



To the Minister of Health, Welfare and Sport

Subject : Presentation of advisory letter *Vaccination against seasonal influenza*
Your reference : -
Our reference : U-6740/HH/cn/693-W4 Publication no. 2011/21E
Enclosure(s) : 1
Date : September 28, 2011

Dear Minister,

The influenza virus has been causing human death and disease for more than 500 years, and possibly even more than 1000 years. There are substantial variations in the extent and severity of epidemics and pandemics but some characteristics of influenza are strikingly constant over time.¹ Recovery from the acute symptoms of the disease usually takes around a week but complications leading to death sometimes occur.

Where possible, the government provides vulnerable groups in the population with protection against influenza. Vaccines based on the entire inactivated influenza virus have been available since 1945 and protein vaccines since 1973. The World Health Organisation (WHO) has been recommending influenza vaccination for certain medical risk groups since 1958. In the Netherlands, a specific policy has long been in place to offer and administer vaccination to people at risk of developing complications in the event of influenza infection, such as elderly people and patients with chronic cardiac or lung dysfunction. In 2003 the Health Care Insurance Board (CVZ) published the results of the PRISMA study, an examination of the cost-effectiveness and efficiency of the National Influenza Prevention Programme (NPG).^{2,3} The main conclusion was that the NPG was a successful prevention programme, with major beneficial health effects. The value of influenza vaccination has also been confirmed by other studies conducted in the Netherlands.⁴

At the time of the influenza A/H1N1 2009 pandemic, the Health Council produced various advisory reports on vaccination against the pandemic influenza virus concerned. The Health Council looks back on that exceptional situation in an evaluating advisory report due to be published soon. In the aftermath of that pandemic, the clinical utility of vaccination against seasonal influenza became a point of discussion in some quarters. Therefore, in accordance with



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your oral request, I have once again summarised the Health Council's grounds for the recommendations in favour of this vaccination.

Below, in section I, I have provided an overview of previous Health Council advisory reports on influenza vaccination; section II includes an overview of systematic reviews by the Cochrane Collaboration in this field, and section III contains my considerations and recommendations.

I. Previous Health Council advisory reports on influenza vaccination

The Health Council's first advisory report on vaccinating people in medical risk groups against influenza was published in 1959. In 1978 advice on influenza vaccination was given a more structural basis with the establishment of the Influenza Vaccination Committee, which produced an annual advisory report in 1978, 1979 and between 1981 and 1998, on the vaccine's composition and the target groups for vaccination.

The Health Council examined the existing recommendations for target groups in its advisory report *Influenza vaccination: revision of the indications* (2007), and assessed whether it would be advisable to add new target groups or whether the vaccination of certain existing groups could end.⁵ The aforementioned advisory report formed the starting point for the overview below of the Health Council's scientific data and recommendations.

Influenza vaccination: revision of the indication (2007)

Assessment framework

For its 2007 review of the target groups for influenza vaccination, the Health Council used the assessment framework for a vaccination's inclusion in a public programme, which it published in its advisory report *The future of the National Immunisation Programme: towards a programme for all age groups* (2007). Seven criteria enable systematic discussion of arguments for and against the inclusion of specific vaccinations. The criteria are formulated with a view to providing protection for the entire population and groups within it (the risk groups) for which protection has priority. Each criterion requires a sound assessment of the scientific reference literature and the arguments arising from it.



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The evidential value of the scientific data on, for example, clinical utility (criterion 2) and safety (criterion 3), can be classified on the basis of the type and quality of the research conducted. Randomised and placebo-controlled studies (randomised controlled trial, RCT) have the highest evidential value but are not always possible and results from such trials are therefore not always available. Non-randomised, observational studies may provide important and relevant knowledge but it is always important to be prepared for possible bias. The Health Council's recommendations are based on the available scientific data; the evidential value and limitations of the available results of studies are taken into account in the grounds for the recommendations.

The Health Council used the aforementioned framework and associated criteria to assess whether target groups should be added to the NPG or whether vaccination of certain target groups should end.

Situation prior to 2007: existing target groups

The Health Council was of the opinion that influenza vaccination for the following target groups continues to meet all the criteria for public vaccination programmes:

- Patients with abnormalities and functional disorders of the airways and lungs
- Patients with a chronic cardiac function disorder
- Patients with diabetes mellitus
- Patients with chronic renal insufficiency
- Patients who have recently undergone a bone marrow transplant
- People infected with HIV
- Children and adolescents from six months to eighteen years of age who take salicylates for a prolonged period
- People with mental retardation who live in residential institutions
- People aged 65 and older
- People with reduced resistance to infections, owing to, cirrhosis, (functional) asplenia, autoimmune diseases, immunosuppressive medication and chemotherapy
- The residents of nursing homes who do not fall into one of the aforementioned categories.



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*Points for discussion in 2007***Asthma patients**

As there are discussions among experts about the clinical utility of influenza vaccination in preventing asthma-related complaints or complications, the Committee spoke extensively about continuing to offer influenza vaccination to children with asthma. Earlier publications pointed to increased mortality as a result of influenza in this group and suggested that vaccination had a beneficial effect which was measurable as a reduction in respiratory infections and visits to a general practitioner. These results were not confirmed in the only randomised study of which the Committee was aware, which was conducted in the Netherlands. However, given the study's limitations, it was unclear which conclusions could be drawn from it. The Health Council was of the opinion that the possibility of vaccination having a beneficial effect cannot be dismissed. Additional and more convincing evidence would be required before the influenza vaccination currently offered to this at-risk group could be stopped. Further research into the clinical utility of influenza vaccination for children with asthma was recommended.

Patients with furunculosis

The existing recommendation for the vaccination of patients with furunculosis (recurrent boils) and members of their family could not be scientifically substantiated and has been withdrawn.

People aged 60 to 64 years

Vaccination was already recommended for people aged 65 and older. The basis for this recommendation includes a randomised placebo-controlled trial conducted by people aged 60 years and older. Specific end points were chosen in the trial, such as serologically confirmed influenza. This trial showed that vaccination of elderly people halved the incidence of influenza.⁶ Because the trial was conducted in the Netherlands, it is relatively easy for us to generalise. The size of the trial precluded the possibility of making statements about infrequently occurring end points, such as mortality.

The aforementioned trial showed that the health benefits of vaccination clearly increase from the age of 60 years. On the grounds of this fact and the results of model-based studies of the



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frequency of hospital admissions and mortality attributable to influenza in people aged 60 to 64 years, the Health Council recommended lowering the lower age-related limit for an influenza vaccination indication from 65 to 60 years.

Shortly after publication of the advisory report *Influenza vaccination: revision of the indication* (2007) an article appeared in *The Lancet Infectious Diseases*, questioning the benefits of influenza vaccination in elderly people.⁷ The authors were of the opinion that the benefits of influenza vaccination in elderly people were largely attributable to the fact that especially healthy and not the most vulnerable elderly people arrange to be vaccinated against influenza and to the fact that many studies use non-specific end points, such as all-cause mortality. In his letter of 4 October 2007, the President of the Health Council referred to various Dutch observational studies which showed that the NPG in the Netherlands had resulted in a sharp decrease in hospital admissions and mortality, also among elderly people. He also referred to studies showing that there were no indications in the Netherlands of relatively low participation in the programme by elderly people at high risk.⁸

Healthy pregnant women

The Health Council took the view that there is no extra burden of disease as a result of influenza in healthy pregnant women. Unlike in many other countries, the Health Council saw no reason to add healthy pregnant women to the target groups for influenza vaccination.

Healthy children

The Health Council took the view that influenza did lead to additional morbidity and mortality in children younger than two years old. The existing vaccines have not been tested and authorised for children younger than six months. Vaccine is available for children in the age group from 6 months to 2 years but its clinical utility has not been demonstrated; a recent publication of Finnish research can only partially fill this gap.⁹ In periods when the influenza virus is in circulation, the number of hospital admissions of children aged two years and older only increases slightly. Influenza vaccination for these children is effective but not necessary. On the basis of this, the Health Council saw no reason to add healthy children to the target groups for vaccination.



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Healthcare personnel

Healthcare personnel themselves exhibit no clearly increased burden of disease as a result of influenza. The main reason for vaccinating them is to protect the patients they treat or look after. In its 2007 advisory report, the Health Council was of the opinion that healthcare personnel who have regular, close contact with patients at increased risk have a special responsibility in this regard. The Health Council also deemed it important to point out that vaccination of the patients themselves would not provide full protection. While formulating its opinion the Health Council had access to three randomised studies conducted in the United Kingdom, in which clinical utility for patients in nursing homes and residential care homes was investigated. A 2006 Cochrane Review concluded that there was no credible evidence for the cost-effectiveness of vaccinating employees in the care sector, as the results for influenza-like illness were not statistically significant. However, they were significant in the third randomised study published subsequently: higher vaccination coverage among nursing home personnel resulted in a reduction in mortality, along with reductions in influenza-like illness, hospital admissions and visits to general practitioners.

Given the demonstrated impact, the Health Council is of the opinion that healthcare personnel in hospitals, residential care homes and nursing homes should be added to the target groups for influenza vaccination. An additional concern is the need to safeguard the continuity of adequate care for these patients; vaccination of healthcare personnel will also lead to a reduction in sickness-related absence. The Health Council takes the view that special responsibility also extends to other healthcare personnel (such as GPs and home care workers), namely when the personnel concerned have direct contact with patients who face an increased risk of severe disease or death as a result of influenza. The recommendation was therefore that healthcare personnel working in the cure sector or care sector who have direct contact with patients should be vaccinated against influenza.

The recommendation to vaccinate healthcare personnel against influenza is in line with the relevant recommendation of the World Health Organisation (WHO). This recommendation has been adopted in many countries.



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Other target groups

In its 2007 advisory report the Health Council also assessed the question of vaccinating other possible target groups against influenza.

On similar grounds to those applicable to healthcare personnel, consideration may also be given to the vaccination of family members of people who face an exceptionally high risk of severe disease or death as a result of influenza. Examples include patients with severe heart or lung abnormalities or dysfunctions, who may face a greater risk of decompensation of cardiac function or pulmonary function despite medication, patients with severe liver or kidney failure, and patients whose immune system is compromised as a result of HIV infection, chemotherapy or immunosuppressive drugs, for example. It is the responsibility of the attending physician to assess the necessity of vaccinating an individual patient's family members.

The Health Council was of the opinion that there were no arguments for vaccinating members of professional groups who come into close contact with the general public, such as teachers. People addicted to drugs or alcohol may have an underlying affliction and consequently belong in one of the usual target groups for influenza vaccination. The Health Council saw no reason for addicts to be added to the target groups for influenza vaccination, if they have no such underlying affliction.

In the absence of an avian influenza epidemic, the Health Council also saw no reason to introduce annual vaccinations for healthy individuals whose work involves close contact with poultry. This would not apply in the event of an outbreak of avian influenza. In that event there would be a risk of genetic material being exchanged between different virus strains and the emergence of a new virus strain which could be highly infectious in humans. It would then be up to the Minister to decide what action to take, possibly on the basis of advice from the Outbreak Management Team (OMT).

Policy decisions

Your predecessor in office adopted almost all of the above recommendations of the Health Council. With regard to employees in the care sector, the Minister decided that in the first instance it is the responsibility of the employer to provide a sound level of care. The Minister therefore decided not to adopt the recommendation for the vaccination of employees in the care sector to be included in the NPG, but to leave the responsibility for vaccination with the employer.



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II. **Systematic reviews by the Cochrane Collaboration**

The methodology of systematic reviews is used to assess and summarise the available scientific evidence. The Cochrane Collaboration is very active in this field. This section provides a summary of the systematic reviews by the Cochrane Collaboration on the clinical utility of influenza vaccination.

Influenza vaccine for patients with chronic obstructive pulmonary disease

A substantial reduction of 30 to 50 percent in the frequency of hospital admissions and mortality was reported in large-scale cohort studies of patients with chronic obstructive pulmonary disease (COPD) who had been vaccinated against influenza; the reduction amongst elderly people was even greater. This systematic review (2006, revised version 2009) focused on RCTs. The results of six trials were available in which the clinical utility of influenza vaccination was examined specifically for patients with COPD. Influenza vaccination resulted in a significant reduction in the number of exacerbations of COPD: weighted average difference -0.37 (95% confidence interval -0.64 – -0.11).¹⁰ These data were taken into account in the Health Council's 2007 advisory report (see above).

Influenza vaccines for preventing coronary heart disease

The Cochrane Collaboration conducted a systematic review of the clinical utility of influenza vaccination for primary and secondary prevention of coronary heart disease (revised version 2008). Various observational studies associated influenza vaccination with a reduced likelihood of primary or repeated myocardial infarction but other studies failed to confirm the link. Two large cohort studies produced contradictory results; the differences were possibly linked to differences in the study populations. In one study conducted among elderly patients, influenza vaccination was found to have a protective effect against hospital admissions and CVA, whereas this was not found in the other study, which was conducted among largely younger patients. The results of only two randomised trials were available but these were too small to enable statements on the effect of influenza vaccination on coronary heart disease.¹¹ These data were taken into account in the Health Council's 2007 advisory report (see above).



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Vaccines for preventing influenza in the elderly

In this systematic review (2006, in revised form 2010), the Cochrane Collaboration concluded that the available scientific data on influenza vaccination among elderly people were of a generally poor quality. Only a few randomised placebo-controlled studies, including the aforementioned Dutch study, were of adequate quality to permit their inclusion in meta-analyses. These showed that vaccination had greater clinical utility than placebo against influenza (vaccine effectiveness (VE) 58%, 95 confidence interval (95%CI) 34-73) and influenza-like disorders (VE 43%, 95%CI 21-58). However, the combined studies lacked the power to enable an assessment of the clinical utility against hospital admissions, complications and mortality. The researchers recommended a large-scale, independent RCT study to enable a better assessment. However, the review's authors themselves indicated that for ethical reasons it would be difficult to conduct such a study. This is because vaccination of elderly people is recommended worldwide and it would be difficult to involve sufficiently large randomly selected study groups. The study would be difficult to conduct for other reasons too, for example – as the researchers also indicated – it would have to be a large-scale study over a number of years.¹² The systematic review included an abundance of non-randomised, observational studies – which were therefore of less evidential value – which practically without exception provided support for the clinical utility of influenza vaccination. This review was taken into account in the Health Council's advisory report of 2007 (see above).

Influenza vaccination for healthcare workers who work with elderly people

In 2006 the Cochrane Collaboration published a systematic review of research into the clinical utility of vaccinating personnel in the care sector against influenza, with a view to indirectly protecting elderly people. This systematic review was taken into account in the Health Council's advisory report of 2007. Unlike the Cochrane Collaboration, the Health Council did have access to the results of the randomised study published in 2006 by Hayward and co-workers.¹³ The Health Council saw evidence in that study for indirect protection of elderly people. However, in a revised publication (2010) the Cochrane Collaboration maintained its objections concerning the available evidence, as a meta-analysis combining the results of the three randomised studies displayed significant differences with regard to non-specific outcomes, such as influenza-like disorders, visits to general practitioners and general mortality but not with regard to laboratory-confirmed influenza infection, pneumonia and mortality as a result of pneumonia.¹⁴



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Vaccines for preventing influenza in people with asthma

In 1998 the Cochrane Collaboration published a systematic review of research into the clinical utility of vaccinating asthma patients against influenza, on the basis of the small number of studies in that field. The conclusion was that there remained uncertainty about the degree of protection vaccination offered against exacerbation of asthma by influenza.¹⁵ This review was taken into account in the Health Council's advisory report of 2007 (see above).

Vaccines for preventing influenza in healthy adults

In 1999 the Cochrane Collaboration published a systematic review of research into the clinical utility of vaccinating healthy adults against influenza (revised version 2010).¹⁶ It was concluded that there were indications of limited protection against influenza-like disorders and work absenteeism but not of protection against complications and hospital admissions. These conclusions are in line with the Health Council's recommendation not to offer vaccination to healthy adults.

Vaccines for preventing influenza in healthy children

In 2006 the Cochrane Collaboration published a systematic review of research into the clinical utility of vaccinating healthy children against influenza (revised version 2008).¹⁷ It was concluded that there was good evidence of the efficacy of influenza vaccines when given to children older than two years but not when given to younger children. In the case of vaccinating children within the scope of public health policy, it would first be necessary to conduct large-scale research into the clinical utility and safety of the various types of vaccines. These conclusions are in line with the Health Council's recommendation in 2007 not to offer vaccination to healthy children.

III. Considerations and recommendations

Since the 1970s considerable experience has been acquired of the clinical utility and safety of influenza vaccines. A great deal of research substantiates the beneficial effects of vaccination. However, this does not mean that improvements are no longer possible. Despite improvements in influenza vaccines over the years, it has to be noted that the efficacy of influenza vaccines is still



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not optimal. One of the reasons for this is that – unlike with most other vaccines – adjuvants (immunestimulating substances) are not generally added to vaccines against seasonal influenza. Various studies and development projects are underway at scientific institutions and industries into influenza vaccines with greater and broader efficacy.¹⁸⁻²²

Influenza vaccines are especially important for people with a medical risk factor and elderly people who face increased risk of complications and death if they contract influenza. This applies to the following groups: people aged 60 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 a bone marrow transplant, people with HIV infection, children aged between 6 months and 18 years who receive long-term salicylate therapy, people with mental retardation who live in residential institutions, people with reduced resistance to infection, and residents of nursing homes. There is convincing evidence for these target groups that influenza vaccination can prevent or limit damage to health. Furthermore, it is cost-effective to offer vaccination as part of a national programme.

With regard to the clinical utility of influenza vaccination, evidence for all risk groups and all end points is not always available from the highest category, namely that of randomised and blind trials. This shows that there are gaps in knowledge of the efficacy of influenza vaccines according to current standards of evidence-based medicine. However, it should not be supposed from this that vaccination has no clinical utility. Claims of no effect would be irresponsible in this case and could result in important interventions being withheld from patients. This has been pointed out by Alderson and Chalmers (of the UK Cochrane Centre), amongst others.²³ It would therefore certainly not be correct to see this lack of knowledge as justification for ending influenza vaccinations for elderly people and medical risk groups. However, it may be seen as an incentive for setting up the required trials for a complete assessment where possible.

Unfortunately, not much more evidential value has been obtained from the new studies conducted since 2007, which have also been taken into account in the systematic reviews of the Cochrane Collaboration. This is not surprising, given the long-standing practice of administering influenza vaccines to protect risk groups. For all new influenza vaccines, data are collected systematically on the extent to which they elicit protective antibodies against influenza and produce side effects among the various target groups. It is the usual way of assessing the vaccines' efficacy and safety in the short time available each year and forms the basis for authorisation by the marketing authorisation authorities for medicines. Influenza vaccines have to be adapted each



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year to the influenza viruses circulating at the time. Little time remains for research once the composition has been determined, as soon afterwards the vaccines have to be produced and be available for use. It is therefore unfeasible to always assess the efficacy of the newly composed influenza vaccines against clinical end points. Sero-immunological knowledge is important for assessing the efficacy of the vaccines but it is not taken into account in the *systematic reviews* of the Cochrane Collaboration.

The fact that influenza vaccines have been administered for many years leaves very little scope for conducting placebo-controlled trials. It will be difficult to assess the clinical utility and safety of influenza vaccines for elderly people by means of a large-scale, publicly funded randomised and placebo-controlled study (RCT), as suggested by the Cochrane Collaboration. The use of RCTs only became standard practice in the period after influenza vaccines had been introduced. Placebo-controlled RCT research, the highest standard of scientific research, can now only be justified for the vaccines against seasonal influenza if there is reasonable doubt about their efficacy. As the effect on influenza has been proven and an effect on the severe complications of influenza is plausible, it would be unethical to withhold vaccination from people in the target groups. In the Netherlands, we have the advantage that we can base policy for the vaccination of elderly people on an RCT which was performed in this country and which was publicly funded. The large-scale RCT requested by the Cochrane Collaboration would supplement the information but, precisely because of the results of that previous RCT, it is unlikely that a medical ethics committee would grant permission for it.

I have asked the Standing Committee on Infection and Immunity whether it saw any reasons for departing from the recommendations in the Health Council's most recent advisory reports on influenza vaccination. I conclude along with the Standing Committee that there are no reasons for doing so at the moment. The recommendation to offer influenza vaccination to the risk groups should certainly be maintained.

Yours sincerely,
(signed)
Professor L.J. Gunning-Schepers
President



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