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Marbus, S.D.; Schweitzer, V.A.; Groeneveld, G.H.; Oosterheert, J.J.; Schneeberger, P.M.; Hoek, W. van der; ... ; Mangen, M.J.

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ORIGINAL PAPER

Incidence and costs of hospitalized adult influenza patients in The Netherlands: a retrospective observational study

Sierk D. Marbus[1] · Valentijn A. Schweitzer[2] · Geert H. Groeneveld[3] · Jan J. Oosterheert[4] · Peter M. Schneeberger[5] · Wim van der Hoek[1] · Jaap T. van Dissel[1,3] · Arianne B. van Gageldonk-Lafeber[1] · Marie-Josée Mangen[1]

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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 hospitalisation 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 €6128 (95% CI €4934–€7737) per patient in 2014–2015 and €8280 (95% CI €6254–€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 hospitalisation costs of €6100–€8300 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.

Keywords Influenza · Hospitalisation · Costs · Incidence

JEL Classification I10 · I11

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 Mio. 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

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✉ Sierk D. Marbus
sierk.marbus@rivm.nl

Extended author information available on the last page of the article

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 hospitalized influenza patients are limited. In the United States (US), the average direct medical costs of seasonal influenza epidemics, based on 2003 US population demographics, were estimated at 10.4 billion dollar annually [7]. Dutch cost estimates are only available for total community-acquired pneumonia (CAP) hospitalized patients, but not further specified for influenza virus infections [8–12]. Moreover, incidence for influenza-like illness (ILI) is 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 hospitalization for influenza virus infections and associated hospitalization 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 hospitalized shorter than 24 h, 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 were 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 into four categories (18–44, 45–64, 65–74 and ≥ 75 years) and by risk of severe or complicated influenza illness into three groups (low, medium and high risk), based on the presence of comorbidities [10, 20, 21] (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 hospitalizations due to respiratory tract infection (RTI) in each hospital by the total hospitalizations 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)

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* (%) (years)				
18–44	7 (6.9)	56 (20.1)	0.00	63 (16.6)
45–64	30 (29.4)	98 (35.3)		128 (33.7)
65–74	16 (15.7)	55 (19.8)		71 (18.7)
≥75	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 (LOS), 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 and 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: $n=0$

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

Hospitalization costs were estimated using a bottom-up approach and included costs for the emergency department (ED) visit, requested diagnostics during stay on the ED, hospitalization 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.

Hospitalization 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 a 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 (2nd/3rd 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 5 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 hospitalization costs per adult influenza patient were estimated and extrapolated to the national level. We attempted to obtain annual national hospitalization 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 hospitalization 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 h influenced our cost analysis. For the sensitivity analysis, we collected additional data on influenza patients admitted shorter than 24 h in one hospital (LUMC). The proportion of patients admitted shorter than 24 h versus admitted longer than 24 h in LUMC was used as a proxy for the other two hospitals (JBH and UMCU). Arithmetic mean hospitalization costs per influenza patient was calculated per subgroup (admitted < 24 h, admitted > 24 h) (supplemental file Table S5).

In addition, to provide more insight into the differences of hospitalization costs between risk groups, we reviewed electronic patients' records for detailed information on complications in a proportion of patients (21%) with the top highest hospitalization 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 hospitalization 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 1000 iterations was used to determine 95% confidence intervals (CI). A p value of < 0.05 was considered significant. Data were analyzed 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 hospitalizations 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 into the medium- and high-risk groups 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 hospitalized influenza patients (0.3 cases per 10,000 persons) peaked at week 7 (supplemental file Figure S1).

Hospitalization costs per patient

The arithmetic mean hospitalization costs per influenza patient was €6128 (95% CI €4934–€7737) in 2014–2015,

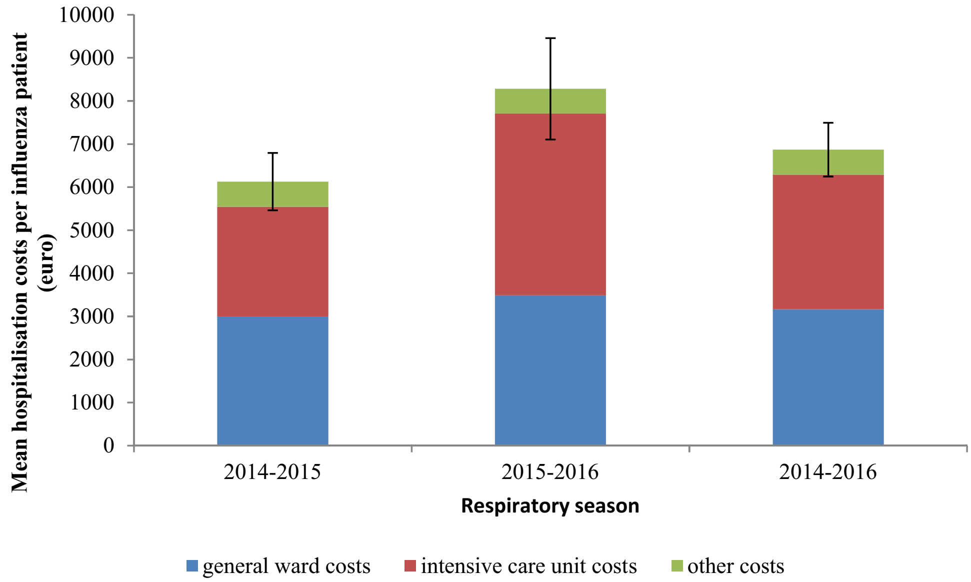

Fig. 1 Arithmetic mean hospitalization costs per influenza patient admitted to three Dutch hospitals during respiratory seasons 2014–2015 and 2015–2016. Error bars indicate the 95% confidence interval as determined by bootstrapping

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

Hospital	Patients (*N*)	Hospitalization costs per patient (2017 euros)*	
		Arithmetic mean	95% CI
General hospital[a]	102	8247	6583–10,206
Academic hospital[b]	278	6365	5078–8132
Total	380	6870	5779–7994

*Statistically significant difference between general hospital and academic hospitals using a Mann–Whitney *U* test; $p=0.00$

[a]JBZ

[b]LUMC and UMCU

€8280 (95% CI €6254–€10,665) in 2015–2016 and €6870 (95% CI €5750–€8071) in 2014–2016 (Fig. 1). No significant differences in hospitalization 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 hospitalization costs per patient. In both respiratory seasons, the arithmetic mean hospitalization costs per patient in the general hospital (€8247, 95% CI €6583–€10,206) were significantly ($p=0.00$) higher than in the university hospitals (€6365, 95% CI €5078–€8132) (Table 2).

The arithmetic mean hospitalization costs were highest for the 45–64-year age group (€8970, 95% CI €6610–€11,694) (Fig. 2, supplemental file Table S8) and

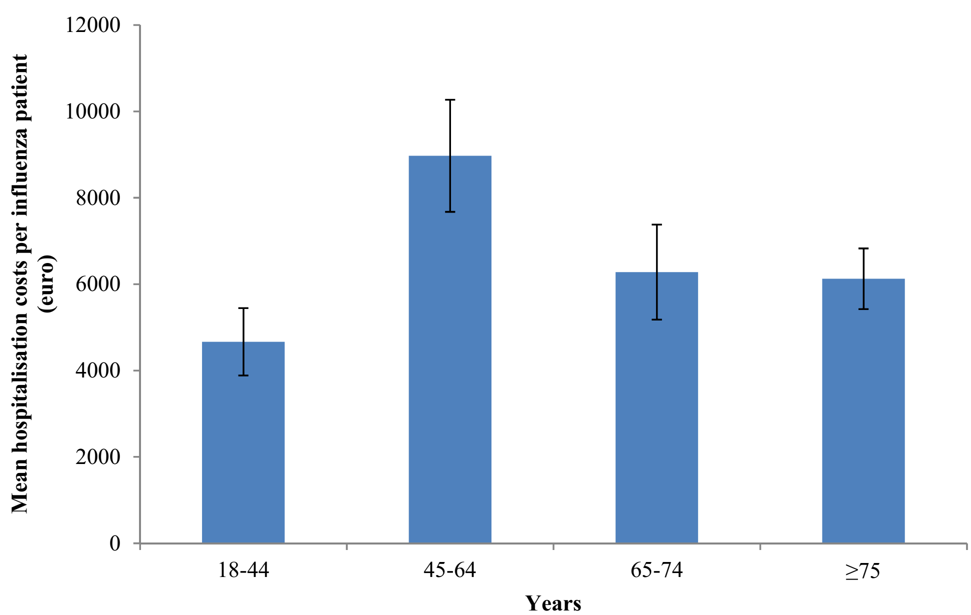

Fig. 2 Arithmetic mean hospitalization costs per age category per influenza patient admitted to three Dutch hospitals during respiratory seasons 2014–2015 and 2015–2016. Error bars indicate the 95% confidence interval as determined by bootstrapping

the low-risk group (€14,249, 95% CI €8798–€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 hospitalization 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 hospitalization costs per influenza patient amounted to €6534 (95% CI €5570–€7510) in 2014–2016.

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 hospitalization costs were used, the total hospitalization costs per influenza patient were €3601 (95% CI €3217–€4030) in 2014–2015, €4099 (95% CI €3398–€4944) in 2015–2016, resulting in €3765 (95% CI €3414–€4151) in 2014–2016 (supplemental file Table S4 and S10).

Taking into account influenza patients admitted less than 24 h and over 24 h, the arithmetic mean hospitalization costs for influenza patients amounted to €6208 in 2014–2016. If compared to hospitalization cost excluding patients admitted less than 24 h (€6870), an arithmetic mean difference of €662 per influenza patient was found (supplemental file Table S5).

Table 3 Arithmetic mean hospitalization 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	8798–21,345
Medium	124	6973	5453–9206
High	208	5132	4230–6246
Total	380	6870	5819–7983

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

[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)

Hospitalization costs on national level

Total hospitalization costs on national level were approximated at €28 Mio. in 2014–2015 and €20 Mio. in 2015–2016. Using the geometric mean, rather than the arithmetic mean, these costs would approximate to €17 Mio. in 2014–2015 and €10 Mio. 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 hospitalization 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 hospitalization costs per influenza patient were €6870 (95% CI €5750–€8071) during respiratory seasons 2014–2016. If extrapolated to national level, the hospitalization costs of influenza patients amounted to 28 Mio. in 2014–2015 and 20 Mio. in 2015–2016. In addition, the general hospital had significantly higher arithmetic mean hospitalization costs than the two academic hospitals. The highest arithmetic mean hospitalization 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 hospitalization for laboratory-confirmed influenza virus infections in Europe is rarely available [31] and hospitalizations 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 hospitalizations 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 specialized care. This is illustrated by a Dutch study showing that the vast majority of CAP patients are managed successfully at GP level without hospitalization [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 (€3219) was reported. Italy reported similar mean hospitalization costs for ILI/lower respiratory tract infection in patients 50 years and older (€3353). In Germany, mean influenza hospitalization costs (€5832, in 2013 euros) were lower than in our study. In Canada, higher hospitalization costs per influenza patient (in 2015 euros) were found (€10,312, 95% CI €9776–€10,848). The longer arithmetic mean LOS (10.8 days) and higher in-hospital mortality (9.3%), taking into account costs for readmissions within 30 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) [9, 10, 45] and invasive pneumococcal disease [10] in, respectively, an adult [9, 45] and elderly population [10]. Vissink et al. [10] reported that mean hospitalization costs of an elderly CAP patient amounted to €8081. In comparison, we found arithmetic mean influenza-related hospitalization costs of €6183 (95% CI €4937–€7625) in the same age group. The higher hospitalization costs found by Vissink et al. could be explained by their inclusion of more detailed cost data on diagnostics and treatment during admission and having an older elderly study population (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 hospitalization costs. This was also illustrated by the study of Spoorenberg et al., showing that CAP caused by *S. pneumoniae* and *S. aureus* is associated with higher hospitalization costs mainly due to longer duration of hospital stay [9]. They estimated a mean hospitalization costs per CAP patient of €4098, which is lower than our hospitalization costs per influenza patient. The difference in mean hospitalization 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 hospitalization 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 hospitalization 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 hospitalization costs.

Similar to the US study of Young-Xu et al. estimating costs of influenza-attributed hospitalizations [46], we found the highest costs in the age group 45–64 years. Although higher hospitalization costs are largely driven by LOS [44], mean LOS in our study was actually higher in the ≥ 75 age group. Nevertheless, the highest hospitalization 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 hospitalization costs per ICU patient with CAP (€16.374) in age group 50–64 years [8].

The low-risk group had the highest hospitalization 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 hospitalization 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 hospitalization 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 hospitalization costs of influenza patients to hospitalization costs of other diseases, our estimations could be put into context. Our estimated total hospitalization costs of influenza on national level (in 2017 euros) is in the same range as gastro-intestinal infections (21 Mio. euros), but lower than for depression (30 Mio., including medication costs) in The Netherlands [49]. In contrast to influenza hospitalization costs, it has to be noted that total hospitalization 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 hospitalized 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, using weighted mean for calculation of hospitalization costs. There are also several limitations that have to be taken into account in this study. Our seasonal cumulative incidence for influenza hospitalizations is based on three Dutch hospitals, which might not be representative for the incidence and associated mean hospitalization costs in the entire Dutch population. It is also important to note that the overall arithmetic mean hospitalization 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 hospitalization costs to some extent. Secondly, excluding influenza patients admitted less than 24 h, underestimated our incidence estimates and our national hospitalization costs as well; whereas, the mean hospitalization cost per admitted influenza patient was overestimated. Thirdly, 'other costs' were underestimated in our analysis, because insufficient data were 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 hospitalization costs. Fourthly, no data were available on hospitalized 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 hospitalization costs per influenza patient. Finally, this study was purely limited to hospitalization 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 hospitalization 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 hospitalization costs.

Conclusions

Influenza virus infections lead to 1.8–3.5 hospitalized patients per 10,000 persons, with mean hospitalization costs of €6100–€8300 per adult patient, resulting in 20–28 Mio. euros annually in The Netherlands. The highest arithmetic mean hospitalization 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.

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Author contributions SM designed the study, analyzed and interpreted the data, and drafted the manuscript. VS, GG, J-JO, PS, RVG-L, and WVDH participated in the design and coordination of the study, and editing the manuscript. JVD participated in editing the manuscript. M-JM participated in the design of the study, performing statistical analysis, interpretation and editing of the manuscript. All authors read and approved the manuscript.

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Data availability Data can be made available for peer review on reasonable request through contacting the corresponding author.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethics approval The Dutch Medical Research Involving Human Subjects Act did not apply to this study, because anonymous data were used and there were no interventions other than routine clinical care. A waiver for full medical ethical review was obtained from the Medical Ethical Committee UMC Utrecht (reference number WAG/mb/16/019885), LUMC (reference number G16.054/NV/nv) and JBZ (reference number 2016.07.06.01).

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Affiliations

Sierk D. Marbus[1] · Valentijn A. Schweitzer[2] · Geert H. Groeneveld[3] · Jan J. Oosterheert[4] · Peter M. Schneeberger[5] · Wim van der Hoek[1] · Jaap T. van Dissel[1,3] · Arianne B. van Gageldonk-Lafeber[1] · Marie-Josée Mangen[1]

Valentijn A. Schweitzer
v.a.schweitzer-2@umcutrecht.nl

Geert H. Groeneveld
g.h.groeneveld@lumc.nl

Jan J. Oosterheert
j.j.oosterheert@umcutrecht.nl

Peter M. Schneeberger
p.schneeberger@jbz.nl

Wim van der Hoek
wim.van.der.hoek@rivm.nl

Jaap T. van Dissel
jaap.van.dissel@rivm.nl

Arianne B. van Gageldonk-Lafeber
rianne.van.gageldonk@rivm.nl

Marie-Josée Mangen
marie-josee.mangen@rivm.nl

[1] Centre for Infectious Diseases Epidemiology and Surveillance, Centre for Infectious Disease Control (CIb), National Institute for Public Health and the Environment (RIVM), PO Box 1, 3720 BA Bilthoven, The Netherlands

[2] Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

[3] Department of Infectious Diseases and Internal Medicine, Leiden University Medical Center, Leiden, The Netherlands

[4] Department of Internal Medicine and Infectious Diseases, University Medical Centre Utrecht, Utrecht, The Netherlands

[5] Regional Laboratory for Medical Microbiology and Infection Prevention, 's-Hertogenbosch, The Netherlands