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Influenza- and respiratory syncytial virus-associated mortality and hospitalisations

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Short title: burden of influenza and RSV

Abstract

Objectives: To estimate influenza- and respiratory syncytial virus-(RSV) associated mortality and hospitalisations, 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 hospitalisation 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 hospitalisation was highest and about equal for 0-1-year-olds and the elderly, and also significant for low-risk adults. Hospitalisation among children was mostly because of respiratory conditions, and among adults cardiovascular complications were frequent. RSV-active periods were associated with excess mortality and hospitalisation among the elderly. The highest RSV-related excess hospitalisation 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 hospitalisation 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.

Key words: hospitalisations, influenza viruses, mortality, respiratory syncytial viruses

Introduction

Almost yearly the influenza virus is held accountable for large numbers of deaths and hospitalisations [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 hospitalisation 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 hospitalisation, especially the influenza-associated burden among low-risk persons $\leq$ 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.

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 base-line 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 base-line 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 base-line period.

During the study period there were 92 influenza 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 hospitalisation rates were provided by Prismant that registers all hospitalisations nationwide according to ICD-9cm (International Classification of Diseases). In this register, all discharge diagnoses were registered per hospitalisation with the first diagnosis marked as primary diagnosis. During the study period, all hospitalisations 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). Hospitalisations 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 hospitalisation, 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 hospitalisation (per 100,000 persons) was calculated in different study periods, i.e. peri-seasonal and summer base-line periods and periods in which influenza virus or RSV predominated. Weekly excess mortality and hospitalisations 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 base-line 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 hospitalisations 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 hospitalisations 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 hospitalisations, 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 hospitalisation was highest in 0-1-year-olds (Table 3). Infants appeared responsible for the largest part of this excess hospitalisation for LRTI, namely yearly on average around 13 to 221 hospitalisations per 100,000 0-year-olds (respectively with the peri-seasonal and summer base-line period as reference) and 13 to 64 hospitalisations per 100,000 1-year-olds. In adults, significant excess hospitalisation 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 hospitalisation for LRTI (Table 3), with yearly on average around 870 to 1063 hospitalisations per 100,000 0-year-olds (with respectively peri-seasonal and summer base-line period as reference) and 104 to 151 per 100,000 1-year-olds. Significant excess hospitalisation was recorded in adults during RSV-active periods, in particular in

elderly (Table 4). The total absolute number of RSV-associated excess hospitalisation was highest and about similar among 0-1-year-olds and elderly (Figure 4).

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 hospitalisation was significant among healthy persons of all age categories and highest for young children and older persons. The highest RSV-associated excess hospitalisation 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 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 hospitalisation 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 hospitalisation 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 hospitalisation was however significant among low-risk 50-64-year-olds. A recent study was not able to demonstrate influenza-associated hospitalisation in this group, but this was probably due to limited statistical power [7]. The hospitalisation rates we found among low-risk 50-64-year-olds were clearly lower than those in young children, but the nature of the hospitalisations may also be important. While in children the excess hospitalisation was mainly due to respiratory conditions, hospitalisations for CVC made up the largest part of the excess hospitalisation among 50-64-year-olds. Obviously, these hospitalisations are expected to have a large impact on the health care system and financial resources. Both influenza-associated excess mortality and hospitalisation, 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 hospitalisation 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 hospitalisation 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 hospitalisation appeared mainly for respiratory indications and to a lesser extent for the indication CVC compared to influenza-associated hospitalisation, 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 hospitalisation 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 base-line 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 hospitalisation and mortality is limited with the peri-seasonal base-line 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 hospitalisation probably lies within the estimations based on the peri-seasonal and summer base-line 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 (See 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 hospitalisation 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 hospitalisation 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 hospitalisation 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.

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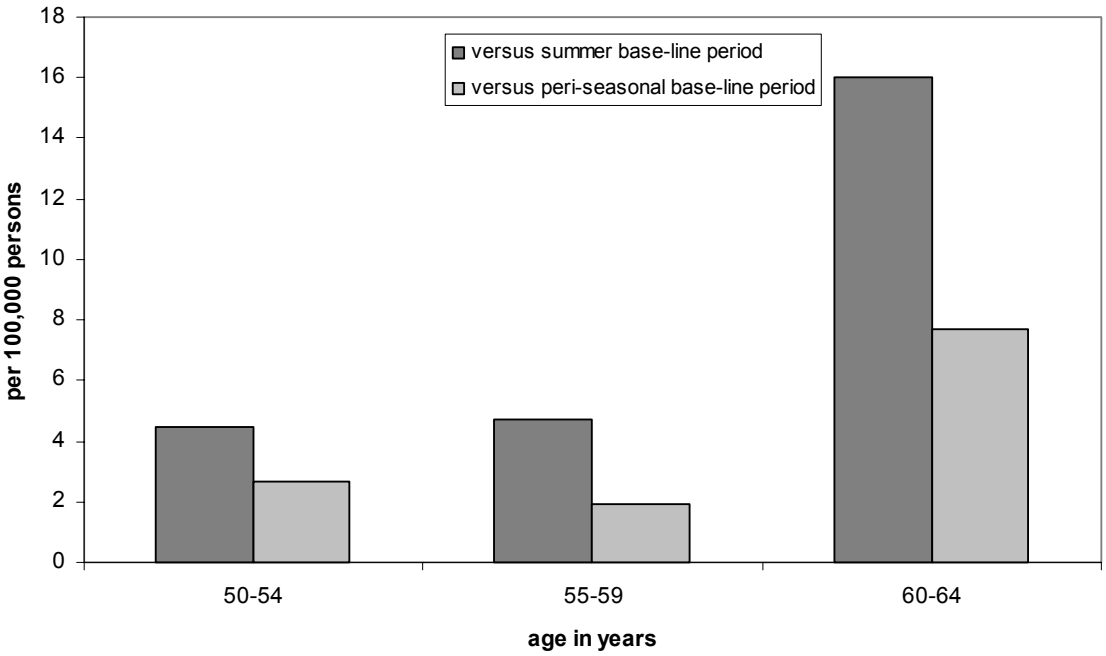
Figure 1: Influenza-associated winter mortality among 50-64-year-olds



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

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

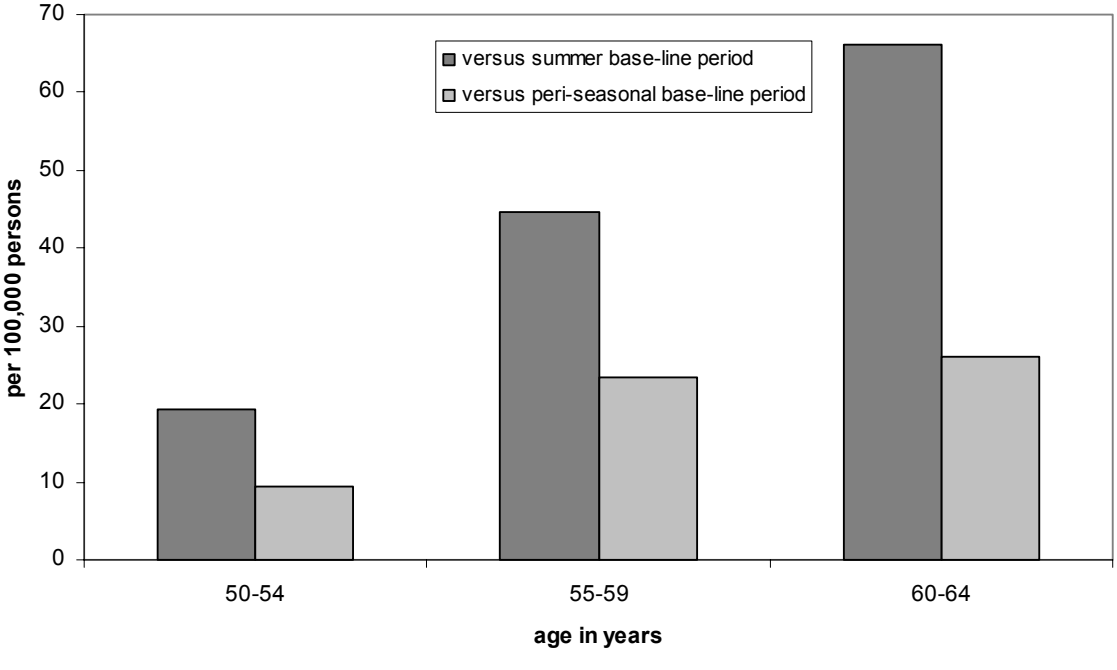


Figure 3: Influenza-associated hospitalisation burden in The Netherlands

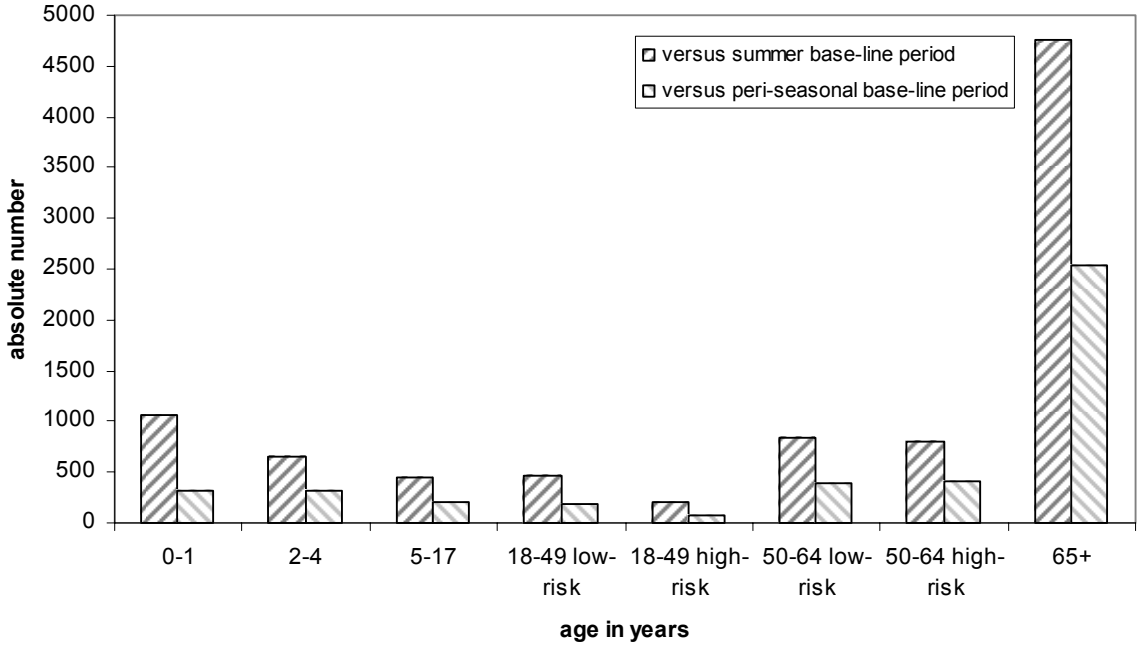
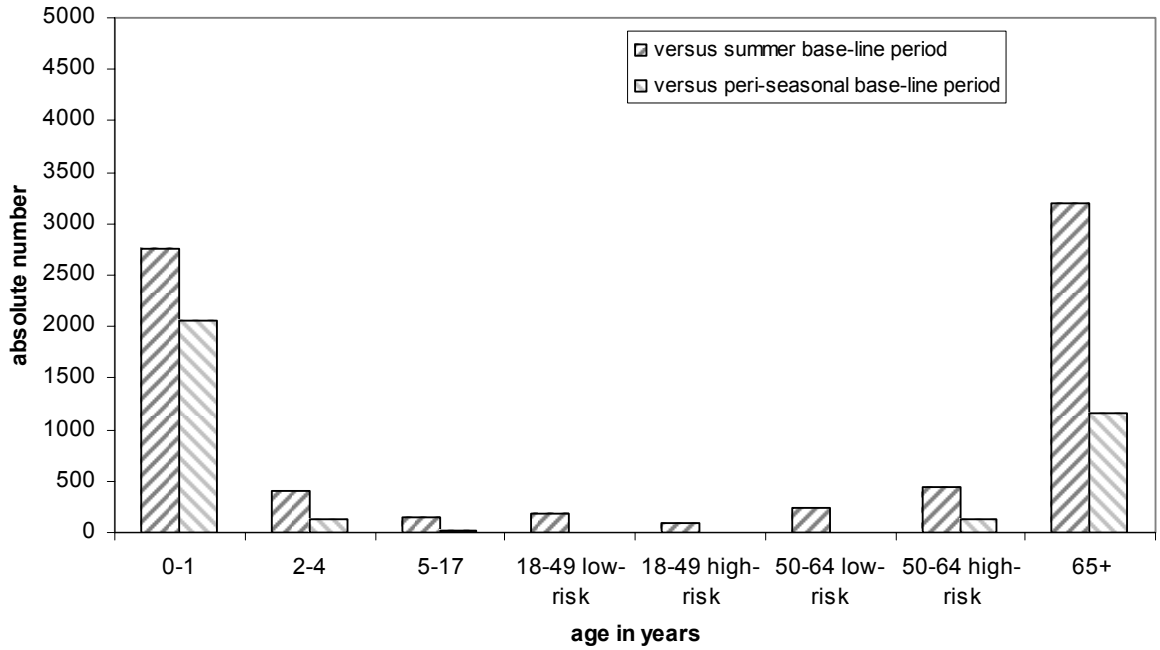
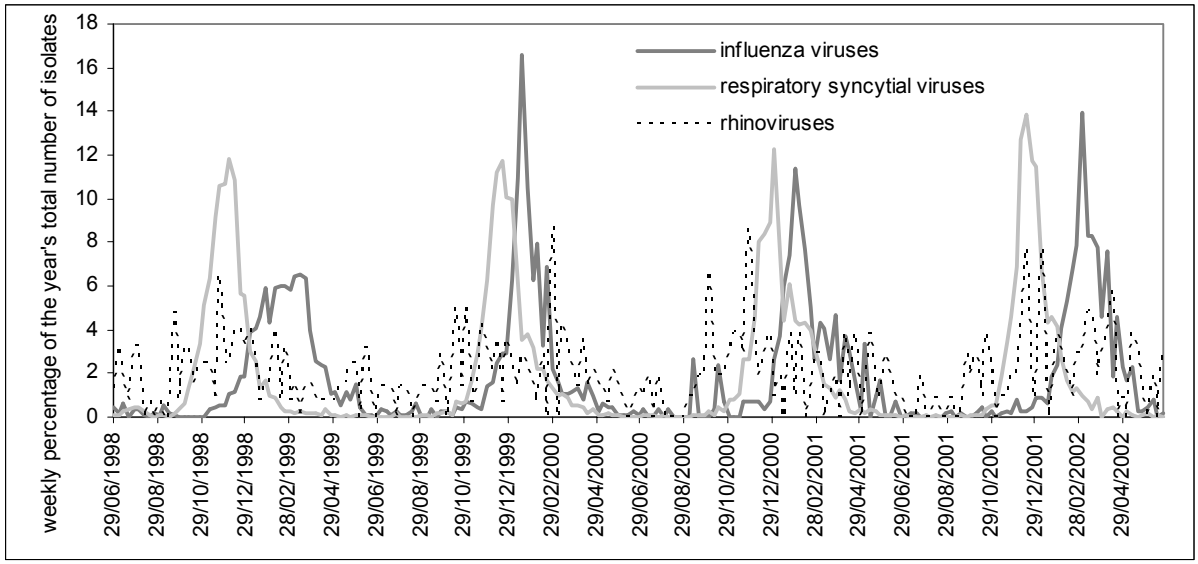
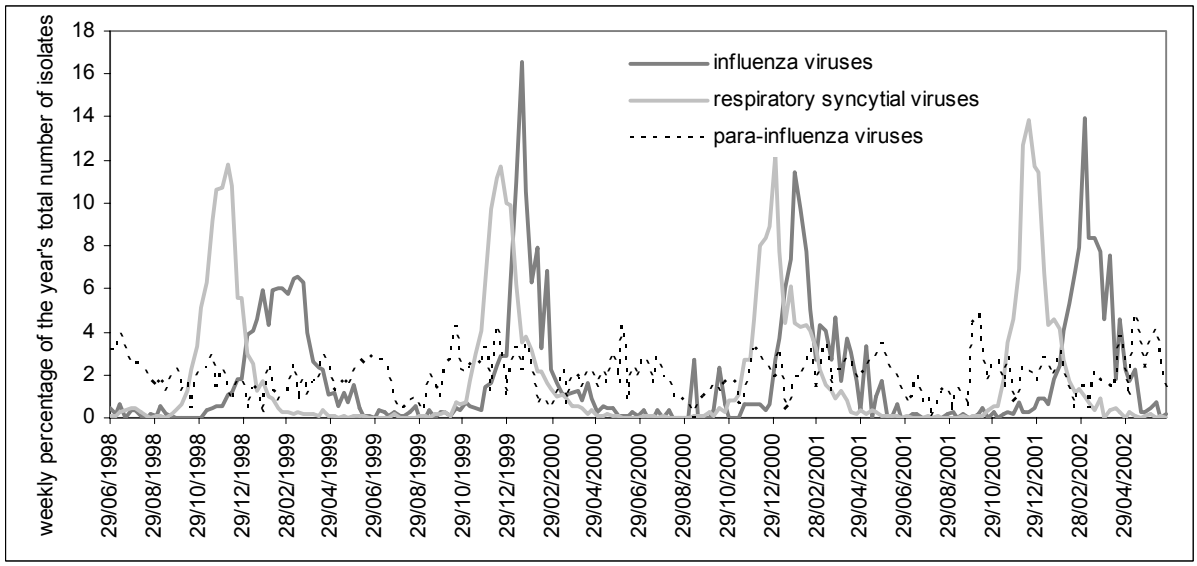


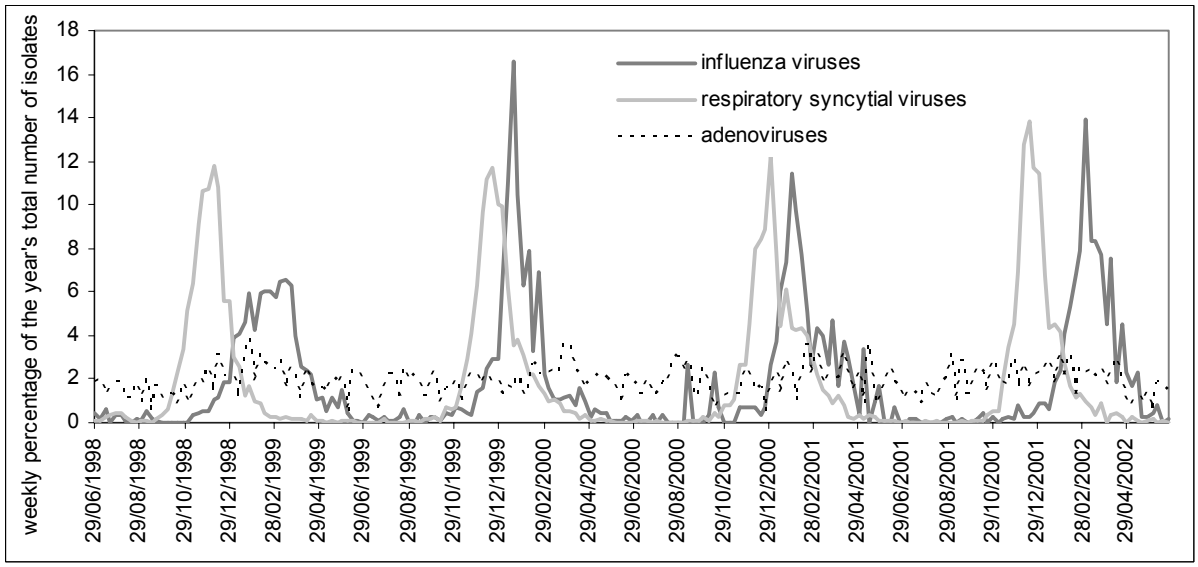
Figure 4: RSV-associated hospitalisation burden in The Netherlands



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







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

Table 1: Influenza virus and RSV surveillance data

		1997-98	1998-99	1999-00	2000-01	2001-02	2002-03
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

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

	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 base-line period	Peri-seasonal base-line period	versus summer base-line period	versus peri-seasonal base-line period	versus summer base-line period	versus peri-seasonal base-line period
0-1 year	5.3	5.0	5.4	5.4	none	none	none	none
2-17 years	0.4	0.3	0.4	0.3	0.1 *(-0.3-0.4)*	0.3 *(0.1-0.7)*	none	none
18-49 years	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 years	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 years	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: Hospitalisation rates and total winter excess hospitalisation among children associated with influenza virus and RSV

	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 base-line period	Peri-seasonal base-line period	versus summer base-line period	versus peri-seasonal base-line period	versus summer base-line period	versus peri-seasonal base-line period
Upper respiratory tract infections								
0-1 year	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 years	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 years	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 and pulmonary disease								
0-1 year	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 years	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 years	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 year	17.1	12.7	13.0	13.3	34.1 *(28.5-39.8)*	31.9 *(26.2-37.6)*	none	none
2-4 years	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 years	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: Hospitalisation rates and estimated total winter excess hospitalisation among adults associated with influenza virus and RSV

		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 base-line period	Peri-seasonal base-line period	versus summer base-line period	versus peri-seasonal base-line period	versus summer base-line period	versus peri-seasonal base-line period
					Upper respiratory tract infections				
18-49	**non high-risk**	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
years	**high-risk**	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	**non high-risk**	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
years	**high-risk**	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	**non high-risk**	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
years	**high-risk**	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	**non high-risk**	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
years	**high-risk**	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)*

Table 4: Hospitalisation rates and estimated total winter excess hospitalisation among adults associated with influenza virus and RSV, cont. I

Cardiovascular complications									
18-49	**non high-risk**	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
years	**high-risk**	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	**non high-risk**	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
years	**high-risk**	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	**non high-risk**	0.6	0.5	0.5	0.5	0.2 *(-0.1-0.4)*	0.3 *(0.1-0.5)*	none	none
years	**high-risk**	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	**non high-risk**	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)*
years	**high-risk**	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)*

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.