Extending Recommendations for Respiratory Vaccines:

Experimental and Non-Experimental studies

Extending recommendations for respiratory vaccines:
experimental and non-experimental studies

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Extending recommendations for respiratory vaccines:

experimental and non-experimental studies

Verruiming van de adviezen voor respiratoire vaccins:

experimentele en non-experimentele studies

(met een samenvatting in het Nederlands)

Proefschrift

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CHAPTER 1

General Introduction

Respiratory tract infections (RTI) continue to be the leading cause of acute illness worldwide.[1] With increasing knowledge about the etiology of RTI, attention has shifted from treatment to prevention of such infections. Influenza viruses and *Streptococcus pneumoniae*, both responsible for a vast part of respiratory morbidity in the population, are members of a selected group of pathogens causing RTI that may be vaccine-preventable. The main rationale behind implementing large-scale vaccination programs is both the prevention of serious infectious disease or its complications at an individual level and the prevention of an infectious disease that (potentially) strikes a large proportion of the population (See Box 1). Consequently, knowing the potentially vaccine-preventable burden in the population and the effects of the vaccine is of utmost importance to guide vaccine policy.

Box 1

Seven criteria to guide decision making regarding the inclusion of vaccinations into the national vaccination program:

1)	*The infectious disease leads to a substantial disease burden in the population:**
	a. *The infectious disease is severe for the individual, and:*
	b. *The infectious disease (potentially) strikes a large group of people*
2)	*Vaccination leads to a considerable reduction of the disease burden in the population.*
	a. *The vaccine is effective in preventing the disease or symptom reduction**
	b. *The needed vaccination coverage (when the aim is to exterminate the disease or herd immunity) is achieved.*
3)	*Any disadvantageous health effects of the vaccination are outweighed by its health gain in the population.*
4)	*The trouble experienced by the individual due to the vaccination itself is outweighed fairly by the health gain for the individual and the population as a whole.*
5)	*The trouble experienced by the individual due to the total vaccination program is outweighed fairly by the health gain for the individual and the population as a whole.*
6)	*The ratio between costs and health gain is favourable in comparison to other possible measures to reduce the burden of the disease.*
7)	*With the decision in favour of vaccination a (potentially) urgent public health matter is served.*

* Criteria addressed in this thesis.

Source: *Health Council of the Netherlands. The future of the national immunisation programme: towards a programme for all age groups. The Hague: Health Council of the Netherlands, 2007; publication no. 2007/02.*

The purpose of this thesis is to study possible extensions of the current vaccination recommendations for respiratory infections. The first part of the thesis describes studies that were initiated partly after incentives of the Health Council of the Netherlands. In the Netherlands, influenza vaccination is recommended for the elderly (≥ 65 years) and persons of any age with high-risk medical conditions like chronic respiratory and cardiac diseases, renal failure and certain immunodeficiencies.[2] In large parts of the world, however, recommendations for influenza vaccination are extending. For example, immunization guidelines from the United States have recently included otherwise healthy 50-64-year-olds and also healthy 6-59-month-olds.[3] In Canada even universal influenza vaccination has been introduced since a few years.[4] Most European countries have vaccination policies similar to the Dutch,[5] and like the other countries, the Netherlands are considering extending recommendations to include otherwise healthy persons younger than 65 years of age. In such a decision, information about the potentially vaccine-preventable burden of influenza in otherwise healthy individuals younger than 65 years of age in the Netherlands is essential. In the first part of the thesis, the influenza-attributable mortality, hospitalization and primary care consultations are estimated among otherwise healthy persons younger than 65 years of age, and especially 50-64-year-olds, using nationwide retrospective data covering multiple years.

The second part of this thesis describes studies on the prevention of RTI in preschool children, which particularly suffer from frequent RTI.[6-8] Attack rates of influenza have proven to be high in this age group.[9] However, few data from randomized controlled trials (RCTs) on the effects of influenza vaccination in preschool children are available.[10] Evidence suggests that influenza virus infections predispose to bacterial superinfection, in particular with *S.pneumoniae*, and that these pathogens interact synergistically.[11] In addition to influenza vaccination, RTI prevention through heptavalent pneumococcal conjugate vaccination (PCV-7) has increasingly gained attention. In the northern American countries, PCV-7 has been recommended for 2-59-month-olds since 2000,[12] and several studies suggest that PCV-7 not only prevents the majority invasive pneumococcal disease like septicemia and meningitis, but also reduces the incidence of pneumonia and acute otitis media (AOM).[13-16] For these reasons, the European Medicines Agency has recently extended the indications for PCV-7 to the prevention of pneumonia and AOM among 2-59-

month-olds.[17] However, studies on the effects of PCV-7 on RTI outside the age of infancy are very scarce and have important limitations in design, i.e. in most studies other designs than RCTs were used which may have led to biased estimates. In the Netherlands, PCV-7 was added to the infant immunisation schedule since April 2006, and no catch-up program was introduced for children less than six years of age.[18] The main aim of the second part of this thesis is to determine the effects of influenza vaccination with or without PCV-7 among preschool children in reducing the occurrence of RTI.

Part I

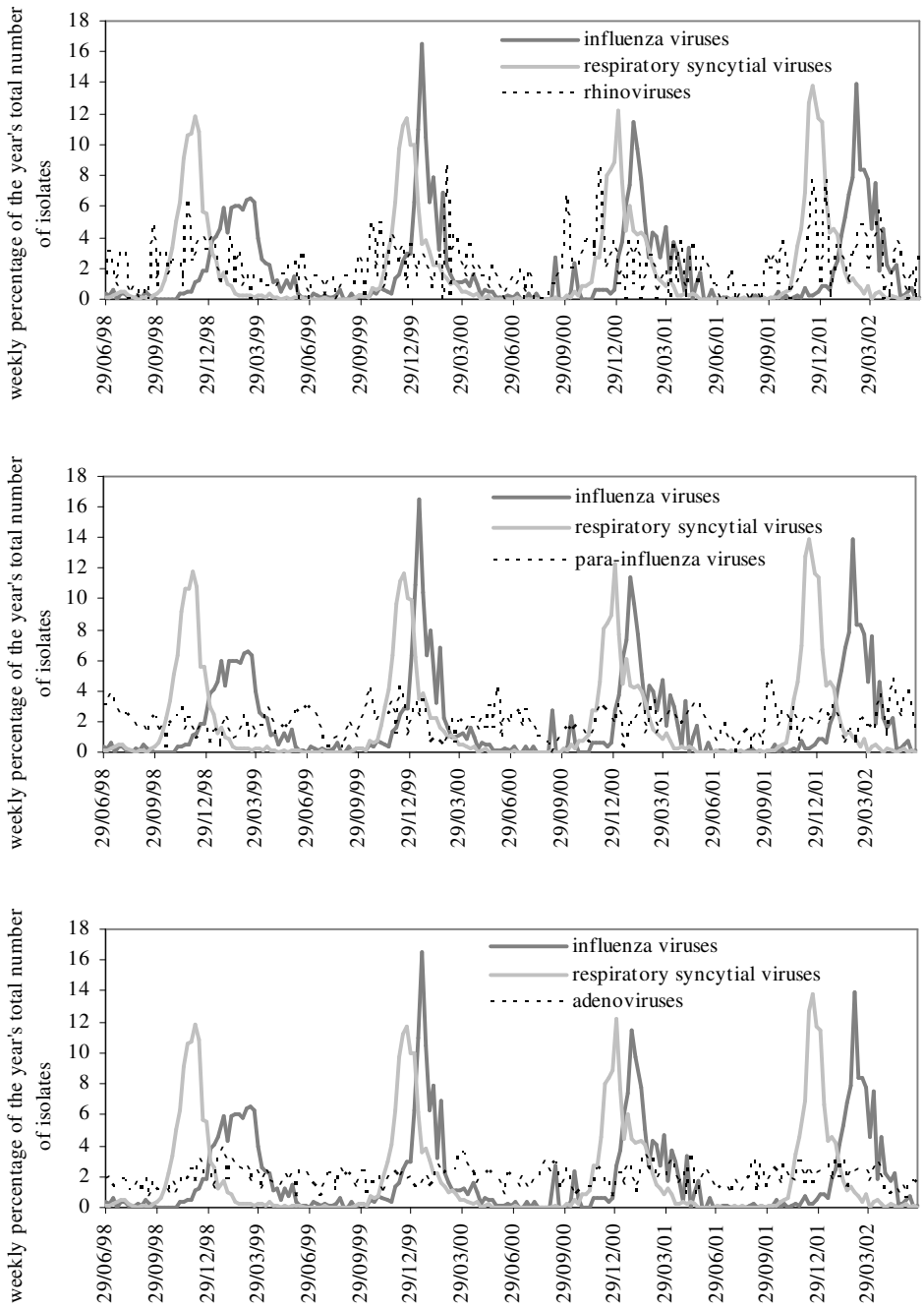
Influenza

Influenza, by people mainly considered a rather innocent illness involving some fever and cough, very much resembling the common cold, is probably one of the most underrated diseases. The most characteristic example of the unpredictable and insidious nature of influenza was the pandemic in 1918 with 50-100 million deaths worldwide, affecting not only elderly and individuals with co-morbid conditions, but also otherwise healthy young individuals.[19-21] The later influenza pandemics of 1957 and 1968 were of a lesser magnitude, but currently avian influenza viruses are a major concern as potential precursor viruses for new influenza pandemics.[22] Nevertheless, influenza viruses are active in smaller epidemics nearly every year and are held responsible for considerable mortality and morbidity.[23-25]

The burden of influenza is difficult to estimate and strictly impossible to measure directly. Influenza is often not clinically recognized, and influenza virus infections are virologically confirmed in only a minority of cases.[26,27] Moreover, influenza virus infections may predispose to secondary illness like bacterial infections and is also thought to trigger cardiovascular disease.[11,28-31] Consequently, direct assessment of the influenza-associated burden by determining the incidence of confirmed influenza, would considerably underestimate the true influenza-associated burden. Several models have been developed to estimate the influenza-associated burden, but these models vary widely in complexity and interpretation.

Earlier studies on influenza-associated disease burden in adults primarily focussed on influenza-associated mortality and morbidity among the elderly.[24,32-37] Only few studies estimated influenza-associated hospitalization among adults younger than 65 years,[25,38,39] and even less focussed on otherwise healthy adults.[40] In contrast, many studies assessed the influenza-associated burden in children, reporting 45 to 282 hospitalizations per 100,000 per year for children less than five years of age.[25,27,41-51] Variations in these estimates may have resulted from the highly variable influenza virus-activity throughout the years, but also from the geographic location, health care system and methods (models) applied to define influenza-associated disease burden. Inherent to modelling and thus indirect estimation is imprecision, and therefore variation appears inevitable. Also, many models estimate the influenza-associated burden by determining excess morbidity/mortality during influenza seasons compared with reference periods. This approach may be prone to disturbance by other seasonal phenomena. Particularly mentioned in this context is respiratory syncytial virus (RSV) which often co-circulates with influenza viruses, and infections with RSV clinically resemble influenza.[52,53] This co-circulation may confound estimations of influenza-associated burden, and therefore these estimations should be corrected for RSV circulation. Other respiratory viruses like rhinoviruses, para-influenza viruses and adenoviruses also co-circulate with influenza viruses, but these viruses show less clear seasonality with rather long periods of marginally increased activity or very short peaks of increased activity (Figure 1).

Figure 1: Respiratory viral activity throughout the years 1998 to 2002



Source: *Weekly Sentinel System of the Dutch Working Group on Clinical Virology*

Respiratory syncytial virus

RSV has traditionally been known as the virus causing bronchiolitis during infancy.[54-56] Infants born prematurely, immunocompromized infants and those with cardiopulmonary disease have a particularly high risk of severe complications from RSV infection. Over the last twenty years, the impact of RSV among the elderly has gained attention, and considerable RSV-attributable mortality has been demonstrated in this age group.[24,57-59] RSV appears however to affect people of all ages with re-infections throughout life, manifesting as both upper and lower RTI.[60] Nevertheless, the impact of RSV over different age categories, especially among adults, is largely unknown. In view of the progress that has been made in the development of the RSV vaccine,[61] insight into the RSV-related burden would be valuable to guide initiatives for further studies.

The last decade, passive protection against RSV with immune prophylaxis has been used in high-risk infants and proved to be effective in reducing the severity of RSV infections.[61] This treatment is however rather expensive and laborious requiring multiple dosages per season, which makes a vaccine against RSV attractive. Developing a vaccine for infants as primary target group has, however, proven to be challenging for several reasons. Besides the relatively immature immune system of infants and potentially interfering maternal antibodies, the immunity to natural RSV infections is incomplete. This makes the design of an immunogenic vaccine complicated.[61] Additionally, studies in the 1960s with a formalin inactivated RSV vaccine not only failed to demonstrate a protective effect but even showed an enhanced disease, which led to reduced efforts in RSV vaccine research.[62] Over the last ten years, however, research in this field has progressed and some novel approaches appear promising. The so-called subunit and peptide vaccines and replicated vector vaccines have been tested in clinical trials and are considered promising for older children and adults.[62] For younger children and infants, the live attenuated vaccine appears promising, as is maternal immunisation.[62]

Effects of influenza vaccination

There is no consensus on how to describe the effects of influenza vaccination. Some researchers define the efficacy of the vaccine as the ability of the vaccine to prevent laboratory-confirmed influenza (confirmed influenza) and effectiveness as the ability of the vaccine to prevent other non-confirmed influenza-associated outcomes.[10] Other researchers state that efficacy means the effects of vaccination found in RCTs, while the effectiveness measures outcomes in daily practice.[63] In this thesis, the terms efficacy and effectiveness will be avoided and instead the collective noun 'effects' will be used.

Influenza viruses mutate very frequently, causing antigenic drift.[64] Currently, specific antibodies are considered the best correlate of protection.[65-68] Every year, new strains circulate that differ more or less from preceding strains, often causing the specific antibodies to be inadequate for protection.[64] This constitutes the need for annual influenza vaccination. Prior to every respiratory season, the World Health Organisation recommends the composition of the forthcoming influenza vaccine, i.e. which strains should be included in the vaccine. The effects of the vaccine therefore not only depend on the immunogenicity of the vaccine itself, defined as the ability to produce adequate antibody levels thought to be protective against influenza strains included in the vaccine, but also on whether the circulating strains match the ones included in the vaccine. Therefore these effects may vary considerably by influenza season. A meta-analysis of (quasi)-randomized studies showed that the vaccine reduced confirmed influenza by 50% (95% confidence interval (CI) 27-65%) to 80% (95% CI 56-91%) in healthy adults.[69] In case of good vaccine matching and high viral activity, the protective effect against clinical symptoms suggestive of influenza, i.e. influenza-like-illness, was demonstrated to be 30% (95% CI 17-41%) in this group.[69] This smaller effect on influenza-like-illness in comparison with that on confirmed influenza is attributable to the fact that influenza-like-illness is less specific for an influenza virus infection, as it may be caused by other respiratory viruses.[51] The effects of influenza vaccination on more serious outcomes such as hospitalization and mortality have mostly been studied in cohort studies since a randomized controlled design generally does not permit assessment of effects on relatively rare outcomes. Cohort studies demonstrated substantial reductions of 16-33% in hospitalizations for acute respiratory, cardiovascular and cerebrovascular events and up to 50% reduction in all-cause mortality during influenza

seasons.[70-73] The results of these studies have however been criticized because of the potential of healthy-user bias (a type of confounding by indication), with healthy people being vaccinated more often or the reverse with those at highest risk for complication being vaccinated more often.[74-77] Importantly, ecological studies conducted in the United States could not demonstrate decreasing influenza-associated mortality with increasing vaccination coverage in the elderly.[23,34] Yet, these studies may have been hindered by major disparities in vaccination rates by geography as well as by socioeconomic, demographic, and health characteristics making it very difficult to estimate individual benefit from population-level data.

Part II

Respiratory tract infections

Acute respiratory illness is most frequent in young children with on average 5 to 6 episodes in 0-4-year-olds and about 4 in 5-9-year-olds per year.[78] Toddlers attending day-care suffer from common cold-like-illness approximately 23% of the time.[79] Older children and adults experience about 1 to 3 episodes per year.[78] Also primary care consultations for RTI occur most frequently among 0-4-year-olds with an incidence of 47 consultations per 100 person-years.[80] Corresponding figures for older children and adults are about 12 and 11 episodes per 100 person years.[80] Besides upper RTI, also lower RTI occur frequently in young children, with primary care consultations for lower RTI in about the same frequency as in the elderly.[80] Common treatments for (recurrent) RTI are antibiotics and ear-nose-throat surgery, [80,81] but in spite of the frequent use of both treatments only marginal effects have been demonstrated.[82-85] Moreover, the frequent and liberal use of antibiotics appears to induce bacterial resistance.[86] For these reasons, preventive strategies like immunisation are attractive.

Pathogens of respiratory tract infections

Overall, community-based studies demonstrated that most acute respiratory illness has a viral etiology.[78] Among 0-4-year-olds, about 39% of the viral respiratory illness annually is caused by rhinoviruses, 19% by RSV, 18% by para-influenza viruses, 11% by adenoviruses

and 9% by influenza viruses.[78] In older children, 50% of the viral respiratory illness is caused by influenza viruses, 22% by rhinoviruses and 12% by para-influenza viruses.[78] The most common viral pathogen in children of community acquired pneumonia, i.e. pneumonia in a previously healthy person who acquired the infection outside a hospital, is RSV. Dependent on the method of detection in 8-29% of all community acquired pneumonias RSV is involved, while influenza viruses have been reported in 3-4% of the cases.[87-89] Although overall influenza viruses appear to be responsible for only a modest portion of the viral respiratory disease among preschool children, influenza viruses are responsible for a large proportion of disease during the marked period of the influenza season. For example, the cumulative incidence of confirmed influenza has been estimated on average around 20% in this age group during influenza seasons, but may be up to 50%.[9,90] A recent study also demonstrated that in 33% of the nasopharyngeal aspirates taken from children presenting to primary care during winter season with cough and fever for which antibiotics were considered, influenza viruses were detected.[91] Moreover, influenza virus infections may predispose to bacterial superinfection, most commonly acute otitis media (AOM), in particular caused by *S.pneumoniae*.[10,92] Influenza virus infection may lead to damage of the epithelium of the respiratory tract, changes in airway function, up-regulation of receptors and alteration of the innate immune response, all enhancing pneumococcal infection.[10] Moreover, the synergistic effect of influenza viruses and *S.pneumoniae* may be bidirectional with an enhancement of the viral infection because of the bacterial infection.[10] *S.pneumoniae* is known to be the leading cause of AOM, accounting for 28 to 55% of all episodes.[93-96] *S.pneumoniae* is also the most common bacterial pathogen of community acquired pneumonia in preschool children, implicated in 27-37% of cases.[87-89]

Influenza and pneumococcal conjugate vaccination

As previously stated, influenza vaccination among children is only recommended when high-risk medical conditions are present, in the Netherlands. The trivalent inactivated sub-unit influenza vaccine is licensed for children. RCTs assessing the effect of the parenteral inactivated influenza vaccine (PIV) on confirmed influenza episodes among preschool children are scarce. Meta-analyses reported a reduction in confirmed influenza of 62% (95% CI 45-75%) and 65% (95% CI 47-76%) of PIV among healthy children of all ages

following PIV.[62,97,98] Within a subgroup of healthy children aged less than six years, a statistically non-significant reduction of 58% (95% CI -20-86%) in confirmed influenza was observed, based on only two RCTs covering each one influenza season.[62] The effects of PIV on influenza-like-illness among healthy children of all ages estimated from meta-analyses vary from 28% (95% CI 22-33%)) to 45% (95% CI 33-55%).[62,97,98] Based on the same RCTs among children aged less than six years a pooled statistically non-significant reduction of 48% (95% CI -98-86%) in influenza-like-illness was found.[62] A meta-analysis of six (quasi) RCTs reported a non-significant reduction in AOM incidence of 32% (RR 0.68, 95% CI 0.40-1.16%) among healthy children of all ages.[98] Earlier non-randomized and/or unblinded studies in preschool children, observed a statistically significant reduction in AOM by PIV of 40-62% in the influenza season.[99,100]

In the Netherlands PCV-7 is licensed for children. The main reason for the addition of this vaccine to the national infant immunisation schedule in 2006 was its protective effect in infants against invasive pneumococcal disease that was demonstrated in RCTs; i.e. an 88% (95% CI 73-94%) reduction for pneumococcal disease caused by the serotypes covered by the vaccine (vaccine-type pneumococcal disease) and 66% (95% CI 46-79%) for all-serotype pneumococcal disease in 0-2-year-olds.[13] However, also the potentially beneficial effect for the non-vaccinated population of this addition to the infant immunisation schedule, contributed to the decision. Several cohort studies conducted in the United States demonstrated a decline in invasive pneumococcal disease of about 30% among older adults after the introduction of PCV-7 among young children.[101-103] This beneficial effect was supposed to be the result of decreased community transmission of vaccine-type pneumococci by young children,[101] since PCV-7 was shown to reduce nasopharyngeal carriage of vaccine-type pneumococci in children.[104-106] The effect of PCV-7 on mucosal pneumococcal infections appears less; a meta-analysis of four RCTs on the effects of PCV-7 among infants observed a reduction in AOM episodes of 8% (95% CI 5-12%).[12] Studies of PCV-7 in older children are scarce. One previous randomized controlled study on nonavalent PCV among children aged 12-35 months attending day-care, reported a reduction of 15% (95% CI 4-24%) of upper respiratory infections.[107] Another RCT with PCV-7 and a subsequent polysaccharide pneumococcal vaccination failed to demonstrated any beneficial effect among older children with recurrent AOM.[108] The recent extension of

indications for PCV-7 by the European Medicines Agency to include the prevention of pneumonia and AOM among all preschool children, appears therefore based on limited evidence.

Scope of this thesis

The main aims of this thesis are to determine the influenza-associated burden among otherwise healthy persons younger than 65 years of age, especially among 50-64-year-olds, and to determine the effects of influenza vaccination with or without PCV-7 in preschool children on the occurrence of RTI.

In Part I, **Chapters 2 to 5**, the potentially vaccine-preventable burden associated with influenza and RSV in the Dutch community is estimated. In **Chapter 2** a short overview of recently reported models to estimate the influenza-associated burden is provided. Using primary health care data, the rather straight-forward rate-difference model is compared with other more extended regression-based models, and both the influenza- and RSV-associated primary care burden are estimated. In **Chapter 3** the nationwide influenza- and RSV-associated burden of mortality and hospitalization is quantified, using national mortality and hospitalization data. In **Chapter 4**, the impact of the introduction of a nationwide vaccination program among elderly in the Netherlands on influenza-associated mortality is assessed, applying the rate-difference method in time-series, comparing the years before and after the introduction of the program. With the Netherlands being a small but densely and rather homogenously populated country, Dutch data are especially suitable for ecological studies. The stable high influenza vaccination coverage among the Dutch elderly after the introduction of the routine influenza vaccination program further facilitates non-experimental measures to quantify the effects of such programs. In **Chapter 5** the potential relationship between influenza viruses and RSV on the one hand and the occurrence of invasive bacterial disease on the other, is assessed. Although the seasonality of invasive bacterial disease is acknowledged, a role for respiratory virus circulation has not been established.

Part II of the thesis, **Chapters 6 to 9**, reports the effects of influenza vaccination and PCV-7 on RTI among preschool children. In **Chapter 6** the management of RTI among

preschool children in primary care is presented, including age-specific antibiotic prescription and referral behaviour. **Chapters 7, 8 and 9** include the results of the PRIMAKid (Prevention of Respiratory Infections and Management in children)-trial. This is a randomized double-blind controlled trial among preschool children designed to address the hypothesis that, in the light of the accumulating evidence suggesting that influenza viruses and *S.pneumoniae* act synergistically, combined influenza and pneumococcal vaccination might be particularly effective in reducing RTI. **Chapter 7** describes the adverse local and systemic reactions associated with the simultaneous administration of trivalent inactivated influenza vaccination with or without PCV-7 in preschool children. In **Chapter 8** the effects are presented of influenza vaccination with or without PCV-7 on patient-reported febrile RTI-episodes and related confirmed influenza, primary care visits, antibiotic prescriptions and physician-diagnosed AOM during and outside influenza seasons. In **Chapter 9** instruments to measure the functional health status or well-being, an increasingly valued outcome in clinical trials, are validated in preschool children. The effects of influenza and pneumococcal vaccinations on functional health status are also reported in this chapter. Finally, in **Chapter 10**, the results of all chapters are discussed in the light of possible extensions in the recommendations for respiratory vaccines.

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PART I

Influenza- and respiratory syncytial virus-associated mortality and morbidity

CHAPTER 2

Estimating the influenza-associated burden: comparison of models illustrated by primary care consultations associated with influenza and respiratory syncytial virus

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Abstract

Objective: To compare different methods to estimate the influenza-associated disease burden, using influenza- and respiratory syncytial virus-(RSV) primary care data as an example.

Study Design and Setting: In a retrospective study in the Netherlands over 1997 to 2003, primary care-attended respiratory episodes and national viral surveillance data were used to compare the rate-difference method to other, more complex methods.

Results: The influenza-associated excess estimated by the different methods varied. The estimates provided by the rate-difference model lied well within this range. According to the rate-difference method, influenza-associated primary care consultations were present for all ages, including low-risk adults. The highest influenza-associated burden was demonstrated for children below the age of five years. The RSV-associated primary care burden was highest in the youngest age category and well above that associated with influenza. Significant RSV-associated excess was also recorded among adults, particularly in high-risk adults and the elderly.

Conclusion: The straight-forward rate-difference model seemed satisfactory to estimate the influenza-associated burden. Significant influenza-associated excess was demonstrated among persons not yet recommended for influenza vaccination in The Netherlands. The RSV-associated burden was highest for the youngest children, but also significant for adults.

Introduction

Estimating the health burden associated with influenza is challenging. Influenza is clinically not always recognized and is confirmed virologically only in a minority of cases.[1,2] Many people who are ill with influenza do not seek medical care. Furthermore, apart from the primary viral respiratory disease, influenza virus infection may also predispose to bacterial super infection and cardiovascular complications.[3-5] For these reasons, direct estimations of the health burden by determining confirmed influenza in the population will underestimate the true burden. Several models have been developed to assess the influenza-associated burden indirectly. Most models determine the excess health burden during influenza virus-active periods over baseline periods, and consequently these models may be disturbed by other seasonally active factors. In particular respiratory syncytial virus (RSV) often co-circulates with influenza viruses and has increasingly gained attention in causing morbidity not only in young children but also in the elderly.[6-10]

Despite difficulties in determining the influenza-associated disease burden, estimations of this burden form the basis of cost-effectiveness analyses, which more and more guide influenza vaccination policies. Since the development, recommendation and implementation of an influenza vaccination strategy involve people with different backgrounds (like scientists, public health workers, policy makers and clinicians), methods to estimate the influenza-associated burden should allow insight for a broad audience. The interpretation and comprehensiveness may however substantially vary between models. Oppositely to the more extended regression-based models, rate-difference models appear straight-forward and do not require extensive epidemiological or statistical knowledge for comprehension.

The aim of the current study is to compare the rate-difference method with three other recently reported methods for determining the influenza-associated burden, evaluating the differences, potential limitations and advantages of the rate-difference method. As an example, the influenza-associated primary health care burden is presented among otherwise healthy persons younger than 65 years that are not yet recommended for influenza vaccination in the Netherlands. Since Dutch primary care functions as gate keeper to

secondary care, the frequency of primary care visits may be particularly high. Further, in view of the progressing development of vaccines against RSV,[11] also the RSV-associated primary health care burden was assessed.

Methods

Setting and study population

Patient data for this retrospective study were obtained from the computerised medical database of the University Medical Center Utrecht Primary Care Research network, a primary care group comprising about 60,000 patients. Main characteristics of this patient population are representative for the Dutch population as a whole.[12] Medical data of all enlisted patients are recorded using a uniform, structured, contact registration format in the primary care information system ELIAS® (ISoft, Nieuwegein, Netherlands). The participating primary care physicians regularly receive medical education regarding the correct coding of diagnostic information according to the International Classification of Primary Care (ICPC) coding system.[13,14] More than 90% of contacts have received an ICPC-code and accuracy appeared high. For this study all patients enlisted in the participating practices during 1997 to 2003 were included.

Outcomes

All general practitioner-(GP) attended episodes of respiratory tract disease were recorded. A new episode was recorded after a consultation-free interval of at least 28 days. Upper respiratory tract infections (URTI) included the ICPC-codes H71 (otitis media, myringitis), R72 (streptococcal angina / scarlet fever), R74 (acute upper respiratory infection including common cold and pharyngitis), R75 (sinusitis), R76 (acute tonsillitis, peritonsillar abscess), and R77 (acute laryngitis, tracheitis). Lower respiratory tract infections and lung disease (LRTI) included the ICPC-codes R78 (acute bronchi(oli)tis), R80 (influenza), R81 (pneumonia), R82 (pleuritis), R83 (other respiratory tract infections), R91 (chronic bronchitis, bornchiectasias), R93 (pleural effusion), R95 (chronic obstructive airway disease), and R96 (asthma). Apart from the ICPC-code, the date of the first GP-visit during the episode and the age of the patient were recorded. Further, the presence of diseases

associated with a high risk of complicated influenza was recorded. High-risk disease included chronic heart and lung disease, stroke, diabetes mellitus, renal insufficiency, malignancy, immune deficiencies, dementia, and other neurologic disease (ICPC-codes B72-74, B90, D74-77, F74, H75, K70-84, K86-87, K90, K93, L71, N74, N86, P70-71, R70, R84-85, R91, R93, R95-96, T71, T73, T90, U75-77, U88, U99, X75-77, Y77-78).

Viral surveillance

During the study period 1997 to 2003, laboratory-based surveillance for various viruses was conducted by the Weekly Sentinel System of the Dutch Working Group on Clinical Virology in the Netherlands throughout the whole year. Seventeen medical microbiological laboratories reported the absolute weekly number of reported patients either hospitalized or visiting outpatient clinics that tested positive for a certain virus. Surveillance data for the influenza virus type A and B, RSV, rhinoviruses, para-influenza viruses and adenoviruses were used in this study. Most of the laboratory diagnoses were made by virus isolation on cell culture or rapid antigen tests. The weekly virological reports were demonstrated to reflect trends in national viral activity adequately.[15] However, most RSV surveillance data (96%) were reported in children below the age of five years.[16] An influenza virus subtype was considered dominant when it accounted for at least 50% of all isolates that were subtyped in that season.

Models

The principal method illustrated in this study is the rate-difference method (model 1) according to Izurieta and colleagues,[17] and this model was applied to the data of all age categories. For comparison reasons, three other models were applied to a selection of the data, i.e. GP-attended LRTI among non high-risk 50-64-year-olds and the elderly, i.e. persons aged 65 years and older.

All models could be expressed in this regression equation:

$Y_t = \beta_0 + \beta_1 x_{1,t} + \beta_2 x_{2,t} \ldots + \beta_n x_{n,t} + e_t$

where Y_t equals the number of episodes in week t, β stands for the regression coefficient of the explaining variables, $x_{1,t}$ is de value of explaining variable x_1 in week t, and e_t stands for the error in week t (normally distributed with a standard error σ).

Model 1

With minor modifications, study periods were defined according to Izurieta and colleagues.[17] For each winter season from week 40 of one year to week 20 of the next year, influenza virus-active periods were defined as the periods of at least two consecutive weeks in which each week accounted for at least 5% of the season's total number of reported laboratory-confirmed influenza cases.[17] Similarly, RSV-active periods were defined as the periods of at least two consecutive weeks in which each week accounted for at least 5% of the season's total number of reported RSV-positive cases. Periods of influenza virus predominance were defined as influenza virus-active weeks with less than 5% of the season's total number of reported RSV-positive cases.[17] Peri-seasonal baseline period was defined as periods of at least two consecutive weeks within week 40 to 20 in which each week accounted for less than 5% of the season's total number of reported influenza virus- and RSV-positive cases. Summer baseline period was defined as week 21 to 39. Unlike Izurieta and colleagues, weeks in which para-influenza viruses were isolated were not excluded from the study as (sporadic) isolates were reported throughout the year. For the same reason, weeks in which sporadic isolates of the influenza virus and RSV were reported were not excluded during summer baseline period.

Importantly, the viral surveillance data revealed largely separate peaks of influenza virus- and RSV-activity over the years 1997 to 2003 in the Netherlands, which allowed us to quantify the impact of both viruses separately. There were 92 influenza virus- and/or RSV-active weeks; 46 weeks of influenza virus predominance, 42 weeks of RSV predominance, and only four both influenza virus- and RSV-active weeks. Influenza virus A subtype H3N2 was the dominant circulating strain in all seasons except for 2000-01 in which influenza virus A subtype H1N1 was dominant.

For all years together, the weekly rate of GP-attended episodes (per 100,000 persons) was calculated in the baseline periods and the periods in which influenza virus or RSV predominated. The mid-time populations of each consecutive year at January 1st were averaged to determine the population at risk. Weekly excess rates of GP-attended episodes with 95% confidence intervals (95%CIs) associated with influenza and RSV were

determined by subtracting summer and peri-seasonal baseline rates from rates during periods of influenza virus or RSV predominance. The total number of GP-attended episodes per 100,000 persons associated with influenza or RSV during winter season, the cumulative annual winter excess rate, was calculated by multiplying the average weekly excess rate during virus predominance periods with the average number of virus-active weeks during winter season. The excess rates were extrapolated to the national population (Statistics Netherlands, Voorburg/Heerlen, the Netherlands) to estimate the total number of GP-attended episodes associated with influenza and RSV in the Netherlands. For adults under 65 years of age, subset analysis by the presence of high-risk disease was performed. Since the prevalence of high-risk disease among children was relatively low, this was not done for children.

Model 1 could also be expressed in two different reference period-specific (peri-seasonal and summer baseline period) regression equations, each fitted on the respective baseline weeks and the period of influenza virus predominance. In these equations, $x_{1,t}$ stands for the index for the baseline period, with 0 standing for a week within the baseline period and 1 standing for a week within the period of influenza virus predominance.

Model 2

Model 2 was a Serfling-type regression model according to Simonsen et al. with minor modifications.[18] First, the time series was detrended by dividing the weekly number of GP-visits by the average weekly number of visits in summer (June-August). A seasonal regression model was then applied to the detrended series excluding values for the period December to April to obtain a baseline level model, in which $x_{1,t}$ and $x_{2,t}$ were the cosine and sine term, $\cos(2\pi t/52)$ and $\sin(2\pi t/52)$. Influenza epidemic periods were identified by applying this procedure to the reported isolates of influenza. The "epidemic weeks" for each season were defined as those weeks for which the number of influenza virus isolates exceeded the upper 95% confidence limit of that predicted by the model. Next, the model was applied to the rates of GP-attended LRTI. Weekly excess rates were calculated as the observed minus predicted rate for all "epidemic weeks". The seasonal excess was estimated as the sum of weekly excess GP-visits.

Model 3

Model 3 was a multiple linear regression analysis according to Pitman et al. to ascertain the underlying aetiologies of influenza-like-illness and to estimate the proportion attributable to the potentially associated pathogens.[19] The observed temporal trends in laboratory reports of viral agents that could potentially cause influenza-like-illness were compared to the number of GP-attended LRTI. The latter was used as the dependent variable of a multiple regression. The explaining variables were the weekly number of laboratory reports for the viruses, and β_0 represents the background number of episodes associated with other infectious or non-infectious causes. The initial model included all viruses as explanatory variables, and by stepwise regression the optimal model was created. If the p-value was >0.1 or the variable was significant but the resulting coefficient negative (which is biologically implausible) the variable was discarded from the model.

Model 4

Model 4 was the modified version of the multivariable regression model applied by Dushoff et al.[20] Excess GP-visits for LRTI was defined as the total number of visits in a selected set of "influenza weeks" above the weekly average of a set of "baseline months". For the main analysis, we used November to April as the flu months and the remaining six months as the baseline months. The weekly excess GP-attended LRTI was used as the dependent variable, and the explaining variables were the weekly number of laboratory reports for influenza virus type A and B and cold. Cold was measured on a weekly basis as the average number of degrees below a threshold temperature of 10 degrees Celcius.

In both model 3 and 4, episodes attributed to the independent variable (influenza virus) were calculated by the difference between the number of episodes predicted when the independent variable is set to zero.

Akaike's information criterion (AIC) was calculated to indicate the model fit,[21] and in order to compare between models the AIC was readjusted for the difference in the number of data points used by the different models:

$AIC_{adjusted} = n_{adjusted} *$ natural logarithm [sum of squared errors / n] + 2 (p+1)

where $n_{adjusted}$ is the average number of data points that were used by the models, n is the actual number of data points used in the model and p is the number of parameters used in the model. Smaller values of AIC indicate a better fit. Differences in AIC of 0-2 between two models indicate that there is weak evidence that the model with the lower valued AIC is better than the other; larger differences in AIC >10 between two models indicate there is compelling evidence that the model with the lower value of AIC is better than the other. All analyses were carried out with SPSS (version 12.0) and Episheet (Rothman K. Episheet: Spreadsheets for the analysis of epidemiologic data, 2002).

Results

Comparison of models

In Model 1, estimates with the peri-seasonal baseline period as reference were lower than those with the summer baseline period as reference (Table 1). When the peri-seasonal baseline period was applied as reference, the excess rate was indirectly corrected for other seasonal phenomena with a potentially disturbing influence such as cold and other seasonally active pathogens. Additionally, the model also corrected specifically for RSV-activity by excluding RSV-active weeks.

Model 2 determined the baseline rate by excluding the influenza virus-active weeks and assuming that a sine wave describes the true baseline rate adequately. This sine wave with increases in winter seasons and decreases in summer season was also a way to correct for seasonal influences. This model assumed that the excess (residuals) above this normal value was influenza-related. Model 4 was fitted on the excess during influenza virus-active (November-April) months over baseline months (May-October), and taking into account the potential influence of cold, the excess was determined by the model coefficients ignoring the residuals. Model 3 did not model the excess, but the total rate throughout the year and determined the proportion of GP-attended LRTI that could be attributed to each pathogen incorporated into the model. Since influenza isolates were reported during summer period sporadically, influenza was also attributed morbidity during summer period

according to Model 3. In this model, there was no correction for seasonally influences other than the pathogens included in the model.

Overall, the influenza-associated excess GP-attended LRTI determined with Model 1 was within the range excesses estimated by the other models (Table 1). Model 2 provided the lowest estimates while Model 4 provided the highest estimates. The $AIC_{adjusted}$ indicates that for the non high-risk 50-64-year-olds there is compelling evidence that model 1, with the summer baseline period as reference, provides a better, more parsimonious description of the data than the other models. For the elderly there is compelling evidence that both model 1, with the summer baseline period as reference, and model 3 provide a better description of the data than the other models.

Table 1: Influenza-associated primary care episodes according to different models

		Average yearly total excess per 100,000 persons *(95% confidence interval)*	Adjusted Akaike's information criterion*
Lower respiratory tract disease, non high-risk persons aged 50-64-years			
Model 1	**peri-season**	494 *(377–610)*	1584**
	summer	732 *(621–844)*	1533
Model 2		233 *(191-283)*	***
Model 3		1090 *(994-1193)*	1552
Model 4		748 *(669-834)*	1691
Lower respiratory tract disease, persons aged 65 years and older			
Model 1	**peri-season**	759 *(561–957)*	1808
	summer	1501 *(1312–1689)*	1788
Model 2		482 *(421-549)*	***
Model 3		2019 *(1863-2123)*	1786
Model 4		1031 *(941-1127)*	1862

* Akaike's information criterion was adjusted for the differences in number of data points used by the models.
** Smaller values of Akaike's information criterion indicate a better model fit. ******* Oppositely to the other models, Model 2 determined the influenza-associated burden out of the residuals, and therefore Akaike's information criterion was not comparable to that of the other models.

Influenza

According to Model 1, young children had the highest risk of an influenza-associated GP-attended episode (Figure 1, Table 2), especially for URTI. Among 0-1-year-olds the

influenza-associated excess episodes was not statistically significant over peri-seasonal baseline period, but only over summer baseline period (Table 2). Significant excesses GP-attended episodes of acute otitis media and pneumonia were however demonstrated in all children during influenza virus-active periods. Also significant excesses GP-attended episodes were observed among adults without high-risk medical conditions (Table 3), and at population level a major part of the influenza-associated primary care burden occurred in non high-risk 18-64-year olds (Figure 1). The excess among adults increased with age and was highest for LRTI. In The Netherlands, an estimated 109,000 to 260,000 GP-attended RTI episodes (over respectively peri-seasonal and summer baseline period) were associated with influenza.

RSV

Periods of RSV predominance were associated with a higher excess of both GP-attended URTI and LRTI episodes than periods of influenza virus predominance among young children (Table 2). The risk of an RSV-associated GP-attended episode was highest for the youngest (Figure 2, Table 2). However, the RSV-associated excess was also significant for adults (Table 3), and at population level the majority of episodes occurred in adults (Figure 2). At population level, 168,000 to 309,000 GP-attended episodes were associated with RSV (over respectively peri-seasonal and summer baseline period).

Table 2: General practice attended episodes during defined study periods and total winter excess episodes among children associated with the influenza virus and RSV

Age years	Weekly incidence per 100.000 persons				Total winter excess per 100,000 persons* (95% confidence interval)			
					Influenza virus		RSV	
	Period of influenza virus-predominance	Period of RSV-predominance	Summer baseline	Peri-seasonal baseline	over summer baseline	over peri-seasonal baseline	over summer baseline	over peri-seasonal baseline
Upper respiratory tract infections								
0-1	1449	2098	829	1387	5150 *(4298-6002)*	520 *(-397-1438)*	9772 *(8812-10730)*	5477 *(4466-6488)*
2-4	869	1089	444	718	3528 *(2988- 4067)*	1260 *(686-1835)*	4963 *(4390- 5535)*	2859 *(2258-3460)*
5-17	292	268	163	216	1077 *(921-1233)*	630 *(468-793)*	810 *(665-955)*	395 *(245-546)*
Lower respiratory tract infections and pulmonary disease								
0-1	380	893	208	383	1428 *(993-1863)*	none	5275 *(4665-5885)*	3924 *(3290- 4559)*
2-4	259	412	134	220	1037 *(742-1331)*	323 *(8-638)*	2142 *(1794-2490)*	1480 *(1118-1842)*
5-17	117	127	75	97	343 *(243-443)*	162 *(58-267)*	400 *(300-499)*	232 *(129-335)*
Pneumonia								
0-1	43	103	15	25	234 *(93-375)*	152 *(4-301)*	677 *(473-881)*	601 *(393-809)*
2-4	52	74	22	33	256 *(126-386)*	163 *(27-300)*	400 *(254-546)*	314 *(163-464)*
5-17	15	18	7	10	65 *(30-100)*	40 *(3-77)*	80 *(44-116)*	57*(19-94)*
Acute otitis media								
0-1	597	726	317	508	2322 *(1778–2865)*	740 *(161–1319)*	3149 *(2581–3718)*	1682 *(1084–2281)*
2-4	394	505	165	315	1906 *(1549–2264)*	660 *(275–1046)*	2624 *(2239–3009)*	1468 *(1061–1875)*
5-17	81	80	46	60	290 *(208-372)*	170 *(85-256)*	261 *(183-340)*	151 *(69-232)*

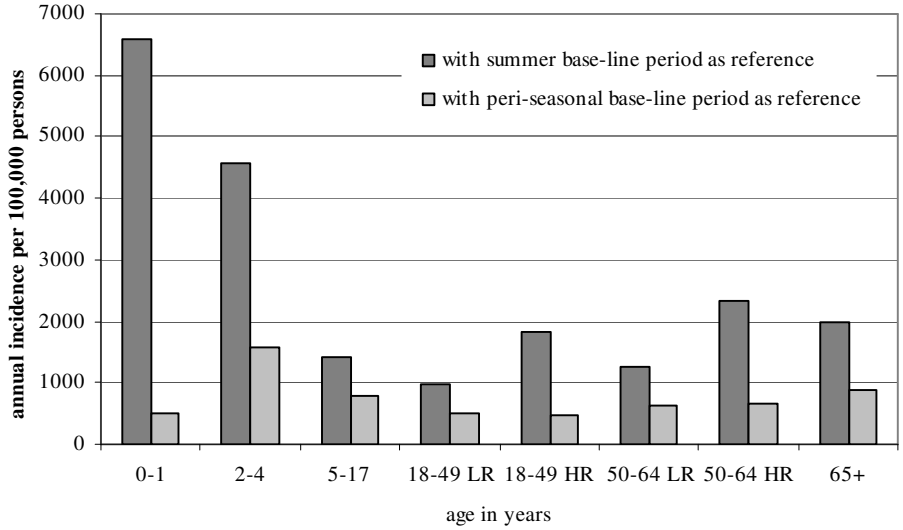
non-significant excesses are given in gray; none means no (non)significant excess

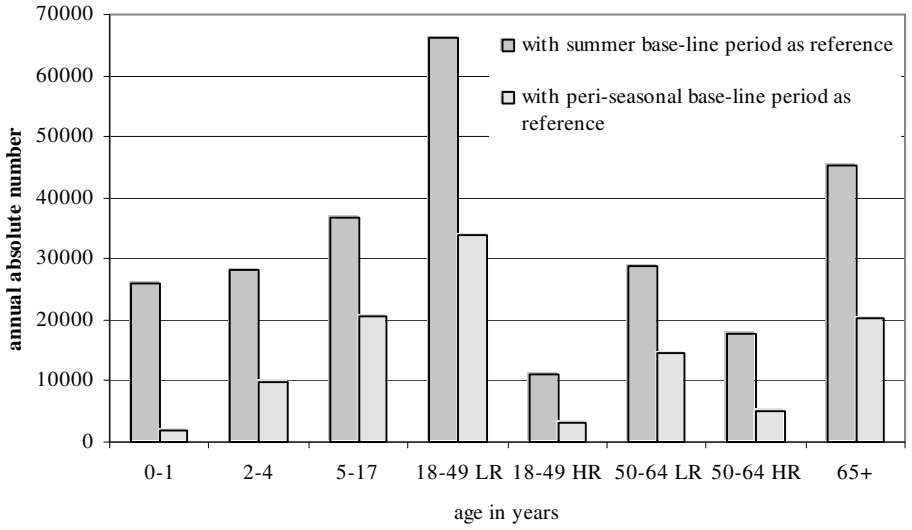
Table 3: Total winter excess episodes among adults associated with the influenza virus and RSV

Age		Weekly incidence per 100.000 persons (95% confidence interval)				Total winter excess per 100,000 persons* (95% confidence interval)			
						Influenza virus		RSV	
		Period of influenza virus-predominance	Period of RSV-predominance	Summer baseline	Peri-seasonal baseline	over summer baseline	over peri-seasonal baseline	over summer baseline	over peri-seasonal baseline
Upper respiratory tract infections									
18-49 years	**LR**	203	206	116	161	722 *(650–794)*	346 *(270–422)*	696 *(626–766)*	347 *(274–420)*
	HR	334	342	195	285	1150 *(843-1457)*	401 *(77–726)*	1130 *(831-1428)*	435 *(121–749)*
50-64 years	**LR**	152	167	89	136	527 *(403–651)*	138 *(6–271)*	601 *(476–725)*	240 *(109–371)*
	HR	217	224	111	195	881 *(627 –1135)*	186 *(-88-459)*	874 *(626–1123)*	229 *(-37-495)*
≥ 65 years		131	145	73	115	478 *(368–588)*	128 *(10–245)*	554 *(443–665)*	229 *(111–346)*
Lower respiratory tract infections and pulmonary disease									
18-49 years	**LR**	64	73	33	46	258 *(218–298)*	155 *(113–197)*	303 *(262–344)*	208 *(166–250)*
	HR	367	385	287	357	667 *(334–999)*	86 *(-261-433)*	757 *(432–1082)*	218 *(-120-556)*
50-64 years	**LR**	133	131	45	74	732 *(621–844)*	494 *(377–610)*	664 *(557–771)*	443 *(331–554)*
	HR	410	486	234	351	1458 *(1106–1811)*	484 *(110–858)*	1936 *(1571–2301)*	1032 *(650–1415)*
≥ 65 years		385	384	204	293	1501 *(1312–1689)*	759 *(561–957)*	1389 *(1207–1570)*	700 *(510–890)*
Pneumonia									
18-49 years	**LR**	9	9	5	6	34 *(19-49)*	27 *(12-43)*	33 *(19-48)*	27 *(12-42)*
	HR	21	31	13	20	65 *(-12-142)*	9 *(-73-91)*	141 *(53-229)*	89 *(-3-181)*
50-64 years	**LR**	27	15	7	13	163 *(113-212)*	111 *(59-163)*	60 *(23-97)*	13 *(-27-52)*
	HR	39	44	16	23	194 *(88-300)*	131 *(21-242)*	216 *(109-324)*	158 *(47- 270)*
≥ 65 years		53	52	26	42	222 *(153–292)*	92 *(18-165)*	201 *(135–268)*	80 *(10-151)*

LR, low-risk; HR, high-risk; non-significant excesses are given in gray; none means no (non)significant excess; * Total winter excess was calculated as the difference between rates during virus-active periods and reference periods multiplied by the average number of virus-active weeks per winter, i.e. 8.3 weeks for influenza virus and 7.7 weeks for respiratory syncytial virus.

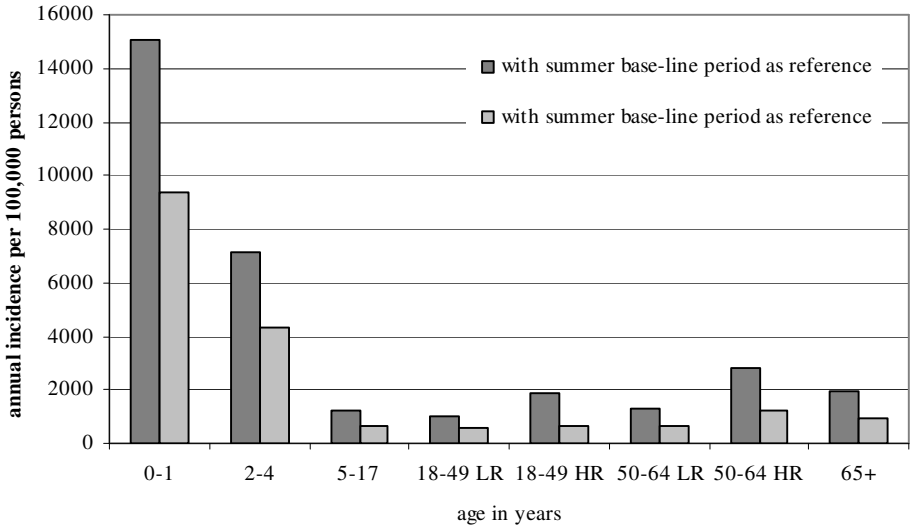
Figure 1: Influenza-associated primary care episodes in the Dutch population

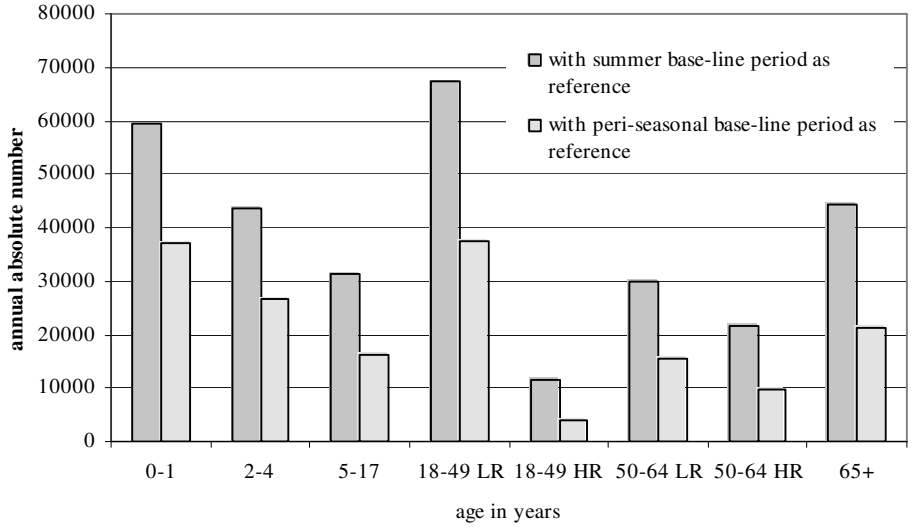




LR, low-risk; HR, high-risk

Figure 2: Respiratory syncytial virus-associated primary care episodes in the Dutch population





LR, low-risk; HR, high-risk

Discussion

Many approaches with varying complexity have been published to estimate the influenza burden indirectly. This six-year retrospective study with primary care consultation data compared estimates of the influenza-associated burden obtained by the straight-forward rate-difference model with those obtained by more complex regression models. We demonstrated that overall the influenza-associated burden determined with the rate-difference model was within the range of burdens estimated by the other models. Influenza virus-active periods were associated with significant excesses GP-attended episodes among children and otherwise healthy 18-64-year-olds that are not yet recommended for influenza vaccination in the Netherlands. Also RSV-active periods were associated with a significant primary health care burden, particularly in young children but also in adults (especially high-risk adults and the elderly).

The estimates of the influenza-associated excess LRTI obtained with the different models in this study demonstrated variation which appears mainly caused by the differences in the definition of influenza virus-active periods and the applied baseline period. It is difficult determining the optimal definition for influenza virus-active periods and baseline periods, and imprecision is inevitable. Model 1 with the summer baseline period as reference appeared to give a better description of the data than the other models. The lowest estimates were obtained by Model 2, possibly explained by the fact that influenza virus was in part responsible for the considered 'normal variation' of baseline activity reflected by a sine wave with increases of LRTI during winter. This may have led to an underestimation of the true influenza-associated burden. Apart from the incorporation of temperature and the broader definition of the influenza season by Model 4, this model resembles Model 1 with the summer period as reference with also rather similar estimates of the disease burden. The highest estimates were obtained with the Model 3. Since this method modelled not the excess rate but the total rate throughout the year, Model 3 is more than others affected by the pathogens incorporated into the model. Unfortunately, we had no data available for bacterial pathogens, and we could therefore not include bacterial infections as explanatory variables. This omission has probably led to an upper estimate of the influenza-associated burden as obtained by this model.

Pitman et al. attempted in their study, on which Model 3 was based, to determine the role of cold in the increase of winter mortality, but they could not determine a consistent relationship.[19] It is also doubtful whether cold should be incorporated in the model. Although cold itself may be responsible for mortality, it may also affect influenza virus-activity, for example by leading to crowding and consequently enhanced influenza virus transmission or by affecting the immune system negatively thereby predisposing to influenza virus infections.[22]

Remarkably, for 0-1-year-olds, the influenza-associated excess GP-attended episodes of acute otitis media and pneumonia separately were significant over peri-seasonal baseline period while excesses for all GP-attended URTI and LRTI together were only significant over summer baseline period and not over peri-seasonal baseline period. This may be explained by the fact that pneumonia and acute otitis media are relatively frequent complications of influenza virus infections in children,[23,24] and consequently particularly these conditions demonstrate clear excesses during influenza seasons. Other conditions defined under URTI or LRTI might be more often caused by other pathogens or other factors (for example allergies) that may be frequent in children during wintertime, which would dilute influenza-associated excesses of RTI over the peri-seasonal baseline period.

Overall, children aged 0 to 4 years had the highest incidences of influenza- and RSV-associated GP-attended episodes with a larger impact of RSV relative to that of influenza, as also was found in previous studies.[25,26] In our study however, the estimated influenza- and RSV-associated burden appeared somewhat lower which may be explained by the previously mentioned differences in models that were applied. Influenza viruses also demonstrate highly variable activity over the years, and consequently the influenza virus-associated health care burden varies throughout seasons. Further, in our study episode-based excesses were determined while other studies counted all GP-visits (and multiple GP-visits may occur in one episode). It should be noted that the influenza-associated primary care burden does not reflect the full extent of the influenza-associated disease burden in the community, since many people with influenza do not seek medical care.[27]

RSV is mainly known as a virus that primarily affects young children.[28,29] However, in our study RSV-active periods were associated with clear excesses GP-attended episodes among adults. The impact of RSV appeared more or less similar to that of influenza among adults at primary care level, which agrees with a recently published study.[19] However, our study underestimated the real influenza-associated burden for high-risk adults and elderly, since annual influenza vaccinations probably has prevented a major part of the influenza-associated burden in these groups.

Some potential limitations of Model 1, the principal method in our study, should be acknowledged. Like in all models, epidemiological data were used to estimate the influenza- and RSV-associated primary care burden, and consequently direct evidence lacked for the aetiology of the GP-attended episode. Since the model provided estimates of the excess versus peri-seasonal and summer baseline period, the margins of the estimates were wide. By applying the summer baseline period as reference, the burden may be overestimated since potentially other seasonally active factors, besides RSV, are not accounted for. On the other hand, if other common causes happen to be absent when influenza is circulating, the burden may be underestimated. Additionally, influenza virus-active periods were defined rather narrow, and therefore the estimated burden may also be an underestimation of the true burden since influenza viruses also circulated outside the weeks with more than 5% of the season's total influenza isolates. Like former studies, we had no access to age-specific viral surveillance data. It is however known that the spread and intensity of influenza virus-activity in community is similar for children and adults. Yet, most of our RSV surveillance data were reported in children, and although we assumed that RSV-activity among adults parallels that in children, this is not exactly known.[30] Therefore, part of the RSV- and influenza-associated morbidity may have been misclassified particularly in adults, as in other excess studies. This stresses the importance for age-specific RSV-surveillance. Finally, the virus surveillance data were primarily obtained in hospital settings. As increased influenza virus-activity may first manifest itself in community as a rise in GP-visits before a rise in influenza-related hospitalisations, the influenza virus-related burden we found may be an underestimation of the true burden. An advantage of our study is that the influenza virus-active periods were determined based on

laboratory-confirmed influenza and not on influenza-like-illness symptoms which have limited predicted value for influenza virus infections.[31,32]

In conclusion, all models estimating the influenza-associated health burden were accompanied by uncertainty. The rate-difference model provided estimates within the range of those obtained by other recently reported models. This model is rather straight-forward, allowing insight into the methods for a broad audience. According to this model, young children were at highest risk for an influenza-associated GP-attended episode, but at population level a large part of the influenza-associated primary health care burden occurred in adults without high-risk medical conditions. This burden may be partly prevented by introducing routine influenza vaccination. Cost-effectiveness analyses with these figures, together with figures of influenza-associated excess mortality and hospitalisation, may be useful to further inform policy makers. Evidence for the effects of influenza vaccination among children younger than two years of age is however limited,[33] and further research on this topic is needed. RSV-active periods were associated with a considerable burden especially in young children, but also in high-risk adults and the elderly. An RSV vaccine in future could therefore play an important role in reducing the primary health care burden.

Acknowledgment

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CHAPTER 3

Influenza- and respiratory syncytial virus-associated mortality and hospitalizations

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Abstract

Objectives: To estimate influenza- and respiratory syncytial virus-(RSV) associated mortality and hospitalizations, especially the influenza-associated burden among low-risk persons ≤ 65 years not yet recommended for influenza vaccination in many European countries.

Methods: Retrospectively during 1997-2003, Dutch national all-cause mortality and hospital discharge figures and virus surveillance data were used to estimate annual average influenza- and RSV-associated excess mortality and hospitalization using rate difference methods.

Results: Influenza virus-active periods were significantly associated with excess mortality among 50-64-year-olds and the elderly, but not in younger age categories. Influenza-associated hospitalization was highest and about equal for 0-1-year-olds and the elderly, and also significant for low-risk adults. Hospitalization among children was mostly because of respiratory conditions, and among adults cardiovascular complications were frequent. RSV-active periods were associated with excess mortality and hospitalization among the elderly. The highest RSV-related excess hospitalization was found in 0-1-year-olds.

Conclusions: Influenza-associated mortality was demonstrated in 50-64-year-olds. Among low-risk persons younger than 65 years of age, influenza-associated hospitalization rates were highest for 0-4-year-olds, but also significant for 5-64-year-olds. These data may further support extension of recommendations for influenza vaccination to include younger low-risk persons. The RSV-associated burden was highest for young children but also substantial for the elderly.

Introduction

Almost yearly the influenza virus is held accountable for large numbers of deaths and hospitalizations,[1-3] in particular among the elderly and persons with high-risk medical conditions. Therefore, most countries recommend influenza vaccination for these groups.[4] Recently the United States extended vaccination to low-risk 50-64-year-olds and young children, and in Canada vaccination for all ages was introduced.[5,6] Many European countries are now considering extending recommendations for influenza vaccination. More information is however needed about the potential impact of such changes in vaccination policy. In particular figures of influenza-associated hospitalization among low-risk adults are scarce.[7]

It is difficult to estimate the influenza-associated health care burden accurately, because influenza virus infections are generally not virologically confirmed and are often not recognized clinically.[8,9] In addition, the influenza virus infection may predispose to other conditions like bacterial superinfection and cardiovascular complications.[10-12] Co-circulation of other respiratory viruses during influenza season, in particular the respiratory syncytial virus (RSV),[13] makes it challenging to estimate the influenza-associated burden indirectly. Several studies suggested that RSV is responsible for considerable morbidity and even mortality not only in children but also among older adults.[2,14-16] Over the last decade the development of vaccines against RSV has progressed,[17] and although a vaccine is not expected in very near future, insight into the RSV-associated health care burden would be valuable.

Oppositely to former studies,[3,7] viral surveillance data in the Netherlands over the years 1997 to 2003 revealed largely separate peaks of influenza virus- and RSV-activity, which allowed quantifying the impact of both viruses separately. The aim of the current study was to assess influenza- and RSV-associated mortality and hospitalization, especially the influenza-associated burden among low-risk persons ≤ 65 years.

Methods

Viral surveillance

During the seasons 1997-98 to 2002-03, laboratory-based surveillance for various viruses was conducted by the Weekly Sentinel System of the Dutch Working Group on Clinical Virology in the Netherlands throughout the whole year. Seventeen virological laboratories weekly reported the absolute weekly number of patients either hospitalized or visiting outpatient clinics that tested positive for a certain virus. Surveillance data for influenza virus and RSV from that system were used in our study. Most of the laboratory diagnoses of influenza virus and RSV infections were made by virus isolation on cell culture or rapid antigen tests. The weekly virological reports were demonstrated to reflect trends in national viral activity adequately.[18] However, most RSV surveillance data (96%) were reported in children below the age of five years.[19] An influenza virus subtype was considered dominant when it accounted for at least 50% of all isolates that were subtyped in that season. The influenza virus and RSV surveillance data are summarised in Table 1. All influenza seasons were subtype A H3N2-dominant, except for season 2000-2001 which was subtype A H1N1-dominant.

Table 1: Influenza virus and RSV surveillance data

Season		**97-98**	**98-99**	**99-00**	**00-01**	**01-02**	**02-03**
No. weeks influenza season		9	10	8	6	9	8
Dominant subtype influenza		H3N2	H3N2	H3N2	H1N1	H3N2	H3N2
No. influenza isolates	**whole year**	777	883	858	298	660	392
	influenza season	532	539	589	141	465	231
No. weeks RSV season		9	9	7	7	6	8
No. RSV isolates	**whole year**	1575	2334	2104	1870	1579	1767
	RSV season	868	1769	1367	1043	1001	1260

Definition of study periods

With minor modifications, study periods were defined according to Izurieta and colleagues.[20] For each winter season from week 40 of one year to week 20 of the next year, the influenza-active period was defined as the periods of at least two consecutive weeks in which each week accounted for at least 5% of the season's total number of laboratory-

confirmed influenza cases.[20] Similarly, the RSV-active period was defined as the periods of at least two consecutive weeks in which each week accounted for at least 5% of the season's total number of RSV-positive patients. The period with influenza predominance was defined as the influenza-active weeks with less than 5% of the season's total number of positive tests for RSV.[20] Peri-seasonal baseline period was defined as periods of at least two consecutive weeks within week 40 to 20 in which each week accounted for less than 5% of the season's total number of influenza and RSV-positive cases. Summer baseline period was defined as week 21 to 40. Unlike Izurieta and colleagues, weeks in which para-influenza virus was isolated were not excluded from the study as (sporadic) isolates were reported throughout the year. For the same reason weeks were not excluded in which sporadic isolates of the influenza virus and RSV were reported during summer baseline period.

During the study period there were 92 influenza virus- and/or RSV-active weeks; 46 weeks of influenza predominance, 42 weeks of RSV predominance, and only 4 weeks of both influenza virus- and RSV-activity.

Mortality data and outcomes

National weekly mortality figures were obtained from Statistics Netherlands, Voorburg/Heerlen, the Netherlands. No information about the presence of high-risk conditions was available in these figures. Weekly hospitalization rates were provided by Prismant that registers all hospitalizations nationwide according to ICD-9cm (International Classification of Diseases). In this register, all discharge diagnoses were registered per hospitalization with the first diagnosis marked as primary diagnosis. During the study period, all hospitalizations with discharge diagnoses indicating acute upper respiratory disease (460-465, 381-384, 034), acute or chronic lower respiratory disease (466, 480-487, 490-496, 510-518, 78609, 7862), cardiovascular disease (410-415, 420-422, 428-429, 7852), cerebrovascular disease (431-437), bacterial invasive disease (036, 038, 041, 320, 3220, 3229, 7280, 7907) or other conditions possibly related to a respiratory infection were collected (293, 323, 390-392, 3483, 7803, 7806, 7784). Hospitalizations were divided in upper respiratory tract infections (URTI), lower respiratory tract infections and pulmonary disease (LRTI), cardiovascular complications (CVC), and others (e.g. bacterial invasive

disease, fever without focus, and delirium). Apart from the discharge diagnosis, the date of hospitalization, the age, and the presence of high-risk conditions was registered. A high-risk risk condition was considered present when at least one of the fourteen subdiagnoses indicated chronic respiratory disease (491-496, 500-508, 516-518, 5199, 71481), chronic cardiac disease (391, 393-396, 402, 404, 410-412, 414, 416, 424-429, 745-747), diabetes mellitus (250-251), renal insufficiency (581-591), haematological malignancy (2031, 2038, 204-208) or HIV/AIDS (042-044). When a chronic cardiac or respiratory condition was marked as primary discharge diagnosis, this was also considered as the presence of a high-risk condition.

Statistical analysis

The population of each consecutive year at January 1st was taken as population at risk, assuming a stable population throughout the year (Statistics Netherlands, Voorburg/Heerlen, the Netherlands). For all years together, the average weekly mortality rate and rate of hospitalization (per 100,000 persons) was calculated in different study periods, i.e. peri-seasonal and summer baseline periods and periods in which influenza virus or RSV predominated. Weekly excess mortality and hospitalizations with 95% confidence intervals (95%CIs) associated with influenza virus and RSV were determined with Episheet (Rothman K. Episheet: Spreadsheets for the analysis of epidemiologic data. 2002), by subtracting summer and peri-seasonal baseline rates from rates during periods of influenza virus or RSV predominance. The total excess per 100,000 persons associated with influenza virus or RSV during winter season, the cumulative annual winter excess rate, was calculated by multiplying the average weekly excess rate during the influenza predominance period with the number of influenza-active weeks during that winter season. The excess rates were applied to the national population of 2005 (Statistics Netherlands, Voorburg/Heerlen, the Netherlands) to estimate the total number of deaths and hospitalizations associated with influenza virus and RSV in the Netherlands. The proportions of the population with high-risk disease, i.e. medical conditions which are associated with a higher risk of complicated influenza virus infections, were obtained from the National Information Network Primary Care (Tacken et al. Monitoring Influenza vaccination campaign 2004, Nivel 2004). Since the prevalence of high-risk disease among children was relatively low, no subset analysis was performed according to the presence of

high-risk disease among children. Subset analysis according to the presence of high-risk disease was also not performed for persons 65 years of age and older, as these persons are already recommended for influenza vaccination.

Results

In total, 839,303 all-cause deaths and 1,551,598 hospitalizations for URTI, LRTI, CVC, and others were registered. Of these all-cause deaths, 1% was reported in 0-17-year-olds, 6% in 18-49-year-olds, 13% in 50-64-year-olds, and 80% in persons aged 65 years and older. For hospitalizations, these figures were respectively 14%, 12%, 23%, and 51%.

Influenza

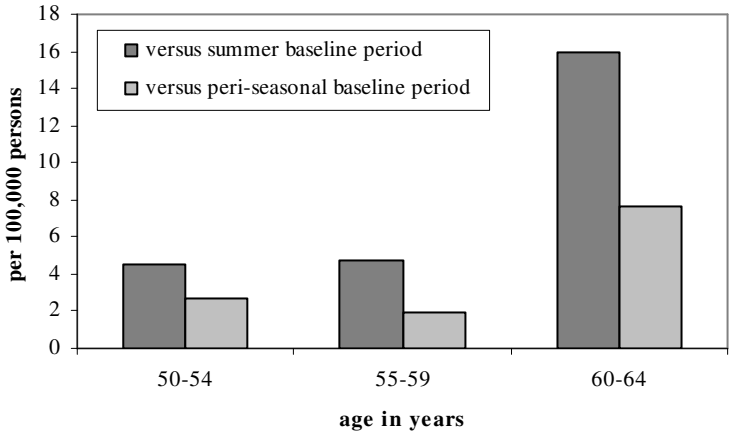
No evident excess mortality was found in the age categories 0-1, 2-17, and 18-49 years during influenza virus-active periods (Table 2). However, among persons aged 50 years and older, significant influenza-associated excess mortality was recorded. Among 50-64-year-olds influenza-associated excess mortality was highest for 60-64-year-olds (Figure 1). Influenza-associated excess hospitalization was highest in 0-1-year-olds (Table 3). Infants appeared responsible for the largest part of this excess hospitalization for LRTI, namely yearly on average around 13 to 221 hospitalizations per 100,000 0-year-olds (respectively with the peri-seasonal and summer baseline period as reference) and 13 to 64 hospitalizations per 100,000 1-year-olds. In adults, significant excess hospitalization for LRTI and CVC was recorded during influenza virus-active weeks (Table 4). Excesses for all diagnosis categories increased with age, also among low-risk 50-64-year olds (Figure 2). In absolute numbers, the highest influenza-associated health care burden occurred in the elderly (Figure 3).

RSV

During RSV-active periods, no evident excess mortality was found in the age categories 0-1, 2-17, and 18-49 years (Table 2). The youngest children appeared to experience the largest RSV-associated excess hospitalization for LRTI (Table 3), with yearly on average around 870 to 1063 hospitalizations per 100,000 0-year-olds (with respectively peri-

seasonal and summer baseline period as reference) and 104 to 151 per 100,000 1-year-olds. Significant excess hospitalization was recorded in adults during RSV-active periods, in particular in elderly (Table 4). The total absolute number of RSV-associated excess hospitalization was highest and about similar among 0-1-year-olds and elderly (Figure 4).

Figure 1: Influenza-associated winter mortality among 50-64-year-olds



* For 55-59-year-olds, influenza-associated winter mortality was not significant with the peri-seasonal baseline period as reference.

Figure 2: Influenza-associated winter hospitalization among low-risk 50-64-year-olds

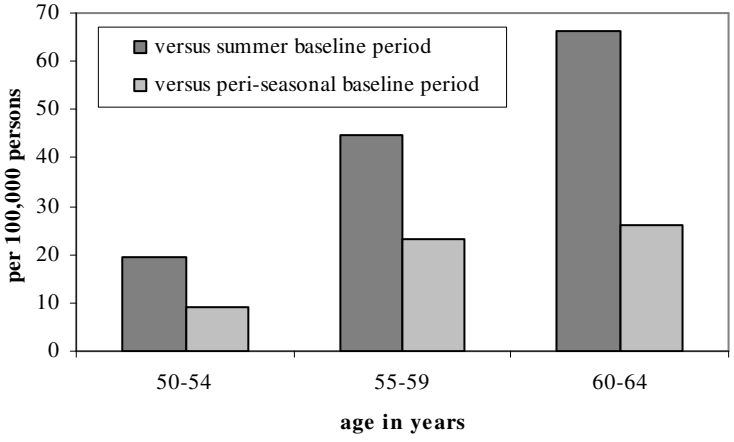


Figure 3: Average annual influenza-associated hospitalization burden in the Netherlands

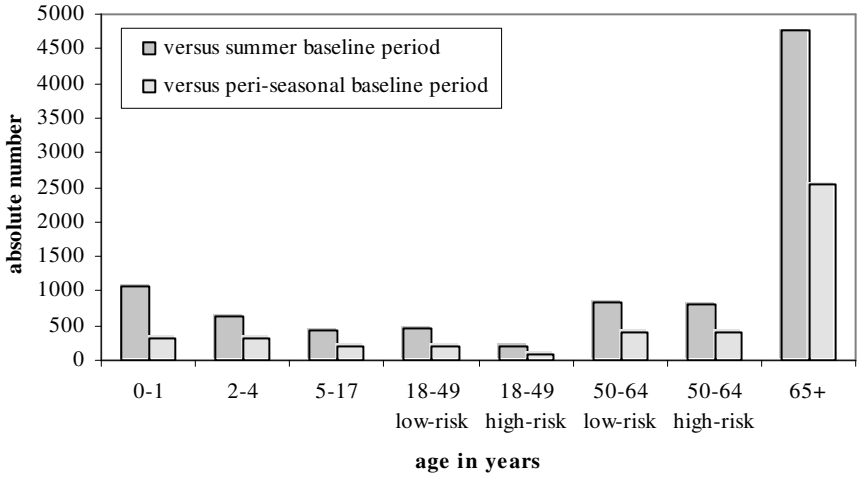


Figure 4: Average annual RSV-associated hospitalization burden in the Netherlands

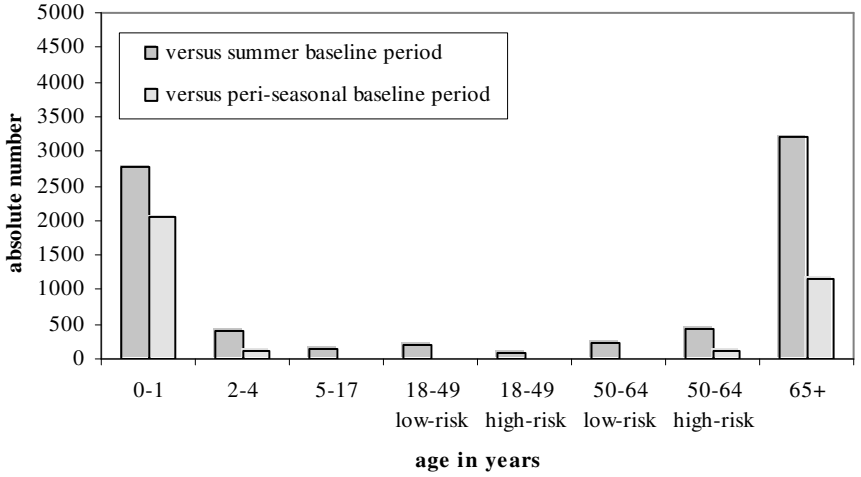


Table 2: Weekly mortality and estimated total winter mortality associated with influenza virus and RSV

Age years	Weekly mortality per 100.000 persons				Total excess winter mortality per 100,000 persons* (95% confidence interval)			
					Influenza virus		RSV	
	Period of influenza virus-predominance	Period of RSV-predominance	Summer baseline period	Peri-seasonal baseline period	versus summer baseline period	versus peri-seasonal baseline period	versus summer baseline period	versus peri-seasonal baseline period
0-1	5.3	5.0	5.4	5.4	none	none	none	none
2-17	0.4	0.3	0.4	0.3	0.1 *(-0.3-0.4)*	0.3 *(0.1-0.7)*	none	none
18-49	2.1	2.1	2.0	2.1	0.7 *(0.2-1.2)*	0.4 (-0.1-0.9)	0.3 *(-0.1-0.8)*	0.1 *(-0.4-0.5)*
50-64	12.8	12.6	11.9	12.3	7.6 *(5.7-9.6)*	3.8 *(1.8-5.7)*	5.4 *(3.5-7.2)*	1.9 *(-0.1-3.7)*
≥ 65	110.5	105.7	92.9	98.9	146.5 *(140.3-152.8)*	96.4 *(90.0-102.8)*	98.7 *(92.8-104.6)*	52.1 *(46.1-58.2)*

non-significant excesses are given in gray; none means no (non)significant excess; * Total winter excess was calculated as the difference between rates during virus-active periods and reference periods multiplied by the average number of virus-active weeks per winter, i.e. 8.3 weeks for influenza virus and 7.7 weeks for respiratory syncytial virus.

Table 3: Hospitalization rates and total winter excess hospitalization among children associated with influenza virus and RSV

Age	Weekly rate per 100.000 persons				Total winter excess per 100,000 persons* (95% confidence interval)			
					Influenza virus		RSV	
years	Period of influenza virus-predominance	Period of RSV-predominance	Summer baseline period	Peri-seasonal baseline period	versus summer baseline period	versus peri-seasonal baseline period	versus summer baseline period	versus peri-seasonal baseline period
Upper respiratory tract infections								
0-1	28.4	28.8	17.1	24.3	94.5 *(87.3-101.6)*	34.2 *(26.6-41.7)*	90.6 *(83.7-97.4)*	34.7 *(27.4-41.8)*
2-4	21.5	17.0	14.0	17.9	61.8 *(56.7-67.0)*	30.1 *(24.8-35.5)*	22.4 *(17.9-27.0)*	none
5-17	6.6	5.6	5.1	5.9	12.1 *(10.7-13.5)*	5.5 *(4.1-7.0)*	3.7 *(2.4-4.9)*	none
Lower respiratory tract infections								
0-1	31.2	93.0	14.0	29.6	142.7 *(135.4-149.9)*	13.0 *(4.9-20.9)*	608.2 *(596.7-619.7)*	487.8 *(475.9-499.7)*
2-4	9.6	11.7	7.3	9.2	19.8 *(16.4-23.3)*	3.8 *(0.2-7.5)*	34.6 *(31.0-38.2)*	19.7 *(16.0-23.5)*
5-17	2.0	2.0	1.7	2.0	2.5 *(1.7-3.2)*	none	1.8 *(1.1-2.5)*	none
Others								
0-1	17.1	12.7	13.0	13.3	34.1 *(28.5-39.8)*	31.9 *(26.2-37.6)*	none	none
2-4	5.9	4.2	3.2	4.1	23.8 *(20.9-26.6)*	16.0 *(13.1-18.9)*	7.6 *(5.5-9.9)*	0.9 *(-1.5-3.2)*
5-17	1.0	0.8	0.7	0.7	2.6 *(2.0-3.1)*	2.5 *(1.9-3.1)*	0.5 *(0.0-0.9)*	0.4 *(-0.1-0.9)*

non-significant excesses are given in gray; none means no (non)significant excess; * Total winter excess was calculated as the difference between rates during virus-active periods and reference periods multiplied by the average number of virus-active weeks per winter, i.e. 8.3 weeks for influenza virus and 7.7 weeks for respiratory syncytial virus.

Table 4: Hospitalization rates and estimated total winter excess hospitalization in adults associated with influenza virus and RSV

		Weekly rate per 100,000 persons				Total winter excess per 100,000 persons* (95% confidence interval)			
						Influenza virus		RSV	
		Period of influenza virus-predominance	Period of RSV-predominance	Summer baseline period	Peri-seasonal baseline period	versus summer baseline period	versus peri-seasonal base-line period	versus summer baseline period	versus peri-seasonal baseline period
Upper respiratory tract infections									
18-49 years	**LR**	0.6	0.4	0.4	0.5	1.2 *(0.9-1.4)*	0.5 *(0.3-0.8)*	0.2 *(0.0-0.4)*	none
	HR	0.4	0.4	0.3	0.3	0.9 *(0.3-1.6)*	0.7 *(0.0-1.3)*	0.5 *(-0.1-1.2)*	0.2 *(-0.4-0.9)*
50-64 years	**LR**	0.7	0.6	0.5	0.6	2.1 *(1.7-2.7)*	1.4 *(0.8-1.9)*	0.8 *(0.3-1.2)*	none
	HR	0.8	0.7	0.4	0.6	3.2 *(2.4-4.2)*	2.1 *(1.2-3.0)*	1.9 *(1.1-2.6)*	0.7 *(-0.2-1.5)*
≥ 65 years		2.0	1.6	1.0	1.2	8.9 *(8.1-9.6)*	6.7 *(5.9-7.5)*	5.2 *(4.5-5.9)*	3.2 *(2.5-3.9)*
Lower respiratory tract infections and pulmonary disease									
18-49 years	**LR**	2.5	2.2	2.0	2.3	4.2 *(3.7-4.7)*	2.1 *(1.5-2.6)*	1.7 *(1.2-2.2)*	none
	HR	14.2	13.1	13.3	11.3	23.7 *(19.8-27.6)*	6.8 *(2.7-10.9)*	13.6 *(9.9-17.2)*	none
50-64 years	**LR**	6.0	5.0	4.4	5.1	12.8 *(11.3-14.3)*	7.0 *(5.5-8.6)*	4.3 *(2.9-5.6)*	none
	HR	24.5	22.3	16.5	20.3	66.5 *(61.6-71.4)*	34.9 *(29.9-40.0)*	44.2 *(39.7-48.7)*	15.0 *(10.2-19.7)*
≥ 65 years		38.4	34.8	24.5	30.0	115.2 *(111.6-118.8)*	69.1 *(65.4-72.9)*	79.7 *(76.4-83.0)*	37.0 *(33.5-40.4)*

LR, low-risk; HR, high-risk; non-significant excesses are given in gray; none means no (non)significant excess; * Total winter excess was calculated as the difference between rates during virus active periods and reference periods multiplied by the average number of virus active weeks per winter, i.e. 8.3 weeks for influenza virus and 7.7 weeks for respiratory syncytial virus.

Table 4, continued

		Weekly rate per 100,000 persons				Total winter excess per 100,000 persons* (95% confidence interval)			
						Influenza virus		RSV	
		Period of influenza virus-predominance	Period of RSV-predominance	Summer baseline period	Peri-seasonal baseline period	versus summer baseline period	versus peri-seasonal baseline period	versus summer baseline period	versus peri-seasonal baseline period
Cardiovascular complications									
18-49 years	**LR**	3.5	3.4	3.3	3.5	1.7 *(1.0-2.2)*	0.3 *(-0.4-0.9)*	0.9 *(0.3-1.5)*	none
	HR	9.6	8.9	8.9	9.1	6.2 *(3.0-9.6)*	4.3 *(1.0-7.6)*	0.2 *(-2.9-3.2)*	none
50-64 years	**LR**	31.0	29.1	28.3	30.0	21.7 *(18.2-25.2)*	8.3 *(4.7-11.9)*	5.5 *(2.2-8.8)*	none
	HR	34.3	32.3	31.3	33.0	24.9 *(18.9-31.0)*	10.8 *(4.6-16.9)*	7.2 *(1.5-12.8)*	none
≥ 65 years		87.2	84.6	77.5	83.3	81.1 *(75.5-86.7)*	32.5 *(26.6-38.2)*	55.1*(49.8-60.5)*	10.0 *(4.5-15.5)*
Others									
18-49 years	**LR**	0.6	0.5	0.5	0.5	0.2 *(-0.1-0.4)*	0.3 *(0.1-0.5)*	none	none
	HR	0.7	0.6	0.6	0.6	0.5 *(-0.3-1.4)*	0.9 *(0.1-1.8)*	0.2 *(-0.6-1.0)*	0.5 *(-0.2-1.4)*
50-64 years	**LR**	1.5	1.4	1.3	1.4	1.4 *(0.7-2.2)*	1.0 *(0.2-1.7)*	0.6 *(-0.2-1.5)*	0.2 *(-0.5-1.0)*
	HR	1.2	0.8	0.9	0.9	2.2 *(1.2-3.3)*	2.1 *(0.8-3.2)*	none	none
≥ 65 years		3.7	3.4	3.3	3.4	2.8 *(1.7-4.0)*	2.7 *(1.5-3.8)*	0.6 *(-0.5-1.7)*	0.5 *(-0.6-1.5)*

LR, low-risk; HR, high-risk; non-significant excesses are given in gray; none means no (non)significant excess; * Total winter excess was calculated as the difference between rates during virus active periods and reference periods multiplied by the average number of virus active weeks per winter, i.e. 8.3 weeks for influenza virus and 7.7 weeks for respiratory syncytial virus.

Discussion

This nationwide retrospective study covering six recent consecutive respiratory seasons showed that mortality associated with influenza was substantial among persons aged 50 years and older. Influenza-associated hospitalization was significant among healthy persons of all age categories and highest for young children and older persons. The highest RSV-associated excess hospitalization occurred also in the youngest, but it was also significant in the elderly in which RSV-active periods were associated with excess mortality as well.

Many models have been described to estimate the influenza-associated burden and most are based on determining the excess rate during influenza virus-active periods versus baseline periods with (lower or) no influenza virus-activity. The rate-difference model has regularly been applied,[7,20,21] and is a straight-forward variant of these models allowing for insight to a broad public. Because of the use of diverse statistical models including the different definitions of viral seasons, and the various definitions of endpoints (e.g. culture confirmed influenza or not), studies are difficult to compare.[1-3,7,9,20-27] Variations of the included study period (and consequently varying influenza virus-activity) and differences in health care systems further lead to poor comparability, as for example primary care in the Netherlands with a gate-keeping function may affect hospitalization rates.

In contrast to previous studies,[2,25] which reported 2-7 influenza-associated deaths per 100,000 among 0-1-year-olds annually and about 1 per 100,000 among 1-4-year-olds, we could not detect excess mortality in children during influenza virus-active periods. Our methods may lack sensitivity to detect small excesses of influenza-associated deaths. We confirmed however that among children and 18-64-year-olds without high-risk medical conditions, the highest influenza-associated excess hospitalization occurs in the youngest children.[3,9,20-24] This suggests that this target group may particularly benefit from influenza vaccination, certainly when also influenza-related primary care visits and parental work absenteeism are taken into account.[27] Additionally, it is also thought that children are the main disseminators of influenza,[28] and vaccinating children may therefore limit the spread of infection in the community. The influenza vaccine is however currently not licensed for

children younger than six months, and evidence for the efficacy and effectiveness of the vaccine in children below two years of age is limited.[29]

Our study indicates that influenza virus-active periods were associated with excess mortality among 50-64-year-olds. Unfortunately, we were not able to estimate which part of this excess occurred in low-risk individuals as information about the risk status was not available in the mortality figures. Influenza-associated hospitalization was however significant among low-risk 50-64-year-olds. A recent study was not able to demonstrate influenza-associated hospitalization in this group, but this was probably due to limited statistical power.[7] The hospitalization rates we found among low-risk 50-64-year-olds were clearly lower than those in young children, but the nature of the hospitalizations may also be important. While in children the excess hospitalization was mainly due to respiratory conditions, hospitalizations for CVC made up the largest part of the excess hospitalization among 50-64-year-olds. Obviously, these hospitalizations are expected to have a large impact on the health care system and financial resources. Both influenza-associated excess mortality and hospitalization, in particular for CVC, increased with age, indicating that 60-64-year-olds would benefit most from annual influenza vaccination. The influenza vaccine has proven to be safe and effective among adults, and it also appears effective in preventing cardiovascular outcomes.[30-33] Apart from potential health gain, cost-effectiveness analyses taking into account both direct and indirect influenza-associated costs, like absenteeism from work, are important to direct decisions to change vaccination policy.

Despite the high influenza vaccination coverage among elderly in the Netherlands (70-80%), influenza-associated mortality appeared high among elderly in our study. It is however known that the immunogenicity of the influenza vaccine decreases with age after the age of 65 years, which may lead to reduced effectiveness.[30,34] This emphasizes the need for further improvement of the protection against influenza particularly in elderly.

As expected, the highest RSV-related excess hospitalization occurred in the youngest,[35,36] and this burden appeared considerably higher than that associated with influenza. We could not demonstrate RSV-related mortality in this age category. For the same power problems applicable to the influenza-related mortality in this study among young children, we cannot

exclude the possibility of RSV-associated mortality in this age category. Previous studies reported 5-8 RSV-associated deaths per 100,000 annually among 0-12-month-olds and about 1 per 100,000 among 1-4-year-olds.[2,25] Significant excess hospitalization was also demonstrated among adults, especially the elderly. Moreover, RSV-active periods appeared associated with excess mortality among 50-64-year-olds and elderly. The RSV-associated hospitalization appeared mainly for respiratory indications and to a lesser extent for the indication CVC compared to influenza-associated hospitalization, which is in agreement with a former study.[24]

To appreciate the results of the current study, some aspects should however be discussed. As epidemiological data were used to estimate influenza- and RSV-related burden, direct evidence was lacking for the causative pathogen that lead to hospitalization or death. Therefore the results should be interpreted cautiously. The burden will however be underestimated by just recording laboratory-confirmed influenza and RSV-infections, due to underdiagnosis/underreporting, but also in case of secondary complications (like bacterial infections or possible other complications such as cardiovascular diseases). Moreover, influenza virus is a pathogen that has extensively been studied and is well-known to be responsible for considerable morbidity and mortality almost annually. In contrast, the role of RSV in causing morbidity and mortality especially among adults is less clear. In our study, a clear excess mortality and morbidity was found during RSV-active periods. However, most of our RSV surveillance data were reported in children, and although we assumed that RSV-activity among adults parallels that in children, this is not exactly known.[37] Possibly, we therefore misclassified some of the RSV- and influenza-associated morbidity, as in all other excess studies. This should be addressed in future studies and also stresses the importance for age-specific RSV-surveillance.

Furthermore, the estimations of virus-related burden strongly depended on the applied reference period, and estimates should therefore be viewed in rather large margins. The peri-seasonal baseline period is the most conservative reference and by applying this reference the virus-related burden is probably underestimated, because excess rates are determined over periods in which influenza virus and RSV are active albeit to a lesser extent (weeks with less than 5% of season's total number of isolates). On the other hand,

the potential role of other respiratory viruses or other seasonal factors such as certain meteorological conditions affecting the rate of hospitalization and mortality is limited with the peri-seasonal baseline period as reference. In other words, by applying the peri-seasonal baseline period as reference we attempted to correct for other potentially important seasonal factors. Therefore, it appears that the true influenza- and RSV-associated excess mortality and hospitalization probably lies within the estimations based on the peri-seasonal and summer baseline period. Nevertheless, it is expected that other viruses like rhinoviruses and coronaviruses cause milder clinical manifestations of respiratory infections which lead to primary care visits. Moreover, surveillance data in the Netherlands during our study period demonstrated that rhinoviruses, adenoviruses and para-influenza viruses appeared to have no clear seasonal pattern like influenza viruses and RSV, with rather long periods of marginally increased activity or very short peaks of increased activity (Appendix Figure 1). Unfortunately, the seasonal pattern of some recently discovered coronaviruses and the human metapneumovirus could not be assessed since no surveillance data were available during the study period.

The major strength of the current study is its nationwide character including large numbers thus allowing subanalysis according to age and the presence of high-risk conditions for hospitalization among adults. With the Netherlands being a small but densely populated country, population characteristics are relatively homogenous nationwide and viral circulation is more or less simultaneous across the country, making ecological studies more reliable. Further, the study period covered six years with different viral attack rates.

In summary, substantial influenza-associated excess hospitalization was found among 0-4-year-olds, although mortality could not be attributed to influenza in this age group. Among low-risk 50-64-year-olds also significant influenza-associated excess hospitalization was recorded, and even excess mortality appeared to be present. Part of this burden might be prevented by introducing annual influenza vaccination. The RSV-associated burden appeared substantial particularly in young children but also in the elderly, and therefore the role of a future RSV vaccine appears promising in reducing this health care burden.

Acknowledgment

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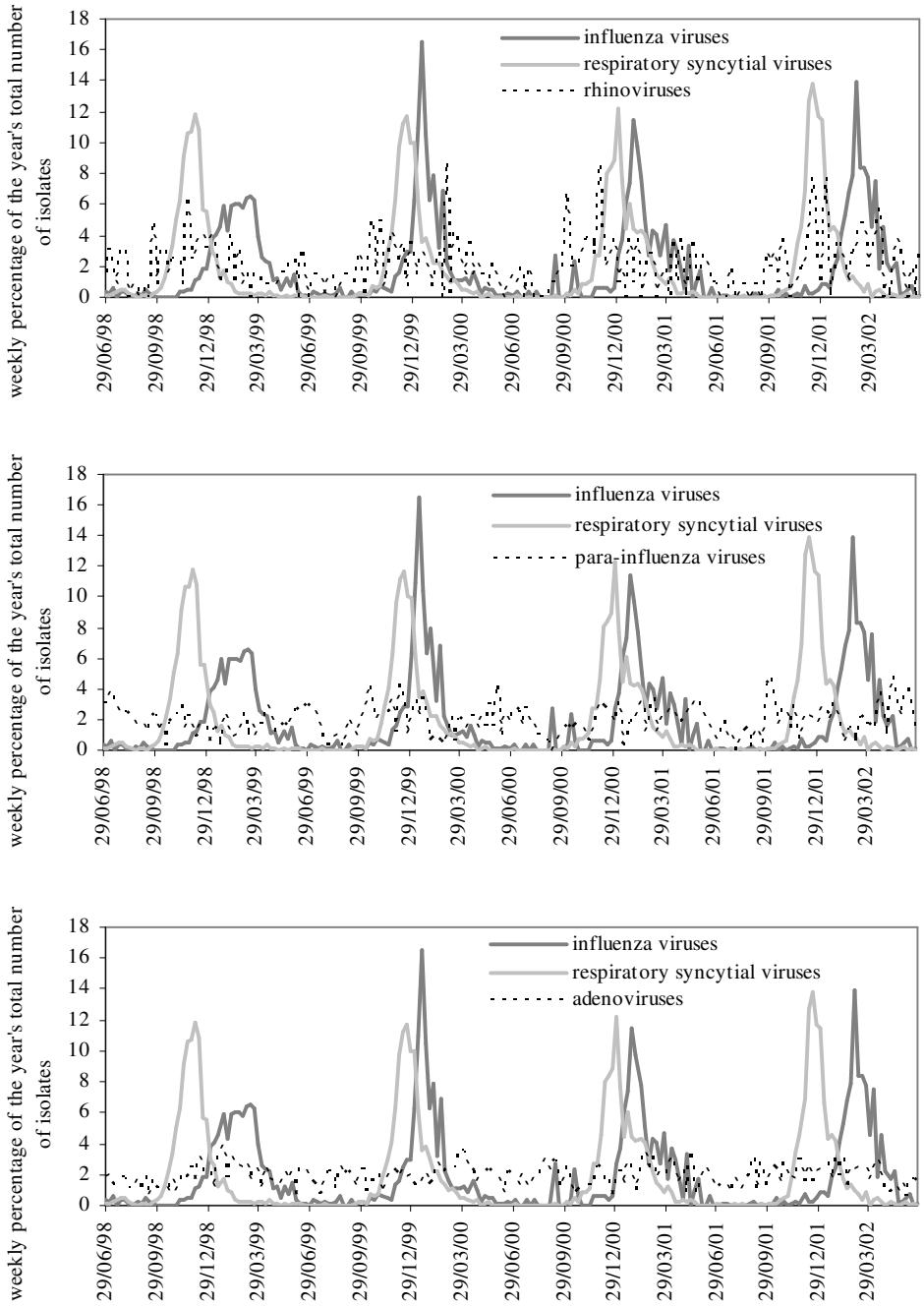
Appendix Figure 1: Respiratory viral activity throughout the years 1998 to 2002



Source: *Weekly Sentinel System of the Dutch Working Group on Clinical Virology*

CHAPTER 4

Decline in influenza-associated mortality among Dutch elderly following the introduction of a nationwide vaccination program

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Abstract

Background: Trend studies could not correlate increasing influenza vaccine uptake with a decline in mortality among the elderly.

Objective: To assess influenza-associated mortality among Dutch elderly before and after the introduction of a nationwide vaccination program.

Methods: Retrospective nationwide study among persons aged 65 years and older over 1992 to 2003. National mortality data and viral surveillance data were used to estimate influenza-associated mortality for each year using rate difference methods. Vaccination coverage before and after the nationwide influenza vaccination program in 1996 was below 50% and 80%. Relative risks of influenza-associated mortality with corresponding 95% confidence interval (95%CI) were estimated using average rates before and after the vaccination program. As a control outcome, the same analyses were performed to estimate respiratory syncytial virus (RSV)-associated mortality rates. We applied a Serfling-type regression analysis to validate the rate difference method.

Results: Before the start of the program, the average annual influenza-associated mortality was 131 (95%CI: 123-139) per 100,000 persons. Over the respiratory seasons from 1996 onwards, this was 105 (95%CI: 99-111) per 100,000 persons (relative risk 0.80, 95%CI: 0.78-0.82). The decline was largest in the age group 65-69 years (relative risk 0.54, 95%CI: 0.50-0.59) and less in those aged 75 years and older. RSV-associated mortality was similar in the 1992-1996 and 1996-2003 respiratory seasons (relative risk 1.03, 95%CI: 0.99-1.06). Serfling-type regression analysis demonstrated similar declines in influenza-associated mortality.

Conclusion: Introduction of routine influenza vaccination among Dutch elderly was associated with a significant decrease in influenza-associated mortality, notably in those aged 65-69 years.

Introduction

Influenza epidemics are held responsible for substantial morbidity and mortality, particularly among the elderly.[1-4] Immunization against influenza was proven to reduce culture confirmed influenza by 50%,[5] and several observational cohort studies reported vaccination to confer substantial reductions in hospitalizations for acute respiratory, cardiovascular, and cerebrovascular events and all-cause mortality during influenza seasons.[6-9] It has therefore been hypothesized that increasing influenza vaccination coverage rates should lead to a decrease in influenza-associated mortality. Surprisingly, data from ecological trend studies conducted in the United States did not support this assumption,[3,10] and the benefits of vaccination have been questioned more and more. Yet, these studies may have been hindered by the major disparities in vaccination rates by geography as well as by socioeconomic, demographic, and health characteristics making it very difficult to estimate individual benefit from population-level data.

The Netherlands encompass a rather homogeneous population, and influenza vaccination approximated 80% after the introduction of routine influenza vaccination among all elderly in 1996. With the current study we aimed to estimate influenza-attributable mortality among elderly over the years 1992 to 2003 and compared the mortality rates before and after the introduction of the vaccination program.

Methods

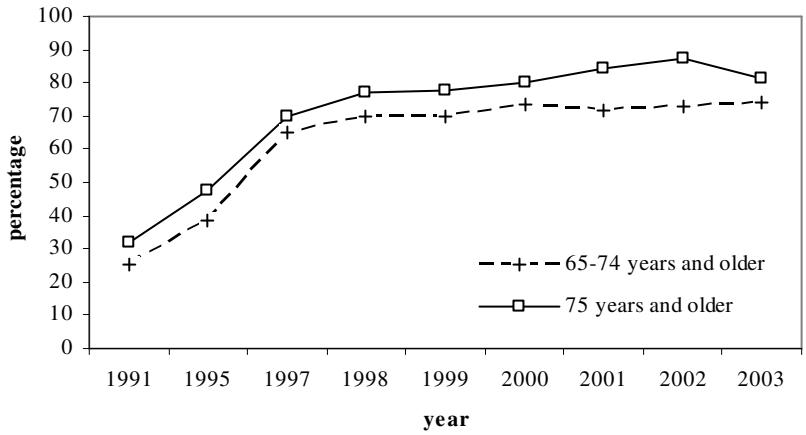
Study population

Weekly all-cause mortality data of all Dutch citizens aged 65 years and older were obtained during the respiratory seasons 1992 to 2003 from Statistics Netherlands, Voorburg/Heerlen, the Netherlands. Each respiratory season started in week 27 of one year and lasted until week 26 of the next year.

The Dutch primary care Influenza vaccination program

Until the respiratory season 1996-1997, influenza vaccination was recommended only for persons with certain high-risk medical conditions in the Netherlands (such as chronic heart, lung and kidney disease). From the respiratory season 1996-1997 onwards, recommendations were extended to include all persons aged 65 years and older for influenza vaccination and a nationwide primary care prevention program was started.[11] Age-specific figures of influenza vaccination coverage were available for the years 1991, 1995, and yearly from 1997 to 2003 from Statistics Netherlands, Voorburg/Heerlen, the Netherlands. Before the introduction of the program, vaccine coverage in those aged 65 years and older was less than 50% and after its start coverage approximated 80% among the elderly (Figure 1); vaccination coverage was 8 to 22% higher in elderly persons without high-risk medical conditions than in those without. Overall vaccination coverage was more or less similar in 5-year age categories from 75 years and older.[12,13]

Figure 1: Influenza vaccination coverage among persons aged 65 years and older



Viral surveillance

From 1992 onwards, whole-year laboratory-based surveillance for various viruses was conducted by the Weekly Sentinel System of the Dutch Working Group on Clinical Virology in the Netherlands. Seventeen medical microbiological laboratories reported their findings in weekly virological reports and these were demonstrated to reflect trends in national viral activity adequately.[14] The reports contained the absolute weekly number of

reported patients either hospitalised or visiting outpatient clinics that tested positive for a certain virus. For this study, data for influenza virus and respiratory syncytial virus (RSV) were obtained. Most laboratory diagnoses were made by virus isolation on cell culture or rapid antigen tests. An influenza virus subtype was considered dominant when it accounted for at least 50% of all isolates that were subtyped during that season.

Definition of study periods

With minor modifications, study periods were defined according to Izurieta and colleagues.[15] For each winter season from week 40 of one year to week 20 of the next year, the influenza virus-active period was defined as the periods of at least two consecutive weeks in which each week accounted for 5% or more of the season's total number of reported laboratory-confirmed influenza virus infections.[15] Similarly, the RSV-active period was defined as the periods of at least two consecutive weeks in which each week accounted for 5% or more of the season's total number of RSV-positive patients. The period with influenza predominance was defined as the influenza virus-active weeks with less than 5% of the season's total number of positive tests for RSV; periods with RSV predominance was defined as the RSV-active weeks with less than 5% of the season's total number of reported influenza virus infections.[15] The peri-seasonal baseline period was defined as periods of at least two consecutive weeks within week 40 to 20, while each week accounted for less than 5% of the season's total number of influenza virus- and RSV-positive cases. The summer baseline period was defined as the period from week 21 to 39.

Eighty-six influenza virus-active weeks, 92 RSV-active weeks, 198 weeks of peri-seasonal baseline period, and 209 weeks of summer baseline period were identified. In total 15 influenza virus- and RSV-active weeks overlapped, of which 10 weeks during the seasons 1993-1994, 1995-1996, and 1996-1997. Influenza A subtype H3N2 was the dominant circulating strain in all seasons except for 1992-1993 and 2000-2001 in which respectively influenza virus B and influenza virus A subtype H1N1 were dominant (Figure 2). Seasons 1994-1995, 2000-2001, and 2002-2003 demonstrated lower influenza virus-activity. Seasons with lower influenza virus-activity were defined as those with a total number of reported laboratory-confirmed influenza cases below the 25th percentile of all study years.

Statistical analysis

The Dutch age-specific population size at January 1st was taken as the population at risk from Statistics Netherlands, Voorburg/Heerlen, the Netherlands. For each year, the weekly mortality rate (per 100,000 persons) was calculated for the different study periods. Weekly excess mortality rates attributable to influenza with 95% confidence interval (95%CI) were determined by subtracting summer and peri-seasonal baseline rates from rates during periods of influenza predominance using Episheet (Rothman K. Episheet: Spreadsheets for the analysis of epidemiologic data, 2002). Total mortality per 100,000 inhabitants attributable to influenza during winter season (cumulative annual winter excess rate) was calculated by multiplying the average weekly excess rate during the influenza predominance period with the number of influenza virus-active weeks during that winter season.

Age-specific relative risks of influenza-associated death with their 95%CI were estimated before and after the introduction of routine influenza vaccination, i.e. the average risk in the respiratory seasons 1996-2003 versus the average risk in 1992-1996. As a "control outcome", also the RSV-associated mortality was determined over the years, since the latter outcome is very unlikely to be influenced by influenza vaccination rates.

Although influenza virus-activity appeared more or less similar over the study years (Figure 2), we also planned sensitivity analyses excluding seasons with lower influenza virus-activity or non-influenza virus A (H3N2) dominant activity. It has been demonstrated that influenza-associated mortality is much higher in seasons dominated by influenza virus A (H3N2) than in seasons dominated by influenza B and A (H1N1) viruses.[1] Furthermore, vaccine effectiveness is much lower during lower influenza virus-activity seasons and non-influenza virus A subtype H3N2 seasons.[16]

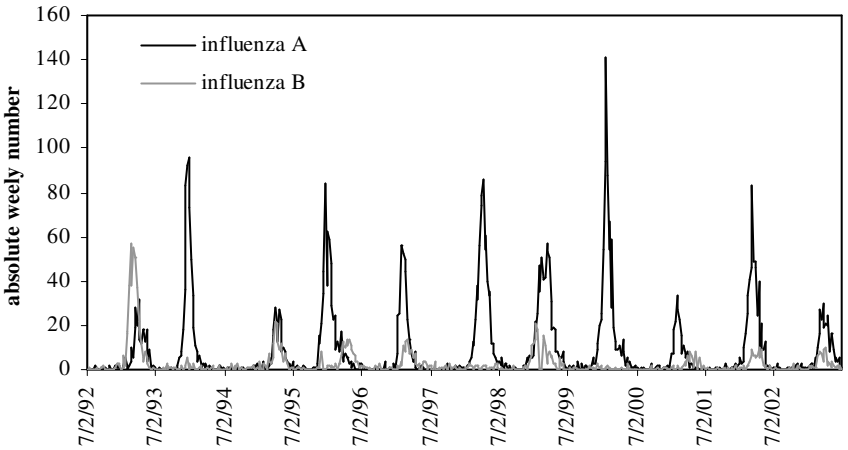
To assess whether our findings were sensitive to the assumptions we made, we validated our analyses by application of a Serfling-type regression model (adapted from the methods of Simonsen et al.[10]). The time series was first de-trended by dividing the weekly number of deaths by the average weekly number of visits in summer (June-August). A seasonal

regression model was then applied to the de-trended series, Yt, excluding values for the period December to April:

$$Yt = a + b\cos(2\pi t/52) + c\sin(2\pi t/52) + e_t,$$

where t is the index for week of death (1-568), and e_t is the error term. Influenza epidemic periods were identified by applying this procedure to the reported isolates of influenza. The "epidemic weeks" for each season were defined as those weeks for which the number of influenza virus isolates exceeded the upper 95% confidence limit of that predicted by the model. Next, the model was applied to the mortality rates. Weekly excess rates were calculated as the observed minus predicted rate for all "epidemic weeks". The seasonal excess was estimated as the sum of weekly excess mortality.

Figure 2: Weekly number of reported laboratory-confirmed influenza cases



Results

Total winter excess mortality attributable to influenza increased about 10-fold from the age category 65-69 years to the category 80 years and older (Table 1, Appendix Table 1). Among all persons aged 65 years and older, influenza-associated mortality decreased over the period from 1992 to 2003 (Figure 3, Appendix Table 2). In the seasons before the introduction of routine influenza vaccination (1992-1996), the average annual cumulative

winter excess mortality attributable to influenza was 131 (95%CI: 123-139) and 172 (95%CI: 163-180) deaths per 100,000 persons aged 65 years and older (with the peri-seasonal and summer baseline period as reference, respectively. Thereafter (1996-2003), influenza-related mortality was on average respectively 105 (95%CI: 99-111) and 151 (95%CI: 145-157) deaths per 100,000 persons (relative risk 0.80 [95%CI: 0.78-0.82] and relative risk 0.88 [95%CI: 0.86-0.90] with the peri-seasonal and summer baseline period as reference).

Table 1: Relative risks of influenza-associated mortality before and after the introduction of routine influenza vaccination in elderly

Age years	Reference baseline period	Total winter excess mortality attributable to influenza per 100,000 persons (95%CI)		Relative risk of influenza - associated death (95%CI)
		Seasons 1996-2003	Seasons 1992-1996	
65-69	peri-season	17 (11-23)	31 (22-40)	0.54 (0.49-0.60)
	summer	26 (20-33)	49 (40-57)	0.54 (0.50-0.59)
70-74	peri-season	35 (26-44)	50 (38-62)	0.70 (0.64-0.76)
	summer	59 (50-67)	74 (63-86)	0.80 (0.75-0.80)
75-79	peri-season	94 (81-107)	114 (96-132)	0.82 (0.78-0.87)
	summer	141 (129-154)	153 (135-171)	0.93 (0.88-0.97)
≥ 80	peri-season	302 (282-321)	371 (345-397)	0.81 (0.79-0.84)
	summer	417 (398-436)	462 (436-388)	0.90 (0.88-0.93)
Within selection of seasons*				
65-69	peri-season	19 (11-27)	53 (39-67)	0.36 (0.32-0.40)
	summer	27 (19-35)	72 (59-86)	0.37 (0.34-0.41)
70-74	peri-season	46 (35-57)	95 (76-114)	0.49 (0.45-0.53)
	summer	67 (56-77)	126 (107-145)	0.53 (0.49-0.57)
75-79	peri-season	123 (107-139)	193 (163-222)	0.64 (0.60-0.68)
	summer	167 (151-183)	240 (211-270)	0.70 (0.66-0.74)
≥ 80	peri-season	375 (351-399)	608 (565-651)	0.62 (0.60-0.64)
	summer	480 (456-504)	722 (679-764)	0.67 (0,65-0.69)

95%CI, 95% confidence interval; * after exclusion of seasons with lower influenza virus-activity (1994-1995, 2000-2001, 2002-2003) or non-influenza virus A (H3N2) dominant activity (1992-93, 2000-01)

Figure 3A: Standardized total winter excess mortality attributable to influenza, peri-seasonal baseline period as reference

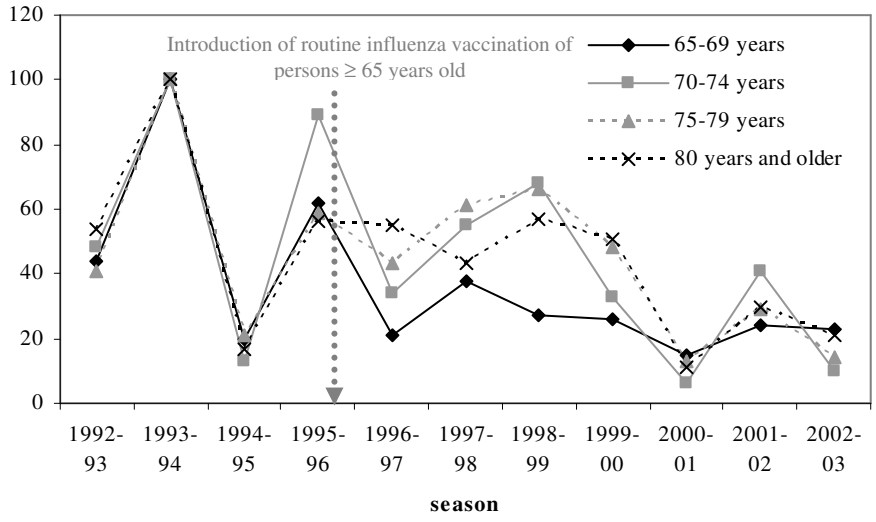
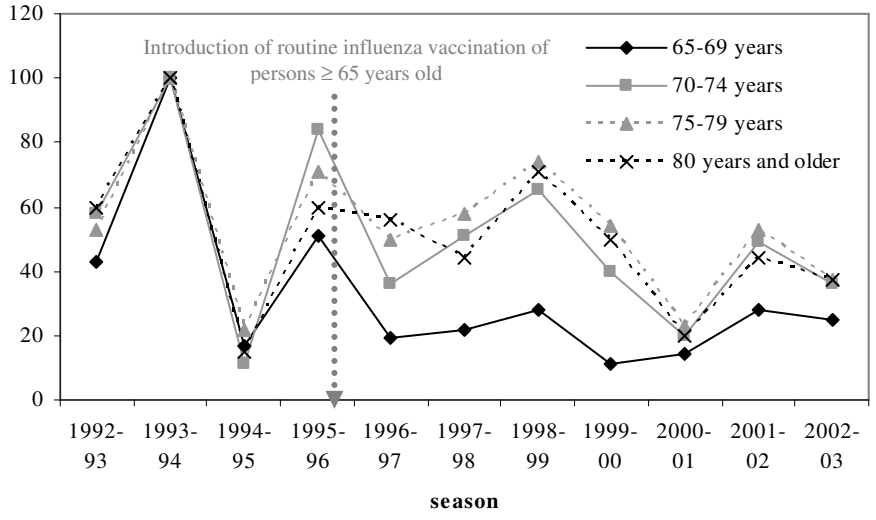


Figure 3B: Standardized total winter excess mortality attributable to influenza, summer baseline period as reference



In a sensitivity analysis in which we excluded the seasons with dominant strains other than influenza virus A subtype H3N2 and seasons with lower influenza virus-activity, the average annual cumulative winter excess mortality attributable to influenza was 220 (95%CI:207-233) and 270 (95%CI: 257-283) deaths per 100,000 persons aged 65 years and older (with the peri-seasonal and summer baseline period as reference, respectively) before the introduction of routine influenza vaccination. After initiation of the nationwide program, these figures were 131 (95%CI: 124-139) and 173 (95%CI: 165-180) per 100,000 persons (relative risk 0.60 [95%CI:0.58-0.61] and relative risk 0.64 [95%CI:0.62-0.65]). Within smaller age categories, 65 to 69-year-olds appeared to show the strongest decline in influenza-associated mortality (Figure 3, Table 1).

During the respiratory seasons 1992-1996, RSV-associated mortality (Appendix Table 3) was yearly on average 61 (95%CI: 52-70) and 116 (95%CI: 107-125) deaths per 100,000 elderly persons (with the peri-seasonal and summer baseline period as reference, respectively). Corresponding figures for the seasons 1996-2003 were 62 (95%CI: 57-68) and 105 (95%CI: 100-111), relative risk 1.03 (95%CI: 0.99-1.06) and 0.91 (95%CI: 0.89-0.93) respectively (Table 2).

Table 2: Relative risks of RSV-associated death before and after the introduction of routine influenza vaccination in elderly

Age years	Reference baseline period	Total winter excess mortality attributable to RSV per 100,000 persons (95%CI)		Relative risk of RSV-associated death (95%CI)
		Seasons 1996-2003	Seasons 1992-1996	
65-69	peri-season	12 (6-18)	10 (0-20)	1.14 (0.98-1.32)
	summer	20 (14-26)	34 (24-44)	0.59 (0.54-0.65)
70-74	peri-season	22 (14-31)	22 (9-35)	1.02 (0.91-1.14)
	summer	45 (37-53)	55 (42-68)	0.82 (0.76-0.88)
75-79	peri-season	46 (33-58)	45 (25-66)	1.02 (0.93-1.11)
	summer	89 (78-102)	98 (78-118)	0.92 (0.86-0.98)
≥ 80	peri-season	185 (167-203)	185 (156-214)	1.00 (0.96-1.04)
	summer	292 (274-310)	309 (280-337)	0.81 (0.79-0.84)

95%CI, 95% confidence interval

Validation of the data by use of a Serfling-type regression model demonstrated similar decreases in influenza mortality in all age categories of the persons ≥65 years over the period from 1992 to 2003 (Appendix Table 4, Appendix Figure 1).

Discussion

This nationally representative ecological study demonstrated a decline in influenza-associated mortality among elderly after the start of the large-scale influenza vaccination program in the Netherlands in 1996, notably in those aged 65 to 69 years.

Alternative explanations for the observed decline, other than the increasing influenza vaccination coverage, are not very likely. Importantly, in the Netherlands pneumococcal vaccination has not been routinely recommended for elderly persons and infants, and therefore it could not have affected mortality figures. Also, influenza virus-activity was more or less similar before and after the introduction of the vaccination program as reflected by the absolute number of influenza cases reported by the laboratories (Figure 2). An alternative explanation for the observed decline may be that the vaccine effort to introduce influenza vaccination among all elderly may have somehow spilled over to the younger population. There is data to suggest that if the very young were vaccinated, this would help reduce the infection rate and the exposure rate to the elderly.[17] This would eventuate in reduction of death in the at risk group. However, in the Netherlands children without high-risk medical conditions (asthma, cardiac conditions, etc.) are not recommended for influenza vaccination, and influenza vaccination coverage among otherwise healthy 0-4-year-olds was less than 3% during our study period,[13] and therefore this could not have affected influenza-associated mortality rates in the elderly. Some may claim that nearly annual waves of influenza virus type A H3N2 led to the development of broad and potent natural immunity among the aged survivors. However, only 5 to 15% of the population is infected with influenza annually. The probability that the same person will be infected in the next years is thus very small and it is unlikely that such a mechanism fully explains these results. Importantly, the type of virus circulating differed substantially over time which caused these annual epidemics. Others may claim that the waves of

influenza virus type A H3N2 depleted the small pool of residents at very high risk of dying, leading to a decline in influenza-associated death over the years. However, if this were true, this would have been demonstrated in previous studies also covering periods with almost annual waves of influenza virus type A H3N2, and these studies could not demonstrate a decline at all.[3,10] Furthermore, we determined RSV-associated mortality over the years as a "control outcome", and no decline was shown in these data with the peri-seasonal baseline period as reference. This further suggests that other environmental or host factors possibly influencing virus-associated mortality were more or less stable during the study years. Yet, a small overall decline of RSV-associated mortality was observed in the data with the summer baseline period as reference. This may be explained by the fact that influenza virus is also active in weeks outside the period of influenza predominance, including periods of RSV predominance. Consequently, in the data with the summer baseline period as reference, we may have attributed part of the influenza-associated mortality to RSV. Excess mortality rates calculated with the peri-seasonal baseline period as reference appear therefore most reliable for observing trends.

The decline in influenza-associated mortality we found might even be an underestimation. Part of the elderly population with high-risk medical conditions was already immunized against influenza before introduction of routine vaccination of elderly. Additionally, over the last decade a growing proportion of elderly has developed diabetes and coronary heart disease (see Appendix Figure 2), conditions that have been associated with a higher risk of influenza complications. Finally, the proportion of persons aged 80 years and over among the elderly increased from 22.7% to 24.5% in the Netherlands during the study period.

Taking into account similar vaccination coverage in the 5-year age categories in the elderly (Appendix Figure 2), our results suggest that the youngest elderly, i.e. 65 to 69-year-olds, benefited more from vaccination than the very old. This is in agreement with the decreasing influenza vaccine immunogenicity with increasing age after the age of 65 years.[18]

Our methods bare some additional limitations. First of all, we based the estimates of deaths attributable to influenza on epidemiological data. These data naturally lack direct evidence for the cause of death. Furthermore, we may have underestimated the mortality associated

with influenza, since we did not take into account the weeks with minor influenza virus-activity, i.e. the weeks with less than 5% of the season's total number of influenza virus isolates.

In light of the potential limitations, conclusions should be carefully drawn. Results from the rate-difference method and validated by the Serfling-type regression model support a protective effect of influenza vaccination against excess mortality among the elderly during influenza virus-active periods.[6-9,18] Nevertheless, influenza still appears to be associated with substantial annual excess mortality in elderly despite high vaccination coverage, especially in the very old and there is a need for improved vaccines.

Acknowledgment

We would like to thank the Dutch Working Group on Clinical Virology for providing the viral surveillance data. This study was funded by the Health Council of the Netherlands.

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Appendix Table 1: Total winter excess mortality attributable to influenza over 1992-2003

Season	Total winter excess mortality attributable to influenza per 100,000 persons - peri-seasonal baseline period as reference (95% CI)					Total winter excess mortality attributable to influenza per 100,000 persons - summer baseline period as reference (95% CI)				
	65-69 years	*70-74 years*	*75-79 years*	*≥ 80 years*	*≥ 65 years*	*65-69 years*	*70-74 years*	*75-79 years*	*≥ 80 years*	*≥ 65 years*
1992-1993	29	48	101	422	138	53	80	150	542	191
	(11-47)	(23-73)	(63-138)	(367-477)	(122-155)	(35-70)	(55-104)	(113-186)	(489-595)	(175-208)
1993-1994	66	101	245	785	276	81	138	282	907	326
	(46-86)	(74-129)	(202-289)	(722-849)	(256-296)	(61-101)	(111-166)	(239-326)	(844-970)	(307-345)
1994-1995	13	13	52	132	48	21	15	61	137	54
	(-2-28)	(-7-33)	(20-83)	(89-176)	(34-62)	(6-36)	(-5-35)	(30-93)	(93-180)	(40-68)
1995-1996	41	90	145	442	168	63	116	199	541	215
	(22-60)	(64-117)	(105-185)	(385-500)	(150-186)	(44-82)	(89-142)	(159-239)	(483-599)	(197-233)
1996-1997	14	34	106	430	135	24	50	141	504	167
	(-7-34)	(6-62)	(63-148)	(366-493)	(115-154)	(4-45)	(22-79)	(98-184)	(441-568)	(147-186)
1997-1998	25	56	149	334	130	27	70	163	397	153
	(7-43)	(31-81)	(112-186)	(279-388)	(113-148)	(11-44)	(47-94)	(129-198)	(355-448)	(137-168)
1998-1999	18	69	162	447	161	35	90	210	641	227
	(-1-37)	(42-95)	(124-200)	(389-506)	(143-179)	(17-53)	(65-115)	(173-246)	(585-696)	(209-244)
1999-2000	17	33	118	397	131	14	55	153	456	157
	(0-34)	(9-56)	(84-153)	(344-451)	(114-147)	(-3-30)	(31-79)	(119-188)	(402-509)	(140-173)
2000-2001	10	6	31	84	31	17	28	66	183	70
	(-5-25)	(-15-26)	(2-61)	(40-129)	(17-45)	(2-32)	(8-49)	(36-96)	(139-228)	(56-84)
2001-2002	16	41	71	239	88	34	67	150	398	154
	(-0-32)	(18-63)	(38-104)	(189-289)	(72-103)	(17-50)	(44-89)	(118-183)	(349-446)	(139-170)
2002-2003	15	10	34	162	54	31	50	103	336	125
	(-1-30)	(-11-32)	(3-66)	(115-208)	(39-68)	(17-46)	(30-70)	(73-133)	(292-380)	(111-140)

95% CI, 95% confidence interval

Appendix Table 2: Mortality rates and estimated cumulative winter excess mortality attributable to influenza in persons aged 65 years and older

	Weekly mortality rate per 100,000 persons (95%CI)			Weekly excess mortality rate/100,000 persons* (95%CI)		Winter excess mortality** per 100,000 persons (95%CI)	
	Period of influenza predominance	**Peri-seasonal baseline**	**Summer base line**	**versus peri-seasonal baseline**	**versus summer baseline**	**versus peri-seasonal baseline**	**versus summer baseline**
92-93	118	101	94	17	24	138	191
	(116-120)	*(100-102)*	*(93-95)*	*(15-19)*	*(22-26)*	*(122-155)*	*(175-208)*
93-94	140	101	94	39	47	276	326
	(138-143)	*(100-102)*	*(93-95)*	*(37-42)*	*(44-49)*	*(256-296)*	*(307-345)*
94-95	107	100	99	7	8	48	54
	(105-109)	*(99-101)*	*(98-100)*	*(5-9)*	*(6-10)*	*(34-62)*	*(40-68)*
95-96	131	103	95	28	36	168	215
	(128-134)	*(102-104)*	*(94-96)*	*(25-31)*	*(33-39)*	*(150-186)*	*(197-233)*
96-97	113	96	92	17	21	135	167
	(111-115)	*(95-97)*	*(91-93)*	*(14-19)*	*(18-23)*	*(115-154)*	*(147-186)*
97-98	111	96	94	14	17	130	153
	(109-112)	*(95-97)*	*(93-95)*	*(13-16)*	*(15-19)*	*(113-148)*	*(137-168)*
98-99	115	99	93	16	23	161	227
	(114-117)	*(98-100)*	*(92-94)*	*(14-18)*	*(21-24)*	*(143-179)*	*(209-244)*
99-00	114	97	94	16	20	131	157
	(112-115)	*(96-98)*	*(93-95)*	*(14-18)*	*(18-22)*	*(114-147)*	*(140-173)*
00-01	105	100	93	5	12	31	70
	(103-107)	*(99-101)*	*(92-94)*	*(3-7)*	*(9-14)*	*(17-45)*	*(56-84)*
01-02	109	100	92	10	17	88	154
	(108-111)	*(99-101)*	*(91-93)*	*(8-11)*	*(15-19)*	*(72-103)*	*(139-170)*
02-03	107	100	91	7	16	54	125
	(105-108)	*(99-101)*	*(90-92)*	*(5-9)*	*(14-17)*	*(39-68)*	*(111-140)*

* Excess rates were calculated as differences between mortality rates during influenza virus-active periods and reference periods. ** Winter excess rates were calculated by multiplying the average excess rate during influenza virus-active by the number of influenza virus-active weeks during the winter season.

Appendix Table 3: Total winter excess mortality attributable to RSV over 1992-2003

Season	Total winter excess mortality attributable to RSV per 100,000 persons - peri-seasonal base-line period as reference (95%CI)					Total winter excess mortality attributable to RSV per 100,000 persons - summer base-line period as reference (95%CI)				
	65-69 years	*70-74 years*	*75-79 years*	*≥ 80 years*	*≥ 65 years*	*65-69 years*	*70-74 years*	*75-79 years*	*≥ 80 years*	*≥ 65 years*
1992-1993	21	24	67	272	89	53	68	134	437	161
	(-1-43)	(-6-54)	(23-112)	(208-336)	(69-109)	(33-74)	(39-97)	(91-177)	(375-498)	(142-180)
1993-1994	14	6	43	180	56	38	64	102	371	134
	(-18-37)	(-25-37)	(-4-91)	(113-247)	(35-77)	(15-60)	(34-94)	(55-148)	(306-437)	(114-155)
1994-1995	none	19	none	36	9	3	21	none	40	15
		(-0-39)		(-7-79)	(-4-23)	(-12-17)	(1-41)		(-3-83)	(1-28)
1995-1996	17	49	115	380	129	50	87	195	528	200
	(-4-37)	(21-77)	(72-158)	(319-442)	(110-149)	(30-71)	(59-115)	(152-238)	(467-590)	(181-219)
1996-1997	33	51	114	355	129	43	68	149	429	161
	(12-54)	(23-80)	(71-157)	(292-417)	(109-149)	(22-64)	(39-97)	(106-193)	(366-492)	(141-181)
1997-1998	5	3	15	64	40	7	17	29	212	62
	(-13-23)	(-22-27)	(-20-50)	(21-107)	(23-56)	(-10-24)	(-6-40)	(-4-62)	(162-261)	(46-77)
1998-1999	5	44	67	204	74	20	64	110	378	133
	(-13-22)	(20-69)	(33-102)	(151-257)	(58-91)	(3-37)	(40-87)	(77-143)	(328-428)	(118-149)
1999-2000	21	43	70	230	88	17	63	101	291	110
	(5-36)	(20-66)	(39-102)	(191-290)	(73-103)	(1-33)	(40-85)	(69-133)	(242-341)	(95-126)
2000-2001	4	8	56	173	56	12	34	96	288	102
	(9-18)	(-14-29)	(24-88)	(125-221)	(41-71)	(-2-25)	(12-56)	(64-128)	(240-336)	(86-117)
2001-2002	17	20	36	135	50	29	37	89	241	95
	(4-30)	(3-37)	(10-62)	(97-173)	(38-62)	(16-41)	(20-55)	(64-114)	(203-278)	(83-107)
2002-2003	5	11	27	97	34	22	51	96	272	106
	(-10-20)	(-10-33)	(-4-58)	(51-144)	(19-49)	(7-36)	(31-71)	(66-126)	(228-316)	(92-120)

95% CI, 95% confidence interval; * Excess rates were calculated as differences between mortality rates during RSV-active periods and reference periods.

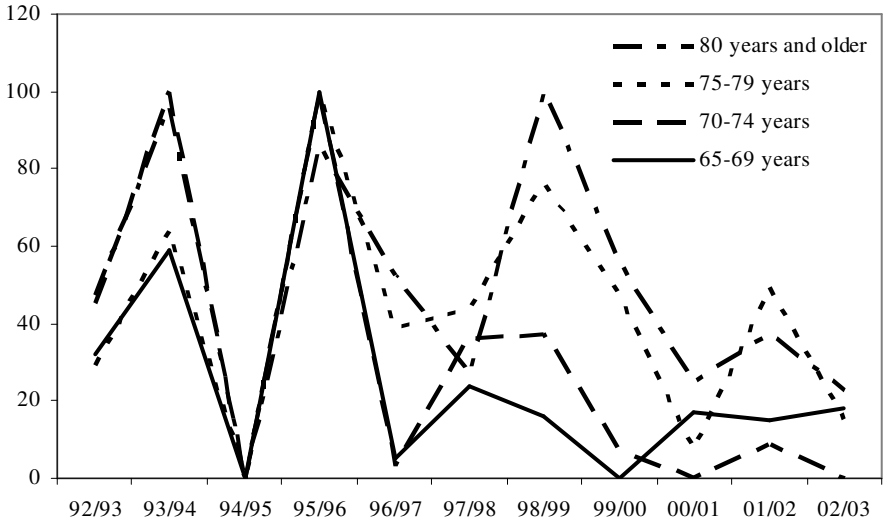
** Winter excess rates were calculated by multiplying the average excess rate during RSV-active weeks by the number of RSV-active weeks during the winter season.

Appendix Table 4: Influenza-associated mortality according to a Serfling-type regression model

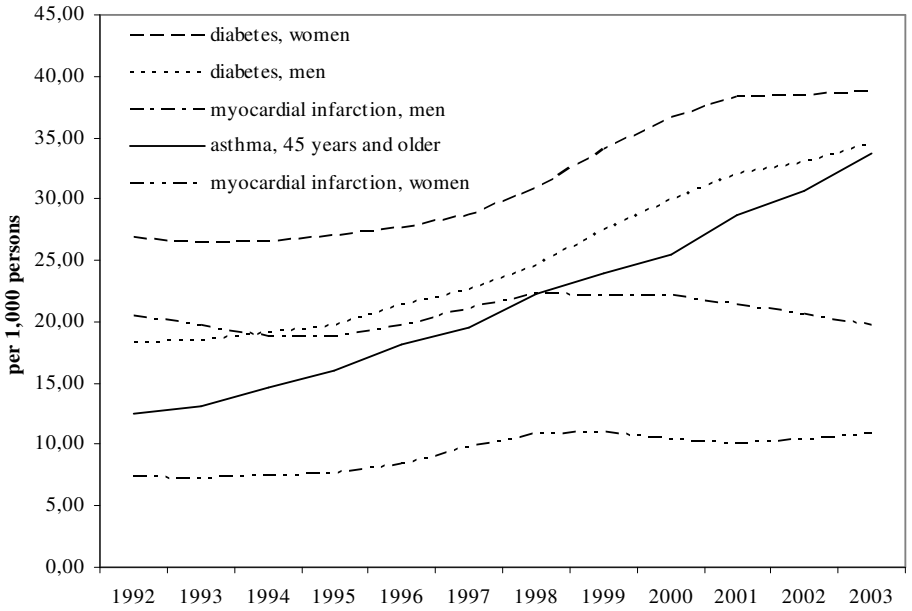
Age (years)	Total winter excess mortality attributable to influenza per 100,000 persons (95%CI)		Relative risk of influenza -associated death (95%CI)
	Seasons 1996-2003	Seasons 1992-1996	
65-69	10 (0-20)	40 (26-54)	0.25 (0.22-0.28)
70-74	7 (-7-21)	36 (16-55)	0.19 (0.17-0.22)
75-79	126 (97-156)	118 (98-137)	0.93 (0.88-0.98)
≥ 80	362 (332-391)	390 (347-432)	0.93 (0.90-0.95)
Within selection of seasons*			
65-69	8 (-5-20)	69 (48-90)	0.11 (0.10-0.13)
70-74	15 (-3-32)	77 (48-106)	0.19 (0.17-0.21)
75-79	153 (128-177)	243 (199-287)	0.62 (0.59-0.66)
≥ 80	434 (396-471)	724 (660-788)	0.60 (0.58-0.62)

95%CI, 95% confidence interval; * after exclusion of seasons with lower influenza virus-activity (1994-1995, 2000-2001, 2002-2003) or non-influenza virus A (H3N2) dominant activity (1992-93, 2000-01)

Appendix Figure 1: Standardized total winter excess mortality attributable to influenza according to a Serfling-type regression model



Appendix Figure 2: Year prevalence of high-risk conditions over the years 1992 to 2003, standardized to the Dutch population of 1990



Source: National Compass National Health, National Institute for Public Health and the Environment, Bilthoven, the Netherlands: http://www.nationaalkompas.nl, June 2006

CHAPTER 5

Invasive pneumococcal and meningococcal disease: association with influenza virus- and respiratory syncytial virus-activity?

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Abstract

Few studies examined the relation between viral activity and bacterial invasive disease, considering both the influenza virus and respiratory syncytial virus (RSV). The current study aimed to assess the potential relation between invasive pneumococcal disease (IPD), meningococcal disease (MD), and influenza virus- and RSV-activity in the Netherlands. Correlations were determined between population-based data on IPD and MD during 1997 to 2003 and influenza virus and RSV surveillance data. Incidence rate ratios of disease during periods of high influenza virus- and RSV-activity over the peri-seasonal and summer baseline periods were calculated. The analyses comprised 7,266 and 3,072 cases of IPD and MD. The occurrence of pneumococcal bacteremia and MD correlated significantly with influenza- and RSV-activity both in children and adults. Periods of increased influenza virus-activity as well as periods of increased RSV-activity were associated with higher rates of pneumococcal bacteremia and MD. Although no causal relation may be inferred from these data, they support a role for influenza virus and RSV in the pathogenesis of IPD and MD.

Introduction

Streptococcus pneumoniae and *Neisseria meningitidis* are leading causes of life-threatening invasive bacterial disease, like meningitis and septicemia. Both invasive pneumococcal disease (IPD) and meningococcal disease (MD) show seasonal patterns with higher incidences during winter months.[1-4] Besides climatic conditions, the circulation of respiratory viruses has been postulated to play a role in this seasonal increase. Viral infections may predispose to bacterial infection by enhancing bacterial adherence for instance by disrupting the respiratory tract epithelium barrier or increased bacterial-cellular interaction.[5] Particularly influenza viruses and respiratory syncytial virus (RSV) with their clear epidemic and seasonal activity during winters are suggested to be causally involved.[6-14]

Few ecological studies examined the epidemiological relationship between invasive bacterial disease and respiratory viral activity in the community, looking both at influenza virus and RSV separately.[1,10,11] Since both viruses often co-circulate, it is usually difficult to differentiate influenza virus-active from RSV-active periods. In the Netherlands over the years 1997 to 2003, however, viral surveillance data revealed largely separate peaks of influenza virus and RSV-activity. With the current study, we aimed to assess the potential relation between IPD, MD, and influenza virus- and RSV-activity.

Methods

Viral surveillance

In the Netherlands, a national representative laboratory-based surveillance for various viruses is conducted by the Weekly Sentinel System of the Dutch Working Group on Clinical Virology throughout the whole year. They weekly provide the absolute number of reported patients either hospitalized or visiting outpatient clinics that tested positive for a certain virus. Data on influenza virus and RSV during the period 1997 to 2003 were used in this study. During the study period, most of the laboratory diagnoses of influenza and

RSV infections were made by virus isolation on cell culture or rapid antigen tests. The weekly virological reports reflect trends in national viral activity adequately.[15] However, most RSV surveillance data (96%) were reported in children below the age of five years.[16]

Pneumococcal and meningococcal isolates

The Netherlands Reference Laboratory for Bacterial Meningitis (NRLBM, Academic Medical Center/National Institute of Public Health and the Environment, Amsterdam, the Netherlands) collects nationwide isolates from cerebrospinal fluid (CSF) and blood from hospitalized patients with proven bacterial meningitis (CSF and possibly blood culture positive), or bacteremia with suspected meningitis (blood culture positive only), bacteremia without suspected meningitis, or isolates from other normally sterile bodily fluids. From week 27 of the year 1997 to week 26 of 2003 all blood and CSF samples sent to the NRLBM and positive for *S.pneumoniae* were considered. For MD the last season (2002-2003) was excluded for analysis because nationwide vaccination against serogroup C meningococci was started for all individuals between one and eighteen years of age in 2002. Pneumococcal vaccination has not been routinely recommended for elderly persons in the Netherlands and heptavalent pneumococcal conjugate vaccination has been introduced in the national immunisation program for infants in 2006.

IPD and MD were defined as all cases in which *S.pneumoniae* or *N.meningitidis* was isolated from blood and/or CSF. IPD was further subdivided in bacteraemia (blood culture positive only) and meningitis (CSF and possibly blood culture positive).

Analyses

The relation between the weekly rate of IPD and MD with the weekly number of laboratory identifications of influenza viruses and RSV was assessed by calculating the Spearman correlation coefficient correcting for long-term trends, with the statistical software SAS version 8.02. In an attempt to quantify the potential relationship between invasive bacterial disease and the circulation of influenza viruses and RSV, the methods of Izurieta et al. were applied with minor modifications.[17] Influenza virus-active periods were defined for each winter season from week 40 to week 20, as the periods of at least two consecutive weeks in which each week accounted for at least 5% of the season's total number of influenza virus

isolates.[17] Periods of influenza virus predominance were defined as the influenza virus-active weeks with less than 5% of the season's total number of positive tests for RSV.[16] Similarly, the RSV-active period was defined as the periods of at least two consecutive weeks in which each week accounted for at least 5% of the season's total number of positive tests for RSV. Periods of RSV predominance were defined as the RSV-active weeks with less than 5% of the season's total number of influenza virus isolates. Peri-seasonal baseline periods were defined as those periods of at least two consecutive weeks with each week accounting for less than 5% of the season's total number of influenza virus isolates and positive tests for RSV during the winter season (week 40 to week 20). Finally, the summer baseline period was defined as week 21 to 39. Unlike Izurieta and colleagues, weeks in which para-influenza viruses were isolated were not excluded from the study as (sporadic) isolates were reported throughout the year. For the same reason, weeks in which sporadic isolates of the influenza virus and RSV were reported during summer baseline period were not excluded. Age-specific incidence rate ratios with 95% confidence intervals of MD and IPD during periods of influenza virus and RSV predominance as compared to the peri-seasonal and summer reference period were calculated with Episheet (Rothman K. Episheet: Spreadsheets for the analysis of epidemiologic data, 2002).

Results

In total 7,266 episodes of IPD were recorded in the 6-year period. Isolated bacteremia accounted for a majority of episodes (81%); meningitis was diagnosed in 19% (1,391 episodes). With respect to MD (3,072 episodes during the 5-year surveillance period), meningitis accounted for 60% of episodes, isolated bacteremia for 39% of cases, and other meningococcal disease for 1%.

Figure 1 demonstrates that the occurrence of pneumococcal bacteraemia peaked when influenza viruses and RSV circulated each year, though invasive bacterial disease already started to rise before the peaks of influenza virus- and RSV-activity. This seasonality was also present for MD among children, although less pronounced (Figure 2).

Figure 1: Invasive pneumococcal disease among all ages together in relation to the circulation of influenza viruses and RSV in the community

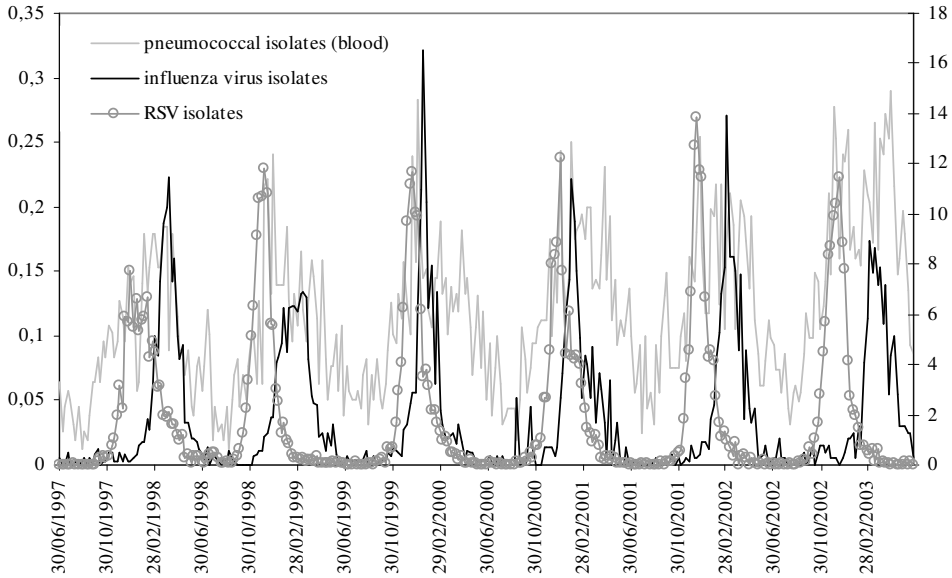
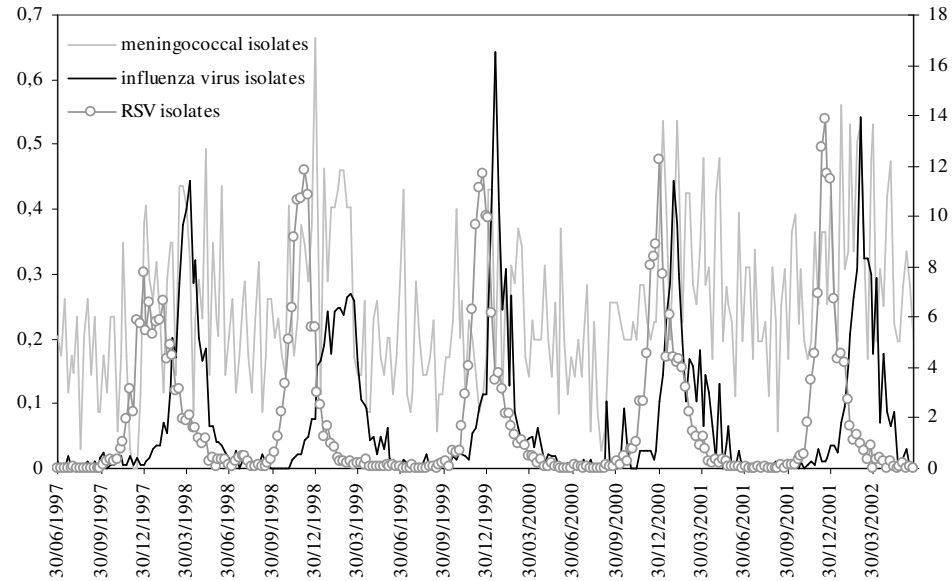


Figure 2: Invasive meningococcal disease among children in relation to the circulation of influenza viruses and RSV in the community



According to the definitions, there were 92 influenza virus and/or RSV-active weeks; 46 weeks of influenza predominance, 42 weeks of RSV predominance, and only 4 weeks of both influenza and RSV-activity during the years 1997 to 2003. Significant positive correlations were found between weekly rates of invasive bacterial disease and the weekly number of laboratory identifications of influenza viruses and RSV among both children and adults (Table 1). Rates of pneumococcal bacteremia and MD were generally higher during both periods of influenza predominance and RSV predominance compared to the peri-seasonal baseline period, but in particular compared to the summer baseline period.

Table 1: Incidence of invasive pneumococcal and meningococcal disease in relation to influenza virus and RSV circulation in the community

Age years	Spearman correlation		Incidence rate ratios (95% confidence interval)			
	Influenza viruses	RSV	Periods of influenza virus predominance		Periods of RSV predominance	
			Versus peri-season	Versus summer	Versus peri-season	Versus summer
Pneumococcal bacteremia						
0-4	0.24 (p<0.01)	0.29 (p<0.01)	1.28 (.97-1.69)	2.48 (1.81-3.39)	1.21 (0.90-1.62)	2.34 (1.69-3.23)
5-17	0.21 (p<0.01)	0.12 (p=0.03)	2.16 (1.30-3.61)	2.18 (1.32-3.59)	1.72 (0.98-3.00)	1.73 (1.00-2.99)
≥ 18	0.62 (p<0.01)	0.59 (p<0.01)	1.23 (1.15-1.33)	2.30 (2.11-2.49)	1.21 (1.12-1.30)	2.45 (2.06-2.25)
Pneumococcal meningitis						
0-4	0.23 (p = 0.01)	0.36 (p<0.01)	0.99 (.76-1.29)	2.45 (1.80-3.33)	1.14 (0.88-1.47)	2.81 (2.08-3.81)
5-17	0.14 (p=0.02)	-	2.58 (1.41-4.69)	2.19 (1.25-3.84)	1.23 (0.57-2.62)	1.04 (0.50-2.16)
≥ 18	0.39 (p<0.01)	0.44 (p<0.01)	1.09 (0.90-1.32)	2.25 (1.81-2.79)	1.30 (1.08-1.56)	2.68 (2.17-3.31)
Meningococcal disease						
0-4	0.32 (p<0.01)	0.35 (p<0.01)	1.37 (1.18-1.59)	1.80 (1.54-2.11)	1.13 (.96-1.34)	1.49 (1.26-1.78)
5-17	0.22 (p<0.01)	0.24 (p<0.01)	1.50 (1.26-1.79)	1.75 (1.46-2.09)	1.96 (1.65-2.31)	2.28 (1.92-2.70)
≥ 18	0.29 (p<0.01)	0.28 (p<0.01)	1.03 (0.83-1.27)	1.51 (1.21-1.89)	1.15 (0.93-1.42)	1.69 (1.35-2.11)

Discussion

In this 6-year retrospective study with largely separate peaks of influenza virus- and RSV-activity in the Netherlands, IPD and MD among both children and adults were demonstrated to correlate directly with the circulation of these viruses in the community. Higher rates of pneumococcal bacteremia were demonstrated among all ages during both influenza virus- and RSV-active periods. Similarly, increased rates of MD among children were found during influenza virus- and RSV-active periods.

Previous studies demonstrated that patients with severe pneumococcal pneumonia and meningococcal disease were more likely than control subjects to show serological evidence of recent influenza virus infection.[7,18] Additionally, some ecological studies reported a significant correlation between influenza virus- and RSV-activity and IPD in adults,[1,10] although others could not confirm this.[11] Among children also significant correlations were reported between IPD and RSV-activity.[1,10,11] The temporal relation between IPD and influenza virus-activity among children appeared less clear;[10,11] only one study reported a significant correlation after incorporation of a lag time.[1] Regarding MD, a significant relationship with influenza virus-activity among infants was reported by one study.[13] In contrast, various other studies assessing the relation between MD and RSV, concluded that no convincing evidence was found for a causal association between RSV and MD.[9,14] In our study, IPD and MD among both children and adults correlated directly with influenza virus- and RSV-activity. We did not incorporate a lag time, since our viral surveillance data originated merely from a hospital population.

Although IPD occurrence in our study appears to be aggravated by the influenza virus- and RSV-activity in the community, IPD rates already seemed to rise before influenza virus- and RSV-activity did. The same appeared to be true for MD. This suggests that apart from viral activity, other seasonal factors may be important in the etiology of invasive bacterial disease and may imply that correction for seasonality is necessary. In our study, we corrected for seasonality by taking the peri-seasonal baseline period as reference. Another study attempted to unravel the seasonality of IPD by comparing rates of IPD and seasonal phenomena within seven different states of the United States.[2] In their study, IPD was

found to be correlated inversely with the temperature ($r = -.82$ with a 1-week lag, $p < 0.01$), although the lowest rates of IPD were found in the coldest states, and no threshold temperature could be identified. They also reported that the seasonal pattern of IPD correlated directly with the sinusoidal variations in photoperiod ($r = .85$ with a 5-week lag) throughout the states and therefore hypothesized that nationwide seasonal changes such as photoperiod-dependent variation, i.e. the variation in hours of day light throughout the seasons, influences host susceptibility and may underlie the seasonality of IPD.[2,19] In our study, IPD and MD correlated with the photoperiod maximally with a time lag of 8 weeks (data on file), which is similar to the study of Dowell et al.[2,19] For MD, wind speed and humidity has been suggested to play a role in the seasonality.[20] When correcting for seasonality, caution is warranted as for example the photoperiod may also lead to an enhanced susceptibility to virus infections including influenza virus and RSV infections, which in turn predispose to bacterial superinfection.[21] Additionally, for example crowding during winter due to low temperatures may enhance transmission of these viruses in the community.[21] By correcting for seasonality one could therefore also inappropriately disturb the potential relation between influenza virus and RSV-activity and invasive bacterial disease.

To appreciate the results of our study, some possible limitations should be discussed. The incidence rate ratios of IPD and MD during influenza virus- and RSV-active periods suggested a relation, but no causal relationship can be inferred from these data since direct evidence for involvement of the viruses in the pathology of the infection is lacking. However, an assessment of the impact of viral seasons solely based on patients with IPD or MD that also tested positive for the influenza virus or RSV would lead to an underestimation since viruses may long be gone in case of bacterial superinfection. The temporal relation we found between influenza virus and RSV isolation and IPD or MD-activity might also have been affected by other seasonally active viruses. However, like previously stated, by taking the peri-seasonal baseline period as reference period, we aimed to limit this possibility. Moreover, other respiratory viruses (rhinovirus, para-influenza virus, and adenovirus) either demonstrated no clear seasonal circulation or very large periods of marginally increased activity (data on file), also limiting their disturbing role in our study. Of note, the observed relation between influenza virus infection and invasive

bacterial disease among elderly may have been underestimated since routine annual influenza vaccination is recommended since 1996 in the Netherlands with vaccination coverages around 70-80% (Statistics Netherlands, Voorburg/Heerlen, the Netherlands) during the study period.

A major strength of the current study is that it assessed IPD and MD nationwide comprising a period of six years with different viral attack rates. Furthermore, since all years showed largely separate peaks of influenza virus and RSV-activity, this allowed the potential relation between IPD, MD, and influenza virus/RSV-activity to be explored separately. Also, with the Netherlands being a small but densely populated country, population characteristics are relatively homogenous nationwide and viral circulation is more or less simultaneous across the country, making ecological studies more reliable. Additionally, due to nationwide surveillance our study included a large number of cases enabling subset analysis by age.

In conclusion, the current study demonstrated that periods of increased influenza virus-activity as well as periods of increased RSV-activity were associated with higher rates of pneumococcal bacteremia and MD. This supports a role for RSV and the influenza virus in the multifactorial pathogenesis of IPD and MD, but it provides however no evidence for a causal relationship. Regarding the accumulating evidence for viral-bacterial interaction and given the broad range of bacterial antigens for which vaccines would be needed, additional approaches to the prevention of invasive bacterial disease may be useful including viral vaccines.

Acknowledgment

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PART III

Effects of combined influenza and pneumococcal conjugate vaccination on respiratory infections in preschool children

CHAPTER 6

Primary care management of respiratory tract infections in Dutch preschool children

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Abstract

Objective: To determine age-specific antibiotic prescription and referral rates in preschool children diagnosed with acute respiratory tract infection (RTI) in primary care.

Design: retrospective cohort study

Setting: research database of the Netherlands University Medical Center Utrecht Primary Care Network

Subjects: All children aged 0-5 years within the database were included, covering 1998 to 2002 (18,801 child-years).

Main outcome measures: Antibiotic prescription and referral rates were determined as percentage of children with at least one prescription or referral within a year, as total number of prescriptions per 1000 child-years, and as percentage of all RTI episodes.

Results: Antibiotics, mostly beta-lactam (80%) and macrolides (16%), were prescribed in 35% of RTI-episodes. Annually 13% of the children received at least one antibiotic following an RTI. Antibiotics were prescribed in more than half of episodes of LRTI, sinusitis, AOM, and acute tonsillitis, and in 12-15% of episodes of asthma exacerbation, acute laryngitis, influenza, and acute upper respiratory infection (including common cold and pharyngitis). Almost 98% of RTI were managed in primary care. On average 1% of the children was referred to a pediatrician or ENT specialist following RTI per year, especially after AOM (59% of referrals). Compared with older children, those under two years of age were more often treated with antibiotics (relative risk [RR] 1.4, 95%CI 1.3-1.6) and referred (RR 2.3; 95% CI 1.8-3.0).

Conclusion: In the Netherlands most episodes of RTI in preschool children were managed in primary care and this often involves prescription of antibiotics. Children younger than two years of age receive more often antibiotics for RTI and are also referred more, especially for AOM.

Introduction

Respiratory tract infections (RTI) are the most common diagnoses in primary care.[1-3] Preschool children in particular suffer from RTI.[3-6] However, only few studies assessed aspects of primary care management of the various RTI and referral to secondary care in these children over a period of several years.

Most childhood RTI have a viral etiology and are self-limiting.[4,7,8] Yet, RTI are the indication for 75% of the total amount of prescribed antibiotics in Western countries and most referrals to secondary care in children are because of respiratory symptoms.[3,9] Besides causing health care costs and side effects, liberal use of antibiotics causes bacterial resistance. In the Netherlands bacterial resistance to antibiotics is still among the lowest in the world, probably due to limited use of antibiotics in that country.[10] In view of the marginal effects of both antibiotics and ear-nose-throat (ENT) surgery for recurrent RTI,[11-13] preventive strategies like immunization need to receive more attention. In assessing the cost-effectiveness of such strategies, baseline information is required about current management and referral rates for RTI. The present study was carried out to gain insight into these matters. Since children below the age of two years are considered to be more prone to RTI due to immaturity of the immune system and the developing anatomy of the airways,[14,15] we also determined potential differences in primary care management among these children as compared with older children.

Methods

Setting and study population

All data for this retrospective cohort study were obtained from the computerized medical database of the University Medical Center Utrecht Primary Care Research network. Twenty general practices, covering a cumulative population of about 60,000 patients, participate in this network. Main characteristics of this patient population are similar to the Dutch population as a whole.[16] Medical data of all enlisted patients have been recorded using a

uniform, structured, contact registration format in the general practitioner information system ELIAS® (ISoft, Nieuwegein, the Netherlands). The participating GPs received education regarding the correct coding of diagnostic information according to the International Classification of Primary Care (ICPC) coding system.[17,18] More than 90% of contacts have received an ICPC-code and accuracy appeared high. Prescribed medication is also recorded in the database, including the Anatomical Therapeutic Chemical (ATC) code.[19]

For this study all children aged 0 to 5 years enlisted in the participating practices between 1998 and 2002 were included. This study population covered 18,801 child years. The size of the cohort did not change substantially over the years.

Outcomes

Outcomes of interest were prescription of antibiotics and rate of referral to the pediatrician or ENT specialist after GP-attended acute RTI. We defined a RTI as a clinical diagnosis of acute otitis media/myringitis (ICPC code H71), acute upper respiratory infection (R74) (including common cold and pharyngitis), sinusitis (R75), acute tonsillitis (R76), acute laryngitis/tracheitis (R77), acute bronchitis (R78), influenza (R80), pneumonia (R81), other RTI (R83), or exacerbation of asthma, defined as asthma (R96) and the use of systemic corticosteroids (H02AB or H02B). Asthma exacerbation was considered as RTI, because it has been shown frequently to be induced by viral infections, most commonly rhinovirus.[20] Lower RTI (LRTI) was defined as acute bronchitis (R78) or pneumonia (R81). A new GP-attended RTI was recorded after a consultation-free interval of at least 28 days. Since there was no direct link in the database between a disease episode and antibiotic prescription or referral, we defined for antibiotic prescription a time window beginning three days before and ending after the RTI episode (maximum of 28 days). Antibiotics (ATC code J01) were subdivided in β-lactam antibiotics including penicillins (J01C), sulfonamides and trimethoprim (J01E), macrolides, lincosamides, and streptogramins (J01F). Referrals from primary care to a pediatrician or ENT-specialist were recorded by review of the medical records.

Analysis

The mid-time population of each consecutive year was determined at 1 July. Age-specific antibiotic prescription and referral were determined on episode level, i.e. the percentage of episodes leading to antibiotic prescription and referral. Antibiotic prescription and referral rates were also calculated per 1000 child years by dividing the number of prescriptions and referrals by the total number of child-years. Additionally we calculated the antibiotic prescription and referral rates on child level, i.e. the percentage of children with at least one prescription or referral per year (children could only contribute once within a year to this percentage). The study population was divided into children younger and older than two years of age, to determine differences in antibiotic prescriptions rates and referral rates between both age groups. Relative risks (RRs) with 95% confidence intervals (95% CI), and 95% CIs for proportions and rates were determined with Episheet (Rothman K. Episheet: Spreadsheets for the analysis of epidemiologic data, 2002).

Results

Antibiotic prescription

In 35% (95% CI 34.5-36.4) of all GP-attended acute RTI antibiotics were prescribed: in 50% or more of episodes of LRTI, sinusitis, AOM, and acute tonsillitis, and in 12-15% of episodes of asthma exacerbation, acute laryngitis, influenza, and acute upper respiratory infection, including common cold and pharyngitis (Table 1). In 80% (95% CI 78.9-81.6) of all RTI episodes in which antibiotics were prescribed, β-lactam antibiotics (including penicillins) were chosen, in 16% (95% CI 15.0-17.5) macrolides, lincosamides, or streptogramins, and in 7% (95% CI 5.8-7.4) trimethoprim or sulfonamines (since sometimes more than one type of antibiotic was prescribed per RTI episode, the sum of these percentages exceeds 100%).

Table 1: Antibiotic prescription for RTI on episode level

Type of RTI	Percentage of antibiotic prescription (episode level)	95% CI
All RTI	35.4%	34.5-36.4
LRTI	57.0%	54.6-59.4
Sinusitis	61.5%	42.5-77.6
AOM	49.7%	48.0-51.4
Acute tonsillitis	47.3%	42.4-52.1
Asthma exacerbation	15.0%	5.2-36.0
Acute upper respiratory infection	14.1%	13.0-15.2
Acute laryngitis / tracheitis	11.7%	8.5-16.0
Influenza	11.6%	5.1-24.5
Other RTI	54.2%	45.3-62.8

On average 13.3% of children (95% CI 12.8-13.9) received antibiotics for a GP-attended RTI at least once yearly. In total 197 courses of antibiotics were prescribed per 1000 child years. Almost 49% of all antibiotics was prescribed because of AOM, followed by 27% for LRTI and 15% for upper respiratory tract infection (including common cold and pharyngitis).

The amount of antibiotics prescribed for RTI was higher in children below two years of age compared with older children; on average 18.0% versus 12.4% of the children received antibiotics at least once yearly, RR 1.45, 95% CI 1.34-1.56 (Table 2). On episode level, however, children below two years of age had a somewhat lower probability of receiving antibiotics for all RTI together than older children (RR 0.87, 95% CI 0.82-0.92), and LRTI (RR 0.77, 95% CI 0.71-0.84). For AOM, however, children below two years of age had a slightly higher probability of receiving antibiotics (RR 1.13, 95% CI 1.06-1.21).

Table 2: Age-specific antibiotic prescription for all RTI together

Age (years)	Percentage of children that received at least 1 antibiotic prescription per year*	Number of prescriptions per 1000 child-years	Percentage of episodes with antibiotic prescription
0	17.2%	258	30.9%
1	18.8%	284	34.9%
2	15.1%	198	36.8%
3	12.8%	157	37.1%
4	13.1%	168	40.0%
5	8.5%	102	38.3%

Referrals

Overall, in 2.2% (95% CI 1.9-2.5) of GP-attended RTI episodes children were referred to secondary care (51% ENT-specialist, 46% pediatrician). For children with tonsillitis this proportion was 4.5%, for AOM and sinusitis 3.8%, and for LRTI 3.3%. On average 1.1% of the children (95% CI 0.9-1.2) were referred at least once per year (including referral to the emergency ward) after a GP-attended RTI. Most referrals were because of AOM (59%) and LRTI (25%); 83% of the referrals to the ENT specialist were because of AOM. Children younger than two years old were referred more often than older children (RR 2.3, 95% CI 1.76-3.05) (Table 3). Episode-based referrals in both age groups were less different from each other (RR 1.27, 95% CI 0.97-1.66), although for AOM (RR 1.41, 95% CI 1.09-1.84) and especially for LRTI (RR 7.99, 95% CI 3.17-20.12) it was higher for children younger than two years of age.

Table 3: Age-specific referral rates for all RTI together

Age (years)	Percentage of children that were referred at least once per year	Number of referrals per 1000 child-years	Percentage of episodes with referral
0	1.7	18.1	2.4
1	1.7	18.6	2.5
2	1.0	10.3	2.0
3	0.8	8.6	2.1
4	0.7	6.9	1.8
5	0.4	4.3	1.7

Discussion

This five-year study demonstrated an overall antibiotic prescription rate of 35% for acute RTI among preschool children in primary care. Almost all GP-attended RTI were managed in primary care; only 2.2% of RTI episodes resulted in referral to a pediatrician or ENT specialist. AOM proved to be by far the most frequent reason for antibiotic prescription and referral. Children below two years of age received more antibiotics and were referred more often as compared with older children.

Antibiotic prescription has proven to be relatively low in the Netherlands compared with other countries.[21-24] Our study also showed lower prescription rates for the various RTI than those reported in many other countries, although these rates are not completely comparable due to the definition of different age groups.[24-26] Except for sinusitis the antibiotic prescription rates found in our study are somewhat higher than those reported by a previous Dutch study.[27] This may be caused by the fact that we used episode-based antibiotic prescription rates in stead of contact-based rates. We defined an RTI-episode to have ended after a consultation-free interval of 28 days, because we hypothesized that most parents would revisit their GP within 28 days if their child continued to have serious respiratory complaints. We also defined a time window for antibiotic prescription lasting for 28 days. This may possibly have lead to a slight overestimation of the antibiotic prescription rate. Besides contact-based instead of episode-based rates and applying slightly different definitions of clinical entities, the discrepancy in prescription rates may be explained by the fact that they determined the rates over one year while we covered five years.[27]

Cultural factors such as habits, patients' expectations, and the structure of the healthcare system may result in differences in clinical practice guidelines between countries.[28] The national guidelines of the Dutch College of General Practitioners are displayed in Table 4. In view of these guidelines, the antibiotic prescription rates in our study may still seem high. Our finding that 15% of the total amount of antibiotics for RTI was prescribed for acute upper respiratory infection (including common cold and pharyngitis), a condition that is generally considered to be self-limiting, suggests that GPs do not always follow these guidelines. We also found that in 15% of the RTI episodes in which antibiotics were

prescribed, macrolides were given. This supports that the use of broad spectrum antibiotics like macrolides is considerable.[10,29,30]

Table 4: Guidelines for antibiotic prescription according tot the Dutch College of General Practitioners

Clinical entity	Indication for antibiotic prescription
AOM	Age ≤6 months
	Abnormal course:
	- progressing illness, decreased fluid intake, increasing ear ache
	- no improvement after three days
	Age <2 years with a recurrence of AOM within 12 months
	Presence of relevant co-morbidity
Acute bronchitis / cough	Age ≤6 months and presence of fever
	Presence of relevant co-morbidity
Pneumonia	Always
Sinusitis	Abnormal course:
	- serious illness, alarm symptoms
	- more than 5 days complaints
	Presence of relevant co-morbidity
Throat infection	Serious illness / serious scarlet fever: peritonsillar infiltrate or abscess-forming lymphadenitis
	Presence of risk factors for complications
Acute upper respiratory infection	No indication

Our study confirms that most RTI are managed in primary care;[3] only 2.2% of GP-attended episodes resulted in referral to secondary care. Since RTI are very common conditions among preschool children, the number of referrals is, however, high, especially in children younger than two years of age. Although the amount of prescribed antibiotics and number of referrals were clearly higher among children younger than two years of age compared with older children, episode-based antibiotic prescription and referral rates were less different. This indicates that the higher amount of antibiotics and number of referrals among children younger than two years of age were mainly caused by the higher frequency of consults for RTI. For LRTI, however, we found that on episode level younger children received antibiotics less often, despite the fact that their immune system is less mature and capable of handling these infections than in older children.[16] In contrast, younger children

were more often referred on episode level for AOM and especially for LRTI. It may be that in younger children compared with older children, GPs are less confident about their diagnosis of RTI in case of lower respiratory symptoms (such as acute bronchitis), and consequently prescribe antibiotics less and refer more.

To appreciate the results of our study, some possible limitations should be discussed. The validity of our study depends on the accuracy with which the participating GPs registered the consultations and prescription of antibiotics. More than 90% of all patient contacts were coded and GPs were trained once yearly to register the conditions and management appropriately. In the Netherlands most inhabitants are registered with a GP. The GP functions as a 'gatekeeper' and a patient may only attend secondary health care when he or she has been referred by the GP. In case of an emergency, the GP may be by-passed. It is therefore possible that antibiotic prescription rates for the more serious LRTI may have been slightly underestimated in our study since medication use resulting from emergency visits or hospital admissions may not have been recorded. However, most RTI do not need such visits.

A major strength of our study is the use of a reliable extended research database including a large study population followed for several years. Further, this is, to our knowledge, the first study assessing antibiotic prescription and referral rates in preschool children in one-year age categories.

In conclusion, although in the Netherlands most episodes of RTI among preschool children are managed in primary care and conservatively, its high frequency results in large antibiotic consumption and many referrals especially in children younger than two years of age. In view of the increasing bacterial resistance to antibiotics and its limited effects on RTI, together with the only marginal effects of surgical interventions for recurrent RTI,[11-13] more attention needs to be paid to the possible role of preventive therapies like immunization. As most RTI are managed in primary care, such preventive strategies may substantially reduce the primary health care burden of these infections in young children.

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CHAPTER 7

Adverse reactions to simultaneous influenza and pneumococcal conjugate vaccinations in children: randomized double-blind controlled trial

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Abstract

In a randomized double-blind controlled trial, the safety was assessed of simultaneous administration of influenza and pneumococcal conjugate vaccines in children with previous physician-diagnosed respiratory tract infections. In total, 579 children aged 18 to 72 months were assigned to receive simultaneous intramuscular influenza and pneumococcal heptavalent conjugate vaccinations (IV+PV), influenza and placebo vaccinations (IV+plac), or control hepatitis B and placebo vaccinations (HepB+plac) in separate extremities. Local and systemic adverse events were recorded in parental diaries for seven days after vaccination. No immediate adverse reactions were recorded. In most children local adverse reactions disappeared two days after vaccination. Local and systemic reactions were more prevalent (30% and 10% more) in the IV+PV group compared with the IV+plac and HepB+plac group. These results are important for designing future vaccination schedules.

Introduction

Respiratory tract infections continue to be the leading cause of acute illnesses worldwide. Especially children are prone to respiratory tract infections. Often these children are treated with courses of antibiotics and ear-nose-throat surgery despite only marginal effects of both treatments.[1-3] Moreover, bacterial resistance to antibiotics is a growing problem.[4] Therefore, preventive strategies like vaccination should be explored.

Influenza virus and *Streptococcus pneumonia* are frequent pathogens of respiratory infections and together they account for considerable morbidity and mortality.[5] The incidence of confirmed influenza has been estimated around 20% during influenza seasons.[6] A recent study demonstrated that in 33% of the nasopharyngeal aspirates taken from children presenting to primary care with cough and fever during winter season, for which the antibiotics were considered, influenza viruses were detected.[7] *S.pneumoniae* is the most common bacterial pathogen of pneumonia in preschool children and is known to be the leading cause of acute otitis media, accounting for 28 to 55% of all episodes.[8-12] Moreover, influenza virus infections appear to predispose to bacterial superinfection like acute otitis media, in particular with *S.pneumoniae*.[13] Evidence suggests that influenza virus and *S.pneumoniae* interact synergistically in causing complicated infections.[5] Given that vaccines for both pathogens are available, combined immunization against the influenza virus and *S.pneumoniae* may be particularly effective. The potential beneficial effect of these immunizations should however be weighed against possible side effects. Since the infant immunization schedule is becoming crowded with an increasing number of pathogens against which children are being immunized, it is important to know whether it is safe to give multiple vaccinations simultaneously. In the Netherlands, only recently (April 2006) pneumococcal conjugate vaccination has been added to the national infant vaccination program without a catch-up program for children less than five years of age. Influenza vaccination is only advised for children with high-risk medical conditions. The current study aimed to assess the safety of simultaneous administration of influenza and heptavalent pneumococcal conjugate vaccines in preschool children by means of a randomized controlled double-blind trial.

Methods

Participants and recruitment

The current study was part of the Prevention of Respiratory Infections and Management (primakid)-study, a randomized double-blind controlled trial that aims to establish the effects of influenza and pneumococcal vaccinations on the occurrence rates of febrile respiratory tract infections among children with previous physician-diagnosed respiratory tract infections.[14] Parents were informed about the study by general practitioners. Parents willing to participate signed a consent form to enrol their child in the study. The study was undertaken in accordance with the European statements for good clinical practice which includes the provisions of the Declaration of Helsinki of 1989. The medical ethical review board of the University Medical Center Utrecht, the Netherlands approved the study protocol.

Children aged 18 to 72 months old with previous respiratory tract infections were selected by general practitioners in the Netherlands within the province Utrecht and surroundings. The characteristics of the population covered by these general practices are similar to the Dutch population as a whole.[15] Inclusion criterion for the study was a history of two or more episodes of general practitioner-diagnosed respiratory tract infections prior to study entry. Respiratory tract infections were defined according to the International Classification of Primary Care:[16,17] acute otitis media (H71), cough (with fever) (R05), acute upper respiratory infection (R74) including common cold and pharyngitis, sinusitis (R75), acute tonsillitis (R76), acute laryngitis/tracheitis (R77), acute bronchitis/bronchiolitis (R78), influenza (R80), pneumonia (R81), pleurisy/pleural effusion (R82), and other respiratory infection (R83). Exclusion criteria were asthma or recurrent wheezing chronically treated with corticosteroids and other disorders predisposing for recurrent respiratory tract infections. Children with clinically significant hypersensitivity to eggs or previous serious adverse reactions to vaccines were also excluded. Furthermore, children who previously had influenza, pneumococcal, or hepatitis B vaccinations were excluded as well as children with conditions for which these vaccinations are recommended.

Procedure and vaccines

The children were randomly assigned in blocks of three to combined influenza and pneumococcal vaccinations (IV+PV), influenza and placebo vaccinations (IV+plac), or control hepatitis B and placebo vaccinations (HepB+plac) in a 1:1:1 ratio. Three cohorts of children were enrolled during the periods October to November of 2003, 2004, and 2005. Inactivated trivalent sub-unit influenza vaccine (Influvac®) was supplied by Solvay, Weesp, the Netherlands. Strains in the 2003-2004 formulation were A/New Caledonia/20/99 (H1N1), A/Moscow/10/99 (H3N2), and B/HongKong/330/01; in the 2004-2005 formulation A/New Caledonia/20/99 (H1N1), A/Fuijan/411/2002 (H3N2), and B/Shanghai/361/2002; and in the 2005-2006 formulation A/New Caledonia/20/99 (H1N1), A/California/7/2004 (H3N2), and B/Shanghai/361/2002. The heptavalent pneumococcal conjugate vaccine (Prevnar®, Wyeth, Vaccines Research Berkshire, United Kingdom) consisted of 2 µg each of capsular polysaccharides of pneumococcal serotypes 4, 9V, 14, 19F, and 23 F, 4 µg of serotype 6B polysaccharide, and 2 µg of serotype 18C oligosaccharide, each conjugated individually to the CRM_{197} protein. The placebo consisted of a standard diluent (0.9% NaCl phosphate buffered, Solvay, Weesp, the Netherlands). Control vaccine was the recombinant hepatitis B vaccine (Engerix-B Junior®, GlaxoSmithkline, Rixenart, Belgium).

Assignments to treatment groups were not revealed to parents, investigators, research personnel involved in follow-up, or non-study health care providers, all of whom remained blinded throughout the study. Administration of the injections was performed by non-blinded research nurses who were not involved in subsequent follow-up of the children. To evaluate blinding, parents of the last two cohorts of included children were asked what vaccinations they thought their child had received just after the vaccinations were set and at the end of the study. Just after the vaccinations, 87% of the parents did not know or mentioned the wrong set of vaccinations, and at the end of the study this was 80% indicating that blinding was successful. All children had a similar vaccination schedule. Children received two sets of vaccinations, administered intramuscularly in deltoid or gluteal muscles (in separate extremities) four to eight weeks apart in the year of inclusion. Pneumococcal and placebo vaccines were administered in the right extremity, and influenza and hepatitis B vaccines were administered in the left extremity.

Safety evaluation

Following vaccinations, children were observed for 15 minutes for immediate hypersensitivity reactions and parents completed diaries for the day of immunization and the six following days recording local and systemic adverse events after the first set of vaccinations. Local reactions solicited included erythema, tenderness, swelling, and interference with limb movement. Systemic events solicited included malaise, headache, and myalgia. Besides these solicited questions, parents were able to write down other complaints in the diary. In addition, parents measured their child's temperature by a tympanic membrane thermometer provided by the trial center (Braun Thermoscan pro 3000® and Braun Thermoscan pro 4000®) on the evening after vaccination and the subsequent six evenings.[18] Parents were asked to contact the researchers directly in case of severe adverse events.

Analysis

The occurrence of adverse events was evaluated after the first set of vaccinations. With an available-case analysis, i.e. study subjects were included that provided valid information, and an intention-to-treat analysis, frequencies of adverse reactions were determined for the three different groups. Risk differences were calculated with Episheet (Rothman K. Episheet: Spreadsheets for the analysis of epidemiologic data, 2002). Furthermore, the course of adverse reactions during the observation period was determined.

Results

Five hundred seventy nine children were randomized, and 567 parents (97.9%) completed the diary (Figure 1). The 12 subjects without follow-up information were equally divided between the study groups. The study groups were similar with regard to age, sex, and medical history (Table 1).

Figure 1: Flow diagram of study groups

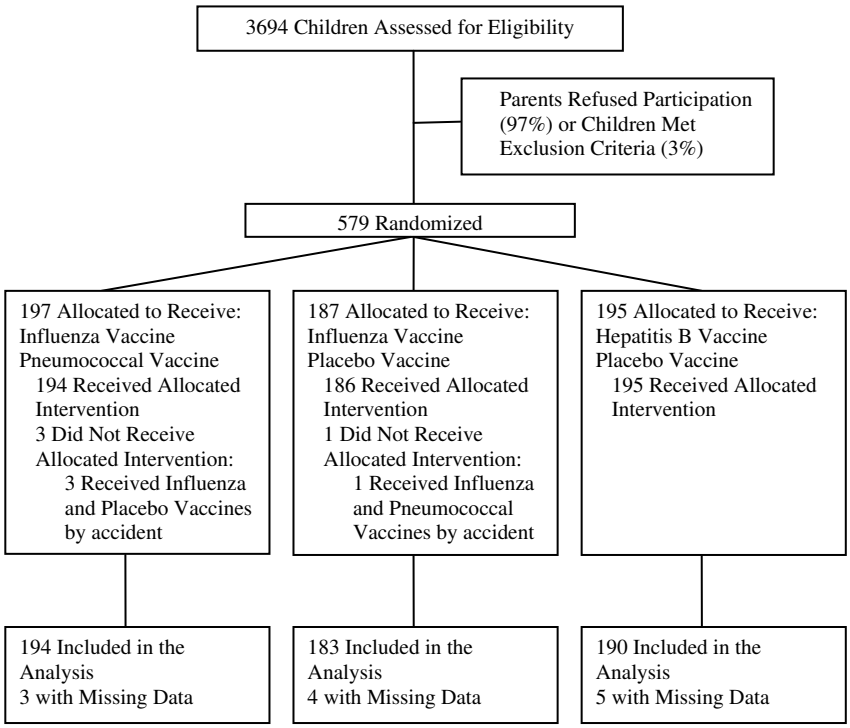


Table 1: Patient characteristics by study group

	IV+PV n = 197	**IV+plac** n = 187	**HepB+plac** n = 195
Sex (% male)	116 (59)	104 (55)	98 (50)
Age (mean)	3.0	3.1	3.1
(History of) Atopy (%)	82 (42.5)	73 (39.9)	81 (43.1)
More than three general practice-attended respiratory tract infections in the year prior to study entry (%)	62 (34.1)	58 (33.5)	62 (30.9)
History of ear-nose-throat surgery* (%)	56 (28.6)	51 (27.6)	56 (29.5)

IV+PV, influenza and pneumococcal vaccines; IV+plac, influenza and placebo vaccines; HepB+plac, hepatitis B and placebo vaccines * i.e. (adeno-)tonsillectomy and / or tympanostomy tubes

No immediate adverse events were recorded. During follow-up, local reactions for at least one day were most reported in the IV+PV group; 66.8% (95% CI 59.9 to 73.1) in the IV+PV group versus 37.8% (95% CI 31.0 to 45.0) in the IV+plac group and 36.0% (95% CI 29.5 to 43.1) in the HepB+plac group (Table 2A). Tenderness was the most prevalent local adverse reaction in all groups, with the highest risk difference between the IV+PV group and the two reference groups.

Table 2A: Local adverse reactions by study group during a follow-up of seven days

	IV+PV (%)	**IV+plac** (%)	Risk difference* (95%CI)	**HepB+plac** (%)	Risk difference** (95%CI)
Erythema	49/189 (25.9)	17/179 (9.5)	**16.4%** (8.9-24.0)	21/185 (11.4)	**14.6%** (6.8-22.3)
Swelling	62/187 (33.2)	32/179 (17.9)	**15.3 %** (6.5-24.1)	17/185 (9.2)	**24.0%** (16.0-31.9)
Tenderness	103/191 (53.9)	54/181 (29.8)	**24.1%** (14.4-33.8)	47/186 (25.3)	**28.7%** (19.2-38.1)
Interference with limb movement	42/188 (22.3)	8/171 (4.5)	**17.9%** (11.2-24.6)	10/176 (5.4)	**17.0%** (10.2-23.7)
Any local reaction	127/190 (66.8)	68/180 (37.8)	**29.1%** (19.3-38.8)	67/186 (36.0)	**30.8%** (21.2-40.4)

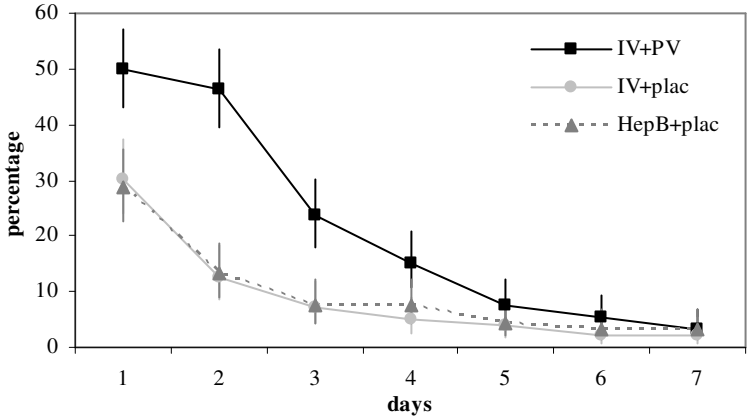
IV+PV, influenza and pneumococcal vaccines; IV+plac, influenza and placebo vaccines; HepB+plac, hepatitis B and placebo vaccines; 95%CI, 95% confidence interval * IV+PV index, IV+plac reference; ** IV+PV index, HepB+plac reference.

The prevalence of local reactions in the IV+PV group was highest during the first two days after immunization (46.3 to 50.0%) after which it decreased to 23.6% at day three and 7.4% at day five (Figure 2A). For the IV+plac and HepB+plac group the course of local reactions was similar, with the highest prevalence at day one (28.7 to 30.2%) thereafter decreasing to 7.1 to 7.4% at day three, and 3.9 to 4.3% at day five after vaccination.

Within the IV+PV group most local reactions were localized in the right extremity where the pneumococcal vaccine was administered. When comparing the local reactions in the left extremity between the IV+PV and IV+plac group, i.e. the extremity in which the IV was administered, IV in the IV+PV group was associated significantly more often with

interference of limb movement, namely 13.2% (95% CI 9.1 to 18.7) in the IV+PV group versus 3.4% (95% CI 1.5 to 7.1) in the IV+plac group.

Figure 2A: Proportion of all subjects experiencing local adverse reactions during the first seven days after vaccination



IV+PV, influenza and pneumococcal vaccines; IV+plac, influenza and placebo vaccines; HepB+plac, hepatitis B and placebo vaccines

During follow-up, any systemic reaction was reported in 63.9% (95% CI 56.8 to 70.5) of the children in the IV+PV group, 52.3% (95% CI 44.9 to 59.7) in the IV+plac group, and 50.9% (95% CI 43.5 to 58.2) in the HepB+plac group (Table 2B). Fever, i.e. temperature of 38.0°C or higher for at least one day, was significantly more reported in the IV+PV group (26.4%, 95% CI 20.4 to 33.4) compared with the HepB+plac group (15.1%, 95% CI 10.5 to 21.2), but not compared with the IV+plac group (21.0%, 95% CI 15.5 to 27.7).

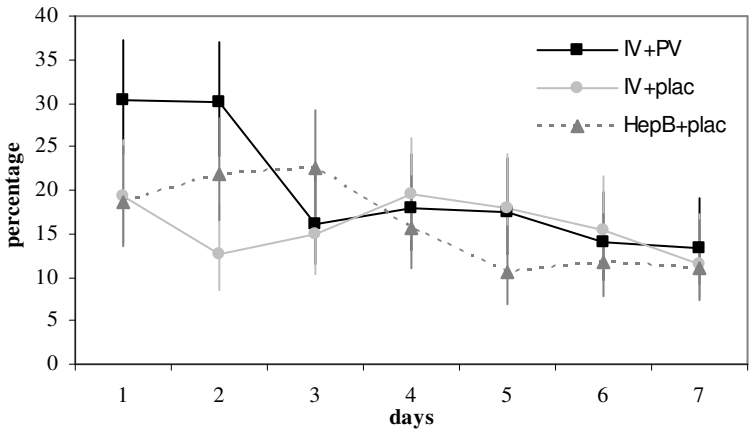
Systemic reactions were more prevalent in the first two days after immunization in the PV+IV group (30.1 to 30.3%) compared with the other study groups (12.6 to 21.9%), but after day two the course of systemic reactions was more or less similar in all three groups (Figure 2B).

Table 2B: Systemic adverse reactions by study group during a follow-up of seven days

		IV+PV (%)	IV+plac (%)	Risk difference* (95%CI)	HepB+plac (%)	Risk difference** (95%CI)
Fever	**≥38 °C**	46/174 (26.4)	35/167 (21.0)	5.5% (-3.5-14.5)	26/172 (15.1)	**11.3%** (2.9-19.8)
	≥39 °C	9/170 (5.3)	6/162 (3.7)	1.6% (-2.9-6.0)	10/169 (5.9)	-0.6% (-5.5-4.3)
Malaise		100/189 (52.9)	79/181 (43.6)	9.3% (-0.9-19.4)	83/187 (44.4)	8.5% (-1.54-18.6)
Headache		15/186 (8.1)	8/179 (4.5)	3.6% (-1.4-8.5)	14/184 (7.6)	0.5% (-5.0-5.9)
Myalgia		18/191 (9.4)	4/181 (2.2)	**7.2%** (2.6-11.9)	9/185 (4.9)	4.6% (-0.6-9.7)
Any systemic reaction		117/183 (63.9)	90/172 (52.3)	**11.6%** (1.4-21.8)	88/173 (50.9)	**13.1%** (2.9-23.3)

IV+PV, influenza and pneumococcal vaccines; IV+plac, influenza and placebo vaccines; HepB+plac, hepatitis B and placebo vaccines; 95%CI, 95% confidence interval * IV+PV index, IV+plac reference; ** IV+PV index, HepB+plac reference.

Figure 2B: Proportion of all subjects experiencing systemic adverse reactions during the first seven days after vaccination



IV+PV, influenza and pneumococcal vaccines; IV+plac, influenza and placebo vaccines; HepB+plac, hepatitis B and placebo vaccines

In 44 children (3.6%), parents reported gastro-intestinal complaints (respectively 10, 19, and 15 in the IV+PV, IV+plac, and HepB+plac group).

In total 14 children (2.4%) reported a visit to their primary care physician during follow-up (3 in the PV+IV group, 8 in the IV+plac group, and 3 in the HepB+plac group). Of these visits 10 were (follow-up) visits because of ear complaints, impetigo, an infected finger, throat infection, or common cold and cough. The other four visits were because of a rash starting on day four after vaccination (HepB+plac group), excessive crying and vomiting starting on day four after vaccination (IV+plac group), and two with coughing and shortness of breath (IV+plac group). In total 21 children (3.6%) withdrew from further immunization following the first vaccination (4 in the IV+PV group, 9 in the IV+plac group, and 8 in the HepB+plac group). Of these children 16 (76.2%) withdrew because of fear for further injections and/or family circumstances. The remaining five children withdrew (partly) because of medical reasons, i.e. 2 in the IV+PV group with rash (1 child with local rash and 1 with generalised rash), 1 in the IV+plac group with generalised rash, and 2 in the HepB+plac group due to malaise lasting for up till three weeks post-vaccination.

Discussion

No immediate anaphylactic or severe adverse reactions were recorded after simultaneous administration of influenza and pneumococcal conjugate vaccines. Most local and systemic reactions were mild and transient. About 30% more often local adverse reactions and 10% more often systemic adverse reactions were reported in the IV+PV group compared with the IV+plac and HepB+plac group during a follow-up of seven days.

Major advantages of the current study are its design (randomized double-blind controlled trial) and the fact that it is, to our knowledge, the first trial presenting the safety of simultaneous influenza and heptavalent pneumococcal conjugate vaccination in preschool children. The study population appeared representative for all preschool children with frequent respiratory tract infections. Age and gender of the included children were similar

to corresponding figures for all eligible children, and the mean number of general practice-attended consultations was only slightly higher in the study population (0.2 consultations more).[14] Additionally, adverse reactions were recorded with standardised diaries provided on the day of immunization which limited recall bias. Finally, adverse reactions were documented during a follow-up of seven days.

However, some possible limitations should be discussed. Firstly, for the parents of the youngest children in our study it may have been hard to assess some of the adverse reactions (particularly headache and myalgia). However, most of the solicited adverse reactions were easy to assess even in small children. Secondly, we did not include a control group with placebo vaccines only. The medical ethical review board of the University Medical Center Utrecht did not allow including a study arm with placebo injections only. We therefore used the hepatitis B vaccine as control, which is not included in the Dutch standard national infant immunization schedule. We did also not include a study group with pneumococcal vaccine only. Consequently, we were not able to assess whether the higher frequency of adverse reactions in the PV+IV group compared with the IV+plac group were solely due to the pneumococcal vaccine or also to the combination of influenza and pneumococcal vaccines. Additionally, it may be claimed that administering the vaccines in the right, mostly dominant, arm may have led to more side effects, and therefore this may have affected blinding. However, we verified that blinding was maintained. Finally, we did not impute missing data. This is unlikely to have affected the results, since the number of children with missing data was small.

Studies on the safety of the inactivated influenza vaccine among young children demonstrate fairly variable designs and presentation of data.[19] Consequently, the results of those studies are difficult to compare with ours. Moreover, the small number of children studied warrants cautious interpretation of the findings.[20] However, generally influenza vaccines appeared well-tolerated and safe in children,[20] which compares favourably with the safety profile of influenza vaccine in this study. A previous study assessing the safety of the heptavalent pneumococcal conjugate vaccine in children aged 24-36 months, reported local reactions (erythema, induration, or tenderness) in 32-40% within 72 hours and fever (≥ 38°C) in about 10% within seven days post-immunization.[21] In our study, erythema was

reported with similar frequency, but tenderness and fever was reported more often in the IV+PV group of our study. We do not know whether the combination of the influenza and pneumococcal had a synergistic effect on causing adverse reactions. However, the fact that the prevalence of interference of limb movement was higher in the extremity where IV was injected in children of the IV+PV group compared with that extremity in children of the IV+plac group supports a synergistic effect.

In adults several studies assessing the safety of simultaneous administration of influenza and pneumococcal vaccines were reported.[22-32] Most of these studies were not randomized or blinded, and in all studies pneumococcal polysaccharide vaccines were used which are not immunogenic in young children. However, simultaneous influenza and pneumococcal vaccination in adults seemed well tolerated and safe,[22-32] although in some studies associated with a higher rate of adverse reactions compared with the administration of either of the vaccines alone.[22,23,27,31,32]

In conclusion, the current study among preschool children demonstrated that adverse reactions were more prevalent in the IV+PV group compared with the IV+plac and HepB+plac groups, although the adverse reactions were non-severe and mostly short-term.

Acknowledgement

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CHAPTER 8

Effects of combined influenza and pneumococcal conjugate vaccination and influenza vaccination alone in preventing respiratory infections in children: a randomised double-blind controlled trial

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Anton M van Loon, Eelko Hak

Abstract

Objective Our objective was to evaluate the effects of combined influenza and heptavalent pneumococcal conjugate vaccination, or influenza vaccination alone on respiratory tract infections (RTI) in preschool children.

Patients and Methods We conducted a randomised double-blind controlled trial with a follow-up of 6 to18 months. 579 children aged 18 to 72 months with a prior history of physician-diagnosed RTI were recruited in primary care centers in three cohorts from 2003 to 2005. They were assigned to two doses of parenteral inactivated trivalent sub-unit influenza and heptavalent pneumococcal conjugate vaccinations (IV+PV), influenza and placebo vaccinations (IV+plac), or control recombinant hepatitis B and placebo vaccinations. Main outcome measures were febrile RTI and related PCR-confirmed influenza, primary care visits, antibiotic prescriptions, and acute otitis media (AOM) episodes.

Results During influenza seasons, the reported incidence of febrile RTI was 5.2 in the IV+PV group, 6.1 in the IV+plac group, and 6.9 per 1,000 child-days in the control group, i.e. reductions in the incidence of 24% (95% confidence interval (95%CI) 2-48%) in the IV+PV group and 13% (95%CI -13-33%) in the IV+plac group compared to the control group. The occurrence of PCR-confirmed influenza was reduced by 52% (95%CI 7-75%) and 51% (95%CI 3-75%) in the IV+PV and IV+plac groups. AOM episodes were reduced by 57% (95%CI 10-80%) in the IV+PV group and 71% (95%CI 29-88%) in the IV+plac group. Outside the influenza seasons no significant effects of vaccinations were demonstrated on the studied outcomes.

Conclusions During three consecutive influenza seasons with relatively mild virus-activity and/or circulating strains that deviated somewhat from the vaccine strains, parenteral influenza vaccination with or without conjugate pneumococcal vaccination reduced confirmed influenza and AOM episodes substantially. The effects on febrile RTI in general appeared less during influenza seasons, and effects were absent outside the influenza seasons.

Introduction

Respiratory tract infections (RTI) continue to be the leading cause of acute illnesses worldwide, particularly in children. Despite their marginal effects, ear-nose-throat surgery and treatment with antibiotics remain common,[1-3] and since frequent use of antibiotics has been associated with increasing bacterial resistance,[4] preventive strategies, in particular immunizations, are attractive.

Among children, influenza viruses and *Streptococcus pneumoniae* are common pathogens in RTI, and both are currently among a limited number of pathogens of respiratory disease that may be vaccine-preventable. In addition, evidence from animal and human studies suggests that influenza virus and *S.pneumoniae* interact synergistically in causing complicated infections,[5] and combined immunization against influenza virus and *S.pneumoniae* may therefore be particularly effective.

The Advisory Committee on Immunization Practices in the United States recently extended recommendations for influenza vaccination to include all infants and preschool children.[6] However, few data from randomised controlled trials on the effects of influenza vaccination in these groups are available.[7-9] In addition, studies on the effects of pneumococcal conjugate vaccination on common RTI in this age group are also scarce and absent for combined influenza and pneumococcal conjugate vaccination.[10,11] In the Netherlands, pneumococcal conjugate vaccination has been added to the national infant vaccination program since April 2006 without a catch-up program for children less than five years of age. For influenza, Dutch immunization guidelines recommend vaccination only for children with high-risk medical conditions such as chronic cardiac or respiratory disease, only. The aim of the current study was to evaluate the effects of combined parenteral influenza vaccination and heptavalent pneumococcal conjugate vaccination, or influenza vaccination alone in preventing RTI in preschool children.[12]

Methods

Participants and recruitment

General practitioners (GP) in the centre area of the Netherlands selected children aged 18 to 72 months old with prior diagnosed RTI, registered according to the International Classification of Primary Care[13,14]: acute otitis media (H71), cough (with fever) (R05), acute upper respiratory infection (R74) including common cold and pharyngitis, sinusitis (R75), acute tonsillitis (R76), acute laryngitis/tracheitis (R77), acute bronchitis/bronchiolitis (R78), influenza (R80), pneumonia (R81), pleurisy/pleural effusion (R82), and other respiratory infection (R83). Exclusion criteria were verified using questionnaires filled out by both GPs and parents. Exclusion criteria were asthma or recurrent wheezing chronically (> 3 months) treated with corticosteroids, other disorders predisposing for recurrent RTI, such as Down's syndrome and cleft palate, and clinically significant hypersensitivity to eggs. Children with previous serious adverse reactions to vaccines were also excluded, as were children who previously received influenza, pneumococcal or hepatitis B vaccinations as well as children with conditions for which these vaccinations are already recommended, such as chronic cardiac or respiratory conditions for influenza vaccination. The medical ethical review board of the University Medical Center Utrecht, the Netherlands approved the study protocol. Parents were informed about the study by their GP, and written informed consent was obtained from the parents for each child prior to enrolment.

Procedures

Three cohorts of children were enrolled during the September to October periods of 2003, 2004, and 2005 (Table 1). The children were randomly assigned in blocks of three to combined influenza and pneumococcal vaccinations (IV+PV), influenza and placebo vaccinations (IV+plac), or control hepatitis B and placebo vaccinations (HepB+plac) in a 1:1:1 ratio. Assignments to treatment groups were not revealed to parents, investigators, research personnel conducting the follow-up or health care providers, all of whom remained blinded throughout the study. Administration of the injections was performed by non-blinded research nurses, who were not involved in subsequent follow-up of the children and who were instructed not to reveal the allocated intervention. The vaccines were administered intramuscularly in deltoid or gluteal muscles (in separate extremities).

Pneumococcal and placebo vaccines were administered in the right extremity, and influenza and hepatitis B vaccines were administered in the left extremity. All three study arms had a similar vaccination schedule (Table 1). Children received two vaccinations four to eight weeks apart in the year of inclusion, and the first two included cohorts of children received a subsequent vaccination in the year thereafter. To evaluate blinding, parents of the last two cohorts of included children were asked what vaccinations they thought their child had received just after the vaccinations were set and at the end of the study. Just after the vaccinations, 87% of the parents did not know or mentioned the wrong set of vaccinations, and at the end of the study this was 80%, indicating that blinding was successful.

Table 1: Vaccination schedule

Cohort	Vaccination groups (n)	First vaccinations (Sept / Oct)	Second vaccinations* (Nov/Dec)	Third vaccinations (Oct next year)	Total follow-up time
2003 and 2004 (n=363)	Combined pneumococcal and influenza vaccinations (122)	IV + PV	IV + PV	IV	18 months
	Influenza vaccinations alone (117)	IV + placebo	IV + placebo	IV	18 months
	Control vaccinations (124)	Hep B+ placebo	Hep B + placebo	Hep B	18 months
2005 (n=216)	Combined pneumococcal and influenza vaccinations (75)	IV + PV	IV + PV	-	6 months
	Influenza vaccinations alone (70)	IV + placebo	IV + placebo	-	6 months
	Control vaccinations (71)	Hep B + placebo	Hep B + placebo	-	6 months

IV, trivalent inactivated influenza vaccine; PV, heptavalent pneumococcal conjugate vaccine; Hep B, recombinant hepatitis B vaccine; * maximally 60 days after the first vaccinations

Vaccines

Inactivated trivalent sub-unit influenza vaccine (Influvac®) was supplied by Solvay, Weesp, the Netherlands. Strains in the 2003-2004 formulation were A/New Caledonia/20/99 (H1N1), A/Moscow/10/99 (H3N2), and B/HongKong/330/01; in the 2004-2005 formulation A/New Caledonia/20/99 (H1N1), A/Fuijan/411/2002 (H3N2), and

B/Shanghai/361/2002; and in the 2005-2006 formulation A/New Caledonia/20/99 (H1N1), A/California/7/2004 (H3N2), and B/Shanghai/361/2002. The heptavalent pneumococcal conjugate vaccine (Prevenar®, Wyeth Vaccines Research, Berkshire, United Kingdom) consisted of 2 μg each of capsular polysaccharides of pneumococcal serotypes 4, 9V, 14, 19F, and 23 F, 4 μg of serotype 6B polysaccharide, and 2 μg of serotype 18C oligosaccharide, each conjugated individually to the CRM_{197} protein. The placebo consisted of a standard diluent (0.9% NaCl phosphate buffered, Solvay, Weesp, the Netherlands). Control vaccine was the recombinant hepatitis B vaccine (Engerix-B Junior®, GlaxoSmithkline, Rixenart, Belgium).

Clinical outcome measures

Follow-up of clinical outcomes for each participant started 14 days after the second set of vaccinations and continued for 18 or 6 months, depending on the year of inclusion (Table 1). Parents were instructed to keep a daily diary with clinical signs or symptoms associated with RTI, i.e. general weakness/malaise, rhinitis, sore throat, earache, coughing, wheezing/shortness of breath, and shivering/muscle ache. They indicated the severity of symptoms by scoring from 1 (mild) to 3 (severe). In case of symptoms, parents measured the child's body temperature (preferably at the end of the day) with a validated electronic tympanic thermometer provided by the trial center.[15] Parents were also asked to mark in the diary when they visited the GP for their child because of RTI-related complaints. In case of such a visit, the GP filled out a form including information on the diagnosis and possible antibiotic prescriptions.

The primary study outcome was the occurrence of a febrile RTI defined as fever (tympanic temperature ≥ 38.0 ºC) for at least two consecutive days accompanied by one or more of the previous mentioned signs or symptoms of RTI with a moderate (i.e. 2) or severe (i.e. 3) severity score (2 or 3). An incident RTI-episode was only counted as such when it occurred after a period of at least five days without fever and RTI symptoms. Secondary outcomes were febrile RTI-related PCR-confirmed influenza (see below), GP visits, antibiotic prescriptions or a physician-diagnosed episode of acute otitis media (AOM). To confirm influenza, parents were instructed to contact the trial center in case their child had fever (tympanic temperature ≥ 38.0 ºC) for more than one day accompanied by at least one RTI-

associated sign or symptom with a severity score of 2 during the influenza season. Within four days after onset of fever and symptoms nasopharyngeal swabs for viral determination were taken by a trained research assistant. The samples were analyzed by real-time PCR for the presence of influenza A and B viruses.[16] Per season, nasopharyngeal swabs were taken maximally once per child. Influenza season was defined as the period with more than 50 GP-visits for influenza-like-illness per 100,000 inhabitants per week in the Netherlands as recorded by the European Influenza Surveillance Scheme (http://www.eiss.org).

Characteristics of influenza seasons

In the Netherlands, the influenza season 2003-04 peaked with 149 patients who visited their GP with influenza-like-illness per 100,000 inhabitants.[17] Almost all isolates were influenza A/H3N2 viruses and appeared closely related to influenza virus A/Fujian/411/02, a variant that already circulated in season 2002-03 and deviated somewhat from the vaccine strain A/Moscow/10/99 and formerly circulating strains.[17] The influenza season 2004-05 peaked with 240 GP-attended influenza-like-illnesses per 100,000 inhabitants.[18] Again most isolates were influenza A/H3N2 viruses and appeared related to the new variant A/California/7/04 that deviated to some extent from the vaccine strains. Although the influenza-A/H1N1-viruses were similar to the vaccine strains, the influenza-B-virus isolates deviated significantly from the vaccine strains.[18] The influenza season 2005-06 included two peaks of activity with 138 and 98 GP-attended influenza-like-illnesses per 100,000 inhabitants.[19] The first peak was mainly caused by influenza B viruses, which differed significantly from the vaccine strain. The second peak of activity was mainly caused by influenza A/H3N2-viruses which generally matched with the vaccine strains.[19]

Statistical aspects

We estimated that we would need at least 163 study subjects per study arm, assuming a hazard rate of the primary outcome of 5.0 per 1,000 days of follow-up during an average influenza season of 60 days, to have 80% power to detect a 45% reduction (hazard rate of 0.55) with a two-sided alpha of .05. Taking into account potential loss-to-follow-up of 15%, 187 persons were required per arm. A more conservative approach was also used, estimating that we would need 200 study subjects per study arm to detect a similar 45% reduction (risk ratio 0.55) in the probability of developing *at least one* febrile RTI ,

assuming a 15% probability of this outcome in the control group, a power of 80% power and a two-sided alpha of .05. Thus, we aimed to include 200 children in each of the three study arms.

All analyses were carried out on an intention-to-treat basis. Relative risks, i.e. proportion of children with at least one febrile RTI and febrile RTI with confirmed influenza during influenza season in the vaccination groups versus the control group, with 95% confidence intervals (95%CI) were determined (Rothman K. Episheet: Spreadsheets for the analysis of epidemiologic data, 2002). With the statistical package SAS (version 8.02), the incidence rates of each outcome (number of events per day) during influenza season and outside influenza seasons were modelled using Poisson regression accounting for potential dependency of observations within individuals. An offset was included in the model to account for different observation times per individual. Incidence rate ratios with 95%CI were based on maximum likelihood estimates and their corresponding standard errors.

Results

Study population

We enrolled a total of 579 children; 171 in the first cohort, 192 in the second, and 216 in the third cohort (Table 1). The distribution of baseline characteristics was similar in the three study arms (Table 2). In total, 471 children (81%) completed the study; 41 (7%) were completely lost to follow-up and 67 (12%) had a partial follow-up (Figure). In general, vaccinations were well tolerated, and no immediate and/or severe adverse events were recorded.

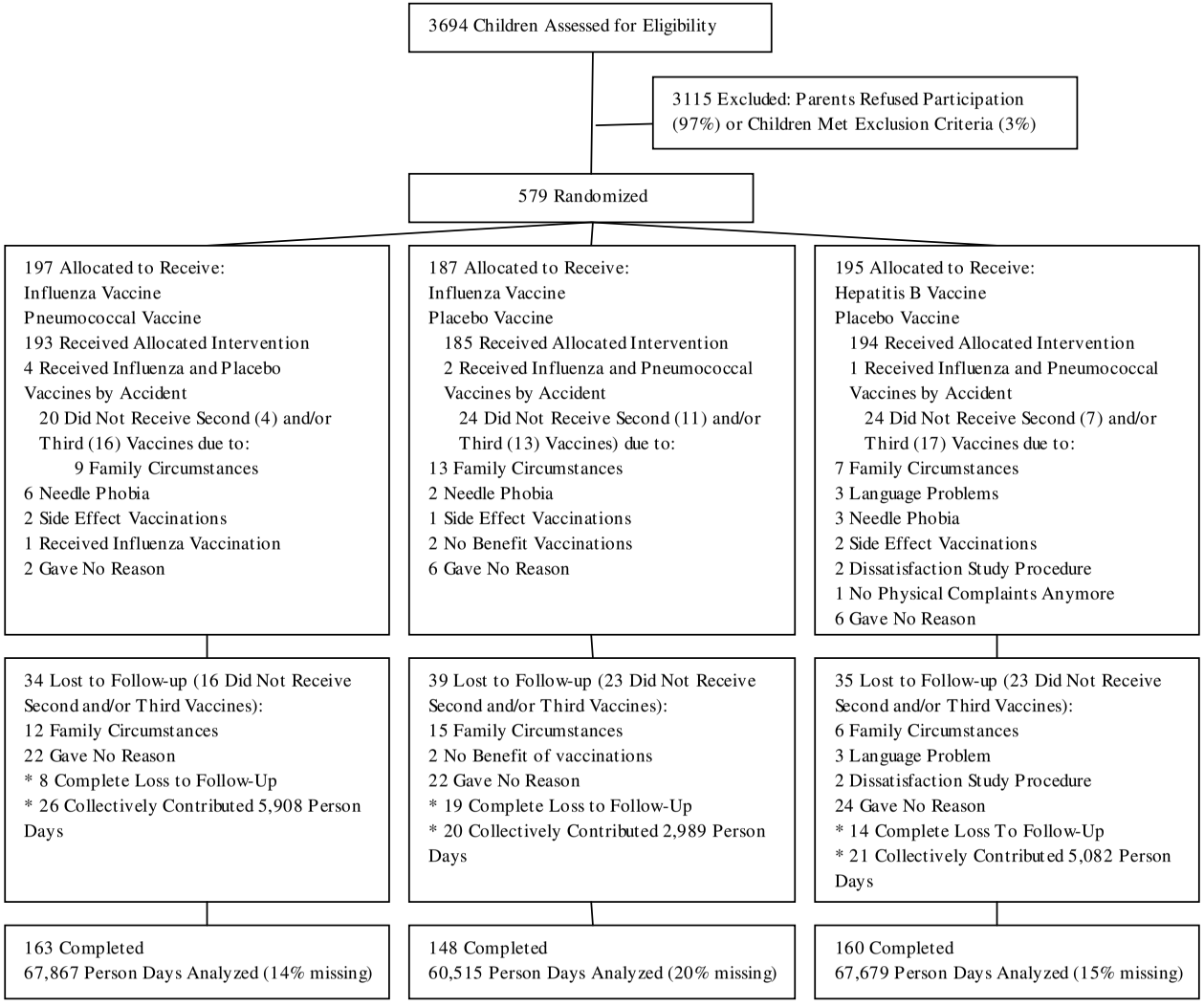
3694 Children Assessed for Eligibility
3115 Excluded: Parents Refused Participation (97%) or Children Met Exclusion Criteria (3%)
579 Randomized
197 Allocated to Receive:
Influenza Vaccine
Pneumococcal Vaccine
193 Received Allocated Intervention
4 Received Influenza and Placebo Vaccines by Accident
20 Did Not Receive Second (4) and/or Third (16) Vaccines due to:
9 Family Circumstances
6 Needle Phobia
2 Side Effect Vaccinations
1 Received Influenza Vaccination
2 Gave No Reason
187 Allocated to Receive:
Influenza Vaccine
Placebo Vaccine
185 Received Allocated Intervention
2 Received Influenza and Pneumococcal Vaccines by Accident
24 Did Not Receive Second (11) and/or Third (13) Vaccines) due to:
13 Family Circumstances
2 Needle Phobia
1 Side Effect Vaccinations
2 No Benefit Vaccinations
6 Gave No Reason
195 Allocated to Receive:
Hepatitis B Vaccine
Placebo Vaccine
194 Received Allocated Intervention
1 Received Influenza and Pneumococcal Vaccines by Accident
24 Did Not Receive Second (7) and/or Third (17) Vaccines due to:
7 Family Circumstances
3 Language Problems
3 Needle Phobia
2 Side Effect Vaccinations
2 Dissatisfaction Study Procedure
1 No Physical Complaints Anymore
6 Gave No Reason
34 Lost to Follow-up (16 Did Not Receive Second and/or Third Vaccines):
12 Family Circumstances
22 Gave No Reason
* 8 Complete Loss to Follow-Up
* 26 Collectively Contributed 5,908 Person Days
39 Lost to Follow-up (23 Did Not Receive Second and/or Third Vaccines):
15 Family Circumstances
2 No Benefit of vaccinations
22 Gave No Reason
* 19 Complete Loss to Follow-Up
* 20 Collectively Contributed 2,989 Person Days
35 Lost to Follow-up (23 Did Not Receive Second and/or Third Vaccines):
6 Family Circumstances
3 Language Problem
2 Dissatisfaction Study Procedure
24 Gave No Reason
* 14 Complete Loss To Follow-Up
* 21 Collectively Contributed 5,082 Person Days
163 Completed
67,867 Person Days Analyzed (14% missing)
148 Completed
60,515 Person Days Analyzed (20% missing)
160 Completed
67,679 Person Days Analyzed (15% missing)

Table 2: Baseline characteristics

		IV+PV (n= 197)	IV+plac (n=187)	HepB+plac (n=195)
Male sex		58.9	55.6	50.3
Mean age, years		3.0	3.1	3.1
Number of RTI episodes in preceding year (%):	**≤ 3**	46	44	42
	4-6	37	40	41
	≥ 7	17	16	17
Number of general practice-diagnosed RTI in preceding year		3.0	3.1	3.2
Number of courses of antibiotics prescribed in preceding year		1.6	1.6	1.8
History of ENT-surgery (%)*		28.6	27.6	29.5
Asthma/wheezing in preceding year (%)		28.3	27.4	31.6
Hay fever / allergic rhinitis in preceding year (%)		16.6	14.1	12.4
Eczema in preceding year (%)		21.6	18.3	22.9
Day care (%)		69.7	62.0	66.3
Mean number of siblings		0.8	0.9	1.0
Breastfeeding < 3 months (%)		58.2	62.7	55.5
Tobacco smoke exposure indoors (%)		22.6	25.9	26.6

RTI, respiratory tract infections; IV+PV, influenza and pneumococcal vaccines; IV+plac, influenza and placebo vaccines; HepB+plac, hepatitis B and placebo vaccines; * i.e. (adeno-)tonsillectomy and / or tympanostomy tubes

Febrile RTI

Influenza season

During the influenza season, 28% in the IV+PV group and 34% in the IV+plac group had at least one febrile RTI episode versus 39% in the control HepB+plac group, corresponding to relative risks of respectively 0.72 (95%CI 0.57-0.92) and 0.88 (95%CI 0.70-1.10). In all three influenza seasons together, a total of 330 episodes of febrile RTI episodes was reported with an incidence rate of 6.1 per 1,000 child-days of follow-up: 5.2 in the IV+PV group, 6.1 in the IV+plac group, and 6.9 per 1,000 child-days in the control HepB+plac group. This relates to reductions of 24% (95%CI 2-42%) in the IV+PV group and 13% (95%CI -13-33%) in the IV+plac group compared to the control group (Table 3). These figures correspond to 9-17 children required to be vaccinated in order to prevent one such

RTI-episode. Of all 330 febrile RTI episodes during influenza seasons, 271 (82%) were in separate children, and nose/throat swabs for influenza virus PCR analysis could be obtained in 117 of these episodes. Influenza virus type A or B was identified in 48 children; 9% of the children in the HepB+plac group, 4% of the children in the IV+PV group (relative risk 0.48, 95%CI 0.25-0.93), and 5% of the children in the IV+plac group (relative risk 0.49, 95%CI 0.25-0.97). This means that in order to prevent one episode of influenza, 20-25 children are required to be vaccinated.

Of all 330 febrile RTI episodes, 128 (39%) resulted in a primary care visit, 66 (20%) in an antibiotic prescription and 39 (12%) in a physician-diagnosis of AOM. For primary care visits and antibiotic prescriptions no significant differences in rates were observed between the IV+PV and IV+plac groups and the control group (Table 3). AOM episodes were reduced by 57% (95%CI 10-80%) in the IV+PV group and 71% (95%CI 29-88%) in the IV+plac group, compared to the control HepB+plac group (Table 3), corresponding to 19-22 children required to be vaccinated to prevent one AOM episode.

Outside influenza seasons

Outside influenza seasons, 504 episodes of febrile RTI and 183 (36%) related GP-visits, 101 (20%) antibiotic prescriptions, and 51 (10%) physician-diagnosed episodes of AOM were recorded. No overall differences between the three study arms were observed in the rates of any of these outcomes (Table 3).

Table 3: Incidence rates of outcomes by follow-up period and treatment group

Condition	Group	Incidence per 1,000 child days (95%CI)	Incidence rate ratio (95%CI)	p-value for overall differences between the three study groups
		INFLUENZA SEASON		
Febrile RTI	*IV+PV*	5.2 (4.2-6.5)	**0.76 (0.58-0.99)**	0.13
	IV+plac	6.0 (5.0-7.2)	0.87 (0.68-1.12)	
	HepB+plac	6.9 (5.9-8.2)		
General practice visit	*IV+PV*	2.2 (1.6-3.0)	0.75 (0.50-1.12)	0.15
	IV+plac	2.0 (1.4-2.7)	0.67 (0.45-1.02)	
	HepB+plac	2.9 (2.3-3.7)		
Antibiotic prescription	*IV+PV*	1.0 (0.6-1.6)	0.73 (0.40-1.32)	0.57
	IV+plac	1.2 (0.8-1.9)	0.89 (0.50-1.61)	
	HepB+plac	1.4 (0.9-2.1)		
Acute otitis media	*IV+PV*	0.5 (0.3-1.0)	**0.43 (0.20-0.94)**	**0.01**
	IV+plac	0.4 (0.2-0.8)	**0.29 (0.12-0.70)**	
	HepB+plac	1.2 (0.8-1.9)		
		OUTSIDE INFLUENZA SEASON		
Febrile RTI	*IV+PV*	4.0 (3.4-4.7)	1.20 (0.95-1.52)	0.29
	IV+plac	3.5 (2.9-4.2)	1.05 (0.82-1.34)	
	HepB+plac	3.3 (2.8-3.9)		
General practice consultation	*IV+PV*	1.2 (0.9-1.6)	0.82 (0.56-1.21)	0.54
	IV+plac	1.2 (0.9-1.7)	0.82 (0.55-1.23)	
	HepB+plac	1.5 (1.1-1.9)		
Antibiotic prescription	*IV+PV*	0.7 (0.5-1.1)	0.89 (0.54-1.44)	0.33
	IV+plac	0.6 (0.4-0.9)	0.67 (0.39-1.16)	
	HepB+plac	0.8 (0.6-1.2)		
Acute otitis media	*IV+PV*	0.5 (0.3-0.7)	**2.00 (1.02-3.93)**	0.13
	IV+plac	0.3 (0.2-0.6)	1.41 (0.65-3.03)	
	HepB+plac	0.2 (0.1-0.4)		

IV+PV, influenza and pneumococcal vaccines; IV+plac, influenza and placebo vaccines; HepB+plac, hepatitis B and placebo vaccines; 95%CI, 95% confidence interval

Discussion

This randomised double-blind controlled trial among 579 children showed that influenza vaccination with or without heptavalent pneumococcal conjugate vaccination was effective against confirmed influenza and AOM episodes during influenza seasons, but appeared less effective against febrile RTI episodes in general. Outside influenza seasons, these vaccinations appeared to have no beneficial effects.

Recent meta-analyses on the effects of influenza vaccination among healthy children of all ages reported reductions of 62% (95%CI 45-75%), 65% (95%CI 45-77%), and 65% (95%CI 47-76%) in confirmed influenza by parenteral inactivated influenza vaccination.[7-9] Within a subgroup of healthy preschool children, a non-significant reduction in confirmed influenza of 58% (95%CI -20-86%) was reported based on two randomised controlled trials covering each one influenza season with a total size of only 132 children.[7] In the current study with 579 children and covering three influenza seasons, we had adequate power to observe a statistically significant effect of 51% (95%CI 3-75%) and 52% (95%CI 7-75%) on confirmed influenza in both vaccination groups which corresponds with the estimates from meta-analyses. We observed a risk difference of 4-5% in febrile RTI-related confirmed influenza between the control and intervention groups, meaning that 20-25 children are required to be vaccinated to prevent one such episode of influenza. However, it should be noted that this number-needed-to-treat may be overestimated since in we only took nose/throat swabs in case of the first febrile RTI episode during the influenza seasons, which probably has led to an underestimation of the influenza attack rate.

The effects on influenza-like-illness among healthy children of all ages reported by meta-analyses vary from reductions of 28% (95%CI 22-33%) to 45% (95%CI 33-55%),[7-9] and among preschool children aged less than six years a statistically non-significant reduction in influenza-like-illness of 48% (95%CI -98-86%) was found.[7] A recent randomised study among preschool children covering one season found significant reductions of 33 an 22% in upper and lower RTI, 26% in febrile respiratory illness, and 32% in antibiotic prescriptions by influenza vaccination. Such reductions are, however, difficult to interpret since the control group did not receive placebo or control vaccinations.[20,21] We observed reductions

in febrile RTI of 24% (95%CI 2-48%) in the IV+PV group and 13% (95%CI -13-33%) in the IV+plac group during influenza seasons. These vaccine effect estimates appear low compared to those reported in these previous studies. Our definition febrile RTI, however, is likely to cover more illnesses than those more narrowly defined as influenza-like-illnesses. Typically, less specific definitions of diagnoses will result in smaller relative reductions. Obviously, even during the influenza season a large proportion of febrile RTI among children is caused by other pathogens like rhinoviruses, human coronaviruses, para-influenza viruses, adenoviruses and particularly the seasonally active respiratory syncytial virus that often co-circulates with influenza virus.[22,23] Nonetheless, we found reductions in AOM episodes of 57% (95%CI 6-80%) in the IV+PV group and 71% (95%CI 30-88%) in the IV+plac group, which indicates a pivotal role of influenza viruses in this condition. Our results are in agreement with previous non-randomised and/or unblinded studies in preschool children that reported a reduction in AOM by parenteral inactivated subunit influenza vaccination of 40 to 62%.[24.25] A meta-analysis of six (quasi) randomised controlled trials reported also a reduction in AOM of 32% (95%CI -16-60%) by parenteral inactivated influenza vaccination among healthy children of all ages.[9]

Although pneumococcal conjugate vaccinations have been demonstrated to be highly effective against invasive pneumococcal disease and to a lesser extent also against pneumonia,[26] their effect on mucosal infections like upper RTI including AOM appears less. A recent meta-analysis of four randomised controlled trials on pneumococcal conjugate vaccinations among infants reported reductions in AOM of 8% (95%CI 5-12%).[27] Studies of pneumococcal conjugate vaccinations in older children are scarce. One previous double blind, randomised, controlled study on nonavalent pneumococcal conjugate vaccinations among children aged 12-35 months attending day-care, reported a reduction of 15% (95%CI 4-24%) of upper respiratory infections, 16% (95%CI 2-28%) in lower respiratory problems, and 17% (95%CI -2-33%) in AOM episodes.[10] However, another study with heptavalent pneumococcal conjugate vaccinations followed by a pneumococcal polysaccharide vaccination in children with recurrent AOM, could not observe a beneficial effect on AOM at all.[11] We found no overall significant difference in the occurrence of GP-diagnosed AOM episodes between the study groups outside influenza seasons. Although our study was not adequately powered to detect relatively small effects

like 8% reduction, the incidence rate ratio of the IV+PV group over the control group suggested rather an increase in the vaccination group. The lack of an effect on either all-cause RTI or physician-attended AOM episodes by pneumococcal conjugate vaccinations may have in part been caused by changes in nasopharyngeal carriage after vaccination, with a shift from serotypes covered by the vaccine to non-vaccine serotypes and other colonising bacteria of the nasopharynx.[28-30] While rates of vaccine serotype RTI may decrease, replacing pathogens may have pathogenic potential,[31] even causing an increase in rates of RTI by non-vaccine serotype pneumococci and other nasopharyngeal colonising flora.[30,32] This replacement phenomenon may particularly affect older children.[11,33] Future studies should further address this.

A potential limitation of the current study is the fact that influenza virus-activity was mild during the seasons 2003-04 and 2005-06, and the circulating influenza virus A subtype H3N2 strain sub-optimally matched with the vaccine strain in the seasons 2003-04 and 2004-05 as was also the case for the influenza B viruses in 2004-05 and 2005-06.[17-19] This mild influenza virus-activity and suboptimal vaccine matching may have led to an underestimation of the effect of influenza vaccination during a severe epidemic. However, these phenomena are inherent to the unpredictable nature of influenza viruses with antigenic drift. This not only further underscores the need for the inclusion of multiple influenza seasons in trials, but also a continuing effort to improve influenza vaccines.

Major strengths of the current study are its randomised double-blind controlled design and the fact that it covered three influenza seasons. Importantly, the current study is to our knowledge the first study on combined influenza and pneumococcal vaccinations in children.

In summary, our study indicated that parenteral inactivated influenza vaccination with or without heptavalent pneumococcal conjugate vaccinations were effective against confirmed influenza and AOM episodes, but less effective against all febrile RTI in general during influenza seasons. Outside influenza seasons, no significant benefits were observed from vaccinations. Influenza vaccination may play an important role in the prevention of AOM.

Acknowledgments

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CHAPTER 9.1

Functional health in children with prior physician-diagnosed respiratory tract infections: validation of measures

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Abstract

Background: The child's well-being and functional health status (FHS) should be considered as an important outcome in both medical practice to guide treatment and in trials evaluating the effect of treatment. Despite the high occurrence of respiratory tract infections (RTI), the impact of RTI on the child's well-being is largely unknown. The objective of the current study was to validate instruments assessing functional health status (FHS) in children with prior-diagnosed RTI, thereby evaluating the child's well-being.

Methods: The generic measure Rand General Health Rating Index for Children (RAND-GHRI), and the disease-specific measures Otitis Media-6 (OM-6) and the Respiratory Tract Infection-6 (derived from OM-6) were validated. Children aged 1.5-6 years with prior RTI in primary care, recruited for a trial on the effectiveness of influenza and pneumococcal vaccination (N=356), were included. Responsiveness was assessed when children had a febrile RTI during influenza epidemics (N=100). Test-retest reliability was measured in 64 children.

Results: The RAND-GHRI demonstrated high internal consistency, test-retest reliability, construct, and discriminant validity, but limited responsiveness. The OM-6 was not responsive at all to new RTI episodes. The RTI-6 showed a good test-retest-reliability, construct, and discriminant validity, and was most responsive.

Conclusions: The RAND-GHRI and RTI-6 appeared valid questionnaires to measure FHS in preschool children with prior-diagnosed RTI. RTI seemed to affect functional health.

Introduction

In developed countries, acute respiratory tract infections (RTI) are the leading cause of morbidity.[1] Toddlers attending day-care suffer from a cold-like illness on average 23% of the time, and many young children suffer from recurrent upper RTI.[2-4] Although the incidence of RTI is high, the impact of RTI on the child's well-being or functional health status (FHS) has gained little attention. Frequent RTI may mimic a chronic condition and negatively affect the child's well-being by causing pain and distress, impairing daily activities, and along with this parental stress. The child's FHS should be considered as an important outcome both in medical practice to guide treatment and in trials evaluating the effect of treatment.

The PRIMAKid-trial aspires to determine the effects of influenza and pneumococcal vaccination in children with prior physician-diagnosed RTI.[5] Aim of the current study was to validate FHS measures for children with prior physician-diagnosed RTI in order to use them as outcome measures in the trial, thereby assessing the child's well-being. A major factor influencing the implementation of FHS measures both in practice and in trials is their ease of use. Therefore the Rand General Health Rating Index for Children (RAND-GHRI) was selected. It is a short generic general health questionnaire, validated in the Netherlands, and proven to be reliable in asthmatic children.[6,7] Generally, disease-specific questionnaires are regarded as more sensitive to change than generic questionnaires, since they pay attention to the specific impairments that may accompany a certain disease.[8,9] Although no RTI-specific questionnaire is available, the short questionnaire Otitis Media-6 (OM-6) developed for use in children with recurrent otitis media,[10,11] was also selected for the current study. Finally, the OM-6 was modified into the Respiratory Tract Infection-6 (RTI-6) questionnaire, more suitable for children with RTI.

Methods

Setting and study population

This study was part of the Prevention of Respiratory Infections and Management (PRIMAKid) randomized placebo-controlled trial that aims to establish the effects of influenza and pneumococcal vaccinations in children with prior physician-diagnosed RTI.[5] General practitioners (GPs) in the centre area of the Netherlands selected children aged 18 to 72 months old with prior diagnosed RTI, registered according to the International Classification of Primary Care:[12,13] acute otitis media (H71), cough (with fever) (R05), acute upper respiratory infection (R74) including common cold and pharyngitis, sinusitis (R75), acute tonsillitis (R76), acute laryngitis/tracheitis (R77), acute bronchitis/bronchiolitis (R78), influenza (R80), pneumonia (R81), pleurisy/pleural effusion (R82), and other respiratory infection (R83). Exclusion criteria were asthma or recurrent wheezing chronically (> 3 months) treated with corticosteroids, other disorders predisposing for recurrent RTI, such as Down's syndrome and cranio-facial malformations, and clinically significant hypersensitivity to eggs. Children with previous serious adverse reactions to vaccines were also excluded, as were children who previously received influenza, pneumococcal or hepatitis B vaccinations as well as children with conditions for which these vaccinations are already recommended, such as chronic cardiac or respiratory conditions for influenza vaccination.

At inclusion in September 2003 and September 2004, a selection of FHS questionnaires was validated, and FHS was cross-sectionally assessed in a total of 356 children recruited during the first two inclusion rounds of the PRIMAKid trial (337 caregivers (95%) completed all questionnaires). To determine responsiveness to clinical change of the measures, we compared score changes in trial participants between baseline and at time they experienced a febrile (>38°C) RTI during the influenza epidemics of 2003-2004 or 2004-2005 (N=100). Additionally, 263 caregivers of children with rRTI who fulfilled the inclusion criteria of the PRIMAKid-trial but refused to participate were approached to assess test-retest reliability. Of these caregivers 111 (42%) responded and completed the questionnaires twice within a period of 30 days. In order to include only children with an equal situation at the two different measurement points, 47 children had to be excluded due

to a RTI at baseline (the previous four weeks) or at the second time the questionnaires were completed. This resulted in 64 children who were appropriate for test-retest analysis.

Instruments

The RAND-GHRI developed at the RAND corporation, has been translated and validated for Dutch children.[6,7] It assesses general health perceptions of caregivers regarding their child with seven items covering parental worrying, current and prior health, physical suffering, and susceptibility/resistance to illness. We changed the time horizon from 3 months into 4 weeks to enable comparison with the other used questionnaires that also consider a time horizon of 4 weeks. The total score of the RAND-GHRI is equal to the sum score ranging from 7 to 32, with higher scores indicating better health (see Appendix for the studied questionnaires).

The OM-6 is a parent-assessed disease-specific measure of FHS and has been developed for use in children with recurrent acute otitis media (AOM) and otitis media with effusion.[10,11] This questionnaire has already been validated and translated into Dutch [Brouwer, C.N. (2003) Health related quality of life in children with recurrent acute otitis media. Thesis. University Medical Center Utrecht, the Netherlands]. The OM-6 is a six-item questionnaire with each item representing a different domain, concerning physical suffering, speech problems, hearing loss, emotional distress, activity limitation, and parental worrying, all caused by AOM. Because of its shortness and ease of use, we adapted the OM-6 for RTI creating the respiratory tract infection-6 (RTI-6) questionnaire. The total score of both the OM-6 and RTI-6 can be calculated by adding up the different item scores, with higher scores indicating better FHS. As the RTI-6 is a modification of the OM-6, we did not perform a full forward-backwards translation procedure (see Appendix for the studied questionnaires).

Analysis

We conducted complete case analysis with SPSS statistical software (version 12.0) since the proportion of missing data was low (5%). To compare the scores of the different questionnaires we standardized all scores to a 0-100 scale, with higher scores indicating better FHS. For each instrument the distribution of scores was evaluated by calculating the

mean, median, standard deviation, and inter-quartile range (IQR). Parametric tests were used for normally distributed variables and corresponding non-parametric tests were used for skewed distributions. Floor and ceiling effects were estimated and expressed as percentage of respondents that had minimum and maximum scores, respectively.

Internal consistency of the questionnaires was assessed by calculating the inter-item correlations and Cronbach's alpha.[14] Item-total correlations were calculated with the formula given by Nunally.[15] Rule of thumb is that items with item-total correlations lower than 0.20 should be discarded.[15] Cronbach's alpha should be higher than 0.70. In order to assess test-retest reliability Pearson correlation coefficients as well as the intra-class correlation coefficients (ICC's) were calculated.[16]

Construct validity was assessed by comparing predicted correlations with the estimated correlations (Spearman) between questionnaires and related items. Strong correlations were predicted between the RAND-GHRI and RTI-6, and moderate correlation between the RAND-GHRI and OM-6. Items covering similar subjects were predicted to have moderate to strong correlations. The OM-6 measures a construct different from the RTI-6 because it is not specific for all RTI but only otitis media. Therefore the correlation between OM-6 and RTI-6 was predicted to be weak to moderate. Correlations between questionnaire score and the number of parent-reported RTI in the year prior to inclusion were predicted to be moderate to strong for the RAND-GHRI and RTI-6. Again, with regard to the different construct that the OM-6 measures, this correlation was predicted to be weak. A correlation <0.30 was defined as weak, 0.30-0.50 as moderate and >0.50 as strong.[17,18]

Discriminant validity was determined by comparing scores between children with ≤ 3 and ≥ 4 parent-reported RTI episodes during the year prior to study entry. We chose 4 episodes as cut-off since the mean number of episodes was 4.28 with a median of 4.00. The Mann Whitney U-test was used to evaluate significance of the differences. To evaluate responsiveness the standardized response mean (SRM), defined as the ratio of the mean change score to the standard deviation of that change score, was calculated.[15,17,19] A SRM of >0.2 reflects a small change, >0.5 a moderate change and > 0.8 a large change.[19]

Results

The mean age of the 356 children at baseline was 36.6 months (SD 15.1) and 56.5% had a male gender. In 42% of the children atopic symptoms were diagnosed in the past, 26% underwent adenoidectomy, 8% tonsillectomy, and in 18% of the children tympanostomy tubes were placed. The mean number of parent reported RTI episodes in the year prior to study entry was 4.28 (SD 2.69); 45.5% had 3 or less episodes, 26.1% 4-5 episodes, and 28.4% 6 or more episodes.

Scores on the RAND-GHRI and RTI-6 were lower at time of illness than at baseline whereas scores on the OM-6 were similar at both occasions (Table 1). At baseline, floor effects were absent in all instruments whereas ceiling effects were moderately high with the RTI-6 and OM-6 (Table 1).

Table 1: Distribution of questionnaire scores

Questionnaires	**N**	**Absolute score mean (median; SD)***	**Standardized score mean (median; SD)****	**IQR *****	**Min. Score (%)**	**Max. Score (%)**
Baseline						
RAND-GHRI	348	23.1 (23.0; 4.1)	64.38 (64.0; 16.5)	20	0	0.3
OM-6	344	38.7 (41.0; 5.2)	90.90 (97.2; 14.5)	14	0	48.8
RTI-6	344	35.9 (37.0; 5.8)	83.03 (86.1; 16.0)	22	0	24.1
At time of a febrile RTI						
RAND-GHRI	99	21.2 (22.0; 4.8)	56.7 (60.0; 19.1)	24	1	0
OM-6	98	39.0 (40.9; 4.7)	91.1 (97.2; 13.2)	12	0	40.8
RTI-6	99	33.0 (34.0; 5.9)	75.0 (77.8; 16.5)	19	0	5.1

* Absolute score range RAND-GHRI 7-32, OM-6 6-42, RTI-6 6-42. ** Scores are standardized according to a score range of 0-100. *** Inter-quartile range

Cronbach's alpha was more than 0.80 for all measures (Table 2). Inter-item and item-total scores were moderate to high, except for the RTI-6 in which the hearing and speaking items had poor inter-item correlations. Pearson correlation coefficients and ICC's were largely in agreement and were high for all questionnaires, reflecting excellent test-retest reliability.[15] The mean differences in standardized scores between baseline and at time of illness varied between 5.3 in the RAND-GHRI to 9.0 in the RTI-6. This change in score is small to moderate reflected by their SRM. The OM-6 did not show any responsiveness.

Table 2: Internal consistency, test-retest reliability, and responsiveness

Internal consistency				
	N	**Cronbach's alpha**	**Inter-item correlation**	**Item-total correlation**
RAND-GHRI	348	0.82	0.27-0.75	0.47-0.67
OM-6	344	0.87	0.23-0.84	0.32-0.82
RTI-6	344	0.83	0.13-0.81	0.24-0.79
Test-retest reliability				
	N	**Pearson correlation**	**p-value**	**ICC****
RAND-GHRI	63	0.91	0.01	0.90
OM-6	64	0.84	0.01	0.84
RTI-6	63	0.91	0.01	0.91
Responsiveness				
	N	**Mean difference (median)***	**Wilcoxon, p- value**	**SRM*****
RAND- GHRI	99	5.3 (4.0)	.001	.32
OM- 6	98	.04 (.00)	.805	.02
RTI- 6	98	9.0 (7.9)	.000	.45

* Mean difference and median of the standardized scores (range 0-100), ** intra-class correlation coefficients, *** standardized response mean

The RTI-6 correlated strongly with both the RAND-GHRI (Spearman correlation 0.59) and the OM-6 (0.62). The RAND-GHRI correlated only moderately with the OM-6 (0.32). All these correlations were significant at a p-level of 0.01. The correlation between items covering parental worrying and pain/discomfort of the child, were moderate between RAND-GHRI and OM-6, and strong between RAND-GHRI and RTI-6 (Table 3). These item-correlations between OM-6 and RTI-6 were moderate. The scores on the

questionnaires correlated all moderately with the number of RTI episodes, except for the OM-6 which correlated very weakly (Table 3).

Table 3: Construct validity

	Spearman correlation*
Correlations between pairs of items	
- Parental worries about child's health	
RAND-GHRI & OM-6	.31
RAND-GHRI & RTI-6	.58
OM-6 & RTI-6	.40
- Pain/discomfort	
RAND-GHRI & OM-6	.32
RAND-GHRI & RTI-6	.71
OM-6 & RTI-6	.42
- Emotional distress OM-6 & RTI-6	.39
- Activity limitation OM-6 & RTI-6	.36
Correlations between total scores and number of RTI	
RAND-GHRI	-.40
OM-6	-.16
RTI-6	-.34

*All correlations are significant at 0.01 level

All four measurements were able to discriminate between children with ≤ 3 and ≥ 4 parental reported RTI (Table 4).

Table 4: Questionnaire scores according to frequency of respiratory tract infections

	≤ 3 RTI per year absolute score; standardized score (N)*	**≥ 4 RTI per year** absolute score; standardized score (N)*	**p-value (Mann Whitney U-test)**
RAND-GHRI	24.6; 70.5 (150)	22.0; 59.8 (183)	$p < 0.001$
OM-6	39.6; 93.3 (152)	38.2; 89.5 (179)	$P = 0.023$
RTI-6	37.8; 88.2 (152)	34.5; 79.1 (179)	$p < 0.001$

* Absolute score range RAND-GHRI 7-32, OM-6 6-42, RTI-6 6-42. Standardized score range 0-100.

Discussion

The RAND-GHRI appeared adequate to measure general FHS in preschool children with prior physician-diagnosed RTI, although responsiveness was limited. The disease-specific RTI-6 showed besides good internal consistency, test-retest reliability, construct and discriminant validity, better responsiveness, and consequently the RTI-6 seems most adequate to measure disease-specific FHS. RTI appeared to affect functional health.

A previous study reported RAND-GHRI scores in asthmatic and control children of respectively 22.4 (SD 5.4) and 26.4 (SD 4.0),[7] while in our study children with ≤ 3 RTI episodes per year had a mean score of 24.6 (SD 3.9) and children with ≥ 4 RTI episodes per year 22.0 (SD 3.9). This suggests that frequent RTI have an impact on general health. Regarding the comparability of our study with this study, we need to say that we changed the time horizon in two questions from 3 months into 4 weeks. Our study population was also younger. This age difference may possibly have functioned as confounder, with younger children having lower scores.[7] However, in our study age did not correlate to RAND-GHRI scores.

It is difficult to draw conclusions from the scores on the other questionnaires (OM-6 and RTI-6) since our study group contained no normative population and the disease specificity of the questionnaires does not allow comparison with other questionnaires considering other kinds of diseases. However, the negative correlation between the frequency of RTI and the scores on the RTI-6 together with a decrease in score with an acute episode, support a negative influence of RTI on FHS.

The hearing and speaking items within the RTI-6 had poor inter-item correlations and after removal the questionnaire showed a higher Cronbach's alpha. It is nevertheless not inconceivable that in a more severely affected population (children with more frequent RTI including otitis media) these items will still be useful. The RTI-6 demonstrated the highest sensitivity to change probably due to its disease-specificity. However, this responsiveness was still borderline moderate, which was probably caused partly by the fact that while estimating the responsiveness we did not pay attention to the disease state at baseline

(whether the child had an RTI at baseline). Consequently, the mean change of scores between baseline and time of illness might have been diluted by children who were ill at baseline. Therefore we expect the true responsiveness to be higher.

To appreciate the results of ours study, some possible limitations should be discussed. First of all we did not impute our missing data (5%). Because of the small percentage we expect, however, that this had no important influence on the results. Secondly, the number of RTI considered with the discriminant validity is parent reported. It relies on the parent's recall of RTI during the last 12 months and may have been subjectively influenced. Finally, not all eligible children entered the PRIMAKid-trial and consequently participated in the current study. This might have influenced the generalizability of the results. However, the test-retest population that consisted of the children who refused to participate in the trial, had questionnaire scores comparable with those of the participating children although the mean number of parent reported RTI prior to inclusion was with 3.90 somewhat lower than that of the participants (4.28).

Originally, the OM-6 was developed as a health related quality of life (HRQoL) measure. Like FHS, HRQoL embraces physical symptoms, psychological or emotional, and social functioning.[8,9,20] Additionally, HRQoL incorporates a person's valuation of his life.[8,9,20] Although the OM-6 certainly assesses domains of HRQoL, it merely assesses functional health.[21] However, it may be questioned whether parent rating of a child's QoL truly reflects the QoL, since the crucial element in the description of QoL is the subjective perception of the functional effects of the disease by the patient himself.[9] As young children do neither have the vocabulary nor the ability of abstract reasoning, an evaluation of their own QoL is strictly impossible. Therefore, QoL measures have to rely on proxy ratings. In attempting to evaluate QoL in these children, caregivers seem to be the best informants.[22-24]

Several studies indicated that the impact of certain variants of RTI, like AOM and community acquired pneumonia, and symptoms comparable with some RTI like allergic rhinitis, have a substantial impact on HRQoL and FHS.[10,25-30] However, these studies mostly dealt with a very specific population (often the most severely affected children e.g. needing ear-nose-throat-surgery). The strength of our study is that it was conducted in a

general practice setting and involved children with a history of all sorts of physician-diagnosed RTI, which may allow for applicability to all children with a history of RTI.

In preschool children with prior physician-diagnosed RTI, the RAND-GHRI and the RTI-6 were demonstrated to be valid, reliable, and feasible questionnaires to measure general and disease-specific FHS. These measures seemed suitable for evaluating treatment effects in trials. RTI seemed to affect FHS, and the scores on the RAND-GHRI in children with a more severe history of physician-diagnosed RTI appeared comparable with those of children suffering from a chronic disease like asthma. This should be a reason to pay more attention to the management of RTI and the development of preventive strategies like immunization.

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CHAPTER 9.2

Effects of combined influenza and pneumococcal conjugate vaccination and influenza vaccination alone on functional health status in children: a randomized double-blind controlled trial

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Abstract

Objective To determine the effects of combined influenza and pneumococcal vaccination or influenza vaccination alone on functional health status in preschool children.

Methods Randomized double-blind controlled trial of 579 children aged 18 to 72 months with a prior history of physician-diagnosed respiratory tract infections (RTI). The children were recruited in primary care centers in three cohorts from 2003 to 2005. Participants were randomly assigned to receive two doses of parenteral inactivated trivalent sub-unit influenza and heptavalent pneumococcal conjugate vaccinations (IV+PV), influenza and placebo vaccinations (IV+plac), or control recombinant hepatitis B and placebo vaccinations (HepB+plac). The functional health status was measured with the generic questionnaire Rand General Health Rating Index for children (RAND-GHRI) and the disease-specific questionnaire Respiratory Tract Infection-6 (RTI-6) (derived from the Otitis Media-6) at baseline and after a follow-up of eight to twelve months, and scores were standardized. When normally distributed, the mean follow-up scores were compared between the study groups, while considering the baseline scores. For skewed scores, the change scores were compared.

Results The mean RAND-GHRI score at follow-up was 64.5 in the IV+PV group, 63.3 in the IV+plac group and 65.7 in the HepB+plac group; at follow-up corresponding figures were 68.6, 70.0 and 69.5 indicating no differences between the study groups (p-values of 0.5 and 0.8 for IV+PV and IV+plac group versus control HepB+plac group, respectively). Corresponding mean change scores of the RTI-6 were 2.5, 4.3 and 3.1 (p-value of 0.7).

Conclusion After a follow-up of eight to twelve months, influenza vaccination with or without pneumococcal vaccination appeared to have no effect on functional health status in preschool children.

Introduction

Respiratory tract infections (RTI) continue to be the leading cause of acute illness worldwide, particularly in children. The marginal effects of current treatments for RTI (ear-nose-throat surgery and antibiotics) and the growing problem of bacterial resistance against antibiotics have made preventive strategies attractive.[1-4] Influenza viruses and *Streptococcus pneumoniae* are common pathogens of RTI and are currently among a limited number of pathogens of respiratory disease that may be vaccine-preventable.[5]

Frequent RTI may mimic a chronic condition and negatively affect the child's well-being by causing pain and distress, impairing daily activities, and along with this parental stress.[6] Assessment of the influence of a disease and interventions on well-being or functional health status (FHS) has become an essential part of evidence-based medicine.[7-12] The FHS reflects the physical, psychological or emotional and social functioning.[13] The current study aimed to determine the effects of combined influenza and pneumococcal vaccination or influenza vaccination alone on FHS in preschool children.

Methods

The current study was part of the PRIMAKid-study, a randomized double-blind controlled trial that aspired to determine the effects of combined influenza and pneumococcal vaccination or influenza vaccination alone on the occurrence of RTI in preschool children with previous physician-diagnosed RTI.[14]

Participants and recruitment

General practitioners (GP) in the centre area of the Netherlands selected children aged 18 to 72 months old with prior diagnosed RTI, registered according to the International Classification of Primary Care:[15.16] acute otitis media (H71), cough (with fever) (R05), acute upper respiratory infection (R74) including common cold and pharyngitis, sinusitis (R75), acute tonsillitis (R76), acute laryngitis/tracheitis (R77), acute bronchitis/bronchiolitis

(R78), influenza (R80), pneumonia (R81), pleurisy/pleural effusion (R82), and other respiratory infection (R83). With questionnaires filled out by both GPs and parents it was verified that exclusion criteria were absent. Exclusion criteria were asthma or recurrent wheezing chronically (> 3 months) treated with corticosteroids, other disorders predisposing for recurrent RTI, such as Down's syndrome and cleft palate, and clinically significant hypersensitivity to eggs. Children with previous serious adverse reactions to vaccines were also excluded, as were children who previously had influenza, pneumococcal or hepatitis B vaccinations as well as children with conditions for which these vaccinations are already recommended, such as chronic cardiac or respiratory conditions for influenza vaccination. The medical ethical review board of the University Medical Center Utrecht, the Netherlands approved the study protocol. Parents were informed about the study by their GP, and written informed consent was obtained from the parents for each child prior to enrolment.

Procedures

Three cohorts of children were enrolled during the September to October periods of 2003, 2004, and 2005. The children were randomly assigned in blocks of three to combined influenza and pneumococcal vaccinations (IV+PV), influenza and placebo vaccinations (IV+plac), or control hepatitis B and placebo vaccinations (HepB+plac) in a 1:1:1 ratio. Assignments to treatment groups were not revealed to parents, investigators, research personnel conducting the follow-up or health care providers, all of whom remained blinded throughout the study. Administration of the injections was performed by non-blinded research nurses who were not involved in subsequent follow-up of the children. The vaccines were administered intramuscularly in deltoid or gluteal muscles (in separate extremities). All three study arms had a similar vaccination schedule. Children received two vaccinations four to eight weeks apart in the year of inclusion. To evaluate blinding, parents of the last two cohorts of included children were asked what vaccinations they thought their child had received just after the vaccinations were set and at the end of the study. Just after the vaccinations, 87% of the parents did not know or mentioned the wrong set of vaccinations, and at the end of the study this was 80%, indicating that blinding was successful.

Vaccines

Inactivated trivalent sub-unit influenza vaccine (Influvac®) was supplied by Solvay, Weesp, the Netherlands. Strains in the 2003-2004 formulation were A/New Caledonia/20/99 (H1N1), A/Moscow/10/99 (H3N2), and B/HongKong/330/01; in the 2004-2005 formulation A/New Caledonia/20/99 (H1N1), A/Fuijan/411/2002 (H3N2), and B/Shanghai/361/2002; and in the 2005-2006 formulation A/New Caledonia/20/99 (H1N1), A/California/7/2004 (H3N2), and B/Shanghai/361/2002. The heptavalent pneumococcal conjugate vaccine (Prevenar®, Wyeth Vaccines Research, Berkshire, United Kingdom) consisted of 2 µg each of capsular polysaccharides of pneumococcal serotypes 4, 9V, 14, 19F, and 23 F, 4 µg of serotype 6B polysaccharide, and 2 µg of serotype 18C oligosaccharide, each conjugated individually to the CRM_{197} protein. The placebo consisted of a standard diluent (0.9% NaCl phosphate buffered, Solvay, Weesp, the Netherlands). Control vaccine was the recombinant hepatitis B vaccine (Engerix-B Junior®, GlaxoSmithkline, Rixenart, Belgium).

FHS measures

FHS was measured with the generic general health questionnaire Rand General Health Rating Index for children (RAND-GHRI) and the RTI-specific FHS questionnaire RTI-6, which was derived from the otitis media-specific questionnaire OM-6 (See Appendix).[17-20] The RAND-GHRI assesses general health perceptions of caregivers regarding their child, covering parental worrying, current and prior health, physical suffering and susceptibility/resistance to illness. The time horizon of this measure, i.e. the period over which the parents were asked to grade the FHS of their child, was changed from three months to four weeks to enhance comparability with the RTI-6 which also considers a time horizon of four weeks. The RTI-6 questionnaire covers physical suffering, speech problems, hearing loss, emotional distress, activity limitation and parental worrying, all RTI-related. Both measures were validated in the PRIMAKid-study population. The RAND-GHRI was demonstrated to have high internal consistency, test-retest reliability, construct and discriminant validity, but responsiveness to the occurrence of RTI was limited. The RTI-6 was shown to have a good test-retest-reliability, construct and discriminant validity, and appeared more responsive.

Parents were asked to fill in the RAND-GHRI and RTI-6 at baseline and after a follow-up of twelve months for cohorts 2003 and 2004, and for cohort 2005 at the end of the study, i.e. after a follow-up of eight months.

Statistical analysis

All analyses were carried out on an intention-to-treat basis. The sum scores of each questionnaire were standardized to a 0-100 scale to enhance comparability between scores, with higher scores indicating a better FHS. To assess the difference between the mean follow-up scores of the three study groups taking into account the mean scores at baseline, analysis-of-covariance was used for normally distributed questionnaire scores, and analysis-of-variance for mean change scores was applied when questionnaire scores had a skewed distribution.[21] A p-value <0.05 was considered to indicate statistical significance. All analyses were done with the statistical package SPSS version 12.0.

Results

A total of 579 children was enrolled; 171 in cohort 2003, 192 in cohort 2004 and 216 in cohort 2005. The baseline characteristics were similar in the vaccine and control groups (Table 1). In total, 560 (97%) RAND-GHRI questionnaires and 557 (96%) RTI-6 questionnaires were analyzed at baseline and 509 (88%) of both questionnaires at follow-up. The proportion of missing questionnaires did not differ appreciably between the study groups (Figure 1).

Figure 1: Flow diagram

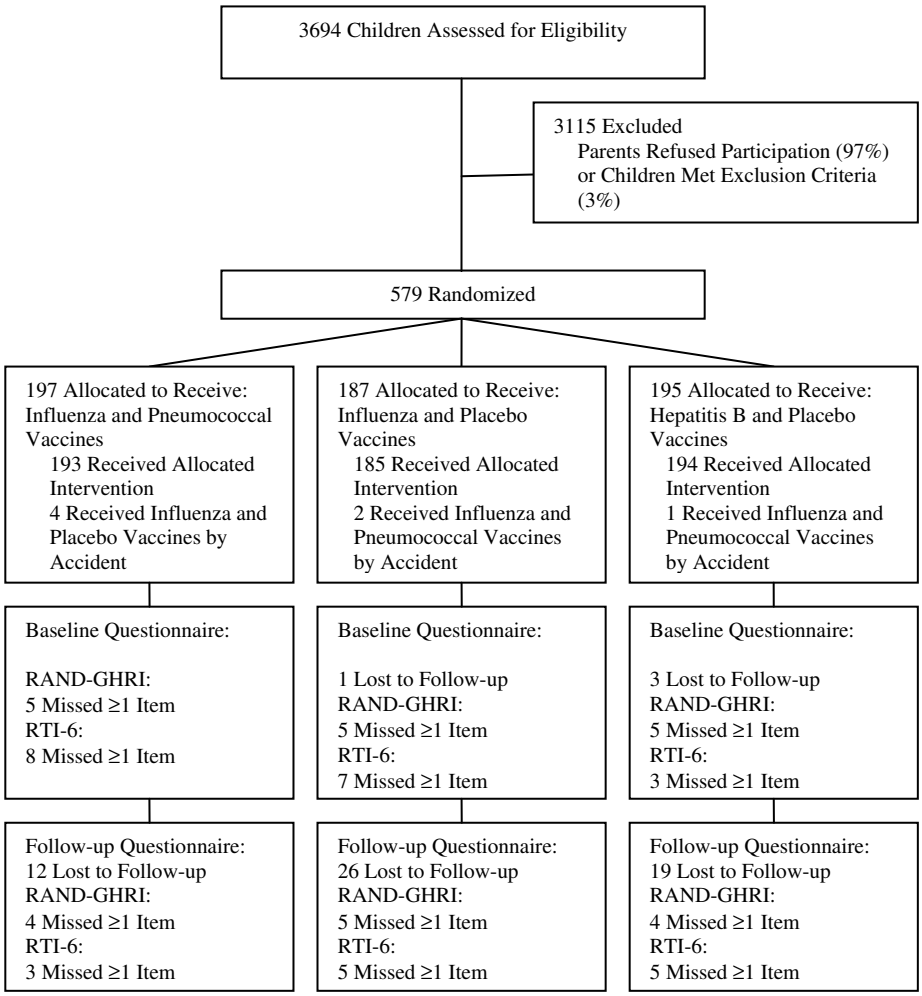

Table 1: Baseline characteristics

		IV+PV (n= 197)	IV+plac (n=187)	HepB+plac (n=195)
Male sex		58.9	55.6	50.3
Mean age, years		3.0	3.1	3.1
Number of RTI episodes in preceding year (%):	**≤ 3**	46	44	42
	4-6	37	40	41
	≥ 7	17	16	17
Number of general practice-diagnosed RTI in preceding year		3.0	3.1	3.2
Number of courses of antibiotics prescribed in preceding year		1.6	1.6	1.8
History of ENT-surgery (%)		28.6	27.6	29.5
Asthma/wheezing in preceding year (%)		28.3	27.4	31.6
Hay fever / allergic rhinitis in preceding year (%)		16.6	14.1	12.4
Eczema in preceding year (%)		21.6	18.3	22.9
Day care (%)		69.7	62.0	66.3
Mean number of siblings		0.8	0.9	1.0
Breastfeeding < 3 months (%)		58.2	62.7	55.5
Tobacco smoke exposure indoors (%)		22.6	25.9	26.6

RTI, respiratory tract infection; IV+PV, influenza and pneumococcal vaccines; IV+plac, influenza and placebo vaccines; HepB+plac, hepatitis B and placebo vaccines

The scores of the RAND-GHRI were normally distributed, and therefore analysis-of-covariance could be applied to look for differences in the mean follow-up scores between the study groups. The mean scores at follow-up for the RAND-GHRI taking into account mean scores at baseline, did not demonstrate significant differences (Table 2). The scores on the RTI-6 had a right-skewed distribution and therefore analysis of variance was used to look for potential differences in change scores. This analysis did not indicate any significant difference between the study groups (Table 2).

Table 2: Standardized scores (0-100) on functional health measures in the different treatment groups

	IV+PV	IV+plac	HepB+plac
RAND-GHRI			
Score at baseline: mean (standard deviation)	64.5 (16.7)	63.3 (16.0)	65.7 (16.2)
Score at follow-up: mean (standard deviation)	68.8 (16.6)	70.0 (17.7)	69.5 (16.2)
Change score: mean (standard deviation)	3.8 (18.6)	5.9 (18.3)	5.0 (17.2)
Analysis of co-variance, p-value	0.5	0.8	
RTI-6			
Score at baseline: mean (standard deviation)	84.8 (15.2)	83.4 (16.1)	85.1 (16.5)
Score at follow-up: mean (standard deviation)	88.0 (15.8)	87.7 (15.5)	88.9 (15.3)
Change score: mean (standard deviation)	2.5 (18.9)	4.3 (18.8)	3.1 (20.2)
Analysis of variance on change scores, p-value	0.7		

IV+PV, influenza and pneumococcal vaccines; IV+plac, influenza and placebo vaccines; HepB+plac, hepatitis B and placebo vaccines

Discussion

This randomized double-blind controlled trial among 579 children assessed the effects of combined influenza and pneumococcal conjugate vaccination and influenza vaccination alone on the FHS of preschool children with a history of physician-diagnosed RTI. No effects were observed from influenza vaccination with or without pneumococcal vaccination on the FHS after eight to twelve months follow-up.

Some previous studies assessed the effect of influenza or pneumococcal vaccination on FHS, but none of these assessed the combination of influenza and pneumococcal vaccinations.[22,23] Also the study population differed, i.e. asthmatic children or children with recurrent otitis media, in stead of children with prior physician-diagnosed RTI like in our study. A randomized double-blind placebo-controlled study among asthmatic children aged 6-18 years attempted to assess the effects of parenteral inactivated influenza vaccination on health-related quality of life,[22] another measure of health which is often equated to the FHS but adds a valuation or affective response to this functioning.[13] They found that influenza vaccination had a moderately beneficial effect on quality of life in influenza-positive weeks

of illness. However, no differences in study groups were found for quality of life in all weeks of illness or for respiratory symptoms throughout the seasons.[22] The results of our study also indicated that influenza vaccination had no beneficial effect on FHS, at least not over the total follow-up period. However, the lack of effect of influenza vaccination on FHS in our study may have been caused by the fact that we did not assess FHS separately over influenza seasons, despite the fact that influenza vaccination is of most benefit during this season.[24-26] Particularly outside influenza seasons, other causes of RTI are likely to have diluted the potential effects of vaccinations in our study.

An earlier randomized controlled trial that assessed the effect of pneumococcal conjugate vaccination followed by a booster pneumococcal polysaccharide vaccination on both health-related quality of life and FHS in children with recurrent acute otitis media, concluded that pneumococcal vaccination had no beneficial effect compared with control vaccination on either of the outcomes, which was in accordance with the results of our study.[23] This same study found no beneficial effect clinically from vaccinations.[27] Pneumococcal conjugate vaccinations have been demonstrated to have a modest beneficial effect on mucosal infections like acute otitis media particularly when administered early in infancy.[28] The apparent lack of effect of pneumococcal vaccination on acute otitis media when it was administered in older children as in the study of Veenhoven et al.[27], was attributed to the fact that in older children nasopharyngeal pneumococcal carriage has already been established and remained similar because non-vaccine serotypes had replaced vaccine serotypes. In that study, it was suggested that previous episodes of acute otitis media might have led to changes in nasopharyngeal and middle ear conditions, which predisposed the children to additional AOM episodes, regardless of the pneumococcal serotype in the nasopharynx. Since we also vaccinated older children, this may explain the lack of effect on FHS measurements. In contrast, in younger children, pneumococcal conjugate vaccination may delay vaccine-type pneumococcal carriage and thereby vaccine-type pneumococcal AOM, since these serotypes are the dominant pathogens early in life.[27]

Although we found no overall differences in FHS after a follow-up of eight to twelve months between the study groups, FHS scores appeared to improve compared with the baseline score in all three study groups. A former study observed a similar trend.[23]

Apparently, either FHS improves with age reflecting a favourable natural course, or it improves by trial participation in itself.[29]

Some limitations of the current study should be acknowledged. We did not impute missing data. We expect however that this had no important influence on the results, since the percentage missing data was relatively low. Further, because we did not assess the FHS separately over influenza seasons, a beneficial effect of pneumococcal conjugate vaccination during influenza seasons, besides that of influenza vaccination, cannot be excluded. In view of the potentially synergistic interaction of influenza viruses and *S.pneumoniae*,[5] the effect of pneumococcal vaccination may also be highest during influenza seasons.[30] On the other hand, pneumococcal vaccination is supposed to be active also outside the influenza season, and therefore effects from pneumococcal vaccination should have been detectable also outside the seasons, with *S.pneumoniae* being the most frequent bacterial cause of acute otitis media, sinusitis and pneumonia.[31-34] Additionally, a suboptimal responsiveness of the used questionnaires (see Methods) may have hindered detection of marginal differences in FHS between the study groups. Finally, it may be questioned whether measures of FHS are suitable in individuals with intermittent disease like frequent RTI, rather than more chronic stable diseases.[35] In other words, in children with recurrent RTI FHS may vary through time (with the presence or absence of a RTI) more than other chronic stable diseases. This underscores the need for a questionnaire with a rather long time horizon.

In summary, our study indicated that parenteral inactivated influenza vaccination with or without heptavalent pneumococcal conjugate vaccination had no effect on overall FHS measured over the total follow-up period.

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Appendix

Otitis Media – 6 item (OM-6)

1. How much pain or unease had your child suffered during the past four weeks as a result of middle-ear infections? *Here we have in mind earpain, ear discomfort, ruptured eardrum, high fever or poor balance.*
2. How much hearing discomfort has your child experienced in the past four weeks? *Here we have in mind difficulty hearing, questions must be repeated, frequently says "what" or television is excessively loud.*
3. How many problems with speech did your child experience in the past four weeks? *Here we have in mind delayed speech, poor pronunciation, difficulty to understand, or unable to repeat words clearly.*
4. To what degree during the past four weeks was your child upset because of middle-ear infections? *Here we have in mind being irritable, frustrated, sad, or poor appetite.*
5. How often during the past four weeks was your child restricted in his or her activities by middle-ear infections? *Here we have in mind playing, sleeping, doing things with friends/family, attending school or day care.*
6. How often during the past four weeks have you as a parent or guardian been concerned about or inconvenienced by your child's middle-ear infections?

Respiratory Tract Infections – 6 item (RTI-6)

1. How much pain or unease had you child suffered during the past four weeks as a result of a respiratory infection? *Here we have in mind an acute infection with fever, having a cold with fever, sinusitis, throat infection, ear infection, influenza, bronchitis, pseudocroup, or pneumonia*.
2. How much hearing discomfort has your child experienced in the past four weeks? *Here we have in mind difficulty hearing, questions must be repeated, frequently says "what" or television is excessively loud.*

3. How many problems with speech did your child experience in the past four weeks? *Here we have in mind delayed speech, poor pronunciation, difficulty to understand, or unable to repeat words clearly.*
4. To what degree during the past four weeks was your child upset because of respiratory infections? *Here we have in mind being irritable, frustrated, sad, or poor appetite.*
5. How often during the past four weeks was your child restricted in his or her activities by respiratory infections? *Here we have in mind playing, sleeping, doing things with friends/family, attending school or day care.*
6. How often during the past four weeks have you as a parent or guardian been concerned about or inconvenienced by your child's respiratory infections?

Rand General Health Rating Index for children (RAND-GHRI)

1. In general, would you say this child's health is excellent, good, fair, or poor?
2. During the last four weeks, how much have you worried about the child's health?
3. During the last four weeks, how much pain or distress has this child's health caused him or her?
4. This child's health is excellent.
5. This child seems to resist illness very well.
6. This child seems to be less healthy than other children I know.
7. When there is something going around, this child usually catches it.

CHAPTER 10

Summary & General Discussion

Part I of the thesis

Until 2007, influenza vaccination was recommended for all inhabitants of the Netherlands with high-risk co-morbidity, e.g. chronic cardiac or respiratory disease, and those aged 65 years and older, similar to many other European countries.[1,2] Recently, however, recommendations have been extending in several countries around the world.[3,4] The major aim of the first part of this thesis was to determine the influenza-associated burden among otherwise healthy persons younger than 65 years of age in the Netherlands, especially among 50-64-year-olds, in order to guide policy decisions concerning possible extension of recommendations for influenza vaccination. The studies will be first summarized, and next the results will be discussed in the light of future recommendations for influenza vaccination.

Summary

With influenza frequently being under-diagnosed and -reported and leading to secondary complications,[5-10] it appears that one has to rely on indirect measures to determine the influenza-attributable burden. In **Chapter 2**, the principal method used in this thesis to estimate the influenza-associated burden of disease, the rate-difference model, was compared with other recently reported models. The rate-difference model determines the excess health burden during influenza virus-active periods over baseline periods (peri-season and summer) by subtracting baseline rates from rates during influenza virus-active periods. This method is therefore straight-forward and provides insight for a broad audience. We found that it provided estimates within the range of those obtained by other more extended linear regression-based models.[11-13] In all models, one should be cautious for the influence of other seasonal phenomena such as co-circulating viruses that may affect rates of outcomes during influenza virus-active periods.[14-15] In contrast to influenza viruses, rhinoviruses, adenoviruses and para-influenza viruses appeared to have no clear seasonal pattern like influenza viruses (see also Figure 1 on page 12). The rate-difference model that we applied in our studies did however account for the alleged most important co-circulating virus, i.e. RSV, that has increasingly been implicated in causing morbidity and even mortality in both children and adults as was also shown in our studies.[14,17-20] Unfortunately, the seasonal pattern of some recently discovered coronaviruses and the human

metapneumovirus could not be assessed since no surveillance data were available during the study period.[16] Partly for these reasons, the precision of the estimations provided by all models is limited. Moreover, estimations depend on how reference periods and influenza virus-active periods are determined, and therefore cautious interpretation remains necessary.

In **Chapters 2 and 3** the influenza-associated health care burden in the Dutch population was estimated by applying the rate-difference model. In **Chapter 2**, the primary health care burden was estimated with data from a primary care research database over the period 1997 to 2003. In **Chapter 3**, influenza-associated mortality and hospitalization was estimated with national data of all-cause mortality and hospital admission rates over the same period. In short, no clear influenza-associated mortality could be demonstrated for the age categories 0-1, 2-4, 5-17 and 18-49 years old. Some influenza-associated mortality may however still be present in these age categories, since our method might have lacked sensitivity to detect very low numbers of influenza-associated deaths, such as for example the annual rates of 0.4-1.1 per 100,000 as previously reported for 1-4-year-olds.[17, 21,22] In the age categories 50-64 years and 65 years and older, influenza-associated mortality was present. Among 50-64-year-olds the major part of the mortality was present among 60-64-year-olds. Since no information about co-morbidity was available in the weekly mortality figures, it was impossible to determine what proportion of this excess mortality occurred in otherwise healthy persons. For optimal monitoring of influenza-associated mortality in future research, recording of weekly mortality figures within co-morbidity categories appears of utmost importance. Also, the introduction of a personal anonymous registration number, which is already in use in Scandinavian countries, would enhance monitoring mortality, but also health care consumption and the surveillance of diseases.

In contrast to mortality, considerable influenza-associated hospitalizations and primary care visits were present in all categories. In otherwise healthy persons younger than 65 years, the rates were highest for children up to 4 years old and decreased with age, but increased again after age 50. Regarding incidence, the influenza-associated hospitalization burden was highest in young children, with about four to seven times higher incidences of influenza-associated hospitalizations among 0-1-year-olds than among otherwise healthy 50-64-year-

olds. Also among 2-4-year-olds, rates were about three times higher. While among children most of these hospitalizations were because of respiratory conditions, particularly upper respiratory conditions, the major part of the influenza-associated hospitalizations among otherwise healthy 50-64-year-olds were related to cardiovascular and lower respiratory conditions. Similar to the mortality figures, 60-64-year-olds accounted for the major part of influenza-associated hospitalization among otherwise healthy 50-64-year-olds, and a similar pattern, although less pronounced, was observed for influenza-associated primary care visits. Remarkably, despite routine influenza vaccination among those aged 65 years or over, the influenza-associated burden was substantial in this age group (see below for further discussion), with by far the highest influenza-associated mortality and with incidences of influenza-associated hospitalizations similar to those in 0-1-year-olds. Table 1 summarizes the average annual influenza-associated burden in all age categories.

Table 1

age category		total influenza-associated winter excess per 100,000 persons	
		vs. summer baseline period	vs. peri-seasonal baseline period
Mortality			
0-1 year		None	None
2-17 years		0.1 (non-significant)	0.3
18-49 years		0.7	0.4 (non-significant)
50-64 years		7.6	3.8
≥ 65 years		146.5	96.4
Hospitalizations			
0-1 year		271.2	79.0
2-4 years		105.4	50.0
5-17 years		17.2	8.0
18-49 years	**non high-risk**	7.1	3.1
	high-risk	31.3	12.7
50-64 years	**non high-risk**	38.0	17.7
	high-risk	96.9	49.9
≥ 65 years		208.0	111.0

Table 1, continued

		Primary care visits	
0-1 year		6578.2	520.5 (non-significant)
2-4 years		4564.4	1583.3
5-17 years		1420.1	792.6
18-49 years	**non high-risk**	980.0	501.2
	high-risk	1816.7	487.4
50-64 years	**non high-risk**	1259.5	632.0
	high-risk	2339.2	670.0
≥ 65 years		1978.7	886.2

In **Chapter 4** the impact of influenza vaccination on influenza-associated mortality in the elderly was assessed. Recommendations for influenza vaccination have changed in the Netherlands in 1996. Prior to the respiratory season 1996-97, Dutch guidelines recommended influenza vaccination in persons with high-risk medical conditions, e.g. chronic cardiac and respiratory disease, only.[75] From the seasons 1996-97 onwards, recommendations were extended to include all elderly, and a nationwide primary care prevention program was initiated.[1] Influenza vaccination coverage among the elderly improved from 50% to 80% after the start of the program (Statistics Netherlands, Voorburg/Heerlen, The Netherlands). With the rate-difference model, the influenza-associated mortality over the seasons 1992-93 to 2002-03 was determined, again using national all-cause mortality data. Comparison of the influenza-associated mortality over the years before and after the start of the prevention program showed 20-40% decline in influenza-associated mortality. The decline was largest in the age group 65-69 years and less in those aged 75 years and older.

As previously stated, RSV often co-circulates with influenza viruses, and recently its potential role in causing a seasonal increase in morbidity in both children and adults has repeatedly been stressed.[17-20] For these reasons, the RSV-associated burden was also included in **Chapter 2 and 3** and was estimated in a similar way as for influenza viruses. As expected, the RSV-associated burden of hospitalization and primary care visits was particularly high in the youngest age categories, with rates clearly higher than those associated with influenza in this age group.[23,24] Furthermore, in all older age categories

RSV appeared to be associated with a health burden. This burden was about equal to that of influenza regarding primary care visits, but considerably less or absent for hospitalizations. Particularly among 50-64-year-olds with co-morbidity and the elderly, RSV was associated with substantial numbers of hospitalization and primary care visits. Moreover, RSV appeared to be associated with mortality in the elderly. Therefore, an RSV-vaccine, if available, may achieve a relevant reduction in the health burden, not only in infants and young children, but also in high-risk older adults and the elderly. However, the actual knowledge about the role of RSV in causing morbidity in adults is still limited in comparison with the existing knowledge about influenza in adults. Most RSV surveillance data, on which we based RSV-active periods, were reported in children. However, the epidemiology of RSV in adults is largely unknown, i.e. it is not exactly known whether the activity of RSV in children parallels in time that among adults, which was assumed in our studies. Age-specific active surveillance for RSV is warranted in the Netherlands to confirm and support our estimates. Table 2 summarizes the average annual RSV-associated burden in the Netherlands.

Table 2

age category		total RSV-associated winter excess per 100,000 persons	
		vs. summer baseline period	vs. peri-seasonal baseline period
		Mortality	
0-1 year		None	None
2-17 years		None	None
18-49 years		0.3 (non-significant)	0.1 (non-significant)
50-64 years		5.4	1.9 (non-significant)
≥ 65 years		98.7	52.1
		Hospitalizations	
0-1 year		698.7	522.5
2-4 years		64.7	20.6
5-17 years		5.9	0.4
18-49 years	**non high-risk**	2.8	None
	high-risk	14.4	0.8 (non-significant)
50-64 years	**non high-risk**	11.2	0.2 (non-significant)
	high-risk	53.2	15.7
≥ 65 years		140.7	50.7

Table 2, continued

		Primary care visits	
0-1 year		15047.3	9401.5
2-4 years		7104.9	4339.3
5-17 years		1209.4	627.2
18-49 years	**Non high-risk**	999.0	554.8
	high-risk	1887.0	653.7
50-64 years	**Non high-risk**	1265.0	682.8
	high-risk	2810.5	1261.6
≥ 65 years		1942.3	928.8

Increasing evidence suggests bacterial-viral interaction, with viral infection predisposing to bacterial superinfection, but also a synergistic effect between viruses and bacteria.[7] Influenza viruses and RSV have also been postulated to play a role in the etiology of bacterial invasive disease of which *S.pneumoniae* and *Neisseria meningitidis* are the major pathogens.[25-34] In **Chapter 5** the temporal relationship between the occurrence of pneumococcal and meningococcal invasive disease, and the circulation of influenza viruses and RSV in the community was assessed. Over de period 1997-2003, correlations between viral circulation and the occurrence of bacterial invasive disease were calculated, and incidence rate ratios were determined during influenza virus- and RSV-active periods versus baseline periods. The occurrence of pneumococcal bacteremia and meningococcal disease correlated significantly with influenza virus- and RSV-activity both in children and adults; periods of increased influenza virus-activity as well as periods of increased RSV-activity were associated with higher rates of pneumococcal bacteremia and MD. It should be realized, however, that such correlations cannot be considered unequivocal proof of causality, but they do suggest that viral infections predispose to invasive bacterial disease. With the rate-difference method we further attempted to quantify the potential relation; influenza viruses may be associated with 21-58% of the cases of pneumococcal bacteremia among persons 18 years and older during influenza seasons (versus peri-seasonal and summer baseline period, respectively), and RSV may be associated with 17-56% during RSV seasons. Corresponding figures for meningococcal disease among 0-4-year-olds were 27-45% and 12-34%.

Reasons to extend recommendations for influenza vaccination?

Currently, a phased extension of the recommendations for influenza vaccinations, with extensions first targeted to the groups most severely affected by influenza, appears to be the best solution. Although the influenza-associated burden of influenza is highest among the youngest children, only few randomized controlled trials assessed the effects of influenza vaccination in this age groups.[35] Our PRIMAKid-trial among preschool children provided additional evidence and will be discussed in detail in part II of this chapter, as will the possible extension of influenza vaccination in preschool children. In older children and otherwise healthy 18-49-year-olds, the influenza-associated burden appears rather mild (mainly primary care visits) and the incidences of influenza-associated hospitalizations are low compared with the other age categories. Within the group of otherwise healthy 50-64-year-olds, the highest influenza-associated mortality, hospitalization and primary care visits occurred among the 60-64-year-olds. Therefore, otherwise healthy 60-64-year-olds are the most likely candidates to be included in an annual vaccination program. Cost-effectiveness analyses may be further of value in guiding the decision whether to extend influenza vaccination recommendations. Recently, partly based on the figures of the influenza-associated burden as presented in this thesis and additional cost-effectiveness analyses, the Health Council of the Netherlands has advised to extend recommendations for influenza vaccination to otherwise healthy 60-64-year olds starting in 2007.[36]

The fact that in all otherwise healthy persons younger than 65 years of age, influenza-associated morbidity was recorded, suggests that influenza vaccination might be beneficial to all. One may wonder whether this justifies annual influenza vaccination for all, certainly in view of the safety of the influenza vaccine.[37] In other words, with the availability of a vaccine, why not try to prevent as much disease as possible? Besides the huge financial resources required for annual influenza vaccination for all, however, one may also question whether there would be enough willingness among people, especially the otherwise healthy young adults, to get vaccinated. Influenza mostly is self-limiting in these persons and only very rarely leads to complications. Nevertheless, influenza has been associated with considerable secondary effects, e.g. school/work absenteeism,[76-80] and therefore there might

be a task for employers to further stimulate and finance influenza vaccination for employees.

Reflections on influenza vaccination in the elderly

The current extent of the influenza-associated burden among the elderly may seem remarkable, taking into consideration the high influenza vaccination coverage of about 80% in the elderly (Statistics Netherlands, Voorburg/Heerlen, The Netherlands). Some researchers even questioned the benefits of influenza vaccination on serious influenza-associated morbidity and mortality,[50,51] since recent studies could not correlate increasing vaccination coverage among the elderly with a decline in excess mortality in the United States during winter seasons.[11,17] Yet, these studies may have been hindered by the major disparities in vaccination rates by geography as well as by socioeconomic, demographic, and health characteristics making it very difficult to estimate individual benefit from population-level data. Additionally, several cohort and case-control studies indicated that the beneficial effect of influenza vaccination on both influenza-associated mortality and morbidity is substantial.[70-73] Our study assessing the influenza-associated mortality over the seasons 1992-93 to 2002-03 further supported these studies and showed a decline in influenza-associated mortality after the introduction of routine influenza vaccination for all elderly in the Netherlands. Nevertheless, the influenza-associated burden is still substantial among the elderly, emphasizing the need for further improvement of preventive strategies. One way to improve protection against influenza is to further increase coverage among the elderly. However, in the Netherlands vaccination coverage is compared with other European countries already relatively high with about 75-80% (Statistics Netherlands, Voorburg/Heerlen, The Netherlands),[82] and vaccination coverage is slightly higher among elderly with co-morbid conditions than those without.[83] Although the endeavour to maintain and even increase coverage among the elderly should be continued, the beneficial effect of this strategy seems limited.

Another option to improve protection would be to improve the vaccine. It is well-known that the antibody response to vaccine components in many elderly reduces with age.[38] High-dose influenza vaccination enhances the antibody response and may therefore lead to improved protection against influenza.[39] The most frequently advocated strategy lately

mentioned to improve protection against influenza among the elderly is herd immunity, i.e. indirect protection by vaccinating one group to reduce exposure of another. Vaccinating healthcare workers who work with the elderly might therefore be of benefit to the elderly, although this has not been clearly proven.[40] Yet, influenza vaccination is currently recommended for health care workers in the Netherlands.[37] In addition, particularly school children were proven to be frequent introducers of influenza viruses into the household and are therefore instrumental in the spread of influenza viruses in the community.[41] Several non-experimental studies demonstrated a decline in the burden of influenza in all ages when schoolchildren were immunized.[41] A well-known example is the analysis of the Japanese school program in which a dampening of the wintertime mortality peaks was observed in the period when influenza vaccination was mandatory among schoolchildren in Japan.[42] However, like most non-experimental studies, this study had some potential limitations in the methods and interpretation in the way that other potential determinants of the observed trend, like improved hygiene and economic conditions, could not be excluded.[43-45] Therefore, the concept of herd immunity warrants more research, but certainly appears a promising additional approach to reduce influenza-associated morbidity and mortality.

Part II of the thesis

Respiratory tract infections (RTI) are especially prevalent among preschool children. Both influenza vaccination and pneumococcal conjugate vaccination have been advocated as a potentially powerful intervention to facilitate RTI prevention, but data from randomized controlled trials on the effects of these vaccinations on RTI in preschool children are scarce. The major aim of the second part of this thesis was to determine the effects of influenza vaccination with or without pneumococcal conjugate vaccination on the occurrence of RTI in preschool children. Below, the studies addressing this issue will be summarized, and the results will be discussed with reference to possible consequences for daily practice.

Summary

Primary care management of RTI in preschool children was assessed with data from a primary care research database covering the years 1998 to 2002 (**Chapter 6**). It was

demonstrated that almost all of the RTI (98%) among preschool children were managed by general practitioners (GPs). Nevertheless, because of the high frequency of primary care visits for RTI the number of referrals to secondary care, i.e. to a pediatrician and ear-nose-throat-specialist, was still considerable. Overall, about a third of GP-attended RTI episodes resulted in an antibiotic prescription; for GP-attended acute otitis media episodes this was even higher: in about 50% of episodes. This high burden of RTI further underscores the need for preventive measures, not only to reduce the health burden, but also to reduce antibiotic prescriptions. Although the Netherlands are known to be rather restrictive in prescribing antibiotics for upper RTI compared with other countries, the large amount of antibiotic prescriptions in children for RTI in children we observed certainly contributes to the rapidly increasing problem of antimicrobial resistance in bacteria.[52]

The results of the PRIMAKid-study, a randomized double-blind controlled trial among 579 children over three respiratory seasons, were described in **Chapters 7, 8 and 9**. In the PRIMAKid-study, the effects of combined influenza and pneumococcal conjugate vaccination or influenza vaccination alone on the occurrence of RTI in preschool children with prior physician-diagnosed RTI were assessed. In **Chapter 7** it was demonstrated that the administration of parenteral inactivated influenza vaccination with or without simultaneous pneumococcal conjugate vaccination was generally well tolerated in preschool children, and no serious or immediate adverse events were recorded. However, simultaneous administration of the vaccinations was associated with twice as many local adverse reactions and slightly more systemic adverse reactions compared with simultaneous influenza and placebo vaccinations. Since we did not include a study arm with simultaneous pneumococcal conjugate and placebo vaccinations it was impossible to determine whether the pneumococcal conjugate vaccination itself was responsible for the higher prevalence of adverse events or whether this observation was attributable to the combination of influenza and pneumococcal vaccines. Nevertheless, the observed adverse reactions were rather mild and transient, indicating the tolerability of simultaneously administered parenteral inactivated influenza and pneumococcal conjugate vaccinations. Since, in contrast to the influenza vaccine, pneumococcal vaccinations need not to be administered prior to the influenza season, there is no absolute need for simultaneous

administration of the vaccines. Nevertheless, combining the two may be logistically attractive.

Chapter 8 demonstrated that influenza vaccination with or without pneumococcal conjugate vaccination reduced febrile RTI-related laboratory-confirmed influenza by respectively 52% (95% CI 7-75%) and 51% (95% CI 3-75%); febrile RTI-related GP-diagnosed AOM episodes were reduced by respectively 57% (95% CI 10-80%) and 71% (95% CI 29-88%) during the influenza seasons. The vaccinations were less effective against all febrile RTI episodes combined during influenza seasons, with a reduction of 24% (95% CI 2-48%) for combined influenza and pneumococcal vaccination and 13% (95%CI -13-33%) for influenza vaccination only. Outside the influenza seasons, vaccinations conferred no clear beneficial effects.

In **Chapter 9** generic and disease-specific measures of functional health, i.e. well-being, were validated in the study population of the PRIMAKid-study. The generic measure 'RAND Generic Health Rating Index for Children' and the disease-specific 'Respiratory Tract Infection-6' (derived from the otitis media-specific 'Otitis Media-6' measure),[53-56] appeared valid questionnaires to measure functional health in preschool children despite limited responsiveness. In accordance with the absence of a statistically significant effect on clinical outcomes outside the influenza seasons, no evidence was found of an effect of the vaccinations on overall functional health. Data restricted to the influenza seasons were not available.

Are the effects of influenza vaccination disappointing?

The study period of the PRIMAKid-trial included seasons with mild influenza virus-activity and/or suboptimal matching of the strains included in the influenza vaccine and the circulating strains.[57-59] Despite this, the effect on febrile RTI-related confirmed influenza and GP-diagnosed AOM was substantial during influenza seasons, suggesting that these effects might even be larger in seasons with higher influenza virus-activity and optimal matching of the vaccine. Also the effect on febrile RTI will probably be higher in such seasons. It should be emphasized, however, that the seasons in the PRIMAKid-trial do reflect reality. Because of the nature of influenza viruses with antigenic drift, viral activity

and circulating strains are not easy to predict for the forthcoming season,[60] and this continues to be a challenge for further research. Suboptimal vaccine effects and mild influenza virus-activity should therefore be taken into account both in practice and the design of randomized trials. It further underscores the need to include multiple influenza seasons in studies assessing the effects of vaccinations.

The observed effects of influenza vaccination on all febrile RTI episodes combined may have been lower than expected, but the effect on febrile RTI-related GP-diagnosed AOM was substantial in the PRIMAKid-trial. A meta-analysis reported that the pooled results of randomized controlled trials among healthy children of all ages indicated a statistically non-significant reduction of 32% in AOM episodes by trivalent inactivated influenza vaccination.[36] An earlier open randomized trial among day care attendees aged one to three years, demonstrated however a statistically significant 40% reduction in AOM following influenza vaccination.[69] Our study revealed an even larger reduction, 71% in AOM episodes during influenza seasons, but the 95% confidence interval was relatively wide: 30-88%. In our study on influenza-associated burden (**Chapter 2**) we estimated that 20-58% of all GP-attended AOM episodes (versus respectively peri-seasonal and summer baseline period) were associated with influenza during influenza season. This further indicates that the point effect estimate of 71% may be too high. On the other hand, influenza virus infection may cause disturbances in the bacterial flora of the middle ear, potentially initiating a cascade of bacterial infections.[7] By preventing an influenza virus infection, this cascade may therefore be prevented as well. Consequently, also bacterial AOM may be prevented by influenza vaccination.

Recently, live attenuated, cold-adapted vaccines have gained popularity in young children. These vaccines are administered intranasally and contain viruses that can only multiply in the cooler nasal passages. Since live attenuated vaccines induce an immune response through viral replication, these vaccines have been anticipated to provide better protection from disease than trivalent inactivated parenteral vaccines, particularly in children who have never had influenza and have little or no pre-existing immunity.[46] Indeed, meta-analyses reported a better protective effect against confirmed influenza of these intranasal vaccines than the inactivated sub-unit vaccine among children, although the effect on

influenza-like-illness appeared similar.[36,47,48] A very recent randomized study among 6-59-month-olds compared the effects of the live attenuated vaccine and the inactivated vaccine.[49] In the group that received live attenuated vaccine, there were 55% fewer cases of confirmed influenza than in the group receiving inactivated vaccine. However, particularly in 6-11-month-olds more episodes of wheezing were noted within 42 days after administration of the live attenuated vaccine. Moreover, also hospitalization rates were higher. The live attenuated vaccine is not licensed for use in the Netherlands. Although this vaccine seems to achieve a higher protective effect against confirmed influenza than the inactivated vaccine in young children, more studies on its safety profile in children are required to assess its value in clinical practice.

Should we recommend influenza vaccination in preschool children to reduce RTI?
No statistically significant effect was found on febrile RTI, but there was insufficient power to detect the 13% reduction observed in our study. A 13% reduction in the occurrence of RTI during an influenza season of on average 9.3 weeks may be too low to recommend routine influenza vaccination of preschool children. Yet, the estimated 71% reduction in AOM episodes during the same period appears substantial. Since the 95% confidence interval of this point estimate was rather wide, this finding should be confirmed in future studies.

Naturally, it is important is to address the generalizability of the PRIMAKid-trial findings before the consequences for vaccination strategies can be considered. Inclusion criteria of the trial were the age between 18 and 72 months and a history of prior GP-diagnosed RTI. The mean age of the included children was 3.1 years and the mean number of GP-diagnosed RTI in the year prior to study entry was 3.1. Can these participants be considered 'average healthy' children? Some studies indicate that children with severe recurrent AOM, i.e. otitis-prone children with four or more AOM episodes per year, may have subtle immune deficiencies that may result in a (slightly) altered response to vaccinations.[84] However, participants of the PRIMAKid-trial had on average 1.3 AOM episodes in the year prior to study entry, and only 9% of the participants had four or more GP-diagnosed AOM in the year prior to study entry. Moreover, children with conditions predisposing to or associated with recurrent RTI were excluded from the study, such as asthmatic children

chronically treated with corticosteroids, children with cystic fibrosis, cranio-facial malformations, Down's syndrome or haematological disorders. Therefore the study population of the PRIMAKid-trial appears quite 'healthy' indicating that such children with a history of AOM in the prior year might benefit from influenza vaccination.

Does pneumococcal conjugate vaccination (combined with influenza vaccination) have an effect on RTI?

The PRIMAKid-trial gives no support to our hypothesis that combined influenza and pneumococcal conjugate vaccination would be more effective in preventing RTI than influenza vaccination alone. Although the point estimate of the effect on febrile RTI and related antibiotic prescriptions during influenza season indicated a slightly, but not statistically significantly, higher beneficial effect in the combined influenza and pneumococcal vaccination group, the opposite was true for the outcomes febrile RTI-related GP-visits and AOM episodes. Our study had insufficient power to detect relatively small additional effects of pneumococcal vaccination compared with influenza vaccination alone. Nevertheless, outside the influenza seasons, the results of the PRIMAKid-trial do not suggest any beneficial effect of the addition of pneumococcal conjugate vaccinations at all. Because the PRIMAKid-trial did not include a treatment arm including pneumococcal conjugate vaccinations alone, strictly no conclusions about effects of these vaccinations alone can be drawn. When assuming, however, that the influence of influenza vaccination outside the influenza season is small (which was also demonstrated by the fact that the effects of influenza vaccination alone outside the influenza seasons were all non-significant), and knowing there is no evidence of a negative influence of influenza vaccination on the effect of pneumococcal conjugate vaccinations, it may be safe to assume that the effects observed outside the influenza seasons are attributable to pneumococcal conjugate vaccination only. No beneficial effects were observed outside the influenza season, indicating that pneumococcal conjugate vaccination confers no substantial preventive effect on febrile RTI.

Outside the influenza seasons, pneumococcal conjugate vaccination even seems to be associated with a higher rate of febrile RTI and related AOM episodes as compared with influenza vaccination only or control vaccination, although overall statistically non-

significant. This would be in agreement with an earlier Dutch study assessing the effect on AOM of pneumococcal conjugate vaccination followed by a booster polysaccharide pneumococcal vaccination in children aged 1-7 years with recurrent AOM, which found also an increasing trend in AOM episodes in the vaccinated children.[61] This lack of effect or even an increasing trend in AOM has been attributed to a change in nasopharyngeal carriage from vaccine-type to non-vaccine-serotype pneumococci after pneumococcal conjugate vaccinations.[62-65] The replacing pneumococci may have pathogenic potential, especially in older children that already developed an AOM prone condition.[61] Despite the increasing trend in AOM episodes outside influenza seasons, it is not completely fair to neglect the possible effect of pneumococcal vaccination during influenza seasons, because it may be particularly beneficial during respiratory virus-active periods by preventing bacterial superinfections. Over the whole follow-up, i.e. follow-up during influenza seasons and outside influenza seasons together, no increasing trend in AOM episodes was demonstrated with an incidence rate ratio over the control group of 0.97 (0.61-1.54). However, further research should address the potential pathogenicity of replacing bacteria after pneumococcal conjugate vaccination, especially in older children (after the age of infancy).

Are there reasons to extend recommendations for pneumococcal conjugate vaccinations in preschool children to reduce RTI?

The previous described results of the PRIMAKid-trial among children aged 18-72 months do not support the recent decision of the European Medicines Agency to extend the indications to include the prevention of AOM for pneumococcal conjugate vaccination in all preschool children.[81] Our study had, however, insufficient power to assess the effects of pneumococcal vaccination in the prevention of the relatively rare outcome pneumonia, which was also added to the indications for pneumococcal conjugate vaccination. Although our study did not find clear evidence for a beneficial effect of pneumococcal conjugate vaccination on RTI in preschool children, the impact of pneumococcal conjugate vaccination on invasive pneumococcal disease is beyond discussion, and pneumococcal conjugate vaccination should be recommended for all young children, particularly below 2 years of age, to prevent these serious pneumococcal infections. Since pneumococcal conjugate vaccination appears to affect nasopharyngeal carriage in a rather complex way,

the effects of this vaccination on RTI may be age-specific. Consequently, it may well be that pneumococcal conjugate vaccination given in infancy has a beneficial effect on RTI, as earlier studies among infants already indicated.[66-68] Also, a pneumococcal conjugate vaccine including more serotypes than those included in the heptavalent vaccine, may have a larger impact in the prevention of RTI. Furthermore, vaccination of infants may induce herd immunity, leading to lower rates pneumococcal invasive disease and RTI caused by pneumococci in other age categories, as was indicated in previous studies.[67,68,74] Future monitoring studies comparing occurrence rate of RTI before and after the introduction of pneumococcal conjugate vaccination in the infant immunisation schedule in 2006 are thus warranted.

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NEDERLANDSE SAMENVATTING

Nederlandse samenvatting voor niet-ingewijden

Luchtweginfecties (LWI) vormen nog steeds de meest voorkomende acute ziekte wereldwijd. Met het groeien van de kennis over de oorzaken van LWI is de aandacht verschoven van behandeling naar preventie van deze infecties, bijvoorbeeld door vaccinatie. De omvang van de ziektelast die te voorkomen zou zijn tezamen met de effectiviteit van de vaccinatie zijn essentieel om het vaccinatiebeleid richting te geven. Het doel van dit proefschrift was gegevens te leveren om de adviezen voor vaccinaties ter preventie van infecties van de luchtwegen te kunnen optimaliseren. Influenzavirussen (ook wel "griep" in de volksmond) en de bacterie *Streptococcus pneumoniae*, ook wel pneumokok genaamd, zijn samen verantwoordelijk voor een aanzienlijk deel van de luchtweginfecties en zijn momenteel de enige verwekkers van LWI waarvoor vaccins beschikbaar zijn. Ook een ander virus, het respiratoir syncytieel virus (RSV) lijkt tevens verantwoordelijk voor een grote ziektelast zowel bij kinderen als (oudere) volwassenen. Alhoewel er nog geen vaccin is tegen RSV, zijn er de laatste tijd belangrijke stappen gemaakt op dit vlak.

Deel I

Tot 2007 werd in Nederland influenzavaccinatie aanbevolen voor iedereen met hoog-risico aandoeningen zoals chronische aandoeningen van de luchtwegen of het hart, nierfalen en bepaalde stoornissen van de afweer, alsmede alle ouderen (65 jaar en ouder). De adviezen voor influenzavaccinatie zijn echter in veel landen recentelijk verruimd. In de Verenigde Staten bijvoorbeeld, worden 50-64-jarigen en kinderen van 6 maanden tot 6 jaar zonder hoog-risico aandoeningen nu ook geadviseerd zich jaarlijks te laten vaccineren tegen influenza. De meeste Europese landen hebben een vergelijkbaar vaccinatiebeleid als Nederland, maar een eventuele verruiming van de adviezen voor influenzavaccinatie wordt in de meeste landen overwogen. Er wordt met name gedacht om 50-64-jarigen zonder hoog-risico aandoeningen te gaan vaccineren. De effecten van influenzavaccinatie bij gezonde volwassenen zijn uitgebreid bekend, namelijk een 50-80% reductie van

laboratorium-bevestigde influenza. Echter, er is er nog maar beperkte informatie over de omvang van de werkelijke ziektelast, zoals sterfte, ziekenhuisopnames en huisartsbezoeken, door influenza bij deze volwassenen. Betere informatie hierover is van belang bij de besluitvorming wel of geen jaarlijkse influenzavaccinatie voor deze groep in te voeren.

Influenza wordt vaak ondergediagnosticeerd en -gerapporteerd, en bovendien lijkt influenza geassocieerd met complicaties zoals bacteriele infecties (met name ook door pneumokokken) en hart- en vaataandoeningen. Om de omvang van de ziektelast in kaart te brengen, maakt men daarom gebruik van indirecte metingen. In **Hoofdstuk 2** werd de 'rate-difference method', ofwel de incidentie-verschil-methode, die in dit proefschrift is gebruikt om de influenza-gerelateerde ziektelast in te schatten, vergeleken met andere gerapporteerde methoden (modellen). De incidentie-verschil-methode bepaalt de overmaat aan ziekte gedurende periodes dat influenzavirussen heersen in het land in vergelijking met andere periodes zoals de overige weken tijdens het winterseizoen (peri-seizoen) of de zomerperiode. De overmaat van ziekte door het influenzavirus wordt bepaald door incidenties van aandoeningen tijdens vergelijkingsperiodes af te trekken van die tijdens influenzavirus-actieve periodes. Deze methode is algemeen geaccepteerd, toegankelijk en inzichtelijk voor een breed publiek. Wij toonden aan dat met deze methode schattingen worden verkregen die liggen binnen de range van de schattingen verkregen met andere methodes. Voor alle modellen geldt echter dat men bedacht moet zijn op de invloed van andere seizoensgebonden factoren zoals andere virussen die ook actief zijn tijdens het influenzaseizoen. Met name RSV kan een rol spelen. Echter, de incidentie-verschil-methode houdt rekening met RSV. Bovendien waren we in staat om apart de RSV-gerelateerde ziektelast bepalen. Ondanks inachtneming van RSV, blijft de nauwkeurigheid van de schattingen verkregen door de verschillende modellen altijd beperkt, aangezien niet alle mogelijke invloeden meegenomen kunnen worden in het model. Daarom moeten de resultaten met enige voorzichtigheid worden geïnterpreteerd, mede doordat de omvang van de schattingen afhankelijk is van welke vergelijkingsperiode wordt gekozen en welke periodes worden gedefinieerd als het 'influenzaseizoen' met influenzavirus-activiteit.

Met de methoden zoals beschreven in **Hoofdstuk 2** werd verder met wekelijkse data van een eerstelijns onderzoeksdatabank (Huisartsen Netwerk Utrecht) over de periode van 1997

tot en met 2003 de influenza- en RSV-gerelateerde ziektelast die voorkwam in de huisartspraktijk berekend. In **Hoofdstuk 3** werden vervolgens de influenza- en RSV-gerelateerde sterfte en ziekenhuisopnames geschat met behulp van landelijke cijfers van sterfte (ongeacht de oorzaak) van het Centraal Bureau voor de Statistiek en ziekenhuisopnames (Landelijke Medische Registratie, Prismant) welke per week zijn geregistreerd in het influenzaseizoen en vergelijkingsperioden. Samengevat kon er geen duidelijke influenza-gerelateerde sterfte aangetoond worden in de leeftijdscategorieën onder de 50 jaar, maar mogelijk is de incidentie-verschil-methode niet gevoelig genoeg om slechts enkele influenza-gerelateerde sterfgevallen in deze bevolkingsgroepen op te sporen. In de leeftijdscategorie 50-64-jarigen werd *wel* influenza-gerelateerde sterfte aangetoond, namelijk gemiddeld ongeveer 4 tot 8 sterfgevallen per 100.000 per jaar. Deze sterfte vond vooral plaats bij 60-64-jarigen. Bij personen van 65 jaar en ouder met jaarlijks ongeveer 96 tot 147 sterfgevallen per 100.000 inwoners, was de influenza-gerelateerde sterfte aanzienlijk. Omdat er geen informatie beschikbaar was over de eventuele aanwezigheid van hoog-risico aandoeningen bij de sterftecijfers, was het niet mogelijk om te bepalen welk deel van de influenza-gerelateerde sterfte plaatsvond bij 50-64-jarigen zonder hoog-risico aandoeningen.

In tegenstelling tot influenza-gerelateerde sterfte werden wel influenza-gerelateerde ziekenhuisopnames en huisartsbezoeken aangetoond voor alle leeftijdscategorieën. Van de personen jonger dan 65 jaar zonder hoog-risico aandoeningen werden de hoogste aantallen influenza-gerelateerde ziekenhuisopnames en huisartsbezoeken gevonden bij 0-4-jarigen. Zo waren er per jaar gemiddeld ongeveer 79 tot 271 influenza-gerelateerde ziekenhuisopnames per 100.000 0-1-jarigen en 50 tot 105 per 100.000 2-4-jarigen. Deze aantallen daalden met het toenemen van de leeftijd, maar stegen weer vanaf de leeftijd van 50 jaar, met een gemiddeld jaarlijks voorkomen van ongeveer 18 tot 38 per 100.000 50-64-jarigen zonder hoog-risico aandoeningen. Terwijl de influenza-gerelateerde ziekenhuisopnames bij kinderen vaak geassocieerd waren met aandoeningen van de bovenste luchtwegen (zoals middenoorontsteking), was het grootste deel van de opnames bij 50-64-jarigen zonder hoog-risico aandoeningen vooral geassocieerd met cardiovasculaire aandoeningen en lage luchtwegaandoeningen (zoals bronchitis en

longontsteking). De grootste ziektelast was wederom te vinden onder de 60-64-jarigen in deze categorie.

Onder senioren ouder dan 65 jaar in Nederland is de influenza-gerelateerde ziektelast en sterfte nog steeds substantieel, ondanks een hoge influenzavaccinatiegraad van bijna 80%. Dit benadrukt de noodzaak voor een verdere verbetering van strategieën voor de preventie van influenza. De laatste tijd wordt steeds meer aandacht geschonken aan de mogelijke waarde van groepsimmuniteit. Bij groepsimmuniteit worden ongevaccineerden beschermd doordat gevaccineerden in de omgeving de ziekte niet meer overdragen. In deze context raadt de Gezondheidsraad gezondheidsverwerkers al aan om zich te laten vaccineren. Ook met name kinderen worden genoemd doordat zij de belangrijkste verspreiders zijn van influenza. Echter, verdere studies naar de effecten van zo'n aanpak zijn echter noodzakelijk.

Naast de influenza-gerelateerde ziektelast hebben we ook de RSV-gerelateerde ziektelast berekend. Zoals verwacht, was de RSV-gerelateerde ziektelast van huisartsbezoeken en ziekenhuisopnames het hoogst in de jongste leeftijdscategorie, met een gemiddelde jaarlijkse ziektelast van ongeveer 9402 tot 15047 huisartsenbezoeken en 522 tot 699 ziekenhuisopnames per 100.000 0-1-jarigen. Deze last was duidelijk hoger dan de influenza-gerelateerde ziektelast op deze leeftijd. Bij oudere kinderen en 18-49-jarigen was er met name sprake van een RSV-gerelateerde ziektelast door huisartsbezoeken; RSV-gerelateerde ziekenhuisopnames waren er veel minder of zelfs helemaal niet. Echter, onder 50-64-jarigen met hoog-risico aandoeningen en senioren boven de 65 jaar was sprake van een substantiële RSV-gerelateerde ziektelast, met respectievelijk jaarlijks gemiddeld ongeveer 16 tot 53 en 51 tot 141 opnames per 100.000 personen. Ook werd RSV-gerelateerde sterfte aangetoond.

Hoofdstuk 4 beschrijft de impact van een in 1996 geïmplementeerde verandering in het influenzavaccinatiebeleid voor ouderen in Nederland. Vanaf dit jaar (winterseizoen 1996-1997) werden alle senioren van 65 jaar en ouder geadviseerd om zich te laten vaccineren, terwijl dit in de jaren ervoor alleen werd aangeraden voor ouderen met hoog-risico aandoeningen. Door deze verandering in vaccinatiebeleid steeg het percentage ouderen dat

zich had laten vaccineren van minder dan 50% tot ongeveer 80%. Deze stijging in de vaccinatiegraad ging gepaard met een 20-40% daling in de influenza-gerelateerde sterfte. De afname was het grootst onder 65-69-jarigen.

Virale infecties als influenza en RSV-infectie lijken de weg vrij te maken voor bacteriële infecties. Met name pneumokokkeninfecties treden vaak op na een virale infectie. In **Hoofdstuk 5** is de mogelijke relatie onderzocht tussen het heersen van influenzavirussen en RSV in de bevolking en het optreden van invasieve pneumokokken- en meningokokkenziekte, de meest voorkomende vormen van hersenvliesontsteking en bloedvergiftiging tegenwoordig in Nederland. Zowel bij kinderen als volwassenen bleek het optreden van deze invasieve bacteriële infecties geassocieerd met influenzavirus- en RSV-activiteit. Men moet zich realiseren dat deze associatie niet zo maar beschouwd mag worden als bewijs voor een oorzakelijk verband. De gegevens zijn wel suggestief voor een bevorderende rol van virale infecties bij bacteriële infecties en mogelijk zal vaccinatie tegen virussen dus ook bacteriële infecties kunnen voorkomen.

Alle informatie in ogenschouw nemend, is de vraag of er reden is om de adviezen voor influenzavaccinatie te verruimen. Vooralsnog heeft de Gezondheidraad in Nederland gekozen voor een gefaseerde verruiming van de adviezen, met de verruiming allereerst gericht op de groepen die het meest getroffen lijken te zijn door influenza. In omvang is de influenza-gerelateerde ziektelast het hoogst onder jonge kinderen. De effecten van influenzavaccinatie voor deze leeftijd zijn echter veel minder goed bekend. De PRIMAKid-trial, beschreven in Deel II van dit proefschrift, moest hierover aanvullende informatie verschaffen en wordt hieronder beschreven. Onder 50-64-jarigen zonder hoog-risico aandoeningen leek de ziektelast het hoogst onder 60-64-jarigen; ook de influenza-gerelateerde sterfte was het hoogst in deze leeftijdscategorie. Recentelijk heeft de Gezondheidsraad geadviseerd aan de Minister, deels op basis van de in dit proefschrift genoemde schattingen en aanvullende kosteneffectiviteitsanalyses, de aanbevelingen voor een jaarlijkse influenzavaccinatie te verruimen naar 60-64-jarigen zonder hoog-risico aandoeningen.

Het feit dat in alle leeftijdscategorieën, ook zonder dat er sprake is van hoog-risico aandoeningen, een influenza-gerelateerde ziektelast aanwezig lijkt, suggereert dat influenzavaccinatie iedereen ten goede zou kunnen komen. Zeker met het oog op de gebleken veiligheid van het vaccin, zou dit wellicht een jaarlijkse influenzavaccinatie voor iedereen rechtvaardigen. Echter, naast het grote financiële budget noodzakelijk voor jaarlijkse influenzavaccinatie voor iedereen, is het de vraag of er voldoende bereidheid onder de bevolking bestaat, met name bij de jongvolwassenen zonder hoog-risico aandoeningen, om zich te laten vaccineren. Deze groep maakt influenza meestal door zonder de noodzaak tot behandeling of complicaties. Aan de andere kant is influenza wel geassocieerd met aanzienlijke secundaire effecten zoals absentie van school en werk, en daarom is er misschien een taak voor de werkgever weggelegd om influenzavaccinatie te financieren en te stimuleren onder haar werknemers.

Kijkend naar de omvang van de gevonden RSV-gerelateerde ziektelast bij baby's, hoog-risico oudere volwassenen en senioren ouder dan 65 jaar zou vaccinatie tegen RSV in de toekomst een relevante reductie in deze ziektelast kunnen betekenen. Echter, tot op heden is de feitelijke kennis over de rol van RSV in het veroorzaken van ziekte bij volwassenen nog relatief beperkt, zeker in vergelijking met de uitgebreide kennis over influenzavirussen op dit vlak. Zo zijn de meeste RSV-surveillance data afkomstig van kinderen en het is eigenlijk niet precies bekend of de RSV-activiteit onder kinderen in de gemeenschap in de tijd echt gelijk loopt met die onder volwassenen, wat overigens in onze studies wel werd aangenomen. Leeftijdspecifieke actieve surveillance voor RSV in Nederland is noodzakelijk om onze schattingen te bevestigen.

Deel II

Vooral bij kinderen tot de leeftijd van 6 jaar komen LWI veel voor. In **Hoofdstuk 6** is de behandeling van LWI bij kinderen tot 6 jaar in de huisartspraktijk onderzocht. Bijna alle LWI (98%) blijken door de huisarts zelf te worden behandeld; slechts een heel klein deel werd verwezen naar een kinderarts of KNO-arts. Echter, juist vanwege de hoge frequentie waarin LWI optreden bij kinderen is het aantal verwijzingen wel substantieel. Bij ongeveer

eenderde van de LWI-episodes waarvoor een huisarts werd geconsulteerd, werden antibiotica voorgeschreven. Voor acute middenoorontsteking apart was dit nog hoger: de helft van de kinderen kreeg een antibioticakuur. Het hoge aantal verwijzingen en antibioticavoorschriften onderstreept de noodzaak voor preventieve maatregelen, niet alleen om te ziektelast te verminderen, maar ook om het aantal antibioticavoorschriften te reduceren. De hoeveelheid antibiotica die wordt voorgeschreven voor LWI bij kinderen draagt namelijk zeker bij aan het groeiende probleem van resistentie van bacteriën tegen antibiotica.

Zowel influenzavaccinatie als vaccinatie tegen pneumokokken worden genoemd als mogelijkheid om LWI te voorkomen. Aanvankelijk was er alleen een vaccin bestaande uit de suikerkapsels tegen pneumokokken dat bij jonge kinderen onvoldoende opbouw van afweerstoffen gaf. Sinds een aantal jaren is echter het zogenaamde zeven-valente pneumokokken conjugaatvaccin (PCV-7) beschikbaar, dat ook bij jonge kinderen leidt tot voldoende afweerstoffen tegen de zeven meest voorkomende type pneumokokken. De effecten van zowel influenzavaccinatie als PCV-7 op LWI zijn voor de leeftijdsgroep tot 6 jaar slechts in een beperkt aantal studies onderzocht. Bovendien hadden deze studies veelal een suboptimale opzet; vaak waren ze niet gerandomiseerd en ontbrak een controlegroep.

Hoofdstuk 7, **8** en **9** beschrijven de resultaten van een grote vaccinatiestudie, het PRIMAKid ('Prevention of Respiratory Infections and Management in children')-onderzoek. Deze studie had als belangrijkste doel het evalueren van de effecten van influenzavaccinatie al dan niet gecombineerd met PCV-7 op het optreden van LWI bij kinderen. In totaal werden voor de start van drie opeenvolgende influenzaseizoenen 579 kinderen in de leeftijd van 18 tot 72 maanden geïncludeerd die een voorgeschiedenis hadden van door de huisarts gediagnosticeerde LWI. Het toeval bepaalde (randomisatie) of de kinderen een combinatie van influenzavaccinatie en PCV-7, influenzavaccinatie alleen of Hepatitis B vaccinatie kregen. Deze laatste groep kinderen die alleen Hepatitis B vaccinaties kreeg was de controlegroep aangezien Hepatitis B vaccinatie geen effecten heeft op LWI. **Hoofdstuk 7** beschrijft de bijwerkingen van de vaccinaties. De vaccinaties werden over het algemeen goed verdragen en er werden geen ernstige of direct-optredende bijwerkingen waargenomen. Echter, gelijktijdige influenzavaccinatie en PCV-7 gaf twee

keer zo veel lokale bijwerkingen (roodheid, pijn, zwelling, etc.) en iets meer systemische bijwerkingen (malaise, koorts, hoofdpijn) dan influenzavaccinatie alleen of Hepatitis B vaccinatie. De meeste bijwerkingen waren echter mild en van snel-voorbijgaande aard; ze verdwenen twee dagen na vaccinatie. Onze studie kon niet laten zien of het vaker voorkomen van bijwerkingen te wijten was aan de toevoeging van PCV-7 alleen, of aan juist de combinatie van de influenzavaccinatie en PCV-7. Aangezien in tegenstelling tot influenzavaccinatie de toediening van PCV-7 niet seizoensgebonden is, is er geen noodzaak tot het gelijktijdig toedienen van deze vaccins, al zou het om logistieke redenen aantrekkelijk zou kunnen zijn.

De kinderen die geïncludeerd waren in de studie gedurende de eerste twee jaren werden 18 maanden gevolgd en die in het derde inclusiejaar 6 maanden. Door de ouders werden dagboeken bijgehouden om gegevens te verzamelen over het voorkomen van symptomen die samengaan met luchtweginfecties (koorts, malaise, verkouden, keelpijn, oorpijn, hoesten, kortademigheid/piepen). Deze symptomen werden gescoord van mild (1) tot ernstig (3). Tijdens het influenzaseizoen werd in geval van deze symptomen (koorts plus een ander symptoom) een neus-keel-wat afgenomen welke werd onderzocht op de aanwezigheid van influenzavirussen. Tevens hielden ouders bij of ze voor deze symptomen de huisarts consulteerden. In geval van een huisartsbezoek vulde de huisarts een formulier in met de diagnose en eventuele behandeling. **Hoofdstuk 8** beschrijft de effecten van influenzavaccinatie al dan niet in combinatie met PCV-7 op het optreden van LWI-episodes en daaraan gerelateerde laboratorium-bevestigde influenza, huisartsbezoeken, antibioticavoorschriften en acute middenoorontsteking. Wij definieerden een LWI-episode als tenminste twee dagen koorts (≥ 38°C) met daarbij één of meer van de eerdergenoemde symptomen met tenminste een score van 2. Tijdens het influenzaseizoen trad zowel in de groep kinderen die alleen influenzavaccinatie had gekregen als in de groep kinderen met gecombineerde influenzavaccinatie en PCV-7 de helft minder laboratorium-bevestigde influenza op in vergelijking met de groep kinderen die alleen controle Hepatitis B vaccinatie had gekregen. Dit betekent dat er 20 tot 25 kinderen gevaccineerd moeten worden om één zo'n episode te voorkomen. LWI-episodes waarbij acute middenoorontsteking voorkwam traden 57% minder op in de groep kinderen met gecombineerde influenzavaccinatie en PCV-7 en 71% minder in de groep met alleen

influenzavaccinaties. De influenzavaccinaties en PCV-7 hadden minder effecten op alle LWI-episodes gecombineerd in het influenzaseizoen, met een reductie van 24% bij gecombineerde influenzavaccinatie en PCV-7 en een reductie van 13% bij influenzavaccinatie alleen. Deze laatste verschillen konden niet met met voldoende precisie aangetoond worden. Buiten het influenzaseizoen lieten de vaccinaties geen duidelijke effecten zien; LWI-episodes en daaraan gerelateerde huisartsbezoeken, antibioticavoorschriften en acute middenoorontstekingen kwamen niet minder vaak voor bij de groepen kinderen die influenzavaccinatie al dan niet in combinatie met PCV-7 hadden gekregen, in vergelijking met de groep kinderen die Hepatitis B vaccinatie had ontvangen.

In **Hoofdstuk 9** worden de effecten van influenzavaccinatie al dan niet in combinatie met PCV-7 beschreven op de functionele gezondheidstoestand, dat het fysiek, psychologisch of emotioneel en sociaal functioneren van het kind weerspiegelt. Zowel de algemene als de specifiek aan LWI gerelateerde functionele gezondheidstoestand zijn gemeten buiten het influenzaseizoen. Overeenkomstig met de afwezige effecten van influenzavaccinatie en PCV-7 op LWI-episodes buiten het influenzaseizoen, waren er geen effecten van deze vaccinaties merkbaar op de functionele gezondheidstoestand.

De vraag is of het effect van influenzavaccinatie teleurstellend waren, aangezien relatief weinig effect werd gezien van influenzavaccinatie op het totale aantal LWI-episodes tijdens het influenzaseizoen. Echter, de studieperiode van de PRIMAKid-studie bevatte seizoenen met slechts milde influenzavirus-activiteit en/of suboptimale ‘matching’ van het influenzavaccin. ‘Matching’ wil zeggen de mate waarin het vaccin influenzavirusstammen bevat die ook daadwerkelijk circuleren in de gemeenschap. Bij een suboptimale match circuleren er virusstammen die niet geheel gedekt worden door het vaccin en hierdoor zullen de afweerstoffen opgebouwd door het vaccin geen optimale bescherming bieden. Ondanks ‘suboptimale’ omstandigheden waren er duidelijke effecten op laboratorium-bevestigde influenza aanwezig en het aantal acute middenoorontstekingen tijdens het influenzaseizoen leek substantieel te dalen door influenzavaccinatie. Dit suggereert dat de effecten gevonden in de PRIMAKid-studie beter hadden kunnen uitvallen bij een hogere influenzavirus-activiteit en een optimale vaccin-match. Het moet echter worden benadrukt dat de seizoenen waarin de PRIMAKid-studie werd uitgevoerd wel de realiteit

weerspiegelen. Aan de hand van de voorspellingen door verschillende onderzoeksgroepen over de wereld welke types virusstammen zullen gaan circuleren, adviseert de Wereld Gezondheids Organistie welke virusstammen in het vaccin dienen te worden geïncludeerd voor komend seizoen. Influenzavirussen hebben echter de eigenschap te kunnen variëren in de twee belangrijke oppervlakte-eiwitten hemagglutinine en neuraminidase. De varianten waartegen in de bevolking de minste antistoffen zijn, hebben een voordeel en kunnen zich daarom beter verspreiden in de gemeenschap en tot een hoger niveau van virus-activiteit komen. Dit fenomeen wordt ook wel antigene drift genoemd en hierdoor kan het voorkomen dat de circulerende stammen en de daaraan verbonden mate virus-activiteit moeilijk te voorspellen zijn voor het komend seizoen. Er moet daarom rekening gehouden worden met de mogelijkheid van een suboptimale vaccin-match en een sterk variërende influenzavirus-activiteit zowel in de praktijk als bij het ontwerpen van studies.

De vraag is of de PRIMAKid-studie aanleiding zou moeten geven om influenzavaccinatie te adviseren voor alle kinderen in de leeftijd van 18 tot 72 maanden met een voorgeschiedenis van LWI. Van influenzavaccinatie alleen werd geen duidelijk effect aangetoond op het totaal aantal LWI-episodes tijdens het influenzaseizoen. De studie was te klein om de gevonden vermindering van 13% in het optreden van LWI-episodes met voldoende precisie te kunnen aantonen. Echter, misschien is een vermindering van 13% gedurende het influenzaseizoen van gemiddeld 9,3 weken überhaupt onvoldoende basis om jaarlijkse influenzavaccinatie voor kinderen van deze leeftijd te rechtvaardigen. Aan de andere kant lijkt een 71% reductie van acute middenoorontsteking gedurende het influenzaseizoen wel een duidelijke winst. Of de resultaten van de PRIMAKid-studie van toepassing zijn op alle kinderen in de leeftijd van 18 tot 72 maanden hangt af van hoe representatief de PRIMAKid-populatie is voor kinderen met deze leeftijd in het algemeen. Deze representativiteit lijkt bevredigend aangezien de kinderen gemiddeld slechts drie huisarts-gediagnosticeerde LWI in het jaar voor de start van de studie hadden. Bovendien zijn alle kinderen geëxcludeerd die aandoeningen hadden gepaard gaand met een verhoogd risico op het krijgen van herhaalde LWI zoals bijvoorbeeld astmatische kinderen die chronisch behandeld worden met corticosteroïden, kinderen met het Down-syndroom of taaislijmziekte.

De PRIMAKid-studie toont aan dat een combinatie van influenzavaccinatie en PCV-7 niet effectiever is bij de preventie van LWI dan influenzavaccinatie alleen. Alhoewel de grootte van de studie niet toeliet relatief kleine additionele effecten aan te tonen van gecombineerde influenzavaccinatie en PCV-7 bovenop die van influenzavaccinatie alleen, lijken de puntschattingen hiervoor ook geen aanwijzingen te geven tijdens het influenzaseizoen. Aannemende dat alleen PCV-7 werkzaam is buiten het influenzaseizoen in de groep kinderen met gecombineerde influenzavaccinatie en PCV-7, lijken er buiten het influenzaseizoen geen positieve effecten van PCV-7 waarneembaar. Dit gebrek aan een positief effect van PCV-7 op LWI zou toegeschreven kunnen worden aan een verandering in de bacteriële flora van de neus-en-keelholte na vaccinatie. Kinderen en met name jonge kinderen zijn vaak drager van pneumokokken en andere mogelijk ziekmakende bacteriën in de neus-en-keelholte. Eerder is aangetoond dat na PCV-7 dit dragerschap vaak verandert van dragerschap met type pneumokokken die wel vertegenwoordigd zijn in PCV-7 naar typen die *niet* in dit vaccin zitten en andere bacteriën. Deze vervangende bacteriën kunnen mogelijk ziekmakend zijn, met name bij oudere kinderen die al LWI hebben doorgemaakt. Verder onderzoek is echter nodig naar dit fenomeen.

Hoewel de PRIMAKid-studie geen bewijs vond voor een positief effect van PCV-7 bovenop influenzavaccinatie op het voorkomen van veelvoorkomende LWI bij kinderen van 18 tot 72 maanden, was de studie te klein om het effect van PCV-7 te bepalen op zeldzamere uitkomsten zoals longontsteking te bestuderen. De toevoeging van PCV-7 aan het Rijks Vaccinatie Programma in 2006 staat overigens in het geheel niet ter discussie. Het beschermend effect van dit vaccin tegen ernstige invasieve pneumokokkeninfecties als meningitis en bloedvergiftiging is uitgebreid aangetoond onder baby's. PCV-7 lijkt het dragerschap van pneumokokken in de neus-keelholte op een complexe wijze te beïnvloeden en daarom zouden de effecten van PCV-7 ook kunnen afhangen van de leeftijd waarop dit vaccin wordt gegeven. Oudere kinderen dragen vaak ook weer andere type pneumokokken mee in de neus-en-keelholte dan de zeven die geïncludeerd zijn in PCV-7 en die met name onder de 3 jaar een rol spelen. Zo zou het kunnen dat PCV-7 gegeven in de zuigelingenleeftijd wel een positief effect geeft op LWI, zoals eerdere studies ook lijken aan te tonen. Studies naar het voorkomen van LWI voor en na de introductie van PCV-7 in het vaccinatieprogramma kunnen hierover meer duidelijkheid geven.

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Curriculum vitae

Angelique Jansen was born on December 24th, 1979 in the Noordoostpolder, the Netherlands. In 1998, after graduating secondary school ('gymnasium') at the Zuyderzee College in Emmeloord (cum laude), she attended one year of the pre-medical major program at the University College of the University Utrecht. She started to study medicine in 1999 at the Erasmus University Rotterdam where she graduated for her doctoral exam in 2003 and obtained her Medical Degree in July 2005. Subsequently, she started her PhD-project at the Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, under the guidance of Prof.dr. E.A.M. Sanders, Prof.dr. A.W. Hoes and dr. E. Hak. She obtained her Master of Science in Epidemiology at the University Utrecht in August 2007. As of in April 2007, she works on several vaccine studies under supervision of Prof.dr. E.A.M. Sanders at the Wilhelmina Children's Hospital of the University Medical Center Utrecht.