Severe acute respiratory infections, the missing link in the surveillance pyramid

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CHAPTER 4

Incidence and costs of hospitalised adult influenza patients in the Netherlands: a retrospective observational study

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ABSTRACT

OBJECTIVE

Influenza virus infections cause a high disease and economic burden during seasonal epidemics. However, there is still a need for reliable disease burden estimates to provide a more detailed picture of the impact of influenza. Therefore, the objectives of this study is to estimate the incidence of hospitalisation for influenza virus infection and associated hospitalization costs in adult patients in the Netherlands during two consecutive influenza seasons.

METHODS

We conducted a retrospective study in adult patients with a laboratory confirmed influenza virus infection in three Dutch hospitals during respiratory seasons 2014–2015 and 2015–2016. Incidence was calculated as the weekly number of hospitalised influenza patients divided by the total population in the catchment populations of the three hospitals. Arithmetic mean hospitalisation costs per patient were estimated and included costs for emergency department consultation, diagnostics, general ward and/or intensive care unit admission, isolation, antibiotic and/or antiviral treatment. These hospitalisation costs were extrapolated to national level and expressed in 2017 euros.

RESULTS

The study population consisted of 380 hospitalised adult influenza patients. The seasonal cumulative incidence was 3.5 cases per 10,000 persons in respiratory season 2014–2015, compared to 1.8 cases per 10,000 persons in 2015–2016. The arithmetic mean hospitalisation cost per influenza patient was €6,128 (95% CI €4,934–€7,737) per patient in 2014–2015 and €8,280 (95% CI €6,254–€10,665) in 2015–2016, potentially reaching total hospitalisation costs of €28 million in 2014–2015 and €20 million in 2015–2016.

CONCLUSIONS

Influenza virus infections lead to 1.8–3.5 hospitalised patients per 10,000 persons, with mean hospitalization costs of €6,100–€8,300 per adult patient, resulting in 20–28 million euros annually in The Netherlands. The highest arithmetic mean hospitalisation costs per patient were found in the 45–64 year age group. These influenza burden estimates could be used for future influenza cost-effectiveness and impact studies.

INTRODUCTION

Influenza virus infections cause a high disease and economic burden during seasonal epidemics. The World Health Organization (WHO) estimated that seasonal influenza epidemics caused annually 3-5 million cases of severe disease.[1] Estimates of global seasonal influenza-associated respiratory deaths amount to 4.0-8.8 per 100,000 persons annually, but wide variation between countries exists.[2] The highest burden of disease due to influenza is seen in the specific high risk groups: children aged 0-4 years and elderly with underlying comorbidities.[3]

In Europe, influenza is the infectious disease with the highest estimated annual burden, responsible for 30% of the total burden caused by 31 selected infectious diseases.[4] In the Netherlands, the burden was estimated at 16,316 disability-adjusted life years (DALY) in 2016, using an incidence- and pathogen-based approach and corrected for underreporting and under-ascertainment.[5] To provide a more detailed picture of the impact of influenza, reliable influenza incidence and cost estimates are necessary. This could help making informed decisions about allocating resources, such as vaccines and antivirals, and planning influenza intervention strategies to limit the spread of influenza and minimize the costs.[6]

However, data on direct medical costs and incidence of hospitalised influenza patients are limited. In the United States (US) the average direct medical costs of seasonal influenza epidemics, based on 2003 US population demographics, was estimated at 10.4 billion dollar annually.[7] Dutch cost estimates are only available for total community-acquired pneumonia (CAP) hospitalised patients, but not further specified for influenza virus infections.[8-12] Moreover, incidence for influenza-like illness (ILI) are limited to patients visiting their general practitioner in primary care.[13] Since, reliable influenza incidence calculations and influenza-associated economic costs in secondary care are unavailable in the Netherlands, we estimated incidence of hospitalisation for influenza virus infections and associated hospitalisation costs for the first time.

METHODS

STUDY POPULATION AND PERIOD

The study population consisted of adult patients with a laboratory-confirmed influenza virus infection admitted to three Dutch hospitals (Jeroen Bosch Hospital (JBZ), Leiden University Medical Center (LUMC), and University Medical Center Utrecht (UMCU)) during the two respiratory seasons 2014-2015 and 2015-2016. The respiratory season was defined as the period from week 40 through week 20 the following year. Influenza

A(H3N2) was the dominating influenza virus in season 2014-2015, while influenza A(H1N1)pdm09 was dominant in season 2015-2016.[14,15] JBZ is a large regional hospital with 575 beds in the south-eastern part of the Netherlands. LUMC (585 beds) and UMCU (±1100 beds) are large tertiary academic hospitals, situated in the western part (LUMC) and central part (UMCU) of the Netherlands. The inclusion criteria for patients were: 1) hospital admission for severe acute respiratory infection (SARI) according to the WHO SARI case definition[16], 2) being 18 years or older, and 3) having a positive influenza virus test using real-time polymerase chain reaction (RT-PCR).[17] Taking into account the Dutch Working Party on Antibiotic Policy (SWAB) guidelines[18] (JBZ and UMCU) and local hospital guidelines (LUMC), all influenza virus tests were requested at the discretion of the treating physician depending on the differential diagnosis. It has to be noted that the SWAB guidelines on influenza primarily focus on the preferred swabbing location, antiviral treatment, and antibiotic treatment of *S. aureus* in ICU patients during the influenza season. Patients hospitalised shorter than 24 hours, readmissions within ten days, and patients with hospital-acquired pneumonia were excluded. In case of a readmission within ten days, the initial admission was included and only the re-admission excluded. In the Netherlands, an influenza epidemic is declared if the incidence of medically-attended ILI in primary care is above the threshold of 5.1 per 10,000 persons per week for at least two consecutive weeks in combination with the detection of influenza virus in combined nasal and throat swabs from a selection of ILI patients.[19]

DATA COLLECTION

Data was collected retrospectively from electronic patient records in all three hospitals. The dataset consisted of age, gender, comorbidities (for details see supplemental file Table S1), influenza virus type (A/B), length of hospital stay (LOS) in days, intensive care unit (ICU) admission (yes/no, and length of ICU stay in days), droplet and contact isolation (yes/no), antibiotic therapy (yes/no), oseltamivir treatment (yes/no), and in-hospital mortality (yes/no, date) (Table 1). Patients were stratified by age in four categories (18-44, 45-64, 65-74 and ≥75 years) and by risk of severe or complicated influenza illness in three groups (low, medium and high risk), based on the presence of comorbidities[20,21,10] (supplemental file Table S1). It was not feasible to collect data on influenza vaccination status, because it is not routinely documented in electronic patient records and a national influenza vaccination registry is not in place in the Netherlands.

INCIDENCE ESTIMATE

Incidence per respiratory season was calculated as the number of influenza patients admitted to the hospital per week, divided by the catchment population of the three hospitals and expressed per 10,000 persons. The catchment population was calculated by dividing the total number of hospitalisations due to respiratory tract infection (RTI) in each hospital by the total hospitalisations because of RTI in the Netherlands and multiplying this proportion by the total Dutch population size for each year available.[22] It is important to note that it concerns the catchment population for RTI only, and is therefore not applicable for incidence calculations related to other type of disease.[6] The data required for the calculation of the catchment population of each hospital were provided by the National Register of hospital discharge diagnosis (Dutch Hospital Data) (supplemental file Table S2). 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 each hospital for the years 2014, 2015 and 2016 (supplemental file Figure S1 footnote).[22,23] Taking into account the non-normal distribution of the catchment population over the available respiratory seasons, we used the *median* value for our incidence calculations.

COSTS ESTIMATES

Hospitalisation costs were estimated using a bottom-up approach and included costs for the emergency department (ED) visit, requested diagnostics during stay on the ED, hospitalisation stay in a general ward and the ICU, medication costs for antibiotic and oseltamivir treatment, isolation in general ward rooms and associated costs. Associated isolation costs involve the use of gloves, Free Flight Phase 1 (FFP1) masks, and additional work load for medical and cleaning personnel and were not included in the daily costs of admission on a regular ward or ICU.

Hospitalisation costs were calculated by multiplying recorded units of used healthcare resources with corresponding unit prices (supplemental file Table S3). Unit prices for laboratory tests were retrieved form the Dutch Healthcare Authority[24], medication prices from the National Health Care Institute[25], and medical consultations and hospital admissions were estimated using Dutch reference prices[26], using the weighted mean unit cost for hospital admission. The weighted mean unit cost takes into account the distribution of general ward and academic hospital beds in the Netherlands. Diagnostics for patients with an RTI on an emergency ward were assumed to include a chest X-ray and laboratory diagnostic tests, including full blood examination, respiratory viral PCR panel, and urine analysis (see supplemental file, Table S3). The urine analysis included an urine screening test and a pneumococcal urinary antigen test. For ICU patients, diagnostics, isolation and medication costs were already included in the total ICU admission costs. Costs for antibiotic treatment on the general ward were calculated for average antibiotic therapy course of one week in line with the most recent SWAB guidelines.[18] Different antibiotic SWAB treatment regimens on the general ward for mild and moderate severe CAP (β-lactam antibiotic) versus severe CAP ($2^{nd}/3^{rd}$ generation cephalosporin) were chosen for costs estimations of antibiotic treatment.[27] Medication costs for oseltamivir on the general ward were calculated for the duration of five days according to SWAB guidelines. A bottom-up calculation was done for the additional costs for isolation in the first week of admission in the general ward, including residing in single rooms, additional associated workload for medical personnel, and usage of FFP1 masks.[28,29]

Arithmetic mean hospitalisation costs per adult influenza patient were estimated and extrapolated to the national level. We attempted to obtain annual national hospitalisation costs attributable to influenza by multiplying the estimated influenza incidence with the estimated average hospital costs per influenza patient. We could not exclude that the number of more severely affected patients, resulting in an extremely prolonged hospital stay, might have been overrepresented in our study sample. Therefore, geometric mean hospitalisation costs were calculated and used as a sensitivity analysis to take into account skewed data with several outliers (supplemental file Table S4). Costs were presented in 2017 euros and, if necessary, updated using the Dutch Consumer Price index.[30]

We performed a sensitivity analysis to examine to what extent the exclusion of influenza patients admitted shorter than 24 hours influenced our cost analysis. For the sensitivity analysis, we collected additional data on influenza patients admitted shorter than 24 hours in one hospital (LUMC). The proportion of patients admitted shorter than 24 hours versus admitted longer than 24 hours in LUMC was used as a proxy for the other two hospitals (JBH and UMCU). Arithmetic mean hospitalisation costs per influenza patient was calculated per subgroup (admitted <24 hours, admitted>24 hours) (supplemental file Table S5).

In addition, to provide more insight into the differences of hospitalisation costs between risk groups, we reviewed electronic patients records for detailed information on complications in a proportion of patients (21%) with the top highest hospitalisation costs.

STATISTICS

Descriptive statistics were used for reporting the baseline characteristics of the study population, such as total number, percentage per category, median and interquartile range (IQR). Arithmetic and geometric means were used for hospitalisation cost data. A Chi-square test was used to compare categorical variables. A Mann-Whitney U test, Kruskal-Wallis test, or unpaired T-test was performed for numerical variables depending on their distribution and number of groups. Missing values were imputed using multiple imputation, creating five imputed datasets. Bootstrapping with 1,000 iterations was used to determine 95% confidence intervals (CI). A p-value of <0.05 was considered significant. Data were analysed using IBM SPSS Statistics, Version 24.

RESULTS

STUDY POPULATION

A total number of 380 influenza patients were admitted to the three Dutch hospitals (catchment population 718,000 persons) during respiratory seasons 2014-2015 and 2015-2016 (Table 1). The median number of all-cause hospitalisations was approximately 31,000 in the three hospitals in the period 2014-2016. The study patients had a median age of 65 years and most patients belonged to the 45-64 and ≥75 age groups (respectively 34% and 31%). The influenza patients had a median of two comorbidities and were classified in the medium and high risk group in respectively 33% and 55% of the cases. The most prevalent comorbidities were cardiovascular disease (50%), followed by immunodeficiency due to disease or medication (35%) and chronic respiratory disease (35%). The median length of hospital stay was 5 days and 18% of the patients were admitted to ICU. In both respiratory seasons, influenza A virus was the most common influenza type. A high proportion of influenza patients were treated with antibiotics (79%), because of a suspected bacterial superinfection as a complication of influenza. The total in-hospital mortality for influenza patients was 6% during two consecutive respiratory seasons (supplemental file Table S6).

INCIDENCE

In respiratory season 2014-2015, the seasonal cumulative incidence was 3.5 cases per 10,000 persons and the incidence peaked at 0.3 cases per 10,000 persons in week 5. The seasonal cumulative incidence was 1.8 cases per 10,000 persons in respiratory season 2015-2016 and the incidence for hospitalised influenza patients (0.3 cases per 10,000 persons) peaked at week 7 (supplemental file Figure S1).

HOSPITALISATION COSTS PER PATIENT

The arithmetic mean hospitalisation costs per influenza patient was €6,128 (95% CI €4,934 - €7,737) in 2014-2015, €8,280 (95% CI €6,254 - €10,665) in 2015-2016 and €6,870 (95% CI €5,750 - 8,071) in 2014-2016 (Figure 1). No significant differences in hospitalisation costs between the two seasons were found (p=0.58) (supplemental file Table S7). General ward and ICU costs accounted for respectively 46% and 45% of the mean hospitalisation costs per patient. In both respiratory seasons, the arithmetic mean hospitalisation costs per patient in the general hospital (€8,247, 95% CI €6,583 - €10,206) was significantly (p=0.00) higher than in the university hospitals (€6,365, 95% CI €5,078 - €8,132) (Table 2).

Table 1. Baseline characteristics of influenza patients during respiratory seasons 2014-2015 and 2015-2016

	General hospital	Academic hospitals	p-value*	Total
Admission, n	102	278		380
Age, median (IQR)	75 (59-84)	62 (48-74)	0.00	64.5 (52-77)
Age category n (%)				
• 18-44 years	7 (6.9)	56 (20.1)	0.00	63 (16.6)
• 45-64 years	30 (29.4)	98 (35.3)		128 (33.7)
• 65-74 years	16 (15.7)	55 (19.8)		71 (18.7)
• ≥75 years	49 (48.0)	69 (24.8)		118 (31.1)
Male, n (%)	48 (47.1)	170 (61.2)	0.01	218 (57.4)
Female, n (%)	54 (52.9)	108 (38.8)		162 (42.6)
Risk group, n (%)				
• Low	17 (16.7)	31 (11.1)	0.00	48 (12.6)
• Medium	58 (56.9)	66 (23.7)		124 (32.6)
• High	27 (26.5)	181 (65.1)		208 (54.7)
Number of comorbidities, median n (IQR)[a]	1 (1-2)	1 (1-3)	0.53	2 (1-2)
ICU, n (%)	20 (19.6)	50 (18.0)	0.72	70 (18.4)
Length of hospital stay, median (IQR)	9 (5-15)	4 (2-8)	0.00	5 (3-11)
• General ward days per patient	8 (5-13)	3 (2-6)	0.00	5 (3-11)
• ICU days per ICU patient	5 (2-11)	5 (2-11)	0.97	5 (2-10)
Influenza virus, n (%)				
• Type A	80 (78.4)	214 (77.0)	0.15	294 (77.4)
• Type B	22 (21.6)	54 (19.4)		76 (20.0)
• Type A & B	0 (0)	10 (3.6)		10 (2.6)
Antibiotic treatment, n (%)[b]	73 (73.7)	224 (80.6)	0.15	297 (78.8)
Oseltamivir treatment, n (%)[c]	46 (46.5)	142 (51.1)	0.43	188 (49.9)
In-hospital mortality, n (%)	5 (4.9)	16 (5.8)	0.75	21 (5.5)

*Statistical difference tested between general hospital and academic hospitals using unpaired t-test, Mann-Whitney U test, Kruskal-Wallis test or Chi-square test.

[a]missing general hospital: n=0, academic hospital: n=118.

[b]missing general hospital: n=3, academic hospital: n=0.

[c]missing general hospital: n=3, academic hospital: n=0.

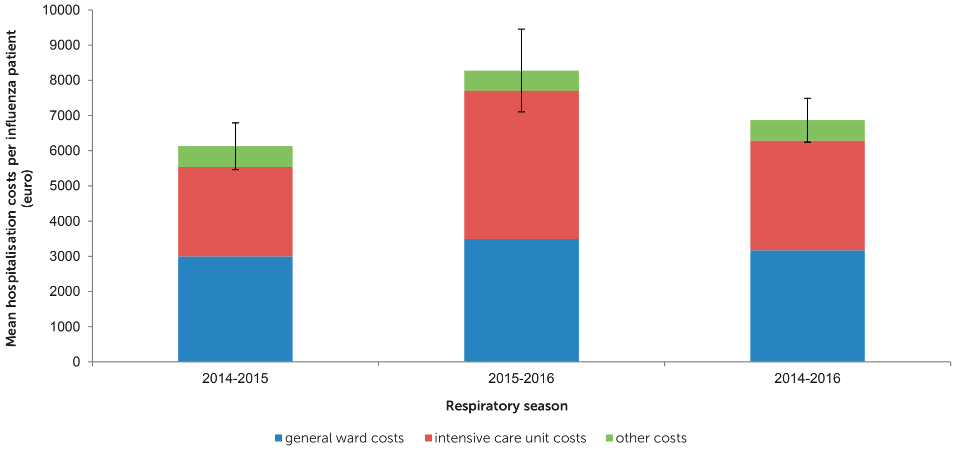

Figure 1. Arithmetic mean hospitalisation costs per influenza patient admitted to three Dutch hospitals during respiratory seasons 2014-2015 and 2015-2016

*Error bars indicate the 95% confidence interval as determined by bootstrapping.

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Table 2. Arithmetic mean hospitalisation costs per hospital type (general and academic) per influenza patient during respiratory seasons 2014-2015 and 2015-2016

Hospital	Patients (n)	Hospitalisation costs per patient (2017 euros)*	
		Arithmetic mean	95% CI
General hospital[a]	102	8,247	6,583 - 10,206
Academic hospital[b]	278	6,365	5,078 - 8,132
Total	380	6,870	5,779 - 7,994

[a]JBZ.
[b]LUMC and UMCU.
*Statistically significant difference between general hospital and academic hospitals using a Mann-Whitney U test; p=0.00.

The arithmetic mean hospitalisation costs was highest for the 45-64 year age group (€8,970, 95% CI €6,610 - €11,694) (Figure 2, supplemental file Table S8) and the low risk group (€14,249, 95% CI €8,798 - €21,345) during respiratory seasons 2014-2015 and 2015-2016 (Table 3). The 45-64 year age group had the highest percentage of ICU admissions (8.4%) and the longest median ICU stay per admitted ICU patient (8 days). The low risk group had the longest median LOS per patient (7 days) and longest median stay in ICU (18 days) (supplemental file Table S9). Analysis within the low risk group with high hospitalisation costs reported an outlier (€134,395) in 2014-2015, which belonged to a 53-year old ICU patient with the longest LOS (86 days; including both ward and ICU days). If this patient was excluded from the analysis, the arithmetic mean hospitalisation costs per influenza patient amounted to €6,534 (95% CI €5,570 - €7,510) in 2014-2016.

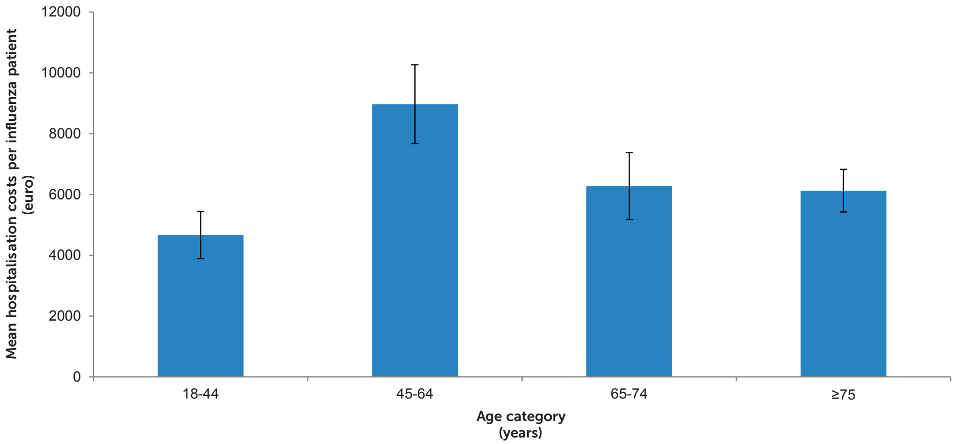


Figure 2. Arithmetic mean hospitalization costs per age category per influenza patient admitted to three Dutch hospitals during respiratory seasons 2014-2015 and 2015-2016

*Error bars indicate the 95% confidence interval as determined by bootstrapping.

Table 3. Arithmetic mean hospitalisation costs per risk group per influenza patient admitted to three Dutch hospitals during influenza seasons 2014-2016

Risk group[a]	Total (n)	Arithmetic mean costs (2017 euros)*	95% CI
Low	48	14,249	8,798 - 21,345
Medium	124	6,973	5,453 - 9,206
High	208	5,132	4,230 - 6,246
Total	380	6,870	5,819 - 7,983

[a]Risk group classification of severe or complicated influenza illness in three groups (low, medium and high risk), based on the presence of comorbidities (supplemental file, Table S1).

*Statistically significant difference between risk groups using a Kruskal-Wallis test; p=0.01.

Acute respiratory distress syndrome (ARDS), as a complication of an influenza virus infection, was diagnosed more frequently in the low risk group (26%) versus the medium (12%) and high risk group (1%). In comparison to influenza patients with other complications (e.g. sepsis, acute renal injury requiring dialysis, heart failure) ARDS patients also had the longest median LOS (29 days).

If geometric mean hospitalisation costs were used, the total hospitalisation costs per influenza patient were €3,601 (95% CI €3,217 - €4,030) in 2014-2015, €4,099 (95% CI €3,398 - €4,944) in 2015-2016, resulting in €3,765 (95% CI €3,414 - €4,151) in 2014-2016 (supplemental file Table S4 and S10).

Taking into account influenza patients admitted less than 24 hours and over 24 hours, the arithmetic mean hospitalisation costs for influenza patients amounted to €6,208 in

2014-2016. If compared to hospitalisation cost excluding patients admitted less than 24 hours (€6,870), an arithmetic mean difference of €662 per influenza patient was found (supplemental file Table S5).

HOSPITALISATION COSTS ON NATIONAL LEVEL

Total hospitalisation costs on national level were approximated at €28 million in 2014-2015 and €20 million in 2015-2016. Using the geometric mean, rather than the arithmetic mean, these costs would approximate to €17 million in 2014-2015 and €10 million in 2015-2016 (supplemental file Table S4).

DISCUSSION

PRINCIPAL RESULTS

To our knowledge, this is the first Dutch study reporting influenza burden estimates in secondary care with regard to incidence and hospitalisation costs. Based on seasonal cumulative and peak incidence from three Dutch hospitals, the season 2014-2015 was considered more severe than the season 2015-2016. The arithmetic mean hospitalisation costs per influenza patient were €6,870 (95% CI €5,750 - €8,071) during respiratory seasons 2014-2016. If extrapolated to national level, the hospitalization costs of influenza patients amounted to 28 million in 2014-2015 and 20 million in 2015-2016. In addition, the general hospital had significantly higher arithmetic mean hospitalisation costs than the two academic hospitals. The highest arithmetic mean hospitalisation costs per patient were found in the 45-64 year age group and in the low risk group.

COMPARISONS WITH OTHER STUDIES

Incidence

Incidence of hospitalisation for laboratory-confirmed influenza virus infections in Europe is rarely available[31] and hospitalisations are mostly reported as absolute numbers without denominator.[32] The US Centers for Disease Control and Prevention (CDC) reported an incidence for laboratory-confirmed influenza hospitalisations of 6.4 cases per 10,000 persons in season 2014-2015 and 3.2 per 10,000 in season 2015-2016.[33] The incidence estimates are considerably higher than reported in our study, which could be due to different available healthcare system in both countries. In the Dutch healthcare system, the general practitioners (GPs) have a gatekeeping role for specialised care. This is illustrated by a Dutch study showing that the vast majority of CAP patients are managed successfully at GP level without hospitalisation.[34] In contrast, in the US approximately two thirds of the adult hospitalized patients with CAP were in a low risk group with respect to the risk of death, suggesting a low threshold for admitting CAP patients to hospital.[35,36]

Costs

Comparison with other studies is difficult due to differences in healthcare system, applied resource unit cost, case definition, study population, and/or taking readmissions into account.

Differences in healthcare system and resource unit prices[37-40] are illustrated by a Spanish[41], Italian[42], German[43] and Canadian study[44]. In Spain, despite a longer arithmetic mean LOS (11.1 days), a lower arithmetic mean costs per influenza hospitalization (in 2015 euros) in patients aged ≥65 years (€3,219) was reported. Italy reported similar mean hospitalisation costs for ILI/lower respiratory tract infection in patients 50 years and older (€3,353). In Germany, mean influenza hospitalisation costs (€5,832, in 2013 euros) were lower than in our study. In Canada, higher hospitalisation costs per influenza patient (in 2015 euros) were found (€10,312, 95% CI €9,776 – €10,848). The longer arithmetic mean LOS (10.8 days) and higher in-hospital mortality (9.3%), taking into account costs for readmissions within thirty days may also account for the difference with our study.

Differences in case definition and study population are illustrated by Dutch studies, which focused mainly on community-acquired pneumonia (CAP)[10,45,9] and invasive pneumococcal disease[10] in respectively an adult[45,9] and elderly population.[10] Vissink et al.[10] reported that mean hospitalisation costs of an elderly CAP patient amounted to €8,081. In comparison, we found arithmetic mean influenza-related hospitalisation costs of €6,183 (95% CI €4,937 - €7,625) in the same age group. Several explanations are responsible for the difference in hospitalisation costs. In contrast to our study, Vissink et al. took readmissions into account, had detailed cost data on diagnostics and treatment during admission, an older elderly population with a majority of patients ≥75 years (56% versus 31% in our study). An additional explanation is that CAP has a great variation of causative pathogens that may result in a longer hospital stay (12.0 days versus 8.5 days in our study) and higher in-hospital mortality (11.1% versus 5.5% in our study) with consequently higher hospitalisation costs. This was also illustrated by the study of Spoorenberg et al., showing that CAP caused by *S. pneumoniae* and *S. aureus* are associated with higher hospitalisation costs mainly due to longer duration of hospital stay.[9] They estimated a mean hospitalisation costs per CAP patient of €4,098, which is lower than our hospitalisation costs per influenza patient. The difference in mean hospitalisation costs could be explained by the exclusion of all immunocompromised patients and a lower percentage of ICU admissions (7.5% versus 18.4% in our study) in the study by Spoorenberg et al.

The differences in hospitalisation costs between the general and academic hospitals found in our study are attributed to a longer LOS in the general hospital (JBZ), mainly caused by longer length of stay on the general ward. Although we do not have a definite explanation for this result, several hypotheses could be made. Firstly, it is possible that pressure on hospital beds during influenza epidemics is higher in academic hospitals, resulting in different policies with respect to supported early discharge between the general and academic hospitals. Secondly, the amount of patient transfers to other hospitals could be higher in academic hospitals than in general hospitals. Thirdly, academic hospitals have a lower threshold for admitting immunocompromised patients, who are therefore less ill and require a shorter LOS, leading to lower hospitalisation costs. On the other hand, general hospitals more often admit patients without significant comorbidities, but are more severely ill and require a longer LOS, with higher associated hospitalisation costs.

Similar to the US study of Young-Xu et al. estimating costs of influenza-attributed hospitalisations[46], we found the highest costs in the age group 45-64 years. Although higher hospitalisation costs are largely driven by LOS[44], mean LOS in our study was actually higher in the ≥75 age group. Nevertheless, the highest hospitalisation costs per patient in the age group 45-64 years can be partly explained by the highest percentage of ICU admissions and the longest stay per admitted ICU patient. In agreement with this result, Rozenbaum et al. found the highest mean hospitalisation costs per ICU patient with CAP (€16,374) in age group 50-64 years.[8]

The low risk group had the highest hospitalisation costs, which could largely be explained by the longest median LOS per patient and ICU days per ICU patient. The higher proportion of ARDS patients found in the low risk group, compared to the medium and high risk group, is most likely responsible for this result. In addition, the main outlier in hospitalisation costs belonged to an influenza patient in the low risk group and in the age group 45-64 years. This influenza patient without comorbidities was admitted to the ICU with sepsis and acute renal failure, requiring dialysis. In contrast to our results, other studies[41,42,46] stated that underlying medical conditions contributed to an increase in total hospitalisation costs for adults and elderly. Only one US study in children found lower costs in high-risk patients, but this difference was not significant.[47,48]
By comparing extrapolated mean hospitalisation costs of influenza patients to hospitalisation costs of other diseases, our estimations could be put into context. Our estimated total hospitalisation costs of influenza on national level (in 2017 euros) is in the same range as gastro-intestinal infections (21 million euros), but lower than for depression (30 million, including medication costs) in the Netherlands.[49] In contrast to influenza hospitalisation costs, it has to be noted that total hospitalisation costs due to gastro-intestinal infections include multiple causative pathogens.

STRENGTHS AND LIMITATIONS

A strength of this study is that we could dispose of accurate catchment populations of each hospital. Therefore, for the first time, we could report incidence of hospitalised influenza patients in the Netherlands. Another strength is that we took differences in unit prices for admission to the general ward, in both general as academic hospital settings, into account, by using weighted mean for calculation of hospitalisation costs. There are also several limitations that have to be taken into account in this study. Our seasonal cumulative incidence for influenza hospitalisations is based on three Dutch hospitals, which might not be representative for the incidence and associated mean hospitalisation costs in the entire Dutch population. It is also important to note that the overall arithmetic mean hospitalisation costs per influenza patient are likely to be an underestimation of the true costs, caused by unavailable cost indicators. Firstly, we did not take into account patient transfers to other hospitals because of capacity problems during the influenza epidemic or readmissions of the influenza patient. This could have underestimated our mean hospitalisation costs to some extent. Secondly, excluding influenza patients admitted less than 24 hours, underestimated our incidence estimates and our national hospitalisation costs as well, whereas the mean hospitalisation cost per admitted influenza patient was overestimated. Thirdly, 'other costs' were underestimated in our analysis, because insufficient data was collected on treatment and diagnostics during admission. To compensate for this, assumptions had to be made for the duration of isolation, empiric antibiotic therapy and duration, and oseltamivir treatment. Data on additional treatment and use of diagnostics because of complications during hospital admission were not available in our dataset and therefore disregarded in our cost estimate. For one severe outlier, we retrieved additional information on complications during hospital stay resulting in better insight in the mean hospitalisation costs. Fourthly, no data were available on hospitalised patients with an RTI with negative influenza virus test results. Even with RT-PCR, false-negative test results may occur due to improper or poor sample collection, handling and/or processing.[50] False-negative influenza test results could have underestimated the total hospitalisation costs per influenza patient. Finally, this study was purely limited to hospitalisation costs. Information on healthcare use before and after hospital admission, on patient costs and related productivity losses were absent and therefore not considered in the current study. Extrapolation of mean hospitalisation costs of influenza patients to national level is a rough estimation and has to be interpreted with caution, because the representativeness of the study hospitals is unknown and outliers could have resulted in overestimation of the total hospitalisation costs.

CONCLUSIONS

Influenza virus infections lead to 1.8-3.5 hospitalised patients per 10,000 persons, with mean hospitalisation costs of €6,100 - €8,300 per adult patient, resulting in 20-28 million euros annually in the Netherlands. The highest arithmetic mean hospitalisation costs per patient were found in the 45-64 year age group. These influenza burden estimates could be used for future influenza cost-effectiveness and impact studies.

REFERENCES

1. WHO: Influenza (seasonal) fact sheet. http://www.who.int/news-room/fact-sheets/detail/influenza-(seasonal) (2018). Accessed 8-October-2018
2. Iuliano, A.D., Roguski, K.M., Chang, H.H., Muscatello, D.J., Palekar, R., Tempia, S., Cohen, C., Gran, J.M., Schanzer, D., Cowling, B.J., Wu, P., Kyncl, J., Ang, L.W., Park, M., Redlberger-Fritz, M., Yu, H., Espenhain, L., Krishnan, A., Emukule, G., van Asten, L., Pereira da Silva, S., Aungkulanon, S., Buchholz, U., Widdowson, M.A., Bresee, J.S.: Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. Lancet 391(10127), 1285-1300 (2018). doi:10.1016/s0140-6736(17)33293-2
3. Heymann, D.L.: Control of communicable diseases manual. American Public Health Association, Washington, DC (2015)
4. Cassini, A., Colzani, E., Pini, A., Mangen, M.J., Plass, D., McDonald, S.A., Maringhini, G., van Lier, A., Haagsma, J.A., Havelaar, A.H., Kramarz, P., Kretzschmar, M.E., On Behalf Of The, B.C.: Impact of infectious diseases on population health using incidence-based disability-adjusted life years (DALYs): results from the Burden of Communicable Diseases in Europe study, European Union and European Economic Area countries, 2009 to 2013. Euro surveillance : bulletin Europeen sur les maladies transmissibles = European communicable disease bulletin 23(16) (2018). doi:10.2807/1560-7917.es.2018.23.16.17-00454
5. RIVM: State of infectious diseases in the Netherlands. https://www.rivm.nl/en/Documents_and_publications/Scientific/Reports/2018/september/State_of_infectious_diseases_in_the_Netherlands_2017 (2017). Accessed 8 October 2018
6. WHO: A Manual for Estimating Disease Burden Associated With Seasonal Influenza. http://www.who.int/influenza/resources/publications/manual_burden_of_disease/en/ (2015). Accessed 8 October 2018
7. Molinari, N.A., Ortega-Sanchez, I.R., Messonnier, M.L., Thompson, W.W., Wortley, P.M., Weintraub, E., Bridges, C.B.: The annual impact of seasonal influenza in the US: measuring disease burden and costs. Vaccine 25(27), 5086-5096 (2007). doi:10.1016/j.vaccine.2007.03.046
8. Rozenbaum, M.H., Mangen, M.J., Huijts, S.M., van der Werf, T.S., Postma, M.J.: Incidence, direct costs and duration of hospitalization of patients hospitalized with community acquired pneumonia: A nationwide retrospective claims database analysis. Vaccine 33(28), 3193-3199 (2015). doi:10.1016/j.vaccine.2015.05.001
9. Spoorenberg, S.M., Bos, W.J., Heijligenberg, R., Voorn, P.G., Grutters, J.C., Rijkers, G.T., van de Garde, E.M.: Microbial aetiology, outcomes, and costs of hospitalisation for community-acquired pneumonia; an observational analysis. BMC infectious diseases 14, 335 (2014). doi:10.1186/1471-2334-14-335
10. Vissink, C.E., Huijts, S.M., de Wit, G.A., Bonten, M.J., Mangen, M.J.: Hospitalization costs for community-acquired pneumonia in Dutch elderly: an observational study. BMC infectious diseases 16, 466 (2016). doi:10.1186/s12879-016-1783-9
11. Mangen, M.J., Rozenbaum, M.H., Huijts, S.M., van Werkhoven, C.H., Postma, D.F., Atwood, M., van Deursen, A.M., van der Ende, A., Grobbee, D.E., Sanders, E.A., Sato, R., Verheij, T.J., Vissink, C.E., Bonten, M.J., de Wit, G.A.: Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. Eur Respir J 46(5), 1407-1416 (2015). doi:10.1183/13993003.00325-2015
12. Mangen, M.J., Rozenbaum, M.H., Huijts, S.M., van Werkhoven, C.H., Postma, D.F., Atwood, M., van Deursen, A.M., van der Ende, A., Grobbee, D.E., Sanders, E.A., Sato, R., Verheij, T.J., Vissink, C.E., Bonten, M.J., de Wit, G.A.: Supplementary material - Cost-effectiveness of adult pneumococcal conjugate vaccination in the Netherlands. Eur Respir J 46(5), 1-26 (2015).
13. NIVEL: NIVEL Primary Care Database. https://www.nivel.nl/en/nivel-primary-care-database (2018). Accessed 8 October 2018
14. Teirlink, A.C., van Asten, L., Brandsema, P.S., et al: Annual report Surveillance of influenza and other respiratory infections in the Netherlands: winter 2014/2015. In. National Institute for Public Health and the Environment (RIVM), Bilthoven, (2015)
15. Teirlink, A.C., van Asten, L., Brandsema, P.S., et al: Annual report Surveillance of influenza and other respiratory infections in the Netherlands: winter 2015/2016. In. National Institute for Public Health and the Environment (RIVM), Bilthoven, (2016)
16. WHO: WHO surveillance case definitions for ILI and SARI. http://www.who.int/influenza/surveillance_monitoring/ili_sari_surveillance_case_definition/en/ (2014). Accessed 13 March 2018
17. Boivin, G., Cote, S., Dery, P., De Serres, G., Bergeron, M.G.: Multiplex real-time PCR assay for detection of

influenza and human respiratory syncytial viruses. Journal of clinical microbiology 42(1), 45-51 (2004).
18. Stichting·Werkgroep·Antibiotica·Beleid: SWAB - onderste luchtwegen. https://www.swab.nl/swab/cms3.nsf/uploads/6A6E127F9A2C1168C125816F004A013A/$FILE/CAP_SWAB_2017-DEF_R5.pdf (2018). Accessed 11 June 2018
19. Vega, T., Lozano, J.E., Meerhoff, T., Snacken, R., Beaute, J., Jorgensen, P., Ortiz de Lejarazu, R., Domegan, L., Mossong, J., Nielsen, J., Born, R., Larrauri, A., Brown, C.: Influenza surveillance in Europe: comparing intensity levels calculated using the moving epidemic method. Influenza and other respiratory viruses 9(5), 234-246 (2015). doi:10.1111/irv.12330
20. WHO: People at High Risk of Developing Serious Flu–Related Complications. https://www.cdc.gov/flu/about/disease/high_risk.htm (2018). Accessed 10 October 2018
21. Mertz, D., Kim, T.H., Johnstone, J., Lam, P.P., Science, M., Kuster, S.P., Fadel, S.A., Tran, D., Fernandez, E., Bhatnagar, N., Loeb, M.: Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. Bmj 347, f5061 (2013). doi:10.1136/bmj.f5061
22. Dutch Hospital Data. https://www.dhd.nl/klanten/Paginas/home.aspx (2019). Accessed 18 April 2019
23. WHO: Classification of Diseases (ICD) - ICD-10 online versions. http://www.who.int/classifications/icd/icdonlineversions/en/ (2018). Accessed 26 July 2018
24. Dutch·Healthcare·Authority: Overview of the Dutch Healthcare Authority. https://www.nza.nl/english (2018). Accessed 15 June 2018
25. National·Health·Care·Institute. https://english.zorginstituutnederland.nl/ (2018). Accessed 15 June 2018
26. Hakkaart-van Roijen, L., van der Linden, N., Boumans, C., Kanters, T., Tan, S.S.: Costing manual: Methodology of costing research and reference prices for economic evaluations in healthcare [in Dutch: Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidzorg]. In. (2015)
27. SWAB: Management of community-acquired pneumonia in adults: 2016 guideline update from the Dutch Working Party on Antibiotic Policy (SWAB) and Dutch Association of Chest Physicians (NVALT). https://www.swab.nl/swab/cms3.nsf/uploads/6A6E127F9A2C1168C125816F004A013A/$FILE/CAP_SWAB_2017-DEF_R5.pdf (2017). Accessed 19 July 2018
28. Hubben, G., Bootsma, M., Luteijn, M., Glynn, D., Bishai, D., Bonten, M., Postma, M.: Modelling the costs and effects of selective and universal hospital admission screening for methicillin-resistant Staphylococcus aureus. PloS one 6(3), e14783 (2011). doi:10.1371/journal.pone.0014783
29. Wassenberg, M.W., Kluytmans, J.A., Box, A.T., Bosboom, R.W., Buiting, A.G., van Elzakker, E.P., Melchers, W.J., van Rijen, M.M., Thijsen, S.F., Troelstra, A., Vandenbroucke-Grauls, C.M., Visser, C.E., Voss, A., Wolffs, P.F., Wulf, M.W., van Zwet, A.A., de Wit, G.A., Bonten, M.J.: Rapid screening of methicillin-resistant Staphylococcus aureus using PCR and chromogenic agar: a prospective study to evaluate costs and effects. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 16(12), 1754-1761 (2010). doi:10.1111/j.1469-0691.2010.03210.x
30. Statistics·Netherlands: Dutch Consumer Price index. http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=71905ned&D1=a&D2=0,95-117&HDR=T&STB=G1&VW=T (2018). Accessed 8 February 2018
31. Gefenaite, G., Pistol, A., Popescu, R., Popovici, O., Ciurea, D., Dolk, C., Jit, M., Gross, D.: Estimating burden of influenza-associated influenza-like illness and severe acute respiratory infection at public healthcare facilities in Romania during the 2011/12-2015/16 influenza seasons. Influenza and other respiratory viruses 12(1), 183-192 (2018). doi:10.1111/irv.12525
32. ECDC: Seasonal influenza - Annual Epidemiological Report for 2015-16 season. https://ecdc.europa.eu/sites/portal/files/documents/AER_for_2015-influenza-seasonal_0.pdf (2017). Accessed 5 July 2018
33. CDC: Laboratory-Confirmed Influenza Hospitalizations. https://gis.cdc.gov/GRASP/Fluview/FluHospRates.html (2018). Accessed 5 July 2018
34. Snijders, B., van der Hoek, W., Stirbu, I., van der Sande, M.A., van Gageldonk-Lafeber, A.B.: General practitioners' contribution to the management of community-acquired pneumonia in the Netherlands: a retrospective analysis of primary care, hospital, and national mortality databases with individual data linkage. Primary care respiratory journal : journal of the General Practice Airways Group 22(4), 400-405 (2013). doi:10.4104/pcrj.2013.00085
35. Jain, S., Self, W.H., Wunderink, R.G., Fakhran, S., Balk, R., Bramley, A.M., Reed, C., Grijalva, C.G., Anderson, E.J., Courtney, D.M., Chappell, J.D., Qi, C., Hart, E.M., Carroll, F., Trabue, C., Donnelly, H.K., Williams, D.J., Zhu, Y., Arnold, S.R., Ampofo, K., Waterer, G.W., Levine, M., Lindstrom, S., Winchell, J.M., Katz, J.M., Erdman, D., Schneider, E., Hicks, L.A., McCullers, J.A., Pavia, A.T., Edwards, K.M., Finelli, L.: Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults. The New England journal of medicine

373(5), 415-427 (2015). doi:10.1056/NEJMoa1500245

36. Marcos, P.J., Restrepo, M.I., Anzueto, A.: Community-Acquired Pneumonia Requiring Hospitalization. The New England journal of medicine 373(24), 2380-2381 (2015). doi:10.1056/NEJMc1511751
37. WHO: Estimates of unit costs for patient services for Spain. http://www.who.int/choice/country/esp/cost/en/ (2018). Accessed 13 September 2018
38. WHO: Estimates of unit costs for patient services for Canada. http://www.who.int/choice/country/can/cost/en/ (2018). Accessed 8 October 2018
39. WHO: Estimates of unit costs for patient services for Italy. https://www.who.int/choice/country/ita/cost/en/ (2020). Accessed 2 February 2020
40. WHO: Estimates of Unit Costs for Patient Services for Germany. https://www.who.int/choice/country/deu/cost/en/ (2020). Accessed 3 February 2020
41. Torner, N., Navas, E., Soldevila, N., Toledo, D., Navarro, G., Morillo, A., Perez, M.J., Dominguez, A., Working Group of the Project, P.I.: Costs associated with influenza-related hospitalization in the elderly. Hum Vaccin Immunother 13(2), 412-416 (2017). doi:10.1080/21645515.2017.1264829
42. Trucchi, C., Paganino, C., Orsi, A., Amicizia, D., Tisa, V., Piazza, M.F., Gallo, D., Simonetti, S., Buonopane, B., Icardi, G., Ansaldi, F.: Hospital and economic burden of influenza-like illness and lower respiratory tract infection in adults >/=50 years-old. BMC health services research 19(1), 585 (2019). doi:10.1186/s12913-019-4412-7
43. Haas, J., Braun, S., Wutzler, P.: Burden of influenza in Germany: a retrospective claims database analysis for the influenza season 2012/2013. Eur J Health Econ 17(6), 669-679 (2016). doi:10.1007/s10198-015-0708-7
44. Ng, C., Ye, L., Noorduyn, S.G., Hux, M., Thommes, E., Goeree, R., Ambrose, A., Andrew, M.K., Hatchette, T., Boivin, G., Bowie, W., ElSherif, M., Green, K., Johnstone, J., Katz, K., Leblanc, J., Loeb, M., MacKinnon-Cameron, D., McCarthy, A., McElhaney, J., McGeer, A., Poirier, A., Powis, J., Richardson, D., Sharma, R., Semret, M., Smith, S., Smyth, D., Stiver, G., Trottier, S., Valiquette, L., Webster, D., McNeil, S.A., Serious Outcomes Surveillance Network of the Canadian Immunization Research Network, I., Toronto Invasive Bacterial Diseases Network, I.: Resource utilization and cost of influenza requiring hospitalization in Canadian adults: A study from the serious outcomes surveillance network of the Canadian Immunization Research Network. Influenza and other respiratory viruses 12(2), 232-240 (2018). doi:10.1111/irv.12521
45. van Werkhoven, C.H., Postma, D.F., Mangen, M.J., Oosterheert, J.J., Bonten, M.J., group, C.-S.s.: Cost-effectiveness of antibiotic treatment strategies for community-acquired pneumonia: results from a cluster randomized cross-over trial. BMC infectious diseases 17(1), 52 (2017). doi:10.1186/s12879-016-2179-6
46. Young-Xu, Y., van Aalst, R., Russo, E., Lee, J.K., Chit, A.: The Annual Burden of Seasonal Influenza in the US Veterans Affairs Population. PloS one 12(1), e0169344 (2017). doi:10.1371/journal.pone.0169344
47. Ortega-Sanchez, I.R., Molinari, N.A., Fairbrother, G., Szilagyi, P.G., Edwards, K.M., Griffin, M.R., Cassedy, A., Poehling, K.A., Bridges, C., Staat, M.A.: Indirect, out-of-pocket and medical costs from influenza-related illness in young children. Vaccine 30(28), 4175-4181 (2012). doi:10.1016/j.vaccine.2012.04.057
48. Federici, C., Cavazza, M., Costa, F., Jommi, C.: Health care costs of influenza-related episodes in high income countries: A systematic review. PloS one 13(9), e0202787 (2018). doi:10.1371/journal.pone.0202787
49. Statistics_Netherlands: Costs of disease 2015. https://statline.rivm.nl/#/RIVM/nl/dataset/50040NED/table?graphtype=Table&ts=1512975518824. Accessed 12 September 2018
50. CDC: Information on Rapid Molecular Assays, RT-PCR, and other Molecular Assays for Diagnosis of Influenza Virus Infection. https://www.cdc.gov/flu/professionals/diagnosis/molecular-assays.htm (2018). Accessed 10 September 2018

SUPPLEMENTAL MATERIAL

Table S1. Risk group classification of severe or complicated influenza illness in three groups (low, medium and high risk), based on the presence of comorbidities

Medium risk	High risk
Chronic cardiovascular disease[a]	Chronic renal failure[c]
Chronic pulmonary disease[b]	Malignancy[d]
Diabetes mellitus	Immunocompromised due to disease or medication[e]
	Chronic liver disease[f]

[*]comorbidities not listed in the table are classified as low risk.

[a]examples given: hypertension, heart failure, heart valve disease, heart rhythm disorder, peripheral vascular disease.

[b]examples given: chronic obstructive pulmonary disease, interstitial pulmonary disease, asthma, obstructive sleep apnea syndrome.

[c]chronic renal failure stage 3-5 (estimated glomerular filtration rate ≤30 ml/min).

[d]malignancy: solid and haematological cancer.

[e]examples given: human immunodeficiency virus, auto-immune disease, solid organ or stem cell transplant, immunosuppressants.

[f]example given: liver cirrhosis.

4

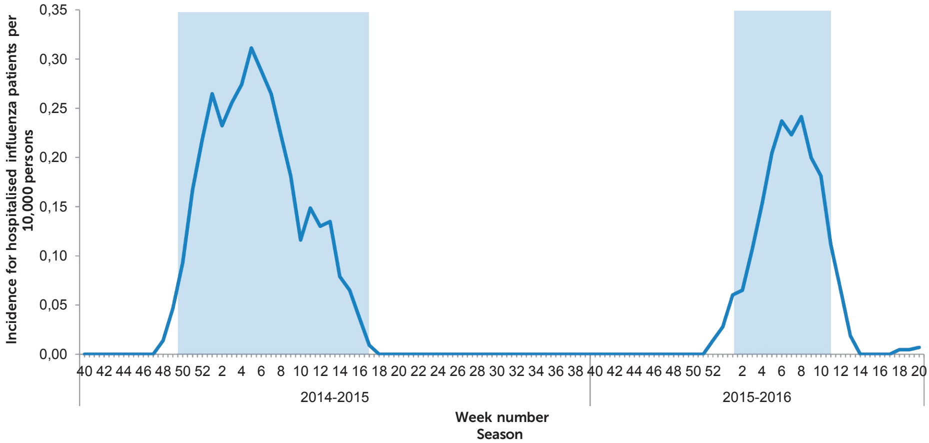
Table S2. Variables used for calculation of the catchment population of three Dutch hospitals in patients with a respiratory tract infection in the years 2014, 2015 and 2016

Variables	Description
Institution code	Unique identification code care provider
Year	Year of discharge clinical admission (2014, 2015 and 2016)
Postal code	Four-digit postal code
Clinical admissions	Number of clinical admissions • per study hospital (LUMC, UMCU, JBH) • all Dutch hospitals

Note: only aggregated data of International Classification of Diseases and Health-related Problems (ICD-10) codes are provided.

Calculation example:

$$\textit{Catchment population hospital X in year (yyyy)}$$
$$= \left(\frac{\text{Total number of admissions in hospital X}}{\text{Total number of admissions in all Dutch hospitals}}\right) * \text{total Dutch population in year (yyyy)}$$



4

Figure S1. Incidence of hospitalised influenza patients in three Dutch hospitals during respiratory seasons 2014-2015 and 2015-2016

Note: The catchment populations for the three Dutch hospitals were respectively: 323,000 (JBZ), 183,000 (LUMC) and 212,000 (UMCU) persons. Depicted areas reflect the influenza epidemic during season 2014-2015 and 2015-2016.

Table S3. Cost unit prices in 2017 euros

Cost type	Cost details		Cost unit price (euro)	Source
Medication[a] (per treatment)	Antibiotics[b]	amoxicillin	21.83	[16, 24, 40]
		ceftriaxone	255.41	
		average[c]	106.35	
	Oseltamivir[d]		22.40	[16, 24, 48]
Emergency department (per admission)	consultation (1x)		265.11	[24]
	diagnostics[e]		222.76	[10, 49-52]
Hospitalisation (per day)	general ward[f]			[24]
	weighted arithmetic mean		487.23	
	intensive care unit[g]		2062.53	[24]
	additional isolation costs[h]		15.06	[26, 27]

[a]average costs/treatment including delivery fees.

[b]total antibiotic therapy course of one week in line with the most recent Dutch Working Party on Antibiotic Policy (SWAB) guidelines.

[c]average antibiotic therapy costs assuming that 30% are severe cases and treated with ceftriaxone and 70% mild to moderate severe cases and treated with amoxicillin.

[d]total oseltamivir therapy course of five days according to the most recent Dutch Working Party on Antibiotic Policy (SWAB) guidelines.

[e]diagnostics include chest X-ray, blood examination (Hb, MCV, Ht, leucocytes, thrombocytes, ASAT, ALAT, GGT, AF, LD bilirubin, creatinine, urea, sodium, potassium, chloride, calcium, total protein, glucose, CRP), urine examination (urine screening test), and multiplex PCR test respiratory pathogens.

[f]general ward hospitalisation costs per day included costs for medical specialists, hoteling and overhead. No medication and diagnostics costs are included.

[g]intensive care unit hospitalisation costs per day including costs for diagnostics, isolation and medication.

[h]additional isolation costs include material costs and additional work load of maximum 7 days. Additional isolation costs are only applicable for the general ward, because isolation costs for the intensive care are already included in the total cost unit price.

Table S4. Extrapolated hospitalisation costs of influenza patients to national level

Season	Hospitalisation costs per patient (2017 euros)		Hospitalisation costs per population (million euros)	
	Arithmetic mean	Geometric mean*	Arithmetic mean	Geometric mean
2014-2015	6,128	3,601	28	17
2015-2016	8,280	4,099	20	10

*Statistical difference tested between seasons using Chi-square test: p=0.69.

Table S5. Differences between arithmetic mean hospitalisation costs per influenza patient admitted less than and over 24 hours during respiratory seasons 2014-2015 and 2015-2016

Hospital (n)	Arithmetic mean hospitalisation costs (2017 euros)	Hospital (n)	Arithmetic mean hospitalisation costs (2017 euros)	Hospital (n)	Arithmetic mean hospitalisation costs (2017 euros)
admitted >24 hours		*admitted <24 hours*		*admitted overall*[a]	
LUMC (n=133)	6,745	LUMC (n=17)[b]	1,072	LUMC (n=150)	6,102
UMCU (n=145)	6,016	UMCU (n=19)	1,072	UMCU (n=164)	5,444
JBH (n=102)	8,247	JBH (n=13)	1,072	JBH (n=115)	7,436
Total (n=380)	6,870	Total (n=49)	1,072	Total (n=429)	6,208

[a]admitted overall: influenza patients admitted <24 hours and >24 hours.

[b]proportion influenza patients admitted <24 hours (LUMC) : 17/133=0.13 (proxy for the proportion of admitted influenza patients in UMCU and JBH).

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Table S6. Baseline characteristics of influenza patients during respiratory seasons 2014-2015 and 2015-2016

	Respiratory season 2014-2015	Respiratory season 2015-2016	p-value*	Total
Admission, n	249	131		380
Age in years, median (IQR)	66.0 (56-80)	59.6 (47-70)	0.00	64.5 (52-77)
Age category, n (%)			0.00	
• 18-44 years	34 (13.7)	29 (22.1)		63 (16.6)
• 45-64 years	76 (30.5)	52 (39.7)		128 (33.7)
• 65-74 years	47 (18.9)	24 (18.3)		71 (18.7)
• ≥75 years	92 (36.9)	26 (19.8)		118 (31.1)
Male, n (%)	145 (58.2)	73 (55.7)	0.64	218 (57.4)
Female, n (%)	104 (41.8)	58 (44.3)		162 (42.6)
Risk group, n (%)			0.44	
• Low	26 (10.4)	22 (16.8)		48 (12.6)
• Medium	92 (36.9)	32 (24.4)		124 (32.6)
• High	131 (52.6)	77 (58.8)		208 (54.7)
Number of comorbidities, median n (IQR)[a]	2 (1-2)	2 (1-2)	0.54	2 (1-2)
Comorbidities, n (%)				
Chronic respiratory disease	93 (37.3)	39 (29.8)	0.14	132 (34.7)
Cardiovascular disease	137 (55.0)	52 (39.7)	0.01	189 (49.7)
Diabetes mellitus	36 (21.1)	18 (19.8)	0.81	54 (20.6)
Chronic renal disease	28 (16.4)	15 (16.5)	0.98	43 (16.4)
Cancer	32 (18.1)	23 (23.0)	0.32	55 (19.9)
Immunodeficiency	78 (31.1)	56 (42.7)	0.03	134 (35.3)
ICU admission, n (%)	39 (15.7)	31 (23.7)	0.06	70 (18.4)
Length of hospital stay in days, median (IQR)[b]	5 (3-10)	5 (2-12)	0.97	5 (3-11)
• General ward days per patient	5 (3-9)	4 (2-10)	0.66	5 (3-9)
• ICU days per ICU patient	5 (2-9)	4 (2-14)	0.87	5 (2-10)
Influenza virus				
• Type A	202 (81.1)	92 (70.2)	0.01	294 (77.4)
• Type B	39 (15.7)	37 (28.2)		76 (20.0)
• Type A and B	8 (3.2)	2 (1.5)		10 (2.6)
Antibiotics treatment, n (%)[c]	194 (78.2)	103 (79.8)	0.72	297 (78.8)
Oseltamivir treatment, n (%)[d]	118 (47.6)	70 (54.3)	0.22	188 (49.9)
In-hospital mortality, n (%)	11 (4.4)	10 (7.6)	0.19	21 (5.5)

*Statistical difference tested between respiratory season 2014-2015 and 2015-2016 using unpaired t-test, Mann-Whitney U test, Kruskal-Wallis test or Chi-square test.

[a]Missing 2014-2015: n=78, 2015-2016: n=40.

[b]Arithmetric mean LOS 2014-2015: 7.8 days, 2015-2016: 9.7 days, 2014-2016: 8.5 days; geometric mean LOS 2014-2015 5.2 days, 2015-2016 5.4 days, 2014-2016: 5.2 days.

[c]Missing 2014-2015: n=1, 2015-2016: n=2.

[d]Missing 2014-2015: n=1, 2015-2016: n=2.

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Table S7. Arithmetic mean hospitalisation costs per influenza patient admitted to three Dutch hospitals during respiratory seasons 2014-2015 and 2015-2016

Season (Number of patients)	Arithmetic mean hospitalisation costs (2017 euros)				
	General ward	Intensive care unit	Other[a]	Total*	95% CI
2014-2015 (n=249)	2,999	2,543	585	6,128	4,934 - 7,737
2015-2016 (n=131)	3,486	4,220	575	8,280	6,254 - 10,665
Total (n=380)	3,167	3,121	582	6,870	5,750 - 8,071

[a]Other: emergency department costs (including diagnostics), empiric antibiotic treatment costs, oseltamivir costs, isolation costs.

*Statistical difference tested between seasons using Chi-square test: p=0.58.

Table S8. Arithmetic mean hospitalisation costs per age category per influenza patient admitted to three Dutch hospitals during respiratory seasons 2014-2015 and 2015-2016

Age category (years)	Number of patients (N)	Arithmetic mean costs (2017 euros)*	95% CI
18-44	63	4,666	3,259 - 6,313
45-64	128	8,970	6,610 - 11,694
65-74	71	6,279	4,274 - 8,593
≥75	118	6,125	4,870 - 7,626
All ages	380	6,870	5,750 - 8,071

*Statistically significant difference between age categories using Kruskal-Wallis test; p=0.03.

Table S9. Total and intensive care unit admissions per age category and risk group of influenza patients admitted to three Dutch hospitals during respiratory seasons 2014-2015 and 2015-2016

	Total admissions[a]		Intensive care unit admissions[b]	
	n (%)	Length of hospital stay median (IQR) days	n (%)	ICU days per ICU patient median (IQR)
Age category				
18-44 years	63 (16.6)	4 (2-7)	7 (1.8)	6 (1-9)
45-64 years	128 (33.6)	5 (2-9)	32 (8.4)	8 (2-19)
65-74 years	71 (18.7)	5 (2-11)	16 (4.2)	3 (1-5)
≥75 years	118 (31.1)	7 (3-13)	15 (3.9)	5 (1-8)
Risk group				
Low	41 (11.2)	7 (3-18)	12 (18.6)	18 (7-24)
Medium	164 (43.2)	5 (3-11)	35 (34.3)	4 (2-8)
High	161 (42.4)	4 (3-10)	21 (47.1)	3 (1-10)
Total	380	5 (3-11)	70 (18.4)	5 (2-10)

[a]Missing total admissions: n=14.

[b]missing intensive care unit admissions: n=2.

Table S10. Differences between arithmetic and geometric mean for length of hospital stay and total hospitalisation costs per influenza patient during respiratory seasons 2014-2015 and 2015-2016

	Respiratory season(s)		
	2014-2015	**2015-2016**	**2014-2016**
Cumulative seasonal incidence	3.5	1.8	5.3
Arithmetic mean (±SD)			
Length of hospital stay (days)	7.8 (±8.9)	9.7 (±12.6)	8.5 (±10.3)
• General ward (days per patient)	6.6 (±6.4)	7.7 (±10.2)	7.0 (±7.9)
• ICU (days per ICU patient)	7.9 (±10.5)	8.7 (±9.2)	8.2 (±9.9)
Hospitalisation costs per patient (2017 euros)			
Total[a]	€6,128	€8,280	€6,870
Geometric mean (± geometric SD)			
Length of hospital stay (days)	5.2 (±2.5)	5.4 (±2.9)	5.2 (±2.6)
• General ward (days per ward patient)	4.7 (±2.3)	5.0 (±2.7)	4.8 (±2.4)
• ICU (days per ICU patient)	4.5 (±2.8)	4.7(±3.2)	4.6 (±2.9)
Hospitalisation costs per patient (2017 euros)			
Total[a]	€3,600	€4,099	€3,765

[a]Weighted mean unit cost prices.