MAJOR ARTICLE

Mortality Attributable to 9 Common Infections: Significant Effect of Influenza A, Respiratory Syncytial Virus, Influenza B, Norovirus, and Parainfluenza in Elderly Persons

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(See the editorial commentary by Simonsen and Viboud, on pages 625–7.)

Background. Because there may be substantial hidden mortality caused by common seasonal pathogens, we estimated the number of deaths in elderly persons attributable to viruses and bacteria for which robust weekly laboratory surveillance data were available.

Methods. On weekly time series (1999–2007) we used regression models to associate total death counts in individuals aged 65–74, 75–84, and ≥85 years (a population of 2.5 million) with pathogen circulation—influenza A (season-specific), influenza B, respiratory syncytial virus (RSV), parainfluenza, enterovirus, rotavirus, norovirus, *Campylobacter,* and *Salmonella*—adjusted for extreme outdoor temperatures.

Results. Influenza A and RSV were significantly ($P < .05$) associated with mortality in all studied age groups; influenza B and parainfluenza were additionallyassociated in those aged ≥75 years, and norovirus was additionally associated in those aged ≥85 years. The proportions of deaths attributable to seasonal viruses were 6.8% (≥85 years), 4.4% (75–84 years), and 1.4% (65–74 years), but with great variations between years. Influenza occasionally showed lower impact than some of the other viruses.

Conclusions. The number of different pathogens associated with mortality in the older population increases with increasing age. Besides influenza A and RSV, influenza B, parainfluenza and norovirus may also contribute substantially to elderly mortality.

Mortality exhibits clear seasonality mainly caused by an increase in deaths in elderly persons in winter [1]. However, accurately assigning causes or contributing causes to a death remains a universal challenge, especially in elderly persons with underlying disease. Cause-of-death statistics commonly record the underlying cause of death, whereas direct causes of death, such as extreme heat in summer and influenza infection in winter, are often attributed to underlying circulatory disorders [1, 2]. Estimating the number of deaths attributable to influenza or other pathogens is therefore usually performed using regression models [3, 4–9]. These models can incorporate multiple viruses [9–12], bacteria, pure seasonal trends [7], and temperature [13], but most studies have not included all of these components simultaneously, nor have most incorporated the time-varying effect of influenza A, for which the severity depends on the main circulating subtype per season [10]. In this study, we include all of the above pathogens and factors and stratify by different age groups (65–74,

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75–84, ≥85 years) to estimate the mortality attributable to common infections in elderly persons.

Although winter peaks in overall death counts are largely attributed to influenza and sometimes cold temperatures, the contribution of other common seasonal viruses and bacteria to these peaks in mortality in elderly persons is not entirely clear. Studies of overall mortality mostly studied either respiratory pathogens (often influenza alone) or gastroenteritis pathogens separately. Reports show that respiratory syncytial virus (RSV) may have been greatly underappreciated as a contributor to overall winter mortality next to influenza A [10, 14–16]. Regarding common gastroenteritis bacteria, a clear link with longer-term mortality has been demonstrated for *Salmonella*, *Campylobacter*, *Yersinia enterocolitica*, and *Shigella*, with the largest numbers of deaths linked to the first 2 [17]. Other recent studies suggest an impact on winter mortality due to noroviruses, especially in recent years when new variants emerged [18–20]. Pathogens for which the number of attributable deaths in elderly is more obscure are rotavirus (mainly known for mortality in children [21, 22]), enterovirus (for which the mortality is on the rise in non-European countries [23]), and parainfluenza (which may be involved more often in severe influenza-like illness and acute respiratory tract infections than previously assumed [3, 24, 25]). Further, low outdoor temperatures [26, 27] and heat waves [28, 29] have been associated with increases in deaths, but those models were mostly unadjusted (or only crudely so) for the activity of seasonal infections.

MATERIALS AND METHODS

Per age group, we modeled time series of weekly overall number of deaths (outcome variable) depending on available weekly time series of common seasonal viruses and bacteria at the population level, temperature, and baseline cyclical (ie, seasonal) trends available from 3 data sources from week 1 of 1999 to week 52 of 2007 (Table 1). Ethical approval was not required.

Data Sources
Mortality Data
Yearly population size and weekly numbers of deaths covering the total Dutch population (16.3 million) were obtained from Statistics Netherlands. We restricted analyses to the elderly population (aged ≥65 years), aggregating weekly numbers of deaths by 10-year age groups (65–74, 75–84, and ≥85 years).

Data on Viruses and Bacteria from Laboratory Surveillance
We used weekly time series for common pathogens for which stable lab surveillance was available: influenza A, influenza B, RSV, parainfluenza, enterovirus, and rotavirus from the Weekly Sentinel Surveillance System of the Dutch Working Group on Clinical Virology, *Campylobacter* and *Salmonella* from the Laboratory Surveillance of Infections, and norovirus outbreak notifications [30] from the norovirus outbreak

Table 1. Characteristics of the Study Population and Laboratory Reports (1999–2007)

| Age Group, Years | Population Size[a] | Total Deaths (1999–2007) | Average Number of Deaths, Mean (IQR) | | | |
			Per Year		Per Week	
65–74	1 231 181	230 006	25 600	(24 300–26 800)	490	(455–523)
75–84	768 083	405 826	45 100	(44 900–45 800)	865	(804–916)
≥85	235 811	367 837	40 900	(40 200–41 800)	784	(713–844)

| Lab Reports[b] | | Total Reports (1999–2007) | Average Number of Reports, Mean (IQR) | | | |
			Per Year		Per Week	
Influenza A		4484	498	(349–648)	10	(0–10)
RSV		16 237	1804	(1567–2120)	2	(0–2)
Influenza B		825	92	(46–143)	35	(1–43)
Norovirus outbreak		879	98	(30–161)	2	(0–2)
Parainfluenza		3227	359	(325–385)	7	(4–9)
Enterovirus		8128	903	(777–1027)	17	(8–23)
Rotavirus		10 355	1150	(1011–1251)	22	(3–33)
Campylobacter		30 525	3391	(3406–3454)	65	(42–82)
Salmonella (non-*Typhi*)		15 698	1744	(1580–2047)	33	(19–44)
Salmonella (*Typhi*)		198	22	(16–26)	<1	(0–1)

Abbreviation: IQR, interquartile range.

[a] Population size and death information from Statistics Netherlands (average of the 1999–2007 time period).

[b] Pathogen information from Weekly Sentinel Surveillance System of the Dutch Working Group on Clinical Virology and the Laboratory Surveillance of Infections.

surveillance system. These series are considered to reflect pathogens in circulation at the national level [31], although the coverage varies by pathogen, and young children are probably overrepresented.

Temperature

Daily mean temperatures were downloaded from the website of the Royal Netherlands Meteorological Institute and aggregated to the weekly average (from 1 central location because the climate is similar across the country).

Statistical Analyses

We used regression models with a Poisson error to relate overall mortality to laboratory pathogen counts. We used the identity link function because we expect that the association between the number of pathogens and the expected number of deaths is additive instead of multiplicative, and a scale parameter was added to take the overdispersion into account. To avoid overestimation of the regression coefficients for the pathogens and to avoid spurious associations, we included baseline periodic trends, assuming that these sine and cosine terms represented seasonal variation in mortality of unknown cause. We did this because many health variables show systematic and coinciding variation over the course of a year even if these variables may not be causally related [32]. To account for the variation in the severity of the main circulating influenza A strain, we used time-dependent variables that allowed parameter estimates for influenza A to vary by season.

For each age group, we built a separate model for which we first checked whether a significant ($P \le .05$) increasing or decreasing linear trend with time was present and whether a significant seasonal trend (sine and cosine terms) was present. Next, using a forward stepwise selection, we checked which additional explanatory pathogens contributed significantly to the pattern in death counts. We also evaluated the association with the lagged values of the pathogens (up to 4 weeks backward in time), building each increment in the model by adding all possible lags of all pathogens and selecting the lag with the best fit (assessed with the deviance) until no more pathogens contributed significantly to the model. Each appropriately lagged pathogen was included in the model only once (we did not consider lags other than the lag with the best fit). We then added temperature variables when significant: one for low temperatures, given by max(0, 5 − T), the other for high temperatures, given by max(0, T − 17). We assumed no effect between 5°C and 17°C (17°C was the upper cutoff estimated in a study of temperature-related mortality in the Netherlands [13]). We did not consider weekly lags because, to date, deaths are considered to be acutely linked to temperature, especially for extremely hot days.

Negative associations were not included to avoid overmodeling of the data, with the underlying consideration that pathogens can cause disease and death but generally do not decrease disease burden. The best model (per age group) was determined with 1 overall coefficient for influenza A; for the final model, we then replaced the overall influenza A variable with season-specific variables allowing the estimation of season-specific influenza A coefficients.

The following regression model was used:

$$\text{Deaths}_t \sim \text{Poisson}(\lambda_t)$$

$$\begin{aligned}
\lambda_t = {} & \beta_0 + \beta_1 t + \beta_2 \sin\left(\frac{2\pi t}{52}\right) + \beta_3 \cos\left(\frac{2\pi t}{52}\right) \\
& + \beta_4 \max(0, 5 - T_t) + \beta_5 \max(0, T_t - 17) \\
& + \beta_6 \text{InflA}_{1999}(t - \text{lagInflA}) + \beta_7 \text{InflA}_{2000}(t - \text{lagInflA}) \\
& + \cdots + \beta_{13} \text{InflA}_{2006}(t - \text{lagInflA}) + \beta_{14} P_{1,(t-\text{lag}P1)} \\
& + \beta_{15} P_{2,(t-\text{lag}P_2)} + \cdots + \beta_m P_{k,(t-\text{lag}Pk)}
\end{aligned}$$

In this equation, λ_t denotes the number of deaths per week and t takes on discrete values. β_0 is the regression parameter associated with the baseline number of deaths, β_1 the parameter associated with a linear trend in time, β_2 and β_3 the parameters associated with the periodic time trends, and β_4 and β_5 the parameters associated with low and high temperature effects. Parameters $\beta_6, \beta_7, \ldots, \beta_m$ are the parameters of interest, describing the association between the (lagged) number of pathogens $P_1, P_2, \ldots, P_k$ and the expected number of deaths. For influenza A, each season-year gets its own coefficient.

RESULTS

Characteristics

The weekly number of deaths was highest in the 2 oldest age groups (490–865 weekly deaths) (Table 1), varying largely by season, especially in the 2 oldest age groups (Figure 1). Laboratory reports of the different pathogens varied from an average of 2–65 per week with large interquartile ranges due to the strong seasonality in their prevalence (Table 1; Figure 2).

Model Results

The association between mortality and explanatory variables varied largely by age: the older the age group the more pathogens (all viruses, mostly active in winter) were significant ($P < .05$) predictors of mortality (Table 2). Influenza A and RSV were associated with mortality in all elderly age groups, and influenza B and parainfluenza associated with mortality in the oldest 2 age groups (75–84 and ≥85 years). Additionally, norovirus activity was a predictor of mortality in the oldest individuals (aged ≥85 years). None of the considered bacteria were significant ($P < .05$) in any of the age groups. In the final models, we adjusted for high temperature only because low
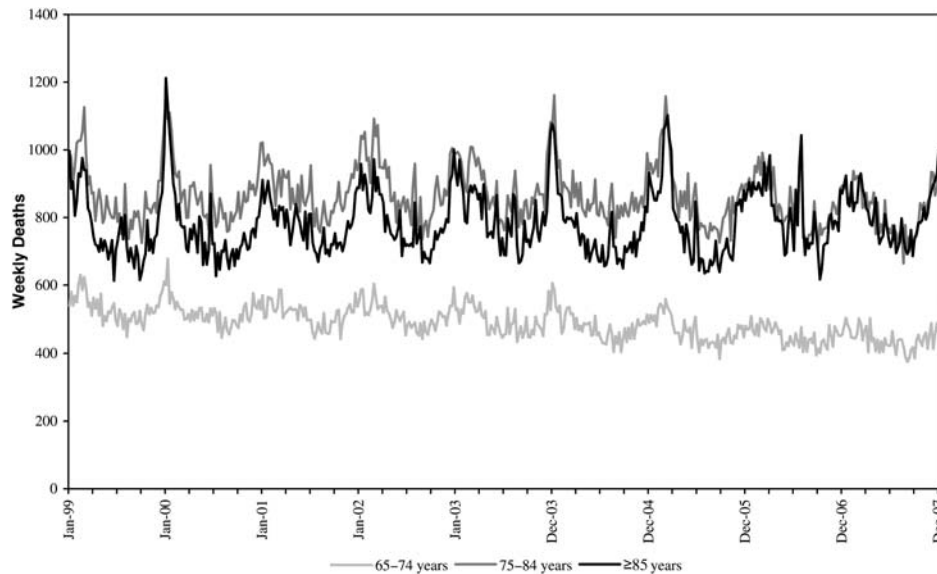
Figure 1. Overall weekly mortality by age group, 1999–2007.

temperature was not associated (and probably already captured in the sine and cosine terms).

Influenza A showed the best fit in all age groups when it was directly associated with mortality (ie, without delay in subsequent mortality), whereas RSV showed an optimal fit when deaths were lagged 2–3 weeks after RSV activity. For parainfluenza, the optimal lag varied by age, with a longer lag in the oldest age group (3 weeks) (see Table 2). Additionally, norovirus was associated with subsequent mortality 4 weeks later in the eldest age group. The fit of the models seemed adequate (visual inspection) but with seemingly slight periodicity remaining in the distribution of the residuals (see Figure 3 for the oldest individuals) for which unknown factors may be accountable. Observed winter peaks were sometimes slightly higher than our models predicted, but non-winter seasons also sometimes showed peaks in mortality not completely explained by our models.

Estimated Numbers of Attributable Deaths

All Pathogens Combined

In the oldest age group (≥85 years), 6.8% of all mortality was attributed to multiple winter viruses (influenza A and B, RSV, parainfluenza, norovirus) (Table 3). This proportion increased with increasing age (65–74 years: 1.4%; 75–84 years: 4.4%), and with increasing age, more viruses were significant ($P > .05$) predictors of death (but always including influenza A and RSV). The absolute numbers of deaths associated with the significant viruses varied by season-year (July 1st–June 30th), with the following minimum and maximum estimates: 177–

545 (65–74 years); 1207–2800 (75–84 years), and 1829–3647 (≥85 years) (Table 4, differences of 1 are due to rounding).
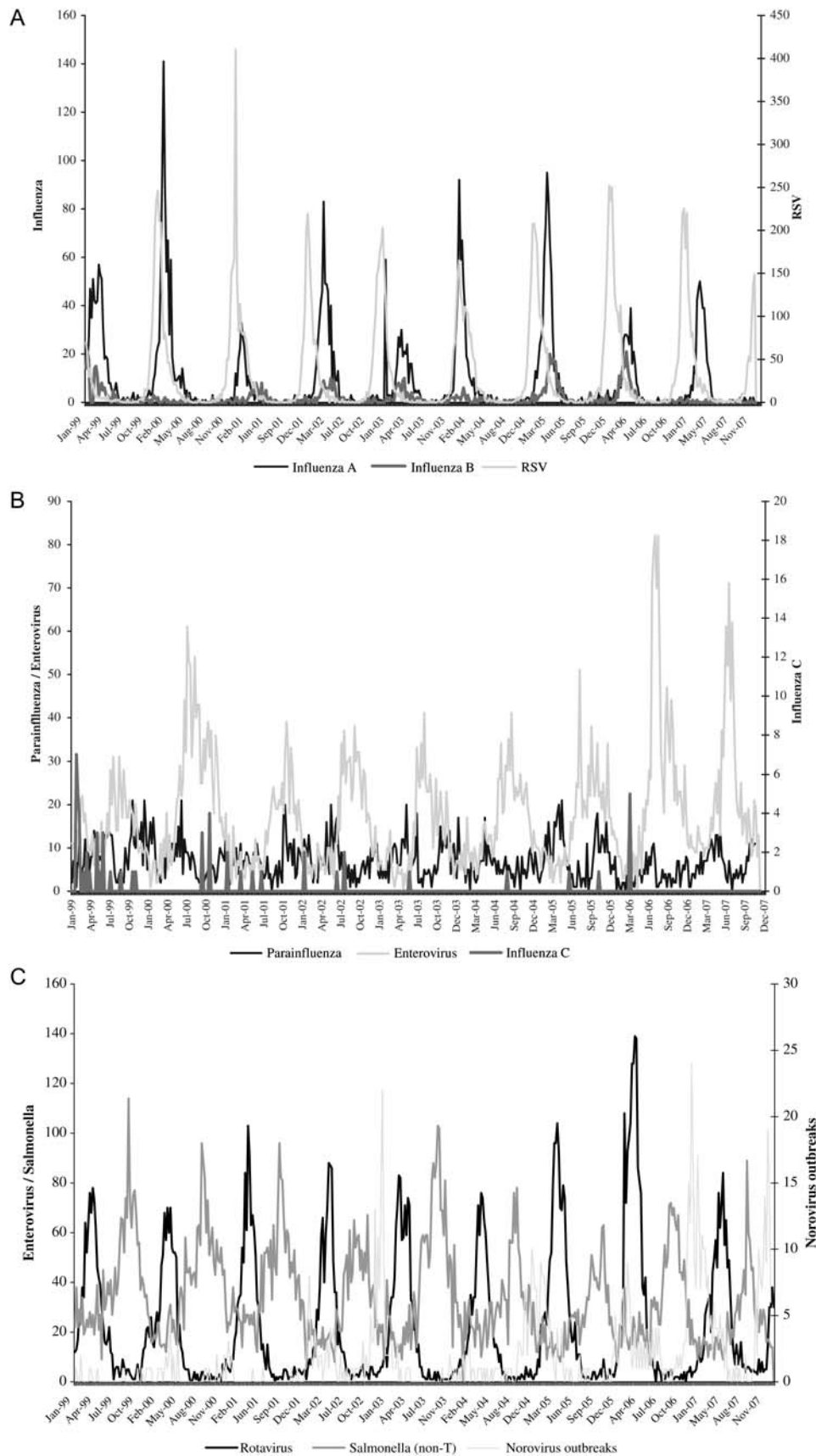
Influenza A and RSV

Influenza A and RSV were associated with the largest numbers of deaths. Overall, the number of deaths attributed to RSV was almost as high as the number attributed to influenza A (Table 3), but their attributable proportions varied largely by season-year (Table 4): the yearly numbers of deaths associated with influenza A were much more variable (eg, 70–1313 or 0.3%–5.9% in the oldest group) than the numbers attributed to RSV in the oldest group (703–1028 or 3.1%–4.4%). For 3 of the 8 included complete season-years (2000–2001, 2005–2006, and 2006–2007), the estimated contribution of RSV to mortality was considerably higher than that of influenza A (Table 4, bold script; also Figure 4).

Influenza B

The number of deaths attributable to influenza B varied from 123–862 in the oldest age group and overall was lower than for influenza A, although interestingly more deaths were attributable to influenza B than to influenza A in the 2000–2001 (very mild influenza A season) and the 2005–2006 seasons (Table 4). Influenza B was not a significant contributor to deaths in the youngest age group (65–74 years) (Table 2).

Parainfluenza

In the 2 oldest age groups, the mortality associated with parainfluenza displayed winter peaks that were much smaller than for most other viruses associated, but as the attributable

Figure 2. *A*, Laboratory reports of influenza A, influenza B, and respiratory syncytial virus in the Netherlands, 1999–2007. *B*, Laboratory reports of parainfluenza, enterovirus, and influenza C in the Netherlands, 1999–2007. *C*, Laboratory reports of rotavirus, salmonella, and norovirus (outbreaks).

Table 2. Predictors of Overall Mortality From Separate Models per Age Group (1999–2007)

| Age Group Predictor	≥85 Years			75–84 Years			65–74 Years		
	Beta	95% CI	Delay[a]	Beta	95% CI	Delay[a]	Beta	95% CI	Delay[a]
Intercept	703.81	690–717	NA	841.90	827–855	NA	533.87	527–539	NA
Linear trend	0.06	.03–.10	NA	− 0.10	− .14 to − .07	NA	− 0.22	− .24 to − .21	NA
Sine	27.44	18.63–36.25	NA	32.98	24.70–41.27	NA	18.84	14.74–22.94	NA
Cosine	41.85	32.25–51.46	NA	45.44	35.88–55.01	NA	20.78	15.38–26.18	NA
Temperature ≥ 17°C	2.35	1.97–2.73	NA	1.73	1.37–2.10	NA	0.44	.24–.64	NA
Viruses									
Influenza A									
1998–1999	1.60	.86–2.34	0	1.06	.33–1.78	0	0.32	− .07 to .72	0
1999–2000	1.59	1.08–2.09	0	0.91	.46–1.36	0	0.21	− .03 to .46	0
2000–2001	0.31	− 1.37 to 2.00	0	0.39	− 1.19 to 1.97	0	0.22	− .66 to 1.10	0
2001–2002	1.26	.56–1.97	0	2.17	1.47–2.87	0	0.61	.24–.98	0
2002–2003	2.42	1.29–3.56	0	2.35	1.27–3.44	0	0.74	.15–1.33	0
2003–2004	2.33	1.66–3.00	0	2.07	1.44–2.70	0	0.76	.42–1.10	0
2004–2005	1.56	.92–2.20	0	1.81	1.21–2.41	0	0.58	.30–.87	0
2005–2006	1.54	.04–3.04	0	1.26	− .15 to 2.67	0	0.32	− .34 to .98	0
2006–2007	1.30	.37–2.23	0	0.40	− .44 to 1.25	0	0.05	− .41 to .50	0
RSV	0.46	.33–.58	3	0.32	.21–.43	2	0.08	.02–.14	0
Influenza B	4.74	2.66–6.81	0	2.68	.76–4.59	0	…	…	
Parainfluenza	1.39	.34–2.43	3	1.30	.29–2.30	0	…	…	
Norovirus outbreaks	2.12	.20–4.05	4	…	…	…	…	…	

Abbreviations: CI, confidence interval; NA, not applicable; RSV, respiratory syncytial virus.

[a] Delay in deaths (weeks).

deaths were more spread out over the year, the total proportion of those deaths was comparable to or slightly larger than that for influenza B (1.2% vs 1.1%, and 1.0% vs 0.5%, in the 2 oldest groups, respectively) (Table 3).

Norovirus

Norovirus outbreaks were significantly associated with mortality in the oldest age group (≥85 years) (Table 3), with peaks coinciding with the emergence of new norovirus variants
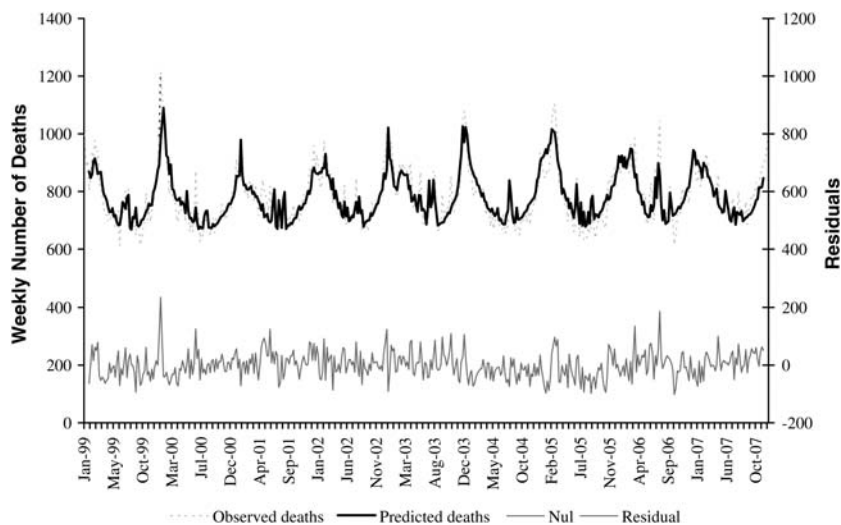
Figure 3. Observed and predicted weekly deaths and model residuals in individuals aged ≥85 years. Predicted weekly overall deaths were calculated using the parameter estimates from a regression model that included influenza A, RSV, influenza B, norovirus outbreaks, parainfluenza, and high temperature.

Table 3. Estimated Numbers of Deaths Attributable to Pathogens During Total Study Period (1999–2007) by Age Group, Adjusted for Temperature[a]

Virus	Lab Reports	≥85 Years Estimated Deaths	%[b]	75–84 Years Estimated Deaths	%[b]	65–74 Years Estimated Deaths	%[b]	All Ages (≥65) Estimated Deaths	%[b]
Influenza A	4484	7201	2.0	6382	1.6	1935	0.8	15 519	1.5
RSV	16 237	7425	2.0	5171	1.3	1305	0.6	13 902	1.4
Influenza B	825	3907	1.1	2209	0.5			6116	0.6
Parainfluenza	3227	4479	1.2	4179	1.0			8658	0.9
Norovirus outbreak	879	1868	0.5					1868	0.2
All viruses		24 881	6.8	17 942	4.4	3241	1.4	46 063	4.6

Abbreviation: RSV, respiratory syncytial virus.

[a] Adjusted for high temperatures (≥17°C).

[b] Percentage of total mortality in the respective age group.

starting in 2002–2003 [33] and with up to 550 norovirus associated deaths in 2006–2007, similar to the influenza A burden that year (Table 4; Figure 4, black areas).

Rotavirus, Enterovirus, Campylobacter, and Salmonella

Rotavirus, enterovirus, *Campylobacter*, and *Salmonella* showed no significant association with mortality in elderly persons, although when leaving out adjustment for high temperature, enterovirus did become a significant predictor in the oldest age group.

DISCUSSION

Our study shows that seasonal mortality in elderly persons is attributable to multiple viruses, including not only influenza A and RSV but also influenza B, norovirus, and parainfluenza. Together, these viruses were associated with up to 6.8% of all deaths in the oldest age group (≥85 years). Influenza A was overall, but not always, associated with the highest numbers of deaths; in some seasons other respiratory viruses (RSV and/or influenza B and/or parainfluenza) had a greater impact on mortality. The number of viruses that contributed to overall mortality increased with increasing age (probably due to increasing vulnerability with age [34]) but always included influenza A and RSV. Overall mortality in the oldest individuals is also attributed to viruses previously thought to cause mild, self-limiting illness, such as influenza B and norovirus activity. The longest delays in death after (noninfluenza) infection are seen in the oldest age group, which might be due to later circulation of pathogens in seniors compared with the overall lab trends that we used [11]

As demonstrated by several previous reports [10, 14–16] our models confirm the large role of RSV in elderly mortality next to influenza A. In some seasons even more deaths were attributed to RSV than to influenza A (although all years included

in the study were relatively mild influenza A years). The role of influenza B may, to date, have been underappreciated because it is generally considered to cause mild illness. Particularly in the oldest elderly, the estimated number of influenza B–attributable deaths was half that estimated for influenza A or higher during 5 of the 8 seasons. High influenza A vaccination uptake in elderly persons (approximately 75% throughout the years under study) might be another reason why some of the seasons show lower mortality associated with influenza A than with RSV or influenza B (although vaccination uptake is not necessarily linked to vaccination effectivity). Further, whereas we estimated season-specific effects for influenza A, the coefficients for the other viruses were assumed constant over the total study period so as not to overstretch the data with too many variables, although their effect might also vary with time. Despite its less serious pathogenesis, influenza B might possibly trigger death in the older and frail populations suffering from other (chronic) illnesses, or misattribution may occur if RSV and influenza B circulation in children coincide with influenza A activity in seniors. We assumed that the RSV laboratory data reflected RSV activity in all age groups, even though laboratory diagnostics for RSV are known to be mostly performed in children [35]. However, we still expect the effect of RSV to remain large because influenza A and RSV seasons are not overlapping for the majority of the years under study (Figure 2) and the overall estimate for influenza A hardly changed when removing RSV from the models, confirming that in our model RSV does not compete with influenza A. With the 3-week lag for RSV in our model, we might lag RSV into the influenza period and misattribute influenza deaths to RSV. However when not lagging RSV, the model did not clearly improve. An additional validation of the best lag would be future analyses on 2009–2010 data, for which influenza unusually preceded the RSV epidemic instead of vice versa.

Table 4. Estimated Numbers of Deaths Attributable to Viruses and High Temperature by Age and Season-Year (July 1st–June 30th)

Season	1999–2000		2000–2001		2001–2002		2002–2003		2003–2004		2004–2005		2005–2006		2006–2007	
	Absolute	Rate[a]	Absolute	Rate[a]	Absolute	Rate[a]	Absolute	Rate[a]	Absolute	Rate[a]	Absolute	Rate[a]	Absolute	Rate[a]	Absolute	Rate[a]
65–74 years																
Influenza A	174	0.1	49	0.0	338	0.3	265	0.2	408	0.3	386	0.3	96	0.1	20	0.0
RSV	169	0.1	**165**	0.1	123	0.1	141	0.1	137	0.1	159	0.1	**181**	0.1	**158**	0.1
Temperature ≥17°C	135	0.1	47	0.0	114	0.1	126	0.1	130	0.1	125	0.1	95	0.1	192	0.2
75–84 years																
Influenza A	753	1.0	87	0.1	1204	1.6	845	1.1	1114	1.5	1195	1.5	376	0.5	161	0.2
RSV	671	0.9	**653**	0.9	489	0.7	558	0.7	541	0.7	629	0.8	**716**	0.9	**624**	0.8
Influenza B	70	0.1	**185**	0.3	262	0.4	241	0.3	139	0.2	487	0.6	**407**	0.5	37	0.0
Parainfluenza	632	0.9	**416**	0.6	531	0.7	460	0.6	467	0.6	488	0.6	344	0.4	**385**	0.5
Temperature ≥17°C	528	0.7	185	0.3	448	0.6	492	0.7	509	0.7	491	0.6	370	0.5	751	0.9
≥85 years																
Influenza A	1313	5.9	70	0.3	701	3.1	870	3.8	1255	5.4	1031	4.4	459	1.9	519	2.1
RSV	964	4.4	**937**	4.2	703	3.1	801	3.5	777	3.3	903	3.9	**1028**	4.3	**896**	3.6
Influenza B	123	0.6	**327**	1.4	464	2.0	426	1.8	246	1.1	862	3.7	**720**	3.0	66	0.3
Parainfluenza	697	3.2	**457**	2.0	548	2.4	491	2.1	518	2.2	534	2.3	358	1.5	419	1.7
Norovirus outbreak	57	0.3	38	0.2	123	0.5	278	1.2	57	0.2	317	1.4	193	0.8	**550**	2.2
Temperature ≥17°C	715	3.2	251	1.1	606	2.7	666	2.9	689	3.0	664	2.9	501	2.1	1016	4.1

Bolded numbers indicate that the indicated virus was associated with more deaths than influenza A during that time period.

Abbreviation: RSV, respiratory syncytial virus.

[a] Per 1000 individuals
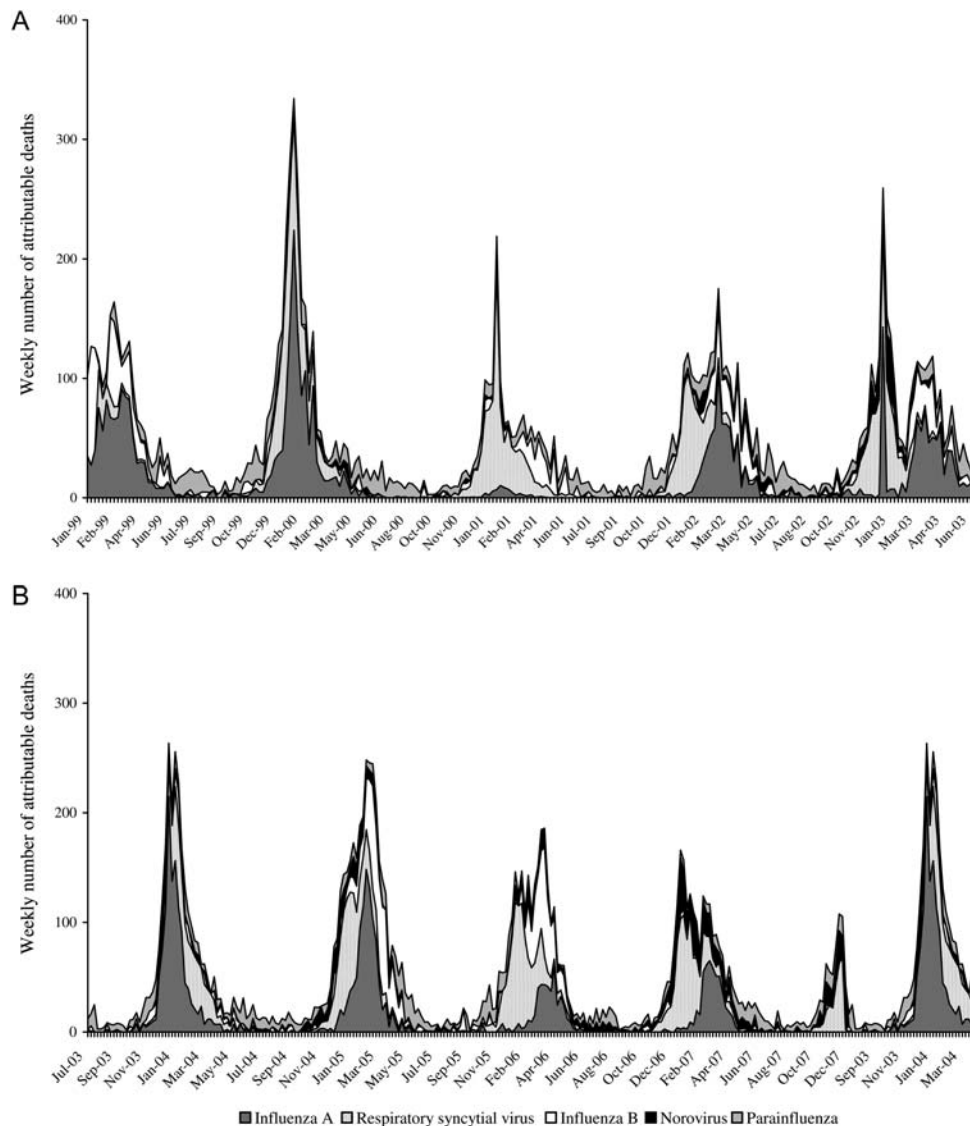
Figure 4. Deaths attributable to respiratory and gastrointestinal viruses in individuals aged ≥85 years for 1999–2003 (*A*) and 2003–2007 (*B*) (stacked).

Comparing our influenza mortality results (adjusted for many pathogens) with other studies in the Netherlands (on influenza mortality adjusted for RSV activity) [36, 37] is difficult because those studies used different models in different (but partially overlapping) time periods and with differently defined age-group categories. In one overlapping age group (aged 65–74 years), we found lower estimates of influenza A attributable deaths than Jansen et al [36], which might be expected because their model does not distinguish between influenza subtypes (although we found no association with influenza B or C in this age category). Compared with influenza-like illness mortality [37], we found reasonably similar magnitudes of influenza-attributable deaths. However, again the comparison is limited because influenza-like illness is a

measure not distinguishing between influenza subtypes and may sometimes include some spillover influenza-like illness caused by other respiratory pathogens.

Another interesting finding is that mortality is also attributed to norovirus outbreaks in the oldest age group and to parainfluenza in the 2 oldest age groups. When adding shorter baseline cycles to the model (sine and cosine terms), these cycles competed with these pathogens. Studies on norovirus mortality are scarce, but norovirus has recently been suggested to be associated with gastroenteritis deaths for which a causative pathogen was unknown (no diagnostics performed) [19, 20], and it has been associated with deaths due to infectious intestinal disease in another study [18]. Recently, sporadic deaths have been linked to norovirus, and this possible

association has also received media attention after deaths in nursing homes during norovirus outbreaks [38]. Studies on the association between parainfluenza and mortality are even more sparse [3], suggesting that this is either a novel finding or a spurious association. One recent study suggests the former because it estimated a surprising association of parainfluenza type 2 with deaths in children [3]. Further support for such an association is a study that demonstrated parainfluenza is the third most prevalent virus in patients with influenza-like illness, cocirculating with influenza A and more likely to be included in mixed infections [24].

Although *Campylobacter* and *Salmonella* infections have a demonstrated association with increased mortality [17], we found no significant association between these 2 pathogens and mortality in our observational population study. A probable reason for this is the relatively small numbers of deaths associated with these pathogens (compared with the number of respiratory virus deaths) combined with the fact that these deaths can occur up to a year after infection (we examined a maximal lag of 4 weeks). The large variation in time to death also dilutes the seasonality in *Campylobacter*- and *Salmonella*-associated deaths and thus also dilutes the correlation with the seasonal occurrence of the initial infections.

As long as many infectious diseases remain unrecognized and underreported as a (contributing) death cause on death notification forms, the only way to estimate the proportion of deaths attributable to infections is indirectly through modeling. However, in such models, relating time series with each other can be tricky because they can be correlated to a certain degree even if there is no biological association. There is no absolute solution for this problem, but we chose to add periodic components to our model and additional adjustments for extreme outdoor temperature. We assumed that these cyclical dynamics represented a baseline seasonal trend of weekly deaths that was not explained by the variation in pathogen circulation. Excluding temperature and periodicity could possibly lead to an overestimation [39] of the pathogen effects. Leaving out the periodic terms lead to much higher regression parameter values for all viruses in all age groups, except for influenza A, which showed moderately higher estimates in the 2 oldest age groups (25% and 37% higher when modeled overall; ie, non–time dependent). But whether adding the periodic components helps avoid overestimation of pathogen effects or whether they actually lead to underestimation of pathogen-attributable mortality is unknown. However, even though we included adjustments for periodicity and temperature in our models, we cannot rule out spuriously generated relationships caused by collinearity between any of the other included explanatory variables [40]. For this reason, the associations that we found between mortality and influenza B [41], norovirus [18, 20], and especially parainfluenza require further confirmation in studies from other countries. Leaving out all pathogens

except influenza A increased the influenza A parameter in half of the years and decreased it in the other years ($\geq$85 years age group). For temperature, the use of cutoff values instead of a continuous temperature variable avoids the introduction of a relatively perfect periodic component that could lead to transferring effects away from the pathogens [40]. This would be inappropriate if the weather attribution is in fact due to (or partially due to) increasing circulation, transmission, and/or survival of cold weather pathogens.

An important limitation of our study is that there may be other pathogens with a (currently) unknown association with mortality and/or for which robust time series were not available, which could also play a role in elderly mortality, but which we cannot detect. These might, however, be included indirectly by the periodic component in our model. One example is rhinovirus infection, one of the most common causes of the common cold, with potentially severe consequences in elderly persons [42, 43]. Another example is *Clostridium difficile* ribotype 027 infections, which were not considered in our analyses because they were not available per week (the time unit in our study) and which only recently surfaced with an outbreak in 2005 [44] in the Netherlands. Also pneumococcus infection may be expected to explain some of the seasonality in elderly deaths [45].

Further Research

Besides estimating attributable fractions, understanding historic mortality patterns is also important for understanding mortality dynamics in prospective surveillance systems, which many countries recently have set up [46, 47]. In our study, several peaks in winter are largely but not fully explained by our models and therefore pose interesting points for further research because they could be associated with hitherto unknown viruses or factors, represent a diagnostic deficit of known viruses in certain time periods, or represent a lack of full understanding of multiple lag times between pathogen activity and mortality. Of further interest are the periodic terms in our model, which represent a pure seasonal trend (unattributed to any pathogen activity considered in this study) that is possibly (partially) explained by currently unknown factors or pathogens.

Notes

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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