the circulation of the virus within the target group, or within the population as a whole

This consideration is usually cited in connection with the part played by children in the transmission of influenza, and with how this might be affected by influenza vaccination. Evidence from a number of studies indicates that the administration of an influenza vaccination to children reduces transmission of the influenza virus.[65-67] However, the available data on this issue is still very limited, in both scope and clarity. This is confirmed by the Scientific Panel on Vaccines and Immunisation of the European Centre for Disease prevention and Control (ECDC).[37] Nor is it clear what effect an annual influenza vaccination at an early age would have on the course of influenza later in life. What is needed, therefore,

is a well-designed study to evaluate both these potential indirect effects and the long-term effects of influenza vaccination in children.

Contribution to preparations for a pandemic

In the Committee's view, the only way in which influenza vaccination could contribute to preparations for a pandemic would be by boosting influenza vaccine production capacity. This is because past experience has demonstrated the adequacy of the Netherlands' existing infrastructure for large-scale vaccination campaigns. A recent example is the inclusion of vaccination against group C meningococci in the NVP.[68] However, the Committee has been unable to find any information in the scientific literature to indicate that the severity of a possible pandemic could be directly influenced by widening the vaccination coverage for epidemic influenza.

Chapter 4

Widening vaccination coverage

In this section, the Committee examines a number of options for widening influenza vaccination coverage among the target groups. For the aspects in question, this has been specifically investigated in terms of influenza vaccination. For general recommendations concerning public information campaigns on vaccination see the advisory report entitled ‘De toekomst van het Rijksvaccinatieprogramma: naar een programma voor alle leeftijden’ [The future of the National Immunisation Programme (RVP): Towards a programme for all age-groups].[13]

4.1 Current vaccination coverage

Influenza vaccination coverage in the Netherlands is reasonably stable, involving approximately 20 percent of the total population each year. In the total at-risk population for which influenza vaccination is recommended, this is equivalent to approximately 75-80 percent.[69,70] In 2001, 81 percent of all individuals over 65 years of age were vaccinated. In those cases where there was only an age-related indication, vaccination coverage was 73 percent. In those where there was one or more additional indication, vaccination coverage was 85 percent, or even higher.[69] Each year, vaccinations are administered to approximately 70 percent of individuals between 18 and 65 years of age with a disorder which leads to increased risk.[49]

There is less certainty regarding vaccination coverage in individuals below the age of 18 who have an increased risk of developing complications or of dying

as a result of influenza. The CVZ report stated that these individuals had a vaccination coverage of 55 percent.[1] Vaccination coverage in this group therefore appears to be a little below average, so it merits greater consideration.

In general, vaccination coverage in the Netherlands can therefore be described as extremely acceptable. In the following sections, ways in which this vaccination coverage can be maintained and, where possible, expanded, will be discussed.

4.2 Public information campaigns

A questionnaire study carried out by NIVEL (Netherlands Institute for Health Services Research) in 2002 (for the purposes of the CVZ report) found that the major reason for participating in influenza vaccination programmes was either a chronic disorder or being aged 65 or above.[1,71.] This was the reason given by 96 percent of elderly people who had been vaccinated (81 percent gave their age as the reason, while 15 percent said that this was in connection with a chronic disorder) and by 76 percent of those with an increased risk who were below the age of 65. Fifty six percent of vaccinated healthy adults gave a chronic disorder as the reason for obtaining a vaccination.

The major reason that people gave for not taking part in the vaccination programme was that they were not eligible – or that they mistakenly believed this to be the case. No less than 38 percent of unvaccinated individuals below the age of 65 with a chronic disorder leading to increased risk believed that they were not eligible for vaccination.

Some of the other major reasons that people gave for not obtaining influenza vaccine were: ‘adequate resistance to influenza’ (32 percent), ‘my GP thought that it was not necessary’ (7 percent), ‘influenza is not serious’ (9 percent), ‘vaccination is unnecessary’ (6 percent) and ‘bad experiences with vaccination in the past’ (e.g. catching influenza even after being vaccinated or suffering influenza-like symptoms for a protracted period following vaccination) (6 percent).[71,72]

It is worth noting that similar studies in other European countries (Poland, Sweden, Germany, Spain, Italy and Great Britain) have shown that all of these reasons were also put forward in these countries.[73,74] In addition to the factors mentioned above, an earlier Dutch study in healthy elderly people (indication for influenza vaccination purely on the basis of age) showed that existing myths about the adverse effects of the vaccine also constitute a major reason for people to refuse influenza vaccination.[75]

What implications does this have for the public information campaigns? In the context of attempts to achieve more extensive vaccination coverage within

the at-risk groups, these campaigns should also focus on those who are unaware that vaccination is recommended for people in their situation. Patient associations should certainly get involved in this. Furthermore, vaccination coverage could be expanded still further by providing information about the risks of influenza, the effectiveness of the vaccination, and the limited adverse effects.

4.3 Methods of inviting people to attend for vaccination

The above-mentioned study by NIVEL in 2002 showed that 85 percent of the individuals in an at-risk group opted for vaccination on the advice of their GP. Seventy one percent of these individuals received a personal invitation from their GP to attend for vaccination. Only sixteen percent did not respond to the invitation.[72] The GP therefore plays an important part, and a personal invitation significantly increases vaccination coverage.

In addition to a personal invitation from their GP, sending out reminders may also be important in terms of vaccination coverage. This was borne out by one study which revealed a correlation between the introduction of the practice of sending reminders and an increase in the vaccination coverage.[76] Another study showed that vaccination coverage in practices that sent out reminders was greater than in practices which did not do so.[69]

Evidence has also been found which bears out the usefulness of automated selection of patients with an indication for influenza vaccination.[77] To this end, GPs can make use of the influenza module of the GP information system (HIS). The personal invitations can be printed out automatically, as can the reminders.

4.4 Provision

The Minister of Health, Welfare and Sport has asked the Health Council to identify scientific arguments for and against the provision of influenza vaccination free of charge.

Studies carried out in other countries show that where people are required to meet some or all of the cost of the influenza vaccine, this can result in financial barriers to participation. In Poland, for example, 25 percent of the unvaccinated individuals in groups with an increased risk (indication for influenza vaccination on the basis of age and/or the presence of a disorder) cited this as the reason for not obtaining an influenza vaccination.[73]

In order to clarify the situation, the Committee feels it important that influenza vaccination for all target groups that are eligible for vaccination should be

available without any financial thresholds. This would allow current vaccination coverage to be maintained and possibly even increased.

4.5 The GP's role

The NIVEL study that was carried out for the purposes of the CVZ report shows that 94 percent of all influenza vaccines are administered by GPs.[72] This means that GPs are the most important distribution channel for influenza vaccination. While six percent of vaccinated individuals collected the vaccine on the advice of a medical specialist, the vaccination itself was usually carried out by the GP.

Given current vaccination coverage, it is appropriate to view GPs as the appropriate institution for administering influenza vaccinations. In this connection, good organisation is essential. This is because studies have shown that in GP's practices where both GPs and their assistants administer the vaccinations, vaccination coverage is higher than when this task is performed exclusively by the former, or exclusively by the latter.[69]

If it is not feasible for the vaccination to be carried out by the GP, then it is vital that there are clear agreements about who will take responsibility for administering the influenza vaccination.

4.6 Nationwide support

The continued success of the National Influenza Prevention Programme (NPG) is still largely dependent on nationwide support, as provided by the National Institute of Public Health and the Environment (RIVM). This will allow the general public information campaign to retain its structure, while facilitating the coordination of the programme at national level.

4.7 Focus on special target groups

Of all the new target groups for influenza vaccination discussed in this advisory report, healthcare personnel is one that requires special consideration. In this case, for instance, vaccination by the GP is not a logical option. In this target group, influenza vaccinations can best be administered at the place of work, possibly by occupational health service staff.[78]

However, research carried out abroad has shown that increasing vaccination coverage among healthcare personnel is no easy matter, despite the use of active information campaigns and the provision of free vaccine.[79,80] It has also been shown that a number of factors contribute to the acceptance of influenza vaccina-

tion among healthcare personnel.[78,81-83] To some extent this was a matter of perception, particularly in relation to the risk involved and the seriousness of the illness in question. There was also the matter of people's confidence in the effectiveness and safety of the vaccine, and in claims that it had no adverse effects.

Other important factors were that vaccination was free of charge and that there were sufficient opportunities to attend for vaccination. However, the questions of whether or not these determinants also apply to the Dutch situation, and if so to what extent, were not investigated. An investigation of these issues can have major implications for the development of an effective information campaign.

Individuals aged 60 to 65, like those above the age of 65, can have the influenza vaccination administered by their GP.

In the case of children suffering from a disorder that can heighten the risk of morbidity and mortality resulting from influenza, vaccination coverage appears to be a little below average. A striking feature is that 23 percent of these children elect to be vaccinated on the advice of a medical specialist.[72] Here it would seem that the medical specialist's advice is even more important than in the case of adults with an increased risk. However, the vaccination itself is administered at the GP's surgery. Accordingly, in this group of children, it is a matter of the utmost importance that the medical specialist and the GP in question should be able to communicate effectively with one another.

Another group that merits extra consideration consists of chronically ill individuals who, to a large extent, are treated by medical specialists rather than by their GP. In their case too, effective communication between the medical specialist and the GP is essential. By this means, the risk that they might not be offered an influenza vaccination can be minimised.

Chapter 5

Conclusions and recommendations

This chapter contains a summary of the Committee's conclusions and recommendations.

5.1 Target groups for influenza vaccination

Offer to fifteen target groups

The situation remains unchanged with regard to the recommendation concerning influenza vaccination for the following target groups:

- patients with abnormalities and function disorders of the airways and lungs (even if they are below the age of 18)
- patients with a chronic disorder of cardiac function
- patients with diabetes mellitus
- patients with chronic renal insufficiency
- patients who have recently undergone a bone marrow transplant
- individuals who are infected with HIV
- children and adolescents from six months to eighteen years of age who use salicylates for a prolonged period
- mentally handicapped individuals living in intramural facilities
- individuals aged 65 and above

- individuals with reduced resistance to infections (as a result of cirrhosis of the liver, asplenia (including functional asplenia), autoimmune diseases, chemotherapy or drugs that suppress the immune system)
- those resident in nursing homes who are not covered by these categories.

New target groups for which influenza vaccination is recommended are:
- individuals aged from 60 to 65
- the staff of nursing homes, residential care homes and hospitals
- healthcare personnel who have direct contact with patients
- family members of individuals with a very high-risk of serious morbidity and mortality resulting from influenza.

Withdraw the offer of vaccination

For patients with furunculosis and members of their family, the recommendation concerning influenza vaccination is withdrawn.

Do not add

No recommendation concerning influenza vaccination is made for the following groups that have been discussed:
- individuals from 50 to 59 years of age
- pregnant women
- healthy children
- professions that involve intensive contacts with the population
- professions that involve intensive contacts with poultry
- drug addicts
- people with alcohol addiction.

It should be mentioned that any individuals in these latter groups who fall into one of the fifteen target groups for influenza vaccination will, of course, be eligible for influenza vaccination.

5.2 Other recommendations

5.2.1 Widening vaccination coverage

In general, the Netherlands already has extensive vaccination coverage with regard to influenza. In order to maintain or even improve this vaccination coverage, the following points are important:

- target information campaigns on individuals in at-risk groups who are unaware that vaccination is recommended for them
- provide information about the risks of influenza, and the effectiveness and limited adverse effects of influenza vaccination
- maintain the pivotal role played by GPs and promote:
  - the automated selection of patients
  - personal invitations from GPs to attend for vaccination
  - sending out reminders
- maintaining the principle that influenza vaccine should be available for all target groups, without any financial thresholds
- if it is not feasible for the vaccination to be carried out by the GP, then clear agreements must be reached about who will take responsibility for administering the influenza vaccination
- maintain nationwide support for the National Influenza Prevention Programme (NPG)
- initiate research into the acceptance of influenza vaccination among healthcare personnel in the Netherlands and the development of an effective information campaign
- see to it that there is effective communication between the medical specialist and the GP concerning:
  - influenza vaccination for children in at-risk groups
  - influenza vaccination for chronically ill individuals who, to a large extent, are treated by medical specialists.

For general recommendations concerning public information campaigns on vaccination see the advisory report entitled *'De toekomst van het Rijksvaccinatieprogramma: naar een programma voor alle leeftijden'* [The future of the National Immunisation Programme (RVP): Towards a programme for all age-groups], which was produced by the National Vaccination Programme Review Committee.[13]

5.2.2 *Recommendations for further research*

The Committee recommends that the following studies be carried out:

- research into the effectiveness of influenza vaccination in children aged from six months to two years
- further research into the effectiveness of influenza vaccination in juvenile asthma sufferers
- research into the possible indirect effects of influenza vaccination in healthy children (as a result of reduced transmission)
- research into the long-term effects that annual influenza vaccination at an early age may have on the clinical course of influenza later in life
- continuation and intensification of research aimed at improving the effectiveness of influenza vaccines.

References

1 Kroes ME. Nationaal Programma Griepppreventie: het succes van de griepprik. 162. 2003.

2 World Health Organisation. Influenza vaccines. Wkly Epidemiol Rec. 2007; 75: 281-288.

3 Macroepidemiology of Influenza Vaccination (MIV) Study Group. The macro-epidemiology of influenza vaccination in 56 countries, 1997--2003. Vaccine. 2005; 23: 5133-5143.

4 Centers for Disease Control and Prevention. Prevention and Control of Influenza: Recommendations of the Advisory Committee on Immunization Practises (ACIP). MMWR Early Release. 2006; 55: 1-41.

5 Gezondheidsraad: Commissie Vaccinatie tegen influenza/ Health Council of the Netherlands: committee on influenza vaccination. Vaccinatie tegen influenza seizoen 1998-1999/ Influenza vaccination season 1998-1999. 1998/17. 1998. Rijswijk, Gezondheidsraad/ Health Council of the Netherlands.

6 van Essen GA, Sorgdrager YCG, Salemink GW *et al.* NHG-standaard Influenza en influenzavaccinatie. 1996. http://nhg.artsennet.nl/

7 Cools HJM, Herngreen JJ, de Jong RE *et al.* NVVA richtlijn Influenzapreventie in verpleeghuizen en verzorgingshuizen. 2004.

8 van Essen GA, Berg HF, Bueving HJ *et al.* NHG-standaard Influenzapandemie. 2007. http://nhg.artsennet.nl/

9 Nicholson KG, Wood JM, Zambon M. Influenza. Lancet. 2003; 362: 1733-1745.

10 Fouchier RA, Munster V, Wallensten A *et al.* Characterization of a novel influenza A virus hemagglutinin subtype (H16) obtained from black-headed gulls. J Virol. 2005; 79: 2814-2822.

11 Sprenger MJ, Mulder PG, Beyer WE *et al.* Impact of influenza on mortality in relation to age and underlying disease, 1967-1989. Int J Epidemiol. 1993; 22: 334-340.

12 Raad voor de Volksgezondheid en Zorg. Zinnige en duurzame zorg. Advies nr. 06/06. 2006. Den Haag, Raad voor de Volksgezondheid en Zorg.
13 Gezondheidsraad/ Health Council of the Netherlands. De toekomst van het Rijksvaccinatieprogramma: naar een programma voor alle leeftijden. publicatie nr 2007/02. 2007. Den Haag/ The Hague, Gezondheidsraad/ Health Council of the Netherlands.
14 European medicines Agency (EMEA). Note for guidance on harmonization of requirements of influenza vaccines CPMP/BWP/214/96, 1997. www.emea.eu.int/pdfs/human/bwp/021496en.pdf.12-3-1997.
15 Juurlink DN, Stukel TA, Kwong J *et al.* Guillain-Barre syndrome after influenza vaccination in adults: a population-based study. Arch Intern Med. 2006; 166: 2217-2221.
16 Verweij M, Dawson A. Ethical principles for collective immunisation programmes. Vaccine. 2004; 22: 3122-3126.
17 Gezondheidsraad/ Health Council of the Netherlands. Vaccinatie van zuigelingen tegen pneumokokkeninfecties/ Vaccination of infants against pneumococcal infections. publicatie nr. 2005/ 13. 2005. Den Haag/ The Hague, Gezondheidsraad/ Health Council of the Netherlands.
18 Demicheli V, Rivetti D, Deeks JJ *et al.* Vaccines for preventing influenza in healthy adults. Cochrane Database Syst Rev. 2004; CD001269.
19 Bridges CB, Thompson WW, Meltzer MI *et al.* Effectiveness and cost-benefit of influenza vaccination of healthy working adults: A randomized controlled trial. JAMA. 2000; 284: 1655-1663.
20 Wilde JA, McMillan JA, Serwint J *et al.* Effectiveness of influenza vaccine in health care professionals: a randomized trial. JAMA. 1999; 281: 908-913.
21 Nichol KL, Lind A, Margolis KL *et al.* The effectiveness of vaccination against influenza in healthy, working adults. N Engl J Med. 1995; 333: 889-893.
22 Turner DA, Wailoo AJ, Cooper NJ *et al.* The cost-effectiveness of influenza vaccination of healthy adults 50-64 years of age. Vaccine. 2006; 24: 1035-1043.
23 Rothberg MB, Rose DN. Vaccination versus treatment of influenza in working adults: a cost-effectiveness analysis. Am J Med. 2005; 118: 68-77.
24 Postma MJ, Jansema P, Scheijbeler HW *et al.* Scenarios on costs and savings of influenza treatment and prevention for Dutch healthy working adults. Vaccine. 2005; 23: 5365-5371.
25 Lee PY, Matchar DB, Clements DA *et al.* Economic analysis of influenza vaccination and antiviral treatment for healthy working adults. Ann Intern Med. 2002; 137: 225-231.
26 Nichol KL. Cost-benefit analysis of a strategy to vaccinate healthy working adults against influenza. Arch Intern Med. 2001; 161: 749-759.
27 Muennig PA, Khan K. Cost-effectiveness of vaccination versus treatment of influenza in healthy adolescents and adults. Clin Infect Dis. 2001; 33: 1879-1885.
28 Black SB, Shinefield HR, France EK *et al.* Effectiveness of influenza vaccine during pregnancy in preventing hospitalizations and outpatient visits for respiratory illness in pregnant women and their infants. Am J Perinatol. 2004; 21: 333-339.

29 Hartert TV, Neuzil KM, Shintani AK *et al.* Maternal morbidity and perinatal outcomes among pregnant women with respiratory hospitalizations during influenza season. Am J Obstet Gynecol. 2003; 189: 1705-1712.

30 Acs N, Banhidy F, Puho E *et al.* Pregnancy complications and delivery outcomes of pregnant women with influenza. J Matern Fetal Neonatal Med. 2006; 19: 135-140.

31 Neuzil KM, Reed GW, Mitchel EF *et al.* Impact of influenza on acute cardiopulmonary hospitalizations in pregnant women. Am J Epidemiol. 1998; 148: 1094-1102.

32 Munoz FM, Greisinger AJ, Wehmanen OA *et al.* Safety of influenza vaccination during pregnancy. Am J Obstet Gynecol. 2005; 192: 1098-1106.

33 Neuzil KM, Mellen BG, Wright PF *et al.* The effect of influenza on hospitalizations, outpatient visits, and courses of antibiotics in children. N Engl J Med. 2000; 342: 225-231.

34 Izurieta HS, Thompson WW, Kramarz P *et al.* Influenza and the rates of hospitalization for respiratory disease among infants and young children. N Engl J Med. 2000; 342: 232-239.

35 Hoberman A, Greenberg DP, Paradise JL *et al.* Effectiveness of inactivated influenza vaccine in preventing acute otitis media in young children: a randomized controlled trial. JAMA. 2003; 290: 1608-1616.

36 Jefferson T, Smith S, Demicheli V *et al.* Assessment of the efficacy and effectiveness of influenza vaccines in healthy children: systematic review. Lancet. 2005; 365: 773-780.

37 Technical report of the scientific panel on vaccines and immunisation. Infant and children seasonal immunisation against influenza on a routine basis during inter-pandemic period. European Centre for Disease prevention and Control (ECDC). 2007.

38 Neuzil KM, Dupont WD, Wright PF *et al.* Efficacy of inactivated and cold-adapted vaccines against influenza A infection, 1985 to 1990: the pediatric experience. Pediatr Infect Dis J. 2001; 20: 733-740.

39 McMahon AW, Iskander J, Haber P *et al.* Adverse events after inactivated influenza vaccination among children less than 2 years of age: analysis of reports from the vaccine adverse event reporting system, 1990-2003. Pediatrics. 2005; 115: 453-460.

40 Negri E, Colombo C, Giordano L *et al.* Influenza vaccine in healthy children: a meta-analysis. Vaccine. 2005; 23: 2851-2861.

41 Heikkinen T, Silvennoinen H, Peltola V *et al.* Burden of influenza in children in the community. J Infect Dis. 2004; 190: 1369-1373.

42 White T, Lavoie S, Nettleman MD. Potential cost savings attributable to influenza vaccination of school-aged children. Pediatrics. 1999; 103: e73.

43 Cohen GM, Nettleman MD. Economic impact of influenza vaccination in preschool children. Pediatrics. 2000; 106: 973-976.

44 Neuzil KM, Wright PF, Mitchel EF, Jr. *et al.* The burden of influenza illness in children with asthma and other chronic medical conditions. J Pediatr. 2000; 137: 856-864.

45 Bueving HJ, Bernsen RM, de Jongste JC *et al.* Influenza vaccination in children with asthma: randomized double-blind placebo-controlled trial. Am J Respir Crit Care Med. 2004; 169: 488-493.

46 Bueving HJ, van der Wouden JC, Raat H *et al.* Influenza vaccination in asthmatic children: effects on quality of life and symptoms. Eur Respir J. 2004; 24: 925-931.

47 Fleming DM, Monto AS. Influenza Vaccination in Children with Asthma: No Reason to Change Current Recommendations (correspondence). Am J Respir Crit Care Med. 2005; 171: 931.

48 Smits AJ, Hak E, Stalman WA *et al.* Clinical effectiveness of conventional influenza vaccination in asthmatic children. Epidemiol Infect. 2002; 128: 205-211.

49 Hak E, Buskens E, van Essen GA *et al.* Clinical effectiveness of influenza vaccination in persons younger than 65 years with high-risk medical conditions: the PRISMA study. Arch Intern Med. 2005; 165: 274-280.

50 Cates CJ, Jefferson TO, Bara AI *et al.* Vaccines for preventing influenza in people with asthma. Cochrane Database Syst Rev. 2004; CD000364.

51 Bueving HJ, Bernsen RM, de Jongste JC *et al.* Does influenza vaccination exacerbate asthma in children? Vaccine. 2004; 23: 91-96.

52 Meltzer MI, Neuzil KM, Griffin MR *et al.* An economic analysis of annual influenza vaccination of children. Vaccine. 2005; 23: 1004-1014.

53 Dayan GH, Nguyen VH, Debbag R *et al.* Cost-effectiveness of influenza vaccination in high-risk children in Argentina. Vaccine. 2001; 19: 4204-4213.

54 Kramarz P, Destefano F, Gargiullo PM *et al.* Does influenza vaccination prevent asthma exacerbations in children? J Pediatr. 2001; 138: 306-310.

55 Mulder J. Furunculose en staphylococcus-bronchopneumonie bij influenza/ Furunculosis and staphylococcal bronchopneumonia in association with influenza (article in Dutch). Ned Tijdschr Geneeskd. 1956; 100: 2106-2109.

56 Goslings WR, Mulder J, Djajadiningrat J *et al.* Staphylococcal pneumonia in influenza in relation to antecedent staphylococcal skin infection. Lancet. 1959; 2: 428-430.

57 Potter J, Stott DJ, Roberts MA *et al.* Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. J Infect Dis. 1997; 175: 1-6.

58 Carman WF, Elder AG, Wallace LA *et al.* Effects of influenza vaccination of health-care workers on mortality of elderly people in long-term care: a randomised controlled trial. Lancet. 2000; 355: 93-97.

59 Burls A, Jordan R, Barton P *et al.* Vaccinating healthcare workers against influenza to protect the vulnerable-Is it a good use of healthcare resources? A systematic review of the evidence and an economic evaluation. Vaccine. 2006; 24: 4212-4221.

60 Thomas RE, Jefferson T, Demicheli V *et al.* Influenza vaccination for healthcare workers who work with the elderly. Cochrane Database Syst Rev. 2006; 3: CD005187.

61 Jefferson T, Rivetti D, Rivetti A *et al.* Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. Lancet. 2005; 366: 1165-1174.

62 Hayward AC, Harling R, Wetten S *et al.* Effectiveness of an influenza vaccine programme for care home staff to prevent death, morbidity, and health service use among residents: cluster randomised controlled trial. BMJ. 2006; 333: 1241-1246.

63 Weingarten S, Staniloff H, Ault M *et al.* Do hospital employees benefit from the influenza vaccine? A placebo-controlled clinical trial. J Gen Intern Med. 1988; 3: 32-37.

64 Saxen H, Virtanen M. Randomized, placebo-controlled double blind study on the efficacy of influenza immunization on absenteeism of health care workers. Pediatr Infect Dis J. 1999; 18: 779-783.

65 Cauchemez S, Carrat F, Viboud C *et al.* A Bayesian MCMC approach to study transmission of influenza: application to household longitudinal data. Stat Med. 2004; 23: 3469-3487.

66 Jordan R, Connock M, Albon E *et al.* Universal vaccination of children against influenza: Are there indirect benefits to the community? A systematic review of the evidence. Vaccine. 2006; 24: 1047-1062.

67 Weycker D, Edelsberg J, Halloran ME *et al.* Population-wide benefits of routine vaccination of children against influenza. Vaccine. 2005; 23: 1284-1293.

68 Gezondheidsraad/ Health Council of the Netherlands. Algemene vaccinatie tegen meningokokken C en pneumokokken. publicatie nr 2001/27. 2001. Den Haag/ The Hague, Gezondheidsraad/ Health Council of the Netherlands.

69 Tacken MAJB, Braspenning JCC, de Bakker DH. De influenzavaccinatiegraad in de huisartspraktijk. Infectieziekten Bulletin. 2003; 14.

70 Hak E, van Loon S, Buskens E *et al.* Design of the Dutch prevention of influenza, surveillance and management (PRISMA) study. Vaccine. 2003; 21: 1719-1724.

71 Kroneman MW, van Essen GA, Tacken MA *et al.* Does a population survey provide reliable influenza vaccine uptake rates among high-risk groups? A case-study of The Netherlands. Vaccine. 2004; 22: 2163-2170.

72 Kroneman MW, Verheij R. De griepprik in nederland: motivatie voor deelname en distributiekanalen. 2003. Nivel.

73 Kroneman M, van Essen GA, John PW. Influenza vaccination coverage and reasons to refrain among high-risk persons in four European countries. Vaccine. 2006; 24: 622-628.

74 Szucs TD, Muller D. Influenza vaccination coverage rates in five European countries-a population-based cross-sectional analysis of two consecutive influenza seasons. Vaccine. 2005; 23: 5055-5063.

75 van Essen GA, Kuyvenhoven MM, de Melker RA. Why do healthy elderly people fail to comply with influenza vaccination? Age Ageing. 1997; 26: 275-279.

76 Hak E, Hermens RP, Hoes AW *et al.* Effectiveness of a co-ordinated nation-wide programme to improve influenza immunisation rates in The Netherlands. Scand J Prim Health Care. 2000; 18: 237-241.

77 Hak E, van Essen GA, Stalman WA *et al.* Improving influenza vaccination coverage among high-risk patients: a role for computer-supported prevention strategy? Fam Pract. 1998; 15: 138-143.

78 Habib S, Rishpon S, Rubin L. Influenza vaccination among healthcare workers. Isr Med Assoc J. 2000; 2: 899-901.

79 Dey P, Halder S, Collins S *et al.* Promoting uptake of influenza vaccination among health care workers: a randomized controlled trial. J Public Health Med. 2001; 23: 346-348.

80 Canning HS, Phillips J, Allsup S. Health care worker beliefs about influenza vaccine and reasons for non-vaccination--a cross-sectional survey. J Clin Nurs. 2005; 14: 922-925.

81 Harrison J, Abbott P. Vaccination against influenza: UK health care workers not on-message. Occup Med (Lond). 2002; 52: 277-279.

82 Mah MW, Hagen NA, Pauling-Shepard K *et al.* Understanding influenza vaccination attitudes at a Canadian cancer center. Am J Infect Control. 2005; 33: 243-250.

83 McEwen M, Farren E. Actions and beliefs related to hepatitis B and influenza immunization among registered nurses in Texas. Public Health Nurs. 2005; 22: 230-239.

Annexes

Annex **A**

The request for advice

The Minister of Health, Welfare and Sports wrote to the President of the Health Council on 16 August 2004 (letter reference POG/ZP 2.498.210):

I hereby submit a request for advice concerning the possible expansion/downsizing of the *annual* influenza vaccination, and various other aspects. As we have already discussed, I assume that the requisite activities will be incorporated into your 2005 work programme, details of which have yet to be fixed. The following is a brief explanation of the current situation, details of some relevant developments, and the specific question being posed for the advisory report.

The current situation

Traditionally, influenza vaccination has been provided for specifically identified at-risk groups. In the past, you submitted annual reports on which at-risk groups were eligible for an influenza vaccination. The professionals concerned were appraised of these at-risk groups on an annual basis. Since 1993, this vaccination has come to resemble a programme, in the sense that active information campaigns were set up to inform the general public. Partly on the basis of the recommendations that you made in 1996, this programme has been expanded to include vaccination for the entire category of elderly people above 65 years of age. From 1997 onwards, on the basis of the Exceptional Medical Expenses Act (AWBZ), the Health Care Insurance Board (CVZ) subsidised the annual influenza vaccination for individuals from a number of at-risk groups and for elderly people above 65 years of age, provided that they had received an invitation from their GP to attend for vaccination. Since then, the pro-

gramme has been referred to as the National Influenza Prevention Programme (NPG). Responsibility for administering the vaccinations has been placed in the hands of GPs.

The NPG has been highly successful. Vaccination coverage has increased substantially within a very short period of time. For a number of years now it has been stable at 75-76% of the entire target group, on average. These figures mean that this vaccination coverage is one of the highest in the world. In 2001, approximately 2,735,000 vaccinations were administered. This influenza vaccination has had major health effects.

Relevant developments

Despite the success of the current National Influenza Prevention Programme (NPG) there have been some developments that raise questions concerning expansion/downsizing of the target group:

2 In May 2003, the Health Care Insurance Board (CVZ) issued a report entitled “The National Influenza Prevention Programme: the success of influenza vaccination”, which it presented to me. This contains the results of a study into the management and cost effectiveness of the programme. This report, which contained a number of appendices, indicated that the Influenza Prevention Programme produces major health effects and that, to a large extent, it even produces cost savings.

   The CVZ recommended that the National Influenza Prevention Programme be continued.

   The CVZ’s study also demonstrated that:

   - it would not be efficient to vaccinate high-risk individuals below the age of 18 against influenza, and;
   - the vaccination of healthy individuals aged 50 to 65 might well be cost effective;

3 For several years, the WHO has recommended that medical staff should be vaccinated against influenza. This was in connection with a potential limitation of the annual influenza epidemics by preventing transmission of the influenza virus to patients. In addition, this might permit faster diagnosis in the event of a possible outbreak of SARS. The same applies to individuals in professions that involve frequent and intensive contact with other individuals (e.g. teachers).

4 At international level, influenza vaccination is often administered to other target groups than those identified in the Netherlands (e.g. pregnant women, children below the age of two).

Request for advice

Partly in view of the CVZ report, I intend to continue the National Influenza Prevention Programme.

I would like you to advise me about whether there are any scientific reasons for amending the current target groups that are eligible for influenza vaccination.

In view of the above, what I have in mind is

- extending the list of target groups to include:
  - the category of 50 to 65-year olds;
  - health workers, professions that involve intensive contacts with the population;
  - pregnant women;
  - children below the age of two, and:
- downsizing of the target groups by excluding:
  - high-risk individuals below the age of 18.

I would ask that you include in your recommendation details of whether, in scientific terms, there are any arguments concerning the best way to provide this vaccination, such as public information campaigns, targeted invitations to attend for vaccination, and whether or not there should be a charge. In this connection, cost effectiveness is a major consideration.

I assume that you will be able to incorporate this advice in the 2005 work programme. Accordingly, I look forward to receiving your recommendation at the end of 2005.

Yours sincerely,
Minister of Health, Welfare and Sport
(signed)
W.G. H. Hoogervorst

Annex **B**

The committee

Influenza vaccination: revision of the indication committee

- Prof. J.A. Knottnerus, *chairman*
  Health Council President, The Hague, Professor of General Practice Medicine, University Medical Centre, Maastricht
- G. van ’t Bosch, *adviser*
  Ministry of Health, Welfare and Sport, The Hague
- Dr. G.A. van Essen
  GP, Julius Center for Health Sciences and Primary Care, University Medical Centre, Utrecht
- G. Frijstein
  occupational health physician, Academic Medical Centre, Amsterdam
- Dr. K. Groeneveld, *adviser*
  Health Council, The Hague
- Prof. R. de Groot
  Professor of Paediatrics, St. Radboud University Medical Centre, Nijmegen
- Dr. E. Hak
  GP, Julius Center for Health Sciences and Primary Care, University Medical Centre, Utrecht
- Prof. J.W.M. van der Meer
  Professor of Internal Medicine, St. Radboud University Medical Centre, Nijmegen

- Prof. J. van der Noordaa
  Emeritus Professor of Virology, Weesp
- Dr. W. Opstelten
  GP, Netherlands Society of General Medical Practitioners (NHG), Utrecht
- Prof. A.D.M.E. Osterhaus
  Professor of Virology, Erasmus MC, University Medical Center Rotterdam
- Prof. M.J. Postma
  Professor of Pharmaco-Economics, Groningen University Institute for Drug Exploration (GUIDE), Groningen
- Dr. J.E. van Steenbergen
  physician/epidemiologist, National Infectious Disease Control Coordination Structure (LCI), National Institute of Public Health and the Environment (RIVM), Bilthoven
- Dr. A.C.G. Voordouw
  Physician, Master of Public Health, Medicines Evaluation Board (CBG), The Hague
- Dr. J. Wallinga
  Population biologist, National Institute of Public Health and the Environment (RIVM), Bilthoven
- I. Looijmans, *secretary*
  Health Council, The Hague

The Health Council and interests

Members of Health Council Committees are appointed in a personal capacity because of their special expertise in the matters to be addressed. Nonetheless, it is precisely because of this expertise that they may also have interests. This in itself does not necessarily present an obstacle for membership of a Health Council Committee. Transparency regarding possible conflicts of interest is nonetheless important, both for the President and members of a Committee and for the President of the Health Council. On being invited to join a Committee, members are asked to submit a form detailing the functions they hold and any other material and immaterial interests which could be relevant for the Committee's work. It is the responsibility of the President of the Health Council to assess whether the interests indicated constitute grounds for non-appointment. An advisorship will then sometimes make it possible to exploit the expertise of the specialist involved. During the establishment meeting the declarations issued are discussed, so that all members of the Committee are aware of each other's possible interests.

Annex **C**

Experts consulted

The Committee consulted the following experts:

- Dr. H.J. Bueving,
  head of the General Practice Programme, Department of General Practice Medicine, Erasmus MC, University Medical Center Rotterdam
- Dr. W.E.P. Beyer,
  clinical medical microbiologist, National Influenza Centre, Rotterdam
- Dr. H. Houweling,
  secretary of the National Vaccination Programme Review Committee (RVP), Health Council, The Hague
- Prof. E.J. Ruitenberg,
  chairman of the National Vaccination Programme Review Committee (RVP), Health Council, The Hague, Professor of International Public Health,VU University Amsterdam
- Dr. J.C. van der Wouden,
  associate professor, Department of General Practice Medicine, Erasmus MC, University Medical Center Rotterdam

Annex **D**

Elaborating the criteria for public vaccination programmes

Table D1a Elaborating the criteria for public vaccination programmes.

Potential target group	Healthy 50 to 65-year-olds	Pregnant women
Purpose of vaccination	Prevention of influenza and associated complications	Prevention of influenza and associated complications
Criterion 1: Is the disease serious for individuals and does it affect many people?	Information derived from the excess study conducted by the Julius Center at the behest of the Health Council: For all 50 to 65-year-olds, an over-mortality was found of between 3.8 and 7.6 per 100,000 individuals per winter. Over-mortality primarily occurs among 60 to 65-year-olds: 7.7 - 16 per 100, 000 individuals per winter = an excess of 63 to 132 deaths per winter. Excess hospital admissions between 17.7 and 38.0 per 100,000 individuals per winter (in 60 - 65-year-olds: 26.1 – 66.2/ 100,000 individuals/winter = an excess of 130 - 327 hospital admissions per winter). Allowing for various uncertainties, this appears to show a substantial burden of disease in 60 to 65-year-olds.	No Hospital admissions in healthy pregnant women during the influenza season are rare, and there are no indications of mortality. [28,31] Influenza does not result in an increased risk of pregnancy complications.[29,30] Pregnant women with a high-risk disorder do have an increased risk hospital admissions during the influenza season.[29,31]

Criterion 2: Is the vaccine known to substantially reduce disease burden?	Yes Not specifically investigated in 50 – 65-year-olds, but the vaccine's effectiveness has been demonstrated in all healthy adults below the age of 65: [18-21] - Serological/Virological influenza: 50-90 percent reduction. - Clinical influenza: ILI: ±30 percent reduction. URI: 10-25 percent reduction. As a result, it is plausible that the vaccine is also effective in 50 to 65-year-olds.	No Research shows that there is no difference between vaccinated and unvaccinated pregnant women in terms of the chance that they will visit their GP in connection with an influenza-like illness. [28]
Criterion 3: Do adverse reactions significantly detract from the health benefit attainable?	No Adverse effects are generally localised and transient. About 59 percent of vaccinated subjects experienced a local adverse effect. No significant, frequently occurring systemic adverse effects were found. [18]	No No evidence to suggest that influenza vaccination during pregnancy is associated with additional adverse effects, pregnancy complications, or congenital defects.[28,32]
Criterion 4: Is the discomfort associated with each separate vaccination in reasonable proportion to the health benefit for the recipient and the population as a whole?	Only for 60 to 65-year-olds Given that they appear to suffer a substantial burden of disease, in combination with the effectiveness of the vaccine.	No Given that there is no substantial burden of disease and the effectiveness of the vaccine has not been demonstrated.
Criterion 5: Is the discomfort associated with the vaccination programme as a whole in reasonable proportion to the health benefit for the recipient and the population as a whole?	Only for 60 to 65-year-olds Given that they appear to suffer a substantial burden of disease, in combination with the effectiveness of the vaccine.	No Given that there is no substantial burden of disease and the effectiveness of the vaccine has not been demonstrated
Criterion 6: Is the ratio between the cost and the health benefit favourable compared with other options for preventive reduction of the disease burden?	Yes In connection with the ‘excess’ study, a cost-effectiveness study has been conducted by the Julius Center. From this, it follows that vaccination of the entire group is expected to cost € 9,000 to € 28,000 per year of life gained (including the costs of lost productivity). These costs of influenza vaccination for individuals in the 60 to 65 age group are expected to range approximately from € 4,000 to € 16,000 per year of life gained. So vaccination of this group is, at any rate, cost effective. Previous studies have shown that, in healthy adults, vaccination is better than antiviral therapy in terms of the relationship of costs to health gains.[24,27]	Unknown There is no data from cost-effectiveness analysis in healthy pregnant women.
Criterion 7: Does the decision to proceed with vaccination currently serve a potentially urgent public health interest?	Only for 60 to 65-year-olds.	No Given that there is no substantial burden of disease and the effectiveness of the vaccine has not been demonstrated.

Remarks	Serological and clinical effectiveness demonstrated in healthy adults below the age of 65, so also plausible in 50 to 65-year-olds. - The excess study that was carried out reveals a substantial burden of disease in 60 to 65-year-olds. - Vaccination of individuals in the 60 to 65 age group is expected to be cost effective.	Pregnant women who make up part of an at-risk group for which vaccination is recommended will, of course, be eligible for vaccination on that basis. Consideration could be given to offering influenza vaccination to pregnant women, in order to protect their newborn children. This consideration is discussed in relation to children < six months.
Advisory report	The addition of healthy 60 to 65-year-olds to the target groups for influenza vaccination.	No addition of healthy pregnant women to the target groups for influenza vaccination.

Table D1a Continued.

	Children		
	≤ 6 months	6 mths-2 yrs	> 2 yrs
	Prevention of influenza and associated complications	Prevention of influenza and associated complications	Prevention of influenza and associated complications
Criterion 1: Is the disease serious for individuals and does it affect many people?	Yes During the influenza season, infants below the age of six months have an increased risk of being admitted to hospital.[33]	Yes: The study conducted by the Julius Center into disease burden and mortality in children below the age of two found excess hospital admissions (79 to 271 per 100,000 individuals per winter) and visits to GPs (520 to 6578 per 100,000 individuals per winter). The majority of these involved infants up to the age of six months. There are no indications of excessive mortality.	No: American studies have shown that, during the influenza season, there is only a limited increase in the number of hospital admissions of children above the age of two.[33,34] The study conducted by the Julius Center into disease burden and mortality found no extra burden of disease in children aged two and above.
Criterion 2: Is the vaccine known to substantially reduce disease burden?	No Influenza vaccines have not been tested in infants below the age of six months. Vaccination of pregnant women has no beneficial effect in terms of the risk of newborn children having to be seen by a doctor or admitted to hospital in connection with influenza or pneumonia.[28]	No The effectiveness of influenza vaccination in children aged from six months to two years has not been demonstrated.	Yes Results on effectiveness in reducing serological or virological influenza vary from 58 to 72 percent. In terms of clinical influenza, the reduction varies from 28 to 59 percent.[36,40]

Criterion 3: Do adverse reactions significantly detract from the health benefit attainable?	No Influenza vaccines have not been tested in infants below the age of six months. No evidence to suggest that influenza vaccination during pregnancy is associated with additional adverse effects, pregnancy complications, or congenital defects.[28,32]	Unclear There has only been a limited amount of research into the adverse effects of influenza vaccination in children. Nevertheless, the limited amount of data available does indicate that there are mild adverse effects.	Unclear There has only been a limited amount of research into the adverse effects of influenza vaccination in children. Nevertheless, this limited amount of data available does indicate that there are mild adverse effects.
Criterion 4: Is the discomfort associated with each separate vaccination in reasonable proportion to the health benefit for the recipient and the population as a whole?	No Cannot be assessed, as there is no proof of the effectiveness of influenza vaccination in pregnant women, in order to protect their newborn children.	No As there is no proof of the effectiveness of influenza vaccination in children aged from six months to two years.	No Given that there is no substantial burden of disease in children aged two and above.
Criterion 5: Is the discomfort associated with the vaccination programme as a whole in reasonable proportion to the health benefit for the recipient and the population as a whole?	No Cannot be assessed, as there is no proof of the effectiveness of influenza vaccination in pregnant women, in order to protect their newborn children.	No As there is no proof of the effectiveness of influenza vaccination in children aged from six months to two years.	No Given that there is no substantial burden of disease in children aged two and above.
Criterion 6: Is the ratio between the cost and the health benefit favourable compared with other options for preventive reduction of the disease burden?	Unknown Cannot be assessed, as there is no data from cost-effectiveness analysis in healthy pregnant women.	Unknown There are no Dutch cost-effectiveness studies on influenza vaccination in children aged from six months to two years. Cost-effectiveness studies carried out in larger age-groups in other countries may not be applicable, as there is no proof of effectiveness in children aged from six months to two years.	Unknown From cost-effectiveness studies in other countries it has been concluded that, if direct and indirect costs are included in the calculations, influenza vaccination in children would very probably be cost saving.[42,43] No Dutch analyses are available. These are certainly important, however, given the differences in care and social insurance.
Criterion 7: Does the decision to proceed with vaccination currently serve a potentially urgent public health interest?	No Cannot be assessed, as there is no proof of the effectiveness of influenza vaccination in pregnant women, in order to protect their newborn children.	No There is no proof of effectiveness.	No Given that there is no substantial burden of disease in children aged two and above.

Remarks	Influenza vaccines have not been registered or tested in infants below the age of six months: so this group cannot be directly vaccinated against influenza. As their most important future contact within the family, the pregnant woman can infect them. It is conceivable that influenza vaccination of the mother during pregnancy could prevent this and possibly also provide extra protection for the child in the form of maternal antibodies passed from mother to unborn child via the placenta. However, the effectiveness of this approach has not been demonstrated.		
Advisory report	No addition of healthy pregnant women to the target groups for influenza vaccination for the protection of infants below the age of six months.	No addition of children aged from six months to two years to the target groups for influenza vaccination.	No addition of children aged two and above to the target groups for influenza vaccination.

Table D1b Elaborating the criteria for public vaccination programmes.

Potential target group	Asthma ≤18 years of age	Furunculosis
Purpose of vaccination	Prevention of influenza and associated complications	Prevention of influenza and associated complications
Criterion 1: Is the disease serious for individuals and does it affect many people?	Yes During the influenza season, high-risk individuals below the age of fifteen are associated with extra hospital admissions, visits to GPs, and prescriptions of antibiotics.[44]	No Basis for previous recommendations: 1) a 1956 case report: four cases of post-influenza secondary staphylococcal pneumonia when furunculosis is present in the patient or their partner.[55] 2) selected clinical case series where in 14 of 40 (35 percent) cases of post-influenza staphylococcal pneumonia the same strain was cultured from the sputum and a skin lesion of the patient or of a family member. No attempt at a statistical analysis.[56] While the risk of furunculosis sufferers developing post-influenza secondary staphylococcal pneumonia cannot be derived from these studies, the Committee takes the view that it is probably very slight.

Criterium 2: Is the vaccine known to substantially reduce disease burden?	Yes Various observational studies found evidence for a reduction of clinical influenza to GPs.[1,48,49,54] In a randomised study, carried out in the Netherlands, vaccinated children exhibited no reduction in the number or severity of asthma attacks, but did experience a better quality of life during the bout of influenza. [45, 46] The possibility that influenza vaccination may have a beneficial effect for asthma sufferers up to the age of 18 cannot be dismissed at this moment in time. Additional and more convincing evidence would be required.	No There is no data concerning the effectiveness of influenza vaccination in patients with furunculosis.
Criterium 3: Do adverse reactions significantly detract from the health benefit attainable?	No Adverse effects are generally localised and transient. Administering of influenza vaccinations to asthma sufferers does not result in exacerbations.[50]	No No supplementary data pertaining to healthy adults, in which adverse effects are generally localised and transient.
Criterion 4: Is the discomfort associated with each separate vaccination in reasonable proportion to the health benefit for the recipient and the population as a whole?	Yes Given that influenza vaccination may have a relevant effect in juvenile asthma sufferers, it cannot be dismissed at this moment in time.	No Given that there is no evidence of a substantial burden of disease from influenza vaccination specifically in furunculosis sufferers.
Criterion 5: Is the discomfort associated with the vaccination programme as a whole in reasonable proportion to the health benefit for the recipient and the population as a whole?	Yes Given that influenza vaccination may have a relevant effect in juvenile asthma sufferers, it cannot be dismissed at this moment in time.	No Given that there is no evidence of a substantial burden of disease from influenza vaccination specifically in furunculosis sufferers.
Criterion 6: Is the ratio between the cost and the health benefit favourable compared with other options for preventive reduction of the disease burden?	Yes The cost-effectiveness studies in the CVZ report gave an average of € 2,574 per prevented GP treatment (these studies only addressed the direct medical costs excl. hospital admissions and mortality).[1] Studies carried out in other countries which also addressed the indirect costs, find that the vaccination of all high-risk children produces cost savings.[52,53]	No details available.

Criterion 7:		
Does the decision to proceed with vaccination currently serve a potentially urgent public health interest?	Yes Since there is a substantial burden of disease and the possibility that influenza vaccination may have a relevant effect in juvenile asthma sufferers cannot be dismissed at this moment in time.	No Given that there is no evidence of a substantial burden of disease or of the effectiveness of influenza vaccination in furunculosis sufferers.
Remarks	If this involves individuals up to the age of 18 who, on the basis of a diagnosis other than asthma, make up part of an at-risk group, the Committee feels that there can be no doubt concerning the importance of influenza vaccination. The Committee also believes that the possibility that influenza vaccination may have a relevant effect in juvenile asthma sufferers cannot be dismissed at this moment in time and that additional and more convincing evidence is required for possible suspension of the current recommendation concerning juvenile asthma sufferers.	The Committee feels that the identification of all carriers of *Staphylococcus aureus* is not feasible, especially as so few of them will actually be suffering from furunculosis. However, the Committee would urge therapists to be alert to the possibility of bacterial superinfections by *Staphylococcus aureus* in furunculosis patients.
Advisory report	For the time being, no suspension of the recommendation concerning influenza vaccination in juvenile asthma sufferers. Further research into the effectiveness of influenza vaccination in juvenile asthma sufferers is recommended	Ending the inclusion of furunculosis sufferers and members of their families in the target groups for influenza vaccination.

Table D1b Continued.

	Healthcare personnel	Family members of individuals in at-risk groups
	Prevention of influenza and associated complications	Prevention of influenza and associated complications
Criterion 1:		
Is the disease serious for individuals and does it affect many people?	Yes Given that healthcare personnel are generally among the healthier members of the population, this group would not be expected to experience serious morbidity or mortality. However, if the patients cared for by these healthcare personnel belong to a high-risk group then the latter will be at increased risk of serious morbidity or mortality resulting from influenza.	To be expected In healthy adults there is no serious morbidity or mortality resulting from influenza. If a contact within the family belongs to a high-risk group, however, this individual will be at increased risk of serious morbidity or mortality resulting from influenza.

Criterion 2: Is the vaccine known to substantially reduce disease burden?	Yes With regard to indirect protection, two randomised trials carried out in Britain found a reduction in patient mortality following an increase in vaccination coverage among nursing home personnel.[57,58] On the basis of these two studies, the authors of a 2006 systematic review concluded that vaccinating healthcare personnel appears to confer indirect protection on their patients.[59] A more recent randomised trial carried out in Britain found that higher vaccination coverage among nursing home personnel was associated with a significant reduction in patient mortality, and in influenza-like illness, as well as in hospital admissions and visits to GPs in connection with influenza-like illness.[62] It seems reasonable to assume that effectiveness among healthcare personnel themselves will not differ from that seen among healthy adults (as mentioned in relation to healthy individuals in the 50 to 65 age group).	Possible The effectiveness of influenza vaccination in healthy adults has been demonstrated. However, there is no supplementary data specifically pertaining to individuals with family contacts in a high-risk group.
Criterion 3: Do adverse reactions significantly detract from the health benefit attainable?	No No supplementary data pertaining to healthy adults, in which adverse effects are generally localised and transient.	No No supplementary data pertaining to healthy adults, in which adverse effects are generally localised and transient.
Criterion 4: Is the discomfort associated with each separate vaccination in reasonable proportion to the health benefit for the recipient and the population as a whole?	Yes Partly in view of this special responsibility of healthcare personnel who are in contact with high risk patients (in relation to reduced transmission and continuity of care).	Yes Discomfort is acceptable, given the voluntary nature of participation and the special responsibility regarding family contacts in high-risk groups (in relation to reduced transmission).
Criterion 5: Is the discomfort associated with the vaccination programme as a whole in reasonable proportion to the health benefit for the recipient and the population as a whole?	Yes Partly in view of this special responsibility of healthcare personnel who are in contact with high risk patients (in relation to reduced transmission and continuity of care).	Yes Discomfort is acceptable, given the voluntary nature of participation and the special responsibility regarding family contacts in high-risk groups (in relation to reduced transmission).
Criterion 6: Is the ratio between the cost and the health benefit favourable compared with other options for preventive reduction of the disease burden?	Yes Influenza vaccination among healthcare personnel is cost effective, and probably even results in cost saving.[59]	No details available.

Criterion 7: Does the decision to proceed with vaccination currently serve a potentially urgent public health interest?	Yes Given that healthcare personnel who are in direct contact with high risk patients have a special responsibility (in relation to reduced transmission and continuity of care) and because these patients suffer a substantial burden of disease.	Possible On the basis of the available data, in combination with expert opinion, influenza vaccination of individuals with family contacts who are at *very* high risk of serious morbidity and mortality resulting from influenza would be expected to be beneficial. Some examples would be: patients with serious abnormalities and dysfunctions of the cardiac function or lung function who, despite their medication, are at great risk of decompensation; patients with severe liver or kidney failure; patients whose immune system is compromised (see section 3.9 of this advisory report for more details).
Remarks		In view of the lack of data, the Committee feels that influenza vaccination for all individuals with family contacts in a high-risk group would be excessive. On the basis of the available data, in combination with expert opinion, influenza vaccination of individuals with family contacts who are at *very* high risk of serious morbidity and mortality resulting from influenza would nevertheless be expected to be beneficial. This *very* high-risk group is described in more detail in section 3.9 of this advisory report.
Advisory report	Addition to the target groups for influenza vaccination of the staff of nursing homes, residential care homes and hospitals, and other healthcare personnel who, in the course of their work in the cure and care sector, have direct patient contact.	Addition to the target groups for influenza vaccination of individuals with family contacts who would be at very high risk of serious morbidity and mortality were they to catch influenza.

Table D1c Elaborating the criteria for public vaccination programmes.

Potential target group	Professions that involve intensive contacts with the population	Professions that involve intensive contacts with poultry
Purpose of vaccination	Prevention of influenza and associated complications	Prevention of influenza and associated complications
Criterion 1: Is the disease serious for individuals and does it affect many people?	No There is no reason to assume that individuals who have many contacts with others have an increased risk of acquiring an influenza infection or of suffering complications. Nor is there any reason to assume that this group has an increased risk of infecting high-risk individuals.	No The available scientific literature contains no data to show that healthy individuals who, in the performance of their duties, have intensive contacts with poultry are at increased risk of acquiring an epidemic influenza infection or of serious morbidity or mortality as a result. The creation of a new strain of virus through simultaneous infection with avian influenza and epidemic influenza does represent a potential hazard to for society. However, in the absence of an outbreak of avian influenza, there is only a negligible risk of this happening.
Criterion 2: Is the vaccine known to substantially reduce disease burden?	Yes The anticipated effectiveness is the same as that in healthy adults (see healthy 50 to 65-year-olds).	Yes The anticipated effectiveness is the same as that in healthy adults (see healthy 50 to 65-year-olds).
Criterion 3: Do adverse reactions significantly detract from the health benefit attainable?	No The anticipated adverse effects will be the same as those seen among healthy adults, which means that they will generally be localised and transient.	No The anticipated adverse effects will be the same as those seen among healthy adults, which means that they will generally be localised and transient.
Criterion 4: Is the discomfort associated with each separate vaccination in reasonable proportion to the health benefit for the recipient and the population as a whole?	No Given that there is no reason to assume that there is an increased risk of acquiring an influenza infection or of suffering complications. Nor is there any reason to assume that this group has an increased risk of infecting high-risk individuals.	No Little discomfort, but the risk of simultaneous infection with avian influenza and epidemic influenza is virtually nil, in the absence of an outbreak of avian influenza.
Criterion 5: Is the discomfort associated with the vaccination programme as a whole in reasonable proportion to the health benefit for the recipient and the population as a whole?	No Given that there is no reason to assume that there is an increased risk of acquiring an influenza infection or of suffering complications. Nor is there any reason to assume that this group has an increased risk of infecting high-risk individuals.	No Little discomfort, but the risk of simultaneous infection with avian influenza and epidemic influenza is virtually nil, in the absence of an outbreak of avian influenza.

Criterion 6:		
Is the ratio between the cost and the health benefit favourable compared with other options for preventive reduction of the disease burden?	No details available.	Probably not: It can reasonably be expected that, with the current policy (influenza vaccination in the event of an outbreak of avian influenza and contact with the poultry in question), the cost-benefit relationship is more favourable than the preventive vaccination of staff on an annual basis.
Criterion 7:		
Does the decision to proceed with vaccination currently serve a potentially urgent public health interest?	No Given that there is no reason to assume that there is an increased risk of acquiring an influenza infection or of suffering complications. Nor is there any reason to assume that this group has an increased risk of infecting high-risk individuals.	No In view of the fact that the risk of simultaneous infection with avian influenza and epidemic influenza is virtually nil, in the absence of an outbreak of avian influenza.
Remarks		If there is an outbreak of avian influenza, then there is a risk of simultaneous infection with avian influenza and epidemic influenza. In that case, there may well be a reason to administer influenza vaccinations to any veterinary personnel and poultry farmers involved. However, this is a decision that the Minister would have to make at the time, if necessary with the advice of the Outbreak Management Team (OMT).
Advisory report	No addition of individuals with intensive contacts with the population to the target groups for influenza vaccination.	No addition of professions with intensive contacts with poultry to the target groups for influenza vaccination.

Table D1c Continued.

Potential target group	Drug addicts	People with alcohol addiction
	Prevention of influenza and associated complications	Prevention of influenza and associated complications
Criterion 1:		
Is the disease serious for individuals and does it affect many people?	No Only if a drug addict is suffering from an underlying affliction, (e.g. an HIV infection) might we be dealing with an immune compromised patient i.e. someone at increased risk of serious morbidity or mortality resulting from influenza. In this group, however, influenza vaccination is already recommended on the basis of the underlying affliction. If there is no underlying affliction, there is no reason to expect extra morbidity or mortality resulting from influenza in this group.	No Only if an alcohol addict is suffering from an underlying affliction, (e.g. cirrhosis of the liver) might we be dealing with an immune compromised patient i.e. someone at increased risk of serious morbidity or mortality resulting from influenza. In this group, however, influenza vaccination is already recommended on the basis of the underlying affliction. If there is no underlying affliction, there is no reason to expect extra morbidity or mortality resulting from influenza in this group.
Criterion 2:		
Is the vaccine known to substantially reduce disease burden?	Yes The anticipated effectiveness is the same as that in healthy adults (see healthy 50 to 65-year-olds).	Yes The anticipated effectiveness is the same as that in healthy adults (see healthy 50 to 65-year-olds).

Criterion 3: Do adverse reactions significantly detract from the health benefit attainable?	No The anticipated adverse effects will be the same as those seen among healthy adults, which means that they will generally be localised and transient.	No The anticipated adverse effects will be the same as those seen among healthy adults, which means that they will generally be localised and transient.
Criterion 4: Is the discomfort associated with each separate vaccination in reasonable proportion to the health benefit for the recipient and the population as a whole?	No Little discomfort, but there is no reason to assume that there will be any serious morbidity or mortality resulting from influenza.	No Little discomfort, but there is no reason to assume that there will be any serious morbidity or mortality resulting from influenza.
Criterion 5: Is the discomfort associated with the vaccination programme as a whole in reasonable proportion to the health benefit for the recipient and the population as a whole?	No Little discomfort, but there is no reason to assume that there will be any serious morbidity or mortality resulting from influenza.	No Little discomfort, but there is no reason to assume that there will be any serious morbidity or mortality resulting from influenza.
Criterion 6: Is the ratio between the cost and the health benefit favourable compared with other options for preventive reduction of the disease burden?	No details available.	No details available.
Criterion 7: Does the decision to proceed with vaccination currently serve a potentially urgent public health interest?	No Given that there is no reason to assume that there is any serious morbidity or mortality resulting from influenza.	No Given that there is no reason to assume that there is any serious morbidity or mortality resulting from influenza.
Remarks	In individuals suffering from an underlying affliction, (e.g. cirrhosis of the liver) on the basis of which might we be dealing with immune compromised patient, influenza vaccination is recommended on the basis of the underlying affliction.	In individuals suffering from an underlying affliction, (e.g. an HIV infection) on the basis of which might we be dealing with immune compromised patient, influenza vaccination is recommended on the basis of the underlying affliction.
Advisory report	No addition of drug addicts to the target groups for influenza vaccination.	No addition of people with alcohol addiction to the target groups for influenza vaccination.

Annex **E**

Summary of ‘excess’ study

Estimate of the burden of disease and mortality caused by the influenza virus and the respiratory syncytial virus in the Netherlands from 1997 to 2003: an epidemiological approach

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This study was funded by a grant from the Health Council.

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The full report of this study can only be obtained by submitting a request to the Health Council.

Summary of ‘excess’ study

Background

The indication for influenza vaccination continues to expand, especially in the United States. However, very little is known about the potential gains associated with this expansion. In addition, very little is known about the potential gains associated with the vaccine against respiratory syncytial virus (RSV) that is currently under development.

Objectives

Primary: Estimating the burden of disease and mortality caused by the influenza virus, in particular among infants up to 12 months of age and “non high-risk” individuals in the 50 to 64 age group (without any disorders that would already make them eligible for vaccination). *Secondary:* 1. Estimating the burden of disease and mortality related to the influenza virus in the rest of the population. 2. Estimating the burden of disease and mortality related to RSV.

Methods

A retrospective cohort study of the entire population of the Netherlands, for the period 1997-2003. Periods in which the influenza virus and RSV were active were defined on the basis of virus surveillance data provided by the Dutch Working

Group on Clinical Virology. Weekly mortality figures were obtained from Statistics Netherlands, while figures on hospital admissions were obtained from Prismant (the research and advisory agency for the Dutch Health Care Service). Information on visits to GPs was obtained from the Utrecht Network of General Practitioners. Over the six-year period of the study, the average annual excess mortality, hospital admissions and visits to GPs during periods of influenza virus or RSV predominance (i.e. weeks containing 5% or more of the total number of influenza virus patients or RSV-positive patients reported during the season in question) were determined relative to two defined reference periods, namely the peri-influenza season and the summer base period.

Results

Influenza

The influenza-related winter excess mortality, hospital admissions and visits to GPs are illustrated in table 1.

RSV

On an annual basis, periods in which RSV was active appeared to coincide with an approximate average over-mortality of between 1.9 and 5.4 per 100,000 50 to 64-year-olds and between 52 and 99 per 100,000 over 65s (with regard to the peri-influenza season and the summer base period respectively). The approximate average excess hospital admissions among infants up to 12 months of age was between 522 and 699 per 100,000. The corresponding figures for the over-65s were 51 and 141 per 100,000. As far as visits to GPs were concerned, the excess was highest in young children. The average values ranged from 9401 to 15047 per 100,000 infants up to 12 months of age, and from 4339 to 7105 per 100,000 children aged from 2 to 4.

Conclusion

Among infants up to 12 months of age and ‘non high-risk’ individuals in the 50 to 64 age group, periods in which the influenza virus was active coincided with excess hospital admissions and visits to GPs. While there are no indications of excessive mortality in infants up to 12 months of age, there was evidence of this among individuals in the 50 to 64 age group. The effectiveness of influenza vaccination in infants up to 12 months of age has not yet been demonstrated. How-

ever, it may be possible to avoid some of the influenza virus-related morbidity and mortality among individuals in the 50 to 64 age group by introducing routine influenza vaccination. A cost-effectiveness analysis is useful for the purpose of further informing decision-making concerning the introduction of routine influenza vaccination among individuals in the 50 to 64 age group.

The influenza-related burden of disease and mortality among the over-65s is by far and away the highest. Especially in young children, but also in the elderly, periods in which RSV was active appeared to be accompanied by a substantial burden of disease.

Core elements

- This six-year retrospective cohort study demonstrated that, among infants up to 12 months of age, periods in which the influenza virus was active did not coincide with excess hospital admissions and visits to GPs. Using the conservative peri-influenza season base period as a reference point, the average annual figures for this excess in the Netherlands amounted to 312 hospital admissions and 2056 visits to GPs in a period of eight weeks.
- When individuals in the 50 to 64 age group are considered as a whole, periods in which the influenza virus was active coincided with an average annual over-mortality (during the peri-influenza season base period) of approximately 30 deaths among individuals in the 50 to 54 age group, 21 in the 55 to 59 age group, and 63 among 60 to 64-year-olds.
- Data collected by the Utrecht Network of General Practitioners showed that throughout the winter season, among all individuals in the 50 to 64 age group 40% of deaths occurred in the non high-risk category. Calculations based on this percentage show that, on average, there are 12 influenza virus-related deaths among ‘non high-risk’ individuals in the 50 to 54 age group in the Netherlands. The corresponding figures for individuals aged from 55 to 59, and from 60 to 64 are 8 and 25.
- Among ‘non high-risk’ individuals in the 50 to 64 age group, periods in which the influenza virus was active coincided with excess hospital admissions and visits to GPs (relative to the peri-influenza season base period). In the Netherlands, this amounted to an annual average of approximately 83, 193 and 130 hospital admissions and 6328, 4701 and 2834 visits to GPs among 50 to 54-year-olds, 55 to 59-year-olds, and 60 to 64-year-olds respectively.

- When the exceptionally mild influenza seasons of 2000/01 and 2002/03 were excluded from the analysis, this generally produced an increase in over-mortality and excess hospital admissions for lower respiratory tract disorders among individuals aged 50 and above, but not in infants up to 12 months of age.
- Since nothing is know about the effectiveness of influenza vaccination in infants up to 12 months of age, further research is needed in this area before routine influenza vaccination can be considered.
- Among "non high-risk" individuals in the 50 to 64 age group, routine influenza vaccination could reduce the influenza virus-related burden of disease. Cost effectiveness analyses should be used to investigate the efficiency of this measure.
- The influenza-related burden of disease and mortality among the over-65s is by far and away the highest, despite the extensive vaccination coverage.

Especially in young children, but also in the elderly, periods in which RSV was active appeared to be accompanied by a substantial burden of disease.

Table 1 Results.

			total winter excess per 100,000 individuals (95% BI) related to influenza virus		total winter excess in the Netherlands	
			relative to summer	relative to peri-influenza season	relative to summer	relative to peri-influenza season
up to 12 months	death		none	none	none	none
	hospital admissions	upper respiratory tract	94 (87-102)	34 (27-42)	373	135
		lower respiratory tract	143 (135-150)	13 (5-21)	564	51
		other	34 (28-40)	32 (26-38)	135	126
		total	271	79	1072	312
	visits to GPs	upper respiratory tract	5150 (4298-6002)	520 (-397-1438)	20348	2056
		lower respiratory tract	1428 (993-1863)	none	5642	none
		total	6578	520	25990	2056
50-54 years	death		4.5 (2.2-6.9)	2.7 (0.3-5.2)	50	30
50-54 years, non high-risk	hospital admissions	upper respiratory tract	1.6 (0.8-2.2)	1.7 (0.9-2.3)	14	15
		lower respiratory tract	8.8 (6.9-10.8)	4.7 (2.7-6.8)	79	42
		cardiovasc. compl.	8.1 (3.9-12.2)	2.2 (-1.9-6.5)	72	20
		other	0.8 (-0.2-1.7)	0.7 (-0.3-1.7)	7	6
		total	19	9.3	172	83
	visits to GPs	upper respiratory tract	513 (332-694)	176 (-15-267)	4610	1581
		lower respiratory tract	717 (557-876)	528 (362-694)	6438	4747
		total	1230	704	11048	6328

55-59 years	death		4,7 (1,4-8,1)	1,9 (-1,5-5,2)	52	21
55-59 years, non high-risk	hospital admissions	upper respiratory tract	2,8 (1,9-3,7)	1,7 (0,7-2,6)	23	14
		lower respiratory tract	15 (12-17)	8,7 (6,1-11,5)	120	72
		cardiovasc. compl.	25 (19-32)	12 (5-18)	210	96
		other	1,9 (0,6-3,3)	1,3 (0,0-2,7)	16	11
		total	45	23	369	193
	visits to GPs	upper respiratory tract	670 (438-902)	178 (-70-426)	5532	1472
		lower respiratory tract	673 (480-866)	391 (187-595)	5559	3229
		total	1343	569	11091	4701
60-64 years	death		16 (11-21)	7,7 (2,9-12,5)	132	63
60-64 years, non high-risk	hospital admissions	upper respiratory tract	2,3 (1,1-3,5)	0,6 (-0,7-1,8)	11	3
		lower respiratory tract	18 (14-22)	8,9 (4,9-12,9)	90	44
		cardiovasc. compl.	44 (34-54)	16 (6-26)	217	78
		other	1,7 (-0,3-3,8)	0,9 (-1,1-3,0)	9	5
		total	66	26	327	130
	visits to GPs	upper respiratory tract	361 (107-615)	9 (-260-279)	1790	46
		lower respiratory tract	845 (589-1101)	563 (295-831)	4185	2788
		total	1206	572	5975	2834
> 65 years	death		147 (140-153)	96 (90-103)	3353	2205
	hospital admissions	upper respiratory tract	8,9 (8,1-9,6)	6,7 (5,9-7,5)	203	154
		lower respiratory tract	115 (112-119)	69 (65-73)	2637	1582
		cardiovasc. compl.	81 (75-87)	32 (27-38)	1856	743
		other	2,8 (1,7-4,0)	2,7 (1,5-3,8)	65	61
		total	208	111	4761	2540
	visits to GPs	upper respiratory tract	478 (368-588)	128 (10-245)	10938	2920
		lower respiratory tract	1501 (1312-1689)	759 (561-957)	34349	17362
		total	1979	887	45287	20282

Annex **F**

Summary of cost effectiveness analysis

Influenza vaccination of healthy adults in the 50 to 64 age group; balance between cost and effects

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This study was made possible by means of a grant from the Netherlands Organisation for Scientific Research (NWO) - Netherlands Organization for Health Research (ZonMW).

The full report of this study can only be obtained by submitting a request to the Health Council.

Summary of cost effectiveness analysis

Introduction

The Ministry of Health, Welfare and Sport has asked the Health Council of the Netherlands for its advice about whether the age of eligibility for the National Influenza Prevention Programme should be reduced from 65 to 50. In order to assess this issue, the additional disease episodes and complications of influenza in this population were investigated by means of a cohort study. This was followed by a model-based cost-effectiveness study, using this data and data from the literature on long-term results and related costs.

Model

The existing PRISMA model[1] served as the starting point for this cost-effectiveness study. It was adapted to enable estimates to be made of the cost-effectiveness of influenza vaccination in healthy adults in the 50 to 64 age group.

The incidences of periods of illness and of complications were compared using reference periods. ‘Peri-influenza season’ and ‘summer’ were the two scenarios selected for this purpose. The incidence of influenza-related complications increases with age, which means that cost effectiveness will also vary with age. Accordingly, sub-group analyses were carried out per five-year age cohort.

Results

The prevention of a death delivers a health gain of almost 25 years of life, while the prevention of an incident of cardiovascular disease results in a gain of well over 2.5 years. In view of the absolute number of incidents in the 50-64 age cohort, the prevention of individual cases of cardiovascular disease delivers the largest relative health gains, both in terms of years of life and quality of life.

The results of the 5-year analyses show that the gains deriving from the prevention of death and from the prevention of cardiovascular disorders increase with age.

Peri-influenza season as a reference period

The model-based predictions indicate that, in the current situation (i.e. in the absence of routine vaccination), 47 individuals per annum suffer sudden death as a result of influenza or associated complications. If the vaccination programme were to be expanded, by setting the age limit at 50, this would be expected to prevent 26 deaths. The predicted deaths involve additional mortality, i.e. over and above the age-specific background mortality. Furthermore, vaccination would prevent 103 new cases of cardiovascular diseases. In view of the absolute number of incidents in the age cohort, the prevention of individual cases of cardiovascular disease delivers the largest relative health gains. The total the health gains in terms of years of life gained both through the prevention of deaths and as a result of the prevention of cardiovascular disorders amounts to 643 (discounted).

The incremental cost-effectiveness per year of life gained is € 32,696 (discounted) when the costs of the associated productivity losses are excluded from the calculation and € 28,019 when they are included.

For each of the individual age cohorts (50-54; 55-59 and 60-64), the incremental cost-effectiveness per year of life gained is estimated to be € 52,403; € 43,217 and € 18,504 when the costs of the associated productivity losses are excluded and € 44,558; € 37,632 and € 15,810 when these costs are included.

Summer season as a reference period

The model-based predictions indicate that, in the current situation (i.e. in the absence of routine vaccination), 93 individuals per annum would be expected to die as a result of influenza or associated complications. It is expected that, were the vaccination programme to be expanded, 52 of these deaths could be pre-

vented. The predicted deaths involve additional mortality, i.e. over and above the age-specific background mortality. Furthermore, vaccination would prevent 270 new cases of cardiovascular diseases. In view of the absolute number of incidents in the age cohort, the prevention of individual cases of cardiovascular disease delivers the largest relative health gains. The total health gains in terms of additional years of life both through the prevention of deaths and as a result of the prevention of cardiovascular disorders amounts to 1,395 (discounted).

The incremental cost-effectiveness per year of life gained is € 13,730 (discounted) when the costs of the associated productivity losses are excluded from the calculation and € 9,421 when they are included.

For each of the individual age cohorts (50-54; 55-59 and 60-64), the incremental cost-effectiveness per year of life gained is estimated to be € 26,269; € 16,786 and € 6,830 when the costs of the associated productivity losses are excluded and € 19,036; € 11,151 and € 4,314 when these costs are included.

Budget impact

If the peri-influenza season is used as a reference period, then an expansion of the vaccination programme to include healthy adults aged between 50 and 64 would require an annual investment of approximately 23 million euros. The gains achieved would be a saving elsewhere of 1.7 million, and 4.7 million if indirect non-medical costs are also included. The net investment therefore amounts to approximately 18 million per annum.

The results of the 5-year analyses show that an expansion of the vaccination programme to include healthy adults aged between 60 and 64 would cost approximately 6 million, while an expansion of the vaccination programme to include healthy adults aged between 55 and 64 would cost approximately 14 million. This is counterbalanced by savings in which a distinction can be drawn between medical costs and indirect non-medical costs (e.g. productivity losses). The estimated net investments for the expansion of the vaccination programme therefore amount to 4.7 million and 11.3 million if healthy adults aged between 60 and 64 or between 55 and 64 are added to the programme.

If the summer is used as a reference period, then an expansion of the vaccination programme to include healthy adults aged between 50 and 64 would require an annual investment of approximately 23 million euros. The gains achieved would be a saving elsewhere of 3.7 million, and 9.8 million if indirect non-medical costs are also included. The net investment therefore amounts to approximately 12.9 million per annum.

An examination of the results of the 5-year analyses shows that the costs associated with an expansion of the vaccination programme are equivalent to the costs involved if the peri-influenza season is used as a reference period. The anticipated savings (medical costs and indirect non-medical costs) only become more substantial if the summer is used as the reference period. The estimated net investments for the expansion of the vaccination programme would then amount to 2.9 million and 7.4 million if healthy adults aged between 60 and 64 or between 55 and 64 are added to the programme.

Sensitivity analyses

Using the sensitivity analyses, an investigation was conducted into the extent to which the results for the entire age cohort (individuals in the 50 to 64 age group) are susceptible to changes in a number of major model parameters. The univariate sensitivity analyses involved variations in vaccine effectiveness, vaccination coverage, and the long-term costs for patients suffering from cardiovascular disorders. The results show that using the peri-influenza season as the reference period and a vaccine effectiveness of 50% results in an unfavourable incremental cost-effectiveness ratio (ICER) of € 46,780 per year of life gained (excluding indirect non-medical costs). The results of the remaining univariate sensitivity analyses range from € 25,000 to € 33,000 per year of life gained (excluding indirect non-medical costs). Using the summer as the reference period and a vaccine effectiveness of 50% results in an ICER of about € 20,000 per year of life gained The incremental cost-effectiveness ratios for the results of the remaining univariate sensitivity analyses range from € 10,000 to € 13,000 per year of life gained (discounted).

Accordingly, the results do not appear to be particularly sensitive to changes in the model parameters of vaccine effectiveness and vaccination coverage. However, the results have been shown to be extremely sensitive to long-term costs, which can be expected to be involved in the case of individuals with a cardiovascular disorder.

The results of the univariate sensitivity analyses show that the vaccination strategy is cost neutral if individuals with a cardiovascular disorder spend € 12,250 (using the peri-influenza season as the reference period) or € 3,430 (using the summer as the reference period) on healthcare costs per annum (including indirect non-medical costs). Since the results are so heavily dependent on this parameter, the decision was taken to exclude it from the multivariate sensitivity analyses.

The results of the multivariate sensitivity analyses are expressed in the form of acceptability curves. These can be used to determine the chance that the incremental cost-effectiveness is at or below the limiting amount that policymakers are prepared to pay per year of life gained. If the peri-influenza season is used as a reference period and there is a readiness on the part of policymakers/society to pay € 35,000 per year of life gained, then the vaccination strategy relative to doing nothing is cost effective in approximately 90% of cases. If these groups (policymakers/society) are prepared to pay € 10,000 per year of life gained, then the chance that the vaccination strategy will be cost effective relative to no invention is zero. If the summer is used as a reference period and there is a willingness among policymakers/society to pay € 20,000 per year of life gained, then the vaccination strategy relative to doing nothing is cost effective in almost all cases. If these groups (policymakers/society) are prepared to pay € 2,000 per year of life gained then the chance that the vaccination strategy will be cost effective relative to no invention is zero.

Discussion

The reference period has been a major subject of discussion. In theory, it should not matter which option is selected. The ultimate objective is to arrive at an accurate prediction of the prevented burden of illness and the associated costs. The model's epidemiological input is based on the excess study carried out by Jansen *et al.* That ecological study related the prevention of influenza to the occurrence of acute morbidity and mortality. Although similar studies have failed to demonstrate causality, it is nevertheless assumed that all "extra" morbidity and mortality is caused by influenza. As a result, the effectiveness of vaccination is assumed to equal the extent to which the incidence of "genuine" proven influenza is reduced within the population.

The excess rates and the attack rates are both calculated on the basis of the reported complications over a number of years (1997 to 2003) in which both mild and more serious influenza epidemics are included. The implications of this for the model are that average excess and attack rates are used. The consequence of this is that there will be some years in which the savings will exceed those presented here and other years in which they will fall short.

With regard to cardiovascular disorders, the only excess rates reported are those pertaining to hospitalisations. Excess rates in relation to new cases of cardiovascular disorders in the primary health care system are not reported separately, which may result from the uncertainty in the data. However, it is unlikely that

there are no excess visits to GPs whatsoever as a result of new cardiovascular disorders. Because the prevention of new cases of cardiovascular disorders has a major effect on the ultimate ICERs, and therefore on the decision-making process too, it is recommended that additional research be carried out into the disease burden of new cardiovascular disorders which are only seen in GPs' practices. If virtually every patient is referred on as a matter of course, then the omission of this category of results will only have a limited effect.

Conclusion

The value of the incremental cost-effectiveness ratio is dependent on the reference period chosen.

If the reference period is taken into consideration, then incremental cost effectiveness will exceed € 20,000 per year of life gained in all cases, with the sole exception of healthy adults in the 60 to 64 age group. Accordingly, from the perspective of health economics, it would only be possible to justify the inclusion of individuals in the 60 to 64 age group in the national vaccination programme. Compared to other common interventions (including those for which the costs are refunded), the cost effectiveness of a vaccination programme for adults in the 60 to 64 age group who have been healthy up to that point is relatively favourable. The annual costs (and extra costs) of such a programme are estimated to be 4.7 million if the reference period used is the peri-influenza season, and 2.9 million if the summer is used.

In general, with regard to the budget impact, it can be stated that the greatest gain results from the prevention of productivity losses in this age group. It is therefore justifiable to ask how the financial burdens of the vaccination programme should be allocated. Should the programme be funded entirely from government resources, or might part of the burden be borne by the private sector (e.g. employers)? All of these elements should be taken into consideration during the final assessment of the pros and cons.