International Journal of Infectious Diseases 124 (2022) 181–186

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

The effect of absent or deferred antibiotic treatment on complications of common infections in primary care

Elin Dahlén[1,2], Julius Collin[3], Jenny Hellman[3], Christer Norman[3], Pontus Nauclér[4,5], Anders Ternhag[3,5,*]

[1] Public Healthcare Service Committee, Stockholm County Council, SE-104 25 Stockholm, Sweden
[2] Department of Clinical Science and Education, Södersjukhuset, SE-118 83 Stockholm, Sweden
[3] Public Health Agency of Sweden, SE-171 82 Solna, Sweden
[4] Department of Infectious Diseases, Karolinska University Hospital, SE-171 76 Stockholm, Sweden
[5] Department of Medicine, Karolinska Institutet, Solna, SE-171 77 Stockholm, Sweden

ARTICLE INFO

Article history:
Received 29 June 2022
Revised 8 September 2022
Accepted 30 September 2022

Keywords:
Respiratory tract infection
UTI
Complications
Antibiotic treatment

ABSTRACT

Objectives: The objective of this study was to compare the incidence rate for complications to upper respiratory tract infections (URTIs), including acute bronchitis and lower urinary tract infections (UTIs), for those treated with antibiotics compared to those who were not.
Methods: This was a population-based retrospective cohort study in Sweden. Patients diagnosed with otitis, pharyngotonsillitis, sinusitis, acute bronchitis, and lower UTI in primary care between 2014 and 2020 were included. Data on prescribed and dispensed antibiotics and comorbidities for each subject were collected. The outcome we investigated was the number of infectious complications within 30 days and if antibiotic treatment had any effect on risk reduction.
Results: There were 202,995 episodes of otitis, 388,158 pharyngotonsillitis, 125,792 sinusitis, 220,960 bronchitis, and 377,954 lower UTIs in our cohort. No increased risk for complications was seen for untreated compared with treated cases with URTI. For lower UTI, the adjusted odds ratio for febrile UTI or bloodstream infection was 1.53 (95% confidence interval 1.39-1.68).
Conclusion: The risk for infectious complications from common URTIs is low and not modified by antibiotic treatment. On the contrary, patients diagnosed with UTI in whom antibiotics were withheld had an increased 30 days risk for severe infections.

Introduction

There has been a significant downward trend in the use of antibiotics in the community in many European countries from 2010 to 2019 (2019). This may be a result of years of antimicrobial stewardship programs, including awareness campaigns for the public. This reduction in antibiotic consumption in the community, which has been going on for many years has accelerated sharply in 2020 due to COVID-19. A recent review of studies from several countries found a 42% decline in health care visits during the pandemic compared with before (Moynihan *et al.*, 2021). Consultations for upper respiratory and urinary tract infections (UTIs) have decreased, particularly among children (Rezel-Potts *et al.*, 2021). The reduced number of visits have resulted in fewer prescribed and dispensed antibiotics. For example, in a US study, they found that the number of dispensed antibiotic prescriptions decreased to 39% in April and 42% in May 2020 compared with the same months in 2017-2019 (King *et al.*, 2020).

Complications due to upper respiratory tract infections (URTIs), such as mastoiditis after otitis media, peritonsillar abscess after pharyngotonsillitis, bacterial meningitis/intracranial abscess after sinusitis, are rare and any protective effect of antibiotic treatment are low (Cars *et al.*, 2017; Petersen *et al.*, 2007). Antibiotic treatment for acute bronchitis may have a small effect on the reduction of symptoms, although, in most cases, not clinically relevant (Little *et al.*, 2013a). There are also findings from the United Kingdom that indicate that general practices with low rates of URTIs consultations with antibiotics prescribed may have higher incidence rates of pneumonia (Gulliford *et al.*, 2016). For lower UTI, it was observed that for patients aged ≥65 years with symptoms

* Corresponding author: Anders Ternhag, Karolinska Institutet, Department of Medicine Solna, 171 77, Stockholm, Sweden, Tel: +46-707 34 76 64
E-mail address: anders.ternhag@ki.se (A. Ternhag).

https://doi.org/10.1016/j.ijid.2022.09.036

of lower UTI, deferred antibiotics or no treatment increased the risk of bloodstream infection and all-cause mortality (Gharbi *et al.*, 2019).

The unnecessary use of antibiotics contributes to the development of resistance. In a review that examined what affects misprescriptions of antibiotics, doctors' fear of possible complications was one of them (Lopez-Vazquez *et al.*, 2012).

To make guidelines addressed to general practitioners on how antibiotics should be used to be credible and reliable, regular measurements of prescriptions and complications are needed. In a previous study from our group, we concluded that bacterial complications after URTIs are rare, and that antibiotics may lack protective effects in preventing bacterial complications (Cars *et al.*, 2017). Since then, the number of antibiotic prescriptions has decreased even further. In addition, it is not known how complications after lower UTIs may be affected. Therefore, our aim with the current study was to compare the incidence rate for complications from URTI, including acute bronchitis and lower UTI, for those treated and not treated with antibiotics.

Methods

Patient population and study setting

This was a population-based retrospective cohort study. All patients living in the greater Stockholm area, Sweden, with 2.3 million inhabitants, formed the study base. Those who sought primary care (both private and public health care providers and emergency services in outpatient care) for URTIs, including acute cough symptoms, and lower UTI and had an International Classification of Diseases (ICD), Tenth revision (ICD-10) code, which complied with otitis, pharyngotonsillitis, sinusitis, acute bronchitis, and lower UTI were included in the cohorts (Table S1). Emergency services in outpatient care were open during evenings and weekends, in contrast to health care clinics, which were open during office hours. Those with life-threatening illnesses and the patients with severe cases were handled at the hospital's emergency departments and were not included in this study.

The time period used was January 1, 2014 to December 31, 2020. Patients of all ages were eligible for inclusion.

The study was approved by the Swedish Ethical Review Authority (Dnr 2019-06503).

Data sources and definitions

Data were obtained from Stockholm region's health care databases. This is primarily a data warehouse that stores information on health care events at the individual-patient level. Data from different care providers within one or more health care episodes are recorded, including information from primary care. Demographics, ICD-10 codes for inclusion and outcomes, and the Charlson comorbidity index (CCI) (Quan *et al.*, 2005) were retrieved from the databases (Table S2). Information on prescribed antibiotics dispensed at pharmacies were also collected from the same data warehouse. The data contain information on all prescribed drugs dispensed at pharmacies for the residents of Stockholm, with a unique identification number for all citizens. The linkage between the different databases in the Stockholm region was possible due to this identification number. Prescribed antibiotics had to be dispensed by a pharmacy within 2 days of the doctor's visit to be counted as exposure (*i.e.,* the doctor's visit is day 0, and antibiotics must be dispensed on day 0, 1, or 2). The database in Stockholm is a regional copy of the national Swedish Prescribed Drug Register (Wallerstedt *et al.*, 2016). The antibiotics were classified according to the Anatomic Therapeutic Chemical system (2021). They were categorized into groups of antibiotics commonly used to treat respiratory tract infections (RTIs) and UTIs (Table S3).

Outcomes

The number of infectious complications within 30 days was investigated. These were identified in both primary as well as outpatient specialized care (including emergency departments), and patients admitted to the hospital. For lower UTIs, we calculated the number of cases with febrile UTIs. This included the categories of upper UTIs and pyelonephritis. The ICD-10 codes used for the identification of these adverse outcomes are shown in Table S1. We calculated and compared the proportion of complications for those who received antibiotics and those who did not. To distinguish different infectious episodes for the same patient and to rule out any patients with recurring or chronic infections, we used a 180-day washout period before every primary care visit for each cohort. One reason for choosing 180 days was that recurrent UTI is defined as two UTIs in the last 6 months or at least three UTIs per year (European Association of Urology (EAU), 2022). If there were any consultations or specialized care within this time period (regarding the cohort definitions), we used this date of visit and performed the same washout once again until there was no previous visit for the same disease within 180 days.

Data on the use of antibiotics were collected within 2 days of each index date of a new episode.

Statistical analysis

Odds ratios (ORs) for complications within 30 days were calculated and adjusted for sex, age, and CCI, together with 95% confidence intervals (CIs). For complications due to lower UTI, additional interaction analyses were performed between exposure to antibiotics and sex, age, and CCI, respectively. In the multivariable analysis, data over a 3-year period preceding each episode were used to create CCI; thus, the analysis included only episodes from 2017 to 2020. Estimates were further validated by a marginal effects model, accounting for multiple infectious episodes for certain individuals. We also calculated adjusted ORs, excluding the year 2020, as a sensitivity analysis to see if the COVID-19 pandemic affected the results.

Statistical analyses were performed in SAS 9.4 and R version 4.0.3.

Results

Patient characteristics

There were 202,995 infectious episodes with otitis, 388,158 with pharyngotonsillitis, 125,792 with sinusitis, 220,960 with bronchitis, and 377,654 with a diagnosis of lower UTI included between January 2014 and December 2020 in the study.

The median age was low for those with otitis, which was 6 years (interquartile range 2-25 years) (Table 1). Also, cases with pharyngotonsillitis were young, with a median age of 22 years (interquartile range 8-37 years). For the other, cohorts median age was between 40 and 50 years. Women were in the majority in all cohorts. Furthermore, the included patients did not have many comorbidities: median CCI was zero for all cohorts. Those with a diagnosis of bronchitis and lower UTI had more comorbidities than the others, especially chronic pulmonary disease for those with bronchitis and dementia and malignancies for lower UTI cases (Table 1).

Table 1
Patient characteristics at doctor's visits in the bronchitis, pharyngotonsillitis, otitis, sinusitis and urinary tract infection cohorts.

	Otitisn = 202,995, n[a] = 107,437	Pharyngotonsillitisn = 388,158,n[a] = 191,216	Sinusitisn = 125,792, n[a] = 62,758	Bronchitisn = 220,960, n[a] = 111,963	Urinary tract infectionn = 367,964, n[a] = 196,096
Patient characteristics					
Male sex, n (%)	99,063 (48.8)	167,365 (43.1)	37,836 (30.1)	91,295 (41.3)	44,370 (12.1)
Age, median (IQR), years	6 (2-25)	22 (8-37)	42 (32-55)	48 (29-64)	49 (30-69)
0-4, n (%)	86,211 (42.5)	52,042 (13.4)	293 (0.2)	19,963 (9.0)	n/a
5-19	58,373 (28.8)	123,853 (31.9)	7618 (6.1)	20,140 (9.1)	35,604 (9.7)
20-69	54,799 (27.0)	205,308 (52.9)	108,952 (86.6)	143,755 (65.1)	245,577 (66.7)
≥70	3612 (1.8)	6955 (1.8)	8929 (7.1)	37,102 (16.8)	86,783 (23.6)
CCI[a], median (IQR), points	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-1)	0 (0-1)
0-1, n (%)	98,132 (91.3)	175,706 (91.9)	55,006 (87.7)	93,143 (83.2)	157,555 (80.4)
2-4, n (%)	2186 (2.0)	4143 (2.2)	3656 (5.8)	11,036 (9.9)	23,342 (11.9)
>5, n (%)	7119 (6.6)	11,367 (5.9)	4096 (6.5)	7784 (7.0)	15,199 (7.8)
Any of the comorbidities below, n[a] (%)	20,539 (19.1)	32,292 (16.9)	15,147 (24.1)	35,932 (32.1)	61,939 (31.6)
Specific comorbidities					
Myocardial infarction, n[a] (%)	130 (0.1)	199 (0.1)	196 (0.3)	669 (0.6)	1261 (0.6)
Congestive heart failure, n[a] (%)	351 (0.3)	485 (0.3)	528 (0.8)	2782 (2.5)	5855 (3.0)
Peripheral vascular disease, n[a] (%)	143 (0.1)	229 (0.1)	255 (0.4)	1110 (1.0)	2446 (1.3)
Cerebrovascular disease, n[a] (%)	415 (0.4)	632 (0.3)	680 (1.1)	2668 (2.4)	6302 (3.2)
COPD, n[a] (%)	518 (0.5)	819 (0.4)	1045 (1.7)	3800 (3.4)	6796 (3.5)
Other chronic pulmonary disease, n[a] (%)	10,989 (10.2)	15,497 (8.1)	5962 (9.5)	14,288 (12.8)	15,972 (8.1)
Rheumatic disease, n[a] (%)	1237 (1.2)	2625 (1.4)	1979 (3.2)	4251 (3.8)	8240 (4.2)
Dementia, n[a] (%)	64 (0.1)	77 (0.0)	56 (0.1)	1035 (0.9)	2744 (1.4)
Hemiplegia, tetraplegia, n[a] (%)	252 (0.2)	299 (0.2)	139 (0.2)	670 (0.6)	1831 (0.9)
Diabetes, n[a] (%)	19 (0.0)	59 (0.0)	20 (0.0)	51 (0.1)	105 (0.1)
Diabetes with end organ damage, n[a] (%)	434 (0.4)	740 (0.4)	690 (1.1)	2021 (1.8)	4094 (2.1)
Moderate or severe kidney disease, n[a] (%)	419 (0.4)	845 (0.4)	563 (0.9)	2087 (1.9)	5177 (2.6)
Mild liver disease, n[a] (%)	239 (0.2)	518 (0.3)	338 (0.5)	842 (0.8)	1381 (0.7)
Moderate or severe liver disease, n[a] (%)	27 (0.0)	40 (0.0)	49 (0.1)	123 (0.1)	260 (0.1)
Peptic ulcer disease, n[a] (%)	118 (0.1)	264 (0.1)	196 (0.3)	491 (0.4)	1148 (0.6)
Any malignancy including leukemia and lymphoma, n[a] (%)	1103 (1.0)	2229 (1.2)	2276 (3.6)	6523 (5.8)	14,209 (7.3)
Metastatic cancer, n[a] (%)	5 (0.0)	13 (0.0)	20 (0.0)	41 (0.0)	105 (0.1)
HIV/AIDS, n[a] (%)	7007 (6.5)	11,221 (5.9)	3912 (6.2)	6798 (6.1)	12865 (6.6)
Antibiotics, n[a] (%)	167,552 (82.5)	269,931 (69.5)	81,856 (65.1)	74,008 (33.5)	311,386 (84.6)

[a] Truncated to 2017-2020.

Infectious complications of those untreated compared to those treated with antibiotics

Whether antibiotics or not, infectious complications were uncommon for those with URTIs 0.47% (1699/361,411) and for lower UTIs 0.99% (1939/196,996). Among those diagnosed with bronchitis. 2.95% (3301/111,963) were diagnosed with pneumonia or a bloodstream infection (BSI) caused by *Streptococcus pnemoniae, Haemophilus influenzae,* or *Staphylococcus aureus* during follow-up. For otitis and pharyngotonsillitis, no increased risk for infection complications within 30 days was seen for those untreated compared with those treated with antibiotics (Table 2. For the number of complications in each age-group, see Table S4). Among individuals with sinusitis, there was an increased risk of complications among the untreated (OR 5, 95% CI 1.3-18.7). However, the number of complications (brain abscess) in the sinusitis cohort was very low, 8 of 43,928 (0.018%) among untreated and 3 of 81,802 (0.0037%) among antibiotic-treated cases, which hampered comparisons. In the unadjusted analysis of patients with bronchitis, no increased risk for pneumonia and BSI was seen. Those treated with penicillin V had a higher complication risk (8.07%; 785/9723) than those who received any of doxycycline, amoxicillin, amoxicillin with enzyme inhibitor, cephalosporin, or a macrolide (4.21%; 919/21,853; OR 2.0, 95% CI 1.9-2.2) (Table 2). Persons diagnosed with lower UTI had a higher risk for febrile UTI and BSI if untreated with antibiotics (OR 1.6, 95% CI 1.4-1.7). Pivmecillinam, compared with trimethoprim, fluoroquinolones, or nitrofurantoin, showed a lower risk for complications in 30 days (OR 0.3, 95% CI 0.3-0.3).

In the analysis of the risk for complications adjusted for age, sex, and comorbidities, we could not find any increased complication risk for untreated cases of otitis, pharyngotonsillitis, sinusitis, or bronchitis. However, for those with lower UTI, the adjusted OR of those untreated was 1.3 (95% CI 1.1-1.4) for febrile UTI and OR 4.3 (95% CI 3.0-6.1) for BSI (Table 3).

We performed a multivariable analysis for cases of lower UTI and included interactions between treatment with antibiotics and sex, age, and CCI, respectively, presented as a forest plot (Figure 1). Females more than men and patients who were 5-19 years or ≥70 years old compared with those aged 20-69 years were at higher risk for complications when untreated with antibiotics.

Discussion

This observational study of 937,905 infectious episodes of otitis, pharyngotonsillitis, sinusitis, or bronchitis of patients of all ages between 2014 and 2020 could not find any increased risk for infectious complications within 30 days of follow-up in patients who were untreated compared with those who were treated with antibiotics. Patients diagnosed with lower UTI who were not treated with antibiotics had an increased risk for febrile UTI and BSI. This was seen in all sex, age, and comorbidity strata.

Table 2
Outcomes complications within 30 days in the bronchitis, pharyngotonsillitis, otitis, sinusitis and urinary tract infection cohorts, unadjusted ORs.

Variable	Patient characteristics	OtitisOR (95% CI)[a]	PharyngotonsillitisOR (95% CI)[a]	SinusitisOR (95% CI)[a]	BronchitisOR (95% CI)[a]	Urinary tract infectionOR (95% CI)[a]
Sex	*Males* vs *Females*	0.8 (0.5, 1.2)	1.3 (1.2, 1.4)	2.8 (0.9, 9.1)	1 (1, 1.1)	3.0 (2.8, 3.2)
Age, years	*0-4*	0.3 (0.1, 0.5)	0.1 (0.1, 0.1)	n/e[c]	0.8 (0.7, 0.9)	n/a[d]
	5-19	Reference	Reference	Reference	Reference	Reference
	20-69	1.1 (0.7, 1.7)	1.9 (1.7, 2.1)	0.1 (0, 0.2)	1.2 (1.1, 1.3)	0.6 (0.6, 0.7)
	≥70	2 (0.7, 5.7)	1.9 (1.4, 2.4)	n/e	1.9 (1.7, 2.2)	1 (0.8, 1.1)
Antibiotics	*No* vs *Yes*	1.1 (0.6, 1.9)	0.5 (0.5, 0.6)	5 (1.3, 18.7)	0.4 (0.4, 0.4)	1.6 (1.4, 1.7)
	PcV vs *other*	0.5 (0.3, 1)	0.5 (0.4, 0.5)	0.2 (0, 2.6)	2 (1.9, 2.2)	n/a
	Amoxicillin vs *other*	1.7 (0.9, 3.2)	0.5 (0.4, 0.7)	n/e	1.3 (1.2, 1.4)	n/a
	Doxycycline vs *other*	n/e	0.7 (0.4, 1.2)	7.6 (0.7, 84.3)	0.5 (0.5, 0.5)	n/a
	Pivmecillinam vs *other*	n/a	n/a	n/a	n/a	0.3 (0.3, 0.3)
	Nitrofurantoin vs *other*	n/a	n/a	n/a	n/a	0.8 (0.7, 0.8)
Charlson comorbidity index[b]	*0*	Reference	Reference	Reference	Reference	Reference
	1	1.3 (0.6, 2.8)	0.8 (0.7, 1)	n/e	1.3 (1.2, 1.4)	1.1 (1.0, 1.3)
	2-3	2 (0.5, 8.2)	1.4 (1.1, 1.9)	n/e	1.8 (1.6, 2)	1.5 (1.3, 1.8)
	4-5	10.3 (1.4, 74.8)	1.5 (0.6, 4.1)	n/e	2.6 (2.1, 3.1)	2.6 (2.1, 3.2)
	≥6	0.3 (0, 2.1)	0.6 (0.5, 0.8)	n/e	1.4 (1.2, 1.6)	1.1 (0.9, 1.3)

[a] Unadjusted OR for any complications within 30 days in respective patient cohorts.
[b] Truncated to 2017-2020.
[c] n/a refers to "not applicable".
[d] n/e refers to "not estimable". Abbreviations: OR, odds ratio; PcV, penicillin V.

Table 3
Outcomes complications within 30 days in the bronchitis, pharyngotonsillitis, otitis, sinusitis, and UTI cohorts, adjusted ORs.

Patient cohorts	Complications	Treatment with antibiotics		Adjusted OR[a]	Lower 95% CI	Upper 95% CI	*P*-value
		Untreated, c/n[b] (%)	Treated, c/n (%)				
Otitis	Mastoiditis	6/18,242 (0.03)	35/89,195 (0.04)	0.840	0.352	2.001	0.69
	Bacterial meningitis	4/18,242 (0.02)	8/89,195 (0.01)	3.259	0.978	10.859	0.05
	BSI	1/18,242 (0.01)	2/89,195 (0)	3.010	0.268	33.844	0.37
	Total	11/18,242 (0.06)	43/89,195 (0.05)	1.327	0.682	2.580	0.40
Pharyngotonsillitis	Peritonsillar abscess	299/62,383 (0.48)	1290/128,833 (1)	0.427	0.377	0.485	<.0001
	Retro- parapharyngeal abscess	27/62,383 (0.04)	44/128,833 (0.03)	1.053	0.651	1.703	0.83
	Rheumatic fever	0/62,383 (0)	0/128,833 (0)	.	.	.	
	Necrotizing fasciitis	2/62,383 (0)	2/128,833 (0)	1.488	0.206	10.762	0.69
	BSI	6/62,383 (0.01)	5/128,833 (0)	2.029	0.616	6.684	0.24
	Total	321/62,383 (0.51)	1318/128,833 (1.02)	0.448	0.396	0.507	<.0001
Sinusitis	Brain abscess	4/23,451 (0.02)	2/39,307 (0.01)	2.734	0.499	14.977	0.25
Bronchitis	Pneumonia	1594/80,387 (1.98)	1703/31,576 (5.39)	0.377	0.352	0.405	<.0001
	BSI	7/80,387 (0.01)	1/31,576 (0)	3.312	0.404	27.185	0.26
	Total	1597/80,387 (1.99)	1704/31,576 (5.4)	0.378	0.352	0.405	<.0001
UTI	Febrile UTI	417/33,536 (1.24)	1430/162,560 (0.88)	1.275	1.141	1.424	<.0001
	BSI	63/33,536 (0.19)	59/162,560 (0.04)	4.254	2.971	6.092	<.0001
	Total	469/33,536 (1.4)	1470/162,560 (0.9)	1.389	1.250	1.544	<.0001

[a] Adjusted OR for a complication within 30 days. No antibiotics compared to Antibiotics. Adjusted for sex, age, comorbidities. 2017-2020.
[b] c/n refers to the number of cases of complications over the total number of infectious episodes. Abbreviations: BSI, blood stream infection; OR, odds ratio; UTI, urinary tract infection.

Our findings of increased risk for infectious complications due to untreated lower UTI is in line with the findings of a large cohort study of patients aged 65 years or older with lower UTI in primary care in the United Kingdom (Gharbi *et al.*, 2019). They found an OR 8.08 (95% CI: 7.12-9.16) of BSI within 60 days after the diagnosis of lower UTI. However, they did not limit their classification codes used to identify BSI to gram-negative bacteria, which is the common cause of urosepsis, and included codes for sepsis due to *S. pneumoniae* and sepsis due to *Staphylococcus*, among others. Their use of a more liberal inclusion of BSI pathogens probably explains the higher OR for BSI in their study compared with ours. There are at least three published randomized clinical trials that have compared treatment with nonsteroidal anti-inflammatory drugs (NSAIDs) with antibiotics in women with lower UTIs (Gágyor *et al.*, 2015; Kronenberg *et al.*, 2017; Vik *et al.*, 2018). These studies all show a longer time for symptom relief in the NSAID groups. Also, the number of complications with pyelonephritis is higher among women treated with NSAIDs than those who received antibiotics across all three trials. This is likely due to a protective effect of antibiotics rather than the harm caused by NSAIDs, but it could be that paracetamol is a safer option to use as pain relief in UTIs (Vik *et al.*, 2018).

In a UK study, they compared general practices with high and low rates of antibiotic prescription for RTI. They found no association between practices with a low proportion of RTI consultations with antibiotics prescribed and complications, such as mastoiditis, empyema, meningitis, intracranial abscess, and Lemierre syndrome (Gulliford *et al.*, 2016). For pneumonia, there was a slightly increased risk at general practices with a low prescription rate (<115 per 1000) compared with a higher rate (≥147 per 1000). However, data from randomized controlled trials of lower RTI and treatment with amoxicillin or placebo in patients where pneumonia is not suspected shows little benefit from treatment. In a primary care study, where 2061 adults were randomized to amoxicillin 1 g three

	Untreated Cases / Infections	Treated Cases / Infections	OR
Gender			
Female	296 / 27036	1057 / 143258	1.48
Male	173 / 6500	413 / 19302	1.24
Age			
5 - 19 years	66 / 3351	158 / 15760	1.76
20 - 69 years	219 / 21190	889 / 106107	1.13
>=70 years	184 / 8995	423 / 40693	1.74
CCI			
0	259 / 22612	935 / 111545	1.25
1	41 / 3792	194 / 19606	0.98
2-3	101 / 3680	181 / 17025	2.38
4-5	30 / 954	58 / 2913	1.47
>=6	38 / 2498	102 / 11471	1.5
Total	**469 / 33536**	**1470 / 162560**	**1.39**

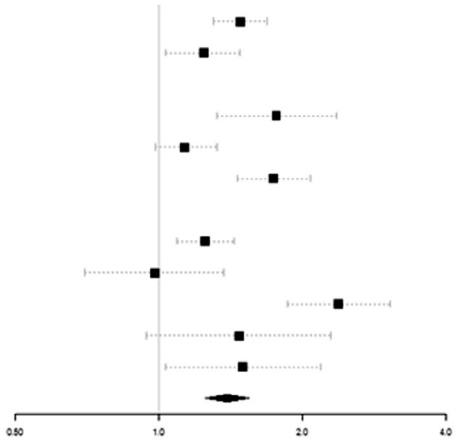

Figure 1. Forrest-plot urinary tract infection interactions with antibiotics and sex, age and Charlson comorbidity index, respectively. Abbreviations: CCI, Charlson comorbidity index; OR, odds ratio.

times daily for 7 days or placebo, no effect on the duration of symptoms rated "moderately bad" or worse, and no increased risk for hospitalization or mortality was seen (Little *et al.*, 2013a). In our study, 33.5% of those with acute bronchitis were treated with antibiotics. This is despite clinical guidelines that advise against initiating antibiotic therapy for acute bronchitis (Harris *et al.*, 2016). In our pharyngotonsillitis cohort, 69.5% were given antibiotic treatment. European clinical guidelines (European Society of Clinical Microbiology and Infectious Diseases) advise against antibiotics for those with less severe presentation (0-2 Centor criteria) (Pelucchi *et al.*, 2012). For patients with >2 centor criteria, benefits should be weighed against side effects, and prevention against suppurative complication is not a treatment indication according to the European Society of Clinical Microbiology and Infectious Diseases guideline. Built-in computer-assisted decision support in the electronic health records may be one way to help primary care doctors in their treatment decisions (Gonzales *et al.*, 2013). Improving antibiotic prescription in outpatient care must be an ongoing project. Conditions where antibiotics are not needed (acute bronchitis, viral pharyngitis) but still prescribed are obvious areas for improvement. Methods that increase the use of evidence-based guidelines for diagnosis and management of URIs in practice, together with regular feedback to clinicians of antibiotic prescribing practices are established features in current outpatient antibiotic stewardship programs (Mölstad *et al.*, 2017; Sanchez *et al.*, 2016).

The findings of a lower adjusted OR for complications in those not treated with antibiotics in the bronchitis and pharyngotonsillitis cohort were most likely an effect of confounding by indication. Patients with sore throat who have fever or pus on tonsils are more likely to be given antibiotics than those who lack these signs (Little *et al.*, 2013b). The same signs are also associated with more complicated course; thus, disease severity (which we unfortunately lacked information on) confounded our estimates.

The COVID-19 pandemic started in Sweden, with the first notified cases in late February 2020. The pandemic had great effect on the health care system. Because this was a sensitivity analysis, we calculated the adjusted ORs for complications, excluding the year 2020. The results did not change in any significant way (Table S5).

Strengths and limitations

The study population comprised all patients consecutively diagnosed in primary care in the Stockholm region during a 7-year period. But to verify generalizability, confirmation of the findings is warranted in patients from other geographical regions and health care settings. Data on diagnoses were collected from patient records, which depend on correct diagnoses and data entry by health care staff and may carry a risk of misclassification (Ludvigsson *et al.*, 2011). The quality of the data on prescriptions is high because the information is gathered automatically. The coverage of the data is over 99% (Wallerstedt *et al.*, 2016). On the other hand, all prescriptions dispensed are not used by the patient.

Conclusion

No increased risk for suppurative infectious complications was seen within 30 days after diagnosis with otitis, pharyngotonsillitis, sinusitis, or acute bronchitis among cases treated with antibiotics compared with those who were not. Based on our data, antibiotic use has limited benefits for reducing the risk of URTI complications. For lower UTI, an increased risk for febrile UTI and BSI was evident, especially for women, children, and those age 70 and older. A careful risk-benefit analysis is needed for guidelines recommending no antibiotic or deferred antibiotic treatment for cystitis.

Author contributions

ED, JH, CN, AT: Study concept and design. **JC:** Statistical analysis. **ED, JC, CN, PN, AT:** Acquisition, analysis, or intepretation of data. **ED, JC, AT:** Drafting of the manuscript. **All authors:** Critical revision of the manuscript for important intellectual content.

Funding

This study was financed by internal means only.

Ethical approval

This study was approved by the Swedish Ethical Review Authority, Dnr 2019-06503.

Declaration of Competing Interest

The authors have no competing interests to declare.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.09.036.

References

Cars T, Eriksson I, Granath A, Wettermark B, Hellman J, Norman C, et al. Antibiotic use and bacterial complications following upper respiratory tract infections: a population-based study. BMJ Open 2017;7.

European Center for Disease Prevention and Control. Antimicrobial consumption in the EU/EEA. Annual Epidemiological Report for 2019. https://www.ecdc.europa.eu/sites/default/files/documents/Antimicrobial-consumption-in-the-EU-Annual-Epidemiological-Report-2019.pdf, 2020 (accessed 7 June 2021).

European Association of Urology (EAU). Guidelines on urological infections https://uroweb.org/guidelines/urological-infections, 2022 (accessed 7 June 2022).

Gágyor I, Bleidorn J, Kochen MM, Schmiemann G, Wegscheider K, Hummers-Pradier E. Ibuprofen versus fosfomycin for uncomplicated urinary tract infection in women: randomised controlled trial. BMJ 2015;351:h6544.

Gharbi M, Drysdale JH, Lishman H, Goudie R, Molokhia M, Johnson AP, et al. Antibiotic management of urinary tract infection in elderly patients in primary care and its association with bloodstream infections and all cause mortality: population based cohort study. BMJ 2019;364:l525.

Gonzales R, Anderer T, McCulloch CE, Maselli JH, Bloom FJ, Jr Graf TR, et al. A cluster randomized trial of decision support strategies for reducing antibiotic use in acute bronchitis. JAMA Intern Med 2013;173:267–73.

Gulliford MC, Moore MV, Little P, Hay AD, Fox R, Prevost AT, et al. Safety of reduced antibiotic prescribing for self limiting respiratory tract infections in primary care: cohort study using electronic health records. BMJ 2016;354:i3410.

Harris AM, Hicks LA, Qaseem A. High Value Care Task Force of the American College of Physicians and for the Centers for Disease Control and Prevention. Appropriate antibiotic use for acute respiratory tract infection in adults: advice for high–value care from the American College of Physicians and the Centers for Disease Control and Prevention. Ann Intern Med 2016;164:425–34.

King H, Xing J, Dean HD, Holtzman D. Trends in prevalence of protective levels of hepatitis B surface antibody among adults aged 18-49 years with risk factors for hepatitis B virus infection-United States, 2003-2014. Clin Infect Dis 2020;70:1907–15.

Kronenberg A, Bütikofer L, Odutayo A, Mühlemann K, da Costa BR, Battaglia M, et al. Symptomatic treatment of uncomplicated lower urinary tract infections in the ambulatory setting: randomised, double blind trial. BMJ 2017;359:j4784.

Little P, Stuart B, Moore M, Coenen S, Butler CC, Godycki-Cwirko M, et al. Amoxicillin for acute lower-respiratory-tract infection in primary care when pneumonia is not suspected: a 12-country, randomised, placebo-controlled trial. Lancet Infect Dis 2013a;13:123–9.

Little P, Stuart B, Hobbs FD, Butler CC, Hay AD, Campbell J, et al. Predictors of suppurative complications for acute sore throat in primary care: prospective clinical cohort study. BMJ 2013b;347:f6867.

Lopez-Vazquez P, Vazquez-Lago JM, Figueiras A. Misprescription of antibiotics in primary care: a critical systematic review of its determinants. J Eval Clin Pract 2012;18:473–84.

Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450.

Mölstad S, Löfmark S, Carlin K, Erntell M, Aspevall O, Blad L, et al. Lessons learnt during 20 years of the Swedish strategic programme against antibiotic resistance. Bull World Health Organ 2017;95:764–73.

Moynihan R, Sanders S, Michaleff ZA, Scott AM, Clark J, To EJ, et al. Impact of COVID-19 pandemic on utilisation of healthcare services: a systematic review. BMJ Open 2021;11.

Pelucchi C, Grigoryan L, Galeone C, Esposito S, Huovinen P, Little P, et al. Guideline for the management of acute sore throat. Clin Microbiol Infect 2012;18:1–27.

Petersen I, Johnson AM, Islam A, Duckworth G, Livermore DM, Hayward AC. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. BMJ 2007;335:982.

Quan H, Sundararajan V, Halfon P, Fong A, Burnand B, Luthi JC, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Med Care 2005;43:1130–9.

Rezel-Potts E, L'Esperance V, Gulliford MC. Antimicrobial stewardship in the UK during the COVID-19 pandemic: a population-based cohort study and interrupted time-series analysis. Br J Gen Pract 2021;71:e331–8.

Sanchez GV, Fleming-Dutra KE, Roberts RM, Hicks LA. Core elements of outpatient antibiotic stewardship. MMWR Recomm Rep 2016;65:1–12.

Vik I, Bollestad M, Grude N, Bærheim A, Damsgaard E, Neumark T, et al. Ibuprofen versus pivmecillinam for uncomplicated urinary tract infection in women-A double-blind, randomized non-inferiority trial. PLOS Med 2018;15.

Wallerstedt SM, Wettermark B, Hoffmann M. The first decade with the Swedish prescribed drug register-a systematic review of the output in the scientific literature. Basic Clin Pharmacol Toxicol 2016;119:464–9.

WHO Collaborating Center for Drug Statistics Methodology. Guidelines for ATC classification and DDD assignment 2021, https://www.whocc.no/filearchive/publications/2021_guidelines_web.pdf, 2021 (accessed 1 Sept 2021)