Respiratory tract infection: prevention, early detection and attenuation of immune response
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Acute respiratory infections in secondary care versus influenza-like illness in primary care in the Netherlands: hospital incidence peaks first.

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ABSTRACT

Background

Surveillance of acute respiratory infections (ARI) in the Netherlands and other European countries is based mostly on primary care data, with little insight into the severe spectrum of the disease. We analyzed time-trends for ARI in secondary care, influenza-like illness (ILI) in primary care, and crude mortality, to assess the potential value of hospital data for surveillance.

Methods

We calculated the incidence of ARI in secondary care (Leiden University Medical Center), ILI in primary care (NIVEL Primary Care data base), and crude mortality (Statistics Netherlands) using three historical databases (2008-2016).

Results

Over eight years, the seasonal incidence peaks of ARI in secondary care occurred earlier than ILI incidence peaks, except during the influenza pandemic season of 2009/2010 and the post-pandemic season of 2010/2011. In the six seasons in which the ARI peak preceded the ILI peak, the median time-lag was eight weeks. The crude mortality peak lagged a median five weeks behind the ARI peak in all eight seasons.

Conclusions

In most seasons, the incidence peaks for ARI in secondary care preceded the peaks for ILI in primary care with a considerable time-lag. This is crucial information for preparedness and emergency control. Adding microbiological test results to these incidence data would be of great value in explaining the whole spectrum of ILI in primary care, ARI in secondary care, and mortality.

BACKGROUND

Most European countries have a well-established weekly near-real-time surveillance system for influenza-like illness (ILI) or acute respiratory infections (ARI) in primary care. In contrast, real-time surveillance data is rarely available on severe acute respiratory infections (SARI), i.e. those requiring hospital admission. The limited available historic and real-time data on severe respiratory infections, such as pneumonia as a complication of influenza, became apparent especially during the 2009 influenza A(H1N1) pandemic. In response, the World Health Organization (WHO) and European Centre for Disease Prevention and Control (ECDC) recommended the establishment of national SARI-surveillance systems to gain insight into the severity of epidemics and enable earlier detection of potential epidemics and pandemics.[1-3]

Surveillance is a vital tool to monitor shifts in the occurrence and burden of infections and diseases in the population, which is necessary for prevention and control.[4,5] In the Netherlands, weekly surveillance of ILI by sentinel general practitioners (GPs) was established in 1970 and virological test results were added in 1992, providing robust longitudinal data on incidence of ILI and influenza virus infection in the general practice population. The Dutch mortality monitoring system provides data on the total number of deaths from all causes, stratified by age group and region, with a weekly analysis of excess mortality.[6] It is a near-real-time surveillance system, but the weekly mortality data are not disease-specific.

SARI-surveillance has been the missing link in the existing respiratory infections surveillance systems in the Netherlands. The Dutch Hospital Data (DHD), a national register collecting the medical diagnoses of patients admitted to a Dutch hospital, provides data on hospital admission for SARI.[7] However it is available with a one-year time-lag and therefore not suitable for real-time surveillance. In 2015, a pilot study by the National Institute for Public Health and the Environment (RIVM) started in two hospitals, Leiden University Medical Center (LUMC) and Jeroen Bosch Hospital (JBH), with the main objective to set up SARI surveillance.[8,9] To assess the value of routinely collected data on respiratory infections in hospitals, it is essential to explore how it relates to data from already existing surveillance systems. Therefore, using historical data derived from the passive surveillance system at LUMC, we conducted an observational study on hospital consultations for ARI in the period 2008-2016, with two objectives:

1| validating the potential of routinely collected data for respiratory infection surveillance in hospitals
2| comparing time-trends for ARI in secondary care, ILI in primary care, and crude mortality monitoring data

METHODS

ARI in secondary care database

Data on patients with an ARI in secondary care during the period between week 40 of 2008 and week 20 of 2016 were provided by the LUMC, a tertiary university teaching hospital in Leiden, South Holland, with 585 beds and a catchment population of 323,269 persons.[10] The catchment population was calculated by dividing the total number of hospitalisations due to respiratory tract infection (RTI) by the total hospitalisations due to RTI in the Netherlands and multiplying this proportion by the total Dutch population size. The data required for the calculation of the catchment population was provided by the National Register of hospital discharge diagnosis (Dutch Hospital Data) (Appendix 1, Figure 4). A selection of International Statistical Classification of Diseases and Related Health Problems (ICD-10) codes related to RTI (J00-J22, A15, A16, A48.1, A70 and A78) was determined for the LUMC for the years 2014, 2015 and 2016. Taking into account the non-normal distribution of the catchment population over the available years, we used the median value for our incidence calculations.

Patients with ARI were defined as those consulting the LUMC emergency department (ED) or outpatient clinic who were registered with diagnostic codes corresponding to a RTI. These codes were based on the Dutch financial coding system (DBC/DOT), applied by the national Dutch Healthcare Authority (NZa) and used by all health care facilities in the Netherlands.[9] Depending on ARI severity, these patients were admitted to an intensive care unit (ICU) or regular ward or discharged for treatment at home. Patients discharged without admission do not fulfil the WHO SARI case definition[11], but we were unable to distinguish outpatients from admitted patients. Therefore, we used 'ARI in secondary care' as a proxy for SARI. The database included consultation date, gender, age category, and ward of admission (ICU/non-ICU)[9], but not microbiological data.

ILI in primary care database

Data from the Sentinel Practices of NIVEL Primary Care Database were used to calculate the incidence of ILI in primary care from week 40 of 2008 to week 20 of 2016.[12] The participating GPs (n=40) report on the weekly number of patients consulting them for ILI, which is defined as 1) sudden onset of symptoms, 2) fever, and 3) at least one of the following symptoms: cough, rhinorrhoea, sore throat, frontal headache, retrosternal pain or myalgia. The population covered by this sentinel network is approximately 0.8% (137,000 persons) of the Dutch population (17.2 million persons) and is representative for age, gender, regional distribution and population density.[13]

Crude mortality monitoring database

Deaths are reported to municipalities and then reported to Statistics Netherlands.[14] During the 2009 influenza pandemic, RIVM and Statistics Netherlands initiated a weekly monitoring system for crude mortality. It monitors the total reported number of deaths from all causes, stratified by age group and region. The presence of excess mortality is verified and reported weekly.[6] For our observational study, all-cause mortality data were collected from Statistics Netherlands for the province of South Holland with over 3.6 million persons (Appendix 1, Figure 4) in the period from week 1 of 2009 though week 20 in 2016.[15] It was not feasible to obtain crude mortality data specifically for the LUMC catchment area, because such data can only be extracted by province from the Statistics Netherlands database.

Statistical analysis

Data are presented for both the 'respiratory year' and 'respiratory season', defined respectively as the period from week 40 through week 39 of the following year and the period from week 40 through week 20 the following year. Data for 2015/2016 is limited to the respiratory season (week 40 of 2015 through week 20 of 2016). The incidence for ARI in secondary care was calculated as the number of patients consulting the hospital per week, divided by the total number of persons in the LUMC catchment population, and expressed per 10,000 persons. To calculate ARI incidence in secondary care as stratified by age groups (0-4, 5-59, and ≥ 60 years old), it was assumed that the age distribution of the total Dutch population in 2008-2016 was similar to the LUMC catchment population. However, it should be noted that the age categories used by Statistics Netherlands differ slightly from those in the LUMC and NIVEL databases (0-5, 5-65, and ≥ 65 years old).[15]

The ILI incidence in primary care was calculated as the number of ILI patients consulting the GP per week, divided by the total number of patients enrolled in participating sentinel GP practices, and expressed per 10,000 persons. The crude mortality in South Holland was calculated as the number of deceased patients, divided by the total number of persons of South-Holland and expressed per 10,000 persons. It is important to note that crude mortality was used only for comparing trends, as it reflected a larger population than the LUMC catchment population. Therefore, the magnitude of all-cause mortality per week was not relevant to this study.

Descriptive statistics were used to compare trends in ARI in secondary care, ILI in primary care, and crude mortality, including three-week moving average incidences, cumulative incidence, and peak incidence. The peak incidence per season for ARI, ILI, and crude mortality was defined as the highest incidence in a season. Data are presented for all ages in total and for the three defined age groups separately. The cumulative incidence calculations were limited to seven respiratory years (2008/2009-2014/2015). The time-lag between peak ARI and ILI was defined as the number of weeks between the ARI incidence peak in secondary care and ILI incidence peak in primary care. The time-lag between peak ARI in secondary care and all-cause mortality was defined as the number of weeks between the incidence peak for ARI in secondary care at LUMC and the peak of crude mortality in South Holland. Median and interquartile range (IQR) are used to describe these time-lags. Statistical analysis was performed using SPSS (version 22) and Excel (version 2010).

RESULTS

Hospital and primary care consultations

Three-week moving incidence averages of ARI in secondary care and ILI in primary care showed clear peaks during the respiratory season. On visual inspection of the time series, elevations of ARI in secondary care appear broader than for ILI (Figure 1).

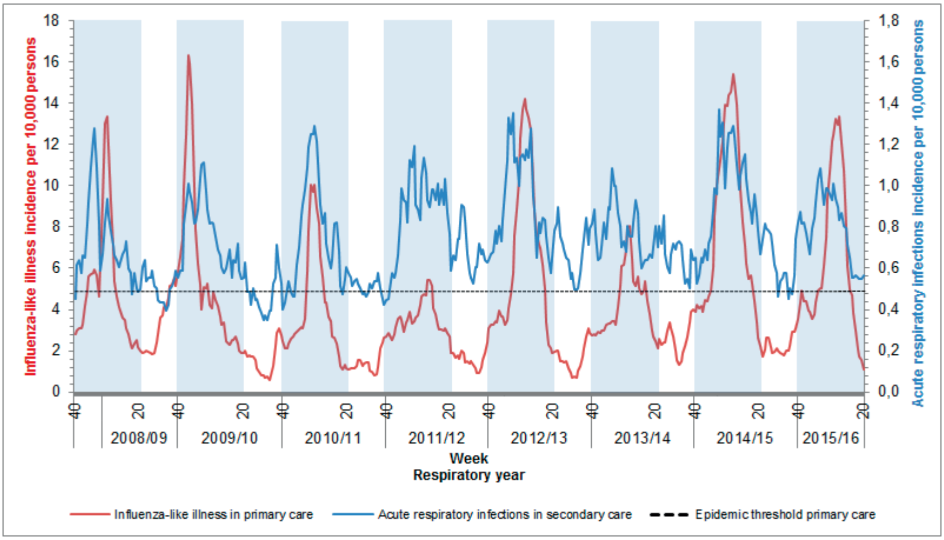

Figure 1. Three-week moving average incidence of acute respiratory infection in secondary care and influenza-like illness in primary care (2008-2016).
The epidemic threshold is 5.1 cases per 10,000 persons and is based primary care data.[16] Blue shading depicts the respiratory season (week 40 through week 20 the following year).

High ILI incidence was confined to the respiratory season (e.g. week 40 through week 20 the following year), whereas ARI incidence in secondary care showed a more diverse pattern, with clear peaks more frequent in winter but not entirely restricted to the respiratory season. The highest peak in weekly incidence for ARI in secondary care was

2.2 cases/10,000 persons (week 1 of 2015), and peak ILI incidence was 19.1 cases/10,000 persons (week 46 of 2009) (Appendix 2, Table 1, and Appendix 3, Table 2). The ARI peaks in secondary care generally occurred earlier than the ILI peaks in primary care, except during the influenza pandemic season of 2009/2010 and the post-pandemic season of 2010/2011. Overall, the median time-lag between ARI and ILI peaks was six and a half weeks (IQR 0 - 9 weeks). During the six seasons in which ARI peaked before ILI, the median time-lag was eight weeks (IQR 6 - 9 weeks). In the respiratory years of 2013/14 and 2015/16, the ARI peak in secondary care was reached earlier than the start of the influenza epidemic, based on ILI and virus diagnostic data from primary care in the Netherlands. Mortality in the province of South Holland as well as ARI in secondary care show winter peaks in the respiratory season. However, crude mortality elevations appear broader with less well-defined peaks than ARI elevations (Figure 2).

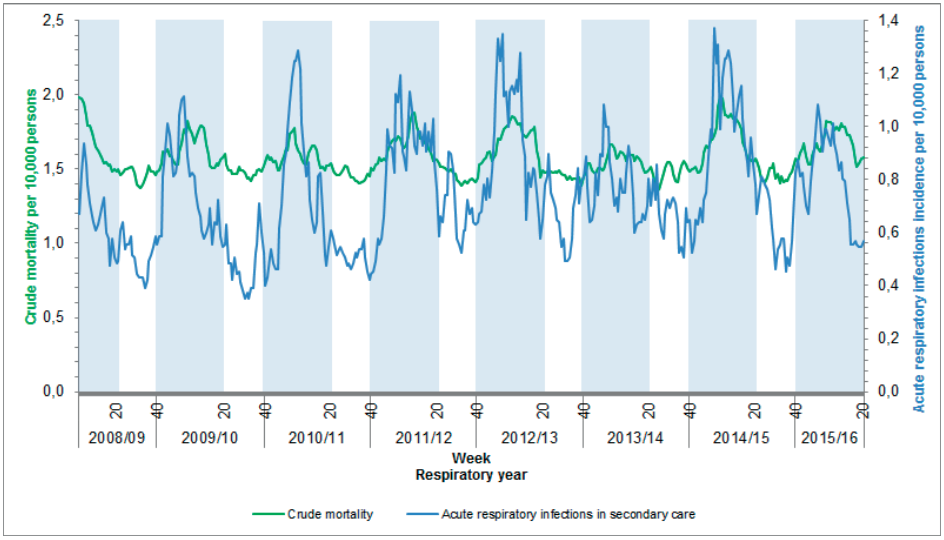

Figure 2. Three-week moving average incidence of acute respiratory infections in secondary care and crude mortality (2008-2016).
Blue shading depicts the respiratory season (week 40 through week 20 the following year).

Mortality almost exclusively occurred among patients 65 years and older. Overall, the crude mortality peak lagged a median 5 weeks behind the ARI peak (IQR 3 - 7 weeks).

Three respiratory seasons (2009/2010, 2011/2012 and 2014/2015) are presented below in more detail to demonstrate the value of routinely collected data on respiratory infections in hospitals.

Respiratory year 2009/2010

During the 2009 influenza pandemic period, ILI incidence in primary care peaked early in the respiratory season (week 46 of 2009), which was not the case for ARI in secondary care (week 52 of 2009). The peak for ARI in secondary care was lowest of all eight respiratory seasons (1.2 cases/10,000 persons). During the pandemic, the highest peaks for ARI in secondary care and ILI in primary care were seen in the 0-4-year olds (Appendix 3, Table 2, and Appendix 4, Table 3). In addition, the pandemic season showed a moderate cumulative incidence for ARI in secondary care (35 cases/10,000 persons), which was within the range of respiratory seasons 2008/2009 and 2010/2011. Compared to the other six respiratory years, the cumulative ILI incidence in 2009/2010 was also in the middle range (Appendix 5 Table 4).

Respiratory year 2011/2012

In the respiratory year 2011/20212, the ILI peak in primary care was low (7.4 cases/10,000 persons), but the peak for ARI in secondary care was considered moderate (1.6 cases/10,000 persons) compared to other eight respiratory years (Appendix 2, Table 1, and Appendix 3, Table 2). The cumulative incidence for ARI in secondary care was the second highest, while ILI cumulative incidence was the lowest of all seven respiratory years (Appendix 5, Table 4).

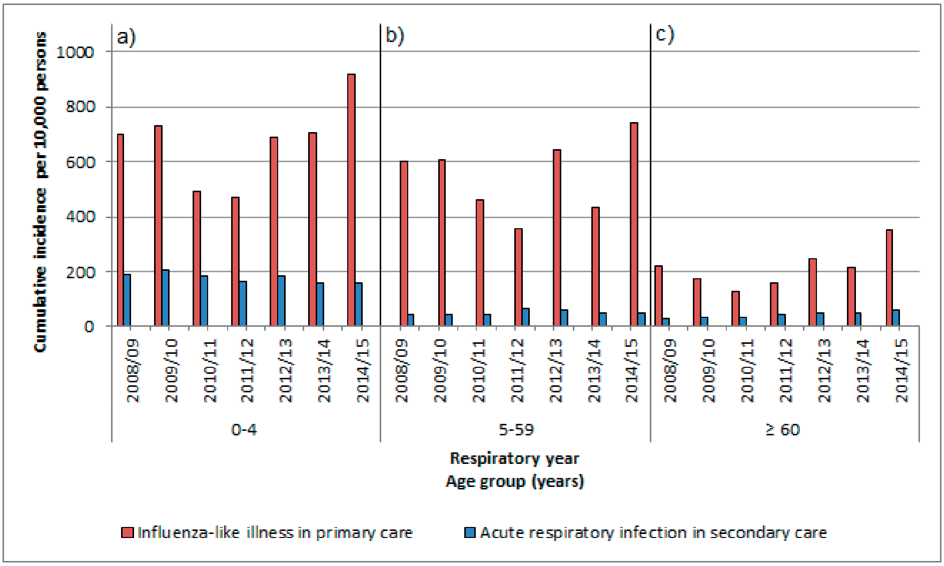

Figure 3. Cumulative incidence of acute respiratory infections in secondary care and influenza-like illness in primary care per age category (2008-2015).

Panel charts a, b and c present the cumulative incidence per age groups (0-4, 5-59, ≥ 60 years old) and respiratory year. The respiratory year 2015/2016 is not included, because data were complete to week 20.

Respiratory year 2014/2015

In the respiratory year 2014/15, a high peak was found for ILI in primary care (16.1 cases/10,000 persons) and ARI in secondary care (2.2 cases/10,000 persons). The highest peak in both primary and secondary care was found among 0-4-year olds, followed by ≥60-year olds (Appendix 3, Table 2 and Appendix 4, Table 3). The cumulative incidence for ILI in 2014/2015 was the highest since 2008/2009 (310 cases/10,000 persons), but cumulative incidence for ARI in secondary care was the lowest since 2008/2009 (31 cases/10,000 persons). All three age groups in primary care showed highest cumulative incidence in this year, while in secondary care this was the case only for ≥60-year olds (Figure 3).

DISCUSSION

This observational study demonstrates that routinely collected data can be used for describing trends of ARI in secondary care and may be suitable for near-real-time SARI-surveillance. We show that ARI incidence in secondary care peaked earlier than ILI incidence in primary care in six of the eight respiratory seasons, with a median time-lag of six and a half weeks. Similar trends were seen in crude mortality, primarily attributable to patients of 65 years and older, and ARI in secondary care.

ARI in secondary care versus ILI in primary care

Our principal finding that ARI in secondary care peaks before ILI in primary care in most respiratory seasons could be explained by high-risk patient groups. We hypothesised that these high-risk groups are elderly patients with comorbidities. As in many European countries, the Dutch population is ageing, and elderly patients with comorbidities increasingly live at home.[17,18] This frail, high-risk patient group is associated with an increased demand for hospital admissions.[19-21] In most seasons, this demand could be reflected in an earlier incidence peak for ARI in secondary care compared to the incidence peak for ILI in primary care. Only for the pandemic and post-pandemic seasons did we find an inverted time-lag, which is hard to explain without additional data on co-morbidities and microbiological test results. However, a disproportionately higher ARI incidence in the younger age versus older age groups is likely to play a role.[22,23]

The finding that ARI incidence in secondary care peaks before ILI in primary care in most respiratory seasons is important for SARI surveillance in terms of preparedness and emergency response.[24,25] Timeliness is critical for detecting outbreaks and taking required public health action to reduce their size, ultimately leading to lower morbidity and mortality [24,26]. Our result confirms the need for SARI surveillance data in the timely detection of future outbreaks and indicates that we cannot depend solely on primary care data.

Our results are consistent with another Dutch study in which respiratory ICU admissions[27] were compared with ILI incidence in primary care from 2007-2015.[28] Its data indicate that in six of the nine seasons studied, increase in respiratory ICU admissions preceded ILI trends with a median time-lag of one week. In contrast to our results, a German study by Buda et al. found that the trend of SARI peaks closely matched the peaks for respiratory infections in primary care in the influenza seasons 2012-2016.[29] Comparison with our study is difficult, because of large differences in methodology and health care systems.

ARI in secondary care versus crude mortality

Comparing ARI incidence in secondary care with crude mortality showed a similar trend, with peaks in winter over a period of eight respiratory years. The incidence peaks for crude mortality in the province of South Holland are probably associated with ARI peaks in secondary care in the LUMC catchment area, but mortality cannot be completely attributed to ARI because disease-specific data were not available to this study. The seasonality of crude mortality has been clearly documented and is primarily caused by increase in deaths in the elderly during winter.[30,31] Van Asten et al. stated that winter peaks of all-cause mortality are often largely attributed to influenza and sometimes cold snaps, but other pathogens, such as respiratory syncytial virus, parainfluenza, and norovirus, may also play a substantial role in the mortality of the elderly.[32]

Historical data on ARI in secondary care

Our results suggest that historical data on ARI in secondary care may be of value for early detection of outbreaks and for providing insight into the severity of epidemics, if used in a near-real-time surveillance system. In particular, the seasons 2009/2010, 2011/2012, and 2014/2015 illustrate their value for SARI surveillance. During the influenza A(H1N1) pandemic season, the cumulative ARI and ILI incidence indicated a relatively moderate season in hospitals and primary care, with the 0-4-year old age group most affected. This aligns with other studies and confirms the moderate impact of the influenza A(H1N1) pandemic.[22,23,33] The 2011/2012 season is of interest, because of a rather severe respiratory year in hospitals even while, based on primary care data, the criteria for an influenza epidemic were not met. The discrepancy went unnoticed at the time, because there was no real-time surveillance of ARI in secondary care. During the influenza A(H3N2)-dominant 2014/2015 season in the Netherlands, the longest influenza epidemic was recorded since the start of surveillance in 1970 and occurred against the background of an influenza vaccine mismatch.[34] Our data show high incidence peaks in both primary and secondary care, especially for patients ≥60 years of age. Such peaks often coincide with a high demand on bed capacity and increased need for qualified medical staff due to sickness absenteeism in hospitals.[35,36] If these data had been available on a weekly basis in 2014/2015, hospitals might have been better prepared for the high number of patients by timely upscaling of bed capacity, using cohort isolation, and recruiting additional medical personnel.

Limitations

Several limitations should be taken into account when interpreting these findings. First, the absence of microbiological diagnostics results is an important barrier to interpreting incidence differences between ILI in primary care and ARI in secondary care. Data on microbiological test results would be needed to explain the whole spectrum of respiratory infections and to better understand the time-lag between ILI, ARI, and mortality per season. For example, the influenza-related SARI could be more accurately defined and make comparisons with ILI more biologically plausible. Together with data on medical history, such as co-morbidities and place of residence (e.g. long-term care facility versus home), it could clarify which patient group is primarily reflected in the peak of ARI incidence in secondary care. In the setting of SARI surveillance, detection of causative pathogens is crucial in mitigating the effect of disease outbreaks by taking timely health care interventions.[37-39]

A second limitation is that we used retrospective data to describe trends for ARI and ILI. Robust 'real-time' SARI-surveillance data are not yet available in the Netherlands. Thirdly, incidence calculations for ARI in secondary care were based on one hospital in the western part of the Netherlands. Although the catchment population of this hospital is large, inclusion of more hospitals with a nationally representative distribution would have increased representativeness and generalisability of the study results. Fourthly, this study used 'acute respiratory infections in secondary care' as a proxy for SARI patients, because no distinction could be made between patients admitted to hospital, reviewed at the outpatient clinic, or discharged home. This could have led to overestimation of incidence calculations.

CONCLUSIONS

This observational study shows that data on ARI in secondary care are of added value for early detection of outbreaks and providing insight into the severity of epidemics, if used in a near-real-time surveillance system. The principal finding is that in most respiratory seasons, the peak of ARI incidence in secondary care preceded the peak of ILI incidence in primary care. This is crucial information for preparedness and emergency control. Adding microbiological test results to these incidence data would be of great value in explaining the whole spectrum of ILI in primary care, ARI in secondary care, and mortality.

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APPENDIX 1

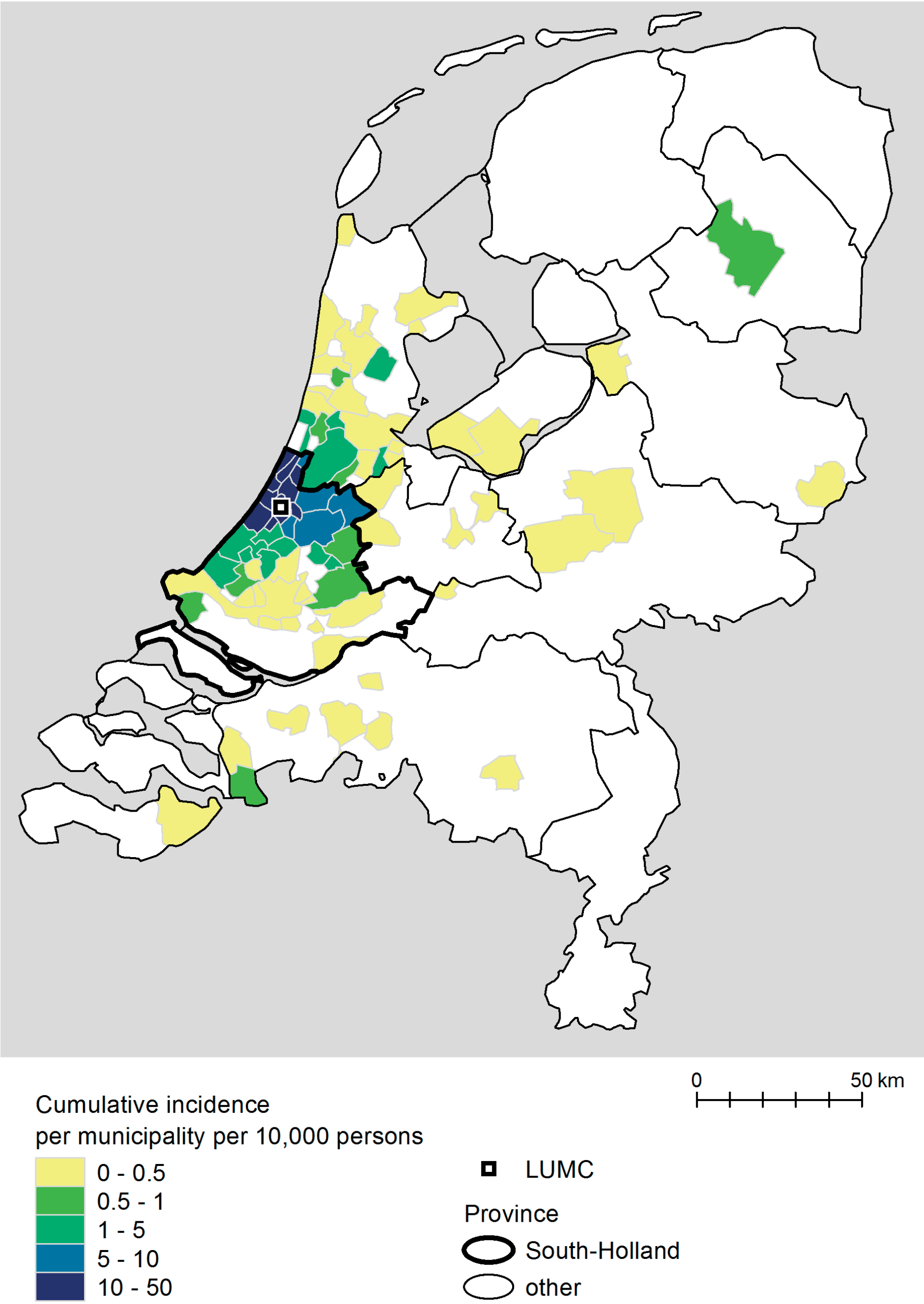

Figure 4 Cumulative incidence of respiratory tract infections per municipality per 10,000 persons in the catchment population of Leiden University Medical Center.

APPENDIX 2

Table 1 Incidence peak, peak week and time-lag for acute respiratory infections in secondary care, influenza-like illness in primary care, and crude mortality in the period 2008-2016.

Respiratory year	Dataset†	Peak (week number)	Time-lag relative to ARI (weeks)	Peak incidence‡
2008/2009	ARI	50		1.39
	ILI	3	5	14.14
	MOR	3	5	
2009/2010	ARI	52		1.21
	ILI	46	-6	19.07
	MOR	3	4	
2010/2011	ARI	5		1.39
	ILI	3	-2	11.34
	MOR	1	-4	
2011/2012	ARI	1		1.64
	ILI	10	9	7.42
	MOR	8	7	
2012/2013	ARI	51	6	1.55
	ILI	5		16.23
	MOR	5	6	
2013/2014	ARI	49		1.24
	ILI	7	10	8.98
	MOR	2	5	
2014/2015	ARI	1		2.23
	ILI	8	7	16.12
	MOR	3	2	
2015/2016	ARI	51		1.30
	ILI	7	9	14.81
	MOR	8	10	

†ARI: acute respiratory infections in secondary care ‡incidence per 10,000 persons
ILI: influenza-like illness in primary care MOR: crude mortality

APPENDIX 3

Table 2. Incidence peak, peak week, and age group for acute respiratory infections in secondary care in the period 2008-2016.

Respiratory year	Age group (years)	Peak (week number)	Peak incidence†
2008/2009	0-4	50	12.58
	5-59	19	0.55
	≥ 60	49	1.32
	Total	*50*	*1.13*
2009/2010	0-4	51	9.73
	5-59	45	0.72
	≥ 60	36	1.38
	Total	*52*	*0.98*
2010/2011	0-4	3	10.83
	5-59	15	0.55
	≥ 60	5	1.80
	Total	*5*	*1.13*
2011/2012	0-4	49	7.22
	5-59	1	0.80
	≥ 60	7	2.32
	Total	*1*	*1.33*
2012/2013	0-4	51	11.84
	5-59	10	0.84
	≥ 60	10	1.95
	Total	*51*	*1.25*
2013/2014	0-4	52	7.82
	5-59	10	0.67
	≥ 60	23	2.02
	Total	*49*	*1.00*
2014/2015	0-4	1	9.04
	5-59	1	0.67
	≥ 60	1	3.54
	Total	*1*	*1.80*
2015/2016	0-4	51	10.46
	5-59	2	0.64
	≥ 60	2	1.54
	Total	*51*	*1.05*

†incidence per 10,000 persons

APPENDIX 4

Table 3. Incidence peak, peak week, and age group for influenza-like illness in primary care in 2008-2016.

Respiratory year	Age group (years)	Peak (week number)	Peak incidence[†]
2008/2009	0-4	3	44.31
	5-59	4	11.79
	≥ 60	3	19.57
	Total	*3*	*14.14*
2009/2010	0-4	46	62.89
	5-59	46	19.70
	≥ 60	1	8.72
	Total	*46*	*19.07*
2010/2011	0-4	3	37.31
	5-59	3	11.17
	≥ 60	1	8.18
	Total	*3*	*11.34*
2011/2012	0-4	51	26.42
	5-59	10	5.93
	≥ 60	10	8.72
	Total	*10*	*7.42*
2012/2013	0-4	5	52.24
	5-59	5	15.07
	≥ 60	8	15.08
	Total	*5*	*16.23*
2013/2014	0-4	7	35.86
	5-59	7	7.51
	≥ 60	11	9.74
	Total	*7*	*8.98*
2014/2015	0-4	7	59.06
	5-59	8	12.65
	≥ 60	8	21.03
	Total	*8*	*16.12*
2015/2016	0-4	5	46.61
	5-59	7	13.86
	≥ 60	9	14.92
	Total	*7*	*14.81*

[†]incidence per 10,000 persons

APPENDIX 5

Table 4. Cumulative incidence of acute respiratory infections in secondary care versus influenza-like illness in primary care in the respiratory years 2008/2009-2014/15

Respiratory year	Cumulative incidence acute respiratory infection secondary care†	Cumulative incidence influenza-like illness primary care†
2008/2009	34	232
2009/2010	35	221
2010/2011	35	161
2011/2012	42	148
2012/2013	43	248
2013/2014	39	192
2014/2015	31	310
Total	*259*	*1513*