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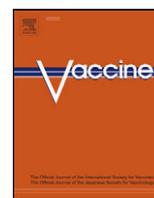
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## Excess drug prescriptions during influenza and RSV seasons in the Netherlands: Potential implications for extended influenza vaccination

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### ABSTRACT

Influenza and respiratory syncytial virus (RSV) infections are responsible for considerable morbidity, mortality and health-care resource use. For the Netherlands, we estimated age and risk-group specific numbers of antibiotics, otologicals and cardiovascular prescriptions per 10,000 person-years during periods with elevated activity of influenza or RSV, and compared these with peri-seasonal rates. Data were taken from the University of Groningen in-house prescription database ([www.iadb.nl](http://www.iadb.nl)) and virological surveillance for the period 1998–2006. During influenza and RSV periods excess antibiotic prescriptions were estimated for all age groups. In the age groups 0–1 and 2–4 years, excess antibiotic prescriptions during periods with elevated RSV activity (65% and 59% of peri-seasonal rates) exceeded the surpluses estimated during the influenza-activity periods (24% and 34% of peri-seasonal rates) while for otologicals excess prescriptions were higher for influenza (22% and 27%) than for RSV (14% and 17%). Among persons of 50 years and older, notably those without medical high-risk conditions, excess prescriptions for cardiovascular medications were estimated during the influenza periods at approximately 10% (this was also already seen in persons aged 45–49). Our results may have implications for influenza vaccination policies. In particular, extension of influenza vaccination to groups of non-elderly adults and young children may lower excess prescriptions during these influenza periods for all three types of drug prescriptions investigated.

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### 1. Introduction

In many countries annual influenza vaccination has been recommended for the elderly and persons with high-risk medical conditions. In the Netherlands until 2007, the age-threshold for such vaccination was 65 years for non-high-risk groups. In 2008, this threshold was lowered to include all persons aged 60 years and older [1]. In addition in the Netherlands, all high-risk groups are vaccinated, including individuals suffering from chronic conditions, respiratory diseases, cardiac diseases, diabetes mellitus, renal failure, those being immunocompromised and individuals aged less than 18 years of age on chronic salicylates use [1]. Vaccination rates among these high-risk groups under 65 years of age ranged from

66% to 83% in the Netherlands in 2005 [2]. Persons of 65 years and older with a medical indication showed higher vaccination coverages compared to those of the same age without such an indication, at 90% and 76% in 2005, respectively [2]. Influenza may cause acute bronchitis and pneumonia in high-risk groups and elderly and may lead to exacerbations of underlying chronic medical conditions such as cardiovascular diseases, asthma and diabetes, potentially leading to hospitalisations and death. Prevention of influenza infection by vaccination is of high importance for these groups with an increased risk for complications from influenza infection [3–5].

Although some countries recommend routine influenza vaccination among children aged 6 months to 2 years, clinical data about the impact of vaccination are limited [1,6]. Yet, vaccination of all healthy children in this age group could be cost-effective or even cost-saving for some societal settings [6]. In the Netherlands, universal influenza vaccination of such children is in debate, however yet the vaccine efficacy and effectiveness for this specific age group is not considered to be sufficiently demonstrated [7–9]. Therefore, the Dutch Health Council concluded in 2007, not yet to start with

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influenza vaccination of these groups [1]. Comparable conclusions were made for healthy children aged 2 years and older. Although vaccination was shown to be effective for these children, influenza was considered not to cause serious morbidity or mortality in the Netherlands in those groups [1].

Next to influenza virus A and B, respiratory syncytial virus (RSV) has been shown to cause similar types of complications, including complications in the respiratory tract. RSV is often recognized as a cause of morbidity and mortality among both children and adults, contributing to a major burden of illness [10–17]. No preventive vaccine is yet marketed for RSV.

In general, it is difficult to estimate the individual contributions of influenza and RSV to the aforementioned disease burdens accurately as influenza and RSV co-circulate during winter seasons. For burden of disease often the label Influenza Like Illnesses (ILI) is considered to primarily comprise disease due to influenza infections, however known to potentially comprise various other agents inclusive RSV, with the identification of the relative contributions of both viruses being strongly hampered [18–21]. In particular, even further viral agents, such as adeno-, parainfluenza-, and corona-viruses may contribute to the burden of ILI [21,22]. For exactly analysing the burdens of disease of influenza and RSV separately, which is the goal of our current paper, ILI is therefore an inappropriate concept. Therefore, we chose to analyse isolates exactly related to the respective causal agents.

Given the potential complications of influenza and RSV, one may expect excess health-care resource utilization during epidemics [23]. Studies estimating such excess resource utilization have previously been directed to hospital admissions and GP-visits, but there is as yet hardly any information on the association between the occurrence of influenza and RSV and the use of medications among the general population [24]. Drug-use for specific complications of influenza and RSV could certainly temporarily be elevated. In particular, prescriptions for antibiotics, otologicals and cardiovascular medication may be elevated, dispensed for otitis media, cardiac complications, respiratory illness and other pulmonary complications. To address this topic, we investigated the association between weekly reported RSV and influenza isolates in the Netherlands and the weekly number of prescription drugs dispensed by Dutch pharmacies, in particular those for antibiotics, otologicals and cardiovascular drugs.

From the preventive point of view, high influenza-associated drug-use may justify more extended use of preventive measures, such as influenza vaccination. In particular, it may enhance the health-economic profile of extended influenza vaccination for currently yet unvaccinated groups. As such, our research may contribute to discussions as to whether, for example, young children should be vaccinated or whether the age limit of the vaccination program should be lowered further.

## 2. Data and methods

### 2.1. Virological surveillance and study period

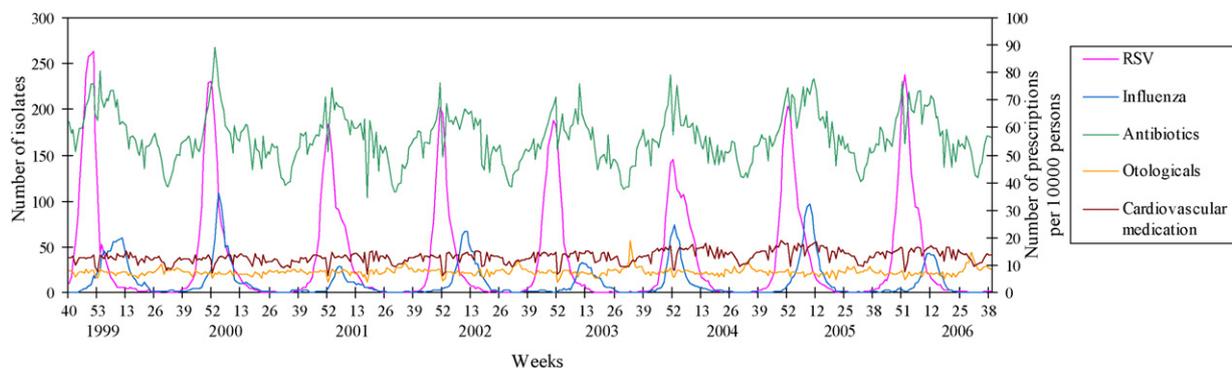
During 1998–2006, the Dutch Working Group on Clinical Virology gathered data from 20 laboratories throughout the Netherlands, testing clinical specimens for respiratory viruses, including RSV and influenza A and B. The number of patients who tested positive for RSV or influenza was reported on a weekly basis. In the absence of any drastic changes in recruiting and testing of specimens the weekly time series can validly be conceived as representing the actual time trend, without requiring any corrections to be applied on the data. To exclude weekly random fluctuations a 3-week moving average was used for presentation (Fig. 1) and for defining the specific weeks exhibiting elevated activity for influenza and RSV.

Two methods for defining weeks with elevated activity of influenza and RSV were applied. The first method defined a week with elevated activity as one with a moving average of more than two times the gross overall average weekly number from week 40 in 1998 onwards to week 39 of 2006 (week 1 obviously being the 1st week in January; week 40 generally being considered as the start of the influenza season). Following Jansen et al., the second method defined the weeks with elevated activity as those weeks from any period of at least 2 consecutive weeks, with each individual week accounting for over 5% of the season's total number of influenza- or RSV-positive specimens [18]. From both methods, it appeared that periods consisting of a number of subsequent weeks resulted, rather than individual weeks or short periods of, for example, 2 weeks only. Such periods would be expected – and were indeed found – to be between week 40 and week 20 in the next year (the non-summer season) [18,25].

The weeks that contained both influenza and RSV activity were excluded for defining the periods with elevated activity, given the difficulty to separate out the individual influences in these weeks with combined activity. As a result, only those weeks with either elevated influenza or RSV were analyzed. Furthermore, a per-season was defined, containing the weeks from week 40 up to and including week 20 of the next year, which did not belong to the influenza or the RSV periods (seasons). The weeks from week 21 up to and including week 39 were labelled “summer”.

### 2.2. Population

Information on drug-use in the population was provided by a University of Groningen in-house prescription database ([www.iadb.nl](http://www.iadb.nl)). The database iadb.nl contains prescription, demographic and population data of 500,000 persons adherent to 50 pharmacies in the North and East of the Netherlands. For analytical purposes, the prescriptions were divided over 5-year age categories.



**Fig. 1.** Number of RSV- and influenza-positive specimens (3-week moving averages), the number prescriptions for antibiotics and otologicals and first prescriptions for cardiovascular medication, all for all age groups aggregated.

The age category 0–4 years was further divided in the ages 0–1 and 2–4, to enable analysis of infants separately. For presentation the following categorization was applied: 0–1, 2–4, 5–19, 20–49, 50–54, 55–59, 60–64 and 65+. The exact age of any person was determined every year on the 1st of October, close to the period in which in the Netherlands the invitations for influenza vaccination for risk groups are sent out by the GPs, supposedly just prior to the season with increased risk for influenza epidemics from October onwards to May. The annual total population sizes were based on estimates for the 1st of January by the local authorities in the places where the pharmacies are located.

Persons who received one of the studied drugs were divided in high-risk and low-risk groups for influenza. The respective populations belonging to both groups were estimated using prescriptions as a proxy, for those medications that are consistent with high-risk indications as specified by the Dutch Health Council [1] and the Dutch GPs (<http://nhg.artsennet.nl>) and that are uniquely prescribed for these indications [26]. For example, dornase alfa, a drug prescribed for cystic fibrosis, was included to define persons with respiratory diseases. Other medications for cystic fibrosis, such as acetylcysteine, are also prescribed for cough and were therefore not included. Table 1 lists these drugs specifically. For heart medication, diuretic sulfonamides were included. Other diuretics used for lowering blood pressure were excluded, as high-blood pressure is not a high-risk identified condition. Furthermore, only calcium antagonists with ATC-code C08D were included as only these are assumed to have cardiac effects. Beta blockers and RAAS system agents were excluded as these are not exclusively prescribed for cardiac diseases, but also, for example, for high-blood pressure only. For renal diseases, medication for the treatment of hyperkalemia and hyperphosphatemia, and antianemic preparations and sulfonamides were included as these are often prescribed for dialysis or renal insufficiency. To identify immunocompromised patients, immunosuppressives were included, which can be prescribed, for example, for patients after organ transplantation. Also HIV medications were included as also HIV-patients are listed as high-risk group.

As mentioned, in the Netherlands, influenza vaccination is recommended to those at the increased risk of complications based on

specific medical conditions. To determine which specific patients should be labelled as belonging to the high-risk group, the recommendations of the Dutch Health Council [1] and the guidelines of the Dutch GPs (<http://nhg.artsennet.nl>, accessed 24th September 2007) for influenza and high-risk indications were used [26]. In particular, persons were labelled belonging to the high-risk group if they had two or more prescriptions from the same group of medications included on the list, on two different dates in the year before the first of October. The latter was supposed to guarantee that the condition would be chronic in that specific year (note that a person's risk status may change from year to year). The population size of the high-risk group was subsequently determined on the 1st of October by counting the number of high-risk persons in iadb.nl; the rest of the population was assumed at low risk.

### 2.3. Classification of prescriptions

We specifically directed our analysis to the drug groups of antibiotics, otologicals and cardiovascular drugs, as these drugs may be considered for those complications of both viral infections that have yet been published in the scientific literature [23,24,27–29]. From iadb.nl, prescriptions of antibiotics (ATC-code J01), otologicals (ATC-code S02) and medications for the cardiovascular system (ATC-code C) were selected.

Antibiotics are commonly prescribed for the treatment of acute otitis media (AOM), in particular for young children in which AOM accounts for approximately half of all antibiotics courses delivered [30–32]. Otologicals may also be prescribed for AOM, despite that they are not recommended by the Dutch College of General Practitioners (NHG) [29]. In addition, more than average numbers of antibiotics may be prescribed for elderly persons with ILI during periods with elevated activity, as particularly this group may develop acute respiratory illnesses (for example, pneumonia) as a complication of the viral infection (trimethoprim and nitrofurantoin were excluded from the analysis as they are prescribed primarily for urinary tract infections) [33]. For antibiotics and otologicals both initial and next prescriptions within the same year were considered.

**Table 1**  
Medications considered to be specific for high-risk indications.

Disease	Medication	ATC code
Respiratory diseases	Drugs for obstructive airway diseases	R03
	Dornase alfa	R05CB13
	Tuberculosis medication	J04A
Cardiac diseases	Acetylsalicylic acid	B01AC06
	Carbasalate calcium	B01AC08
	Clopidogrel	B01AC04
	Organic nitrates	C01DA
	Antiarrhythmics	C01B
	Digoxin	C01AA05
	Diuretics: sulfonamides	C03CA
	Calcium channel blockers	C08D
	Diabetes	Insulin (analogue)
Blood glucose lowering medication		A10B
Chronic renal disease	Drugs for treatment of hyperkalemia and hyperphosphatemia	V03AE
	Other antianemic preparations	B03XA
	Erythropoietin	B03XA01
	Darbepoetin alfa	B03XA02
	Diuretics (sulfonamides only)	C03CA
Immunocompromised	Immunosuppressive agents	L04
	HIV-medication: direct acting antivirals	J05A EFGX
	Oral corticosteroids	H02AB
Children below 18 years old who are taking long term salicylates	Salicylic acid and derivatives	N02BA01 N02BA15 N02BA51

**Table 2**  
Exact weeks defining periods with elevated activity.

Year	Influenza <sup>a</sup> (weeks)	Influenza <sup>b</sup> (weeks)	RSV <sup>a</sup> (weeks)	RSV <sup>b</sup> (weeks)	Peri-season (weeks)	Summer (weeks)
1998–1999	1–14	1–14	44–53	44–53	40–43, 15–20	21–39
1999–2000	51–9	4–9	47–3	47–50	40–46, 10–20	21–39
2000–2001	4–6	–	49–7	49–3, 7	40–48, 8–20	21–39
2001–2002	6–16	6–16	48–3	48–3	40–47, 4–5, 17–20	21–39
2002–2003	9–15	9–15	45–2	45–2	40–44, 3–8, 16–20	21–39
2003–2004	50–5	–	49–7	49, 6–7	40–48, 8–20	21–39
2004–2005	3–14	6–14	49–5	49–2	40–48, 15–20	21–39
2005–2006	9–15	9–15	48–7	48–7	40–47, 8, 16–20	21–39
Total number of weeks	73	54	81	62	131	152

<sup>a</sup> Inclusive weeks with combined activity of both influenza and RSV.

<sup>b</sup> Weeks with combined activity excluded, period used for actual analysis.

It is well known that influenza-related complications are more prevalent among persons with cardiovascular and other chronic diseases than in persons without such underlying conditions [4,34]. In persons of 65 years and older with high-risk conditions an increased rate of hospitalisation for cardiac problems has been reported [17]. Some further recent studies suggest that there might also be an association between cardiovascular problems and influenza epidemics among groups without any cardiovascular history yet, such as the elderly or even among those aged below 65 years of age [23,35]. For analysing cardiovascular medications, only first prescriptions were considered as our current interest was to investigate whether the viral infections were related to new cardiovascular disease and/or exacerbations of existing – yet untreated – background cardiovascular conditions, rather than identify chronic medications for cardiovascular diseases (note that chronic cardiovascular medication use was used as a criterion for assigning persons to the high-risk group). A prescription was defined as a first prescription when a person had not had a prescription for the same drug or a drug from the same subgroup in the year before that specific prescription.

#### 2.4. Statistics

After the various periods of elevated activity were determined, the number of prescriptions in the weeks belonging to the influenza and RSV periods/seasons were compared to the number of prescriptions in the peri-season. For comparative purposes also results for comparing with the summer season are presented. This was done in every age group for the total population, the high-risk group and the low-risk group. Incidence rates were calculated and corresponding 95%-confidence intervals were estimated [36]. The incidence rate ( $I$ ) was calculated as the weekly number of prescriptions per 10,000 person-years:

$$I = \sum_{i=1}^n \frac{P_i}{(Nn)/52} \times 10,000$$

with  $P_i$  being the number of prescriptions in week  $i$  of a season (influenza, RSV, peri or summer),  $n$  the number of weeks of that specific period of interest and  $N$  the population size (per age group, for high risk or for low risk). The division by 52 is to transfer person-week estimates into person-years (for 2 years 53 instead of 52 had to be used). Microsoft Office Excel 2003 was used for processing the data, calculations and graphics.

### 3. Results

#### 3.1. Periods with elevated activity of influenza and RSV

During the study period, the average weekly number of influenza-positive and RSV-positive specimens were 11.77 and

36.90, respectively. The first method for defining the periods of elevated activity using two times the average number of isolates per week as a lower limit (23.54 for influenza and 73.80 for RSV) resulted in Table 2, showing the weeks which were labelled as belonging to the influenza, RSV, peri- and summer periods.

The second method, defining the periods with elevated activity as at least two consecutive weeks in which each week accounted for over 5% of the season's total number of RSV- or influenza-positive specimens yielded comparable results (data not shown). Hereafter, only for those results where both methods differed, the results of both methods are presented otherwise the results of only the first method are shown.

Obviously, periods with elevated activity and the peri-season changed from year to year, both in length (the summer season of course always ranged from week 21 up to and including week 39 of the next year). In some years overlap in influenza and RSV activity weeks were seen, in which case weeks were excluded. In fact, in the years 2000–2001 and 2003–2004 there was no influenza-only period left (although 4 weeks remained in 2000–2001 if the 2nd method was used).

**Table 3**

Person-years during periods of elevated activity per age group for the total population, high-risk group and low-risk group.

Age group	Influenza	RSV	Peri-season	Summer
Total population				
0–1	11499	13452	28651	33044
2–4	17248	20177	42977	49566
5–19	86692	100726	213531	246961
20–49	238725	277212	589120	680702
50–54	32349	37811	80150	92574
55–59	27200	32184	67792	78353
60–64	20977	24538	51696	59863
65+	66848	77534	164202	190012
High-risk group				
0–1	393	454	970	1118
2–4	668	774	1662	1914
5–19	2785	3246	6882	7954
20–49	10871	12823	27188	31349
50–54	4047	4795	10180	11726
55–59	4838	5830	12331	14187
60–64	5243	6210	13052	15089
65+	30724	36035	76397	88201
Low-risk group				
0–1	11106	12998	27681	31926
2–4	16581	19403	41315	47652
5–19	83907	97480	206650	239007
20–49	227853	264389	561932	649353
50–54	28301	33015	69970	80848
55–59	22362	26354	55461	64166
60–64	15734	18328	38644	44774
65+	36124	41499	87806	101811

**Table 4**

Excess drug prescriptions for the periods with elevated activity compared to the peri-season, shown as numbers of prescriptions per 10,000 person-years (as % of peri-seasonal levels).

Seasons	0–1 years	2–4 years	5–19 years	20–49 years	50–54 years	55–59 years	60–64 years	65+ years
<b>Antibiotics</b>								
RSV total	3791 (65%)	2326 (59%)	248 (15%)	236 (10%)	264 (8.9%)	431 (13%)	572 (15%)	669 (13%)
Influenza total	1397 (24%)	1328 (34%)	417 (25%)	407 (18%)	461 (15%)	615 (18%)	796 (21%)	761 (14%)
Influenza high risk	–	–	819 (20%)	761 (13%)	717 (12%)	827 (13%)	1059 (16%)	846 (12%)
Influenza low risk	–	–	404 (25%)	393 (18%)	432 (17%)	586 (22%)	721 (24%)	722 (19%)
<b>Otologicals</b>								
RSV total	79 (14%)	90 (17%)	a	a	a	a	a	a
Influenza total	126 (22%)	142 (27%)	a	a	a	a	a	a
<b>Cardiovascular medication</b>								
RSV total	–	–	a	a	a	a	a	a
Influenza total	–	–	a	b	110 (8.7%)	122 (7.4%)	159 (7.4%)	196 (6.3%)
Influenza high risk	–	–	a	a	a	a	a	130 (3.3%)
Influenza low risk	–	–	a	b	110 (11%)	170 (13%)	163 (10%)	269 (11%)

The number of persons was insufficient for valid estimation.

<sup>a</sup> Result not statistically significant.

<sup>b</sup> Although borderline significant not shown here for the whole age-group as further 5-year age-group specific analyses revealed that significance was related only to a significant and clinically relevant surplus for the age category 45–49: 113.12 (12.95%) and 122.78 (17.06%) for the total population and low-risk group, respectively.

### 3.2. Population

Table 3 presents the number of person-years for the influenza, RSV, peri-season and summer periods per age and risk group. For infants and children aged 2–4, the high-risk group was very small with 393 person-years in the influenza period and 454 person-years for the RSV period, and therefore only the figures for both low- and high-risk groups taken together were used for these ages. Furthermore, in all age groups the number of person-years in the high-risk group was lower than the numbers in the low-risk group. We also note, as expected, that the older age groups contained relatively more person-years in the high-risk group than the younger age groups.

### 3.3. Isolates and prescriptions

Fig. 1 shows the number of positive findings for RSV and influenza per week. The annual influenza and RSV epidemics are clearly seen, as is the overlap in some years. Also the number of (first) prescriptions per 10,000 persons for antibiotics, otologicals and cardiovascular medication is plotted for the total population. In particular, for antibiotics a clear pattern is visible in which during influenza and RSV activity periods a peak in antibiotic use occurs. Additionally, we notice that in the younger age groups amoxicillin was the mostly prescribed antibiotic, whereas from the age group 5–19 onwards other antibiotics were mostly prescribed (data not shown).

### 3.4. Comparative statistics

The excess prescriptions per 10,000 person-years during the influenza and RSV periods are presented in Table 4, as compared to the peri-season. We noted that both methods used for estimating the activity periods showed similar results.

The number of prescriptions for antibiotics was significantly elevated during the activity periods in each age group. For the age groups 0–1 and 2–4, excess prescriptions were highest in the RSV periods, in the older age groups surpluses were higher during the influenza periods. For influenza, the low-risk group showed higher excess prescriptions compared to the high-risk group. Prescription of otologicals was significantly elevated during the periods of elevated activity, however only in the youngest age groups of infants and children aged 2–4 years. In contrast to antibiotics, excess prescriptions were higher during influenza periods than during RSV periods.

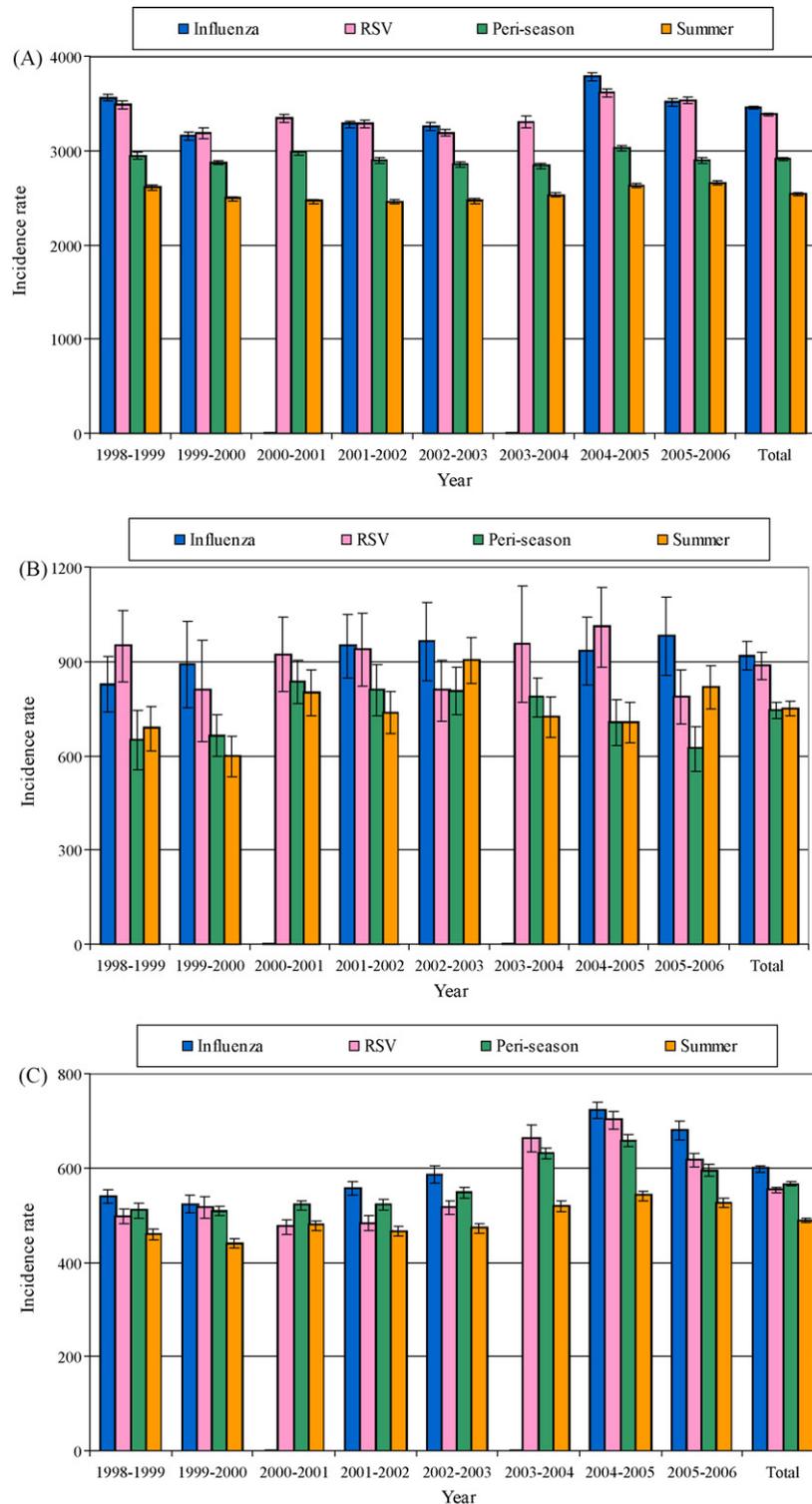
For first cardiovascular medications, the prescription rate in the RSV periods was lower than in the peri-season, although not significant. During the influenza period, higher prescription rates were found for those aged 50 years and older. When the age group of 20–49 was analyzed in 5-year age categories separately, also a significant difference for the age category 45–49 was seen.

Fig. 2 shows the prescription rates per 10,000 person-years and confidence intervals for selected aggregated age groups for the different periods per year separately, as well as for the aggregated years. The incidence rates of antibiotics were increased during the influenza and the RSV periods in comparison with the peri-season (and the summer season). This increase was noticeable for every year. For otologicals, the incidence rate was increased but the confidence intervals were wide and therefore not every year rendered a statistically significant difference during the influenza and RSV periods. For first cardiovascular prescriptions also an increase was noticeable during influenza periods as compared to the peri-season, but again not for every year a significant difference was found. Finally, we note from Fig. 1 that elevations in the influenza and RSV periods are not necessarily followed by relatively lower levels in the peri- and/or summer seasons, suggesting that surpluses detected are actual extra prescriptions that are not “neutralized” by subsequent dips in prescriptions.

## 4. Discussion

Statistically significant excess antibiotic prescriptions during periods with elevated activity of influenza and RSV were found for both viruses in all age groups, each year investigated and irrespective of the method used for exactly defining the influenza or RSV activity periods. For otologicals during both influenza and RSV-active periods, statistically significant surpluses were found in young children only. Oppositely, excess cardiovascular drug prescriptions were identified in adults and elderly in periods with elevated influenza activity.

We generally found a tendency for higher percentages of surpluses in low-risk groups than in high-risk groups. For antibiotics and cardiovascular drugs, this can probably be explained by the fact that individuals belonging to a high-risk group have a higher likelihood of being vaccinated against influenza, lowering the chance of infection and secondary bacterial or cardiovascular complications. This tendency also applied to low-risk elderly as compared to high-risk elderly, despite the fact that this whole group is recommended for vaccination.



**Fig. 2.** Incidence rates and confidence intervals for prescriptions of antibiotics for all ages (A), otologicals for ages 0–4 (B) and cardiovascular medication for ages 45 and older (C).

Some choices in our research should be noted. Specifically, the lower limit for the weekly moving-averaged number of isolates for weeks to be labelled as active was chosen by two different methods. The first used a cut-off of two times the average number of influenza or RSV isolates per week. This limit was chosen to achieve continuous periods per year of weeks subsequently labelled as active, i.e. to guarantee epidemic periods rather than fluctuations. The second method was used to be in concordance with a previously performed

Dutch study using the weeks which accounted for 5% or more of the season's total number of influenza or RSV isolates [18]. In general, both methods resulted in similar results.

By using the influenza and RSV activity periods that excluded weeks of combined activity, possible major influence by the presence of the respective other virus was reduced. However, the exclusion of weeks in which both influenza and RS viruses were active was only necessary in 4 out of the years included in this

analysis. Also, in methodology excluded weeks were not included in counting person-years, so the effect of excluding those weeks maybe limited. Yet, possible influence of any other respiratory virus obviously remains present. However, the impact of these viruses is probably limited, as they may have long periods of marginally increased activity rather than a clear seasonal pattern [18]. Furthermore, complications are expected to be milder compared to influenza and RSV infection [18].

We compared our data for the activity periods with the peri-season, which provided a more conservative estimation of the surpluses than if we would have compared with the summer period. Yet, some underestimation of the surpluses may be introduced in this way. We do feel, however, that comparison with the peri-season is most appropriate, as other potential influences concerning the climate and possibly other viruses that circulate in non-summer periods are probably comparable between the peri-season and the activity periods.

Every year, RSV-positive specimens reached a relatively small and intensive peak around week 52. Earlier studies have shown similar tendencies, with RSV isolates peaking every year around the same time [14,15,37]. This suggests the presence of potential common strict seasonal factors which might increase both the number of isolates and prescriptions; however probably not invalidating the associations and surpluses found in our analyses, which are truly seen and are in line with other studies [14,15,37].

Persons were labelled as belonging to the high-risk group based on specific medication profiles. In particular, persons belonging to the high-risk group were selected based on prescriptions that corresponded rather uniquely to the high-risk indications. Prescriptions potentially meant for other indications, not labelled as high risk, were consistently excluded. Still, it is possible that these selection criteria unjustly labelled individuals as belonging to the high-risk groups. Also, some individuals may have been incorrectly excluded and labelled as non-high-risk.

Finally, one may hypothesize that excess prescriptions are merely shifts in time of extra prescriptions later to be outweighed by dips in prescriptions (sometimes referred to as “the harvesting effect”). Visual inspection of our data however did not give any reason to support this hypothesis in our study. Additionally, a formal statistical comparison of the number of prescriptions during the peri-seasons and during the first 5 weeks after the active seasons did not show any peak-dip pattern (data not shown).

Previously, various investigations have been performed on the association between influenza and RSV epidemics, on the one hand, and hospitalisations, mortality and outpatient visits, on the other [14,17,18,24,33,37–44]. Below, we briefly compare the outcomes, knowing that the validity of making such comparisons between studies is limited due to differences in outcome measurement, statistical models, study period, and health-care system concerned.

Previously, only one study investigated excess antibiotic use during influenza-activity periods in the general population [24]. This study did show that otherwise healthy children get more prescriptions for antibiotics during these influenza periods. However, the surplus reported was relatively low compared to our findings [24]. Two other studies estimated the excess antibiotic prescriptions during both RSV and influenza-active seasons, focussing on specific target groups [33,43]. The first study focussed on patients suffering from chronic lung disease, showing the highest surpluses for the youngest age groups [43]. The latter study showed higher surpluses due to influenza as compared to RSV for those living in nursing homes [33]. Both results are in line with our findings for antibiotics [33,43].

Several other studies indicate that, in general, both during RSV and influenza-activity periods, infants and elderly show the highest morbidity and mortality rates [14,18,24,37,39–44]. This is certainly in line with our findings on excess antibiotic and otological

prescriptions among the youngest age groups and cardiovascular medication surpluses among the older age groups. In contrast to other studies which showed higher morbidity and mortality among the oldest age groups compared with non-elderly adults, our study shows that the elevation in the prescriptions of antibiotics in the oldest age groups (65 years of age and older) is not higher than in the two younger age groups (55–59 and 60–64). Yet, if compared with other adult age groups, a small increase could be seen. For influenza, this slightly deviating finding compared to non-Dutch settings, might be explained by the high vaccination coverage among elderly in the Netherlands.

A recent Dutch study showed that RSV-related excess hospitalisations were considerably higher as compared to those due to influenza [18]. Comparably, a study performed for England and Wales showed greater excess rates for complications during RSV-active periods among the youngest age groups as compared to influenza; similar rates were found for all other age groups [37]. Five other studies focussing on excess morbidity, mortality and hospitalisation among children confirmed these results, showing that RSV was responsible for higher hospitalisation rates than influenza [14,39–42].

For the Netherlands, Jansen et al. recently showed excess hospitalisation for cardiovascular complications among the 50–64 years old, during influenza-active periods but not during RSV-active periods [18]. In line with their findings, we showed a significant surplus in first cardiovascular medication prescriptions during influenza-active periods, but not during RSV-active periods for those aged 45 years and over. Elevated hospitalisation and prescription rates during influenza periods in persons aged around 50 years and beyond suggests that influenza may cause cardiovascular diseases or that it may aggravate existing non-diagnosed cardiovascular diseases in older adults. Another hypothesis explaining this increase might be that increased cardiovascular problems during influenza periods are related to the increased use of analgesics during those periods to alleviate influenza symptoms [45]. Further research is definitely needed into this topic.

Thus, in general, our results seem to be comparable with most other studies relating elevated viral activity to the use of health-care resources, morbidity and mortality. All studies consistently show that the highest excess rates for the youngest age groups are mostly due to RSV, whereas those for influenza are seen in elderly.

Vaccination may prevent part of the excess prescriptions we have found. For example, healthy children are not recommended to be vaccinated against influenza in the Netherlands, while their vaccination might prevent part of the surplus prescriptions found for this group. In particular, vaccination may prevent influenza infection and potential subsequent bacterial super infection(s) and thus avert antibiotics prescribed for the prevention and treatment of such bacterial super infections.

Additionally, reducing the prescription of antibiotics may also be important from the perspective of limiting the development of antibiotic resistance. Such reasoning could be an additional motivation for vaccinating yet uncovered groups against influenza [23]. An effective vaccine against RSV may potentially even prevent more antibiotic prescriptions, especially in young children [37]. Yet the introduction of a vaccine against RSV is not expected in the very near future [18].

## 5. Conclusions

During influenza- and RSV-active periods, elevations in antibiotic prescriptions were identified in all age groups. For otologicals, such an elevation was shown in the age groups of 0–1 and 2–4 years, both during influenza- and RSV-active seasons. By vaccinating young children against influenza, a part of these prescriptions for antibiotics and otologicals may be prevented.

In persons of 50 years and older an elevation of prescriptions for cardiovascular medication was shown during the period of elevated influenza activity only, in particular for the low-risk population. Also for antibiotic prescriptions, the excess found was higher in the low-risk population than in the high-risk population, possibly indicating the effectiveness of the vaccination program in the high-risk group, in which a relatively high coverage rate is reached in the Netherlands.

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