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Burden of infections on older patients presenting to general practice

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Title: Burden of infections on older patients presenting to general practice: a registry-based study.

Short title: Burden of infections on older patients

Article category: Epidemiology

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Key messages:

- Potentially serious infections are common in an older patient population
- Patients affected by a potentially serious infection are on average 76 years
- Older persons had 8% risk of getting a potentially serious infection yearly
- From 2000 to 2015, incidences decreased markedly for influenza like illness
- Patient characteristics differ by infection type

Abstract

Background: Estimates on the incidence rates of infections are needed to assess the burden of disease in the community.

Objectives: To assess incidence rates of potentially serious infections in patients aged 65 years and over presenting to Flemish general practice from 2000-2015, and to describe patient characteristics.

Methods: We performed a retrospective study, based on data provided by the Intego morbidity registry of the KU Leuven, which includes the electronic medical records of 111 general practitioners. Incidence rates were calculated taking person-time at risk into account, and longitudinal trends from 2000 to 2015 were analysed using autoregressive time-series analyses.

Results: On average, a person aged 65 years or older has an 8.0% risk of getting a potentially serious infection each year. Acute cystitis was the most often occurring potentially serious infection (39.8/1000 person-years; 95%CI: 39.4 - 40.2), followed by Influenza Like Illness (ILI, 24.3/1000 person-years; 95%CI: 24.0 - 24.6) and pneumonia (9.7/1000 person-years; 95%CI: 9.5 - 9.9). The incidence rates of pneumonia were higher in older age groups and in men, whereas they were markedly lower for ILI at older ages, in both genders. From 2000 to 2015, overall incidence rates decreased significantly for ILI, while they increased in women for pneumonia, acute cystitis and pyelonephritis. Common chronic comorbidities were non-insulin dependent diabetes, COPD, asthma, heart failure and chronic renal insufficiency.

Conclusion: Potentially serious infections are quite common in an older patient population presenting to primary care. They are accompanied by several chronic comorbidities, which may differ by infection type.

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Key words: communicable diseases; comorbidity; frail elderly; geriatrics; immunosenescence; incidence

Lay summary

The aim of this study was to assess the occurrence of potentially serious infections in patients aged 65 years and over presenting to Flemish general practice from 2000-2015, and to describe the characteristics of these patients.

Potentially serious infections are quite common in older patients presenting to primary care. Annually, about 8% of them get a potentially serious infection. This risk increases with increasing age, reaching a peak around 76 years. Acute cystitis is the most common type of infection, followed by influenza like illness and pneumonia. From 2000 to 2015, we saw that the number of pneumonia infections slightly increased, especially in women, while the number of influenza like illness infections decreased markedly. We also observed a modest increase in the number of acute cystitis and pyelonephritis infections in women over this time period. This increase was not observed in men.

Not every person affected by an infection is alike. For example, patients affected by pneumonia are more often also having several chronic comorbidities, such as type II diabetes, asthma or chronic obstructive pulmonary disease, while patients affected by influenza like illness generally have less chronic comorbidities.

Introduction

Serious infections are important causes of morbidity and mortality in older persons.(1-3) Community-acquired pneumonia is associated with a 30-day in-hospital mortality of 19.4% in patients aged 65 years and older.(4) In 1997, acute pyelonephritis resulted in the hospitalization of 191,566 people in the US, of which only 28% was 60 years or older. However, this relatively small proportion of older persons accounted for 90% of the in-hospital mortality due to this infection.(5)

Whether an acute infection results in a serious outcome such as death or functional decline is not only determined by infection-specific factors but also by the individuals' underlying risk profile and functional status prior to infection.(6) An influenza virus infection for example, can be relatively minor in a healthy 85-year-old, but it could also prove to be fatal to a frail person of the same age who has several comorbidities. Some infections that are considered less serious, such as acute cystitis, may lead to a serious infection in older patients. This is largely determined by the patients' general health.(7)

Information on the occurrence of potentially serious infections in general practice is very limited. Most studies are performed in hospitals, which are based on a selected population.(8-10) Estimates on the incidence rates of infections are needed to assess the burden of disease in the community. This knowledge can serve as an information base for adapting health service delivery to an aging population.

Therefore, the aims of this study were (1) to calculate age-specific incidence rates of infections in older persons, (2) to examine the trends of those incidence rates from 2000 to 2015, and (3) to describe the characteristics of older patients affected by a serious infection.

Methods

Study setting and population

We performed a retrospective, registry-based study, on data provided by the Intego network of the KU Leuven. Intego is a morbidity registration network coordinated by the Academic Centre for General Practice, in which 111 general practitioners (GPs) working in 48 Flemish practices continuously register diagnoses and other data such as drug prescriptions and laboratory test results in their electronic medical records.(11) The participating practitioners are selected on the basis of their registration quality. The patient population in the register is representative of the Flemish population in terms of age and gender.

Information in medical records is automatically extracted and collected in a central database on a yearly basis. Identifiers are recoded to ensure anonymization and protection of patient privacy. The recorded diagnoses are extremely detailed and contain around 70.000 different keywords. Diagnostic keywords are mapped and classified according to the International Classification of Primary Care (ICPC-2) coding system.(11, 12) In case there is no appropriate ICPC-2 code available for a certain infection, or whenever this coding system is too broad, the underlying codification of the electronic medical records is used. A list of pre-selected infections is presented in Supplementary Table 1. From this list, we considered the following infections to be potentially serious, based on a consensus definition of a serious infection in geriatric ambulatory care patients:(6) pneumonia, acute exacerbation of chronic obstructive pulmonary disease, ILI, pyelonephritis, acute cystitis, meningitis/encephalitis, HIV infection/AIDS, appendicitis, acute cholecystitis, *clostridium difficile* enterocolitis, osteomyelitis, infectious arthritis, discitis, and infectious endocarditis. We chose not to include sepsis as a serious infection,

as this diagnosis is most often made in a hospital setting. It is therefore not included in the ICPC-2 coding. Moreover, sepsis could be seen as a potentially life-threatening host response to an infection that is included in this study.

Statistical analyses

For each year, data from all patients aged 65 years and older were included in a dynamic cohort, from 2000 to 2015. In Belgium patients can consult any GP at any time, meaning they are not obliged to register with a practice. It is therefore difficult to establish a practice population. For this reason, we used both the yearly contact group and the estimated practice population as a denominator when calculating incidence rates. The yearly contact group consists of those patients who had at least one contact with their GP during that particular year. The practice population is then estimated by applying a correction factor to the yearly contact group after stratification for age, gender and geographical region, based on data provided annually by the Belgian inter-mutualistic agency.(13)

Incidence rates of all infections, regardless of severity, and their 95% confidence intervals (95% CI) were calculated by dividing the number of new infections by the total person-time at risk. We categorized incidence by age: 65-74y, 75-84y, ≥ 85 years. We also analysed incidence rates by (continuous) age and per gender using a generalized linear model, accounting for the correlation of the observations across ages. Overall incidence rates were directly age-standardized using the mid-year Belgian population estimates from the year 2000.(14) We examined the 95% CI for overlap to assess the difference in incidence rates between subgroups.

Trends of incidence rates of potentially serious infections over subsequent years were analysed by gender using an autoregressive moving average time series analysis(15) because the data were correlated: older patients who contracted a specific infection were at higher risk of contracting the same infection in a subsequent year. Trends of potentially

serious infections were only analysed if at least one event of a particular infection was available each year, to avoid cells containing zeros.

We also described the study-population in more detail by calculating the prevalence (and its 95% CI) of the 10 most often observed chronic comorbidities in patients with a potentially serious infection for the year 2015. The median number of chronic comorbidities (+interquartile range) was calculated by infection, stratifying for age and gender. A radar chart was constructed to give a visual overview of the most frequent comorbidities in patients suffering from one of the four most often occurring potentially serious infections. Each spoke of the radar chart represents a chronic comorbidity. For each infection, the prevalence of the comorbidities was connected with a line, creating a star-shaped surface. The magnitude of the surface gives an indication of the burden of chronic comorbidities in patients suffering from that particular infection in that particular year.

All statistical analyses were performed using R software, Version 3.5.1 (R Core Team, 2019) and SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Population characteristics

From 2000 to 2015, there were on average 23,622 persons aged 65 years or above in the yearly contact group each year. About 56% of the people were women. The age group from 65 years to 74 years was the largest (49.1%), followed by the age group from 75 years to 84 years (36.1%) and those aged 85 and above (14.8%). The number of persons aged 65 years or older included in the registry increased over the years, from 16.877 persons in 2000 to 23.405 in 2015 (yearly contact group). More details on the yearly contact group and on the estimated practice population are presented in **Table 1**.

Incidence rates

Acute upper respiratory tract infection was the most commonly presenting infection, both in men and in women. Acute cystitis was the most common potentially serious infection, but incidence rates differed significantly between genders affecting women 2.5 to 5 times more often than men, depending on age. Incidence rates increased significantly by age in men (on average +5.5/1000 persons every ten years, 95% CI 4.2 to 6.7). After an initial significant increase in women, reaching a maximum at an age of 76 years, it decreased significantly thereafter.

ILI was also a common potentially serious infection. Its incidence rate was significantly lower at older ages, in both genders. In contrast, we observed higher incidence rates of pneumonia in older age groups, especially in men (Figure 1). Figure 2 shows the contrasting evolutions in men and women regarding the acute cystitis, pneumonia and ILI incidence rates. Supplementary Table 3 presents the incidence rates of infections, stratified by age group and gender.

Trends from 2000-2015

Results of the time series analyses are presented in table 2 and figure 3. From 2000 to 2015, incidence rates decreased significantly for ILI, both in women and in men (-4.09% and -5.14% annually, respectively). We observed a significant increase of the incidence rate for pneumonia in women (+1.91% annually, 95% CI +1.22% to +2.61%) but not in men. Similarly, we observed a significant increase of the incidence rate for acute cystitis in women (+1.89% annually, 95% CI +1.20% to +2.58%) and not in men. Pyelonephritis incidence increased significantly in women and decreased in men (+2.94% and -1.19% annually, respectively).

Characteristics of patients with a potentially serious infection

Patients affected by a potentially serious infection were on average 76 years old. At that age, the incidence rate reached a peak of 158.0/1000 persons per year (95% CI 153.0 to 163.0). Patients had a median of 2 chronic comorbidities prior to infection. However, variability across patients was high, and the number of comorbidities per patient was not evenly distributed. Seventy-five percent of all patients with a potentially serious infection had 3 or fewer chronic comorbidities, while 25% of them had 4 to 13. We observed this skewed distribution in all infection types (data not shown). **Supplementary table 2** presents the ten most observed chronic comorbidities in patients with the four most often occurring potentially serious infections.

We did find differences in age, gender and type of comorbidities across infection type. A typical patient with pneumonia is male (61.7%), aged 85 years or older, and affected by a median number of two chronic comorbidities. Pneumonia patients are more often affected by several cardiovascular diseases, by cerebrovascular accidents and by COPD than patients with other types of infection.

In contrast, a patient affected by ILI is on average 65 to 74 years old, female (50.1%) and affected by only one chronic comorbidity. Characteristics of patients with acute cystitis or pyelonephritis do not differ substantially. A typical patient affected by either infection is a woman aged 65 to 84 years, who has one chronic comorbidity.

Supplementary figure S1 shows radar charts for pneumonia, ILI, acute cystitis and pyelonephritis. On visual inspection, the surface of the radar chart star connecting the prevalence of each comorbidity is largest for pneumonia, while the surface and shape of the other charts (ILI, acute cystitis and pyelonephritis) does not differ substantially.

Discussion

Main findings

This registry-based study provides estimates of the burden of infectious diseases in older persons presenting to Flemish general practice. Upper respiratory tract infections and acute bronchitis were the most often occurring infections, with people aged 65 years and older typically having one infection per 5 patient-years. Potentially serious infections are relatively common in this population. People aged 65 years or older can expect to experience at least one potentially serious infection every 12.5 years.

The most common potentially serious infection was acute cystitis, which occurred far more often in women than in men. Pneumonia incidence rates increased by increasing age, both in men and in women. The opposite was true for ILI incidence rates, being the highest in the younger age groups, regardless of gender.

Interpretation

We observed some remarkable trends from 2000 to 2015. While the incidence rates of pneumonia, acute cystitis and pyelonephritis all slightly increased in women, the ILI incidence rate decreased markedly in both genders. In 2000, the incidence rates of pneumonia and ILI differed by at least 20 events per 1000 persons per year, with ILI being by far the most common infection. By 2015 this difference had almost completely disappeared. One reason might be that influenza vaccination rates in Flanders were relatively high over this time period, especially in people aged 85 years and older. However, while vaccination reduces the number of influenza virus infections, it does not necessarily reduce the total number of ILI events,(16) and mortality rates due to pneumonia or ILI have not decreased substantially from 2000 to 2015.(17) Another explanation for the decreasing trend might be a change in recording behaviour by GPs, potentially to justify antibiotic prescribing in ill patients because this is recommended practice for pneumonia but not for ILI. Similarly, we did not observe an increase in the number of alternative diagnoses like acute bronchitis, cough or fever, for which antibiotics are equally not recommended.

As can be expected in this age group, most people suffer from pre-existing comorbidities, such as non-insulin dependent diabetes, COPD, asthma, heart failure and chronic kidney insufficiency. Importantly, patients with pneumonia had more comorbidities, especially COPD, and were on average older than other people with a potentially serious infection. The fact that pneumonia patients suffer more from COPD may of course be caused by an increased prevalence of smoking in pneumonia patients, which is an established risk factor for both pneumonia and COPD.(18) Increasing smoking rates in women over the years may also explain the increasing incidence of pneumonia in women. Unfortunately, smoking records are insufficiently reliable in Intego precluding any analysis to explore such association.(11)

Comparison with other studies

Our findings on pneumonia incidence rates and trends are very similar to those reported by a population-based study performed in the UK, with an overall incidence rate that was only slightly lower than what we observed (8.0/1000 person-years versus 9.7/1000).(19) Differences between age groups were more pronounced in this UK study, with the youngest people having a lower, and the oldest people having a higher incidence rate. A prospective study performed in adults visiting ambulatory care in northern Spain found a pneumonia incidence rate of 9.9 per 1000 person-years in those aged 74 years and older, which is only slightly lower than what we observed.(20) Unfortunately, this study did not report incidence rates per gender.

A similar decreasing trend in ILI incidence rates was observed in UK primary care from 1995 to 2013.(21) The authors state that this decrease was most likely reflecting changing recording behaviour by GPs, while we did not observe this change in coding. The incidence rates of acute cystitis reported by a registry-based study performed in the UK differed substantially from our data.(22) From 2004 to 2014, they found a slightly

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3 increasing trend for both men and women, while we only observed a significant increase
4 of cystitis cases in women. This study did not correct for correlation across years in their
5 analyses, which might explain the difference in statistical significance.
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13 *Strengths and limitations*

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16 Strengths of this study are the follow-up of a large real-world patient population, which is
17 representative for Flanders, over a relatively long and recent time period. The data
18 collection methodology was stable over the reported years.
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23 Some limitations should be discussed as well. The disease events reported in this study
24 are diagnoses made by GPs, which are not necessarily confirmed events. Changes in
25 recording behaviour may also influence the observed trends. This is a typical limitation of
26 a registry-based study, but it also implies that these data are closest to the observations
27 made in clinical practice.
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34 A second limitation is the fact that some important covariates, such as smoking habits or
35 alcohol abuse, are not well recorded in the Intego database. Given the nature of our data,
36 we could not present estimates on sepsis incidence, nor could we perform trend analyses
37 using individual patient data.
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47 *Implications for practice and research*

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50 The presented routine-care data are close to the observations made in clinical practice.
51 They are therefore well suited to serve as an information basis for further research.
52 Potentially serious infections are quite common in older persons. As the population ages
53 this will lead to an increased workload for GPs, and primary care health services will need
54 to be adapted accordingly. A shift towards early diagnosis and preventive medicine will be
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necessary in order to cope with the higher number of older patients, and in order to safeguard their functional independence up to an old age.

Future research should focus more on the relationship between the severity of an infection in older individual and the occurrence of frailty and functional decline before and after such infection. This implies that existing registers, such as Intego, and the GP's underlying registration habits need to be improved to better capture these concepts in a longitudinal and accurate manner.

For Peer Review

Ethics approval

The Intego project is approved by the ethical review board of the Research Ethics Committee of the UZ Leuven University Hospitals (number ML 1723) and by the Belgian Privacy Commission (number SCSZG/13/079). Intego was waived the need for individual informed consent but operates under an opt-out procedure for patients who do not wish their data to be included.

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Conflicts of interest: none declared

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Table 1: Composition of the Yearly Contact Group and Practice Population by age and gender (average number per year, period 2000-2015, and relative increase from yearly contact group to practice population (%))

Gender	Age Group	Yearly Contact Group (N)	Practice Population (N)	% practice population > yearly contact group
MEN	65-74y	5557	6293	+13.2%
	75-84y	3629	3961	+9.1%
	≥85y	1158	1245	+7.5%
	All	10,344	11,499	+11.2%
WOMEN	65-74y	6039	6619	+9.6%
	75-84y	4908	5205	+6.1%
	≥85y	2330	2430	+4.3%
	All	13,277	14,254	+7.4%
ALL	65-74y	11,597	12,912	+11.3%
	75-84y	8537	9166	+7.4%
	≥85y	3488	3675	+5.4%
TOTAL		23,622	25,753	+9.0%

Table 2: Results of the autoregressive moving average time series analysis of trends of potentially serious infections from 2000-2015

Infection	Gender	Annual change in incidence rate ¹ (/1000.persons.y ⁻¹ (95%CI))	Mean annual percent change ² (95%CI)		P-value
Pneumonia	Women	+0.1474 (0.094 to 0.201)	+1.91% (+1.22% to +2.61%)	↑	<0.0001
	Men	+0.025 (-0.084 to 0.134)	+0.32% (-0.68% to +1.09%)		0.650
Influenza like illness	Women	-1.0369 (-1.585 to -0.489)	-4.09% (-6.26% to -1.93%)	↓	0.002
	Men	-1.2403 (-1.671 to -0.809)	-5.14% (-6.93% to -3.35%)	↓	<0.0001
Acute cystitis	Women	+1.1457 (0.726 to 1.565)	+1.89% (+1.20% to +2.58%)	↑	<0.0001
	Men	+0.2057 (-0.118 to 0.529)	+1.44% (-0.83% to +3.71%)		0.220
Pyelonephritis	Women	+0.0714 (0.027 to 0.115)	+2.94% (+1.13% to +4.75%)	↑	0.006
	Men	-0.0136 (-0.025 to -0.002)	-1.19% (-2.19% to -0.19%)	↓	0.032
Acute cholecystitis	Women	-0.0251 (-0.070 to 0.020)	-2.71% (-7.58% to +2.16%)		0.280
	Men	-0.0214 (-0.068 to 0.025)	-2.31% (-7.31% to +2.70%)		0.367

¹Mean annual change in incidence rate as estimated by the model; ²Mean annual percent change in incidence rate, calculated as: (absolute mean annual change/ mean incidence rate over 16 years)*100; Statistically significant changes are indicated in **bold** (p<0.05).

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Figure 1: Incidence rates of potentially serious infections per gender and age group

Figure 2: Observed and predicted incidence rates (per 1000 person-years) of acute cystitis (TOP), influenza like illness (MIDDLE) and pneumonia (BOTTOM) by age, in men and women (including 95% confidence band)

Figure 3: Trends of age-standardized incidence rates of influenza like illness (TOP) and pneumonia (BOTTOM) in men and women aged 65 years and older from 2000 to 2015

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Figure 1: Incidence rates of potentially serious infections per gender and age group.

211x158mm (600 x 600 DPI)

149x295mm (300 x 300 DPI)

Figure 3: Trends of age-standardized incidence rates of influenza like illness (TOP) and pneumonia (BOTTOM) in men and women aged 65 years and older from 2000 to 2015.

264x198mm (350 x 350 DPI)

Table 1: Composition of the Yearly Contact Group and Practice Population by age and gender (average number per year, period 2000-2015, and relative increase from yearly contact group to practice population (%))

Gender	Age Group	Yearly Contact Group (N)	Practice Population (N)	% practice population > yearly contact group
MEN	65-74y	5557	6293	+13.2%
	75-84y	3629	3961	+9.1%
	≥85y	1158	1245	+7.5%
	All	10,344	11,499	+11.2%
WOMEN	65-74y	6039	6619	+9.6%
	75-84y	4908	5205	+6.1%
	≥85y	2330	2430	+4.3%
	All	13,277	14,254	+7.4%
ALL	65-74y	11,597	12,912	+11.3%
	75-84y	8537	9166	+7.4%
	≥85y	3488	3675	+5.4%
	TOTAL	23,622	25,753	+9.0%

Table 2: Results of the autoregressive moving average time series analysis of trends of potentially serious infections from 2000-2015

Infection	Gender	Annual change in incidence rate ¹ (/1000.persons.y ⁻¹ (95%CI))	Mean annual percent change ² (95%CI)		P-value
Pneumonia	Women	+0.1474 (0.094 to 0.201)	+1.91% (+1.22% to +2.61%)	↑	<0.0001
	Men	+0.025 (-0.084 to 0.134)	+0.32% (-0.68% to +1.09%)		0.650
Influenza like illness	Women	-1.0369 (-1.585 to -0.489)	-4.09% (-6.26% to -1.93%)	↓	0.002
	Men	-1.2403 (-1.671 to -0.809)	-5.14% (-6.93% to -3.35%)	↓	<0.0001
Acute cystitis	Women	+1.1457 (0.726 to 1.565)	+1.89% (+1.20% to +2.58%)	↑	<0.0001
	Men	+0.2057 (-0.118 to 0.529)	+1.44% (-0.83% to +3.71%)		0.220
Pyelonephritis	Women	+0.0714 (0.027 to 0.115)	+2.94% (+1.13% to +4.75%)	↑	0.006
	Men	-0.0136 (-0.025 to -0.002)	-1.19% (-2.19% to -0.19%)	↓	0.032
Acute cholecystitis	Women	-0.0251 (-0.070 to 0.020)	-2.71% (-7.58% to +2.16%)		0.280
	Men	-0.0214 (-0.068 to 0.025)	-2.31% (-7.31% to +2.70%)		0.367

¹Mean annual change in incidence rate as estimated by the model; ²Mean annual percent change in incidence rate, calculated as: (absolute mean annual change/ mean incidence rate over 16 years)*100; Statistically significant changes are indicated in **bold** (p<0.05)

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Supplementary material 1: Infections (with their ICPC-2 and Medidoc (Mddc) codes) included in the study. **Potentially serious infections are in bold.**

ICPC-2 code	Description
A77	other viral infection
A78	other viral infection not otherwise specified
B90	HIV infection/AIDS (first infection only)
D70	gastro-intestinal infection
D88	appendicitis
R72	streptococcal angina
R74	acute infection of the upper respiratory tract
R75	acute/chronic sinusitis
R78	acute bronchitis/bronchiolitis
R80	influenza (excl. pneumonia)
R81	pneumonia
R83	other infection of the respiratory tract
U70	pyelonephritis/pyelitis
U71	acute cystitis
Mddc Codes (Intego) ¹	Description
KI3301 KI3816 KI3392 KI3301 KI3308 KI3303 KI3399 KI398B KI0892	infective endocarditis
N3209 N3234 N323901 N32390 N3229 NA869 NA879 N0360 N3201	meningitis/encephalitis
L730011 L730012 L730013 L730014 L730015 L730021 L730022 L730031 L730032 L730033 L730041 L730042 L730043 L730044 L730051 L730052 L730061 L730062 L730063 L730064 L730071 L730072 L730073 L730074 L730075 L730076 L730077 L730081 L730082 L730083 L730084 L730085 L730086 L73009 L7300	osteomyelitis
D57501 D57504 D57519	acute cholecystitis
L72291A L72291B L72291C L72291 LM463	discitis
L7119911 L7119912 L7119913 L7119914 L7119915 L7119921 L7119922 L7119931 L7119932 L7119933 L7119941 L7119942 L7119943 L7119944 L7119951 L7119952 L7119953 L7119961 L7119962 L7119963 L7119964 L7119971 L7119972 L7119973 L7119974 L7119975 L7119976 L7119977 L7119981 L7119982 L7119983 L7119984 L7119985 L7119986 L711999 L71199 L7110	infectious arthritis
DA047	<i>Clostridium difficile</i> enterocolitis
R49691	Acute Exacerbation of COPD (AECOPD) with LRTI

¹ICPC-2: International Classification of Primary Care, second edition; ²An explanatory list of the Medidoc codes is available upon request (Dutch only)

Supplementary material 2: Top 10 most frequently observed comorbidities for the 4 most often occurring potentially serious infections in 2015

	Co-morbidity	Diabetes non-insulin dependent	COPD ²	Asthma	Heart failure	Vitamin/nutritional deficiency	Chronic renal insufficiency ³	Cardiovasc. disease (other)	Stroke/cerebrovasc. accident	Constipation	Ischemic heart disease without angina
Pneumonia (N=331)¹	Prevalence	23.0%	19.9%	16.9%	14.5%	13.9%	13.3%	11.8%	10.3%	9.7%	8.8%
	(95%CI)	(18.5%-7.9%)	(15.8%-4.7%)	(13.0%-1.4%)	(10.9% -8.8%)	(10.4%-8.1%)	(9.8%-17.4%)	(8.5%-15.8%)	(7.2%-14.1%)	(6.7%-13.4%)	(6.0%-12.3%)
Influenza Like Illness (N=527)¹	Co-morbidity	Diabetes non-insulin dependent	Asthma	Depressive disorder	Constipation	Cardiovasc. disease (other)	COPD	Urine incontinence	Vitamin/nutritional deficiency	Obesity	Benign prostatic hypertrophy
	Prevalence	20.5%	13.1%	12.1%	11.6%	7.6%	7.4%	7.2%	7.0%	5.9%	4.9%
	(95%CI)	(17.1%-24.2%)	(10.3%-16.3%)	(9.5% -15.2%)	(9.0%-14.6%)	(5.5%-10.2%)	(5.3%-10.0%)	(5.2%-9.8%)	(5.0%-9.6%)	(4.0%-8.3%)	(3.3%-7.2%)
Acute cystitis (N=1106)¹	Co-morbidity	Diabetes non-insulin dependent	Vitamin/nutritional deficiency	Constipation	Depressive disorder	Asthma	Urine incontinence	Chronic renal insufficiency ³	Cardiovasc. disease (other)	Ischemic heart disease with angina	Stroke/cerebrovasc. accident
	Prevalence	16.8%	12.9%	10.0%	9.8%	9.6%	9.4%	8.3%	7.2%	7.1%	5.8%
	(95%CI)	(14.7%-19.2%)	(11.0%-15.1%)	(8.3%-11.9%)	(8.1%-11.7%)	(7.9%-11.5%)	(7.8%-11.3%)	(6.8%-10.1%)	(5.8%-8.9%)	(5.7%-8.8%)	(4.5%-7.3%)
Pyelonephritis/pyelitis (N=58)¹	Co-morbidity	Diabetes non-insulin dependent	Chronic renal insufficiency ³	Depressive disorder	Constipation	Asthma	Vitamin/nutritional deficiency	Urine incontinence	Ischemic heart disease with angina	Cardiovasc. disease (other)	Malignant neoplasm of skin
	Prevalence	15.5%	12.1%	12.1%	10.3%	8.6%	8.6%	6.9%	5.2%	5.2%	5.2%
	(95%CI)	(7.4%-27.4%)	(5.0%-23.3%)	(5.0%-23.3%)	(3.9%-21.2%)	(2.9%-19.0%)	(2.9%-19.0%)	(1.9%-16.7%)	(1.1%-14.4%)	(1.1%-14.4%)	(1.1%-14.4%)

¹N=the number of new cases registered in the yearly contact group in 2015; ²COPD= Chronic Obstructive Pulmonary Disease; ³Defined as 'estimated Glomerular Filtration Rate <45ml/min'

Supplementary material 3: Incidence rates of (potentially serious) infections, by age group and gender, calculated for both the Yearly Contact Group and the estimated Practice Population as a denominator (per 1000 persons per year). Total incidence rates are age-standardized.

		WOMEN			MEN			ALL
	Denominator	65-74 years (95% CI)	75-84 years (95% CI)	≥85 years (95% CI)	65-74 years (95% CI)	75-84 years (95% CI)	≥85 years (95% CI)	≥65 years (95% CI)
Acute URTI ¹	Yearly contact group	147.59 (145.17 - 150.03)	106.73 (104.46 - 109.03)	68.40 (65.79 - 71.09)	137.59 (135.17 - 140.06)	110.82 (108.14 - 113.56)	71.87 (68.11 - 75.80)	124.36 (123.67 - 125.06)
	Practice population	134.54 (132.35 - 136.77)	100.59 (98.45 - 102.76)	65.58 (63.08 - 68.15)	121.37 (119.22 - 123.54)	101.47 (99.01 - 103.97)	66.79 (63.29 - 70.44)	112.46 (111.80 - 113.12)
Acute bronchitis/ bronchiolitis	Yearly contact group	73.82 (72.11 - 75.55)	71.42 (69.57 - 73.31)	62.82 (60.32 - 65.40)	88.04 (86.10 - 90.01)	95.33 (92.84 - 97.88)	72.66 (68.86 - 76.61)	79.41 (78.86 - 79.97)
	Practice population	67.29 (65.74 - 68.87)	67.30 (65.56 - 69.09)	60.22 (57.82 - 62.70)	77.63 (75.92 - 79.37)	87.24 (84.96 - 89.57)	67.50 (63.97 - 71.17)	71.95 (71.42 - 72.48)
Acute cystitis	Yearly contact group	61.07 (59.52 - 62.64)	64.05 (62.30 - 65.84)	50.49 (48.25 - 52.80)	11.71 (11.02 - 12.43)	17.21 (16.18 - 18.30)	20.09 (18.15 - 22.19)	39.75 (39.36 - 40.15)
	Practice population	55.67 (54.27 - 57.11)	60.36 (58.71 - 62.05)	48.40 (46.26 - 50.62)	10.34 (9.73 - 10.97)	15.77 (14.82 - 16.76)	18.67 (16.87 - 20.62)	36.23 (35.86 - 36.61)
Influenza Like Illness	Yearly contact group	29.93 (28.86 - 31.04)	20.60 (19.62 - 21.61)	10.47 (9.48 - 11.53)	27.18 (26.12 - 28.28)	20.61 (19.48 - 21.80)	12.81 (11.28 - 14.49)	24.28 (23.98 - 24.59)
	Practice population	27.31 (26.33 - 28.31)	19.42 (18.50 - 20.38)	10.04 (9.09 - 11.06)	24.00 (23.06 - 24.97)	18.88 (17.84 - 19.97)	11.91 (10.49 - 13.47)	22.05 (21.76 - 22.35)
Acute/chronic sinusitis	Yearly contact group	20.62 (19.73 - 21.53)	9.46 (8.81 - 10.16)	2.95 (2.45 - 3.53)	12.72 (12.00 - 13.47)	6.90 (6.25 - 7.59)	3.24 (2.52 - 4.11)	12.74 (12.52 - 12.96)
	Practice population	18.81 (18.00 - 19.64)	8.92 (8.30 - 9.57)	2.83 (2.35 - 3.38)	11.23 (10.60 - 11.90)	6.32 (5.73 - 6.95)	3.01 (2.34 - 3.82)	11.52 (11.31 - 11.74)
Pneumonia	Yearly contact group	6.22 (5.74 - 6.73)	9.19 (8.55 - 9.88)	11.63 (10.58 - 12.75)	9.61 (8.99 - 10.27)	14.90 (13.93 - 15.91)	19.01 (17.12 - 21.05)	9.68 (9.49 - 9.87)
	Practice population	5.68 (5.24 - 6.14)	8.67 (8.06 - 9.31)	11.15 (10.15 - 12.22)	8.48 (7.93 - 9.06)	13.64 (12.76 - 14.57)	17.66 (15.91 - 19.56)	8.87 (8.69 - 9.06)
Pyelonephritis/ pyelitis	Yearly contact group	2.64 (2.34 - 2.97)	2.32 (2.01 - 2.67)	1.74 (1.37 - 2.19)	1.02 (0.83 - 1.24)	1.36 (1.09 - 1.68)	1.13 (0.74 - 1.67)	1.85 (1.76 - 1.93)
	Practice population	2.41 (2.13 - 2.71)	2.19 (1.89 - 2.51)	1.67 (1.31 - 2.10)	0.90 (0.74 - 1.10)	1.25 (1.00 - 1.54)	1.05 (0.69 - 1.55)	1.69 (1.61 - 1.77)
Gastro- intestinal infection	Yearly contact group	1.60 (1.37 - 1.87)	1.29 (1.06 - 1.55)	1.58 (1.23 - 2.01)	1.26 (1.05 - 1.50)	1.00 (0.77 - 1.27)	0.76 (0.45 - 1.20)	1.34 (1.27 - 1.41)
	Practice population	1.46 (1.25 - 1.70)	1.21 (1.00 - 1.46)	1.52 (1.18 - 1.93)	1.11 (0.93 - 1.33)	0.92 (0.71 - 1.17)	0.70 (0.42 - 1.12)	1.22 (1.16 - 1.29)
Acute cholecystitis	Yearly contact group	0.81 (0.65 - 1.00)	1.05 (0.84 - 1.28)	0.99 (0.72 - 1.34)	0.82 (0.65 - 1.02)	0.98 (0.76 - 1.25)	1.08 (0.70 - 1.60)	0.90 (0.84 - 0.96)
	Practice population	0.74 (0.59 - 0.91)	0.99 (0.79 - 1.21)	0.95 (0.69 - 1.28)	0.73 (0.58 - 0.90)	0.90 (0.70 - 1.15)	1.00 (0.65 - 1.49)	0.82 (0.77 - 0.88)
AECOPD ²	Yearly contact group	0.62 (0.48 - 0.79)	0.42 (0.30 - 0.58)	0.38 (0.23 - 0.60)	1.26 (1.05 - 1.50)	1.52 (1.23 - 1.85)	1.13 (0.74 - 1.67)	0.88 (0.83 - 0.94)
	Practice population	0.57 (0.44 - 0.72)	0.40 (0.28 - 0.54)	0.36 (0.22 - 0.57)	1.11 (0.93 - 1.33)	1.39 (1.13 - 1.69)	1.05 (0.69 - 1.55)	0.81 (0.75 - 0.86)
Appendicitis	Yearly contact group	0.42 (0.31 - 0.56)	0.38 (0.27 - 0.53)	0.24 (0.13 - 0.42)	0.39 (0.28 - 0.53)	0.31 (0.20 - 0.47)	0.27 (0.12 - 0.55)	0.37 (0.34 - 0.41)
	Practice population	0.39 (0.29 - 0.51)	0.36 (0.25 - 0.50)	0.23 (0.12 - 0.41)	0.35 (0.25 - 0.47)	0.28 (0.18 - 0.43)	0.25 (0.11 - 0.51)	0.34 (0.31 - 0.38)
Clostridium	Yearly contact group	0.23 (0.15 - 0.33)	0.46 (0.33 - 0.62)	0.64 (0.43 - 0.93)	0.20 (0.13 - 0.31)	0.33 (0.21 - 0.49)	0.32 (0.15 - 0.63)	0.31 (0.28 - 0.34)

difficile enterocolitis	Practice population	0.21 (0.14 - 0.30)	0.43 (0.31 - 0.58)	0.62 (0.42 - 0.89)	0.18 (0.11 - 0.27)	0.30 (0.19 - 0.45)	0.30 (0.14 - 0.59)	0.28 (0.25 - 0.32)
Infective endocarditis	Yearly contact group	0.08 (0.04 - 0.15)	0.09 (0.04 - 0.17)	0.03 (0.01 - 0.10)	0.09 (0.05 - 0.16)	0.10 (0.05 - 0.20)	0.05 (0.01 - 0.20)	0.08 (0.07 - 0.10)
	Practice population	0.08 (0.04 - 0.14)	0.08 (0.04 - 0.16)	0.03 (0.01 - 0.09)	0.08 (0.04 - 0.14)	0.09 (0.04 - 0.18)	0.05 (0.01 - 0.19)	0.08 (0.06 - 0.09)
Infectious arthritis	Yearly contact group	0.06 (0.03 - 0.12)	0.13 (0.07 - 0.22)	0.11 (0.04 - 0.24)	0.09 (0.05 - 0.16)	0.02 (0.00 - 0.06)	0.00	0.08 (0.06 - 0.09)
	Practice population	0.06 (0.03 - 0.11)	0.12 (0.07 - 0.21)	0.10 (0.04 - 0.23)	0.08 (0.04 - 0.14)	0.02 (0.00 - 0.06)	0.00	0.07 (0.06 - 0.09)
Osteomyelitis	Yearly contact group	0.09 (0.05 - 0.16)	0.09 (0.04 - 0.17)	0.16 (0.08 - 0.31)	0.03 (0.01 - 0.08)	0.05 (0.02 - 0.12)	0.00	0.07 (0.06 - 0.09)
	Practice population	0.09 (0.05 - 0.15)	0.08 (0.04 - 0.16)	0.15 (0.07 - 0.30)	0.03 (0.01 - 0.07)	0.05 (0.02 - 0.11)	0.00	0.07 (0.05 - 0.08)
Meningitis/ encephalitis	Yearly contact group	0.05 (0.02 - 0.11)	0.01 (0.00 - 0.05)	0.00	0.09 (0.05 - 0.16)	0.00	0.00	0.04 (0.03 - 0.06)
	Practice population	0.05 (0.02 - 0.10)	0.01 (0.00 - 0.04)	0.00	0.08 (0.04 - 0.14)	0.00	0.00	0.04 (0.03 - 0.05)
Discitis	Yearly contact group	0.01 (0.00 - 0.04)	0.01 (0.00 - 0.05)	0.03 (0.01 - 0.10)	0.06 (0.02 - 0.12)	0.00	0.00	0.02 (0.02 - 0.03)
	Practice population	0.01 (0.00 - 0.03)	0.01 (0.00 - 0.04)	0.03 (0.01 - 0.09)	0.05 (0.02 - 0.10)	0.00	0.00	0.02 (0.01 - 0.03)
HIV infection³	Yearly contact group	0.02 (0.01 - 0.06)	0.00	0.00	0.01 (0.00 - 0.04)	0.00	0.00	0.01 (0.01 - 0.02)
	Practice population	0.02 (0.01 - 0.05)	0.00	0.00	0.01 (0.00 - 0.04)	0.00	0.00	0.01 (0.00 - 0.02)

¹Acute Upper Respiratory Tract Infection; ²Acute Exacerbation of Chronic Obstructive Pulmonary Disease; ³HIV infections acquired prior to the year 2000 were included as well

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STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study’s design with a commonly used term in the title or the abstract	1
		(b) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5-6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(a) Cohort study—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Case-control study—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls Cross-sectional study—Give the eligibility criteria, and the sources and methods of selection of participants	NA
		(b) Cohort study—For matched studies, give matching criteria and number of exposed and unexposed Case-control study—For matched studies, give matching criteria and the number of controls per case	NA
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	NA
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding	6
		(b) Describe any methods used to examine subgroups and interactions	6
		(c) Explain how missing data were addressed	NA
		(d) Cohort study—If applicable, explain how loss to follow-up was addressed Case-control study—If applicable, explain how matching of cases and controls was addressed Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy	NA
		(e) Describe any sensitivity analyses	NA

Continued on next page

Results

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	NA
		(c) Consider use of a flow diagram	NA
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	NA
		(c) <i>Cohort study</i> —Summarise follow-up time (eg, average and total amount)	7-8
Outcome data	15*	<i>Cohort study</i> —Report numbers of outcome events or summary measures over time	8
		<i>Case-control study</i> —Report numbers in each exposure category, or summary measures of exposure	NA
		<i>Cross-sectional study</i> —Report numbers of outcome events or summary measures	NA
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	7-9
		(b) Report category boundaries when continuous variables were categorized	7-9
		(c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	NA
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	NA

Discussion

Key results	18	Summarise key results with reference to study objectives	9
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	11-12
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	11-12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12

Other information

Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	15
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*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.