



National Institute for Public Health  
and the Environment  
*Ministry of Health, Welfare and Sport*

## **Influenza vaccination in the Netherlands**

Background information for the Health Council of the  
Netherlands

RIVM Letter report 2019-0002  
T.M. Schurink-van 't Klooster et al.





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## Colophon

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## Synopsis

### **Influenza vaccination in the Netherlands**

Background information for the Health Council of the Netherlands

Among all infectious diseases, influenza causes the highest burden of disease. Vaccination is the main strategy to prevent complications and death from influenza virus infection. Also, vaccination leads to milder infections. The Dutch Health Council is currently preparing a new advice on the target groups for influenza vaccination and the safety and effectiveness of novel vaccines. Potential new target groups are pregnant women and children. To support this advice, the RIVM provides an overview of currently available scientific information on influenza vaccination, including effectiveness, acceptance, impact, safety and cost-effectiveness.

Currently, vaccination in the Netherlands is advised for all individuals aged 60 years or older and individuals with co-morbidity who have an increased risk of complications or death due to this infection. Vaccination against influenza during pregnancy can protect the mother as well as the infant up to the age of six months of age. Vaccinating children can provide herd protection as well as individual protection.

The influenza vaccines in current use in the Netherlands provide only moderate protection. Vaccination prevents about a third to half of the infections. Also, the level of protection decreases with age at vaccination. Recent studies showed that novel vaccines have an improved protective benefit in elderly subjects. These vaccines are not yet used in the Netherlands. From 2019-2020 onwards, a quadrivalent influenza vaccine, rather than the trivalent vaccine, will be used for the current target groups.

Keywords: influenza, flu, vaccination, disease burden, vaccine effectiveness, vaccine efficacy, safety, acceptance, cost effectiveness



## Publiekssamenvatting

### **Influenzavaccinatie in Nederland**

Achtergrond informatie voor de Gezondheidsraad

Van alle infectieziekten veroorzaakt griep de meeste ziekenhuisopnames en sterfgevallen. De belangrijkste manier om dit te voorkomen, is door mensen tegen dit virus te vaccineren. Ook zorgt vaccinatie ervoor dat infecties milder verlopen. De Gezondheidsraad bereidt momenteel een nieuw advies voor over de doelgroepen van de vaccinatie en de veiligheid en effectiviteit van nieuwe vaccins. Hierbij wordt ook gekeken of griepvaccinatie voor zwangere vrouwen en kinderen een goed idee is. Als ondersteuning van dit advies geeft het RIVM een overzicht van beschikbare wetenschappelijke informatie over griepvaccinatie. Onderwerpen zijn onder andere de effectiviteit, acceptatie, impact, veiligheid en kosteneffectiviteit ervan.

Op dit moment wordt in Nederland twee groepen mensen geadviseerd zich tegen de griep te laten vaccineren: alle mensen van 60 jaar en ouder, en mensen die (chronische) aandoeningen hebben en daardoor een hoger risico om complicaties te krijgen of te overlijden door de griep. Vaccinatie tijdens de zwangerschap kan zowel de moeder beschermen als het kind tot zes maanden na de geboorte. Bij kinderen kan de vaccinatie een dubbel effect hebben: zij zijn zelf beschermd tegen de griep en de vaccinatie kan de kans verkleinen dat mensen in hun omgeving de griep krijgen.

Er bestaan veel verschillende vaccins tegen de griep. De vaccins die nu in Nederland worden gebruikt, beschermen matig. Ze voorkomen een derde tot de helft van de infecties. Ook geldt: hoe ouder mensen zijn op het moment dat ze zich laten vaccineren, hoe minder het vaccin hen beschermt. Recente onderzoeken laten zien dat nieuwe vaccins oudere proefpersonen beter beschermen. Deze vaccins worden nog niet gebruikt in Nederland. Vanaf 2019-2020 zal een vaccin tegen vier typen griepvirus worden gebruikt in plaats van het huidige vaccin tegen drie typen.

Kernwoorden: influenza, griep, vaccinatie, ziektelast, vaccineffectiviteit, veiligheid, acceptatie, kosteneffectiviteit





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## Preface

In temperate zones of the Northern Hemisphere, influenza transmission occurs during winter epidemics. Influenza viruses are easily transmitted from person to person, particularly in crowded spaces, including schools or long-term care facilities. Influenza is characterised by a sudden onset of symptoms from which most people recover within 1-3 weeks, without medical attention. However, the infection can cause severe illness or death, especially in people at high risk of complications following infection due to age or underlying conditions. The mortality rate among the elderly makes that of all infectious diseases influenza has the highest burden of disease in the Netherlands and the EU region.

Since 1997, the Dutch National Influenza Prevention Programme (NPG) actively offers influenza vaccination with trivalent subunit or split virion vaccine to specific target groups. In 2007, the Health Council of the Netherlands recommended influenza vaccination for all individuals 60 years or older and those with underlying medical conditions, such as heart or lung disease. The main goal of the programme is to prevent complications from influenza virus infection in these high-risk groups. Additionally, the Health Council advised annual influenza vaccination for healthcare professionals to prevent transmission of the influenza virus to vulnerable patients and to protect the professionals themselves. However, influenza vaccination of healthcare workers is not covered by the NPG and is the responsibility of the employer.

In recent years more information has become available on the efficacy and effectiveness of various influenza vaccine types or formulations in groups other than the current target groups, such as healthy children and healthy pregnant women. WHO now recommends vaccination of all pregnant women because of the increased risk of a severe course of influenza both in the mother and the infant in the first months of life. Furthermore, several countries, including the United States (US) and the UK, have implemented vaccination of healthy children not only for personal protection but also to reduce transmission. A current question is whether the Dutch influenza vaccination programme should likewise include annual vaccination for pregnant women and children.

With respect to the choice of vaccine, in September 2018, The Ministry of Health decided that from 2019-2020 onwards, a quadrivalent influenza vaccine, rather than the trivalent vaccine, will be used in the NPG for the current target groups. The advice was based on discussions in the Outbreak Management Team (OMT), which met after the long and severe 2017-2018 influenza epidemic, in which the influenza B virus of the Yamagata lineage was predominant but not included in the trivalent vaccine. Another recommendation was that the vaccination coverage among healthcare workers should be increased. Study is underway to determine whether compulsory influenza vaccination for newly appointed healthcare professionals is feasible or whether other measures would be preferred to increase vaccine uptake in this group. A third recommendation from the OMT was that better data are needed on severe influenza that requires hospital admission.

The Health Council of the Netherlands is asked to update the current influenza vaccination recommendations based on newly available data. This report provides currently available scientific information on influenza virus infection and vaccination, including data regarding maternal vaccination, childhood vaccination and vaccination of older adults and people with comorbidities. Data cover vaccine efficacy/effectiveness, vaccination acceptance, safety, impact and cost-effectiveness. This report does not consider pandemic influenza vaccination and vaccination of healthcare workers.

# 1 Influenza disease burden

## Summary

Influenza is an important cause of morbidity and mortality in human populations. Worldwide, it has been estimated that between 291,243 and 645,832 seasonal influenza-associated respiratory deaths occur annually. In the Netherlands and the EU, influenza has the highest burden of disease of all infectious diseases.

Influenza is a respiratory disease caused by influenza virus. Influenza type A and B viruses cause seasonal epidemics. The main transmission routes are droplets, aerosols, and direct contact. Most people recover completely within 1 to 3 weeks without medical treatment. However, some people are at increased risk of serious disease and complications after influenza virus infection, like the elderly and those with chronic underlying disease.

Influenza infection is most common in children under five years of age. However, complications and mortality occur mostly in adults 65+ years old, especially those with comorbidities. Pregnant women are at increased risk for hospitalisation due to influenza, especially in the third trimester of pregnancy. Children with asthma have a higher disease burden compared with healthy children. Mortality is low in children and pregnant women.

## 1.1 Pathogen and transmission

Influenza is caused by influenza virus. Influenza viruses (orthomyxoviruses) are classified into types (species) A, B and C based on variation in the nucleoprotein (NP) and matrix (M) antigens [1]. Influenza type A and B viruses cause seasonal epidemics, while type C virus infections are generally mild or asymptomatic. Influenza type C viruses are not thought to cause epidemics [2]. Influenza A viruses are further classified in subtypes according to the combination of the surface glycoproteins hemagglutinin (HA) and neuraminidase (NA) [1]. There are currently 18 hemagglutinin subtypes and 11 neuraminidase subtypes identified: H1 through H18 and N1 through N11, respectively. Only few combinations infect humans; those currently causing seasonal epidemics are A(H1N1)pdm09 and A(H3N2). Influenza B viruses are divided into two phylogenetic lineages that have become antigenically distinct. Currently circulating influenza B viruses belong to one of two lineages: B/Yamagata/16/88 or B/Victoria/2/87 [1, 2].

Influenza viruses are constantly evolving by small changes in the genes of the virus when it replicates. In what is called "antigenic drift," these small changes can result in amino acid changes that affect the antigenic properties of the HA protein but usually result in viruses that are closely related and share the same antigenic properties. Major changes in influenza A viruses, called "antigenic shift," occur less often. Caused by reassortment of genetic material from different A subtypes, they can lead to a new subtype (combination of HA and NA) with possible pandemic potential if there is no pre-existing (cross-reactive) immunity against it. Usually such viruses develop in animals (water birds and pigs) and may transmit to humans [1, 3].

Influenza viruses are easily transmitted from person to person, particularly in crowded areas including schools and long-term care facilities [4, 5]. There are three main routes of transmission:

1. Droplets: these particles can deposit on mucous surfaces of the mouth and nose when inhaled, but are too large to reach the lungs.
2. Aerosols: these particles can deposit on mucous surfaces of the upper respiratory tract when inhaled, but are small enough to reach the lower respiratory tract.
3. Direct contact transmission: infectious viruses are transferred to mucous membranes of the upper respiratory tract via a contaminated object or person.

Influenza virus deposited on surfaces can survive outside the body for a few hours up to several days. The incubation period for influenza is 1-5 days, with an average of 3-4 days [6].

## 1.2 Influenza and disease burden

### ***Influenza surveillance***

*In the Netherlands, influenza surveillance is a collaborative effort of the National Influenza Centre (NIC) (consisting of the National Institute for Public Health and the Environment [RIVM] in Bilthoven and the Erasmus University Medical Centre [EMC] in Rotterdam) and the Nivel Primary Care Database sentinel surveillance in Utrecht. The general practitioners (GPs) participating in the sentinel surveillance report weekly the incidence of influenza-like illness (ILI) according to the case definition provided by Pel (sudden onset of symptoms, fever of at least 38°C and at least one of the following symptoms: cough, rhinorrhoea, sore throat, frontal headache, retrosternal pain, myalgia). From a systematic selection of patients presenting with ILI or another acute respiratory infection (ARI, GPs collect nose and throat swabs for influenza virus detection by real-time RT-PCR at the NIC-RIVM. In addition, diagnostic laboratories forward a selection of influenza virus-positive specimens for subtyping and lineage determination to the NIC-EMC, where a subset of sentinel and non-sentinel influenza viruses is subjected to further genetic and antigenic characterisation.*

*Robust real-time national data on the number of patients admitted to a hospital or intensive care for complications of influenza virus infection, such as pneumonia, are not available in the Netherlands. This has to do with diverse hospital electronic systems and the very low number of patients tested for influenza virus infection. However, there is a severe acute respiratory infection (SARI) surveillance pilot study since the 2015/2016 season in a few Dutch hospitals. Additionally, in the Nivel Primary Care Database, pneumonia is one of the illnesses monitored in this syndromic surveillance. No additional testing is performed in those cases for surveillance purposes. Direct estimates of number of deaths from influenza are also not available. In cause-of-death statistics, the main code is for the underlying cause of death (for example a chronic heart disease), rather than the direct cause of death (which could be influenza virus infection). However, monitoring of weekly excess all-cause mortality is well established in the Netherlands and in the European context (EuroMOMO programme). With these data, the RIVM and EuroMOMO are able to estimate the all-cause mortality during the influenza epidemic period.*

Influenza is a respiratory disease and is characterised by a sudden onset of symptoms including fever, cough, headache, myalgia, joint pain, malaise, sore throat and nasal congestion [1, 7, 8]. The fever can rise within 12 hours to 39°C or higher and in most cases lasts for 3 to 5 days. In very old patients, fever might not be a prominent sign. Inflammation of the mucous membranes can occur in the nose, throat or sinuses, and also the bronchi and lungs. Yet influenza virus infection can be asymptomatic. Most people recover completely in 1 to 3 weeks without medical treatment. For example, in the 2017/2018 influenza season, an estimated 900,000 people experienced illness from an influenza virus infection, but only 184,000 visited their general practitioner [9]. However, some people are at increased risk of serious disease and/or complications after infection with influenza virus, such as the elderly, people with a chronic underlying disease (see §1.2.3) and pregnant women, especially in their third trimester (see §1.2.1).

Worldwide, it has been estimated that between 291,243 and 645,832 seasonal influenza-associated respiratory deaths occur annually [10]. In the Netherlands, there were an estimated 16,000 hospitalisations due to SARI infection and 9,500 excess deaths during the 18 epidemic weeks in the 2017/2018 influenza season [9]. Influenza as well as cold snaps are considered important causes of this estimated excess mortality [9]. However, 2017/2018 was a more severe season, compared to earlier seasons; in four previous seasons the excess mortality during influenza epidemic weeks ranged from 0 to 8,600 [11-14].

Influenza has been long recognised as an important cause of morbidity and mortality in human populations, but deriving precise and reliable estimates of the burden of illness attributable to influenza, either by country/region or globally, is made difficult by numerous methodologic challenges [15]. A recent European study showed that influenza had the highest burden of all studied infectious diseases (30% of the total burden caused by 31 infectious diseases) [16]. In the Netherlands, burden estimates for 38 infectious diseases in the years 2012–2016 showed that the burden of disease caused by influenza was 18% of the total burden of these 38 diseases [17]. The annual burden of influenza was 10,799 disability-adjusted life years (DALYs), which is an estimate of the number of healthy years lost due to ill health, disability or early death [18]. For influenza, it is especially the mortality (years of life lost) among the elderly that contribute to the high DALY estimates.

### 1.2.1 *Influenza during pregnancy*

In 2012, WHO recommended for the first time that pregnant women should be prioritised over others in influenza vaccination campaigns [19]. Pregnancy is associated with biochemical, mechanical, hemodynamic and immunologic changes in the mother that become most pronounced by the third trimester [20]. Regulatory T-cell function is upregulated to suppress allogeneic response directed to the fetus [21]. In general, the more immune-suppressed status of pregnant women increases the risk for severe disease [22, 23]. Also mechanical factors may play a role, in particular in the third trimester when breathing is more shallow and faster due to increasing uterine pressure on the diaphragm and increased progesterone levels lead to decreased muscle tone. [24].

A systematic review, including 152 studies (142 non-ecological and 10 ecological studies) and published in 2017, quantified the association between pregnancy and severe influenza [25]. The majority of the included studies (n=136) containing individual-level information, concerned data on pandemic influenza either alone or in combination with seasonal influenza. Seventeen studies concerned seasonal influenza, with 11 of them reporting on post-pandemic influenza A(H1N1)pdm09. Detailed information follows on mortality and hospitalisations due to influenza during pregnancy using studies with individual-level data. Data on influenza in young infants are described in section 1.2.2.

#### 1.2.1.1 Mortality and hospitalisations due to influenza during pregnancy using studies from the review with individual-level data

##### *Mortality risk due to influenza for pregnant women [25]*

In the systematic review mentioned above, 94 studies reported on mortality, with the majority including only hospitalised patients. Overall, influenza during pregnancy was not associated with an increased risk for mortality (OR 1.04; 95%CI 0.81-1.33). Similar results were found for studies conducted in a community setting (OR 1.79; 95%CI 0.88-3.61), studies among hospitalised pregnant women (OR 1.06; 95%CI 0.78-1.44), and studies among pregnant women admitted to an ICU (OR 0.73; 95%CI 0.43-1.24).

##### *Risk for hospitalisation due to influenza for pregnant women*

##### *Admittance to ICU*

Regarding ICU admission following influenza, the systematic review found no significant differences between pregnant and non-pregnant women (OR 0.85; 95%CI 0.62-1.17) [25]. Likewise, no statistical significantly increased risk was found for pneumonia (OR 1.80; 95%CI 0.72-4.49) or mechanical ventilator support (OR 1.12; 95%CI 0.70-2.08); and a composite outcome, including ICU admission and/or all-cause mortality (OR 0.95; 95%CI 0.59-1.52) was found for pregnant women in comparison to non-pregnant women.

##### *Hospitalisation without ICU admission*

In contrast to mortality and ICU admission, pregnant women did have a significantly increased risk for hospitalisation for influenza compared to non-pregnant women (OR 2.44; 95%CI 1.22-4.87) [25]. A sensitivity analysis including studies with non-pregnant women of reproductive age serving as a comparator likewise showed an increased risk (OR 3.28; 95%CI 0.52-20.6) for hospitalisation for influenza. The small number of included studies (n=2) and their substantial heterogeneity ( $I^2=84\%$ ) probably was the reason that this result was non-significant. The two studies had very different inclusion criteria, partly explaining the large heterogeneity.

#### 1.2.1.2 Mortality and hospitalisations due to influenza during pregnancy using review studies with group-level data

The studies with group-level data [25] all focused on 2009-pandemic influenza A(H1N1)pdm09 and found significantly higher mortality rates, ICU admission, and hospitalisation among pregnant women compared



with non-pregnant patients [25]. However, authors identified several biases that may have overestimated these risk estimates.

#### 1.2.1.3 Reviews on 2009-pandemic influenza A(H1N1) data

An earlier review of 2009-pandemic influenza A(H1N1) data included 120 papers covering 3,110 pregnant women with confirmed pandemic influenza [26] (Table 1.1). Three studies showed an increased risk of hospitalisation for influenza during pregnancy. Furthermore, of seven studies reporting estimates of ICU admission, three showed non-significant results and four showed a significantly increased risk. For mortality, seven out of eight studies showed non-significant differences, whereas one showed a statistically significant increased relative risk.

Similarly, for severe disease, three out of four studies showed non-significant results, whereas one study revealed an increased risk. Thirty percent of the pregnant women had comorbidities such as asthma, diabetes mellitus, or obesity. This last factor has not been previously described as a risk factor for severe disease following seasonal influenza virus infection. The interplay between obesity and pregnancy as risk factors is largely unknown [27]. Pregnancy was also described as a significant risk factor for hospitalisation due to influenza A(H1N1)pdm09 infection (unadjusted relative risk (RR) 3.5-25.3) in a worldwide collection of approximately 70,000 laboratory-confirmed hospitalised influenza A(H1N1)pdm09 patients from 19 countries [28]. However, no increased risk for death was found.

Table 1.1 Relative risk of hospitalisation, ICU admission, death or any severe outcome in pregnant women due to 2009 influenza A(H1N1) [26]

Paper	Risk of hospitalisation	Risk of ICU admission	Risk of death	Risk of severe disease
<b>New south Wales Public Health Network [29]</b>		RR: 5.8 <sup>a</sup>	RR: 10.2 <sup>a</sup>	
<b>ANZIC [30]</b>		RR: 7.4 <sup>a</sup>		
<b>Campbell et al. [31]</b>		RR: 0.7 (0.4-1.2) <sup>a</sup>	RR: 1.1 (0.3-4.1) <sup>a</sup>	RR: 0.7 (0.4-1.3)
<b>Creanga et al. [32]</b>	RR: 7.2 <sup>a</sup>			RR 4.3 <sup>a</sup>
<b>Fuhrman et al. [33]</b>			aOR: 0.3 (0.04-3.0)	aOR: 0.5 (0.2-0.8)
<b>Gérardin et al. [34]</b>		RR: 0.4 (0-2.6) <sup>a</sup>		
<b>Hanslik et al. [35]</b>		OR: 5.2 (4.0-6.9)	OR: 1.4 (0.3-4.2)	
<b>Jamieson et al. [36]</b>	RR: 4.3 (2.3-7.8) <sup>b</sup>			
<b>Kelly et al. [37]</b>	RR: 5.2 (4.6-5.8) <sup>b</sup>	RR: 6.5 (4.8-8.8) <sup>b</sup>	RR: 1.4 (0.4-4.5) <sup>b</sup>	
<b>Koegelenberg et al. [38]</b>			OR: 1.13 (0.14-8.88)	
<b>Oliveira et al. [39]</b>			RR: 1.07 (0.82-1.41) <sup>a</sup>	
<b>Yang et al. [40]</b>			OR: 0.8 (0.2-3.5)	OR: 0.4 (0.2-3.4)
<b>Zarychanski et al. [41]</b>		OR: 3.64 (0.86-15.4) <sup>a,c</sup>		

ANZIC=ANZIC Influenza Investigators and Australian Maternity Outcomes Surveillance System; aOR=adjusted odds ratio; ICU=intensive care unit;

OR=odds ratio; RR=relative risk;

<sup>a</sup> Compare to nonpregnant women of reproductive age;

<sup>b</sup> Compared to general population;

<sup>c</sup> This number reports odds for pregnant women requiring ICU admission compared to requiring only outpatient treatment.

A review of eight studies performed in India (all started during the 2009 pandemic) showed increased mortality and disease severity compared to non-pregnant women in the majority of studies [42]. Increased mortality was associated with a significant delay in presentation to hospital and also presenting with symptoms in the third trimester.

#### 1.2.1.4 Review of birth outcomes following maternal influenza

A systematic review of maternal influenza and birth outcomes included 16 studies on preterm birth, 5 on SGA birth, and two on fetal death [43]. It was published in 2017. Heterogeneity across the studies reporting preterm birth precluded meta-analysis. In a subgroup of the highest quality studies, two reported significantly increased preterm birth (risk ratios [RR] from 2.4 to 4.0) following severe 2009 pandemic H1N1 (pH1N1) influenza illness, whereas those assessing mild-to-moderate pH1N1 or seasonal influenza found no association. Five studies of SGA birth showed no discernible patterns with respect to influenza disease severity (pooled odds ratio 1.24; 95% CI 0.96–1.59). Two fetal death studies were of sufficient quality and size to permit meaningful interpretation. Both reported an increased risk of fetal death following maternal pandemic H1N1 disease (RR 1.9 for mild-to-moderate disease and 4.2 for severe disease). Cesarean delivery occurred frequently, often as an attempt to improve worsening maternal status.

Studies published since the review have confirmed the increased risk of preterm birth (adjusted RR 3.9; 95%CI 2.7-5.6) following severe pandemic influenza during pregnancy, requiring ICU admission [44]. Furthermore, authors found an increased risk of low birth-weight infants (adjusted RR 4.6; 95%CI 2.9-7.5) and Apgar scores  $\leq 6$  at 5 minutes (adjusted RR 8.7; 95%CI 3.6-21.2). For non-hospitalised pregnant women and hospitalised women not admitted to ICU, no elevated risks for adverse infant outcomes were found. A study from Norway, including mainly non-hospitalised pregnant women with pandemic influenza, found no increased risks of pre-eclampsia, preterm birth or SGA birth [45].

**In summary**, influenza during pregnancy is associated with an increased risk of hospitalisation, especially in the third trimester. Non-significant differences for ICU admission and death were found. Differences were more pronounced for pandemic influenza than for seasonal influenza. Furthermore, a severe course of influenza during pregnancy increases the risk of a preterm delivery. Noconsistently increased risks of low birth-weight infants were observed following influenza during pregnancy.

#### 1.2.2 *Influenza in children*

A study in England showed that children under five years of age had the highest rate of influenza-attributable GP consultation, especially children under the age of 6 months [46]. The same is seen in Dutch surveillance data, where in the last five winter seasons the GP consultation rate and the estimated symptomatic influenza incidence was highest among children younger than five years. For children under the age of 6 months, no separate ILI surveillance data are available in the Netherlands; this is unfortunate, as such children might benefit from the possible introduction of maternal vaccination [9, 47].

In the UK, children under 15 years of age accounted for 37% of all influenza-attributable hospital admissions [46]. In the Netherlands, no surveillance system on hospitalisation data per age group is available. Globally it has been estimated that in 2008, between 28,000 and 111,500 deaths in children younger than 5 years were attributable to influenza-associated acute lower respiratory infections, with 99% of these deaths occurring in developing countries [48]. In England, influenza-attributable deaths in children under 15 years is low, with around 12 deaths in hospital per year [46]. In the Netherlands, there was no excess mortality among children during the influenza epidemic over the last five winter seasons [9, 11-14].

A common complication in children with influenza infection is acute otitis media, for which antibiotics can be prescribed. In a Finnish cohort study of children younger than 3 years, 39.7% of the children with culture-confirmed influenza illness developed otitis media, compared to 19.6% of children 3-6 years and 4.4% of children 7-13 years; only one of the 370 children with culture-confirmed influenza illness was hospitalised [49].

In the United States, estimated outpatient influenza-attributable visit rates were higher among children with asthma than among healthy children aged 6 to 59 months. Additionally, annual influenza-attributable hospitalisation rates were higher among children with asthma than among healthy children 6 to 23 months of age, but not among children 24 to 59 years of age [50]. In general, influenza negatively affected health-related quality of life in children with asthma [51]. In the Netherlands, people using maintenance medication, such as inhalation corticosteroids for asthma, are eligible for influenza vaccination [52].

A systematic review of the influenza burden in Western European countries noted that influenza in children led to absenteeism from day care, school, or work for the children, their siblings, and their parents, leading to a high socioeconomic burden [51].

**In summary** children have a high influenza burden in terms of primary care consultations (including consultations for complications like otitis media) and in terms of hospital admissions. However, mortality is low among children in Western countries. The burden of influenza disease is higher among children with asthma than among healthy children.

### 1.2.3

#### *Influenza in elderly and people with comorbidities*

A U-shaped curve is seen for influenza hospitalisation in a study in England, i.e. the highest rate is for children under 5 years, followed by the 65+ year olds [46]. However, this is not seen in the estimated symptomatic influenza incidence in primary care in the Netherlands, where incidence was relatively low for people of 65 years and older [47]. Pneumonia is the most common complication of influenza virus infection [53]. In the pneumonia syndromic surveillance of Nivel Primary Care Database, the pneumonia prevalence was highest among people of 65 years or older in the last five winter seasons. However, no diagnostics are performed for surveillance purposes, so it is unknown how many of the pneumonia cases were caused by the influenza virus [9]. Influenza mortality is highest in the older age groups. In a global study, the

highest mortality rate was estimated among people aged 75+ year olds (51.3-99.4 per 100,000 individuals) [10]. In England, the majority (72%) of influenza-attributable deaths in hospital are estimated to occur in 65+ year olds with comorbidities [46]. The excess mortality observed in Europe in the 2016/2017 influenza season was seen especially among 65+ year olds. Likewise in the Netherlands, the highest influenza mortality is seen among the elderly.

It has been estimated that the influenza mortality burden in terms of years of life lost before age 90 (YLL90) is highest for persons aged 80-84 years (914 YLL90 per 100,000 persons; 95% uncertainty interval: 867, 963). They are followed by persons aged 85-89 years (787 YLL90/100,000; 95% uncertainty interval: 741, 834) [54]. The high mortality from influenza among the elderly translates into high DALY estimates. During the last four influenza seasons, the highest excess mortality was observed among 75+ year olds [9, 12-14]. Seasonal mortality in elderly persons in the Netherlands is attributable to multiple viruses, with highest numbers of deaths associated with influenza virus type A [55].

#### 1.2.3.1 Burden of influenza among the immunocompromised

The immune system of individuals can be compromised by inherited defects or, secondarily, by disease or medication. Disease categories that undermine the immune response are, for example, hematological malignancies (several thousand patients in the Netherlands) and HIV infection (about 20,000 patients in the Netherlands). Many more patients receive immunosuppressive agents because of chronic inflammatory diseases. In the Netherlands, about 200,000 patients with rheumatoid disease and 60,000 patients with inflammatory bowel diseases receive immunosuppressive agents. The therapeutic armamentarium is rapidly expanding, with new agents in the pipeline that target specific cytokines and intracellular pathways.

Furthermore, patients with liver dysfunction and chronic kidney disease are more susceptible to infections. In some, organ deterioration requires hemodialysis or solid organ transplantation. (For example, annually about 1,000 kidneys are transplanted.) These patients then receive combinations of immunosuppressive agents to prevent rejection of the transplanted organ.

Another category of immunocompromised patients is comprised those undergoing cancer treatment, including chemotherapy. Annually, tens of thousands patients are diagnosed with cancer in the Netherlands. Especially hematologic malignancies predispose patients to infections, given the immunodeficiency related to the disease itself and to the required chemotherapy or stem cell transplantation.

In immunocompromised patients, both the susceptibility to influenza virus infection and the incidence of influenza-related complications can be increased. In HIV-infection, increased severity of influenza has been noted in the most severely immunocompromised patients with low CD4 counts [56, 57]. Patients with hematologic malignancies may have an increased susceptibility to influenza virus infection, and complications result in high death rates of up to 33% [58]. In rheumatoid arthritis, a

higher incidence of influenza has been noted, with an increased risk of influenza-related complications compared to healthy controls [59]. A case fatality rate of almost 10% has been reported in cancer patients hospitalised for serious influenza-related complications [60]. Influenza virus infection has been reported to cause acute kidney allograft rejection [58].

Influenza vaccination is indicated for household contacts and direct contacts of immunocompromised persons. Vaccination of household contacts has also been recommended in several international guidelines [61-64].

**In summary,** estimated symptomatic influenza incidence based on GP data is relatively low among the elderly in the Netherlands. However, pneumonia prevalence in primary care is highest in the elderly. Next, influenza hospitalisation rates are highest among children under five years followed by those among adults of 65+ years. Influenza-associated mortality is highest among the elderly, especially among people with comorbidities.

## 2 Influenza vaccination

### Summary

Three types of vaccines are licensed, i.e. inactivated (whole, split and subunit virions), live attenuated, and recombinant HA vaccines. Availability on the Dutch market is dependent on existing supply arrangements for the National Influenza Prevention Programme (NPG) and in 2019 will be limited to two quadrivalent inactivated vaccines. Influenza vaccination is available free of charge via the NPG for target groups previously defined by the Health Council of the Netherlands. Currently, healthy pregnant women and healthy children aged 6–59 months are not target groups for influenza vaccination in the Netherlands.

### 2.1 Influenza vaccines

#### 2.1.1 *Availability of vaccines in the Netherlands*

The Dutch influenza vaccine market consists of two main segments--the National Influenza Prevention Programme (NPG) and the private market. The market share of NPG is about 96% and the private market is 4%. RIVM is responsible for the procurement of the vaccines for the NPG. The strain composition of seasonal influenza vaccines can change each year, making a relatively short time available for vaccine production each year. The WHO vaccine composition recommendation is issued late February, and the vaccine production process takes about half a year. To ensure that annual vaccines are ready despite the short manufacturing timeline, they are procured from two different suppliers.

For the NPG target groups (see §2.2.1), influenza vaccines are free of charge. The majority of these vaccinations take place at each person's GP practice, upon invitation. Each year more than 5,000 GPs receive the vaccines they have ordered directly from the RIVM-DVP-dedicated warehouse. At the end of the annual campaign, the GPs are reimbursed depending on the number of vaccinations given.

People not within the identified NPG target groups can obtain an influenza vaccination, upon payment, from their GP or sometimes their occupational physician. In addition, according to prevailing professional guidelines, hospitals and nursing homes offer vaccines free of charge to their healthcare workers. In these cases outside of the NPG, the influenza vaccines are purchased via wholesalers/ pharmacists in the private market.

Since the private market is small (about 4%; 130,000 doses per season), it is not attractive to manufacturers. Only the influenza vaccine suppliers of the NPG will offer vaccines for the private market. For the season 2019/2020, when quadrivalent inactivated vaccines will be introduced in the NPG, Influvac Tetra (Mylan) and Vaxigrip Tetra (Sanofi) will be available for both NPG and the private market.

Trivalent influenza vaccines will no longer be available for the Dutch market.

Besides the two quadrivalent vaccines that will be available on the Dutch market, other influenza vaccines obtained market authorisation in the Netherlands, but suppliers had not decided at this writing make these vaccines available in the Netherlands.

In Table 2.1 an overview is given of the influenza vaccines currently registered in the Netherlands by the Medicines Evaluation Board (MEB) of the Netherlands and the European Medicines Agency (EMA). In December 2018, Seqirus obtained European market authorisation for Flucelvax Tetra, the only cell-based (MDCK) influenza vaccine so far, which is registered for children  $\geq 9$  years and adults.

**In summary,** the availability of influenza vaccines on the Dutch market is strongly dependent on existing supply arrangements for the NPG. Starting with the 2019/2020 season, it will be limited to two quadrivalent inactivated vaccines.



Table 2.1 Overview of market authorisation of vaccines in the Netherlands (MEB - 26-01-2019)

Product name	Supplier	Type	Trivalent	Quadrivalent	Age group	Remarks
<b>Seasonal influenza vaccines</b>						
<b>Fluenza tetra</b>	Astra Zeneca	Nasal spray, live attenuated		X	Children >24 months, 18 yrs	Is under consideration
<b>Afluria</b>	Seqirus	Inactivated / split virion	X		Children >5 yrs – adults 0.5ml	
<b>Batrevac *)</b>	Mylan Healthcare	Inactivated / subunit	X		Infants 6-36 months 0.25ml Children >36 months + adults 0.5ml	
<b>Batrevac Tetra *)</b>	Mylan Healthcare	Inactivated / subunit		X	Infants 6-36 months 0.25ml Children >36 months + adults 0.5ml	
<b>Fluarix</b>	GSK	Inactivated / split virion	X		Infants 6-36 months 0.25ml Children >36 months + adults 0.5ml	Latest market authorisation 2016/2017
<b>Fluarix Tetra</b>	GSK	Inactivated / split virion		X	Infants > 6 months – adults 0.5ml	
<b>Influvac Junior</b>	Mylan Healthcare	Inactivated / subunit	X		Infants 6-36 months 0.25ml	
<b>Influvac</b>	Mylan Healthcare	Inactivated / subunit	X		Infants 6-36 months 0.25ml Children >36 months + adults 0.5ml	
<b>Influvac Tetra</b>	Mylan Healthcare	Inactivated / subunit		X	Children > 3 years Adults (18 years and older)	In season 2020 also infants 6 months – 3 yrs
<b>Serinfla *)</b>	Abbott Biologicals	Inactivated / subunit	X		Infants 6-36 months 0.25ml Children >36 months + adults 0.5ml	
<b>Vaccinfla *)</b>	Mylan Healthcare	Inactivated / subunit	X		Infants 6-36 months 0.25ml Children >36 months + adults 0.5ml	
<b>Vaxigrip</b>	Sanofi-Aventis	Inactivated / split	X		Infants 6-36 months 0.25ml	

Product name	Supplier	Type	Trivalent	Quadrivalent	Age group	Remarks
<b>Seasonal influenza vaccines</b>						
		virion			Children >36 months + adults 0.5ml	
<b>Vaxigrip Tetra</b>	Sanofi-Aventis	Inactivated / split virion		X	Infants 6 months – 17 yrs 0.5ml Adults 0.5ml	
<b>Xanaflu *)</b>	Mylan Healthcare	Inactivated / subunit	X		Infants 6-36 months 0.25ml Children >36 months + adults 0.5ml	
<b>New: Flucelvac Tetra</b>	Seqirus	Inactivated / subunit Cell-culture based (MDCK)		X	≥ Children 9 years Adults 18 yrs and older	
<b>Pandemic vaccines</b>						
<b>Adjupanix</b>	GSK	Pandemic (H5N1) AS03 adjuvant / split virion	NA	NA	Adults (18 years and older)	Limited data available for 2x half vaccination (day 0 and day 21) infants 3-9 yrs
<b>Aflunoy</b>	Seqirus	Prepandemic (H5N1) MF59 adjuvant / subunit	NA	NA	Adults (18 years and older)	Limited data available for vaccination infants 6 months – 17 yrs
<b>Focivia</b>	Seqirus	Pandemic (H5N1) MF59 adjuvant / subunit	NA	NA	Adults (18 years and older)	Limited data available for vaccination infants 6 months – 17 yrs
<b>Vepacel</b>	Nanotherapeutics (Baxter)	Prepandemic (H5N1) adjuvant / wholevirus Vero-cells	NA	NA	Infants >6 months and adults	Additional monitoring required

\*) These vaccines are identical to Influvac Tetra and are back-up registrations for international marketing purposes

## 2.1.2 *Influenza vaccines*

### 2.1.2.1 Currently available vaccines

Currently three types of vaccines are licensed: inactivated (whole, split and subunit virions), live attenuated, and recombinant HA vaccines. Only the first two types are widely available. Tables on clinical evaluation of influenza vaccines can be found at

[https://www.who.int/immunization/diseases/influenza/clinical\\_evaluation\\_tables/en](https://www.who.int/immunization/diseases/influenza/clinical_evaluation_tables/en).

Inactivated vaccines are the most frequently used, and most are produced by growing the vaccine seed virus on eggs. Cell-based inactivated vaccines are also available, but they are more expensive and supply is limited. The inactivated vaccines can be used in all age groups starting at age 6 months. The influenza viruses in these vaccines have been chemically inactivated to prevent their causing influenza. One intramuscular dose is sufficient, except for children between 6 months and 8 years of age who have not received a seasonal influenza vaccine in the previous year. They should receive two vaccine doses with at least a 4-week interval.

Live attenuated influenza vaccines (LAIV) better mimic a natural infection but are not recommended for use in children under 2 years of age, pregnant women, persons with certain underlying conditions, and immune-compromised individuals. Live attenuated vaccines should be given as a single dose nasal spray. Children between 2 and 8 years of age that did not receive an influenza vaccine in the previous year require two doses. LAIV contains weakened forms of the virus that can cause mild influenza signs or symptoms.

Recombinant HA vaccines are produced with a recombinant-protein-expression system using insect cells and baculovirus. They can be produced within 2 months, whereas other seasonal vaccines require 6-8 months of production time. The vaccine is licensed for use in adults 18 years and older.

Traditionally, seasonal vaccines are trivalent vaccines, i.e. containing three different influenza viruses: two subtypes of influenza A and one lineage of influenza B virus. More recently, quadrivalent vaccines have been developed that protect against four influenza viruses: two influenza A subtypes and two lineages of influenza B virus.

### 2.1.2.2 Development of next-generation vaccines

Several manufacturers are developing seasonal influenza vaccines with improved effectiveness, e.g. using cultured cells instead of eggs for virus preparation to increase NA content of the vaccine. They are also developing novel classes of adjuvants or novel vaccine concepts such as DNA or RNA or virus-like-particle vaccines.

Data suggest that high-dose vaccines with a higher NA content may induce cross-protective antibodies, which would result in broader protection by the vaccine. The advantage of DNA vaccines is that they induce humoral as well as cellular responses, whereas inactivated vaccines mostly rely on antibody production to achieve protection. The ultimate aim is to develop vaccines which could provide long-lasting (over multiple years) protection against a wide range of influenza virus

strains [65]. Several research projects are focussed on this 'universal influenza vaccine', but many years are likely to elapse before such a vaccine is available for routine vaccination programmes.

Table 2.2 Currently internationally available vaccines and vaccines in development

Vaccine type	Trivalent/quadrivalent	adjuvant	Administration route	Produced in	Age recommendation	Advantage	Licensed
Inactivated	Trivalent	none	IM	egg	≥ 6 months, Higher doses > 3 years	Low reactivity	yes
Inactivated	Quadrivalent	none	IM	egg	≥ 3 years	Low reactivity	yes
Inactivated/ High-dose	Trivalent	none	IM	egg	≥ 65 years	Higher antibody levels	yes
Inactivated	Trivalent	Squalene (MF59)	IM	egg	≥ 65 years	Low reactivity Dose-sparing	yes
Inactivated	Quadrivalent	none	IM	cells	≥ 4 years	Low reactivity, No eggs required	yes
Inactivated	Whole virion	AlPO4 gel	IM		≥ 60 years	Early and late T-cell-independent and -dependent responses	Hungary
Live attenuated	Quadrivalent	none	Intra nasal spray		≥ 24 months	Local mucosal admin and response Higher response in children Cross-reactivity Antibody and cellular responses Herd immunity	yes
Recombinant protein	Trivalent	none	IM	cells	≥ 18 years	No eggs required Higher antibody levels	US
RNA/DNA vaccines						No eggs required Non-replicating Added cellular responses	No
Virus-like particle vaccines						Highly effective, long lasting antibody response	No

## 2.2 The current influenza vaccination programme in the Netherlands

Since 1975, the Health Council of the Netherlands has recommended influenza vaccination for people who are at risk for developing complications related to influenza. In 1997, the government introduced the National Influenza Prevention Programme (NPG), making influenza vaccination available for recommended target groups free of charge.

National coordination of the NPG has been delegated by the Minister of Health to the RIVM-CvB. The National Influenza Prevention Programme Foundation (Stichting Nationaal Programma Grieppreventie, SNPG) has arrangements with GPs who invite target-group people within their practice to come for vaccination. Purchasing and distribution of vaccines is the responsibility of the RIVM-DVP.

GPs order influenza vaccines using the web application of SNPG. This application is also used for the financial settlement of the orders. In addition, healthcare organisations such as nursing homes, mental health institutes and rehabilitation centres are allowed to order free influenza vaccines at the SNPG for any residents who are in target groups but do not have a GP. The administration of these vaccines is not reimbursed through the NPG but through the Exceptional Medical Expenses Act (Algemene Wet Bijzondere Ziektekosten, AWBZ).

The Dutch College of General Practitioners (Nederlands Huisartsen Genootschap, NHG) has developed a protocol for GPs in cooperation with the SNPG. An e-learning tool is available for GPs. For patients, an infographic on influenza vaccination was produced by RIVM-CvB and NHG [66].

Until 2018, a trivalent influenza vaccine was used in the NPG. From 2019 onward, a quadrivalent vaccine will be used on the advice of the Outbreak Management Team (OMT). The OMT was organised by RIVM-CIb in response to the long-lasting and severe influenza epidemic of the 2017/18 season, which was dominated by B/Yamgata whereas B/Victoria was included in the trivalent vaccine. The OMT has also advised higher vaccination coverage among healthcare workers, to prevent transmission to patients. Vaccination of healthcare workers is not included in the NPG, however, and its implementation and financing are the responsibility of the employer.

### 2.2.1 *Target groups for influenza vaccination*

Currently influenza vaccination is recommended for the following groups [67-69]:

- 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 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);
- residents of nursing homes who do not fall into one of the categories above;
- family members of very high-risk individuals, e.g. 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;
- healthcare personnel in hospitals, care homes and nursing homes;
- other healthcare personnel with daily direct contact with patients.





### 3 Effectiveness of influenza vaccines and vaccination

#### Summary

##### ***VE of maternal vaccination***

For seven consecutive influenza seasons, maternal influenza vaccination has a mean vaccine effectiveness (VE) of 40% against hospitalisation for influenza during pregnancy. Vaccination against influenza during pregnancy also protects against laboratory-confirmed influenza in newborns up to six months of age (VE 30%-79%).

##### ***VE in healthy children***

VE in children is relatively high compared to other age groups. A meta-analysis of RCTs among children 3-16 years of age, using LAIV, showed a VE of 78%, comparable to results from observational studies.

##### ***VE in elderly individuals***

The current inactivated influenza vaccines provide only moderate protection against seasonal influenza in individuals of 65 years of age and older. The protective benefit of influenza vaccination is especially low for influenza A(H3N2) and decreases with increasing age. An exception is influenza A(H1N1)pdm09, for which vaccination seems to provide relatively good protection.

##### ***Novel vaccines in elderly***

Novel vaccine concepts and techniques such as high-dose vaccines, adjuvanted vaccines and recombinant technique vaccines, show promising results as demonstrated in both post- and pre-authorization studies. All of these vaccines show better protection in elderly subjects, compared with the traditional vaccines. This emphasizes the importance to innovate and invest in new vaccines and vaccine production techniques.

##### ***European VE studies***

It is generally not possible to obtain high-precision VE estimates for the Netherlands only. Pooled European estimates from the I-MOVE network (in which the Netherlands participates) provide more robust estimates. In the seasons 2009/2010 through 2017/2018, the adjusted overall VE estimated by I-MOVE varied between 6 (95%CI -21 – 26) in 2011/2012 and 72 (95%CI 46 - 86) in 2009/2010. Average overall VE for these 9 seasons was 34%.

#### 3.1 Measuring influenza vaccine efficacy and effectiveness

##### 3.1.1 *Vaccine efficacy*

'Influenza vaccine efficacy' traditionally refers to the effect of the vaccine in ideal, regulated circumstances. In general, it is measured in randomised controlled trials (RCT), which in recent years are mainly performed in healthy young persons.

### 3.1.2 *Vaccine effectiveness*

Vaccine effectiveness (VE) refers to the effect of the vaccine in the general population, daily practice, or in the field. In general, this is measured in observational studies, like cohort or case control studies.

These are the definitions that we use in the present report, whereby the acronym 'VE' represents vaccine efficacy as well as vaccine effectiveness. It should be noted that Cochrane reviews use different definitions. They define 'vaccine efficacy' as the reduction in laboratory-confirmed influenza cases, and 'vaccine effectiveness' as the reduction of influenza-like illness, assessed using non-viral endpoints.

A frequently used design for the estimation of influenza VE is the test negative design (TND). It has evolved as an internationally accepted standard that is used in the EU region (I-MOVE), the USA, Canada and Australia. The relatively low number of specimens that is generally available from sentinel GP surveillance results in broad confidence intervals (CI) in influenza VE analyses, especially those analyses that are stratified for age, influenza (sub)types with a low prevalence, vaccine type or brand. To overcome this problem, the RIVM and Nivel participate in the I-MOVE consortium and contribute data to annual multi-country pooled influenza VE analyses [70, 71].

The VE can vary per season and geographical location, depending on the match of the vaccine viruses with the circulating viruses, the individual characteristics of patients, and the type of vaccine used. This variation makes it difficult to compare estimates among studies and countries.

Compared to RCTs, observational studies are more prone to bias due to observed and unobserved confounding. Over the past decade, however, study design and data analysis methods have been developed and validated to limit bias and control as much as possible for confounding. This is particularly true for the TND that has been further developed and harmonised within multi-country influenza VE networks.

## ***Experimental study designs***

### **Randomized controlled trial (RCT)**

A RCT is a non-observational study. In this type of study, persons are randomly assigned to experimental exposure groups. Comparisons that can be made are: exposure vs non-exposure, exposure vs placebo and exposure A vs exposure B. In this setting, 'exposure' refers to the vaccine, and exposure to the influenza virus is not controlled. The exposure groups are followed during a defined period, after which the clinical outcome is observed and compared between the two groups. The most reliable results are obtained if the participants do not know to which exposure group they are assigned (=blinded). Ideally, the researchers who are responsible for measuring the clinical outcome and the data analysis also do not know which persons are assigned to which exposure group (=double blinded).

In the recent literature very few new RCTs have been published that study the efficacy of already existing influenza vaccines in risk groups. However, RCTs that study the efficacy of new types of influenza vaccines

compared to already existing vaccines are still being performed. In these RCTs, the outcome is 'relative efficacy' instead of efficacy itself.

### ***Observational study designs***

#### **Case control study**

A case control study is an observational study design in which the frequency of determinants (exposure) of persons with a disease (cases) is compared with that in persons without the disease (controls). A case control study is a retrospective study. Its typical epidemiological outcome measure is the odds ratio (OR).

#### **Cohort study**

A cohort study is an observational study design in which persons with and without certain exposure factors are compared. These groups are followed during a defined time period, after which the clinical outcome is observed and compared between both groups. A cohort study can have a retrospective or a prospective design. In prospective cohort studies, the persons are followed going forward, whereas in retrospective cohort studies, the clinical outcomes have been established. Because the outcomes have already been reached, the information is collected from such sources as registries or questionnaires. The typical epidemiological outcome measure from this type of study is the relative risk or risk ratio (RR).

#### **Test negative design (TND)**

A study with a TND is a type of case control study that is frequently used for the estimation of influenza VE. Cases are defined as persons with ILI (or ARI) who have tested positive for influenza virus, whereas controls are persons with ILI (or ARI) who have tested negative for influenza virus. Frequencies (or, the odds) of being vaccinated are compared between these groups, resulting in an OR.

### ***Systematic review***

A systematic review is a literature study in which the best available published research on a specific question is compared and summarised.

#### ***Meta-analysis***

A meta-analysis is a literature study in which results from published studies are summarised quantitatively. A meta-analysis is sometimes added to a systematic review.

#### **3.1.3**

##### ***Calculation of influenza VE***

VE is calculated as  $VE = (1 - RR) * 100\%$  in RCTs and cohort studies or as  $VE = (1 - OR) * 100\%$  in case control studies (including TND studies).

A VE higher than 0 means that the vaccine has a protective effect on the measured outcome. The higher the influenza VE, the higher the protective effect. An influenza VE of 0 means there is no effect of the influenza vaccine on the measured outcome. Theoretically, a negative VE means that the vaccine increases the risk for the measured outcome.

However, negative VE point estimates (or a negative value of the lower *bound/boundary* of the 95% confidence interval) are mostly observed in underpowered studies, i.e., in studies that have a sample size too low to be able to demonstrate a significant effect. In this context, it should be borne in mind that the lower the true effectiveness of the vaccine, the higher the sample size required to obtain a significant result. In practice, studies rarely have sufficient power to demonstrate an effect, which is slightly above 0. Therefore, in these situations, negative VEs might be found, simply due to chance.

### 3.2 Vaccine effectiveness of maternal vaccination

The WHO recommends seasonal influenza vaccination of healthy pregnant women, and a growing number of countries provide such vaccination. Among those are Australia, USA, Canada, most countries in South America, South Africa, Scandinavian countries, the UK, Germany, Belgium, France, Spain and Italy. Vaccination coverage in these countries varies between 23% and 96%. The benefit of maternal influenza immunisation for a newborn derives from the sustained reduction in the risk of acquiring disease during the influenza season, typically two to three months every winter in temperate climates. Immunisation status outside this window is irrelevant. This is depicted in Figure 3.1, which shows that only pregnancies starting in about May through July could benefit from maternal vaccination, i.e., children born in the epidemic period, which is typically January through March in the Netherlands [72]. To assess potential benefits, it is critical to know whether the pregnancy is vulnerable to maternal influenza disease at particular time periods during gestation.

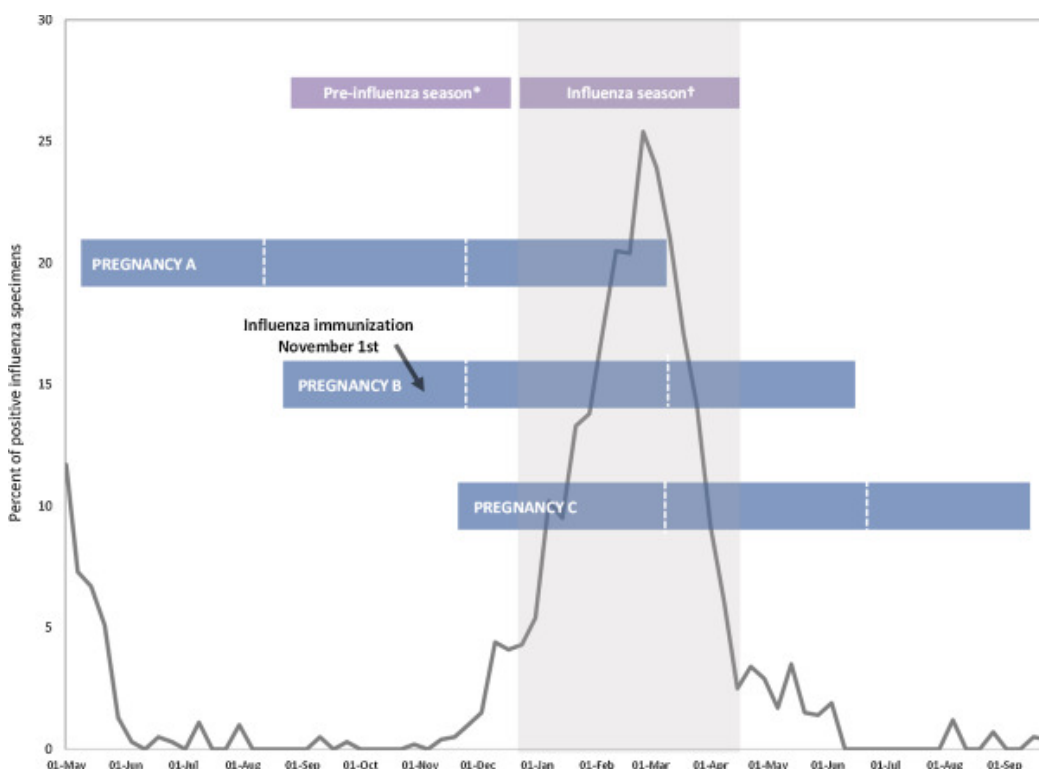


Figure 3.1 Hypothetical temporal alignment of ongoing pregnancies with influenza seasonality

The pre-influenza season represents the time period in which influenza vaccines are typically administered (shown here as September to December). The dark gray line represents the proportion of specimens positive for influenza virus, and the shaded area represents a typical influenza season, in this case defined as the first and last occurrence of two consecutive weeks with  $\geq 5\%$  positive influenza specimens [72].

This phenomenon considerably complicates assessment of benefits of maternal influenza vaccination.

### 3.2.1 *Protection against infant influenza*

#### 3.2.1.1 Randomised controlled trials

The study by Zaman *et al.* paved the way for increased attention to maternal influenza vaccination and its beneficial effects for mother and child [73]. This RCT in Bangladesh showed that maternal influenza vaccination was 63% effective (95%CI 5-85) in preventing infant laboratory-confirmed influenza in infants up to 6 months of age. Furthermore, vaccination reduced infant respiratory febrile illness by 29% and infant clinic visits for that disease by 42%.

Later, similar RCTs were performed in Mali, Nepal and South Africa, with pregnant women vaccinated against influenza in their second or third trimester [74-76]. VE estimates against laboratory-confirmed influenza in infants up to 6 months of age were 33% (95%CI 4-54) and 30% (95%CI 5-48) in Mali and Nepal, respectively [74, 75]. In the South African trial, VE against infant hospitalisation due to all-cause acute lower respiratory tract infection was 43% (95%CI 0-68) [76], and it amounted to 49% (95%CI 12-70) against laboratory-confirmed influenza in infants up to 24 weeks of age [77]. Infant VE decreased over time and conferred most protection in the first two months after birth [74, 75, 78].

The Forest plot of the main outcome of these RCTs, i.e., prevention of laboratory-confirmed influenza infection in infants younger than 6 months, is depicted in Figure 3.2 [79].

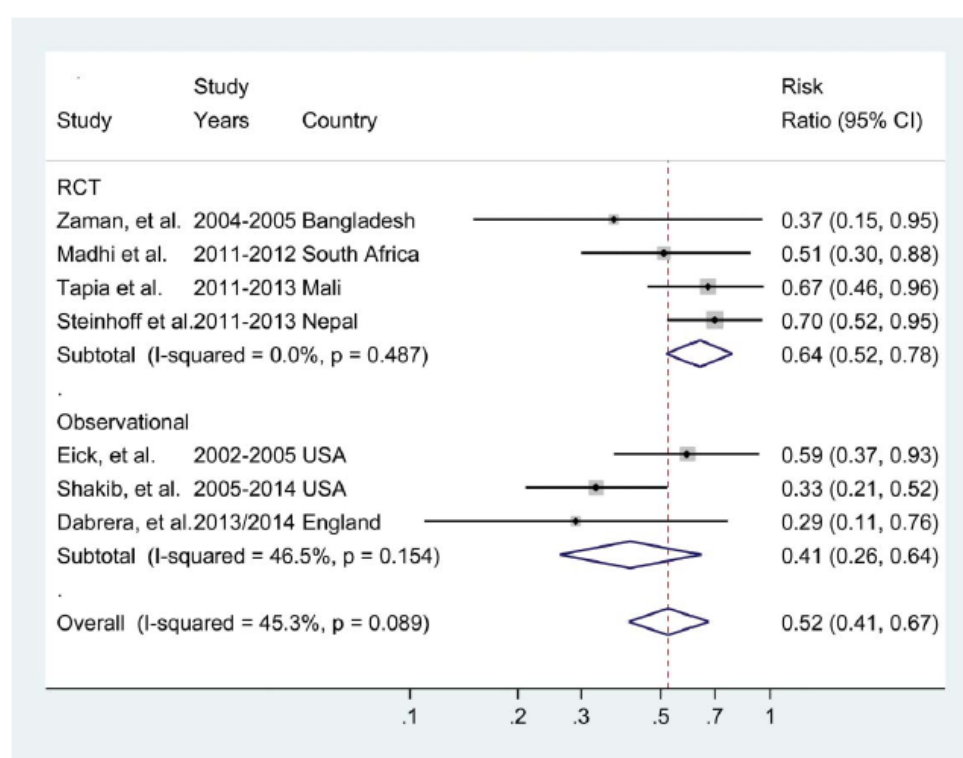


Figure 3.2 Prevention of laboratory-confirmed influenza infection in infants younger than 6 months based on RCTs and observational studies on maternal influenza vaccination (from [79]).

### 3.2.1.2 Observational studies

A recent systematic review of studies on influenza vaccination during pregnancy to protect young infants against influenza, not only included the RCTs described above but also three observational studies [79]. All three studies found a significant protective effect of maternal influenza vaccination in the prevention of influenza in their offspring up to six months of age (Figure 3.2).

In another observational study, performed in Australia and including 31,028 mother-singleton infant pairs, maternally vaccinated infants were less likely to be hospitalised for a severe respiratory infection than infants of unvaccinated mothers (adjusted hazard ratio (HR) 0.75; 95%CI 0.56-0.99) [80]. In the period outside the influenza season, there was no difference in hospitalisation rate for respiratory infections between the groups.

## 3.2.2 Protection against influenza during pregnancy

### 3.2.2.1 Randomised controlled trials

In the RCT performed by Zaman *et al.*, mothers who received influenza vaccination were less likely to have respiratory illness with fever, as compared to the control group (VE 36%; 95%CI 4-57) [73]. In the RCTs performed in Mali, Nepal and South Africa [74, 75], VE against laboratory-confirmed influenza in the pregnant women ranged between 31% (95%CI -10 - +34) and 70% (95%CI 42-86).

### 3.2.2.2 Observational studies

A recently published observational study covering seven consecutive influenza seasons in Australia, Canada, Israel and the United States (Pregnancy Influenza Vaccine Effectiveness Network, PREVENT) showed an overall VE of 40% (95%CI 12-59) against influenza-associated hospitalisation during pregnancy, adjusted for site, season, seasonal timing and high-risk medical conditions [81].

### 3.2.3 *Other benefits of maternal influenza vaccination*

Besides prevention of influenza in mothers and their newborns, other findings are described. Secondary outcomes of two RCTs described in this section suggest that mean birth weight increases after maternal influenza vaccination, especially when the mother is vaccinated in the third trimester and the baby is born during the influenza season [82, 83]. Likewise, an observational study showed a reduced likelihood of prematurity (adjusted OR 0.28; 95%CI 0.11-0.74) and SGA births (adjusted OR 0.31; 95%CI 0.13-0.75) [84]. However, methodological shortcomings may have biased these results. Moreover, in-depth analysis of the possibility of detecting true differences in adverse pregnancy outcomes revealed the need for large sample sizes, which were probably not achieved in the studies described above [85].

**In summary**, for seven consecutive influenza seasons, maternal influenza vaccination had a mean VE of 40% against hospitalisation for influenza during pregnancy. Vaccination against influenza during pregnancy also protects against laboratory-confirmed influenza in newborns up to six months of age (VE 30%-71%).

## 3.3 **Vaccination programme and vaccine effectiveness in healthy children**

### 3.3.1 *Current vaccination programmes*

In the Dutch National Influenza Prevention Programme, healthy children are currently not eligible for vaccination. Only children belonging to one of the target risk groups as listed in paragraph 2.3.1 are offered vaccination.

The WHO, however, recommends vaccination of all children aged 6–59 months [19], and a limited number of countries have implemented this recommendation. In the United States, universal influenza vaccination is recommended for all citizens from 6 months of age. In Europe, eight countries have a vaccination recommendation for children, of which only three (Finland, Latvia, and the United Kingdom [UK]) provide the influenza vaccine to healthy children free of charge [86]. In England, the Joint Committee on Vaccination and Immunisation (JCVI) recommended in 2012 that the seasonal influenza programme be extended to all children aged two to 17 [87]. The roll-out of this extended programme is being phased in over a period of time, in order to ensure a manageable and successful implementation process. Figure 3.3 gives the vaccination schedule for the 2018/2019 season in UK/England.

## Which flu vaccine should children have?



There are two types of flu vaccine available for children in 2018/19 – the 'live' nasal spray vaccine and the inactivated injected flu vaccine. This chart indicates which vaccine children should get.



Figure 3.3 Child influenza vaccination schedule for the 2018/2019 season in England

Available at:

[https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment\\_data/file/735239/Which\\_flu\\_vaccine\\_should\\_children\\_flu\\_vaccine\\_2018\\_.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/735239/Which_flu_vaccine_should_children_flu_vaccine_2018_.pdf)

### 3.3.2 Rationale for vaccination of healthy children

The main rationale for the WHO recommendation of vaccinating healthy children is the high global burden of disease, especially among children less than 2 years of age. By far the largest burden from severe paediatric influenza illness and 99% of influenza-attributable paediatric deaths occurs in developing countries [48]. The rationale to vaccinate school-age children is that these children have the highest annual attack rates for influenza and are the major spreaders of influenza in the community and introducers into the household. Therefore, in addition to the objective of protecting the individual, vaccinating children aims to reduce transmission of influenza virus in the family, school and community and reduce absenteeism of children from school and their parents from work. Initial results from the UK indicate that vaccination of healthy primary school-age children with live-attenuated influenza vaccine (LAIV) at a moderate uptake of 58% is indeed associated with population-level reductions in influenza-related respiratory illness [88]. These indirect effects through herd protection and the other impacts of vaccination of children are covered in chapter 5.1.



### 3.3.3 *Influenza vaccine effectiveness in children*

Two recent systematic reviews on influenza VE in children were published in 2017 and 2018. Caspard *et al.* [89] performed a systematic review and meta-analysis of 29 observational studies that assessed the effectiveness of LAIV against laboratory-confirmed influenza since the 2009 pandemic in children and young adults. In some of the seasons between 2010 and 2016, LAIV was suboptimally effective against A(H1N1)pdm09 and less effective than inactivated influenza vaccine (IIV). LAIV was consistently effective against B strains and matched A(H3N2) strains, but it was not shown to provide significant protection against mismatched A(H3N2) strains in 2014-2015.

The Cochrane review by Jefferson *et al.* [90] concluded from 41 randomised clinical trials that, LAIV or IIV reduce influenza with moderate to high-certainty evidence in children between 3 and 16 years of age. In studies in which virologically confirmed endpoints were used, evidence from RCTs shows that LAIV has an overall VE of 78% (RR 0.22, 95%CI 0.11-0.41; 7,718 children 3-16 years; moderate-certainty evidence). Evidence from RCTs shows that inactivated vaccines have a lower VE of 64% (RR 0.36, 95%CI 0.28-0.48; 1,628 children 2-16 years; high-certainty evidence). The authors of the Cochrane review did not identify a RCT in children under 2 years of age that fulfilled the inclusion criteria. Although this Cochrane review was published in 2018, it included only one recent original study, a RCT with LAIV among children aged 2-4 years in Bangladesh by Brooks *et al.* [91], with a VE estimate of 57.5% (95%CI 43.6%-68.0%).

The most recent original industry-funded RCT, which was not included in the Cochrane review, involved healthy children aged 6-35 months from 13 countries over five influenza seasons. VE of an inactivated QIV with 4 months follow-up was estimated at 63% (97.5%CI 52%-72%), although there were high levels of vaccine mismatch [92]. VE was highest against moderate-to-severe disease.

In a case cohort study in the USA from July 2010 through June 2014, influenza vaccination with any influenza vaccine was associated with reduced risk of laboratory-confirmed influenza-related paediatric deaths [93]. VE against laboratory-confirmed influenza-associated death was 65% (95%CI 54%-74%) in a group of children aged 6 months through 17 years. VE was lower in children with underlying medical conditions. Another US study was conducted with a TND during two influenza seasons (2010-2012) among children aged 6 months to 17 years admitted to 21 US paediatric ICUs. VE was 74% (95% CI 19%-91%) in preventing life-threatening laboratory-confirmed influenza in children requiring admission to the ICU [94]. In New Orleans, Louisiana, USA, with a test-negative design, a combined VE of 61% was found for all influenza vaccines (IIV or LAIV) for three seasons (2013–2016) among children 1-17 years of age [95].

In a study in Canada, VE against laboratory-confirmed influenza hospitalisations among children aged 6-59 months was estimated with the TND in hospitalised children during the 2010/2011 to 2013/2014 influenza seasons [96]. For the four seasons combined, VE was 60% (95%CI 44%-72%).

Annual estimates of influenza VE from observational studies in Europe, including data from the Netherlands, are available from the I-MOVE (Influenza Monitoring Vaccine Effectiveness) consortium, but are not specifically focused on children. In the 2015/2016 season, VE of trivalent inactivated influenza vaccines against influenza A(H1N1)pdm09 was moderate in children 0-14 years (and adults), and low against influenza B [97]. However, confidence intervals of the VE estimates for children are extremely wide due to the very low vaccination coverage among children in Europe.

Countries in Europe (I-MOVE) and on other continents work together in the Global Influenza Vaccine Effectiveness (GIVE) Collaboration to provide interim (in-season) and final VE estimates. These estimates are used by the WHO for the Vaccine Composition Meetings. The GIVE report of 20th September 2018 contains results from observational studies, including interim studies from the Southern Hemisphere 2018 influenza season and final season studies from the Northern Hemisphere 2017/2018 influenza season (Report compiled by the WHO Collaborating Centre for Reference and Research on Influenza, Melbourne, Australia). Final VE against influenza A and B in paediatric outpatients (<18 years) ranged from 43% to 63% in five studies: Canada 43% (95%CI 9%-65%); Europe (I-MOVE) 51% (31-65); Japan 63% (45-76); USA (two different networks) 50% (40-59) and 47% (38-55). However, these estimates may be influenced by large differences among countries in the relative proportions of the different influenza subtypes and circulating lineages and the relative use of TIV, inactivated QIV, or LAIV.

#### 3.3.4 *LAIV controversy*

LAIV is administered intranasally and is often used for vaccinating healthy children. The USA has a long-standing programme of vaccinating children against influenza with use of LAIV. However, when studies showed an apparent lack of VE of LAIV in 2015-2016, particularly against A(H1N1)pdm09, the USA suspended the use of LAIV in the 2016-2017 season. In 2015-2016, the UK and Finland, unlike the USA, found evidence of significant VE of LAIV against laboratory-confirmed influenza, and both the UK and Finland continued to recommend the use of LAIV in children [98]. For the 2018-2019 influenza season, the US Centers for Disease Control and Prevention (CDC) and its Advisory Committee on Immunization Practices (ACIP), after an extensive review of all published studies from the USA and Europe, again listed LAIV (quadrivalent) as a recommended option for children who have no contra-indication for a live vaccine [99]. Also, in 2017, two improved backbones for use in producing vaccine seed viruses for influenza A(H1N1)pdm09 became available for the LAIV vaccine, with improved replicative fitness over previous LAIV influenza A(H1N1)pdm09 vaccine strains. These are the Ann Arbor (American) backbone and the Leningrad (Russian) backbone. However, the Committee on Infectious Diseases [100] of the American Academy of Pediatrics (AAP) recommended an inactivated influenza vaccine, either TIV or QIV, as the primary choice for influenza vaccination of children for the 2018-2019 season because the effectiveness of LAIV against influenza A(H1N1)pdm09 was inferior during past influenza seasons and was unknown for the upcoming season. Evidence is nevertheless accumulating that LAIV with Ann Arbor or Leningrad backbone with an

updated A(H1N1)pdm09 component not only provides improved replication but also elicits immune responses similar to those seen before for LAIV with previous seasonal A(H1N1).

### 3.4 Vaccine effectiveness in the elderly

#### 3.4.1 RCTs

In the most recent Cochrane review published in 2018, Demicheli *et al.* [101] concluded that vaccinating elderly individuals reduces the risk of influenza and ILI. Evidence from RCTs with laboratory-confirmed viral endpoints showed that the risk of influenza is reduced from 6% in unvaccinated elderly to 2.4% following vaccination with an inactivated vaccine (VE 58% [RR 0.42; 95%CI: 0.27-0.66]; n=2,217 elderly; low-certainty evidence). RCTs with non-virological endpoints likewise showed that vaccinated elderly experience less ILI (6% vs 3.5%) (VE 41% (RR 0.59, 95%CI: 0.47-0.73); n=6,894 elderly; moderate-certainty evidence). The authors graded the certainty of this evidence moderate to low due to uncertainties in the way influenza was diagnosed, and they explicitly mention that no firm conclusions can be drawn due to the heterogeneous nature of the vaccines tested (monovalent, trivalent, different strains), as well as the various settings, outcomes, populations and study designs. Additionally, three of the included RCTs assessed the effect of various types of inactivated aerosol vaccines, but the evidence did not show a protective effect against influenza and ILI, probably partly due to the small study population. The authors found no data on hospitalisations for influenza-associated complications, and data on influenza-associated deaths was sparse, limiting the possibility to draw any conclusions. Although this Cochrane review was updated in 2018 with data current to 31 December 2016, the most recent RCT that meets the criteria of eligibility dates from 2004. The absence of any recent RCTs questions the representativeness of the review. In addition, although the Cochrane collaboration does not include observational studies in its reviews due to the suggested low-quality evidence of this study design, the collaboration includes RCTs that report on non-virological endpoints, such as ILI.

#### 3.4.2 Systematic reviews and meta-analyses of observational studies

A recent meta-analysis of TND studies examined the effectiveness of influenza vaccines in preventing severe influenza illness, defined as laboratory-confirmed influenza needing hospitalisation [92]. The authors reported a significantly lower seasonal VE for any type of influenza among adults aged  $\geq 65$  years of age (VE 37%; 95%CI: 30-44) compared to those  $< 65$  years of age (VE 51%; 95%CI: 44-58). Influenza strain-specific estimates showed a lower protection in elderly individuals compared to younger subjects against influenza subtype A(H3N2) (VE 33% vs. VE 50%) and type B (VE 31% vs. VE 45%), while the VE against influenza-related hospitalisations associated with influenza subtype A(H1N1)pdm09 was similar for both age groups.

A recent meta-analysis by Darvishian *et al.* included studies of multiple geographical regions and assessed the seasonal influenza VE in the elderly. They reported a significant effect of influenza vaccination in reducing the risk of laboratory-confirmed influenza among community-dwelling elderly. The VE varied substantially across influenza type and

subtype and was considerably higher when the vaccine matched the circulating strain (matched vaccine; VE 44.4%; 95%CI: 22.6-60.0) compared to seasons with low vaccine match (VE 20.0%; 95%CI: 3.5-33.7). The VE was higher for influenza subtype A(H1N1)pdm09 (VE 53.2%; 95%CI 10.3-75.6) than for A(H3N2) (VE 21.8%; 95%CI: 2.3-37.5). Additionally, adjusted estimates of all influenza types by age showed a protective effect in those younger than 75 years old (VE 33%; 95%CI: 17–45), but not among those older than 75 years (VE 16%; 95%CI: -8-55). The substantial variation in VE across influenza virus types and subtypes among elderly ( $\geq 65$  years) is also reported in the systematic review and meta-analysis by Belongia *et al.* [102]. They reported a VE of 63% (95%CI: 33-79) against influenza type B; a similar protective effect against influenza subtype A(H1N1)pdm09 (VE 62%; 95%CI: 36-78); and lower protection against influenza subtype A(H3N2) (VE 24%; 95%CI: -6–45). Another recent meta-analysis by Rondy *et al.* assessed TND studies and reported a VE of 37% (95%CI: 30-44) against laboratory-confirmed hospitalised influenza among people  $\geq 65$  years of age [103].

### 3.4.3 *European estimates*

For the past 10 years, annual influenza VE estimates for the EU based on routine influenza surveillance systems in the participating countries have been available through the I-MOVE consortium. These European estimates showed a low to moderate VE among the elderly population in different influenza seasons. The VE varied substantially per influenza subtype, with the lowest protection against the influenza A(H3N2) subtype. Pooled data from five European study sites in the 2017-2018 season showed a VE of 35% (95%CI 13-51) against hospitalisations associated with any type of influenza among adults aged 65 years and older [104]. These findings are similar to the overall VE of 39% (95%CI: 22-53) observed in the 2015-2016 European influenza season [105]. Further influenza subtype analysis among those  $\geq 65$  years of age in the 2017-2018 season showed low protection (VE 37%; 95%CI: -40-72) against influenza in primary care and hospitalisation-associated influenza subtype A(H1N1)pdm09 infections compared to those younger (18-64 years of age; VE ranges between 60%-63%) [104]. A low protection against influenza type A(H1N1)pdm09 was also observed in the 2015-2016 season, in which the VE was 42% (95%CI 22-57) for hospitalisations and 13.2% (95%CI -38.0-45.3) for primary-care medically-attended laboratory-confirmed ILI [105, 106]. VE against hospitalisation for influenza type B ranged from moderate in 2015-2016 (VE 52%; 95%CI 24-70) to low in 2017-2018 (VE 34%; 95%CI 8-52). Additionally, vaccination in the 2015-2016 season showed no effect against influenza B laboratory-confirmed ILI (VE 9.3%; 95%CI -44.1-42.9) [106]. Vaccination was not beneficial against influenza subtype A(H3N2) associated hospitalisations in both the 2016-2017 and 2017-2018 season, and showed a low protection at primary-care level as well (VE 23.4%; 95%CI -15.4-49.1)[104, 107].

**In summary,** RCTs and meta-analyses of observational studies show that the current influenza vaccines provide only moderate protection against seasonal influenza in individuals 65 years of age and older, and protection is lower than in younger adults. The protective benefit of influenza vaccination is low for influenza type B and especially for

influenza A(H3N2) and decreases with age. VE is considerably higher against influenza A(H1N1)pdm09.

#### 3.4.4 *Alternative vaccines*

In the last decades, vaccines promising improved protection for the elderly population were developed, including a trivalent inactivated influenza vaccine containing the MF59 immunologic adjuvant (aIIV3) and a high-dose inactivated trivalent vaccine (HD-IIV3) containing a four-fold hemagglutinin level (60 µg instead of the usual 15 µg per vaccine component). In addition, broader coverage quadrivalent inactivated influenza vaccines (QIV/IIV4) were developed to address the antigenic diversification of influenza B viruses. Recombinant vaccines have reduced production time and do not develop egg-adaptations that reduce antigenic likeness with circulating strains. These new vaccines were authorised by the US Food and Drug Administration (FDA) and/or the European Medicines Agency (EMA).

##### 3.4.4.1 Adjuvanted influenza vaccines

Two cohort studies that examined the VE of adjuvanted vaccines among community-dwelling elderly showed a significant impact in preventing ILI (VE 70%; 95%CI 44-84). Both studies combined had only 498 observations and were performed in a year with low viral circulation but with good vaccine match [101]. A meta-analysis of observational studies evaluated the effectiveness of vaccination with MF59-TIV compared to no vaccination against influenza-related outcomes in elderly living in communities or long-term care facilities [108]. MF59-TIV was effective (VE>50%) in preventing hospitalisation for influenza or not virologically tested pneumonia and acute coronary and cerebrovascular events in community settings, adjusted for possible confounders. Adjusted estimates of VE (e.g., for underlying pathologies, sex and age) for laboratory-confirmed influenza in both settings were 68%; however, the 95%CI was broad (5% - 82%). The relative VE of MF59-TIV in comparison with intramuscular non-adjuvant vaccines tended to be significantly higher; however, a meta-analysis for the latter was not feasible due to the different study designs and outcomes.

##### 3.4.4.2 High-dose influenza vaccines

To overcome the reduced immune response following vaccination in the elderly, high-dose (HD) vaccines have entered the market. These contain up to 60 µg of hemagglutinin per strain, rather than the standard 15 µg antigen per strain, thereby potentially increasing the immune response. A meta-analysis performed by Wilkinson *et al.* [109] reviewed RCTs that compared high-dose vaccines to standard-dose (SD) vaccines in community-dwelling elderly ≥65 years of age. The authors concluded that the efficacy of HD vaccines in reducing laboratory-confirmed influenza was 24% greater compared to that in individuals receiving SD vaccination. A more recent meta-analysis assessed the vaccine efficacy and effectiveness of HD-IIV3 among elderly people against more clinically relevant outcomes such as influenza-associated hospitalisations and death [110]. Those authors also demonstrated that HD-IIV3 improved protection against influenza-like illness (VE 19.5%; 95%CI: 8.6-29.0) compared to SD-IIV3. Moreover, HD-IIV3 was found to be more effective in preventing hospitalisations from pneumonia (VE 24.3%; 95%CI: 13.9-33.4), influenza (VE 17.8%; 95%CI: 8.1-26.5),

cardiorespiratory events (VE 18.2%; 95%CI: 6.8-28.1) and all-cause hospital admissions (VE 9.1%; 95%CI: 2.4-15.3).

#### 3.4.4.3 Recombinant influenza vaccines

In recombinant influenza vaccines, the hemagglutinin is produced in insect-cell cultures, avoiding the time-consuming process of generating reassortant virus with high-replicating capacity and growth of virus cultured in eggs or cells. In addition, vaccine viruses grown in eggs are subjected to egg-growth-induced amino acid substitutions in the hemagglutinin that potentially affect antigenicity. Indeed, these have been associated with low VE against influenza subtype A(H3N2) [111]. A recent RCT compared the protective efficacy of a quadrivalent recombinant influenza vaccine with insect-cell-expressed hemagglutinin ((RIV4); 45 µg hemagglutinin per strain) with a SD quadrivalent influenza vaccine ((IIV4); 15 µg hemagglutinin per strain) in adults ≥50 years of age [112]. The trial was performed during the 2014-2015 influenza season in which influenza subtype A(H3N2) predominated and antigenic mismatch of the vaccine strain with the circulating strains resulted in low effectiveness of many vaccines [113]. They found a lower attack rate of laboratory-confirmed ILI in the elderly (≥50 years of age) vaccinated with RIV4 (2.2%) compared to IIV4 (3.2%) and concluded that RIV4-vaccinated individuals were 30% less likely to have ILI. The relative VE of RIV4 over IIV4 in the subpopulation of those aged ≥64 years was not found to be significant (VE 17%; 95%CI: -20 - 43).

**In summary**, adjuvanted and high-dose vaccines provide greater protective benefits in elderly subjects, compared to the traditional vaccines.

### 3.5 Effectiveness and efficacy of the influenza vaccination in people with co-morbidities

People with chronic health conditions are at particular risk for developing severe complications from influenza virus infection, which is an indication for vaccination. Few studies have assessed the effectiveness of influenza vaccination against several clinical outcomes in a population with non-specific co-morbidities. Two case-control studies among adults (≥18 years of age) (one group living in Australia and another in Spain) with at least one chronic condition reported that influenza-associated hospitalisations were reduced about 50% following seasonal vaccination with a trivalent inactivated influenza vaccine (TIV) [114, 115].

#### 3.5.1 *Chronic obstructive pulmonary disorder (COPD)*

In a 2018 Cochrane review [116] of people with COPD, inactivated influenza vaccines (IIV) significantly reduced the total number of exacerbations per patient in two RCTs (n=180). Moreover, based on the same RCTs, VE was 81% (95%CI 52–93) against laboratory confirmed influenza infections. No effect was observed on hospitalisations or overall mortality. Although the review was published in 2018, the most recent RCTs date from more than a decade ago and include a very small number of participants. Nevertheless, similar effects were observed in a recent review by Bekkat-Berkani *et al.* [117] of seven observational studies that assessed the effectiveness of influenza vaccination in patients with COPD in preventing adverse clinical outcomes such as

ARI's, episodes of acute coronary syndromes, hospitalisations due to COPD exacerbations and death. The authors observed a potential benefit of vaccination in people with a mean age of  $\geq 65$  years suffering from COPD, but they reported no outcome numbers, as a meta-analysis was not possible due to the heterogeneity of the studies. The studies in both reviews used mostly the trivalent inactivated influenza vaccine (TIV3) given with standard dose antigen of 15 ug per strain. A trial conducted in Thailand in 2004 among patients with COPD (mean age 68 years), used a 2-fold higher antigen concentration and resulted in a VE of 76% against acute respiratory illness [118]. Increasing the dose could enhance the VE in older and/or more vulnerable groups, especially since other alternatives, such as addition of a live attenuated vaccine, showed no additional benefit in people suffering from COPD [116].

### 3.5.2 *Asthma*

The most recent Cochrane review by Cates and Rowe *et al.* [119] focused on children aged  $\geq 2$  years and adults with stable asthma. The authors included RCTs and pooled the data based on the type of vaccine used, but the results were inconclusive. The review included one trial in children aged 6–18 years that compared trivalent inactivated influenza vaccine (TIV3) with placebo, which showed no significant reduction in the number of asthma exacerbations. However, of the children that became infected, those that had received vaccination reported an improved health-related quality of life score compared to those who were not vaccinated. Another more recent meta-analysis pooled VE data from two TND studies performed in the US during the 2011-2012 and 2012-2013 season and showed that vaccinating people with asthma ( $>6$  months of age) reduced the risk for laboratory-confirmed influenza (VE 45%; 95%CI 31-56;  $n=1,825$ ) [120]. Additionally, these authors reported multiple studies that observed a protective effect of influenza vaccination against asthma attacks and other clinical outcomes. Pooled estimates of LAIV among children in two RCTs showed a VE of 72% (95%CI 20-90;  $n=2,229$ ) against febrile illness, compared to no vaccine. Multiple trials compared the use of LAIV (intranasal) with TIV3 (intramuscular) in children with a history of wheezing and asthma. Fleming *et al.* [121] compared LAIV with TIV during the 2002-2003 season in children aged 6-17 years and found a lower risk of culture-confirmed influenza illness following vaccination with LAIV (VE 35%; 95%CI 4-56), but they observed no difference in the incidence of asthma exacerbations or asthma symptoms. Two other trials that included children aged 2-5 years showed fewer cases of culture-confirmed influenza illness in children receiving LAIV and documented a VE of LAIV over TIV of 46.6% (95%CI 16.6–65.4) [122] and 39.9% (95%CI: -25.9–72.3) [123].

### 3.5.3 *Cardiovascular disease*

Cardiovascular disease includes disorders like coronary heart disease (CHD), cerebrovascular disorders and peripheral arterial disease (PAD). Most literature regarding cardiovascular diseases uses a composite of major cardiovascular events as the primary or secondary endpoint. Such events include cardiovascular death, hospitalisation for myocardial infarction, stroke, unstable angina pectoris and heart failure. Two meta-analyses of RCTs were identified that assessed the evidence of the efficacy of influenza vaccination in patients with known cardiovascular

disease. First, a Cochrane review by Clar *et al.* [124] assessed the potential benefit of influenza vaccination in adults with cardiovascular disease. The pooled results of four RCTs showed that significantly fewer cardiovascular deaths occurred among patients with known heart disease in the vaccination group compared to the placebo group (RR 0.44; 95%CI 0.26–0.76;  $P=0.003$ ). This significant reduction in cardiovascular death was not observed in the specific subgroups of patients with stable angina pectoris (RR 0.35; 95%CI 0.07–1.73) or acute coronary syndrome (RR 0.46; 95%CI 0.05–5.20). The risk for composite outcomes of cardiovascular events tended to be lower, but not significant, when patients were vaccinated for influenza. This is consistent with the results of another meta-analysis where influenza vaccination showed a significant reduction (RR 0.64; 95%CI 0.48–0.86;  $P=0.003$ ) in the risk for composite major cardiovascular events compared to controls [125]. However, no protective effect of vaccination against cardiovascular mortality and all-cause mortality was demonstrated. Additionally, patients with a history of recent acute coronary syndrome were at lower risk of major cardiovascular events following vaccination (RR 0.45; 95%CI 0.32–0.63;  $P<0.001$ ), compared to those with stable coronary artery disease (RR 0.94; 95%CI 0.55–1.61). Neither review could identify significant differences in individual (instead of composite) outcomes.

A number of observational studies have also addressed the VE in patients with known cardiovascular disease. A meta-analysis of case-control studies by Barnes *et al.* [126] aimed to estimate the association between influenza vaccination and acute myocardial infarction. First, the authors showed that recent influenza virus infections, ILI or respiratory tract infections (RTIs) occurred significantly more often in patients with acute myocardial infarction (OR 2.01; 95%CI 1.47–2.76). Second, they documented a significant beneficial association between influenza vaccination and reduced acute myocardial infarction (VE 29%; 95%CI: 9–44). Additionally, a prospective cohort study in Australia among adults with and without previous cardiovascular events reported a protective effect of vaccination (VE 45%; 95%CI 15–65) against acute myocardial infarction [127]. Another recent systematic review assessed the evidence for the prevention of cardiovascular events and observed that vaccination reduces the risk of cardiovascular events, probably by reducing the risk of influenza infection [128]. They summarised the evidence of randomized and non-randomized studies, in which the mean age of patients was 65 years or older, and documented that influenza vaccination seems to reduce the risk of cerebrovascular disease (OR 0.77; 95%CI 0.66–0.89) and all-cause death (OR 0.55; 95%CI 0.46–0.55). This supports a recent study showing that the risk of the development of cardiovascular events increased in the first period after influenza virus infection, thus emphasising the importance of vaccination in this group [129]. These randomised trials were similar to those included in the previously mentioned meta-analyses (Clar *et al.* [124]; Udell *et al.* [125]).

### 3.5.4 Diabetes mellitus

A recent meta-analysis by Remschmidt *et al.* [130] included 11 observational studies and evaluated the effect of influenza vaccination in patients with diabetes type 1 and type 2 in all ages. In diabetic patients



aged 18-64 years, influenza vaccination seems effective in preventing all-cause hospitalisations (VE 58%; 95%CI 6–81) and influenza or pneumonia associated hospitalisations (VE 43%; 95%CI 28–54), although no effect on ILI and all-cause mortality was observed. Influenza vaccination among elderly diabetics ( $\geq 65$  years of age) showed a protective effect against all-cause mortality (VE 38%; 95%CI 32–43) and hospitalisation (VE 23%; 95%CI 1–40), and hospitalisations associated with influenza or pneumonia (VE 45%; 95%CI 34–53%) and ILI (VE 13%; 95%CI 10–16). It should be noted that none of these studies documented data on laboratory-confirmed influenza virus infections, and most did not specify the type of diabetes or a combination of both types. Furthermore, the reports concluded that due to strong confounding in most studies, the evidence was insufficient to determine the actual benefits that patients with diabetes might have from influenza vaccination. Finally, a large retrospective cohort study conducted in England during a 7-year period (2003-2004 through 2009-2010) compared vaccinated vs unvaccinated adult patients with diabetes type 2 [131]. A significant reduction in the risk for hospital admissions due to heart failure (RR 0.78; 95%CI 0.65–0.92), stroke (RR 0.70; 95%CI 0.53–0.91) and pneumonia or influenza (RR 0.76; 95%CI 0.74–0.99) was reported, as well as all-cause death (RR 0.76; 95%CI 0.65–0.83) following vaccination.

### 3.5.5 *Kidney disease*

Remschmidt *et al.* [132] conducted a systematic review of five retrospective cohort studies and assessed the VE in patients that underwent renal replacement therapy (kidney transplantation, peritoneal dialysis, hemodialysis) due to end-stage renal disease. Pooled estimates demonstrated a significant protective effect of vaccination against all-cause mortality (VE 32%; 95%CI 24–39), cardiac death (VE 16%; 95%CI 2–29) and hospitalisations due to influenza or pneumonia (14%; 95%CI 7–20). The authors suggested that this small-to-moderate positive effect of vaccination on influenza-associated clinical outcomes could be considered sufficient, given the high rates of health-threatening events in these patients; however, the quality of the evidence is considered to be low.

A number of studies further addressed the VE in hemodialysis patients, peritoneal-dialysis patients or kidney-transplant recipients. A retrospective cohort study by Cohen-Hagai *et al.* [133] found that influenza type A infections were associated with a worse prognosis among hemodialysis patients, stressing the importance of influenza vaccination. A more recent retrospective ecological study by the same authors assessed the effect of influenza vaccination on the incidence of influenza virus infections among hemodialysis patients in two consecutive seasons (2014-2015 and 2015-2016) [134]. They reported a significantly lower incidence of influenza following vaccination in hemodialysis patients who also had diabetes (17% vs 6.3%), but they observed no significant effect in hemodialysis patients without diabetes (OR 0.63; 95%CI: 0.2–1.7). Furthermore, influenza vaccination is associated with a lower risk of death and transplant failure in kidney-transplant recipients in the first year after transplantation [135]. Following this study, a recent Japanese analysis retrospectively evaluated the effect of influenza vaccination on the rate of influenza

virus infections in kidney-transplant recipients. This study compared patients receiving one or two doses of a quadrivalent influenza vaccine to those unvaccinated, but observed no reduction in the rate of influenza virus infections in the 2016-2017 season [136]. Finally, a retrospective cohort study evaluated the effectiveness of influenza vaccination in patients with end-stage renal disease undergoing peritoneal dialysis [137]. The study showed that the vaccinated group of patients had a 15% (95%CI 8–22) lower rate of hospitalisations. The risk was especially reduced for hospitalisations associated with sepsis (hazard ratio [HR] 0.79; 95%CI 0.65–0.96), cardiovascular disease (HR 0.74; 95%CI 0.63–0.89) and overall mortality (HR 0.66; 95%CI 0.55–0.78).

**In summary**, despite limitations of many studies, there is considerable evidence that influenza vaccination provides important benefits to patients with COPD, asthma, cardiovascular disease, diabetes mellitus, and kidney disease. However, many authors of reviews conclude that there is a need for other vaccines that potentially provide improved and broader protection than the traditional TIV.

### 3.5.6 *Elderly people with comorbidities*

Adults aged  $\geq 65$  years often have one or more conditions that increase the risk of complications from influenza. This was estimated at 74% in a recent American study, compared to 27% among adults aged 18-49 [138]. Elderly individuals comprise the overall majority of influenza-associated hospitalisations and deaths, and those with chronic health conditions have a particularly high risk. The most recent (2018) Cochrane review regarding the effectiveness of influenza vaccination in the elderly included a chapter that assessed the effectiveness in elderly individuals that have one or more of the following underlying conditions: lung disease, heart disease, renal disease, diabetes, immunosuppression, cancer, stroke or dementia, vasculitis or rheumatic disease [101]. It found no significant protective effect of vaccination on clinical outcomes, except on all-cause mortality (VE 61%; 95%CI 3–84;  $n=68,032$  observations; high heterogeneity [ $I^2$  64.1%]). Additionally, the European I-MOVE consortium conducted a multicenter TND case-control study assessing the 2015-2016 influenza VE among community-dwelling elderly ( $\geq 65$  years of age) against influenza A(H1N1)pdm09 and influenza B hospitalisations [105]. It reported a moderate protective effect against influenza type B hospitalisations in people with diabetes mellitus (VE 62%; 95%CI 5-85), lung disease (VE 60%; 95%CI 18-80) and heart disease (VE 36%; 95%CI -23-67), following vaccination with TIV. Vaccination was also moderately protective against influenza subtype A(H1N1)pdm09 in hospitalisations of patients with diabetes mellitus (VE 59%; 95%CI 23-78), lung diseases (VE 43%; 95%CI 8-65), heart diseases (VE 39%; 95%CI 7-60), and cancer (VE 48%; 95%CI 5-71). Another recent meta-analysis of test-negative case-control studies reported that influenza vaccination was associated with a protective effect against laboratory-confirmed influenza among community-dwelling elderly with respiratory (VE 31.2; 95%CI 2.4–51.5) and cardiovascular (VE 31.5%; 95%CI 6.5–49.8) diseases [139].

### 3.5.7 *Immunocompromised patients*

The efficacy of trivalent inactivated influenza vaccine was established in HIV patients in a RCT that demonstrated fewer laboratory-confirmed influenza virus infections but no significant effects on other clinical outcomes [140]. Many reviews evaluating effectiveness have summarised the benefits of the inactivated influenza vaccine in groups of immunocompromised patients. In a review by Hak *et al.*, influenza vaccination was associated with reduced incidence of hospitalisation or death in high-risk elderly patients [141]. An important observation in this analysis was that the absolute risk reduction of influenza-related complications was higher among high-risk elderly persons than among healthy elderly persons, which stresses the importance of vaccination, especially in the immunocompromised patients. Reductions in the incidence of ILI after influenza vaccination have been demonstrated in patients with cancer and solid-organ transplants [142]. In patients with hematological malignancies, inactivated influenza vaccine may reduce respiratory infections and hospitalisation in adults with multiple myeloma or children with leukaemia or lymphoma [143]. An additional benefit of influenza vaccination has been established in patients with advanced colorectal carcinoma; patients who were immunised had fewer chemotherapy interruptions [144]. Data on effectiveness in patients with chronic inflammatory diseases is scarce, but lower rates of hospital admission in vaccinated patients with systemic lupus erythematosus (SLE) has been noted, [145] as well as lower rates of influenza-related complications in patients with rheumatoid arthritis [146].

The immunogenicity of standard-dose inactivated influenza vaccine has been established in cancer patients receiving chemotherapy for solid tumors. Serological studies show that the magnitude of antibody response can be lower in patients receiving chemotherapy compared to healthy controls, but that seroprotection can be achieved in most patients [147]. Serological studies demonstrate lower antibody titers in patients with HIV infection [148] and those with solid organ transplants [149]. Patients receiving immunosuppressive agents because of chronic inflammatory disease may have reduced serological response to influenza vaccine, depending on the type of agent that is used. However, frequently prescribed agents in rheumatoid arthritis, such as methotrexate and anti-TNF drugs, did not markedly depress antibody response [150].

Annual influenza vaccination is recommended by all national and international guidelines for specialists treating hematological or cancer patients [61], HIV patients (NVHB guidelines, EACS: [http://www.eacsociety.org/files/2018\\_guidelines-9.1-english.pdf](http://www.eacsociety.org/files/2018_guidelines-9.1-english.pdf)) and patients with chronic inflammatory diseases [151].

Data on use of high-dose and adjuvanted influenza vaccines in immunocompromised patients are scarce. High-dose trivalent influenza vaccine did result in a significant increase in seroprotective antibody levels in patients with HIV [148]. Clinical effectiveness of high-dose influenza vaccine has been evaluated in patients on hemodialysis, showing lower rates of hospitalisation compared to patients receiving standard-dose influenza vaccine in some years [152]. More studies are needed to determine clinical effectiveness of these vaccines before they

can be recommended to all immunocompromised patients because of increased immunogenicity.

**In summary**, immunocompromised patients have increased susceptibility to influenza virus infection and increased incidence of influenza-related complications. However, data are limited regarding the use of influenza vaccines in the setting of specific immunocompromised states. Effectiveness studies are relatively scarce, and the quality of evidence is low. More data is available about immunogenicity of the standard-dose than high-dose inactivated influenza vaccine. Immunocompromised patients may experience various degrees of decreased immunogenicity on receiving influenza vaccine. Regardless of these findings, reviews as to effectiveness in several high-risk groups consistently demonstrated clinical benefit of annual influenza vaccination. An explanation is that the absolute benefits of vaccination are highest among the high-risk people. Consequently, international guidelines uniformly recommend annual vaccination of immunocompromised patients. The advantages of newer influenza vaccines may be of particular relevance for prevention of influenza and influenza-related complications in these patients.

### 3.6 Vaccine efficacy and effectiveness in the Netherlands

Due to differences in healthcare systems, age distribution of the population, and prevalence of co-morbidities, the estimated effectiveness of a given influenza vaccine might differ among countries. Therefore, we summarize here the most important recent results with regard to influenza vaccine efficacy and effectiveness in the Netherlands. Most of these studies were observational studies (TND as well as ecological studies).

Darvishian *et al.* [153] and Van Doorn *et al.* [154] analysed data from patients with ILI or other ARI from the Dutch sentinel surveillance. They estimated influenza VE against laboratory-confirmed influenza virus infection with a TND for the seasons 2003/2004 through 2013/2014. The adjusted overall VE was 29% (95%CI 11-43). Adjusted VE was lower in seasons with a vaccine mismatch (20%, 95%CI -5-38) compared to seasons with a full or partial vaccine match (40%, 95%CI 18-56). Strikingly, VE was low in seasons when influenza virus type A(H3N2) circulated in high proportions, whereas VE was higher in seasons when influenza A(H3N2) circulated in lower proportions. Subtype/lineage-specific VE for all the influenza seasons covered by this study (2003/2004 through 2013/2014) are shown in Table 3.1. These estimates represent unadjusted estimates because the low numbers did not allow for adding extra parameters in the model after stratifying for subtype/lineage. Still, the 95% CIs are broad. Pooled European estimates from I-MOVE (in which the Netherlands participates) might therefore be regarded as more relevant estimates for the Netherlands than the estimates based on Dutch data only. In the seasons 2009/2010 through 2017/2018, the adjusted overall VE estimated by I-MOVE varied between 6% (95%CI -21–26) in 2011/2012 and 72% (95%CI 46-86) in 2009/2010. Average overall VE for these 9 seasons was 34%.

Table 3.1 Subtype/lineage-specific unadjusted VE: overall estimates for seasons 2003-2004 through 2013-2014

Subtype/lineage	VE (95% CI)
Former A(H1N1)	77% (37-92%)
A(H1N1)pmd09	47% (2-64%)
A(H3N2)	20% (-4 -38%)
B (total)	64% (50-74%)
B Yamagata	59% (30-76%)
B Victoria	not available

Sourced from: Darvishian et al. [153]

Another study by Van Doorn *et al.* [155] on the same data demonstrated that the VE differed when different control groups were used. The overall adjusted VE was 35% (95%CI 15–48) using the control group ‘negative for influenza virus (all influenza negative);’ 64% (95%CI 49–75) using ‘negative for influenza virus, but positive for respiratory syncytial virus, rhinovirus or enterovirus (non-influenza-virus-positive);’ and 21% (95%CI 1–39) using ‘negative for these four viruses (pan-negative)’. The authors conclude: ‘In both the main and subgroup analyses, VE estimates were the highest using non-influenza virus positive controls, likely due to limiting inclusion of controls without laboratory-confirmation of a virus causing the respiratory disease.’ This study shows that methodological choices can have a large impact on the estimate of VE, which should be kept in mind when interpreting TND VE studies. Most studies using the TND method to estimate VE, including I-MOVE, use the ‘negative for influenza virus (all influenza-negative)’ control group, because influenza surveillance usually does not include detection of pathogens other than influenza virus.

Van Beek *et al.* [156] performed a study among a cohort of community-dwelling elderly persons in the winters of 2011-2012 and 2012-2013. Nose and throat swabs were taken when these persons had an episode of ILI and from a control group with the same distribution of age and time within the season. These swabs were tested for a range of pathogens, including influenza virus. VE against all influenza subtypes was 73% (95%CI 26-90) in 2011-2012 and 51% (95%CI 7–74) in 2012-2013 in ILI patients. However, ILI incidence was similar between vaccinated and nonvaccinated participants in both seasons.

Three ecological studies were published in the last decade that analysed the association between influenza vaccination and outcome in the Netherlands [157-159]. The studies of Spruijt *et al.* and Dijkstra *et al.* studied the association between influenza-vaccination coverage and ILI. Dijkstra *et al.* [157] found that ILI incidence in the elderly declined by 1.7 per 10,000 persons ( $P=0.05$ ) per percentage vaccine uptake per season in the period 1991-2005. During the period 1991-2014, Spruijt *et al.* [159] did not find a significant decline in incidence rate per percentage point increase in vaccination coverage for the elderly in the Netherlands. However, they did find a significant negative correlation between vaccine coverage and ILI incidence in the total population ( $p=-0.60$ ,  $p=0.003$ ). Nevertheless, because of the ecological design of both studies, it is not clear whether this association indicates a causal relationship.

### 3.7 Immunity induced by influenza infection and vaccination

Immunity to influenza virus after infection serves three purposes: clearance of the infection, protection against severe disease and protection against subsequent infection. Antibodies produced by B cells with helper T cells can prevent infection. Cytotoxic T cells (CTLs) will interfere with disease progression and limit dissemination of the virus through the host and to other individuals. An important component of the immune response is the generation of memory cells that can be more rapidly recruited on re-infection: this recall response can occur within 5 days, whereas the initial response takes 8-14 days. Because influenza virus changes its surface proteins constantly, long-term sterile protection by antibodies does not occur, and the role for cellular immunity against the less variable internal proteins is therefore essential [160].

In general, inactivated influenza vaccines (IIV, either trivalent [TIV] or quadrivalent [QIV]), which are given intramuscularly, will induce strain-specific serum antibody responses to the included vaccine viruses; associated B cells, including memory B cells; and possibly a limited CD4+ T-cell response [161, 162], but no CTL response.

Live-attenuated influenza vaccines, which are given intranasally, will induce immunity by all arms of the immune system, including innate immunity help; a strong T-cell response, with CTLs and memory cells; and local mucosal immunity.

The effect of LAIV is reduced by existing influenza-specific immunity and is therefore more appropriate for use in vaccine-naïve children.

However, adults and the elderly can benefit from the use of a LAIV vaccine owing to the induction of mucosal immunity by these vaccines [163].

#### 3.7.1 *Role of the different components of the immune system in protection against influenza virus infection induced by vaccination*

##### 3.7.1.1 Innate immunity

The innate immune system is the non-specific first line of defense against influenza viruses and is strongly activated by so-called 'danger signals', which are inherently present in viruses but may also be provided by adjuvants in vaccines. The innate system steers and supports activation of cells of the adaptive immune system. It is a highly complex network of cells and chemicals that offers generally beneficial protection, but only to a limited degree, because influenza virus expresses proteins that counteract the innate responses of the host. In addition, the severity of its response to influenza virus infection can contribute to disease in the airways. The innate system has no immune memory, but it activates the adaptive immune response. It can, however, also respond directly to vaccines, particularly those that are live and adjuvanted, and contribute to reactogenicity to the vaccine.

#### 3.7.2 *Adaptive immune response*

##### 3.7.2.1 Antibodies

Antibodies protect against influenza virus infection by preventing infection of cells. They are generally strain-specific. Antibodies appear within about 2 weeks after vaccination and can circulate for years to

prevent subsequent infections by the same strain of a particular subtype virus, but they become gradually less effective against drifted strains [164]. The first line of antibody defense is at the respiratory epithelium. Antibodies of type IgA that are present in the mucosal layers can neutralize the virus before it ever appears in the host. IgG antibodies induced by intramuscular vaccination are present in the blood and are responsible for systemic and transmucosal responses.

IIVs do not induce IgA antibodies, but high levels of IgG antibodies may reach the mucosal layers and also play a role in local protection. LAIVs do induce IgA. It has been shown that mucosal immunity is not as long-lasting as systemic immunity, but it does extend over the influenza season [165]. IgG antibodies induced by IIVs and most other vaccines circulate in the blood and prevent the spread of the virus.

The usefulness of IIVs for long-term protection against a specific influenza virus subtype strain is limited not only because immunity slowly wanes, depending on the vaccine and on age, but also because influenza virus can escape from induced immunity by continuously changing its surface proteins. In addition, as described in 3.7, repeat IIV vaccination may lead to less potent immune responses. Therefore, much effort is being made to develop vaccines that induce antibodies in regions of influenza surface proteins (mostly HA) that are highly conserved among influenza virus subtypes or even types, such as all A viruses. These regions are considered highly essential for virus viability and therefore cannot be adapted by the virus, but they are poorly immunogenic; thus, clever strategies are needed to force direction of the immune system at those sites. It is estimated that within 10 years these new vaccines may reach the market. Only a large-scale introduction will make it possible to establish whether these regions are truly essential to influenza viruses, such that the virus cannot introduce escape mutations.

### 3.7.3 *Cellular immunity*

Vaccination induces B-cell memory in the antigens in the vaccine. In subunit vaccines, this memory is against the surface proteins HA (primarily since the amount is standardised) and NA (amount not standardised; only the presence is required). In split vaccines and LAIVs, some internal proteins may also be targeted. CD4+ helper T-cells are required to select B-cells that produce high-affinity antibodies. Whether IIVs are efficient in inducing these cells is still a matter of debate, although recent reports demonstrate strong CD4+ responses after vaccination against A(H1N1)pmd09, which are even augmented after repeat vaccinations over 5 years [166]. The effectiveness of IIVs is also suggested to rely on the existence of a memory CD4+ cell pool acquired with earlier infections. LAIVs can efficiently induce CD4+ cells on their own.

CTLs, which are needed to eliminate the virus-infected cells, are not induced by IIVs. Thus, the ability to use this essential arm of the immune system relies on either prior infection or vaccination with LAIVs. It has been suggested that IIV vaccination of children who have not seen an influenza virus before will have the detrimental effect of

depriving them of a CTL capacity to clear infections [167]. To date, this possibility has neither been confirmed nor ruled out.

In contrast to antibodies, CD8+ T-cells (cytotoxic T-cells) can recognize internal influenza virus proteins presented to them by cells that have been either infected or have interacted with virus-infected cells. Internal viral proteins are more conserved between influenza viruses of the same subtypes than the surface proteins; therefore, these T-cells have the advantage of providing cross-protection against disease caused by different strains of the same influenza subtypes.

Evidence is mounting that the first influenza virus encountered in life, either by infection or after LAIV vaccination, confers a preference in the immune response of the host towards that subtype of viruses. This imprinting or 'original antigenic sin,' determines all subsequent responses to different influenza viruses during life. Influenza A viruses are grouped into two major subtypes based on HA similarity, and the imprinting distinguishes these two groups; one group contains the H1, H2, H5, H6, H8, H9, H11, H12, H13, H16, H17, and H18 subtypes, and the second group includes H3, H4, H7, H10, H14, and H15 subtypes. Primary infection with a subtype from one group of influenza viruses will always give better protection against re-infection with subtypes from the same group than subtypes from the other. This has an impact on vaccine responses, as well [168-170], but the underlying mechanism is still unclear.

#### 3.7.4

##### *Effect of age on immunity to influenza virus induced by vaccination*

It is well established that the immune response to influenza vaccines develops with age and is highly heterogeneous among individuals. The immune response of very young children to influenza vaccination has not been well studied. It is known that from 6 months of age (the age at which influenza vaccination is recommended in the USA), children's immune response to LAIVs is broader than to IIVs, but both are protective. Some studies show an induction of memory CD4+ cells [161], but other have failed to detect T-cell immunity after IIV immunisation in this age group [171]. As described, vaccination of young children with IIVs may have a negative effect on the induction of CD8+ cell immunity. For neonates, studies have shown that maternal antibodies that are acquired by the mother after vaccination during pregnancy may protect for up to 6 months against matching influenza strains.

In the elderly, whose immune capacity slowly declines, influenza vaccines less effective than in younger adults or children. This may be overcome partly by different vaccination strategies, such as administration of the vaccine closer in time to the average start of the influenza season [172] or use of other routes of immunisation or higher-dose or adjuvanted vaccines, as was recently demonstrated [173].

Immunological data show that a single influenza vaccine for all ages is unlikely to work optimally. Currently, only inactivated and live attenuated vaccines are available for protection against influenza virus. IIVs have the advantage of easy adaptation to the needs of different ages and groups. For those who have an impaired immune response, such as the elderly or certain risk groups, the doses of IIVs can be



varied; they can be adjuvanted for better protection by recruiting innate help; and their route of administration, which can be either subcutaneous or intramuscular, can be adapted. However, IIVs also have disadvantages, most significantly their inability to induce a CTL response needed to clear infection and limit disease. Their use in naive individuals, particularly children, should be considered with caution. LAIVs have the advantage of producing an immune response that closely resembles that induced by infection, including local mucosal immunity. They have the potential of inducing a broader, more cross-protective immune response. However, a disadvantage of LAIVs is that existing immunity, except for local immunity, may affect their efficacy, which may make them less suitable in adults and the elderly. When no prior immunity exists, such as in children or in a pandemic setting, these vaccines are potentially very effective.

### 3.8 Effect of repeated vaccinations

People with an indication for influenza vaccination should receive the seasonal vaccine every year. This means many vaccinations in a lifetime and an increasing number of vaccinations per individual with expansion of age criteria for vaccination. For example, in the US, annual influenza vaccination is now recommended for all residents  $\geq 6$  months of age, and a child born in the US today can therefore expect to receive 70-80 annual influenza vaccinations. In this context, the effect of repeated vaccination on VE has become an important topic for research and debate.

A possible negative effect of repeated influenza vaccination on VE was first reported by Hoskins *et al.* [174] in an article in the Lancet. In a boy's boarding school in England, there were three outbreaks of influenza in 1972, 1974 and 1976. In every outbreak, vaccination was protective only among boys who were not previously vaccinated. This publication was followed by several studies that showed inconsistent results. Keitel *et al.* [175] performed a multi-season randomized clinical trial that showed some variation in infection rates between vaccine groups given one or more than one annual vaccination, and between years, but no consistent pattern of differences was noted in relation to number of successive years of vaccination.

Since then, several observational studies and meta-analyses have reported inconsistent results of the effect of previous vaccination on current season influenza VE. The review by Belongia *et al.* [176] stated that 'Substantial heterogeneity in repeated vaccination effects is not surprising given the variation in study populations and seasons, and the variable effects of antigenic distance and immunological landscape in different age groups and populations. Caution is required in the interpretation of pooled results across multiple seasons, since this can mask important variation in repeated vaccination effects between seasons. Multi-season clinical studies are needed to understand repeated vaccination effects and guide recommendations'.

Results from the I-MOVE consortium over the years 2011-2012 through 2016-2017 show no clear pattern of previous influenza vaccination effect, and the need for prospective cohort studies documenting

influenza infections, vaccinations and vaccine types to understand previous influenza vaccinations' effects was reiterated [177]. The most recent systematic review and meta-analysis by Bartoszko *et al.* [178] concluded that "Available evidence does not support a reduction in VE with consecutive influenza vaccinations, but the possibility of reduced effectiveness cannot be ruled out due to the very low certainty of this evidence".

Various hypotheses have been proposed to explain an effect of repeated vaccination. The antigenic distance hypothesis was proposed by Smith *et al.* [179] as an explanation for contradictory findings in earlier studies. It implies that the response to antigen in a second vaccine will be partially eliminated by pre-existing cross-reactive antibodies that were induced by the first vaccine. Negative interference from prior vaccination will occur when the antigenic distance between vaccine and circulating strains is large but when the distance between consecutive vaccine components is small. The antigenic distance hypothesis was presented as an explanation for the findings of a Canadian study in which persons vaccinated only in the current season had stronger protection against influenza A(H3N2) infection than those having had repeated vaccination [180]. The alternative original antigenic sin hypothesis suggests that exposure to influenza antigens can preferentially expand pre-existing memory responses to historical virus antigens at the expense of de novo responses to the current vaccine or infecting strain. The infection block hypothesis suggests that previously vaccinated individuals do not have the cross-protective immunity provided by natural infection [181]. The immune exhaustion hypothesis suggests over-activation of negative feedback mechanisms, and finally, the immunosenescence hypothesis is built on the ageing of the immune system. Despite the many studies undertaken, at this point none of the potential immunological hypotheses can be discarded.

Effects of previous vaccination seem to be dependent on several factors, including the circulating influenza strain, with A(H3N2) causing more problems than influenza B and influenza A(H1N1)pdm09; the season, with possible antigenic drift in circulating strains or change in vaccine strain; and individual characteristics such as age, occurrence of other infections, and genetic background.

Fundamental studies on humoral and cellular immunological response to vaccination and infection and large-scale integrated prospective immunological-epidemiological studies would provide more insight. However, such studies are very costly and might be redundant if universal influenza vaccines become available.

### 3.9 Intraseasonal waning of immunity

A common assumption in studies of influenza VE is that individuals for whom the vaccine is effective will remain protected for the entire duration of the influenza season. However, vaccine-induced protection may be lost during a season when the influenza virus is still actively circulating, a phenomenon that is called 'waning intraseasonal immunity' [182]. Although the underlying immunological mechanisms and potential epidemiological biases are not yet clarified, there is increasing evidence

that VE towards the end of the influenza season is lower than in the beginning. In the US Influenza Vaccine Effectiveness Network, pooled data from the 2011-2012 through 2014-2015 influenza seasons showed a maximum VE shortly after vaccination, followed by a decline of about 7% per month [183]. Pooled data from the influenza seasons from 2010 to 2014 in the European I-MOVE network showed a decline in VE for influenza A(H3N2) to 0 after 111 days post-vaccination, and VE for influenza type B declined from 70.7% to 21.4% after the end of the season. VE for influenza A(H1N1)pdm09 remained above 50% [184]. In a study in England, the influenza VE for those vaccinated less than three months previously was 53%, but only 12% for those vaccinated three months or more before the onset of an influenza-like illness [185]. In an Australian general practitioner (GP) sentinel network in the 2012 influenza season, there was a (non-significant) decline in VE from 37% in patients vaccinated <93 days before presenting to their GP to 18% in those presenting with ILI  $\geq 93$  days after vaccination [186].

Waning intraseasonal immunity has obvious public health implications. A better understanding of the underlying mechanisms is needed, and might eventually open a discussion on changes in the timing of vaccine administration.



## 4 Safety and (adverse) consequences of Influenza vaccination

### Summary

Inactivated influenza vaccines have a good safety profile and are recommended for children of six months of age and older, the elderly, asthmatics and those individuals with other high-risk conditions. However, adverse events do occur. Some adverse events, such as fever and febrile seizures, are more common in children than in adults. Symptoms due to adverse events are usually transient. Severe allergic reactions to influenza vaccines are very rare, estimated at less than 1 in a million doses. During some influenza seasons, vaccines have been associated with a slight increase in the risk of Guillain-Barre syndrome in adults, although the findings in several studies are inconsistent. For live-attenuated influenza vaccine, wheezing is one of the most frequent side effects in children aged 6-23 months. As a result, these vaccines are currently not recommended for children aged less than two years.

Influenza vaccination during pregnancy is safe. The tolerability of this vaccination is similar to that in healthy adults who are not pregnant. Furthermore, no increased risks of adverse pregnancy outcomes for mother and child are found, in either the short term or in the long term.

### **GLOSSARY**

#### ***Adverse event (AE)***

Undesirable experiences occurring after immunisation that may or may not be related to the vaccine.

#### ***Adverse event following immunisation (AEFI)***

Any untoward medical occurrence that follows immunisation but does not necessarily have a causal relationship to the vaccine. The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease.

#### ***Adverse reaction***

A classification of AEFI referring to events caused or precipitated by the vaccine when given correctly, caused by the inherent properties of the vaccine.

#### ***Acute adverse event/reaction***

A short-term, intense health effect

#### ***Local adverse event/reaction***

Restricted or limited to a specific body part or region.

#### ***Mild vaccine reaction***

A vaccine reaction that usually occurs within a few hours of injection, resolves after a short time and poses little medical danger.

***Passive surveillance (also referred as spontaneous reporting)***

A surveillance system designed to collect adverse events that follow vaccination. This type of surveillance typically relies on health professionals, patients or relatives of patients who notice and report such events to the NRA or appropriate authority.

***Reactogenicity***

Being able to produce adverse reactions.

***Safety profile***

A summary of the evidence on the safety of a medical product, such as a vaccine or drug, under ideal conditions of use, including the incidence of any adverse reactions relative to the number of doses given.

***Serious adverse event (SAE)***

A regulatory term defined as any untoward medical occurrence following any dose that results in death, requires inpatient hospitalisation or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is life-threatening.

***Solicited data***

Data derived from organised collection systems, which include clinical trials, registries, post-approval named patient use programmes, other patient support and disease management programmes, surveys of patients or healthcare-providers or information gathering on efficacy or patient compliance.

***Systemic***

Relating to a system, or affecting the entire body or an entire organism (e.g., fever).

***Unsolicited data***

Data from spontaneous reports, literature reports and other sources such as lay press, internet or digital media.

**4.1****History and overview of safety of influenza vaccination**

The safety of influenza vaccines is a critical factor in maintaining public trust in the vaccination programme. In many countries, influenza vaccines are recommended for children, adults, the elderly and healthy pregnant women. Since these vaccines are not only administered to risk groups but also to healthy people, they need to comply with a high safety standard.

During the past 80 years, many different production methods have been used to produce influenza vaccines. Some adverse events causally associated with inactivated influenza vaccines have been attributed to differences in production methods. For example, fever was very common in young children following whole-virus influenza vaccines produced many decades ago, and febrile seizures occurred at unacceptable rates. Therefore, these influenza vaccines were rarely used in children [187]. Adverse events with these vaccines were dose-related. In the 1960s, a new type of vaccine, the split vaccine, was authorised in the US after clinical studies demonstrated that it was less reactogenic than whole-virus vaccines, especially in the early years of life [188]. The first subunit vaccine was created between 1976 and 1977. This

innovative tool proved to be well tolerated in humans, especially in children [188]. In the past 20 years, scientific research has resulted in new immunization techniques, which may be better tolerated during administration and thereby reduce adverse events. For example, in 2003 the FDA in the United States authorized the use of a live attenuated vaccine administered intranasally in adults [188]. More recent years saw the development of adjuvanted vaccines, such as those containing alum adjuvants and the oil-in-water adjuvant. In general, these adjuvants are safe and well tolerated, though they may increase local reactions, particularly pain at the injection site. In addition, there have been some rare adverse events with adjuvanted vaccines at a population level. A small risk of Bell's palsy was seen after the intranasal administration of an influenza vaccine with a heat labile enterotoxin as an adjuvant (13 excess cases per 10,000 vaccinees), and narcolepsy has been seen after AS03 adjuvanted vaccination, particularly in individuals with a specific haplotype [189]. In 2011, the FDA first authorized an intradermal influenza vaccine, although local reactions were more common after intradermal administration than after intramuscular injection of regular influenza vaccines [2]. In 2012, the first quadrivalent vaccine was licensed in the USA. This split vaccine contains two influenza A subtype (H1N1pdm09 and H3N2) antigens and influenza B antigens of both lineages, and maintains the same safety profile as standard trivalent vaccines.

Overall, changes in manufacturing processes for influenza vaccines have been made during the past 40 years, which have resulted in decreased rates of fever and local reactions, but most of these changes have not been outlined in the published literature [187]. In the next paragraphs, the safety of TIV, QIV and LAIV are described.

## **4.2 Safety of trivalent inactivated influenza vaccine (TIV)**

### **4.2.1 General**

TIV vaccines are generally considered safe, although transient local reactions at the injection site occur frequently ( $>1/100$ ). Also, fever, malaise, myalgia and other systemic adverse events may affect persons without previous exposure to the influenza vaccine antigens, such as young children [19]. In general, such adverse events occur less frequently in adults [190]. A post-licensure population-based study assessing TIV safety in 251,600 children aged  $<18$  months (including 8476 vaccinations in children aged 6-23 months) did not reveal evidence of important medically-attended events associated with TIV [191]. Similarly, no new safety concerns emerged after a review of 15 years of post-licensure surveillance data covering nearly 750 million TIV vaccinations in the USA [192]. However, in 2010 in Australia, an increase in febrile convulsions was observed, although this involved only one brand of vaccine (i.e., Fluvax and Fluvax Junior) [193]. A review of the safety of TIV administration showed that high fever rates were correlated with this vaccine in young children, although it was not possible to attribute this association to the TIV-strain composition [194]. Another study showed that the incidence of local reactions and systemic adverse events in overweight and obese children after a standard dose (SD) of TIV (i.e., Fluarix) was comparable in these children and normal-weight children [195].

Studies that examined the risk of serious adverse events after TIV are described below.

#### 4.2.1.1 Anaphylaxis

In 2008, a case of anaphylaxis after influenza vaccination was published [196]. Another study investigated the annual frequency of anaphylaxis following immunisation, a rare AE that can be life-threatening and causes hospitalisation within 48 hours after immunisation [197]. The study was conducted on subjects younger than 18 years in Germany between June 2008 and May 2010. During this period, one notification of anaphylaxis after administration of seasonal influenza vaccine was received. In a study using the Vaccine Safety Datalink, the rate of anaphylaxis was 1.35 (95%CI 0.65-2.47) per million doses of TIV [198]. Therefore, administration of TIV is contraindicated in cases of severe allergic reaction (e.g., anaphylaxis) after a previous dose or a reaction to a vaccine component, including egg protein [19, 199].

#### 4.2.1.2 Guillain–Barré Syndrome

During some influenza seasons, TIVs have been associated with a slight increase in the risk of Guillain-Barre syndrome (GBS) in adults (relative incidence 1.45; 95% CI 1.05-1.99) [200]. However, there are inconsistent findings in several studies. In a study of cases recorded in the General Practice Research Database from 1990 to 2005 in the United Kingdom, the relative incidence of GBS within 90 days of vaccination was 0.76 (95% CI 0.41-1.40). In contrast, the relative incidence of GBS within 90 days of an influenza-like illness was 7.35 (95% CI 4.36-12.38) [201]. In addition, the background incidence of GBS in the Netherlands, with a general-practitioner electronic medical record database is estimated at 1.14 per 100,000 per year (95% CI 0.67-1.61) [202]. Inconsistent findings may also be explained by lack of statistical power among negative findings [187]. The biological mechanism(s) for a possible small increased risk following TIV is not understood. Most of the data are from adults, primarily because influenza vaccine recommendations for children are relatively new in many countries. Only two studies provide data on children, and these findings are inconclusive [187, 203, 204]. Precautions for TIV vaccination include GBS <6 weeks after a previous dose of influenza vaccine and moderate or severe acute illness with or without fever [19].

#### 4.2.1.3 Multiple Sclerosis

Although each epidemiologic study of associations between influenza vaccines and multiple sclerosis (MS) reported to date has had relatively low power to rule out an increased risk, these studies as a group provide consistent evidence against a causal association with MS onset or relapse and influenza vaccine in adults. Studies are more limited in children, due in part to the lower risk of disease, but there is no evidence to indicate reason for concern [187].

#### 4.2.1.4 Other

The available evidence does not establish a causal relationship between influenza vaccines and acute disseminated encephalomyelitis (ADEM) or transverse myelitis, but neither can the evidence rule out the possibility of a small increased risk following influenza vaccination. If there is any risk, it is very low [187]. Furthermore, no increased risk is found for



immune thrombocytopenia or inflammatory arthritis associated with influenza vaccines. Despite some suggestion of an increased risk of Bell's palsy, the available evidence does not support an increased risk in any age group [187].

#### 4.2.2 *Safety of brands used in the Dutch NPG*

4.2.2.1 Reports to the spontaneous reporting system in the Netherlands  
Every year, adverse events following influenza vaccination are monitored by means of a spontaneous surveillance system, which is managed by the National Centre for Pharmacovigilance Lareb.

The total number of reports during the last four years has been quite stable. Differences are seen in the number of reports regarding the two vaccines that are used by the NPG, although these may be explained by changes in the ratio of vaccines administered over the years (see Table 3.1) [205-208].

Table 3.1 Number of reports per vaccine and influenzaseason

<b>Vaccine</b>	<b>2014/2015</b>	<b>2015/2016</b>	<b>2016/2017</b>	<b>2017/2018</b>
Vaxigrip	150	95	44	58
Influvac	67	65	108	104
Vaxigrip or Influvac	50	83	66	22
Unknown	16	40	39	46
<b>Total</b>	<b>283</b>	<b>283</b>	<b>257</b>	<b>230</b>
<b>Administered doses [209]</b>	<b>3,242,965</b>	<b>3,115,542</b>	<b>3,034,237</b>	<b>3,078,026</b>
<b>Ratio of administered brands (Vaxigrip vs Influvac)</b>	<b>66.6% vs 33.3%</b>	<b>66.6% vs 33.3%</b>	<b>40% vs 60%</b>	<b>40% vs 60%</b>

Over the years, most reported adverse events are injection-site inflammation (range 77-125), pyrexia (range 38-47), myalgia (range 34-66), headache (range 30-65) and fatigue (range 8-28). No stratification has been made for type of adverse event per vaccine brand.

In 2012, Lareb reported a signal of extensive limb swelling (ELS) after influenza vaccination [210]. Since October 2011, Lareb has received 10 reports of ELS associated with seasonal influenza vaccination, with nine reports concerning vaccines in 2011-2012. The majority (7 out of 10) of the patients involved were children. In the following seasons, Lareb also received reports of ELS after influenza vaccination (range 7-37) [205-208] [211, 212].

#### 4.2.2.2 Lareb Intensive Monitoring

Within the Lareb Intensive Monitoring (LIM), patients who receive influenza vaccination are followed over a specific period of time, with the collection of information about AEFI through web-based questionnaires. The aim is to obtain real-time data and provide insight into profiles of reported adverse drug reactions. Eligible patients are identified by their general practitioner.

Over the years 2015, 2016 and 2017, a total of 1474, 602 and 445 patients, respectively, completed the registration for participation in the LIM study. The patients reported a total of 880, 350 and 488 AEFI, respectively. The 10 most reported AEFI were mostly well-known expected AEFI, with injection site reactions, headache, myalgia and fever most often reported. The pattern of AEFI is comparable with the reported AEFI in spontaneous reports [205-208].

#### 4.2.2.3 International monitoring

Safety data for Vaxigrip that were gathered using diverse methods (i.e., clinical trials, routine spontaneous reporting and active and passive safety surveillance) are consistent and demonstrate the absence of safety signals after Vaxigrip use in all relevant populations. In 2015, the European Medicines Agency (EMA) published a review of Vaxigrip safety in approximately 10,000 individuals aged  $\geq 6$  months [213]. Most reported solicited local reactions were injection site pain and irritability. These reactions were mainly mild to moderate and generally resolved spontaneously within three days of onset. This safety profile re-enforces the positive benefit-risk ratio of Vaxigrip. The most frequently reported solicited systemic adverse event within seven days of Vaxigrip administration was headache in adults, the elderly and children aged 9–17 years and malaise in children aged 3–8 years. Both events were very common. Solicited adverse reactions were generally less frequent in the elderly than in younger adults. In spontaneous reporting systems, no signals have been identified for adverse events of special interest, like anaphylactic reactions, Guillain–Barré syndrome, encephalomyelitis, neuritis, convulsions, vasculitis, and thrombocytopenia [214].

Between 1982 and 2006, 76 clinical studies were performed with the trivalent inactivated subunit influenza vaccine Influvac. In all, 6,415 subjects were vaccinated, of whom 5,034 were eligible for safety evaluation and 4,534 for efficacy evaluation. Treatment-emergent adverse events occurred in 13.7% of subjects. Transient mild-to-moderate local and systemic reactions occurred in up to half of subjects. Post-marketing surveillance confirmed the well-established safety profile reported for Influvac [215]. In addition, Influvac showed in a reactogenicity study a better safety profile compared to another trivalent inactivated influenza vaccine, Fluvax [216].

One study compared the risk of febrile events after vaccination with four brands of inactivated 2010 and 2011 influenza vaccines, i.e. Fluvax, Influvac, Vaxigrip and Fluarix. This study among infants and children in New Zealand showed lower rates of febrile reactions with Influvac (OR 0.54, 0.36-0.81) than with Vaxigrip (OR 0.21, 0.16-0.27) and with Fluarix (OR 0.10, 0.05-0.20), compared to Fluvax [217].

### 4.3 Safety of quadrivalent inactivated influenza vaccine (QIV)

#### 4.3.1 General

The safety of QIV is described in a review by Trombetta [193]. Greenberg *et al.* compared the safety and immunogenicity of a QIV whose formulation contained two influenza B strains versus licensed TIVs containing either a Victoria B-lineage strain (2009-2010 TIV) or a Yamagata B-lineage strain (2008-2009 TIV) [218]. The occurrence of

the different AEs were comparable in all groups. Furthermore, the safety and reactogenicity of QIV have proved similar to those of seasonal influenza vaccines, as demonstrated by Tinoco *et al.* [219]. The most common adverse reactions were pain at the injection site, headache and myalgia, all of which disappeared within 3 days of vaccination. No serious AE or deaths were registered.

Similar results regarding the safety of the first QIV introduced in Australia were reported by Regan *et al.* in a sample of 1,685 healthcare providers [220]. Although 7 days after immunisation no AE was observed in either QIV- or TIV-vaccinated subjects, a slightly but significantly higher percentage of QIV-immunised than TIV-immunised subjects reported pain or swelling at the injection site. That study confirmed the safety of QIV, since its reactogenicity was similar to that of TIV. A meta-analysis also showed no significant differences between the safety profiles of QIV and TIV, except for a slightly higher rate of injection-site pain following QIV immunisation, which may have been due to the higher dose (60 versus 45 mcg), in agreement with the results of the study by Regan [220, 221].

Differences in production methods yielding vaccines of varying composition, in addition to the presence of a further antigen in QIV, may be responsible for the differing frequency of AEs [220]. A systematic review and meta-analysis of randomised controlled trials by Moa *et al.* showed that injection-site pain was more common for QIV compared to TIV, with a pooled RR of 1.18 (95% CI 1.03-1.35) [221].

The safety and reactogenicity profile of inactivated QIV in children aged 18–47 months was evaluated by Rodriguez Weber *et al.* in a phase-2 double-blind study [222]. Reactogenicity was investigated, because QIV contains 60 µg of antigen compared with 45 µg in TIV. SAEs were monitored for 6 months after immunisation. The reactogenicity and safety profiles of QIV were similar to those observed for TIV. Other recent studies also showed that the safety profile of QIV is comparable to TIV [223-225].

In an investigation by the Vaccine Adverse Events Reporting System (VAERS), after vaccination with quadrivalent IIV4 and trivalent IIV3 from 7/1/2013 to 5/31/2015, similar safety profiles between the two vaccines were reported [226]. This observation agreed with the data obtained from pre-licensure studies of IIV4. Most of the AEs reported were not serious. Among the most frequent AEs in persons between 6 months and 17 years of age were fever, injection-site swelling and erythema, whereas in individuals aged 18–64 years pain in the extremities and injection-site pain were most frequent. The most common non-lethal serious events were GBS, seizures, injection-site reactions and anaphylaxis.

Thus, apart from slightly higher rates of transient local reactions, the additional antigen does not appear to alter the safety profile of QIV compared to TIV.

#### 4.3.2 *Safety of brands licensed in the Netherlands*

From 2019-2020 onwards, QIV rather than TIV will be used in the NPG for all people 60 years and older and for certain high-risk groups. Four QIV brands are licensed in the Netherlands: Fluarix Tetra (for ages  $\geq 6$  months), Vaxigrip Tetra ( $\geq 6$  months), Influvac Tetra ( $\geq 18$  years) and Batrevac Tetra ( $\geq 6$  months; identical to Influvac Tetra).

In 2015, the safety and tolerability of Fluarix Tetra was reviewed [227]. Four studies were evaluated, and it was concluded that the safety profile of Fluarix Tetra was similar to the TIV vaccine. No serious side effects related to the vaccine were observed in these studies [222, 228-230]. The summary of product characteristics of Fluarix Tetra also included the vaccine's safety profile. It described the findings from clinical trials that showed the most often reported local adverse reaction after vaccination in all age groups was injection-site pain (15.6% to 40.9%). In adults 18 years of age and older, the most frequently reported general adverse events after vaccination were fatigue (11.1%), headache (9.2%) and myalgia (11.8%). In subjects aged 6 to 17 years, the most frequently reported general adverse events after vaccination were fatigue (12.6%), myalgia (10.9%) and headache (8.0%). In subjects aged 3 to 5 years, the most frequently reported general adverse events after vaccination were drowsiness (9.8%) and irritability (11.3%). In subjects aged 6 months to 3 years, the most frequently reported general adverse events after vaccination were irritability/fussiness (14.9%) and loss of appetite (12.9%). Spontaneous reports of GBS have been received following vaccination with Fluarix and Fluarix Tetra but no causal association between has been established [231].

Reviews regarding the immunogenicity and safety of Vaxigrip Tetra described the results from phase 3 clinical trials [225, 232]. Since Vaxigrip Tetra was developed by a manufacturing process closely related to that used for TIV, the data on the safety profile of TIV are considered to support that of Vaxigrip Tetra. The safety of Vaxigrip Tetra was similar to that of the corresponding licensed TIV. Most adverse events usually occurred within the first 3 days following vaccination and resolved spontaneously within 1 to 3 days after onset. The intensity of these events was mild. The most frequently reported adverse reaction after vaccination in all populations, including all children from 6 to 35 months of age, was injection-site pain (between 52.8% and 56.5% in children from 3 to 17 years of age and in adults; 26.8% in children from 6 to 35 months of age, and 25.8% in elderly). In a subpopulation of children less than 24 months of age, irritability (32.3%) was the most frequently reported adverse event. In a subpopulation of children from 24 to 35 months of age, malaise (26.8%) was the most frequently reported adverse event. Adverse events were generally less frequent in the elderly than in younger adults and children [233]. Vaccine-related unsolicited adverse reactions were uncommon in the phase-3 trials [232]. There are no safety data from post-marketing experience with Vaxigrip Tetra.

Overall, Vaxigrip Tetra is well tolerated, and no safety signals were detected. Data confirm its safety, even in children aged 6-35 months [225].

Safety data regarding the use of Influvac Tetra are based on a clinical study in healthy adults 18 years of age and older in which Influvac Tetra was administered to 1,535 subjects and the trivalent influenza vaccine Influvac to 442 subjects [234]. Similar rates of solicited adverse events were observed in recipients of Influvac Tetra and Influvac. The most frequently reported local adverse reaction after vaccination with Influvac Tetra was pain at the injection site (16.3%). The most frequently reported general adverse events after vaccination with Influvac Tetra were fatigue (11.2%) and headache (10.3%). These reactions usually disappeared within 1-2 days without treatment.

To date, no studies have been published about post-marketing exposure to Influvac Tetra.

#### **4.4 Safety of live-attenuated influenza vaccine (LAIV)**

##### **4.4.1 General**

Studies on the Russian LAIV involving nearly 130,000 children aged 3-15 years did not disclose any serious adverse event (SAE) [235], except for transient febrile reactions occurring in <1% of children after vaccination. The adverse events most commonly associated with the US-manufactured LAIV were transient runny nose or nasal congestion and low-grade fever, although the frequencies were close to those observed in the control groups [19]. LAIVs have been reported to cause adverse effects in 15% of cases. With the exception of fever, which has been reported on the day after vaccination, the symptoms occur 2–3 or 8–9 days after LAIV administration [236]. LAIVs have been reported to cause slightly more troublesome moderate adverse effects than TIV, although the incidence has been low. In one study, the difference was shown to be significantly higher following the first dose, but it disappeared after the second administration [122] and was reduced following subsequent annual vaccinations. Although one of the most frequent side effects in children aged 6-23 months was wheezing, no difference in severity, length of hospitalisation or treatment was observed [122, 236]. Wheezing was not increased in vaccinees 2-5 years of age [122]. As a result, LAIV is currently not recommended for children aged less than two years [1, 19].

Severe consequences have been reported only rarely, and no association with vaccine administration has been proved. McNaughton *et al.* investigated the incidence of adverse effects of interest (AEIs) in children and adolescents upon immunisation with QLAIV in the same influenza season in England. They reported nasal congestion, cough and malaise as the most frequent AEIs. No SAE, hospitalisation or death was reported during the investigation [237]. In a study of trivalent LAIV safety in a large cohort of children, few serious adverse events were detected [238]. Anaphylaxis and syncope occurred following LAIV, although rarely.

Since a higher frequency of fever has been reported after the administration of LAIV than after IIV, a recent prospective observational study investigated the frequency of fever following immunisation of young children with IIV in three community clinics in New York City. A low frequency of fever was found, and no difference between the

vaccines evaluated was observed during the 2013–2014 influenza season [239].

Studies by Carr *et al.* and King *et al.* confirmed the safety of LAIV in children affected by cancer and in HIV-infected adults, respectively [240, 241]. In a South African RCT on the safety of LAIV in adults aged  $\geq 60$  years, reactogenicity events were more frequent among recipients of LAIV than of placebo during 11 days post-vaccination ( $p=0.042$ ); symptoms included runny nose or nasal congestion, cough, sore throat, headache, muscle aches, tiredness, and decreased appetite. However, rates of SAE were similar for recipients of LAIV and placebo [242]. Contraindications for LAIV use included asthma, anaphylactic reactions to eggs, a history of GBS, long-term aspirin therapy in patients aged  $<18$  years, and advanced immunosuppression [19].

#### 4.4.1.1 Quadrivalent vs trivalent LAIV

Findings from a combined paediatric immunogenicity and safety study of QLAIV performed in the USA have shown that the safety profile of QLAIV is similar to that of the TLAIV formulation [243]. The most common adverse event reported within 10 days of vaccination with QLAIV versus TLAIV were runny nose or nasal congestion (31.6 vs 28.1%; difference not significant) and cough (15.2 vs 15.5%; difference not significant). The only significant difference in reported events was fever  $>38^\circ\text{C}$  after the first dose in 5.1 vs 3.1% ( $p=0.04$ ) of children 2-8 years of age who were LAIV-naïve [243]. Overall, 44.9% of children in the QLAIV-group had symptoms compared with 43.3% of subjects who received the TLAIV (ns). Adverse events detected within 28 days were significantly different between QLAIV and TLAIV only for fever (1.7 vs 0.7%;  $p=0.04$ ), headache (0.9 vs 0.2%;  $p=0.04$ ) and throat pain (0.6 vs 0%;  $p=0.03$ ). Overall, the safety profile of QLAIV and TLAIV in children 2 to 17 years of age were similar.

#### 4.4.2 Safety of brands licensed in the Netherlands

Fluenz Tetra is the only LAIV licensed in the Netherlands.

Safety data for Fluenz Tetra are based on data from clinical studies of Fluenz Tetra in 2,231 children and adolescents 2 to 17 years of age; clinical studies of Fluenz in more than 29,000 children and adolescents 2 to 17 years of age, and post-authorisation safety studies of Fluenz in more than 84,000 children and adolescents 2 to 17 years of age. Additional experience has occurred with marketed use of Fluenz. In clinical studies, the safety profile of Fluenz Tetra was similar to the safety profile of Fluenz. The most common adverse event observed in clinical studies was nasal congestion or rhinorrhea [244].

In an active-controlled clinical study, an increased rate of hospitalisations for any cause for 180 days after the final vaccination dose was observed in infants and toddlers 6-11 months of age (6.1% Fluenz versus 2.6% injectable influenza vaccine). Most hospitalisations were due to gastrointestinal and respiratory tract infections and occurred more than 6 weeks after vaccination. The rate of hospitalisations was not increased in Fluenz recipients 12 months of age and older. In the same study, an increased rate of wheezing through 42 days was observed in infants and toddlers 6-23 months of age (5.9%

Fluenz versus 3.8% injectable influenza vaccine). The rate of wheezing was not increased in Fluenz recipients 24 months and older. Fluenz Tetra is not indicated for use in infants and toddlers younger than 24 months.

Very rare reports of GBS and exacerbation of symptoms of Leigh syndrome (mitochondrial encephalomyopathy) have been observed in the post-marketing setting with Fluenz [244].

During the 2014-2015 influenza season, the crude incidence rate of adverse events following Fluenz Tetra vaccination was estimated in children and adolescents in England [237]. No hospitalisations, deaths or other SAEs were reported. No significant change in reactogenicity or other apparent safety signals was detected as part of this study.

## 4.5 Safety of maternal influenza vaccination

Safety of maternal influenza vaccination can be divided in two parts: the tolerability for the mother and the safety for mother and child in the short term (adverse pregnancy outcomes) and long term (negative effects for the child later in life).

### 4.5.1 *Tolerability for the mother*

Several studies have shown that the tolerability of seasonal influenza vaccination in pregnant women is comparable to that in non-pregnant women [245-247]. Data on adverse events in healthy adults, as described in the previous sections, are therefore also applicable to healthy pregnant women.

### 4.5.2 *Short-term adverse pregnancy outcomes*

With respect to adverse pregnancy outcomes, two systematic reviews were published on seasonal and pandemic influenza vaccination that included respectively 7 (studies up to 2013 included) and 21 studies (studies up to 2014 included) [248, 249].

The review by Bratton et al. showed that maternally vaccinated women had a lower risk of stillbirth compared to non-vaccinated women (RR 0.73; 95%CI 0.55-0.96) for seasonal and pandemic influenza vaccination combined [248]. Of the seven studies that reported on stillbirth and were included in this review, four studies found a significantly decreased risk in women who received influenza vaccination during pregnancy, while three studies found insignificant results. Just looking at pandemic vaccination, RR was 0.69 (95%CI 0.53-0.90) [248]. The pooled estimate for spontaneous abortion was 0.91 (95%CI 0.68-1.22), based on one study with a significantly lower risk among maternally vaccinated women, and three studies showing insignificant results.

Likewise, no increased risk of fetal death (at any gestational age [GA], <20w GA or ≥20w GA) was found in the review of Fell *et al.* [249]. All three studies in the review that reported fetal death showed insignificant results. For late fetal deaths, five studies were included, with two reporting significant decreased risks after maternal influenza vaccination and three insignificant results. For preterm birth and maternal influenza vaccination, this review reported on 19 studies. In 18 studies, estimates revealed no increased risk of preterm birth after maternal influenza

vaccination, with four studies reporting a significantly decreased risk [249]. Only one study reported a significantly increased risk among maternally vaccinated women (HR 3.28; 95%CI 1.25-8.63) [250]; the average decrease in gestational length was three days in this study.

A retrospective cohort study, including 58,008 births, confirmed the absence of an increased risk for stillbirth  $\geq 20$ w GA (adjusted HR, 0.49; 95%CI 0.29 - 0.84) [251]. A retrospective cohort study, including 145,869 children, found no association between maternal influenza vaccination and SGA birth, preterm birth, need for mechanical ventilation at birth, respiratory distress syndrome, admission to the neonatal ICU (NICU), low birth weight, or low Apgar score [252]. Likewise, a Dutch study on adverse pregnancy outcomes after the 2009 influenza pandemic did not find an increased risk for preterm delivery (OR 0.98; 95%CI 0.59-1.62), or SGA births (OR 0.84; 95%CI 0.50-1.43) or a composite outcome including low Apgar score, neonatal ICU admission, neonatal resuscitation or perinatal death (OR 0.84; 95%CI 0.44-1.60) [253].

In the case-control arm of a large study on the safety of influenza vaccination during pregnancy in three consecutive influenza seasons, no overall increased risk for preterm delivery was found; an elevated adjusted risk was reported only for second-trimester vaccination during one season (HR 2.60; 95%CI 1.21-5.61), which was a reduction in gestational length of  $< 2$  days. For the 42 specific defects or categories of defects, most adjusted risks were close to 1.0; the highest was 2.38 for omphalocele and the lowest was 0.50 for atrioventricular canal defects. None had confidence boundaries  $> 1.0$ . For each season individually, only one elevated OR had a lower 95% CI  $> 1.0$ : omphalocele (OR 5.19; 95%CI 1.44-18.7) [254]. This estimate was based on five cases. Likewise, in the cohort arm of this study, first-trimester exposure to influenza vaccination was not statistically significant in association with an increased risk for major birth defects (RR 1.87; 95%CI 0.97-3.59), which occurred in 5.6% of exposed first-trimester pregnancies and 2.9% of those un-exposed to the vaccine. No specific pattern of defects was evident in the vaccine-exposed cohort. The overall risk of spontaneous abortion was not elevated (HR 1.09; 95%CI 0.49-2.40). Adjusted HRs for preterm delivery approximated 1.0 (adjusted HR 1.23; 95%CI 0.75-2.02). Relative risk (RRs) for SGA infants in weight, length and head circumference ranged from 1.19 to 1.49 with all 95%CIs including '1' [255].

Similar findings were reported in studies, performed in Finland [256], USA [257], Denmark [258] and Sweden [259]. In contrast, a study performed in Italy revealed a limited increase in the prevalence of gestational diabetes (adjusted OR 1.26; 95%CI 1.04-1.53) and eclampsia (adjusted OR 1.19; 95%CI 1.04-1.39) [260].

#### 4.5.3 *Long-term adverse pregnancy outcomes*

The safety of maternal influenza vaccination for the child later in life was studied in a nationwide Danish cohort. The authors found no increased risk for hospitalisation in children up to 5 years of age whose mothers were vaccinated against 2009 influenza A(H1N1) compared to children with unvaccinated mothers, irrespective of trimester (1<sup>st</sup> trimester RR



1.17; 95%CI 0.94-1.45 and 2<sup>nd</sup> and 3<sup>rd</sup> trimester RR 0.93; 95%CI 0.87-0.99) [261]. This study also assessed the risk of 23 diseases, including infectious diseases, autoimmune diseases, neurologic diseases and behavioural disorders. The authors found a significantly increased risk of other infections after influenza vaccination in the first trimester (RR 1.71; 95%CI 1.08-2.73; IR 16.9 per 1000 person years [py] among exposed vs 9.8 per 1000 py in unexposed). However, after correction for multiple comparisons with Bonferroni-corrected confidence intervals, results were not statistically significant (RR 1.71; 95%CI 0.83-3.56). Likewise, after second- or third-trimester vaccination, increased risks were found for sepsis (RR 1.96; 95%CI 1.26-3.05; IR 1.1 per 1000 py in exposed vs 0.5 per 1000 py in unexposed) and Sjögren syndrome (RR 1.59; 95%CI 1.04-2.44; IR 1.0 per 1000 py among exposed vs 0.7 per 1000 py in unexposed). Again, results became statistically insignificant after correction for multiple comparisons.

In the Netherlands, no differences were found in growth and development between children up to 1 year of age of vaccinated vs unvaccinated mothers [253].

**In summary**, influenza vaccination during pregnancy is safe. The tolerability of this vaccination is similar to that in healthy adults who are not pregnant. Furthermore, no increased risks of adverse outcomes for mother and child have been found in either the short or long term.



## 5 Influenza vaccine uptake and acceptance of vaccination

### Summary

The influenza vaccination coverage among the target groups in the Netherlands has dropped from 53.5% in 2016 to 49.9% in 2017. Since 2008 there has been a decreasing trend in vaccination coverage. The highest vaccination coverage (69.6%) was observed among persons 65 years and older who also have a medical indication for vaccination. The intention to be vaccinated against influenza among the elderly increases with advancing age. The perceived severity of influenza was lowest for participants aged 50-60 years.

Strong predictors for influenza vaccination uptake were vaccination in the last year, no experience with side effects, and general positive attitude towards vaccination. Important factors that were associated with vaccination acceptance in general among older adults were the high risk of mortality in infectious disease, high susceptibility to infectious disease, and high VE. Higher age, influenza vaccination in the preceding year and higher self-perceived health score were identified as personal factors that affected vaccine preference positively.

The vaccination coverage for 2016-2017 in other European member states for older target populations ranged from 2.0% to 72.8%. The vaccine uptake during the pandemic influenza season among pregnant women in the Netherlands was 63%. The most important predictor for uptake was the government's recommendation for vaccination. Thirty-nine percent of women expressed a positive intention for future maternal vaccination. Information on vaccine safety is a very important aspect in their decision-making process. About 15% of Dutch parents had a positive intention to vaccinate their children for seasonal influenza. In general, they believed it was not important to vaccinate their child against influenza because they thought it not to be a severe disease. Dutch youth healthcare workers believed that including vaccination against influenza in the National Immunisation Programme was not necessary.

### 5.1 Vaccine uptake

#### 5.1.1 *Vaccine uptake in the Netherlands*

During the seasonal influenza vaccination campaign of 2017, 17.4% of the Dutch population was vaccinated. The vaccination coverage among all target groups for vaccination was 49.9%. The highest vaccination coverage (69.6%) was observed among persons 65 years and older who also had a medical indication for vaccination. For persons between 60 and 64 years of age without a medical indication, the vaccination coverage was lowest (25.9%). Among groups with a medical indication, the vaccination coverage was highest in the population with diabetes (61.9%) and lowest among the immunocompromised (44.8%). Since 2008, there has been a decreasing trend in the vaccination coverage among the target groups (see Figure 5.1 below) [262].

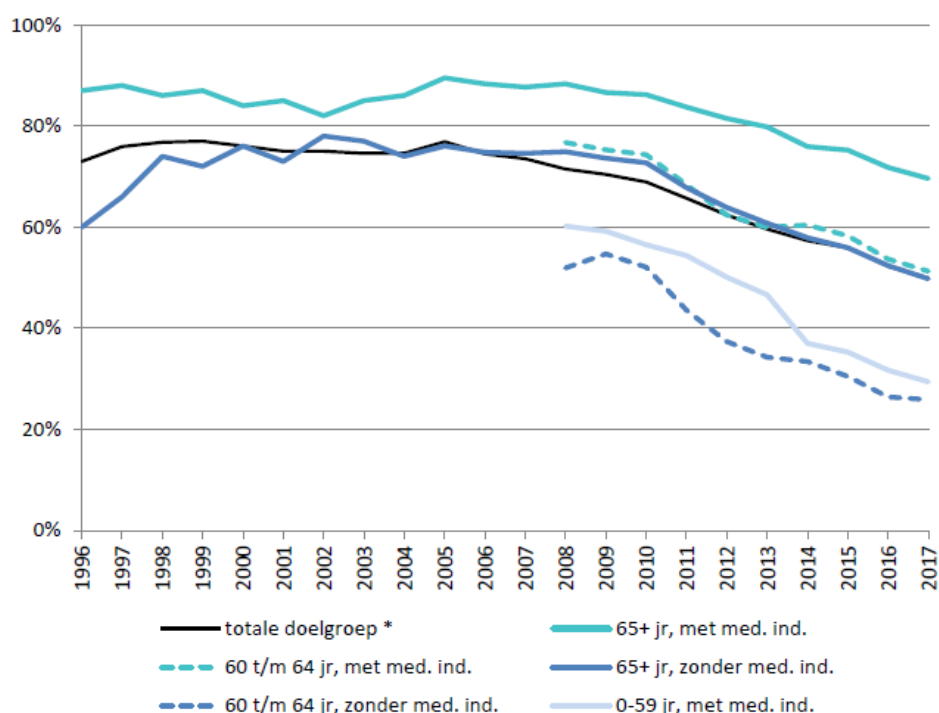


Figure 5.1 Trends in vaccination coverage by age and medical indication, 1996-2017 [262]

Black continuous line are all target groups \*In 2008 the age limit for indication for influenza vaccination has been decreased from 65 years to 60 years. Therefore, the vaccination coverage among all target groups in the years 1996 until 2007 is poorly comparable with those of later years. Dotted lines are 60-64 years old, blue-green colour for those with a medical indication and dark blue colour for those without a medical indication. The continuous lines on the right side are, from top to bottom: 65 years and older with a medical indication; 65 years and older without a medical indication; and 0-59 years old with a medical indication.

### 5.1.2

#### *Vaccine recommendations and uptake in other European countries*

Of 30 responding member states, all recommended seasonal influenza vaccination for older age groups, albeit with different age thresholds. Six member states recommended vaccination for children and adolescents <18 years of age. Of 30 responding member states, 28 recommended vaccination of pregnant women.

Vaccination coverage rates in 2016–2017 for older target populations were known in 19 member states (Denmark, Estonia, Finland, Germany, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, the Netherlands, Norway, Poland, Portugal, Slovakia, Slovenia, Spain, Sweden and the United Kingdom) and ranged from 2.0% to 72.8% (median 47.1%). The coverage for those with chronic medical conditions was provided by seven member states (Czech Republic, France, Ireland, the Netherlands, Norway, Portugal, and the United Kingdom) and ranged from 15.7% to 57.1% (median 44.9%). The coverage for pregnant women was known in nine member states (Belgium, Finland, Hungary, Ireland, Italy, Lithuania, Romania, Slovenia, and the United Kingdom) and ranged from 0.5% to 58.6%, (median 25.0%) [263].

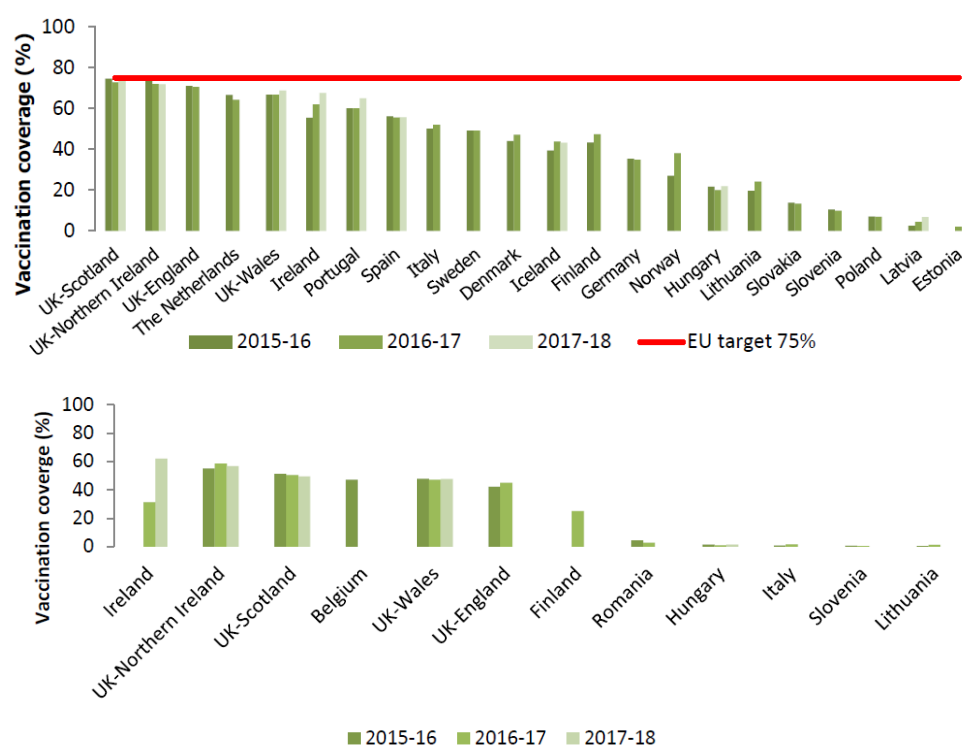


Figure 5.2 Seasonal influenza vaccination coverage rates in older age groups (upper panel) and pregnant women (lower panel) in EU/EEA member states for influenza seasons 2015-2016, 2016-2017 and 2017-2018 (if available)

In the UK, during the 2017-2018 influenza season, the overall vaccine uptake by school year was 61.3%, 60.0%, 59.4%, 54.7 % and 54.5% for children in reception (ages 4 rising to 5 years) and in school years 1, 2, 3 and 4 (ages 5-9), respectively [264].

**In summary**, since 2008, the trend in the vaccination coverage has declined among the target groups in the Netherlands. The vaccination coverage among member states varies widely from 2.0% to 72.8% for older target populations. Most member states also recommend influenza vaccination for pregnant women and six member states recommend vaccination for children and adolescents <18 years of age.

## 5.2 Acceptance of influenza vaccination in the Netherlands

### 5.2.1 Acceptance of maternal influenza vaccination

During the 2009 influenza pandemic, the vaccine against influenza A(H1N1) was available for pregnant women, and the coverage was 63% [265]. Coverage was higher among older birth cohorts, women who had been pregnant before, women with underlying medical conditions and women who reported no defined 'life philosophy'. Protection of the child after birth, the government's advice, and possible harmful effects of the vaccine for the unborn child had the greatest predictive value for vaccination status. With regard to vaccination during future pregnancies, 39% had a positive intention to obtain vaccination and 45% were neutral. The government's advice was the strongest predictor for intention to vaccinate. However, women expressed concern over lack of knowledge about vaccine safety.

### 5.2.2 *Acceptance of influenza vaccination for infants by parents*

An internet survey (November 2012) was performed among parents of infants in the Netherlands. A random sample from the national immunisation register of 1,500 parents was invited, and 491 parents participated (33% response) and completed the questionnaire. The aim was to study the intention of parents to have their child vaccinated against four diseases not currently included in the National Immunisation Programme (NIP) in the Netherlands: varicella, serogroup B meningococcal (MenB) disease, rotavirus gastroenteritis and seasonal influenza. Results showed that the intention to vaccinate was highest for MenB disease (83% positive intention, scores 4-5 taken together on 1-5 Likert scale), followed by rotavirus gastroenteritis (38%), varicella (28%) and lowest for seasonal influenza (15%). Parents did not believe in the importance of vaccinating their child against influenza (mean = 2.1) or in the disease severity (mean = 2.2), although they perceived it rather likely that their child would contract influenza (mean = 3.7). With regard to concerns about side effects of vaccination, the results per disease were similar (mean between 3.1-3.2) [266].

A study of parental reasoning regarding pandemic influenza A(H1N1) vaccination of their children was performed in the Netherlands in December 2009 for acceptors (N = 1227) and in June and July 2010 for decliners (N = 1900). The vaccine response rate was 71% for the first round and 59% for the second round. Most reported reasons for parental acceptance of H1N1 vaccination were "I don't want my child to become sick" (43%), "Mexican flu can be severe" (10%), "The government advises it, so I do it" (6%), and "If I don't do it, I will regret it" (6%). The most reported reasons declining the vaccination were "fear of side effects or harmful consequences" (51%), "Just having a bad feeling about it" (46%), and "The vaccine was not thoroughly tested" (39%). More decliners than acceptors experienced feelings of doubt about their vaccination decision (decliners 63% versus acceptors 51%,  $p < 0.001$ ), and decliners reported more often information-seeking behavior (decliners 76% vs acceptors 56%,  $p < 0.001$ ). Decliners more frequently solicited advice from their social network than acceptors (decliners 72% vs acceptors 61%,  $p < 0.001$ ). In addition, acceptors more often reported social influence on their vaccination decision (acceptors 58% vs decliners 38%,  $p < 0.001$ ) and experienced more negative feelings after their vaccination decision (acceptors 8% vs decliners 2%,  $p < 0.001$ ) [267].

### 5.2.3 *Acceptance of influenza vaccination for infants among youth healthcare workers*

A questionnaire study (December 2013) was conducted among youth healthcare workers to gain more insight into their opinions about vaccines not yet included in the NIP, such as that against influenza. A questionnaire was sent to 1427 youth healthcare workers, and 432 (30%) responded. Results with regard to whether they believed new vaccines were necessary to include (on a Likert scale of 1-7) to include in the National Immunisation Programme showed that they perceived a vaccine against varicella and influenza (mean = 3.1 and 2.8, respectively) less necessary than a vaccine against menB disease, infection caused by respiratory syncytial virus (RSV) and rotavirus gastroenteritis (mean = 4.6, 4.5, and 4.1, respectively) [268].

#### 5.2.4 *Acceptance of influenza vaccination among the elderly*

In December 2014, a postal questionnaire was sent to 1800 people who had been randomly selected by six municipalities, based on four age categories: 50-60 years, 60-70 years, 70-80 years, and 80 years and older. The municipalities differed in the level of urbanisation and geographical location. In total, 735 (41%) people aged 50 years and older returned the questionnaire. The aim was to assess their intention to be vaccinated against influenza, pneumococcal disease, herpes zoster and pertussis and the predictors of their attitude. More than half of all the participants had been vaccinated against influenza in the season preceding this study (61%), and 70% had been vaccinated against influenza at some point in the past. Results showed that participants perceived pneumococcal disease (mean = 6.0 on a Likert scale of 1- 7) as significantly more severe than the other three diseases, while influenza (mean = 4.7) was perceived as significantly less severe than herpes zoster (mean = 5.4) and pertussis (mean = 5.3). Intention to vaccinate was highest for pneumococcal disease (mean = 5.5) and differed significantly from the intention to vaccinate against influenza (mean = 5.0), herpes zoster (mean = 4.9), and pertussis (mean = 4.9). The intention to be vaccinated against influenza increased with increasing age (50-60 years of age (mean = 4.0), 60-70 (mean = 4.9), and 70-80 (mean = 5.4) and >80 (mean = 5.8). The perceived severity for influenza was lowest for participants in the 50-60 age group (mean = 4.3) [manuscript in preparation].

In 2016, a discrete choice experiment (DCE) was performed for which scenarios for influenza vaccination were developed on the basis of five vaccination characteristics: effectiveness, risk of severe side effects, risk of mild side effects, protection duration, and time to activation of the vaccine. From the total of 1,419 panel members aged 60 years and older who participated in the survey, 1,261 (response rate 89%) completed the questionnaire. With the assumption of a base case respondent and a realistic vaccination scenario, the predicted uptake was 58%. The strongest predictors for vaccination uptake were having been vaccinated last year, no experience of side effects, and general positive attitude towards vaccination [269].

In December 2014 another DCE was performed among adults 50 years and older to determine the relative importance of vaccine and disease-specific characteristics and the acceptance of vaccination against pneumococcal disease, herpes zoster, pertussis, and influenza. In the DCE, vaccination scenarios were based on the above four diseases and on six characteristics: clinical symptoms, susceptibility, mortality, VE, side effects, and number of given vaccinations. In total 1,800 potential respondents were selected, and 735 surveys were returned (response rate = 41%). Finally, 610 (34%) respondents were included in the analyses. Important factors associated with vaccination acceptance in older adults were perceptions of high risk of mortality of the infectious disease, high susceptibility for contracting the infectious disease, and high VE. Higher age, influenza vaccination in 2013 and higher self-perceived health score were identified as personal factors that affected vaccine preference positively. Potential vaccination rates of older adults were estimated at 68% for pneumococcal vaccination, 58% for herpes zoster vaccination, 54% for pertussis vaccination and 54% for influenza

vaccination, and the percentages were somewhat higher for persons aged 65 years and older [270].

## **5.3 International acceptance of influenza vaccination**

### **5.3.1 *Acceptance of maternal influenza vaccination***

In concordance with results on acceptance of maternal vaccination in the Netherlands, a systematic review on vaccine hesitancy in relation to maternal vaccinations in general, including 155 articles, revealed the major barriers for vaccination to be vaccine safety; a belief that a vaccine was not needed nor effective; no recommendation from healthcare workers; insufficient knowledge of vaccines; access issues; costs and conflicting advice [271].

A review focusing on more broadly oriented predictors, found that patient-focused predictors of maternal vaccination included provider recommendation; knowledge, attitudes and beliefs; cues to action; and race and ethnicity [272]. Provider-focused predictors included knowledge, attitudes and beliefs; and multi-component intervention packages. Health system predictors included standing-order protocols and practice-site logistics.

Several other reviews and studies also addressed one or more of the barriers mentioned above [273-285]. In nearly all articles, recommendation by healthcare providers played an important role in women's decision-making.

Strategies to promote vaccine acceptance among pregnant women are ongoing education, recommendation, normalisation and maximisation of convenience [274, 279, 286, 287]. These aspects are important to address hesitancy not only among pregnant women themselves but also among healthcare providers [279, 287, 288].

### **5.3.2 *Parental acceptance of influenza vaccination of children***

A cross-sectional online survey was performed in the UK shortly after the 2015-2016 immunization campaign. The aim was to identify predictors of uptake of childhood influenza vaccination in the 2015-2016 influenza season, parental perceptions of side effects from the influenza vaccine and intention to vaccinate one's child in the 2016-2017 influenza season. Participants were parents or guardians of children aged between 2 and 7 years (N = 1001). Factors strongly positively associated with vaccination uptake included having the child previously vaccinated against influenza, perceiving the vaccine to be effective and perceiving the child to be susceptible to influenza. Factors strongly negatively associated with uptake included perception of the vaccine as unsafe, a belief that the vaccine causes short-term side-effects or long-term health problems and a belief that yearly vaccination may overload the immune system. Predictors of intended vaccine uptake in 2016-2017 were similar. Participants whose children experienced side effects after the 2015-2016 vaccination reported being less likely to vaccinate their child the next year [289].

A systematic review of influenza vaccination hesitancy was performed and included articles published between 2005-2016. Following the



PRISMA approach, the authors selected 470 articles and analysed them for significant barriers to influenza vaccine uptake or intention. The barriers reported most often to seasonal influenza uptake for children were sociodemographic variables (age and education) and absence of recommendations from medical personnel to the decision-makers, i.e., parents of children 6-59 months of age. With regard to the 4C framework (factors related to four categories: complacency, convenience, confidence, and calculation), calculation (decreased perception of own benefit of vaccine) and inconvenience (decreased frequency of interaction with health service) were the most prominent reasons for vaccine hesitancy [290].

### 5.3.3 *Acceptance of influenza vaccination among elderly*

A systematic review of factors associated with the uptake of seasonal influenza vaccination in adults included articles published until November 2013. Twenty-three articles met the inclusion criteria and were selected for outcome analysis, 21 of which were quantitative observational studies. Results showed that increasing age and having chronic diseases were strongly predictive of vaccination uptake. In addition, advice from doctors/other health professionals/family and/or close friends and free vaccination were other key factors associated with uptake of vaccination. Furthermore, perceptions of effectiveness and vaccine safety and adverse events were more influential than the level of knowledge regarding influenza and its vaccination [291].

Results from the systematic review of influenza vaccination hesitancy described above showed that the most frequently reported barriers to seasonal influenza vaccine uptake among chronically ill patients were not having been vaccinated previously, having a smoking habit and being younger. The most frequently reported barriers within the chosen framework (i.e. 4C model stands for complacency, convenience, confidence, and calculation factors) for seasonal influenza vaccination were lack of confidence due to a negative attitude and low perceived VE and complacency issues (low perceived severity of disease). Sociodemographic variables (lower age, additional risk factors, less knowledge, being female), psychical variables (smoking habit, high perceived health status) and past negative behaviour were among the most frequently reported barriers to seasonal influenza vaccination uptake among elderly. As in similar studies, other barriers to vaccination uptake concerned the elderly and their living arrangements (e.g., living alone and being single). This association may be mediated by access and cues to action: people who live alone with limited assistance may have less access, irregular preventive health visits, and less support from family members [290].

**In summary,** intention to accept influenza vaccination for infants by parents and by youth healthcare workers in the Netherlands is not high. For both the elderly and pregnant women, vaccine coverage of the 2009 influenza pandemic and seasonal influenza, respectively, was higher among those who were older and those with an underlying medical condition. Furthermore, similar factors influencing vaccination uptake among various groups have been observed, such as perceived VE, vaccine safety, personal susceptibility, severity of the disease and past vaccination behaviour. A clear recommendation from the health

professional and an increase in the frequency of interaction with the healthcare service might increase vaccination uptake.

## 6 Impact of influenza vaccination programmes

### **Summary**

Influenza vaccination aims to protect the vaccinated persons from infection using the direct effect of vaccination. Unvaccinated persons may also benefit indirectly, being less exposed to the virus when its circulation is diminished by vaccination of others. Both direct and indirect effects play a role in the impact of the current vaccination programme. The impact can be expressed as the effect on the infection attack rate (IAR), the percentage of the population infected during an influenza season, or on the number of symptomatic cases, hospitalisations or deaths.

### ***Maternal vaccination programme***

A maternal vaccination programme is aimed at direct protection of pregnant mother and child. Indirect effects are negligible, as the number of additionally vaccinated persons is small. So, the impact will be proportional to the uptake. Even with limited transfer effectiveness from mother to child, the incidence of influenza in newborns to 1-year-old children can be expected to decrease.

### ***Paediatric vaccination programme***

A paediatric vaccination programme is aimed at indirectly protecting vulnerable groups by decreasing virus circulation in children. Modelling studies are a helpful tool to investigate the impact of such a policy change. Published modelling results differ widely in the predicted impact of vaccinating children because of differing model assumptions. The study by Baguelin *et al.* [292] predicts a 52% reduction in population-wide IAR at a 50% coverage in healthy children. However, this result is valid only at the very start of the vaccination programme, as long-term effects are not taken into account. The study by Backer *et al.* [293] is the only model that explicitly addresses long-term effects of vaccination and variability between seasons. The study predicts a more modest reduction of 18% in IAR at 50% coverage in children. Moreover, modelling results show that vaccination of children increases variation in epidemic sizes, i.e., more influenza seasons with a very high incidence and more seasons without any influenza activity. This erratic behaviour could lead to more severe seasons in which healthcare demands exceed available capacity.

### ***Current vaccination programme***

The current vaccination programme is aimed at direct protection of vulnerable groups, such as those with a high risk of complications and the elderly. It is difficult to assess the effect of introducing such a programme from observations. Modelling studies however show that this strategy has only a limited impact on virus circulation, but it is fairly effective in averting hospitalisations and deaths in the target group.

### **6.1 Impact of influenza vaccination programmes on pregnant women**

No literature has been found reporting the effect of vaccination of pregnant women on the IAR in the Netherlands. RCTs and observational

studies from other countries focus mainly on VE, discussed in section 3.2. A rough estimate for the Netherlands can be derived on the assumption that maternal vaccination will have direct effects only on mother and child, with no indirect effects on the population as a whole, since 1) pregnant women make up a very small part of their age class and 2) newborns do not play a major role in influenza transmission as they have few contacts.

Each year, approximately 170,000 women become pregnant in the Netherlands (data CBS [Statistics Netherlands] 2015), 50% of whom would be pregnant in their 2<sup>nd</sup> or 3<sup>rd</sup> trimester, and vaccinated during the annual influenza vaccination campaign. With an average VE of 45% [294] and an average IAR of 7.4% in the age class of 20 to 35 [294], maternal vaccination would avert 2800 infections during pregnancy. The newborns are protected by maternal antibodies up to 6 months, while the epidemic is assumed to last 3 months. Depending on when the epidemic starts, between 25% and 50% of the newborns that are born annually might benefit from maternal vaccination. With an average VE of 48% [79] and an average IAR of 6.4% in newborns to 1-year-old children, 1350-2700 infections, or 68-136 hospitalisations (assuming an influenza hospitalisation rate of 333/100000 [46]), would be averted per season, on average. This rough estimate assumes that the vaccination coverage in eligible pregnant women is 100%. For lower coverages, the impact would decrease proportionally. Similar calculations form the basis of health economic analyses in Belgium [295] and the UK [296], but these studies do not report the achieved impact on the IAR nor averted infections.

## 6.2 Impact of influenza vaccination programmes on healthy children

School-aged children (4-16 years of age) are generally recognised as the epidemic drivers of influenza transmission. This has led to the notion that targeting these groups for vaccination could effectively decrease influenza circulation, and, as an indirect result, protect groups at higher risk of complications. Here we assess the evidence for the intended positive and unintended negative consequences of extending the current Dutch influenza programme with a paediatric programme. We make a distinction between simulation results and observations.

### 6.2.1 *Impact of paediatric vaccination programme based on model studies*

Simulation studies that predict the effect of vaccinating children against influenza differ in model structure and assumptions (Table 6.1). All models predict some reduction in the IAR due to child vaccination, but there is no consensus on the extent of this reduction (Figure 5.1). For instance, at an effective vaccination coverage of 40%, the predicted reduction ranges from 20% to 84%. The earliest models report the highest impacts, either because the vaccine was assumed to be 94% efficacious [297] or to induce protection for 12 years [298, 299].

More recent modelling studies used for evaluation of child vaccination fall roughly into two categories. The first is studies that model a succession of influenza seasons with immunity gains (due to recent infection) and losses (due to antigenic drift) from one season to another ("multiseason dynamics" in Table 6.1). This type of model explores long-term infection dynamics and how they are affected by vaccinating

children against influenza [293, 300-303]. Vaccination decreases the natural immunity levels not only in the target group (due to vaccination) but also in the total population (due to less virus circulation). The infection incidence increases in groups that have just aged out of the child vaccination programme; as these groups have little natural immunity after years of vaccination, they take on the role of epidemic driver [293]. However, many models with a succession of multiple seasons do not allow parameters to vary between seasons. This leads to projections of identical influenza seasons in terms of timing and epidemic size.

The second category contains models that capture the high variation in epidemic size between seasons that is caused by the variation in VE and antigenic drift of the virus ("variability between seasons" in Table 6.1). Studies that analyse single seasons estimate the variable population susceptibility and IAR per season and per age group [292, 304, 305]. However, these models do not capture long-term trends, such as the decline in natural-immunity levels. This may lead to an overly optimistic assessment of the impact of vaccinating children.

One modelling study has combined multiseason dynamics and variability between seasons [293]. This study showed that even though vaccinating children will lower the influenza incidence on average, influenza seasons could become more erratic; seasons with low influenza activity could be followed by large outbreaks due to the build-up of susceptible persons within the population. Such variation of the epidemic size grows with increasing vaccination coverage (Figure 6.2). For example, at a vaccination coverage of 50% in children, the probability of a year without an influenza epidemic is 29%, compared to 4.4% without child vaccination. At the same time, the probability of having a very large epidemic (comparable to season 2014-2015) is 1.5%, compared to 0.2% without child vaccination. These findings imply that planning for required healthcare resources becomes increasingly more difficult, as on average healthcare demands are lower, but they also may exceed available capacity more often.

Table 6.1 Overview of transmission models by model category

Variability Between Seasons: vaccine effectiveness and antigenic drift of the virus can differ between seasons and between age groups	Multiseason Dynamics: starting situation of influenza season depends on the previous influenza season to explore long-term effects			
	No		Yes	
	No	Weycker <i>et al.</i> [297] US	Yes	Vynnycky <i>et al.</i> [298] EW Pitman <i>et al.</i> [299] DE Rose <i>et al.</i> [302] EW/ES/BR/T Gibson <i>et al.</i> [301] W Gerlier <i>et al.</i> [303] BE Gerlier <i>et al.</i> [300] FR
	Yes	Baguelin <i>et al.</i> [292] EW Meeyai <i>et al.</i> [304] TH Weidemann <i>et al.</i> [305] DE		Backer <i>et al.</i> [293] NL

Impacts of paediatric vaccination programme according to these models are shown in Figure 6.1. The model is applied to the following countries: BE (Belgium), BR (Brazil), DE (Germany), ES (Spain), EW (England and Wales), FR (France), NL (The Netherlands), TH (Thailand), TW (Taiwan) and US (United States of America).

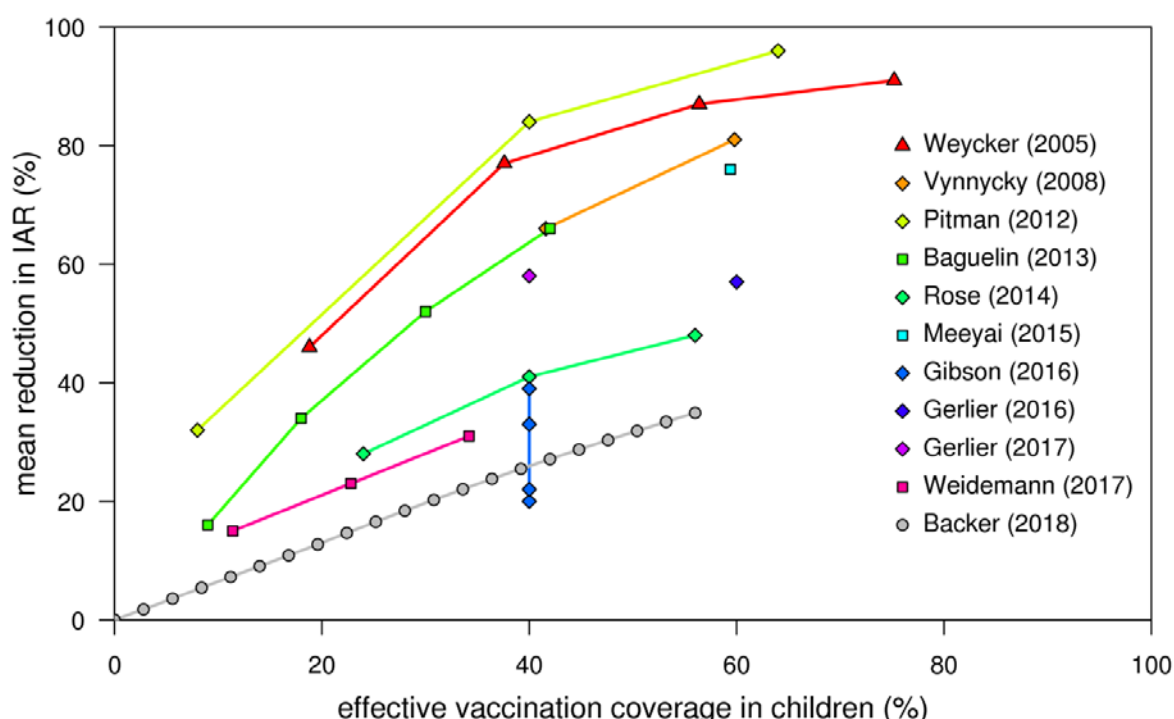


Figure 6.1 Mean reduction in influenza infection attack rate (IAR) as a function of effective vaccination coverage in the paediatric vaccination programme for different transmission models

The effective vaccination coverage is the multiplication of the vaccination coverage and the assumed vaccine efficacy for the target age group. Results are shown for the largest target groups in each study from children 0.5-2 years old to those 16-18 years old. The studies are subdivided into studies with only multiseason dynamics (diamonds), only variability between seasons (squares), neither (triangles) or both (circles). Figure reproduced from Backer *et al.* [293].

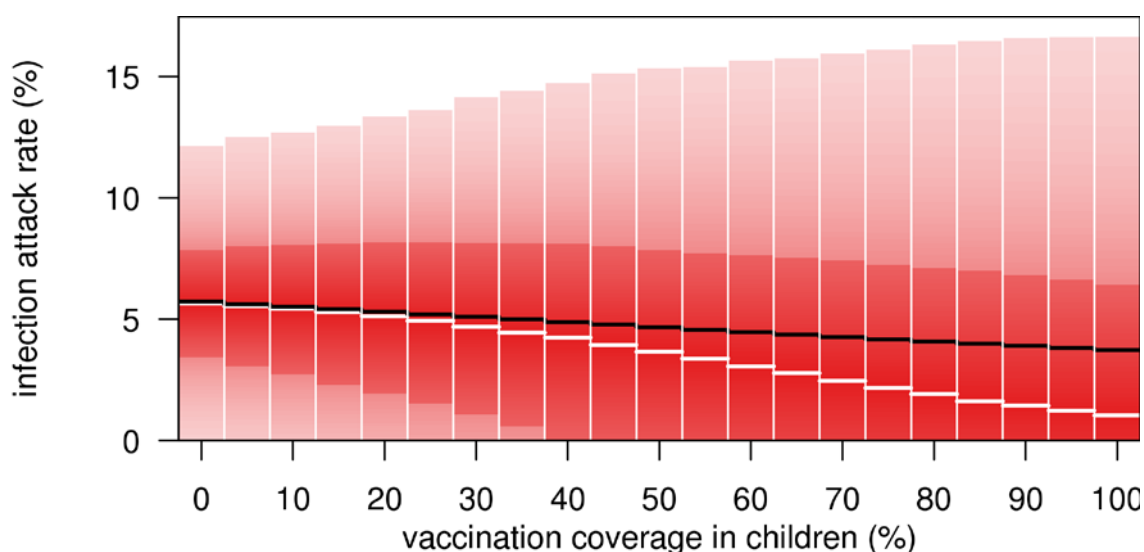


Figure 6.2 Infection attack rate distribution after roll-out of the paediatric vaccination programme for 2-16 year olds as a function of vaccination coverage; mean (black line), median (white line), interquartile range (red area) and 95% range (pink area)

The declining black and white lines show that, as expected, median and mean size of epidemics will decrease with increasing vaccination coverage. The rising top of the pink area shows that, unexpectedly, the occurrence of extremely large epidemics will increase with increasing vaccination coverage. Figure reproduced from Backer *et al.* [293].

For the Netherlands, the impact of child vaccination has been assessed in two other modelling studies the results of which are yet to be published. First, in the European project I-MOVE+ the impact of child vaccination is assessed for several European countries using the model by Baguelin *et al.* [292]. Preliminary findings for the Netherlands suggest a sizeable reduction in the population-wide IAR at a coverage of 50% in healthy children (unpublished manuscript), but this result applies only to the first year of childhood vaccination. Secondly, at the University of Groningen the paediatric programme has been studied with an adapted version of the model by Pitman *et al.* [299], [306], which also suggests a considerable impact on the IAR (unpublished manuscript). However, in this study the variability between influenza seasons is not taken into account.

The Belgian Healthcare Knowledge Centre published a report on targeting children for vaccination in 2013 ([kce.fgov.be/sites/default/files/atoms/files/KCE\\_204Cs\\_Seasonal\\_influenza\\_vaccination\\_partII.pdf](http://kce.fgov.be/sites/default/files/atoms/files/KCE_204Cs_Seasonal_influenza_vaccination_partII.pdf)) that adapted the model by Vynnycky *et al.* [298] to the Belgian setting. At an 80% coverage in children 2 to 17 years old, they estimated a 22% reduction in influenza cases. This is notably lower than that found in the original work, possibly due to the use of more realistic values for VE and duration of protection.

### 6.2.2

#### *Impact of paediatric vaccination programme from observation*

In Japan a vaccination programme for schoolchildren (aged 7-15 years) was in place from 1962 to 1987, with coverage levels ranging from 50 to 85%. In a time-series analysis, Reichert *et al.* [307] found that mortality attributed to pneumonia and influenza dropped significantly in

this period and rebounded after repealing the programme. However, the mortality rates before the start of the vaccination in Japan were much higher than those seen currently in European countries, making the two settings difficult to compare.

A more comparable situation is the paediatric programme in the UK, that was initiated in the 2013-2014 season by gradually increasing the vaccinated cohort. Progress of vaccine uptake levels and impact on several disease indicators are being monitored [88, 308, 309], comparing pilot (full vaccination) with non-pilot (limited vaccination) areas. Most disease indicators such as influenza-confirmed hospitalisations were consistently lower in the pilot areas than in the non-pilot areas, but the differences were mostly non-significant. Hardelid *et al.* [310] compared influenza-associated admission rates to paediatric ICUs before and after the introduction of the paediatric programme. In the target age group, the admission rate increased, and no difference was found for older children. Hence, the authors concluded that the study period was too short to observe a potential long-term effect of the paediatric programme, as it has not yet been fully implemented.

### 6.3 Impact of influenza vaccination programmes for the elderly and persons with co-morbidities

In most European countries, influenza vaccination is recommended for individuals at high risk of complications after influenza infection and for elderly persons above a certain age. Here we give an overview of the published literature on what impact the current programme has had on influenza outcomes, i.e., number of cases, hospitalisations and deaths. We distinguish analyses based on historical observations versus computer simulations.

#### 6.3.1 *Impact of current vaccination programme based on observation*

Analysis of influenza incidence before and after the implementation of the current vaccination programme can suggest the impact of the programme. Initially, the current programme included only the high-risk population. In approximately 2000, the programme was extended in most European countries to the elderly population above a certain age (generally 65 years). Three articles assess the impact of adding the elderly to the vaccination programme:

1. For England and Wales, Mann *et al.* [311] estimated excess mortality using a time series of pneumonia or influenza deaths in a multivariable regression model. They found decreasing mortality trends over the period of study (1975-1976 to 2004-2005), but only weak evidence that the increased vaccination coverage had a role in this decrease.
2. For the Netherlands, McDonald *et al.* [312] attributed influenza cases to ILI cases in a short time series of 4 years before and after policy change. They found no effect after the vaccination of persons 65 years and older began in 1997, but a strong effect when the age limit was lowered to 60 years in 2008. This counterintuitive result may have been caused by the limited number of influenza seasons in the analysis or by long-term trends that were not considered.



3. For Scotland, Corson *et al.* [313] estimated with Poisson regression that 10 influenza-related and 123 COPD-related deaths, as well as 21 influenza- and 425 COPD-related hospitalisations, were prevented annually after the inclusion of persons over 65 years of age in the vaccination programme. However, they did not provide the relative reduction or evidence that these reductions were caused by the change in the vaccination programme.

**In summary**, analyses based on observations are often hampered by a lack of data when only a limited number of seasons before and after the policy change are available and also by changes in circumstances that may confound the analysis. Influenza incidence has been steadily decreasing over the last decades, but it is difficult to quantify to what extent vaccination contributes to that trend.

#### 6.3.2 *Impact of current vaccination programme based on computer simulations*

Many influenza transmission models have been developed. A few have assessed the impact of the current programme by comparing simulations with and without vaccination. Table 6.2 compares the results for six studies. The results for England/Wales and the Netherlands are similar, despite different transmission models. For countries that have a high vaccination uptake, such as the US, a large impact on infections is found mainly through indirect effects [314]. Eichner *et al.* [315] predict a similar high impact with a similar high coverage. For Germany, however, vaccination coverage of approximately 20% as used by Weidemann *et al.* [305] seems to correspond more accurately with current German uptake rates.

*Table 6.2 Comparison of published results on the impact of the current vaccination programme (CP) targeting high-risk groups and the elderly*

	Country #	Overall Coverage	Averted Infections	Averted Hospitalisations	Averted Deaths
<b>Baguelin <i>et al.</i> [316]</b>	EN	-	17%	-	-
<b>Baguelin <i>et al.</i> [292]</b>	EN/WL	18%	16%	-	40%
<b>Eichner <i>et al.</i> [315]</b>	DE	45%	41%	-	-
<b>Weidemann <i>et al.</i> [305]</b>	DE	18%	-	9%	-
<b>Arinaminpathy <i>et al.</i> [314]</b>	US	>45%	38%*	-	-
<b>Backer <i>et al.</i> [294]</b>	NL	21%	13%	24%	35%

Only point estimates or means given.

\* Average over 7 seasons (min: 21%, max: 48%)

# DE (Germany), EN (England), NL (The Netherlands), US (United States of America), WL (Wales)

In the above overview, the focus is on transmission models that take direct and indirect effects of vaccination into account. In other studies, the impact was assumed to be equal to the effective vaccination coverage, i.e., vaccination coverage multiplied by VE. In general, these models can account only for direct effects and will underestimate the effect of vaccination (e.g., Kostova *et al.* [317], Foppa *et al.* [318]). Preaud *et al.* [319] applied this method to the EU27 region and

estimated that under the current vaccine uptake levels, 45,300 to 65,600 hospitalisations, and 25,200 to 37,200 deaths are averted annually by influenza vaccination.

**In summary**, modelling studies show that the current influenza vaccination programme averts a considerable number of influenza-related hospitalisations and deaths, as it directly targets the groups with highest morbidity and mortality. However, evidence from practice that vaccination has changed observed time series of outcomes is weak, due to variability in influenza seasons and changing circumstances.

## 7 Cost-effectiveness of vaccination

### Summary

#### ***Maternal influenza vaccination***

No cost-effectiveness study of maternal influenza vaccination in the Netherlands is available. Cost-effectiveness studies from England and Wales and from Belgium estimated that, from a healthcare payer's perspective, the incremental cost-effectiveness ratio (ICER) of influenza vaccination of healthy pregnant women was between €6,000 and €26,000 per quality-adjusted life year (QALY) gained, which was cost-effective according to each country's national threshold. This conclusion did not change when the efficacy transfer to newborns was excluded. Whether maternal vaccination would be cost-effective in the Netherlands is unclear, as the Dutch conventional cost-effectiveness threshold of €20,000 per QALY gained falls within this estimated range. Moreover, the studies deviate in some aspects from the Dutch cost-effectiveness guidelines with regard to study perspective, discount rates and included cost components. Finally, timing of vaccination seems important, as vaccination was only cost-effective in England and Wales for pregnant women who were vaccinated in their second or third trimester during the months September to December.

#### ***Childhood influenza vaccination***

A dynamic modelling study from the Netherlands estimated that the cost effectiveness of influenza vaccination of children aged 2-16 years was on average €57,045 per QALY gained when health outcomes of the children themselves were accounted for. On average it was €3,944 per QALY gained when health outcomes of the entire population were accounted for when a societal perspective was adopted. This would not be cost-effective for the threshold of €20,000 per QALY gained for the children themselves, but it would be cost effective for the entire population (the latter finding is consistent with cost-effectiveness analyses from other European countries). This discrepancy arises because the main health benefits of childhood vaccination go to the elderly through herd-immunity. Childhood vaccination was also predicted to increase the number of severe influenza seasons, which may lead to problems with a peak demand that may exceed available healthcare capacity. Moreover, this analysis found a non-negligible risk of an unintended perverse outcome, where the overall quality of life will decrease after introduction of the childhood vaccination programme.

#### ***Current vaccination programme***

There are no peer-reviewed publications on the cost effectiveness of the current influenza vaccination programme in the Netherlands. A Dutch cost-effectiveness study that was not peer-reviewed but mentioned in a previous report of the Health Council of the Netherlands in 2007 found that vaccination of persons aged 60 to 64 years was cost effective from a societal perspective, with a corresponding ICER of €15,810 per QALY gained. However, due to the use of a static model, no potential herd effects were included. A static modelling study from Belgium estimated the cost effectiveness of vaccination of high-risk individuals under 65

years of age to be between €14,378 and €24,768 per QALY gained, depending on age. This was cost effective to Belgium's national threshold. Dynamic modelling studies from England and Wales and from Finland found that vaccination of older adults and high-risk patients was highly cost effective as compared to each country's threshold. A recent dynamic modelling study from England and Wales estimated that the cost effectiveness of vaccinating healthy older adults may cease after introduction of the childhood influenza programme due to reduced circulation of the virus. Since 2016, the Dutch cost-effectiveness guideline recommends including so-called indirect healthcare costs (those unrelated to influenza in gained life-years). This has not been taken into account in any published study, but is expected to have considerable impact on the cost effectiveness of the current influenza vaccination programme.

#### ***Quadrivalent influenza vaccine***

No cost-effectiveness study of the quadrivalent influenza vaccine (QIV) as compared to the trivalent influenza vaccine in the Netherlands is available. Results from other European studies suggest that a switch from TIV to QIV is likely to be cost effective according to national thresholds. However, these studies may have limited validity in the Dutch context due to methodological differences such as perspective, discounting and included cost components. A major limitation is that no high-quality data exist on the additional efficacy that QIV provides over TIV. Therefore, all studies have had to estimate the difference, using biologically plausible assumptions. The cost effectiveness depends highly on the vaccine price of QIV. A dynamic modelling study from England estimated that the maximum possible vaccine price to be cost-effective for a threshold of £20,000 per QALY gained was substantially higher for children than older adults, given the relatively higher influenza B burden in children and the herd immunity that is offered by vaccination of this target-group.

## **GLOSSARY**

### ***Cost-effectiveness analysis***

Cost-effectiveness analyses give important information on the efficiency of healthcare interventions by comparing relative costs and outcomes (effects). Consistent evaluation of cost effectiveness over the disease trajectory from prevention to care may provide useful data to support the setting of healthcare priorities.

### ***Quality-adjusted life year***

The quality-adjusted life year (QALY) is often used as a generic measure of effect in cost-effectiveness analysis. It includes both the quality and the quantity of life lived. One QALY is equal to 1 year of life in perfect health. QALYs are calculated by estimating the years of life remaining for a patient following a particular treatment or intervention and weighting each year with a quality-of-life score (on a 0 to 1 scale).

### ***Costs***

Costs are usually distinguished between 1) healthcare costs (e.g. costs of GP visits and hospitalisations), 2) patient costs (e.g., costs of traveling and over-the-counter medication) and 3) productivity losses

(e.g., costs of sick workers who are absent or those who are present but less productive). Since 2016, the Dutch guideline of cost effectiveness in healthcare research recommends including indirect healthcare costs in the cost-effectiveness analysis. These include costs of healthcare use unrelated to the disease that occur during the life-years gained because of the intervention. This approach may have substantial impact on the cost effectiveness of interventions against diseases with considerable mortality, such as influenza. Historically, Dutch analyses and analyses from other countries do not usually include indirect healthcare costs.

### ***Perspective***

The perspective of the analysis determines which costs are included. The two perspectives most often used are that of the healthcare payer, which includes only healthcare costs, and that of society, which includes healthcare costs, patient costs and productivity losses.

### ***Discounting***

Discounting is used to account for time preference, as future costs and effects are valued at less than current costs and effects. The Dutch guideline recommends the use of differential discount rates of 4% per year for costs and 1.5% per year for effects. Most other countries recommend equal discount rates for costs and effects. Use of a higher discount rate for costs than for effects usually results in more optimistic cost-effectiveness outcomes compared to the use of equal discount rates for costs and effects.

### ***Incremental cost-effectiveness ratio***

The incremental cost-effectiveness ratio (ICER) is calculated as follows:

$$ICER = \frac{(Costs_{New\ strategy} - Costs_{Current\ practice})}{(Effects_{New\ strategy} - Effects_{Current\ practice})}$$

### ***Cost-effectiveness threshold***

Interventions are considered cost effective when the ICER falls below the cost-effectiveness threshold. In the Netherlands, no official threshold exists, but the conventional threshold for preventive interventions such as influenza vaccination is €20,000 per QALY gained. For therapeutic interventions, higher thresholds of €50,000 to €80,000 per QALY gained are used. Cost-effectiveness thresholds differ among countries.

### ***Probabilistic sensitivity analysis***

Probabilistic sensitivity analysis is a recommended technique to quantify the level of confidence of the model output in relation to uncertainty in the model inputs. Sets of parameter values are repeatedly (typically 1,000-10,000 times) drawn by random sampling from each input distribution,\* and outputs (costs and effects) are stored. Results can be visualized in a cost-effectiveness plane, and the proportion of cost-effective simulations can be analysed over a range of thresholds (cost-effectiveness acceptability curve).

## **7.1 Cost-effectiveness of maternal vaccination**

No cost-effectiveness analysis of maternal influenza vaccination for the Dutch context is available in the literature. There are, however, two

cost-effectiveness studies available from other countries in Western Europe (Table 7.1).

A study from a healthcare payer's perspective by Jit *et al.* [296] for England and Wales in 2010 estimated the incremental cost-effectiveness ratio (ICER) of maternal vaccination in the second or third trimester at £23,000 (approx. €26,000) per quality-adjusted life year (QALY) gained, when vaccination occurred in the period of September to December. This was not cost-effective to a threshold of £20,000 per QALY gained, but cost-effective to a threshold of £30,000 per QALY gained. The probabilistic sensitivity analysis showed that 69% of the simulations were cost-effective to a threshold of £30,000 per QALY gained. Sensitivity analysis for the period of administration concluded that vaccination outside the period September to December \* was not likely to be cost-effective to this threshold. The analysis assumed a relatively high vaccine efficacy of 80% for pregnant women themselves, and an influenza risk reduction of 71% for their children aged 1-6 months. Excluding the efficacy transfer to children increased the ICER to €28,000 per QALY gained. As pregnant women are not expected to receive a vaccination invitation in the next year, the ICER would decrease to £15,000 per QALY gained when the efficacy in the second year was assumed to be half of the efficacy in the first year. A limitation of this study is that the loss of QALYs due to fetal death was not taken into account.

Also from a health payer's perspective, a study by Blommaert *et al.* [295] for Belgium in 2014 found that the ICER of maternal influenza vaccination in the second or third trimester was €6,616 per QALY gained. This was highly cost effective to Belgium's threshold of €35,000 per QALY gained. The probabilistic sensitivity analysis (PSA) demonstrated that all simulations were below a threshold of €35,000 per QALY gained. The analysis assumed vaccination in mid-November, a vaccine efficacy of 59% for pregnant women and an efficacy transfer from mother to newborn of 50%. Excluding the transfer of vaccine efficacy to the child would double the ICER to approximately €13,000 per QALY gained.

Whether maternal vaccination would be cost effective in the Netherlands is unclear, as the Dutch conventional cost-effectiveness threshold of €20,000 per QALY gained falls within the estimated range of €6,600-€26,000 per QALY gained. Moreover, the Dutch guidelines deviate to some extent from the methodology used in the above studies, as they recommend the inclusion of indirect healthcare costs and the use of a societal perspective. A limitation in both studies is that the potential efficacy transfer from the mother to the newborn seems to be overestimated, as recent clinical trials found an efficacy transfer to infants during the first 6 months of age between 30 to between 30% and 49% [320]. However, both studies estimated that maternal influenza vaccination remained cost effective when the efficacy transfer to newborns was excluded.

Table 7.1 Overview of European studies on the cost effectiveness of vaccination of pregnant women against influenza.

Study	Country	Model type	Analysed population	Comparison	Time-horizon / discount rate	Perspective	Cost items	Health outcomes	Vaccine costs per individual	Cost effectiveness (Cost per QALY gained)
<b>Jit, 2010 [296]</b>	England & Wales	Static	Pregnant women 15-49y	Vaccination of high-pregnant women <i>versus</i> no vaccination	2y / 3.5% for costs and health effects	NHS	Vaccine, administration, GP visits, hospitalisations	QALYs	£13.54	£23,000
<b>Blommaert, 2014 [295]</b>	Belgium	Static	Pregnant women 15-44y	Vaccination of pregnant women <i>versus</i> vaccination of high-risk pregnant women only	1y / 3% for costs and 1.5% for health effects	HCP	Vaccine, GP visits, hospitalisations, deaths	QALYs and life-expectancy	€11.81	€6,616

HCP: Healthcare payer's perspective, NHS: National health service, QALY: Quality-adjusted life year, GP: general practitioner, y: year(s)

## 7.2 Cost effectiveness of childhood influenza vaccination

**7.2.1** *Cost effectiveness of childhood influenza vaccination in the Netherlands*

De Boer et al. assessed the cost effectiveness of a childhood influenza vaccination programme using quadrivalent live attenuated influenza vaccine (Q-LAIV) in the Netherlands (submitted manuscript). Two other unpublished studies also assessed the cost effectiveness of childhood influenza vaccination in the Netherlands. First, in the European project I-MOVE+ the cost effectiveness of this vaccination was assessed for several countries using the model by Baguelin *et al.* [292]. Second, at the University of Groningen the paediatric programme was studied with an adapted version of the model by Pitman *et al.* [306]. As these studies have not yet been submitted, we focus in this document on de Boer et al. Their cost-effectiveness study relied on a dynamic transmission model developed by Backer *et al.* [321] (see paragraph 6.2.1). More details of the cost-effectiveness analysis are given in Table 7.2. The cost-effectiveness analysis was conducted according to the Dutch guideline on health health-economic evaluations, as the societal perspective was used and indirect healthcare costs were included.

*Table 7.2 Main study characteristics and parameter inputs of the cost-effectiveness study of childhood influenza vaccination in the Netherlands*

Study characteristic	Input
<b>Publication of underlying transmission model</b>	Backer et al. 2018 (Netherlands) [294, 321]
<b>Model type</b>	Dynamic, compartmental
<b>Model features</b>	(+) Multiseason dynamics (+) Variability between seasons (-) Subtype specific
<b>Calibration</b>	Influenza-associated GP visits using ILI notifications and viral data from the period 2004-2015 and effectiveness estimates from literature
<b>Time horizon</b>	20 years (annual time-steps)
<b>Discount rates</b>	4% for costs, 1.5% for health effects
<b>Perspective</b>	Societal
<b>Target groups</b>	Children 2-3, 2-12, 2-16 years
<b>Vaccine type</b>	Q-LAIV
<b>Coverage for children</b>	50%
<b>Vaccination costs</b>	€14.95
<b>Included disease-related cost components</b>	
<b>Healthcare costs</b>	GP visits (including prescribed drugs and specialist visits), hospitalisations, indirect healthcare costs
<b>Patient costs</b>	OTC medication, travel costs
<b>Productivity losses</b>	Influenza cases and caregivers of children aged 0-14
<b>QALY losses</b>	Cases, GP visits, hospitalisations, deaths

GP: General practitioner, ILI: Influenza-like-illness, Q-LAIV: Quadrivalent live-attenuated vaccine, HCP: Healthcare payer's perspective, OTC: over the counter

The impact of vaccination of children aged 2-16 years at 50% coverage is shown in Table 7.3. Across 1,000 simulations, extension of current



policy with childhood influenza vaccination resulted in an average annual reduction of 57,266 cases in the general population, preventing 1,288 hospitalisations and 318 influenza deaths. Among children aged 2-16 years, 31,522 cases, 615 hospitalisations and 0.5 deaths were prevented, representing 55% of the total number of averted cases, 48% of the total number of averted hospitalisations and 0.1% of the total number of averted deaths. With regard to cost-effectiveness outcomes, the total discounted net costs increased by €182 million over a period of 20 years. Vaccination costs and healthcare costs in gained life years increased by €286 million and €355 million, respectively, whereas the direct healthcare costs, patient costs and productivity losses decreased by €69 million, €86 million and €303 million, respectively. The total number of discounted QALYs gained was estimated at 43,512, predominantly due to averted mortality. When only outcomes among children aged 2-16 years were considered, the total discounted net cost was €149 million, and the total number of discounted QALYs gained was 2,611.

*Table 7.3 Main model outcomes of a childhood influenza vaccination programme for children aged 2-16 years at 50% coverage in the Netherlands over 20 years. Outcomes are averaged across 1,000 simulations. Costs and QALYs include an annual discount rate of 4% and 1.5%, respectively.*

Outcome	Within total population	Within children aged 2-16y
<b>Average annual clinical outcomes as compared to the current programme (percentage)</b>		
<b>Symptomatic cases</b>	57,266 (18%)	31,522 (36%)
<b>GP visits</b>	13,352 (19%)	7,628 (37%)
<b>Hospitalisations</b>	1,288 (17%)	615 (42%)
<b>Deaths</b>	318 (10%)	0.5 (29%)
<b>Total cost difference (€, millions)</b>	172	149
<b>Vaccination costs (€, millions)</b>	286	286
<b>Direct HC costs (€, millions)</b>	-69	-26
<b>Indirect HC costs (€, millions)</b>	344	0
<b>Patient costs (€, millions)</b>	-86	-47
<b>Productivity losses (€, millions)</b>	-303	-64
<b>Total QALY difference</b>	-43,512	-2,611
<b>QALYs illness</b>	-4,163	-2,277
<b>QALYs mortality</b>	-39,350	-334

Y: years, GP: General practitioner, HC: Healthcare, QALY: Quality-adjusted life year

The cost-effectiveness results by age group are presented in Table 7.4. Vaccination of children aged 2-16 years dominated scenarios of vaccination of children aged 2-3 years and 2-12 years due to a higher QALY gain against a lower ICER. The average ICER of vaccination of children 2-16 years, compared to current practice, was estimated at €3,944 per QALY gained, which was cost effective to the conventional Dutch threshold of €20,000 per QALY gained. When only outcomes in children aged 2-16 years were considered, the ICER of vaccination of children aged 2-16 years was on average €57,054 per QALY gained, which was not cost effective.

Table 7.4 Cost-effectiveness outcomes of childhood influenza vaccination in the Netherlands over 20 years. Outcomes are averaged across 1,000 simulations. Costs and QALYs include an annual discount rate of 4% and 1.5%, respectively.

Scenario	Total costs (€, millions)	Total QALY loss (thousands)	Incremental costs (€, millions)	QALYs gained (thousands)	ICER (€ per QALY gained)
<b>Within total population</b>					
Current programme (CP)	4,127	432.9			
CP + 2-3y	4,150	431.1			Ext. dominance*
CP + 2-12y	4,230	407.2			Ext. dominance*
CP + 2-16y	4,299	389.4	172	43.5	3,944
<b>Within children aged 2-16y</b>					
Current programme (CP)	390	7.32			
CP + 2-3y	416	7.05			Ext. dominance*
CP + 2-12y	510	5.60			Ext. dominance*
CP + 2-16y	539	4.71	149	2.61	57,054

\*A strategy was considered dominant when there was a more effective strategy at lower costs (strict dominance) or lower ICER (extended dominance). ICER: Incremental cost-effectiveness ratio, QALY: Quality-adjusted life year, y: years

The probability sensitivity analysis demonstrated high uncertainty around the absolute impact of the childhood vaccination programme, when outcomes in the entire population were considered. Measured over 20 seasons, the majority of simulations (93.4%) showed that vaccination of children aged 2-16 years was more effective against higher costs, whereas there was a small probability (0.2%) that childhood vaccination was more effective against lower costs (Figure 7.1). However, 6.4% of the simulations showed that introducing a childhood influenza vaccination programme was less effective than the current influenza programme, resulting in a net loss of QALYs.

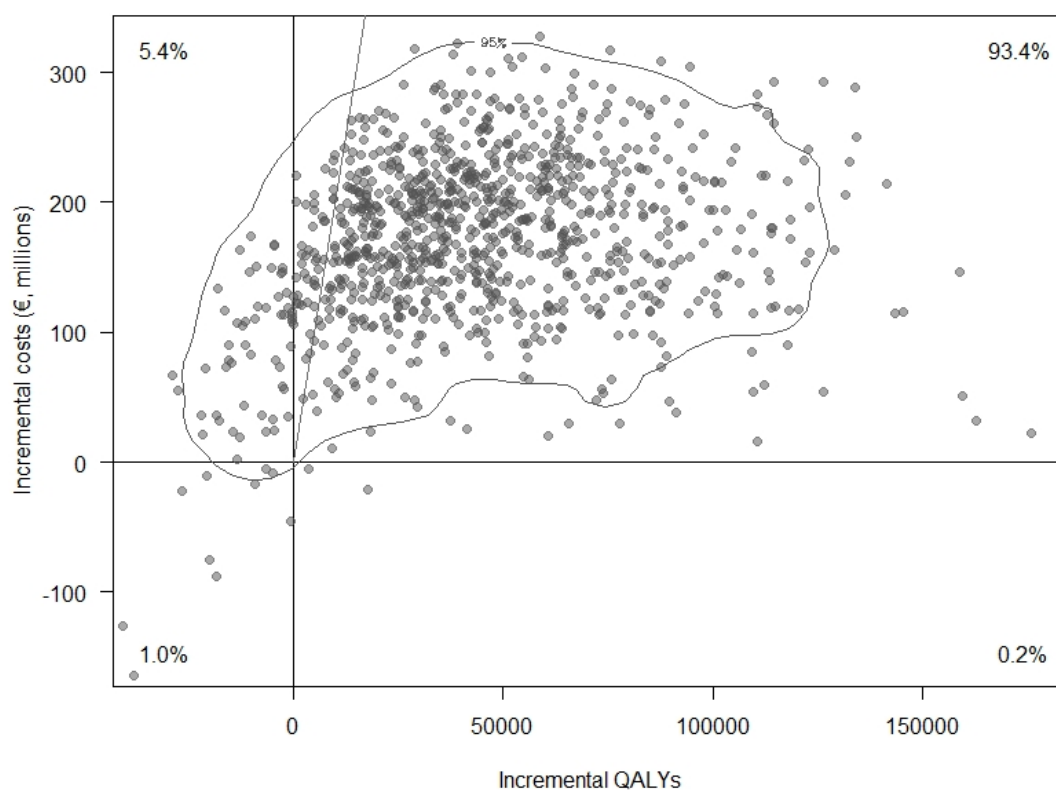


Figure 7.1 Probabilistic sensitivity analysis with 1,000 simulations of vaccination of children aged 2-16 years at 50% coverage in the Netherlands over 20 years. Costs and QALYs include an annual discount rate of 4% and 1.5%, respectively. QALY: Quality-adjusted life year

The cost-effectiveness acceptability curve demonstrates that the current program has the highest probability of being the most cost-effective alternative below a threshold of €5,007 per QALY gained, whereas vaccination of children aged 2-16 years is the most cost effective above this threshold (Figure 7.2). At the conventional threshold of €20,000 per QALY gained, confidence that vaccination of children aged 2-16 years is the most cost-effective alternative is 89%.

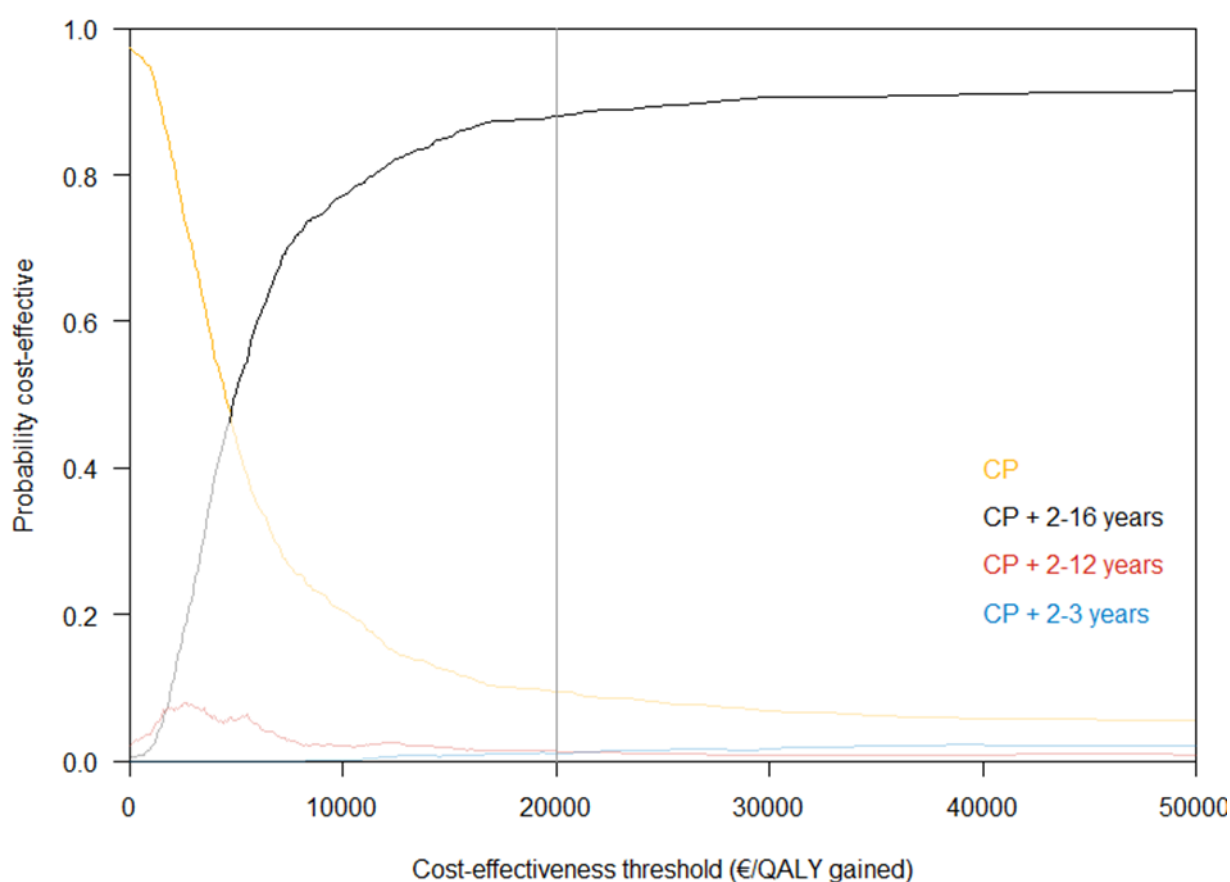


Figure 7.2 Cost-effectiveness acceptability frontier with 1,000 simulations of several childhood influenza vaccination programmes at 50% coverage over 20 years. Costs and QALYs include an annual discount rate of 4% and 1.5%, respectively. CP: Current programme, QALY: Quality-adjusted life year

A univariate sensitivity analysis demonstrated that the coverage in healthy children had limited impact on the ICER, although the absolute impact increased substantially when higher coverages were used. The highest impact on the ICER was found when indirect healthcare costs were excluded in the analysis, changing the average ICER to saving costs as compared to the current programme.

As explained in paragraph 6.2.1, the dynamic model predicted that a childhood influenza vaccination programme would lead to increased variability in size of epidemics. The cost-effectiveness analysis demonstrated that the programme would increase the number of seasons with large influenza epidemics in 23.3% of the simulations. Here, a season with large influenza epidemics was defined as an IAR higher than any observed in the 11 seasons used to calibrate the model. Figure 7.3 shows how the increase of the number of seasons with large influenza epidemics corresponds to the gain of QALYs over 20 seasons. We found that simulations with a higher increase in the number of seasons with large epidemics on average resulted in a lower QALY gain. Furthermore, simulations with an increase in the number of seasons with large influenza epidemics resulted more often in a net QALY loss compared to seasons with no such increase. This suggests that the

health burden in seasons with large epidemics offset the alleviated health burden in the seasons with small epidemics.

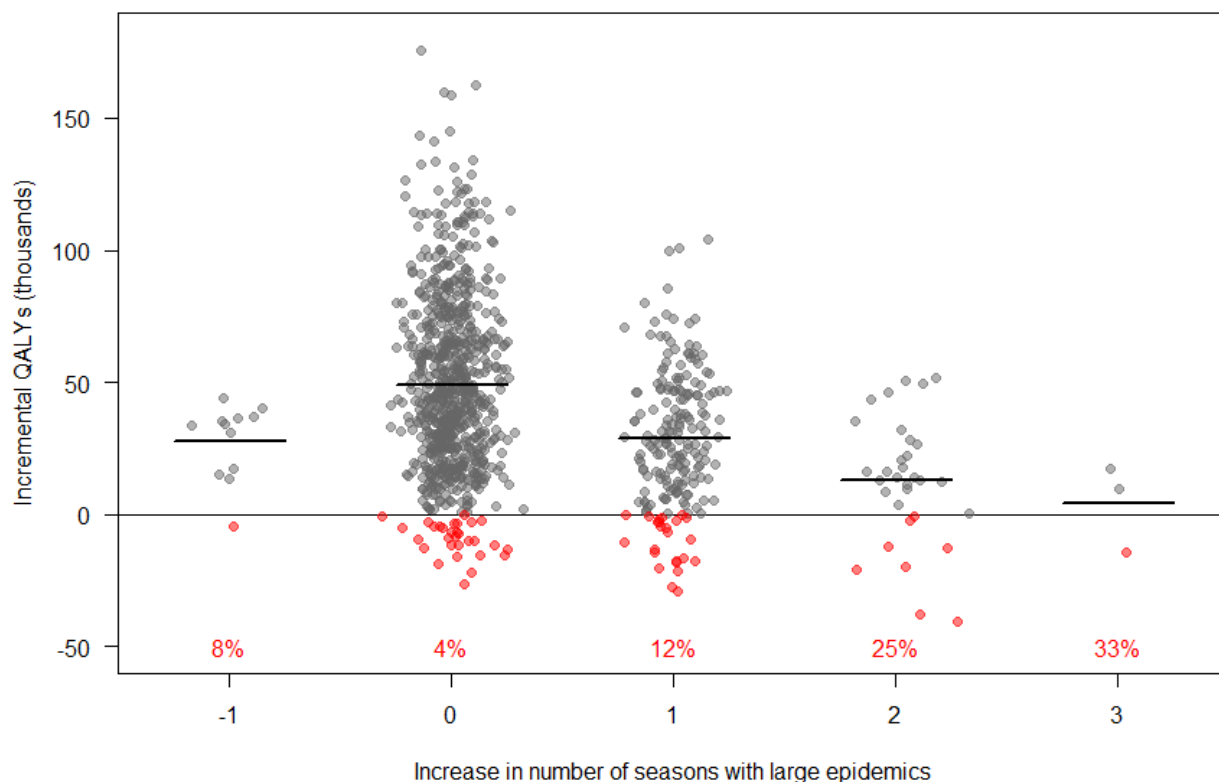


Figure 7.3 Relation between the increase in number of seasons with large influenza epidemics and the incremental quality-adjusted life years (QALYs) following a childhood influenza vaccination programme for children aged 2-16 years at 50% coverage. Results are based on 1,000 simulations of a probabilistic sensitivity analysis. A time horizon of 20 years was used, and costs and QALYs include an annual discount rate of 4% and 1.5%, respectively. Red dots represent 6.4% of the 1,000 simulations that resulted in an overall QALY loss. Red percentages illustrate the proportion of red dots as compared to the total number of dots for that specific increase in the number of large seasons.

**In summary**, on average, the introduction of a childhood vaccination programme is cost effective only if evaluated for the entire population. For the children themselves, vaccination is not cost effective. Moreover, there may be a serious risk that a childhood vaccination programme could have an unintended perverse outcome wherein the overall quality of life would decrease after introduction of the programme due to an increase in severe epidemics.

### 7.2.2

#### *Cost effectiveness of childhood influenza vaccination in other European countries*

Table 7.5 shows an overview of European studies that assessed the cost effectiveness of childhood influenza vaccination using a dynamic transmission model. Three studies were conducted for England and Wales, one study for Germany and one study for Belgium. More details on the epidemiological impact of these studies are available in paragraph 6.2.1.

Overall, the majority of studies found that childhood influenza vaccination was cost effective to the national threshold. A study by Pitman *et al.* [306] found that vaccination of healthy children aged 2-4, 2-10 or 2-17 years ranged between £128-365 per QALY gained from the healthcare payer's perspective, which was cost effective to a threshold of £20,000 per QALY gained. In addition, they found that vaccination with LAIV for children aged 2-4 years was cost-saving, and that strategies with LAIV dominated strategies with TIV (higher QALY gain against lower costs). This was explained by higher efficacy for LAIV compared to TIV, while the vaccine prices were assumed to be equal.

Vaccination was also found to be cost effective (£2,314-5,561 per QALY gained) when only the impact among children aged 2-18 years was considered. A study from the Belgian Healthcare Knowledge Centre (KCE) [322] estimated that vaccination of children aged 12-17, 5-17 and 2-17 years with LAIV ranged between €42,046-44,415 per QALY gained from a healthcare payer's perspective. This was not cost effective to a threshold of €35,000 per QALY gained. The ICER was relatively higher than that found in the study by Pitman *et al.* due to a more conservative assumption regarding the duration of protection of vaccination, which resulted in a lower impact of vaccination and a lower QALY loss per illness. A study by Baguelin *et al.* [323] for England and Wales estimated the ICER of vaccination of children aged 2-4 years, 5-16 years and 2-16 years with LAIV at £1,745-2,612 per QALY gained, from the healthcare payer's perspective, which was cost effective to a threshold of £20,000 per QALY gained.

The most cost-effective policy was vaccination of children 5-16 years old, and childhood vaccination policies were found to be more cost effective than vaccination of older adults and high-risk groups. Vaccination was also cost effective for children aged 2-16 years (£7,713 per QALY gained), when herd effects for other age groups were excluded. A study by Damm *et al.* [324] for Germany found that vaccination of children aged 2-17 years with LAIV was highly cost effective from the healthcare payer's perspective (€1,228-2,265 per QALY gained, depending on cost components included), while vaccination from a societal perspective was cost-saving. Finally, a study by Thorrington *et al.* [325] for England and Wales found that vaccination of children aged 4-10, 11-16 or 4-16 years using LAIV was cost effective from the National Health Service (NHS) perspective (£3,117-16,152 per QALY gained). These findings represent the optimum findings over a range of uptake rates.

Table 7.5 European studies assessing the cost effectiveness of extending the existing programme with vaccination of healthy children

Study	Country	Model type	Comparison	Target group	Vaccine type / uptake	Time horizon / discount rate	Perspective	Vaccination cost per dose <sup>a</sup>	ICER in overall population <sup>b</sup> (Costs per QALY gained)	ICER in target population (Costs per QALY gained)
<b>Pitman et. 2013 [306]</b>	England and Wales	Dynamic	Vaccination for all children <i>versus</i> high-risk children only	2-18y	TIV or LAIV / 50%	200 years / 3.5% for costs and effects	NHS	£38.60 for either TIV or LAIV	TIV: 2-4y: £128 2-10y: £361 2-17y: £365 LAIV: 2-4y: Cost-saving 2-10y: £226 2-17y: £253	TIV: 2-4y: £2,936 2-10y: £4,551 2-17y: £5,561 LAIV: 2-4y: £2,314 2-10y: £4,075 2-17y: £5,305
<b>KCE report, 2013 [322]</b>	Belgium	Dynamic	Vaccination for all children <i>versus</i> high-risk children only	2-17y	LAIV / 50%	NR / 3% costs and 1.5% effects	HCP	€35.13	LAIV: 12-17y: €42,046 5-17y: €44,260 2-17y: €44,280 TIV in <2y and LAIV in 2-17y: €44,415	NR
<b>Baguelin et al. 2015 [323]</b>	England and Wales	Dynamic	Vaccination for all children <i>versus</i> high-risk children only	2-16y	LAIV / 50%	1 year / 3.5% for costs and effects	NHS	£15.85	2-4y: £2,612 5-16: £1,745 2-16: £1,949	2-16: £7,713
<b>Damm et al. 2015 [324]</b>	Germany	Dynamic	Vaccination for all children <i>versus</i> high-risk children	2-17y	LAIV / 50%	10 years / 3% for costs and effects	HCP, HCP broad <sup>b</sup> , societal	€26.67	TPP small: €2,265 TPP broad*: €1,228 Societal: Cost-saving	NR

Study	Country	Model type	Comparison	Target group	Vaccine type / uptake	Time horizon / discount rate	Perspective	Vaccination cost per dose <sup>a</sup>	ICER in overall population <sup>b</sup> (Costs per QALY gained)	ICER in target population (Costs per QALY gained)
			only							
<b>Thorrington et al. 2017 [325]</b>	England and Wales	Dynamic	Vaccination for all children <i>versus</i> high-risk children only	4-16y	LAIV / 0-100	1 year / 3.5% for costs and effects	NHS	£17.03	4-10y: £3,117 (100% uptake) <sup>c</sup> 11-16y: £4,280 (100% uptake) <sup>c</sup> 4-16y: £16,152 (48% uptake in 4-10y, 34% uptake in 11-16y) <sup>c</sup>	NR

<sup>a</sup>Includes vaccine cost and administration costs, <sup>b</sup>HCP broad includes also childcare sickness benefits, <sup>c</sup>Reflects the optimal policy from cost-effectiveness point of view. HCP: Healthcare payer, NHS: National Health Service, NR: Not reported, QALY: Quality-adjusted life year; TIV: trivalent influenza vaccine; LAIV: live attenuated influenza vaccine, Y: year(s), ICER: incremental cost-effectiveness ratio, TPP: Third-party payer



### 7.3 Cost effectiveness of the current vaccination programme

No study is available in the literature on the cost effectiveness of the current Dutch influenza vaccination programme, i.e., vaccination of older adults aged  $\geq 60$  years and individuals aged  $< 60$  years with clinical risk conditions. However, a Dutch study was conducted on the cost effectiveness of programmes in healthy adults aged 50-64 years, and studies from other European countries have evaluated programmes similar to that of the Dutch (Table 7.6). Meijboom *et al.* [326] used a static model to assess the cost effectiveness of vaccination of healthy adults aged 50-64 years in the Netherlands. The authors reported that vaccination of this target group would annually prevent 26 deaths and 103 acute cardiovascular events. The ICER of vaccination of healthy adults aged 50-64 years was €17,418 per QALY gained, from a healthcare payer's perspective, and €14,926 per QALY gained from a societal perspective. Stratification by age showed that vaccination of adults aged 60-64 years was most cost-effective with an ICER of €11,539 per QALY gained from a healthcare payer's perspective and €9,860 per QALY gained from a societal perspective.

Table 7.6 lists also cost-effectiveness studies of target-groups that are currently included in the influenza vaccination programme from other European countries. A study from Belgium using a static model assessed the cost effectiveness of a programme including individuals with clinical risk conditions, from a healthcare payer's perspective [295]. With a relatively high vaccination cost of €35.13 per person, the ICER was estimated at €22,008, €24,768 and €14,378 per QALY gained as compared to no vaccination for individuals aged 0-14, 15-49 and 50-64 years, respectively. This would be cost effective to the Belgian threshold of €35,000 per QALY gained.

Three dynamic modelling studies from England and Wales analysed the cost effectiveness of a vaccination programme for older adults  $\geq 65$  years and individuals aged  $< 65$  years with clinical risk conditions. A study by Baguelin *et al.* in 2012 found that such a programme would lead to a 28% reduction in influenza incidence with a good vaccine match and a 9% reduction with a poor vaccine match, as compared to no vaccination. More than half of the prevented cases occurred in the non-targeted population via herd immunity. From the perspective of the National Health Service, the cost effectiveness of the programme at that time, in a season with a good vaccine match, was estimated at £6,500 per QALY gained for high-incidence seasons and £24,700 per QALY gained for low-incidence seasons. In the event of a poor vaccine match, the ICER was estimated at £19,400 per QALY gained for high-incidence seasons and £72,100 per QALY gained for low-incidence seasons. This implies that the current programme would be cost effective to a threshold range of £20,000-£30,000 per QALY gained, except when the vaccine was poorly matched and the incidence was relatively low. In 2015, with use of the same model fitted to more influenza seasons, Baguelin *et al.* [323] estimated that the ICER of the current programme was on average £7,475 per QALY gained, which was regarded as highly cost effective. A study by Pitman *et al.* found that vaccination of adults aged  $\geq 65$  years and high-risk patients aged  $< 65$  years was cost saving. This more optimistic finding was presumably explained by the

assumption of a long duration of protection through vaccination. Nagy *et al.* [327] in Finland predicted that the cost-effectiveness of vaccinating adults aged  $\geq 65$  years, high-risk individuals aged  $< 65$  years and children aged 0.5-3 years would reduce influenza incidence by 25%. The ICER of this programme was estimated at €5,064 from a healthcare payer's perspective and €7,447 per QALY gained from a societal perspective. In a modelling study for England and Wales, Hodgson *et al.* [328] estimated the cost effectiveness of vaccinating the current target groups, i.e. clinical risk groups and all adults aged  $\geq 65$  years, after the childhood influenza programme was implemented. They found that vaccination of high-risk individuals remained cost effective to a threshold £20,000 per QALY gained in any scenario, but vaccination of low-risk elderly ceased to be cost effective when vaccination of children aged 2-16 years at 90% coverage was added (increase from £12,552 to £29,145 per QALY gained). This was explained by a lower IAR in older adults due to herd immunity resulting from the childhood programme.

The cost effectiveness of the current influenza vaccination programme for the Netherlands is unclear, as no evaluation has been performed. The existing literature suggests that vaccination of older adults and individuals with clinical risk conditions is cost effective. For instance, if vaccination of Dutch adults aged 60-64 appears to be cost effective from a healthcare payer's perspective, it seems highly likely that vaccination of adults  $\geq 65$  years of age is also cost effective due to their higher hospitalisation and mortality rates. Moreover, static models presumably underestimate the impact of vaccination, as herd immunity is not incorporated. A limitation is that indirect healthcare costs were not included, which does not align with the most recent Dutch cost-effectiveness guideline of 2016. Since the influenza-associated mortality among older adults is expected to be considerable, the inclusion of indirect healthcare costs may increase the ICER substantially. Studies from England and Wales may be regarded as conservative because of use of the healthcare payer's perspective, while the Dutch cost-effectiveness guideline recommend the use of societal perspective, which includes the prevention of productivity losses. Finally, the cost effectiveness of the current programme could be affected by a reduction in the spread of influenza resulting from the introduction of a childhood influenza programme. There are, however, no guidelines on how the cost effectiveness of existing vaccination policies should be evaluated.

Table 7.6: Overview of European studies on the cost effectiveness of vaccination of older adults and high-risk individuals.

Study	Country	Model type	Analysed population	Comparison	Time horizon / discount rate	Perspective	Vaccine costs per individual	Cost effectiveness (/QALY gained)
<b>Specific target groups</b>								
<b>Meijboom, 2007 [326]</b>	Netherlands	Static	Healthy adults 50-64y	Vaccination of older adults aged 50-64 years using TIV <i>versus</i> no vaccination	NS/NR?	HCP, societal	NR	HCP: 50-64y: €17,418 50-54y: €23,564 55-59y: €20,391 60-64y: €11,539 Societal: 50-64y: €14,926 50-54y: €20,036 55-59y: €17,756 60-64y: €9,860
<b>Blommaert, 2014 [295]</b>	Belgium	Static	<65y with underlying illnesses	Vaccination of high-risk individuals aged <65y with TIV <i>versus</i> no vaccination	1y / 3% for costs and 1.5% for health effects	HCP	€35.13	0-14y: €22,008 15-49y: €24,768 50-64y: €14,378
<b>Full programme</b>								
<b>Baguelin, 2012 [316]</b>	England & Wales	Dynamic	Total	Vaccination of older adults ≥65 years and individuals <65 years with risk conditions using TIV <i>versus</i> no vaccination	1y / 3.5% for costs and health effects	NHS	£16.37	Well matched: - High incidence: £6,500 - Low incidence: £24,700 Non-well matched: - High incidence: £19,400 - Low incidence: £72,100

Study	Country	Model type	Analysed population	Comparison	Time horizon / discount rate	Perspective	Vaccine costs per individual	Cost effectiveness (/QALY gained)
<b>Pitman, 2013 [306]</b>	England & Wales	Dyna mic	Total	Vaccination of older adults $\geq 65$ years and individuals $< 65$ years with risk conditions using TIV <i>versus</i> no vaccination	200y / 3.5% for costs and health effects	NHS	£38.60	Cost-saving
<b>Baguelin, 2015 [323]</b>	England & Wales	Dyna mic	Total	Vaccination of older adults $\geq 65$ years and individuals $< 65$ years with risk conditions using TIV <i>versus</i> no vaccination	1y / 3.5% for costs and health effects	NHS	£15.85	£7,475
<b>Nagy, 2016 [327]</b>	Finland	Dyna mic	Total	Vaccination of older adults $\geq 65$ years, individuals $< 65$ years with risk conditions and children 0.5-3 years using TIV <i>versus</i> no vaccination	20y / 3% for costs and health effects	HCP, societal	€11.21 for $< 65$ y and €11.34 for $\geq 65$ y	HCP: €5,064 Societal: €7,447
<b>Hodgson,</b>	England	Dyna	Total	Vaccination of	1y / 3.5% for	NHS	£15.55	Increase from £12,552 in

Study	Country	Model type	Analysed population	Comparison	Time horizon / discount rate	Perspective	Vaccine costs per individual	Cost effectiveness (/QALY gained)
2018 [328]	& Wales	mic		low-risk adults ≥65 years, individuals <65 years with risk conditions using TIV and children 2-16 years using LAIV <i>versus</i> vaccination of 2-16 years using LAIV only	costs and health effects			absence of vaccination to £29,145 in presence of vaccination of children aged 12-16 at 90% coverage

HCP: Healthcare payer, LAIV: Live-attenuated influenza vaccine, NHS: National Health Service, NR: Not reported, QALY: Quality-adjusted life year, TIV: Trivalent inactivated vaccine, y: year(s)

## 7.4 Cost effectiveness of quadrivalent influenza vaccine

Studies conducted in Europe were selected from a systematic review of the cost effectiveness of quadrivalent influenza vaccine [329] and updated with the latest literature (Table 7.7). No cost-effectiveness study has been published in the Dutch context, but nine other European studies have been conducted for the UK, Germany, Finland, Spain and Italy [327, 330-337]. Some studies used dynamic models that included indirect effects like herd immunity, whereas other studies used static models without herd effects. Most studies analysed the inactivated vaccine, but others focused on countries with childhood influenza vaccination recommendations (UK and Finland) and explored scenarios of LAIV for children. Overall, the relative reduction of influenza with quadrivalent vaccines as compared to trivalent vaccines varied from 0.67% in the UK to 11.3% in Finland. Dynamic models showed higher reductions as compared to static models due to the impact of herd effect. The systematic review of the cost effectiveness of quadrivalent influenza vaccines indicated that the inclusion of cross-protection, the level of influenza B circulation and the proportion of seasons with a mismatch between TIV and the circulating lineage are important to the impact of QIV as compared to TIV. Although the level of influenza B circulation and proportion of mismatches did not differ dramatically among European countries, assumptions on the level of cross-protection did. For instance, the high impact of QIV in Finland is explained by their not considering cross-protection in their analysis. Studies also show that the impact of QIV may differ by age group. A dynamic modelling study for England and Wales showed that a switch from LAIV to quadrivalent LAIV (Q-LAIV) for children aged 5-12 years was expected to reduce influenza incidence in the general population by 35%. This is explained by the relatively higher burden of influenza B in children and the level of indirect protection in the unvaccinated population that is provided by vaccination of children. After a switch to Q-LAIV for healthy children, the additional impact of changing from inactivated TIV to inactivated QIV for high-risk individuals aged <65 years was 7.5%, and for adults aged ≥65 years, it was 2.2%.

Regarding the cost-effectiveness outcomes, all studies showed results from a healthcare payer's perspective or that of the National Health Service (NHS), and five studies also showed results from a societal perspective. From a healthcare payer's perspective, the ICER of QIV as compared to TIV among static models ranged from €11,118 to £28,443 per QALY gained for various age groups, and a study from Italy found a higher ICER of €131,600 per QALY gained for older adults. The Italian study is explained by a relatively high vaccine price and a conservative estimate of influenza-associated mortality. Dynamic modelling studies showed relatively lower ICERs, ranging from €667 to €14,461 per QALY gained. Use of a societal perspective caused only a small decline in the ICER as compared to the healthcare payer's perspective in static models, as most of the studies focused on vaccination of non-working older adults. Dynamic models, however, found reductions of influenza through the entire population that included working adults. In these studies, a switch to the societal perspective lowered the ICER substantially. For instance, studies in Germany and Finland became cost-saving when the societal perspective was adopted. The study for

England and Wales included a threshold analysis, in which the maximum price difference between QIV and TIV was estimated to remain cost-effective for a threshold of £20,000 per QALY. For the switch of LAIV to Q-LAIV for healthy children aged 5-16 years, the vaccine cost per dose was allowed to increase by £6.36. Extension of this policy to a switch from inactivated TIV to inactivated QIV for high-risk individuals aged  $\leq 65$  years resulted in a maximum price increase of £1.84. The maximum price increase of a switch from inactivated TIV to inactivated QIV for adults aged  $\geq 65$  years was only £0.20.

In consideration of the results in the European literature, all except the Italian study by Capri *et al.* revealed that a switch from TIV to QIV was likely to be cost effective in all age groups according to the various national thresholds. Dynamic modelling studies showed more optimistic cost-effectiveness outcomes as compared to static studies. An age-stratified analysis for England and Wales demonstrated improved cost-effectiveness outcomes with a switch from LAIV to Q-LAIV for children as compared with a switch from TIV to QIV for older adults. Extrapolating results from other European studies to the Dutch setting is hampered by differences in cost-effectiveness guidelines, such as differences in perspective, discount rates and included cost components. For instance, the inclusion of indirect healthcare costs could have considerable impact on the ICER, as influenza is a disease with substantial mortality. Moreover, the vaccination coverage among children in Germany, Finland and the UK is higher than in the Netherlands, which may influence the cost effectiveness due to the herd immunity that children provide for the rest of the population.

Estimations from published studies include several limitations. A major limitation is that no studies have directly compared the efficacy between QIV and TIV. Most cost-effectiveness studies therefore estimated the efficacy of QIV by assuming that the matched efficacy of TIV is applicable to both influenza B lineages. However, there is much uncertainty surrounding the level of cross-protection that TIV provides to the non-included B lineage. Moreover, the level of cross-protection may differ by age group. For instance, a meta-regression study suggested that only young individuals benefit from QIV as older adults have high cross-protection due to existing immunity [338]. This phenomenon was not explored in any study. Finally, the cost effectiveness greatly depends on the price increase of QIV as compared to TIV. Therefore, most studies had to make assumptions on this aspect, as tendered prices of QIV are not yet available.

Table 7.7 Overview of European studies on the cost effectiveness of quadrivalent influenza vaccine as compared to trivalent influenza vaccine

Study	Country	Model type	Target group	Comparison	Time horizon / discount rate	Perspective	Cross-protection TIV	Incremental vaccine cost QIV	Reduction of influenza cases	Cost-effectiveness (/QALY gained) vs. TIV only
<b>Van Bellinghen, 2014 [330]</b>	UK	Static	Adults ≥65y, at risk <65y	TIV to QIV	Lifetime / 3.5% for costs and health effects	NHS	68%	£4.23 <sup>a</sup>	0.69%	£28,443
<b>Meier, 2015 [331]</b>	UK	Static	Adults ≥65y, at risk <65y	TIV to QIV	Lifetime / 3.5% for costs and health effects	NHS, societal	68%	£3.51	1.17%	NHS: £14,645 Societal: £13,497
<b>Thommes, 2015 [332]</b>	UK	Dynamic	All ages	LAIV to Q-LAIV for LR 2-17y; TIV to QIV for HR ≥18y	10y / 3.5% for costs and health effects	HCP	68%	£3.55	1.44%	£7,989
<b>Dolk, 2016 [333]</b>	Germany	Dynamic	All ages	TIV to QIV	20y / 3% for costs and 1.5% for health effects	TPP, societal	60%	€3.87	4.02%	HCP: €14,461 Societal: Cost-saving
<b>Garcia, 2016 [334]</b>	Spain	Static	Adults ≥65y, at risk <65y	TIV to QIV	Lifetime / 3% for costs and health effects	NHS, Societal	67%	€2.50	18,565 cases per average year	NHS: €11,188 Societal: €8,748
<b>Nagy, 2016</b>	Finland	Dynamic	All	S1: TIV to	20y / 3% for	HCP,	0%	€3.59 <sup>b</sup>	11.3%	HCP: S1:



Study	Country	Model type	Target group	Comparison	Time horizon / discount rate	Perspective	Cross-protection TIV	Incremental vaccine cost QIV	Reduction of influenza cases	Cost-effectiveness (/QALY gained) vs. TIV only
[327]			ages	QIV for all ages; S2: TIV to Q-LAIV for 2-17y, other age groups remain on TIV; S3: S2 + TIV to QIV for other age groups	costs and health effects	societal				€3933; S2: €5,667; S3: €6,077 Societal: S1-S3: Cost-saving
<b>Thorrington, 2017 [335]</b>	England & Wales	Dynamic	All ages	S1: LAIV to Q-LIAV for LR 2-11y S2: TIV to QIV for HR <65y, given that S1 is implemented S3: TIV to QIV for HR ≥65y given that S1 and	1y / 3.5% for costs and health effects	NHS	17%	Threshold incremental price to £20,000/QALY	S1: 35% S2: 7.5% S3: 2.2%	S1: £6.36 S2: £1.84 S3: £0.20

Study	Country	Model type	Target group	Comparison	Time horizon / discount rate	Perspective	Cross-protection TIV	Incremental vaccine cost QIV	Reduction of influenza cases	Cost-effectiveness (/QALY gained) vs. TIV only
				S2 are implemented						
<b>Mennini, 2018 [336]</b>	Italy	Static	Adults ≥65y, at risk <65y	TIV to QIV	1y / no discounting of costs, 3% for health effects	HCP, societal	67%	€5,69	5,870 cases per average year <sup>c</sup>	HCP: €23,426 Societal: €21,096
<b>Capri, 2018 [337]</b>	Italy	Static	Adults ≥65y	TIV to QIV	1y / no discounting	NHS	65%	€5,73	1.1% <sup>d</sup>	HCP: €131,600

<sup>a</sup>50% increase of QIV as compared to TIV, <sup>b</sup>50% increase of QIV of tendered TIV prices, <sup>c</sup>sum of avoided non-attending and GP attending cases, <sup>d</sup>based on the reduction in QALYs. HCP: Healthcare payer; HR: High-risk, LAIV: Live-attenuated vaccine, LR: Low-risk, NHS: National Health Service, QALY: Quality-adjusted life year, Q-LAIV: Quadrivalent live-attenuated vaccine, QIV: Quadrivalent inactivated vaccine, S: Strategy, TIV: Trivalent inactivated vaccine, y: year(s), TPP: third-party payer.

## 8 List of abbreviations

AAP	American Academy of Pediatrics
ACIP	US CDC and its vaccines advisory committee
ADEM	acute disseminated encephalomyelitis
AE	adverse event
AEFI	adverse event following immunisation
aIIV3	trivalent inactivated influenza vaccine containing the MF59 immunologic adjuvant
ARI	acute respiratory infection
CHD	coronary heart disease
CI	confidence interval
COPD	chronic obstructive pulmonary disorder
CTLs	cytotoxic T-cells
CVD	Cardiovascular disease
DALY	disability-adjusted life years
ELS	extensive limb swelling
EMA	European Medicines Agency
GA	gestational age
GBS	Guillain-Barre syndrome
GIVE	Global Influenza Vaccine Effectiveness
GP	general practitioner
HA	hemagglutinin
HCPs	healthcare providers
HD	High dose
HD-IIV3	a high-dose inactivated trivalent vaccine
HR	hazard ratio
IAR	infection attack rate
ICER	incremental cost-effectiveness ratio
ICU	intensive care unit
IIV	inactivated influenza vaccine
ILI	influenza-like illness
I-MOVE	Influenza Monitoring Vaccine Effectiveness
I-MOVE+	Integrated Monitoring of Vaccines in Europe
JCVI	Joint Committee on Vaccination and Immunisation
KCE	Belgian Health Care Knowledge Centre
LAIV	live-attenuated influenza vaccine
MS	multiple sclerosis
NA	neuraminidase
NHG	Dutch College of General Practitioners
NHS	National Health Service
NIC	National Influenza Centre
NIP	National Immunisation Programme
NICU	neonatal intensive care unit
NPG	Dutch National Influenza Prevention Programme
OR	odds ratio
PAD	peripheral arterial disease
PPV	polysaccharide pneumococcal vaccine
PREVENT	Pregnancy Influenza Vaccine Effectiveness Network
QALY	quality-adjusted life year
QIV/IIV4	quadrivalent inactivated influenza vaccine

Q-LIAV	quadrivalent live-attenuated influenza vaccine
RCT	randomised controlled trials
RIVM	National Institute for Public Health and the Environment
RIVM-Cib	Centre for Infectious Disease Control of the RIVM
RIVM-CvB	Centre for Population Screening of the RIVM
RIVM-DVP	Department for Vaccine Supply and Prevention Programmes of the RIVM
RIV4	recombinant quadrivalent influenza vaccine
RR	relative risk or risk ratio
RTIs	respiratory tract infections
SAE	serious adverse event
SD	standard dose
SD-IIV	standard dose-inactivated influenza vaccine
SLE	systemic lupus erythematosus
SNPG	National Influenza Prevention Foundation
TIV3	trivalent inactivated influenza vaccine
TND	test negative design
VE	vaccine effectiveness or efficacy
WHO	World Health Organisation

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