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Influenza- and respiratory syncytial virus-associated mortality and hospitalisations

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ABSTRACT: The aim of the current study was to estimate influenza- and respiratory syncytial virus (RSV)-associated mortality and hospitalisations, especially the influenza-associated burden among low-risk individuals ⩽65 yrs old, not yet recommended for influenza vaccination in many European countries.

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.

Influenza virus active periods were significantly associated with excess mortality among 50–64-yr-olds and the elderly, but not in younger age categories. Influenza-associated hospitalisation was highest and about equal for 0–1-yr-olds and the elderly, and also significant for low-risk adults. Hospitalisation among children was mostly due to 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-yr-olds.

Influenza-associated mortality was demonstrated in 50–64-yr-olds. Among low-risk individuals ⩽65 yrs of age, influenza-associated hospitalisation rates were highest for 0–4-yr-olds, but also significant for 5–64-yr-olds. These data may further support extension of recommendations for influenza vaccination to include younger low-risk persons. The respiratory syncytial virus-associated burden was highest for young children but also substantial for the elderly.

KEYWORDS: Hospitalisations, influenza viruses, mortality, respiratory syncytial viruses

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STATEMENT OF INTEREST
None declared.

Almost yearly, the influenza virus is held accountable for large numbers of deaths and hospitalisations [1–3], in particular among the elderly and people with high-risk medical conditions. Therefore, most countries recommend influenza vaccination for these groups [4]. Recently, the USA extended vaccination to low-risk 50–64-yr-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, however, is 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 healthcare burden accurately, because influenza virus infections are generally not virologically confirmed and are often not recognised clinically [8, 9]. In addition, the influenza virus infection may predispose to other conditions, such as 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 10 yrs the development of vaccines against RSV has progressed [17], and although a vaccine is not expected in the very near future, insight into the RSV-associated healthcare burden would be valuable.

Contrary to former studies [3, 7], viral surveillance data in the Netherlands from 1997–2003 revealed largely separate peaks of influenza virus- and RSV-activity that allowed quantification of 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 individuals ⩽65 yrs of age.

For editorial comments see page 1029.

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METHODS

Viral surveillance

During the period 1997–2003, laboratory-based surveillance for various viruses was conducted by the Weekly Sentinel System of the Dutch Working Group on Clinical Virology in the Netherlands. A group of 17 virological laboratories reported weekly on the absolute number of patients, either hospitalised or visiting outpatient clinics, who tested positive for a certain virus. Surveillance data for influenza virus and RSV from that system were used in the current 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 adequately reflect trends in national viral activity [18]. However, most RSV surveillance data (96%) were reported in children <5 yrs old [19]. An influenza virus subtype was considered dominant when it accounted for ⩾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 2000–2001, which was subtype A H1N1-dominant.

Definition of study periods

With minor modifications, study periods were defined according to IZURIETA *et al.* [20]. For each winter season, from week 40 of 1 yr to week 20 of the next, the influenza virus-active period was defined as the periods of at least two consecutive weeks in which each week accounted for ⩾5% of the season's total number of laboratory-confirmed influenza cases [20]. Similarly, the RSV-active period was defined as the period of at least 2 consecutive weeks in which each week accounted for ⩾5% of the season's total number of RSV-positive patients. The period with influenza predominance was defined as the influenza virus-active weeks with <5% of the season's total number of positive tests for RSV [20]. The peri-seasonal baseline period was defined as periods of at least two consecutive weeks within week 40–20 in which each week accounted for <5% of the season's total number of influenza and RSV-positive cases. The summer baseline period was defined as week 21–39. Unlike the study of IZURIETA *et al.* [20], the weeks in which parainfluenza virus was 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 from the study.

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 (Healthcare and Advice Institute, Utrecht, the Netherlands), who register all hospitalisations nationwide according to the International Classification of Diseases-9CM. 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 into upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI) and pulmonary disease, 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 were registered. A high-risk condition was considered present when at least one of the 14 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.

TABLE 1 Influenza virus and respiratory syncytial virus (RSV) surveillance data

	Season					
	1997–1998	1998–1999	1999–2000	2000–2001	2001–2002	2002–2003
Influenza season weeks	9	10	8	6	9	8
Dominant subtype influenza	H3N2	H3N2	H3N2	H1N1	H3N2	H3N2
Influenza isolates						
Whole year	777	883	858	298	660	392
Influenza season	532	539	589	141	465	231
RSV season weeks	9	9	7	7	6	8
RSV isolates						
Whole year	1575	2334	2104	1870	1579	1767
RSV season	868	1769	1367	1043	1001	1260

Data are presented as n.

Statistical analysis

The population of each consecutive year on January 1st was taken as the population at risk, assuming a stable population throughout the year (Statistics Netherlands). For all years taken together, the average weekly mortality rate and rate of hospitalisation (per 100,000 subjects) 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 hospitalisations with 95% confidence intervals (CIs) associated with influenza virus and RSV were determined by subtracting summer and peri-seasonal baseline rates from rates during periods of influenza virus or RSV predominance. The cumulative annual winter excess rate was the total excess per 100,000 subjects associated with influenza virus or RSV during winter season, and 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. The excess rates were applied to the national population of 2005 (Statistics 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 [21]. 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 subjects aged $\geqslant$=65 yrs, as these subjects 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-yr-olds, 6% in 18–49-yr-olds, 13% in 50–64-yr-olds and 80% in those aged $\geqslant$65 yrs. For hospitalisations, these figures were 14, 12, 23 and 51%, respectively.

Influenza

No evident excess mortality was found in the age categories 0–1, 2–17 and 18–49 yrs during influenza virus-active periods (table 2). However, among those aged $\geqslant$50 yrs, significant influenza-associated excess mortality was recorded. Among 50–64-yr-olds, influenza-associated excess mortality was highest for 60–64-yr-olds (fig. 1). Influenza-associated excess hospitalisation was highest in 0–1-yr-olds (table 3). Infants appeared responsible for the largest part of this excess hospitalisation for LRTI, namely a yearly average of ~13–221 hospitalisations per 100,000 infants <1-yr-old (respectively with the peri-seasonal and summer baseline period as reference) and 13–64 hospitalisations per 100,000 1-yr-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 and increased among low-risk 50–64-yr olds (fig. 2). In absolute numbers, the highest influenza-associated healthcare burden occurred in the elderly (fig. 3).

RSV

During RSV-active periods, no evident excess mortality was found in the age categories 0–1, 2–17 and 18–49 yrs (table 2). The youngest children appeared to experience the largest RSV-associated excess hospitalisation for LRTI (table 3), with average annual hospitalisation ~870–1063 per 100,000 infants <1-yr-old (with respectively peri-seasonal and summer baseline period as reference) and 104–151 per 100,000 1-yr-olds. Significant excess hospitalisation was recorded in adults during RSV-active periods, in particular in the elderly (table 4). The total absolute number of RSV-associated excess hospitalisation was highest and approximately similar among 0–1-yr-olds and the elderly (fig. 4).

TABLE 2 Weekly mortality and estimated total winter mortality associated with influenza virus and respiratory syncytial virus (RSV)

Age group	Weekly mortality per 100000 population				Total excess winter mortality per 100000 population#			
					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 yr	5.3	5.0	5.4	5.4	None¶	None¶	None¶	None¶
2–17 yrs	0.4	0.3	0.4	0.3	0.1 (-0.3–0.4)+	0.3 (0.1–0.7)	None¶	None¶
18–49 yrs	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 yrs	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)+
$\geqslant$65 yrs	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)

Data are presented as mean (95% confidence interval), unless otherwise stated. #: 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 RSV; ¶: no nonsignificant excess; +: nonsignificant excess.

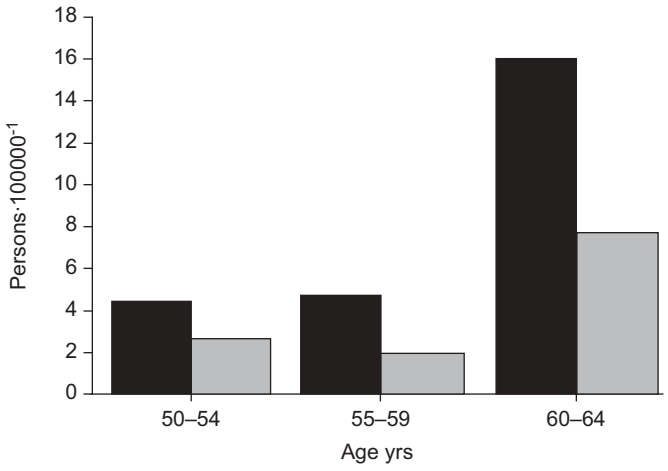

FIGURE 1. Influenza-associated winter mortality among 50–64-yr olds. ■: *versus* summer baseline period; ■: *versus* peri-seasonal baseline period. For 55–59-yr-olds, influenza associated mortality was not significant with the peri-seasonal baseline period.

DISCUSSION

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

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, 22] and a straightforward variant of these models allowing for insight to a broad public. Due to the use of diverse statistical models, including the different definitions of viral seasons and the various definitions of end-points (*e.g.* culture-confirmed or nonconfirmed influenza), studies are difficult to compare [1–3, 7, 9, 20, 22–28]. Variations of the included study period (and consequently varying influenza virus-activity) and differences in healthcare systems further lead to poor comparability, for example primary care in the Netherlands with a gate-keeping function may affect hospitalisation rates.

In contrast to previous studies [2, 26], which reported annual influenza-associated deaths of 2–7 per 100,000 among 0–1-yr-olds and ~1 per 100,000 among 1–4-yr-olds, the current authors could not detect excess mortality in children during influenza virus-active periods. The present methods may lack sensitivity to detect small excesses of influenza-associated deaths. However, the current study confirmed that among children and 18–64-yr-olds without high-risk medical condi-

TABLE 3 Hospitalisation rates and total winter excess hospitalisation among children associated with influenza virus and respiratory syncytial virus (RSV)

	Weekly incidence per 100000 population				Total winter excess per 100000 population#			
					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
URTIs								
0–1 yr	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 yrs	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 yrs	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¶
LTRIs and PDs								
0–1 yr	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 yrs	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 yrs	2.0	2.0	1.7	2.0	2.5 (1.7–3.2)	None¶	1.8 (1.1–2.5)	None¶
Other								
0–1 yr	17.1	12.7	13.0	13.3	34.1 (28.5–39.8)	31.9 (26.2–37.6)	None¶	None¶
2–4 yrs	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 yrs	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)+

Data are presented as mean (95% confidence interval), unless otherwise stated. URTI: upper respiratory tract infection; LRTI: lower respiratory tract infection; PD: pulmonary disease. #: 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 RSV; ¶: no nonsignificant excess; +: nonsignificant excesses.

TABLE 4 Hospitalisation rates and estimated total winter excess hospitalisation among adults associated with influenza virus and respiratory syncytial virus (RSV)

	Weekly incidence per 100000 population				Total winter excess per 100000 population#			
					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
URTIs								
18–49 yrs								
nonhigh-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¶
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 yrs								
nonhigh-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¶
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 yrs	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)
LRTIs and PDs								
18–49 yrs								
nonhigh-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¶
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 yrs								
nonhigh-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¶
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 yrs	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)
Cardiovascular complications								
18–49 yrs								
nonhigh-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¶
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 yrs								
nonhigh-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¶
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)
Other								
18–49 yrs								
nonhigh-risk	0.6	0.5	0.5	0.5	0.2 (-0.1–0.4)+	0.3 (0.1–0.5)	None¶	None¶
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 yrs								
nonhigh-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)+
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)+

Data are presented as mean (95% confidence interval), unless otherwise stated. URTI: upper respiratory tract infection; LRTI: lower respiratory tract infection; PD: pulmonary disease. #: 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 RSV; ¶: no nonsignificant excess; +: nonsignificant excesses.

tions, the highest influenza-associated excess hospitalisation occurs in the youngest children [3, 9, 20, 22–25]. This suggests that this target group may benefit particularly from influenza vaccination, certainly when influenza-related primary care visits and parental work absenteeism are also taken into account [28]. Furthermore, it is also thought that children are the main disseminators of influenza [29], and vaccinating children may therefore limit the spread of infection in the community. The influenza vaccine is, however, currently not licensed for children aged <6 months, and evidence for the efficacy and effectiveness of the vaccine in children under 2 yrs of age is limited [30].

The present study indicates that influenza virus-active periods were associated with excess mortality among 50–64-yr-olds. Unfortunately, the study was not able to estimate which part of this excess occurred in low-risk individuals, as information about risk status was not available in the mortality figures. Influenza-associated hospitalisation was, however, significant among low-risk 50–64-yr-olds. A recent study was not able to

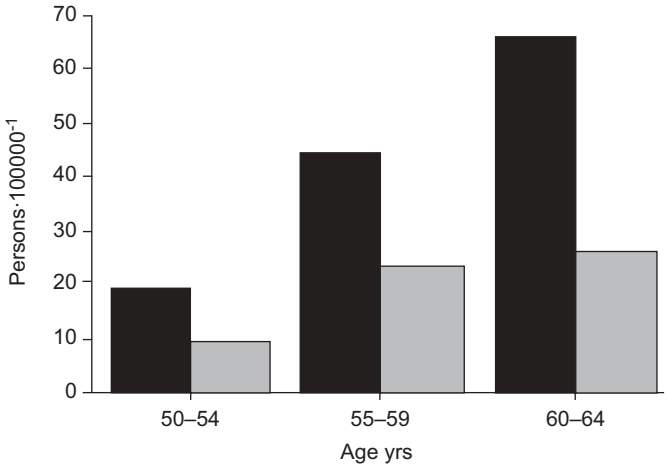

FIGURE 2. Influenza-associated winter hospitalisation among low-risk 50–64-yr olds. ■: *versus* summer baseline period; ■: *versus* peri-seasonal baseline period.

demonstrate influenza-associated hospitalisation in this group, but this was probably due to limited statistical power [7]. The hospitalisation rates found in the current study among low-risk 50–64-yr-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-yr-olds. Obviously, these hospitalisations are expected to have a large impact on the healthcare system and financial resources. Both influenza-associated excess mortality and hospitalisation, in particular for CVC, increased with age, indicating that 60–64-yr-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 [31–34]. Apart from the potential health gain, cost-effectiveness analyses taking into account both direct and indirect influenza-associated costs, like

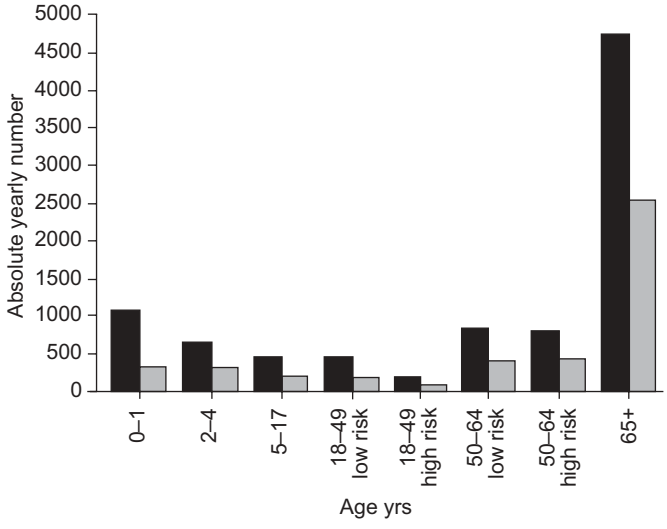

FIGURE 3. Influenza-associated hospitalisation burden in the Netherlands. ■: *versus* summer baseline period; ■: *versus* peri-seasonal baseline period.

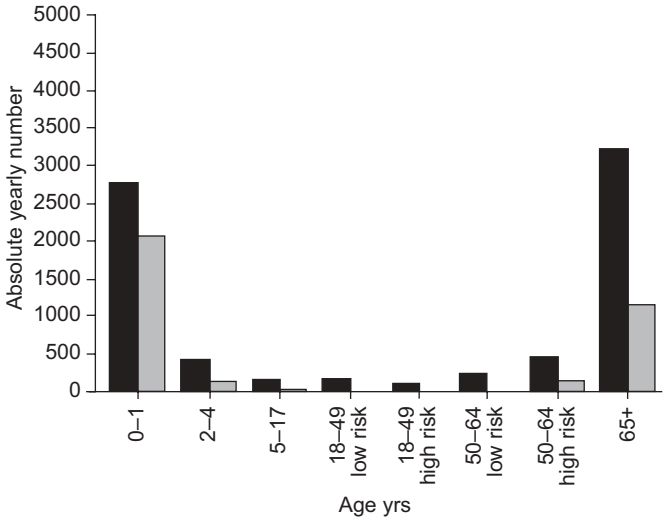

FIGURE 4. Respiratory syncytial virus-associated hospitalisation burden in the Netherlands. ■: *versus* summer baseline period; ■: *versus* peri-seasonal baseline period.

absenteeism from work, are important to direct decisions to change vaccination policy.

Despite the high influenza vaccination coverage among the elderly in the Netherlands (70–80%), influenza-associated mortality appeared high among the elderly in the present study. It is known, however, that the immunogenicity of the influenza vaccine decreases with age after the age of 65 yrs, which may lead to reduced effectiveness [31, 35]. This emphasises the need for further improvement of the protection against influenza, particularly in the elderly.

As expected, the highest RSV-related excess hospitalisation occurred in the youngest age group [36, 37], and this burden appeared considerably higher than that associated with influenza. The RSV-related mortality in this age category could not be demonstrated. Due to the same power problems applicable to the influenza-related mortality among young children in the current study, the possibility of RSV-associated mortality in this age category could not be excluded. Previous studies reported annual RSV-associated deaths of 5–8 per 100,000 among infants aged 0–12-months and ~1 per 100,000 among 1–4-yr-olds [2, 26]. Significant excess hospitalisation was also demonstrated among adults, especially the elderly. Moreover, RSV-active periods appeared associated with excess mortality among 50–64-yr-olds and the elderly. The main RSV-associated hospitalisations were for respiratory indications and, to a lesser extent, for CVC compared with influenza-associated hospitalisation, which is in agreement with a former study [25].

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 led to hospitalisation or death. Therefore, the results should be interpreted cautiously. The burden will, however, be underestimated by only recording laboratory-confirmed influenza and RSV-infections, due to underdiagnosis and under-reporting, but also in the case of secondary complications (like bacterial

infections or other possible complications such as cardiovascular diseases). Moreover, the influenza virus is a pathogen that has been extensively studied and is known to be responsible for considerable annual morbidity and mortality. In contrast, the role of RSV in causing morbidity and mortality, especially among adults, is less clear. In the current study, a clear excess mortality and morbidity was found during RSV-active periods. However, most of the present RSV surveillance data were reported in children, and although the present authors assumed that RSV-activity among adults parallels that in children, this has not yet been suitably proven [38]. It is possible therefore, that some of the RSV- and influenza-associated morbidity could have been misclassified, as in all other excess studies. This stresses the importance for age-specific RSV-surveillance and should be addressed in future studies.

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 the application of this probably underestimated the virus-related burden, because excess rates are determined over periods in which influenza virus and RSV are active albeit to a lesser extent (weeks with <5% of season's total number of isolates). Conversely, 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 baseline period as reference. In other words, by applying the peri-seasonal baseline period as reference, the present authors 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 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 the current 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). Unfortunately, the seasonal pattern of some recently discovered coronaviruses and the human metapneumovirus could not be assessed as no surveillance data were available during the study period.

The major strength of the current study is the nationwide inclusion of 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. Furthermore, the study period covered 6 yrs with different viral attack rates.

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

APPENDIX

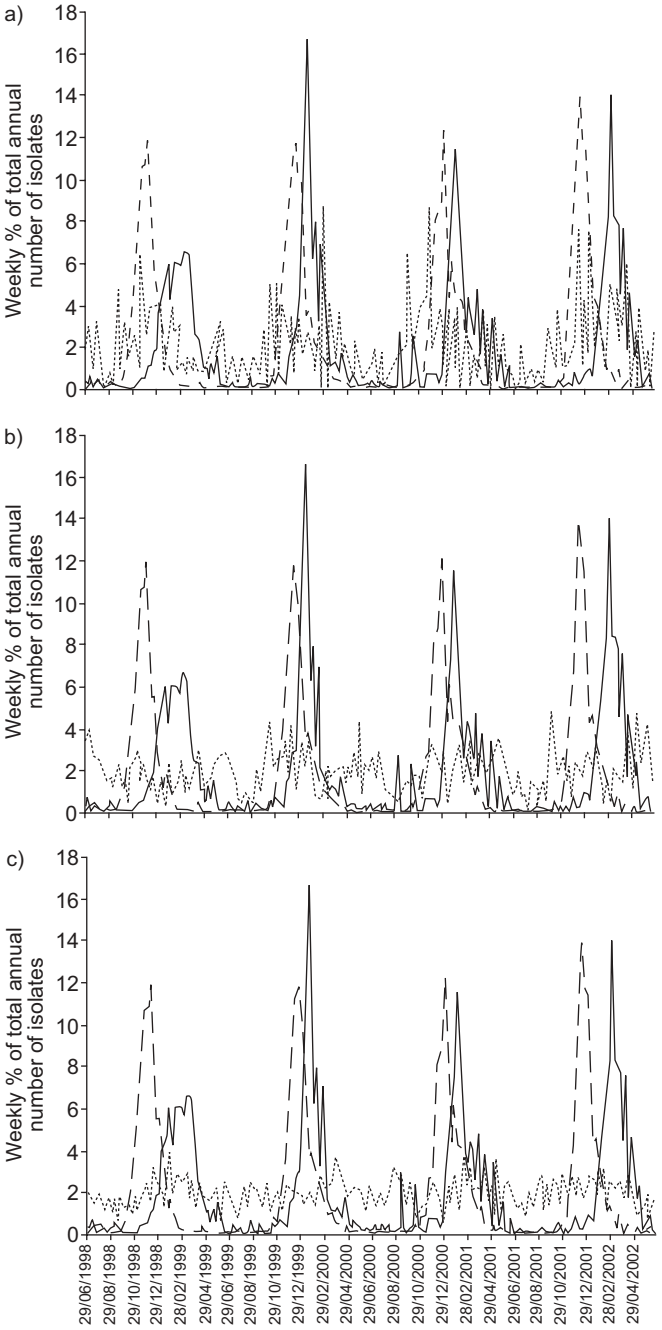

FIGURE 5. Respiratory viral activity in the Netherlands in the period 1998–2002. ——: influenza viruses; – – –: respiratory syncytial virus; · · · · ·: other viruses (a) rhinovirus, b) para-influenza virus, c) adenovirus).

REFERENCES

1 Simonsen L, Clarke MJ, Williamson GD, Stroup DF, Arden NH, Schonberger LB. The impact of influenza epidemics on mortality: introducing a severity index. *Am J Public Health* 1997; 87: 1944–1950.
2 Thompson WW, Shay DK, Weintraub E, *et al.* Mortality associated with influenza and respiratory syncytial virus in the United States. *JAMA* 2003; 289: 179–186.
3 Thompson WW, Shay DK, Weintraub E, *et al.* Influenza-associated hospitalizations in the United States. *JAMA* 2004; 292: 1333–1340.
4 Van Essen GA, Palache AM, Forleo E, Fedson DS. Influenza vaccination in 2000: recommendations and vaccine use in 50 developed and rapidly developing countries. *Vaccine* 2003; 21: 1780–1785.
5 Advisory Committee on Immunization Practices, Smith NM, Bresee JS, *et al*. Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006; 55: 1–42.
6 Groll DL, Thomson DJ. Incidence of influenza in Ontario following the Universal Influenza Immunization Campaign. *Vaccine* 2006; 24: 5245–5250.
7 Mullooly JP, Bridges CB, Thompson WW, *et al.* Influenza- and RSV-associated hospitalizations among adults. *Vaccine* 2007; 25: 846–855.
8 Centers for Disease Control and Prevention. Surveillance for laboratory-confirmed, influenza-associated hospitalizations - Colorado, 2004-05 influenza season. *MMWR Morb Mortal Wkly Rep* 2005; 54: 535–537.
9 Poehling KA, Edwards KM, Weinberg GA, *et al.* The under recognized burden of influenza in young children. *N Engl J Med* 2006; 355: 31–40.
10 Hament JM, Kimpen JL, Fleer A, Wolfs TF. Respiratory viral infection predisposing for bacterial disease: a concise review. *FEMS Immunol Med Microbiol* 1999; 26: 189–195.
11 Davis MM, Taubert K, Benin AL, *et al.* Influenza vaccination as secondary prevention for cardiovascular disease: a science advisory from the American Heart Association/American College of Cardiology. *J Am Coll Cardiol* 2006; 48: 1498–1502.
12 Madjid M, Awan I, Ali M, Frazier L, Casscells W. Influenza and atherosclerosis: vaccination for cardiovascular disease prevention. *Expert Opin Biol Ther* 2005; 5: 91–96.
13 Zambon MC, Stockton JD, Clewley JP, Fleming DM. Contribution of influenza and respiratory syncytial virus to community cases of influenza-like illness: an observational study. *Lancet* 2001; 358: 1410–1406.
14 Han LL, Alexander JP, Anderson LJ. Respiratory syncytial virus pneumonia among the elderly: an assessment of disease burden. *J Infect Dis* 1999; 179: 25–30.
15 Nicholson KG. Impact of influenza and respiratory syncytial virus on mortality in England and Wales from January 1975 to December 1990. *Epidemiol Infect* 1996; 116: 51–63.
16 Falsey AR, Hennessey PA, Formica MA, Cox C, Walsh EE. Respiratory syncytial virus infection in elderly and high-risk adults. *New Eng J Med* 2005; 352: 1749–1759.
17 Venkatesh MP, Weisman LE. Prevention and treatment of respiratory syncytial virus infection in infants: an update. *Expert Rev Vaccines* 2006; 5: 261–268.
18 Van den Brandhof WE, Kroes ACM, Bosman A, Peeters MF, Heijnen MLA. [Reporting virological diagnostics in The Netherlands. Representativity of data from the weekly viral reports.] *Infectieziekten Bulletin* 2002; 13: 110–113.
19 Heijnen MLA, Bartelds AIM, de Jong JC, Rimmelzwaan GF, Wilbrink B. [Influenza and RS virus infections during the winter 2000/2001.] *Infectieziekten Bulletin* 2001; 12: 2.
20 Izurieta HS, Thompson WW, Kramarz P, *et al.* Influenza and the rates of hospitalization for respiratory disease among infants and young children. *N Engl J Med* 2000; 342: 232–239.
21 Tacken M, Verheij R, Mulder J, van den Hoogen H, Braspenning J. Monitoring griepvacinatecampagne 2004. [Monitoring influenza vaccination campaign 2004.] Landelijk Informatie Netwerk Huisartsenzorg, Utrecht, The Netherlands; 2004.
22 O'Brien MA, Uyeki TM, Shay DK, *et al.* Incidence of outpatient visits and hospitalizations related to influenza in infants and young children. *Pediatrics* 2004; 113: 585–593.
23 Schanzer DL, Langley JM, Tam TWS. Hospitalization attributable to influenza and other viral respiratory illnesses in Canadian children. *Pediatr Infect Dis J* 2006; 25: 795–800.
24 Grijalva CG, Craig AS, Dupont WD, *et al.* Estimating influenza hospitalizations among children. *Emerg Infect Dis* 2006; 12: 103–109.
25 Neuzil KM, Zhu Y, Griffin MR, *et al.* Burden of interpandemic influenza in children younger than 5 years: a 25-year prospective study. *J Infect Dis* 2002; 185: 147–152.
26 Fleming DM, Pannell RS, Cross KW. Mortality in children from influenza and respiratory syncytial virus. *J Epidemiol Community Health* 2005; 59: 586–590.
27 Wong CM, Yang L, Chan KP, *et al.* Influenza-associated hospitalization in a subtropical city. *PLoS Med* 2006; 3: e121.
28 Heikkinen T, Silvennoinen H, Peltola V, *et al.* Burden of influenza in children in the community. *J Infect Dis* 2004; 190: 1369–1373.
29 Heikkinen T. Influenza in children. *Acta Paediatr* 2006; 95: 778–784.
30 Smith S, Demicheli V, Di Pietrantonj C, *et al.* Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev* 2006; 1: CD004879.
31 Gross PA, Hermogenes AW, Sacks HS, Lau J, Levandowski RA. The efficacy of infuenza vaccine in elderly persons. A meta-analysis and review of the literature. *Ann Intern Med* 1995; 123: 518–527.
32 Govaert TM, Thijs CT, Masurel N, Sprenger MJ, Dinant GJ, Knottnerus JA. The efficacy of influenza vaccination in elderly individuals. A randomized double-blind placebo-controlled trial. *JAMA* 1994; 272: 1661–1665.
33 Nichol KL, Nordin J, Mullooly J, Lask R, Fillbrandt K, Iwane M. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Eng J Med* 2003; 348: 1322–1332.
34 Vu T, Farish S, Jenkins M, Kelly H. A meta-analysis of effectiveness of influenza vaccine in persons aged 65 years and over living in the community. *Vaccine* 2002; 20: 1831–1836.
35 Goodwin K, Viboud C, Simonsen L. Antibody response to influenza vaccination in the elderly: a quantitative review. *Vaccine* 2006; 24: 1159–1169.

36 Lee MS, Walker RE, Mendelman PM. Medical burden of respiratory syncytial virus and parainfluenza virus type 3 infection among US children. Implications for design of vaccine trials. *Hum Vaccin* 2005; 1: 6–11.

37 Rietveld E, Vergouwe Y, Steyerberg EW, Huysman MW, de Groot R, Moll HA. Hospitalization for respiratory syncytial virus infection in young children: development of a clinical prediction rule. *Pediatr Infect Dis J* 2006; 25: 201–207.

38 Fleming DM, Elliot AJ, Cross KC. Morbidity profiles of patients consulting during influenza and respiratory syncytial virus active periods. *Epidemiol Infect* 2007; 12: 1–10.