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Antibiotic use and bacterial complications following upper respiratory tract infections: a population based study

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Patients were not directly involved in this study. General practitioners, specialists in infection diseases as well as representatives from health authorities were involved in the study design and the development of the outcome measure. There was no direct consumer involvement in this study. All data used in this study were anonymized, thus we do not know who the patients included in our analyses are. Therefore, the study results cannot be directly disseminated to the patients. We will however communicate the findings to the general practitioners and specialists in infection diseases involved in care of patients with upper respiratory tract infections.

Abstract

Objectives

To set up a process for continuous monitoring of the incidence of upper respiratory tract infections (URTIs), antibiotic use and the incidence of bacterial complications following URTIs, using routinely collected healthcare data, in order to monitor if more restricted utilization of antibiotics is associated with an increase in bacterial complications.

Design

Ecological and a prospective cohort study.

Setting

Primary, outpatient specialist and inpatient care in Stockholm County, Sweden. All analyses were based on administrative healthcare data on consultations, diagnoses and dispensed antibiotics from January, 2006, to January, 2016.

Main outcome measures

Ecological study: 10 year trend analyses of the incidence of URTIs, bacterial infections/complications and respiratory antibiotic use.
Prospective cohort study: Incidence of bacterial complications following URTIs in antibiotic-exposed and non-exposed patients.

Results

The utilization of respiratory tract antibiotics decreased by 22% from 2006 to 2015 but no increased trend for mastoiditis (p=0.0933), peritonsillitis (p=0.0544), invasive group A streptococcal disease (p=0.3991), orbital abscess (p=0.9637), extra- and subdural abscess (p=0.4790) and pansinusitis (p=0.3971) were observed. For meningitis and acute ethmoidal sinusitis, a decrease in the numbers of infections from 2006 to 2015 was observed (p=0.0038 and p=0.0003, respectively) and for retropharyngeal and parapharyngeal abscess an increase was observed (p=0.0214). Bacterial complications following URTIs were uncommon both in antibiotic-exposed (less than 1.5 per 10 000 episodes) and non-exposed patients (less than 1.3 per 10 000 episodes) with the exception of peritonsillitis after tonsillitis (risk per 10 000 tonsillitis episodes: 32.4 and 41.1 in patients with no antibiotic treatment and patients treated with antibiotics, respectively).

Conclusions

Bacterial complications following URTIs are rare and antibiotics may lack protective effect in preventing bacterial complications. By using data of updated population based health care data one can provide continuous feedback on the number of URTIs, antibiotic use, and hospital complications to patients, prescribers and policymakers.

Strengths and limitations of this study

Data used in this study are population based and include information from primary, outpatient specialist and inpatient care as well as data on all drugs dispensed in ambulatory care

Data are continuously updated and loss to follow-up is minimal (only when an individual moves out of the region)

Antibiotic exposure assessment is based on the information from the drug dispensation database; no information on antibiotics administered in hospitals was available for these analyses

Outcome definitions are based on recorded diagnoses thus this study relies on the accuracy and completeness of diagnoses data

It is unknown whether the individual completed the prescribed course of antibiotic treatment

Introduction

The use of antibiotics contributes to the emergence and spread of drug-resistant bacteria(1-3). Curbing antibiotic resistance requires coordinated action at the global, national and regional levels(4). In Sweden, a comparatively low level of antibiotic utilization(5, 6) has been achieved through years of strategic work at the national and regional level that has included surveillance of antibiotic utilization and resistance trends, development and implementation of treatment guidelines as well as educational activities targeted at healthcare professionals, patients and the general public(7).

Most antibiotics prescribed in the Swedish primary care are used for treatment of respiratory tract infections(8). Over the past 20 years such use in Sweden has gradually declined(9). Most of this decline has been attributed to limiting the inappropriate antibiotic use in viral respiratory tract infections or mild self-healing bacterial infections(10) by the implementation of stricter guidelines, for example for pharyngotonsillitis and sinusitis(11-13). However, we know still that a substantial number of antibiotic prescriptions are issued by doctors “just in case” in fear of complications(14, 15). There is therefore a need for large studies on rare complications of upper respiratory tract infections (URTIs) in order to quantify these risks and hopefully to reduce some of the uncertainty for primary care physicians and their patients.

The objective of this study was to develop a process for continuous monitoring of the incidence URTIs, antibiotic use and the incidence of bacterial complications using routinely collected administrative healthcare data in order to monitor if more restricted utilization of antibiotics is associated with an increase in bacterial complications. First, we present results from an ecological analysis assessing whether the reduction in antibiotic use in URTIs were associated with a change in the incidence of bacterial complications in a large geographically defined population. Second, we present findings from a prospective cohort study based on individual patient level data describing the incidence of bacterial complications in antibiotic-exposed and non-exposed patients with URTIs.

Methods

Setting

We conducted both an ecological and a prospective cohort study in Stockholm County, Sweden, using administrative healthcare data from 1 January, 2006, to 31 January, 2016. The study was approved by the regional ethics committee at Karolinska Institutet, Sweden (Ref. no. 2015/158-31).

Data sources

We used data from the regional healthcare data warehouse of Stockholm County (VAL)(16) and the Swedish Prescribed Drug Register(17). VAL contains comprehensive administrative healthcare data for all Stockholm County residents (around 2.2 million people, approximately 23% of the population of Sweden). From VAL we obtained the following information: demographic data (patient age and sex), diagnoses in primary care, outpatient specialist- and inpatient care (diagnoses are coded using the International Classification of Diseases [ICD-10] codes), consultation dates (for both in-person and phone consultations), hospital admission and discharge dates, as well as migration and death records. From the Swedish Prescribed Drug Register we obtained data on dispensed antibiotics (drugs are coded using the Anatomical Therapeutic Chemical [ATC] codes).

Ecological study

For the ecological analyses we used aggregate level antibiotic utilization data (exposure) and data on the incidence of bacterial complications (outcome) between 1 January, 2006, and 31 December, 2015. We also assessed data on the incidence of URTIs during this period. We matched the exposure and outcomes data based on the year in which they were recorded. The list of antibiotics classified as those used to treat URTIs is provided in Supplement 1. The utilization of antibiotics was expressed as the defined daily dose (DDD) per 1000 inhabitants per day(18).

We studied the following bacterial complications: mastoiditis, meningitis, retropharyngeal and parapharyngeal abscess, invasive group A streptococcal disease, acute pansinusitis, acute ethmoidal sinusitis, orbital abscess, extradural abscess- and subdural abscess documented in inpatient care. For peritonsillar abscess, diagnoses recorded both in outpatient and in inpatient setting were included. The lists of ICD-10 codes used to define bacterial complications and primary URTIs are provided in Supplement 2 and Supplement 3, respectively.

Prospective cohort study

Inclusion and exclusion criteria

In the prospective cohort study we included all patients with a diagnosis of acute otitis media, tonsillitis, sinusitis or acute upper respiratory tract infections of multiple and unspecified sites diagnosed in the outpatient setting (primary care or outpatient specialist care) from 1 January, 2006, to 31 December, 2015 (see Supplement 3 for ICD-10 codes used to define the cohorts). The selected population was stratified into four sub-cohorts to study the incidence of bacterial complications in the antibiotic-exposed and non-exposed individuals: 1) acute otitis media cohort to study the incidence of mastoiditis and meningitis; 2) tonsillitis cohort to study the incidence of peritonsillar abscess, retropharyngeal and parapharyngeal abscess and invasive group A streptococcal disease; 3) acute sinusitis cohort to study the incidence of acute pansinusitis, orbital abscess and extra- and subdural abscess; 4) cohort of patients with sinusitis and acute upper respiratory tract infections of multiple and unspecified sites in combination to study the incidence of orbital cellulitis (without formation of abscess). This last combination cohort allowed

identifying complications to acute rhinosinusitis, mainly of ethmoidal origin not included in the acute sinusitis cohort (the majority of this combination cohort are children). In the widespread Swedish clinical practice children displaying symptoms and signs of an orbital complication in relation to an URTI (often of viral origin) are designated as cases of acute ethmoidal sinusitis (or other types of acute sinusitis) based on the clinical findings(19). In this paper and internationally, these complications are referred to as orbital cellulitis. The cohort selection flow chart can be found in Supplement 4.

Episode definition

Since more than one diagnosis of an URTI can be recorded for the same patient, an episode was created to combine data on diagnoses and treatment attributed to the same URTI and the start and the end dates were defined for each episode (

Figure **1**).

The episode start date (index date) was defined as the date of the first recorded diagnosis within the episode. If there was more than a month (30 day period used in all calculations) between diagnoses, the later diagnosis was attributed to a new URTI episode. The 30 day period was based on the Swedish guidelines on URTIs (sinusitis, acute otitis media, tonsillitis) stating that new symptoms within 30 days are a relapse and not a new episode. If a dispensation of antibiotic occurred within 3 days after the latest recorded diagnosis attributed to an episode (reflecting the strategy of watchful waiting), the date of antibiotic dispensation constituted the episode end date. If a bacterial complication occurred, the date of complication diagnosis constituted the episode end date.

If a bacterial complication occurred on the same date as the episode start date this episode was excluded from our analyses. Furthermore, episodes with less than one month of follow-up were also excluded.

For all bacterial complications, if more than 6 months passed between recorded diagnoses it was defined as an incident bacterial complication. The 6 month period was chosen in order to not miss any late bacterial complications. If more than 6 months passed since the primary URTI it is highly unlikely that any new signs and symptoms would be due to the primary URTI.

Exposure groups

Patients were considered exposed to respiratory tract antibiotics if a prescription was dispensed within the episode. An episode was not considered exposed to antibiotic if the first antibiotic prescription was dispensed on the same day as the suspected bacterial complication.

Outcomes

The follow-up of patients for study outcomes started at the episode start date (index date) and continued for a one month period after the episode end date.

The study outcomes included: 1) mastoiditis and meningitis diagnosed in inpatient setting (acute otitis media cohort); 2) peritonsillar abscess diagnosed in either outpatient or inpatient setting, retropharyngeal and parapharyngeal abscess and invasive group A streptococcal disease diagnosed in inpatient setting (tonsillitis cohort); 3) pansinusitis, orbital abscess and extra- and subdural abscess diagnosed in inpatient setting (sinusitis cohort); 4) orbital cellulitis diagnosed in inpatient setting (sinusitis and acute upper respiratory tract infections of multiple and unspecified sites in combination cohort). ICD-10 codes used to define bacterial complications are provided in Supplement 2.

Statistical analyses

For the ecological study, aggregate level of respiratory antibiotic utilization data (DDD per 1000 inhabitants per day, DID), number of bacterial complications per year as well as number of primary URTI episodes per year were plotted over time.

Trends for bacterial complications and respiratory antibiotic utilization (using DDD as the measure of utilization) were investigated using negative binomial regression models with annual Stockholm County population counts (as of December 31 each year) as the offset variable.

For the prospective cohort study, we calculated the number of patients experiencing episodes of URTIs and stratified these patients by age and antibiotic treatment (no antibiotic treatment group and treated with antibiotics group). We then calculated the number of bacterial complications occurring in these patients and risk of bacterial complications per 10 000 patients.

Data management and analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC).

Results

The volumes of dispensed respiratory tract antibiotics in Stockholm County declined by 22% from 2006 to 2015 (Figure 2**). The number of acute otitis media and sinusitis episodes declined and the number of tonsillitis episodes was increasing from 2006 to 2012 and then sharply declined and remained stable from 2013 to 2015. (Tables**

Table 1). The proportion of patients treated with antibiotics declined in the cohorts of acute otitis media (from 88% in 2006 to 81% in 2015), sinusitis (from 86% in 2006 to 71% in 2015) and sinusitis/acute URTI unspecified (from 36% in 2006 to 18% in 2015), and remained stable for tonsillitis (73% in 2006 and 73% in 2015).

In the ecological analyses we observed a significant decrease in the volumes of dispensed antibiotics from 2006 to 2015 ($p<0.0001$). During the same time period there was no significant trend in the number of the following bacterial complications: mastoiditis ($p=0.0933$), peritonsillitis ($p=0.0544$), invasive group A streptococcal disease ($p=0.3991$), orbital abscess ($p=0.9637$), extra- and subdural abscess ($p=0.4790$) and pansinusitis ($p=0.3971$). For meningitis and acute ethmoidal sinusitis, a decrease in the numbers of infections from 2006 to 2015 was observed ($p=0.0038$ and $p=0.0003$, respectively) and for retropharyngeal and parapharyngeal abscess an increase was observed ($p=0.0214$). Data are presented in

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Using individual patient level data we identified 515 156 acute otitis media, 866 378 tonsillitis, 269 215 sinusitis, and 2 015 595 sinusitis/acute upper respiratory tract infections of multiple and unspecified sites episodes (see Supplement 4 for cohort selection flow charts).

Table 2 provides information on the number of bacterial complications, stratified by age and antibiotic treatment. Our data showed that all bacterial complications in URTI patients were infrequent (less than 1.5 per 10 000 episodes) with the exception of peritonsillitis after tonsillitis (risk per 10 000 tonsillitis episodes: 32.4 and 41.1 in patients with no antibiotic treatment and patients treated with antibiotics, respectively). Peritonsillitis was most common in adults aged 15 to 64 years old (risk per 10 000 tonsillitis patients aged 15 to 64: 42.2 and 67.4 in patients with no antibiotic treatment and patients treated with antibiotics, respectively).

Discussion

The volumes of dispensed URTI antibiotics in Stockholm County decreased by 22% over a ten-year period from 2006 to 2015. Our ecological analyses covering the entire population in a large region showed that restricted use of antibiotics was not associated with an increase in bacterial complications of mastoiditis, meningitis, peritonsillar abscess, invasive group A streptococcal disease, acute pansinusitis, acute ethmoidal sinusitis, orbital abscess and extradural abscess and subdural abscess. Moreover, the number of meningitis and acute ethmoidal sinusitis complications decreased over the study period. For retropharyngeal and parapharyngeal abscess an increase was observed.

The analyses of individual level data revealed that the incidence of bacterial complications following primary URTIs was very low: the risk per 10 000 URTI episodes was less than 1.5 (average for all age groups) for all analyzed bacterial complications (with the exception of peritonsillitis) for both patients with no antibiotic treatment and patients treated with antibiotics. We observed a slightly higher risk of bacterial complications in the antibiotic treated group in 3 out of 9 bacterial complications studied. This can possibly be explained by the presence of selection bias: patients prescribed antibiotics likely had a more severe primary URTI thus were at a higher risk of both being prescribed an antibiotic and progressing to bacterial complications.

Our findings of no association between more restricted antibiotic use and the incidence of bacterial complications are in line with previous studies(10, 20-22). A previous Swedish study(23) showed that there were no increase in acute mastoiditis since 2000, when new guidelines recommending restrictive use of antibiotics for AOM were introduced. In 2010 new revised guidelines with an even more restrictive recommendation were issued (24). Our study includes data on mastoiditis in Stockholm County before and after these most restrictive recommendations, thus providing a first update on the impact of further restriction of antibiotic use in treatment of AOM.

Differences in definitions used can explain discrepancies with other observational studies (20, 25). Our definition of bacterial complication only included bacterial complications recorded in inpatient care and therefore was more strict than those used in other studies (for example in comparison to analyses by Petersen et al.). Furthermore, our definition of the antibiotic-exposed group included patients receiving an antibiotic anytime during their URTI episode (to account for the watchful waiting approach) thus likely resulting in a more complete capture of patients treated with antibiotics.

We also found that a large proportion of diagnosed bacterial complications analyzed in this study were not preceded by patients seeking care for URTIs. A short duration from the onset of primary URTI to progression to bacterial complication could be an explanation for this as patient would have already developed a bacterial complication by the time of the first contact with healthcare professionals. In children, for example, the onset of symptoms and signs of mastoiditis is often very quick (within 24 hours). In this case a rapid progress of the disease is likely related to the virulence of pathogenic airway bacteria. It has also been noted that peritonsillitis, the most common bacterial complication among adults in our study, often occurs without a preceding typical tonsillitis(26). Alternate routes of infection, for example oral pathogenic bacteria, may play a role in etiology of peritonsillitis.

The decline in meningitis and acute ethmoidal sinusitis observed in our analyses is in line with previous studies demonstrating a similar decrease in these infections after the introduction of conjugated anti-pneumococcal vaccine in the general vaccine schedule in Stockholm in 2007(27).

All data used in our study are population-based and include complete information on diagnoses in primary, outpatient specialist and inpatient care as long as they were recorded by healthcare professionals, as well as on all dispensations of antibiotics in ambulatory care. These data are updated on a monthly basis thus enabling a real-time patient follow up. Using administrative data however carries a number of known limitations, including reliance on the accuracy and completeness of recorded diagnoses, lack of information on antibiotics administered in the inpatient setting and inability to assert whether the patient completed the prescribed course of antibiotic treatment.

Our study demonstrated that routinely collected administrative healthcare data can be used in continuous monitoring of antibiotics use and related patient outcomes. We found that more restrictive use of antibiotics for common infections of the upper respiratory tract has not led to an increased number of severe bacterial complications. Our ongoing follow up model enables the provision of continuous feedback to patients, prescribers and policy makers and can be adapted for other Swedish counties with similar data sources or internationally.

Contributorship statement

TC, IE, AG, BW, JH, CN, AT contributed to the design of the study. TC extracted the data, wrote statistical programs and led statistical analyses. TC, IE, AG, BW, JH, CN, AT participated in the interpretation of data. TC had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. TC and IE drafted the paper. TC, IE, AG, BW, JH, CN, AT critically revised the paper for important intellectual content and approved the final version to be published.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the

submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

Additional data are available by emailing the corresponding author.

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Tables

Table 1. Number of episodes and antibiotic treatment for acute otitis media (cohort 1), tonsillitis (cohort 2), sinusitis (cohort 3) and sinusitis/acute upper respiratory tract infections of multiple and unspecified sites in combination (cohort 4) in Stockholm County from 2006 to 2015

	Acute otitis media		Tonsillitis		Sinusitis		Sinusitis/acute URTI unspecified	
	No antibiotic treatment	Treated with antibiotics	No antibiotic treatment	Treated with antibiotics	No antibiotic treatment	Treated with antibiotics	No antibiotic treatment	Treated with antibiotics
	n, %	n, %	n, %	n, %	n, %	n, %	n, %	n, %
2006	6 414(12)	47 657(88)	20 496(27)	54 998(73)	3 744(14)	23 586(86)	108 735(64)	61 658(36)
2007	6 971(12)	53 050(88)	23 262(26)	66 098(74)	4 364(14)	26 703(86)	123 484(64)	68 564(36)
2008	8 374(13)	55 350(87)	25 857(27)	71 041(73)	5 065(17)	25 057(83)	138 906(69)	62 195(31)
2009	8 260(15)	47 543(85)	27 007(29)	67 040(71)	5 942(22)	21 440(78)	149 417(74)	51 323(26)
2010	10 266(18)	47 248(82)	27 024(28)	68 774(72)	7 361(26)	20 737(74)	160 610(76)	52 044(24)
2011	8 773(18)	41 111(82)	23 635(25)	70 060(75)	7 531(28)	19 497(72)	167 915(77)	50 351(23)
2012	9 464(19)	39 697(81)	24 299(24)	78 428(76)	8 377(30)	19 988(70)	172 164(78)	49 398(22)
2013	7 933(19)	33 613(81)	20 069(27)	54 321(73)	7 150(29)	17 245(71)	160 925(80)	39 023(20)
2014	8 271(19)	35 656(81)	20 794(28)	53 111(72)	6 453(28)	16 376(72)	161 070(81)	38 395(19)
2015	7 858(19)	34 437(81)	19 956(27)	53 786(73)	6 949(29)	16 771(71)	172 759(82)	38 556(18)
2006-2015	**82 584(16)**	**435 362(84)**	**232 399(27)**	**637 657(73)**	**62 936(23)**	**207 400(77)**	**1 515 985(75)**	**511 507(25)**

Table 2. Risk of bacterial complications in the month after diagnosis of upper respiratory tract infections

	No antibiotic treatment			Treated with antibiotics		
	No of patients	No of complications	Risk per 10000	No of patients	No of complications	Risk per 10000
Mastoiditis after acute otitis media						
0-4	45 473	6	1.32	243 141	23	0.95
5-14	21 294	3	1.41	88 741	13	1.46
15-64	12 676	1	0.79	93 582	9	0.96
65+	2 412	0	-	7 809	1	1.28
Total[1]	**81 864**	**10**	**1.22**	**433 273**	**46**	**1.06**
Meningitis after acute otitis media						
0-4	45 476	2	0.44	243 151	1	0.04
5-14	21 292	1	0.47	88 746	0	-
15-64	12 676	1	0.79	93 581	13	1.39
65+	2 412	0	-	7 808	4	5.13
Total[1]	**81 865**	**4**	**0.49**	**433 286**	**18**	**0.42**
Peritonsillits after pharyngotonsillitis						
0-4	20 772	4	1.93	116 785	15	1.28
5-14	44 609	57	12.8	156 170	183	11.7
15-64	157 178	663	42.2	347 424	2 340	67.4
65+	9 167	27	29.5	12 552	61	48.6
Total[2]	**231 749**	**751**	**32.4**	**632 933**	**2 599**	**41.1**
Retropharyngeal and parapharyngeal abscess after pharyngotonsillitis						
0-4	20 772	0	-	116 811	2	0.17
5-14	44 585	0	-	156 332	3	0.19
15-64	156 805	24	1.53	349 240	76	2.18
65+	9 154	4	4.37	12 627	9	7.13
Total[2]	**231 339**	**28**	**1.21**	**635 012**	**90**	**1.42**
Invasive group A streptococcal disease after pharyngotonsillitis						
0-4	20 772	0	-	116 811	0	-
5-14	44 585	0	-	156 333	2	0.13
15-64	156 806	4	0.26	349 255	8	0.23
65+	9 155	3	3.28	12 632	1	0.79
Total[2]	**231 341**	**7**	**0.30**	**635 033**	**11**	**0.17**
Orbital abscess after sinusitis						
0-4	199	0	-	679	0	-
5-14	1 791	1	5.58	4 333	0	-
15-64	54 811	0	-	181 930	1	0.05
65+	5 637	0	-	19 832	0	-
Total[3]	**62 441**	**1**	**0.16**	**206 774**	**1**	**0.05**

	No antibiotic treatment			Treated with antibiotics		
	No of patients	**No of complications**	**Risk per 10000**	**No of patients**	**No of complications**	**Risk per 10000**
Extra- and subdural abscess after sinusitis						
0-4	199	0	-	679	0	-
5-14	1 791	0	-	4 333	1	2.31
15-64	54 811	1	0.18	181 930	1	0.05
65+	5 637	0	-	19 832	0	-
Total[3]	**62 441**	**1**	**0.16**	**206 774**	**2**	**0.10**
Acute pansinusitis after sinusitis						
0-4	198	0	-	679	0	-
5-14	1 790	0	-	4 330	1	2.31
15-64	54 812	7	1.28	181 923	15	0.82
65+	5 637	0	-	19 832	2	1.01
Total[3]	**62 440**	**7**	**1.12**	**206 764**	**18**	**0.87**
Acute ethmoidal sinusitis after sinusitis / acute upper respiratory tract infections of multiple and unspecified sites						
0-4	419 540	39	0.93	70 887	15	2.12
5-14	208 157	21	1.01	34 173	13	3.80
15-64	778 900	4	0.05	347 041	6	0.17
65+	100 201	1	0.10	56 669	0	-
Total[4]	**1 506 825**	**65**	**0.43**	**508 770**	**34**	**0.67**

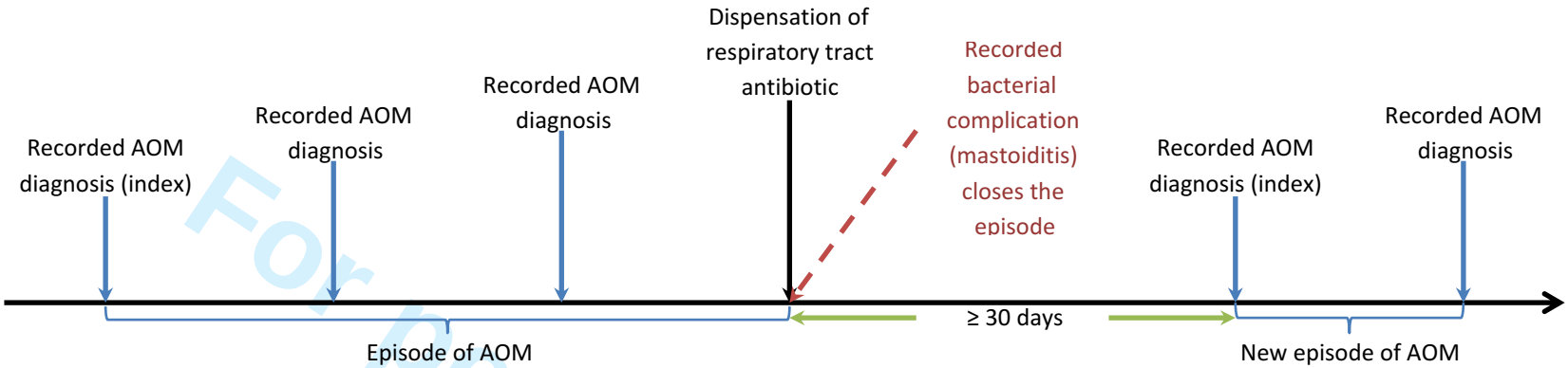
1. Missing information on age for 9 episodes of acute otitis media
2. Missing information on age for 25 episodes of tonsillitis
3. Missing information on age for 3 episodes of sinusitis
4. Missing information on age for 27 episodes of sinusitis

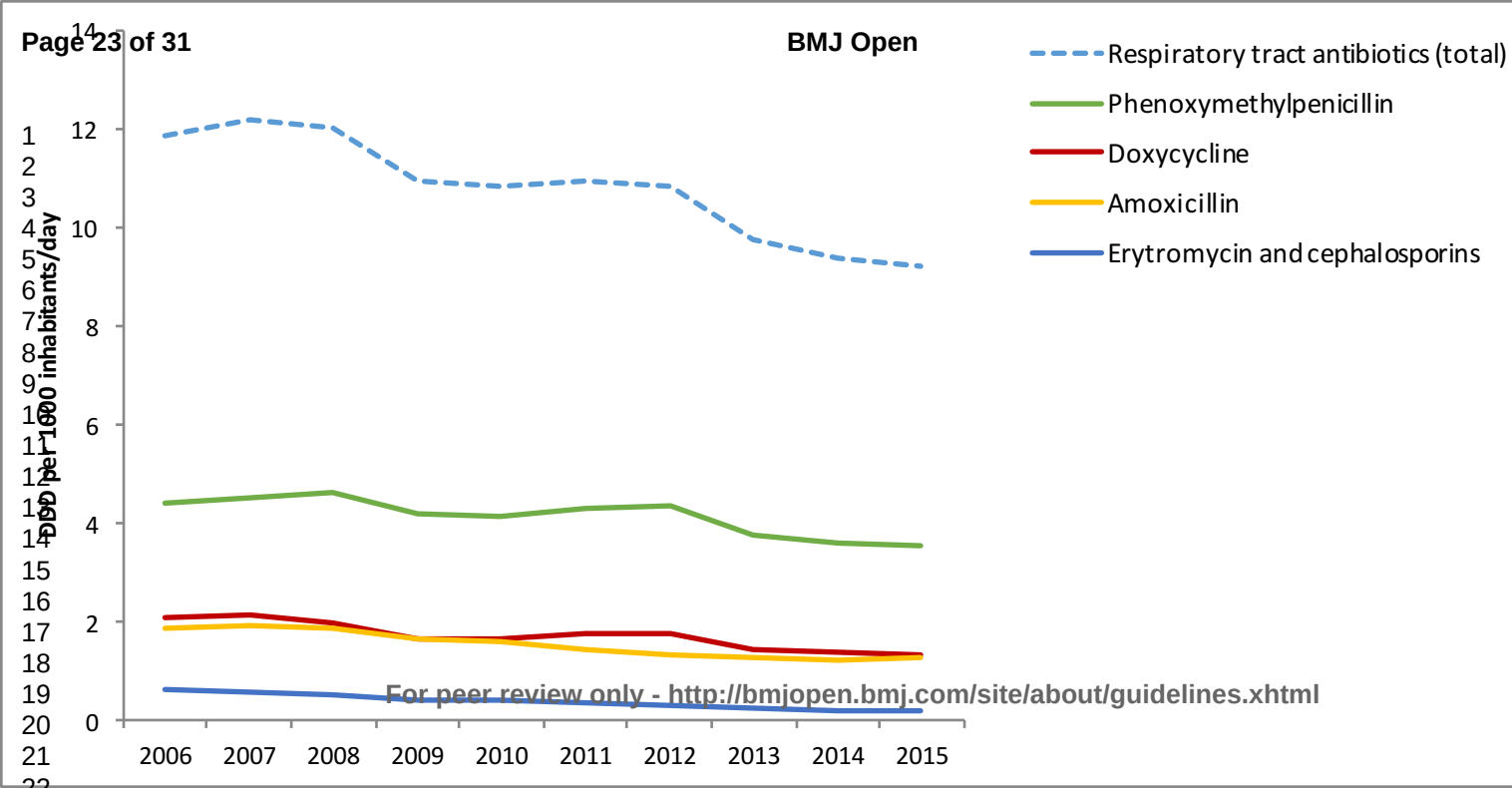
Figure legends

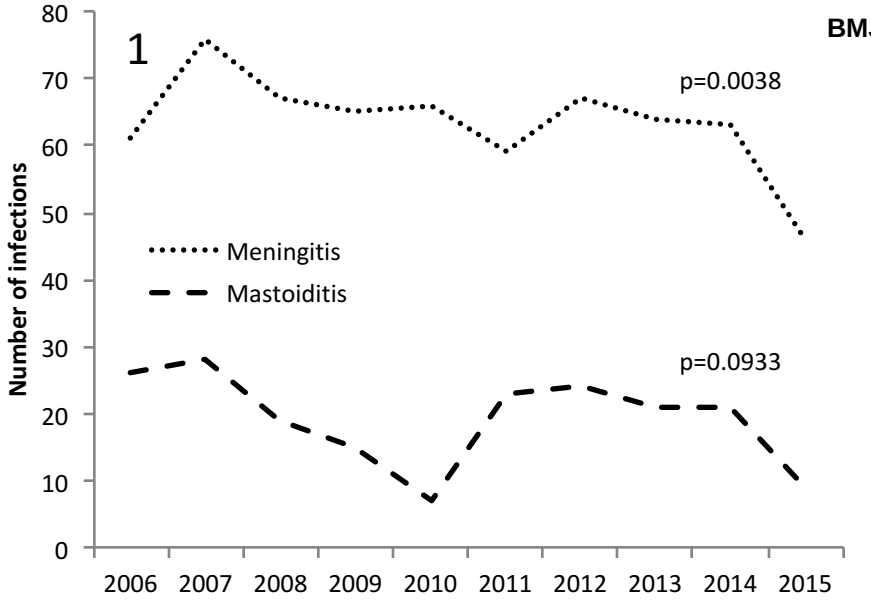
Figure 1. Definition of an episode of upper respiratory tract infection (here exemplified with acute otitis media (AOM) and mastoiditis)

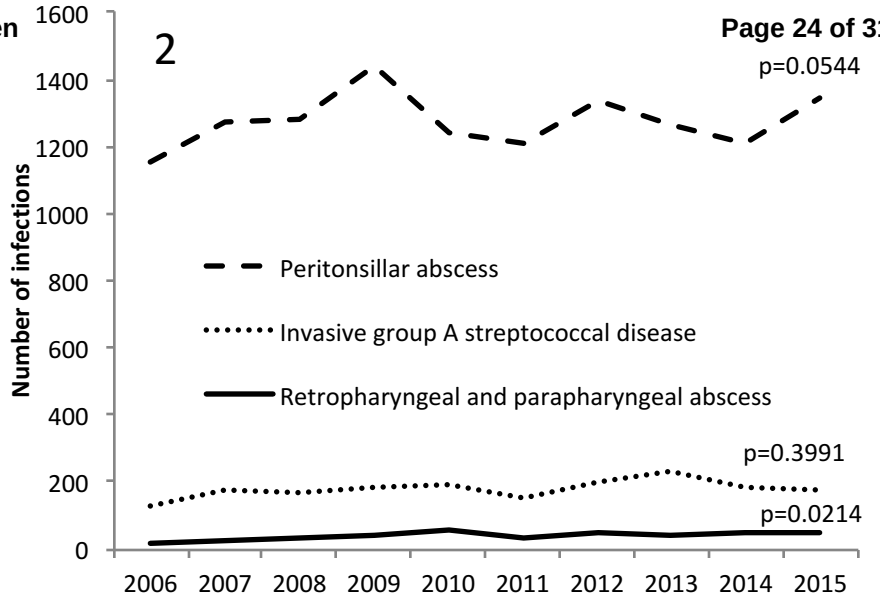
Figure 2. Trend for respiratory tract antibiotic utilization in Stockholm County from 2006 to 2015

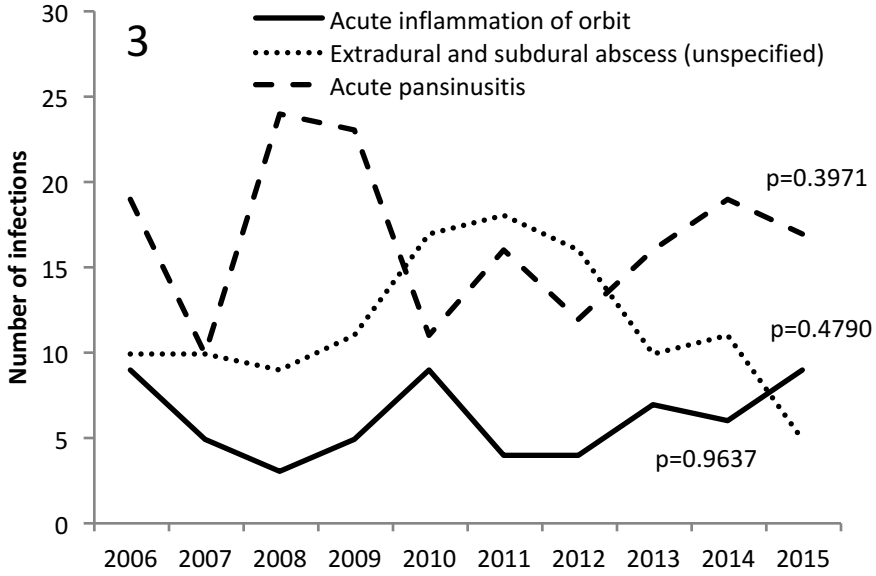
Figure 3. Trend for bacterial complications in Stockholm County from 2006 to 2015.











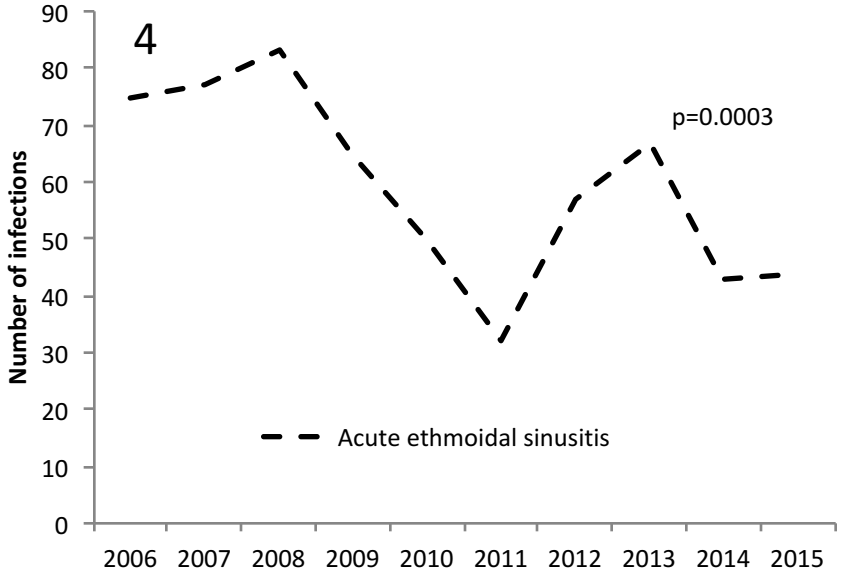


Figure 3 presents trends for bacterial complications in Stockholm County from 2006 to 2015. The four panels (1-4) corresponds to the complications we also assess in the four cohorts of the prospective cohort study ((1) acute otitis media cohort, (2) tonsillitis cohort, (3) sinusitis cohort and (4) sinusitis and acute upper respiratory tract infections of multiple and unspecified sites cohort. P-values present test for trend.

Supplements

Supplement 1. Antibiotics used to treat upper respiratory tract infections

ATC code	Name of substance	ATC code	Name of substance
J01AA01	demeclocycline	**J01DD01**	cefotaxime
J01AA02	doxycycline	**J01DD04**	ceftriaxone
J01AA04	lymecycline	**J01DD08**	cefixime
J01AA06	oxytetracycline	**J01DD13**	cefpodoxime
J01AA07	tetracycline	**J01DD54**	ceftriaxone, combinations
J01AA08	minocycline	**J01DE01**	cefepime
J01AA12	tigecycline	**J01DE02**	cefpirome
J01BA01	chloramphenicol	**J01DH02**	meropenem
J01CA01	ampicillin	**J01DH03**	ertapenem
J01CA02	pivampicillin	**J01DH04**	doripenem
J01CA04	amoxicillin	**J01DH51**	imipenem and enzyme inhibitor
J01CA06	bacampicillin	**J01DI02**	ceftaroline fosamil
J01CA12	piperacillin	**J01EE01**	sulfamethoxazole and trimethoprim
J01CE01	benzylpenicillin	**J01FA01**	erythromycin
J01CE02	phenoxymethylpenicillin	**J01FA06**	roxithromycin
J01CE08	benzathine benzylpenicillin	**J01FA09**	clarithromycin
J01CR02	amoxicillin and enzyme inhibitor	**J01FA10**	azithromycin
J01CR05	piperacillin and enzyme inhibitor	**J01FA15**	telithromycin
J01CR50	combinations of penicillins	**J01FF01**	clindamycin
J01DA10	cefotaxime	**J01FF02**	lincomycin
J01DB01	cefalexin	**J01FG01**	pristinamycin
J01DB03	cefalotin	**J01FG02**	quinupristin/dalfopristin
J01DB04	cefazolin	**J01MA02**	ciprofloxacin
J01DB05	cefadroxil	**J01MA12**	levofloxacin
J01DC01	cefoxitin	**J01MA14**	moxifloxacin
J01DC02	cefuroxime	**J01RA01**	penicillins, combinations with other antibacterials
J01DC04	cefaclor	**J01XA01**	vancomycin
J01DC06	cefonicid	**J01XA02**	teicoplanin
J01DC08	loracarbef	**J01XX08**	linezolid
		J01XX09	daptomycin

Supplement 2. ICD-10 codes used to identify bacterial complications

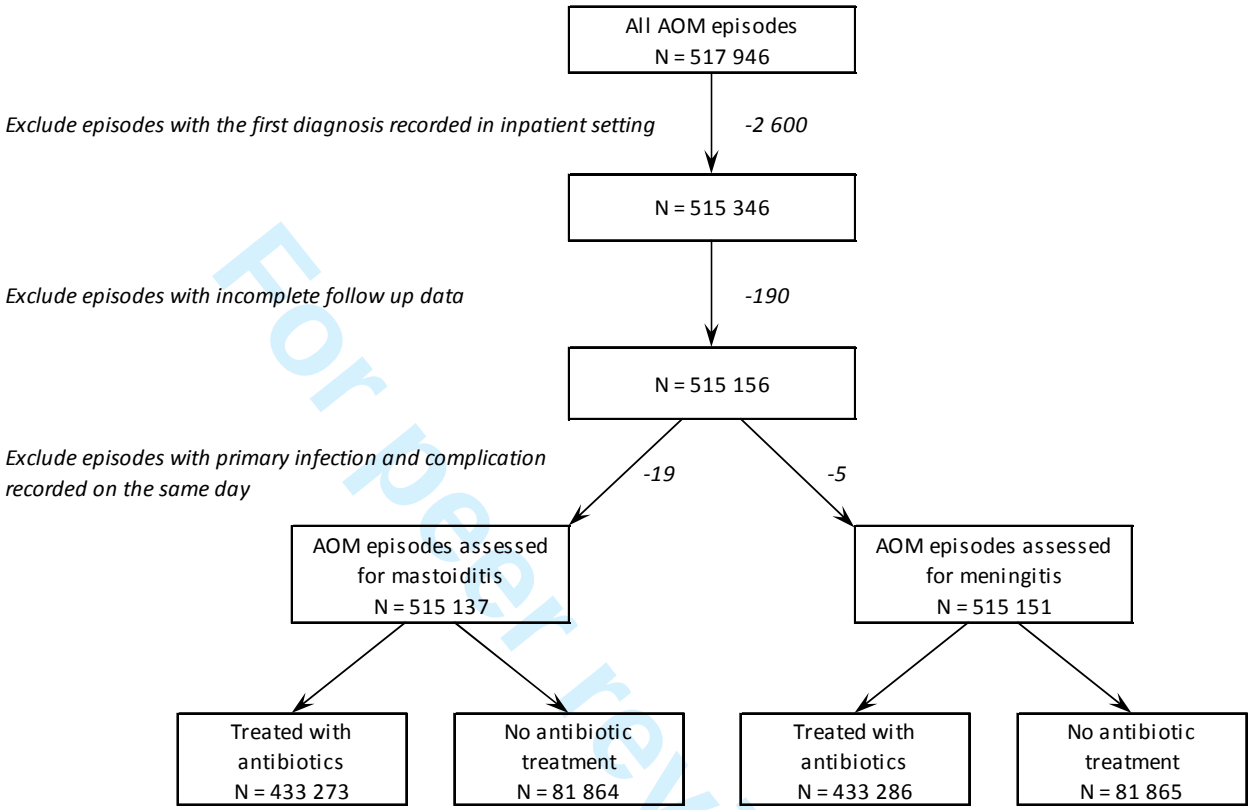
Bacterial complication	ICD-10 code	ICD-10 text
Mastoiditis	H70.0	Acute mastoiditis
	H70.2	Petrositis
	H70.9	Mastoiditis, unspecified
Meningitis	G00.0	Haemophilus meningitis
	G00.1	Pneumococcal meningitis
	G00.2	Streptococcal meningitis
	G00.3	Staphylococcal meningitis
	G00.9	Bacterial meningitis, unspecified
Peritonsillar abscess	J36	Peritonsillar abscess
Retropharyngeal and parapharyngeal abscess	J39.0	Retropharyngeal and parapharyngeal abscess
Invasive group A streptococcal disease	A40.0	Sepsis due to streptococcus, group A
	A40.9	Streptococcal sepsis, unspecified
	M72.6	Necrotizing fasciitis
Pansinusitis	J01.4	Acute pansinusitis
Orbital abscess	H05.0	Acute inflammation of orbit
Extra- and subdural abscess	G06.2	Extradural and subdural abscess, unspecified
Acute ethmoidal sinusitis	J01.2	Acute ethmoidal sinusitis

Supplement 3. ICD-10 codes used to identify primary URTIs

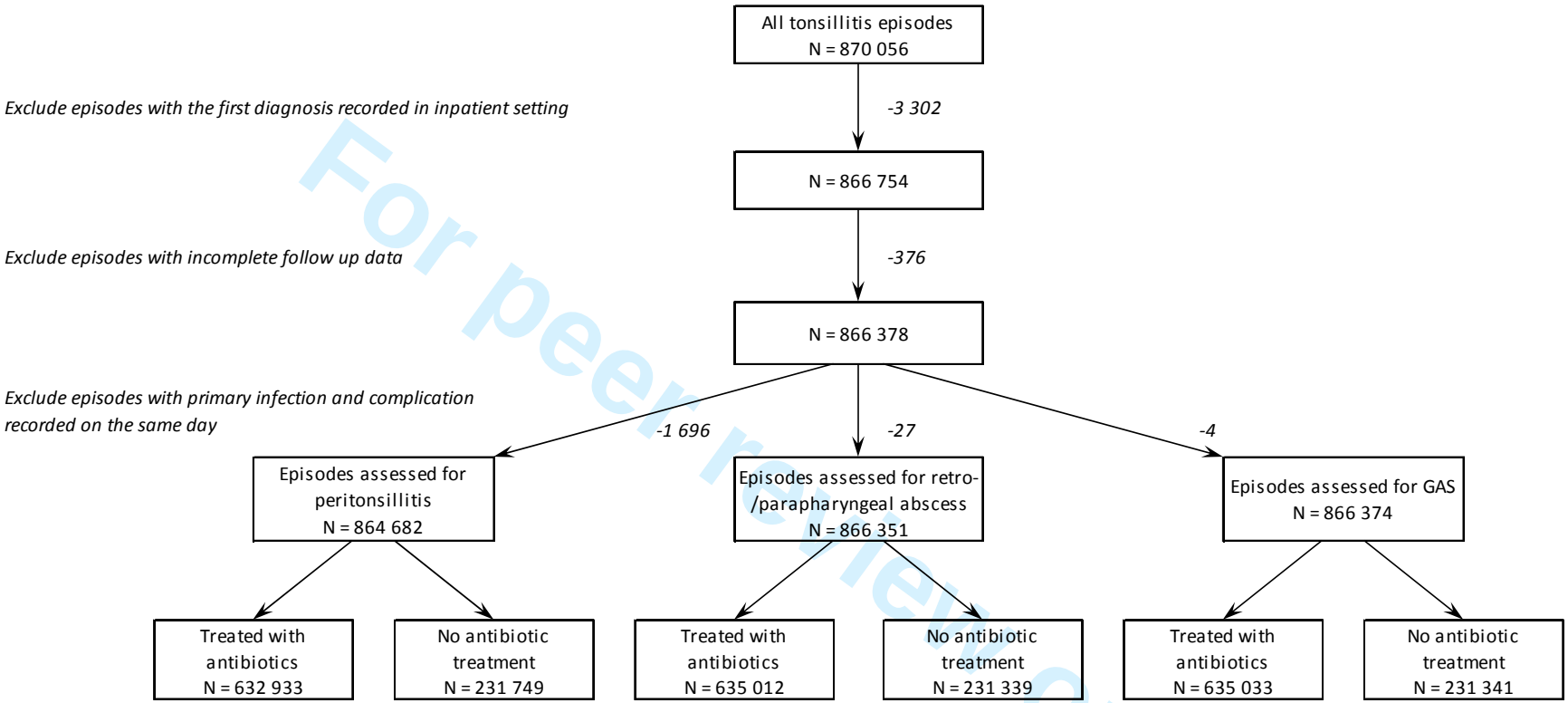
Primary URTIs	ICD-10 code	ICD-10 text
Acute otitis media	H66.0	Acute suppurative otitis media
	H66.9	Otitis media, unspecified
Tonsillitis	J02	Acute pharyngitis
	J03	Acute tonsillitis
Sinusitis	J01.0	Acute maxillary sinusitis
	J01.9	Acute sinusitis, unspecified
	J01	Acute sinusitis (for primary care records only)
Sinusitis and acute upper respiratory tract infections of multiple and unspecified sites	J01.0	Acute maxillary sinusitis
	J01.9	Acute sinusitis, unspecified
	J01	Acute sinusitis (for primary care records only)
	J06.0	Acute laryngopharyngitis
	J06.9	Acute upper respiratory infection, unspecified
	J06	Acute upper respiratory infections of multiple and unspecified sites (for primary care records only)

Supplement 4. Cohort selection flow-chart

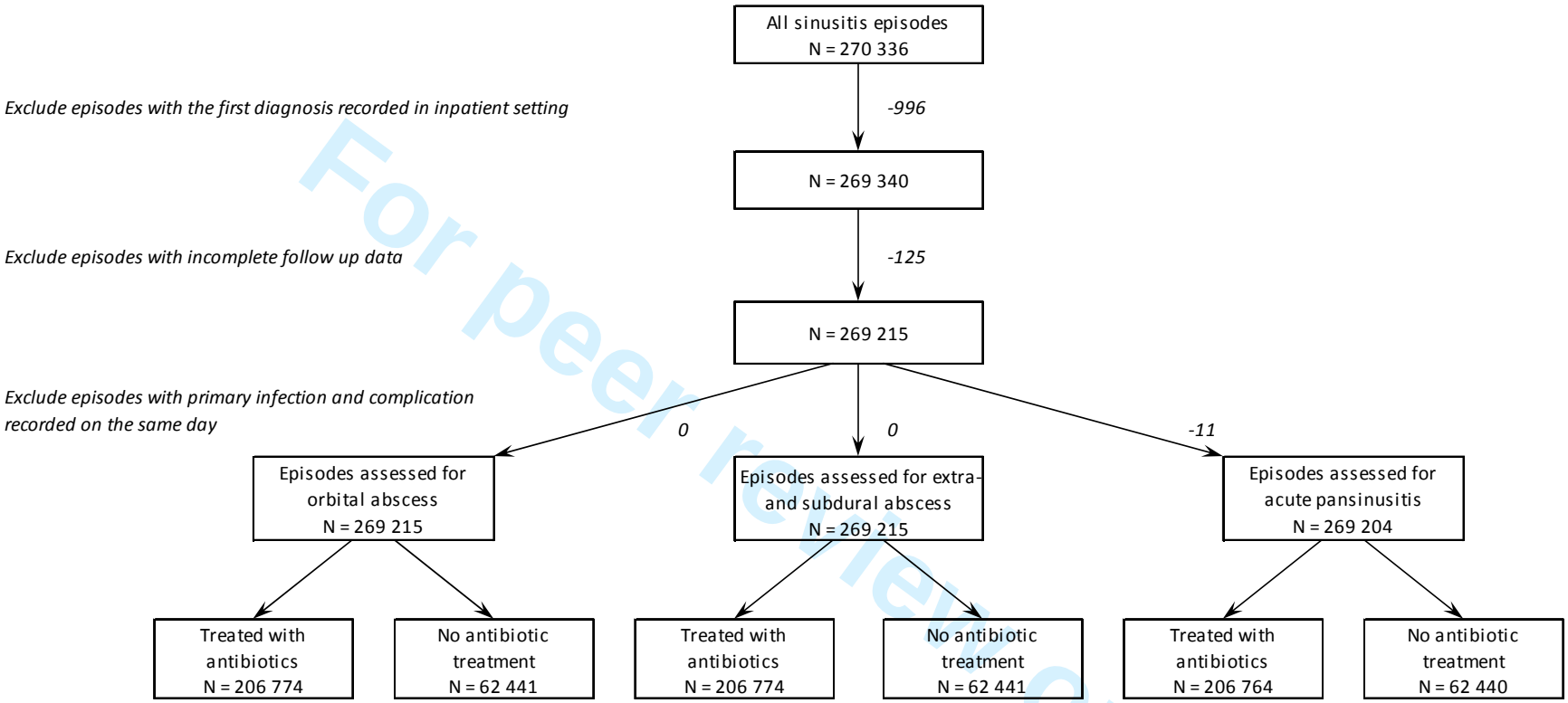
1. Acute otitis media (AOM) cohort



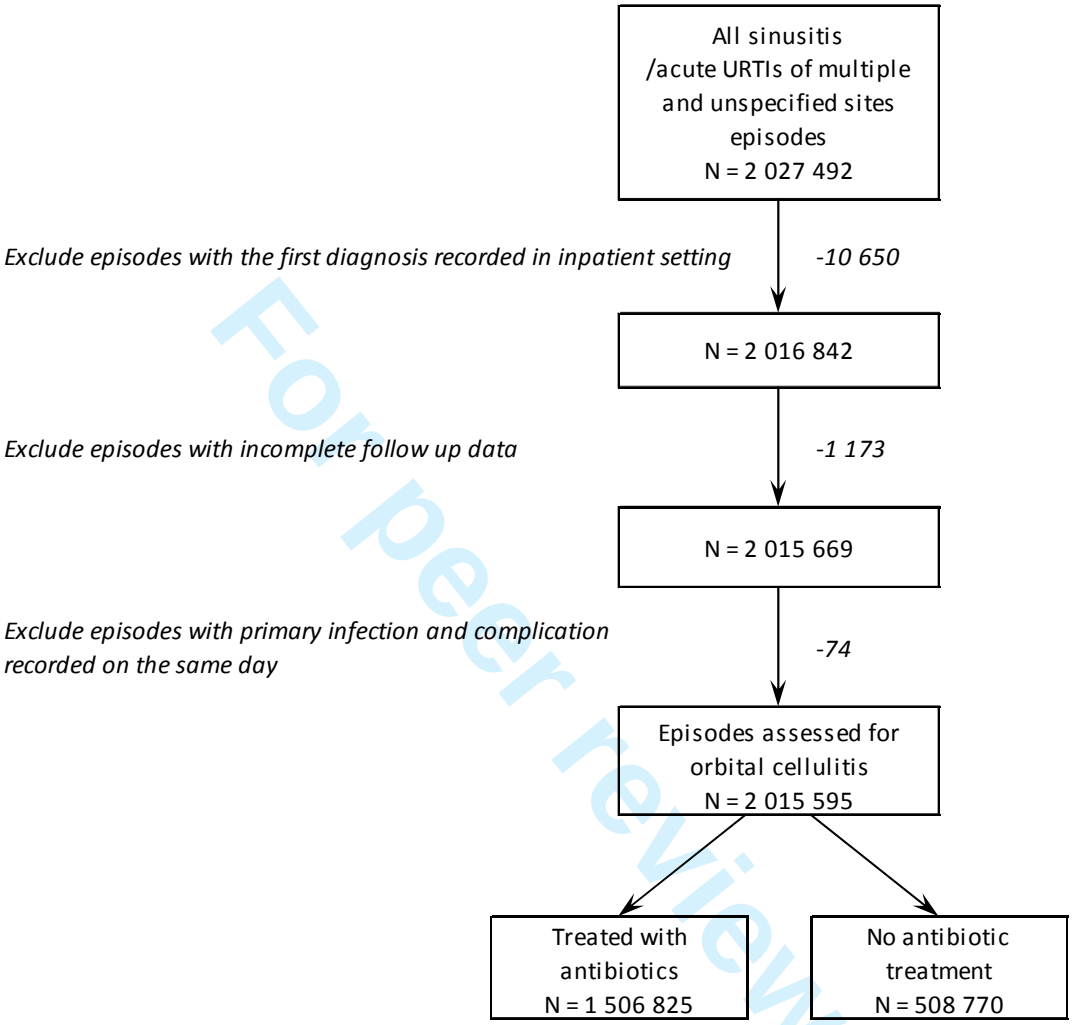
2. Tonsillitis cohort



3. Acute sinusitis cohort



4. Acute sinusitis / acute upper respiratory tract infections of multiple and unspecified sites cohort



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Antibiotic use and bacterial complications following upper respiratory tract infections: a population based study

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Patients were not directly involved in this study. General practitioners, specialists in infection diseases as well as representatives from health authorities were involved in the study design and the development of the outcome measure. There was no direct consumer involvement in this study. All data used in this study were anonymized, thus we do not know who the patients included in our analyses are. Therefore, the study results cannot be directly disseminated to the patients. We will however communicate the findings to the general practitioners and specialists in infection diseases involved in care of patients with upper respiratory tract infections.

Abstract

Objectives

To investigate if use of antibiotics was associated with bacterial complications following upper respiratory tract infections (URTIs).

Design

Ecological time-trend analysis and a prospective cohort study.

Setting

Primary, outpatient specialist and inpatient care in Stockholm County, Sweden. All analyses were based on administrative healthcare data on consultations, diagnoses and dispensed antibiotics from January, 2006, to January, 2016.

Main outcome measures

Ecological time-trend analysis: 10-year trend analyses of the incidence of URTIs, bacterial infections/complications and respiratory antibiotic use.
Prospective cohort study: Incidence of bacterial complications following URTIs in antibiotic-exposed and non-exposed patients.

Results

The utilization of respiratory tract antibiotics decreased by 22% from 2006 to 2015 but no increased trend for mastoiditis (p=0.0933), peritonsillar abscess (p=0.0544), invasive group A streptococcal disease (p=0.3991), orbital abscess (p=0.9637), extra- and subdural abscess (p=0.4790) and pansinusitis (p=0.3971) were observed. For meningitis and acute ethmoidal sinusitis, a decrease in the numbers of infections from 2006 to 2015 was observed (p=0.0038 and p=0.0003, respectively) and for retropharyngeal and parapharyngeal abscess an increase was observed (p=0.0214). Bacterial complications following URTIs were uncommon both in antibiotic-exposed (less than 1.5 per 10 000 episodes) and non-exposed patients (less than 1.3 per 10 000 episodes) with the exception of peritonsillar abscess after tonsillitis (risk per 10 000 tonsillitis episodes: 32.4 and 41.1 in patients with no antibiotic treatment and patients treated with antibiotics, respectively).

Conclusions

Bacterial complications following URTIs are rare and antibiotics may lack protective effect in preventing bacterial complications. Analyses of routinely collected administrative healthcare data can provide valuable information on the number of URTIs, antibiotic use, and bacterial complications to patients, prescribers and policymakers.

Strengths and limitations of this study

Data used in this study are population based and include information from primary, outpatient specialist and inpatient care as well as data on all drugs dispensed in ambulatory care

Data are continuously updated and loss to follow-up is minimal (only when an individual moves out of the region)

Antibiotic exposure assessment is based on the information from a drug dispensation database; no information on antibiotics administered in hospitals was available for these analyses

Outcome definitions are based on recorded diagnoses thus this study relies on the accuracy and completeness of diagnoses data

It is unknown whether the individual completed the prescribed course of antibiotic treatment

Introduction

The use of antibiotics contributes to the emergence and spread of drug-resistant bacteria(1-3). Curbing antibiotic resistance requires coordinated action at the global, national and regional levels(4). In Sweden, a comparatively low level of antibiotic utilization has been achieved through years of strategic work at the national and regional level that has included surveillance of antibiotic utilization(5, 6) and resistance trends, development and implementation of treatment guidelines as well as educational activities targeted at healthcare professionals, patients and the general public(7).

Most antibiotics prescribed in the Swedish primary care are used for treatment of respiratory tract infections(8). Over the past 20 years such use in Sweden has gradually declined(9). Most of this decline has been attributed to limiting the inappropriate antibiotic use in viral respiratory tract infections or mild self-healing bacterial infections(10) by the implementation of stricter guidelines, for example for pharyngotonsillitis and acute otitis media(11-13). However, we know that a substantial number of antibiotic prescriptions are still issued by doctors “just in case” in fear of complications(14, 15). There is therefore a need for large studies on rare complications of upper respiratory tract infections (URTIs) in order to quantify these risks and hopefully to reduce some of the uncertainty for primary care physicians and their patients.

The objective of this study was to investigate if use of antibiotics was associated with bacterial complications following URTIs. First, we present results from an ecological time-trend analysis assessing whether the reduction in antibiotic use in URTIs was associated with a change in the incidence of bacterial complications in a large geographically defined population. Second, we present findings from a prospective cohort study based on individual patient level data describing the incidence of bacterial complications in antibiotic-exposed and non-exposed patients with URTIs.

Methods

Setting

We conducted both an ecological time-trend analysis and a prospective cohort study in Stockholm County, Sweden, using administrative healthcare data from 1 January, 2006, to 31 January, 2016. Because this study used only anonymized administrative healthcare data, informed consent was not required. The study was approved by the regional ethics committee in Stockholm, Sweden (Ref. no. 2015/158-31).

Data sources

We used data from the regional healthcare data warehouse of Stockholm County (VAL) (16)and the Swedish Prescribed Drug Register(17). VAL contains comprehensive administrative healthcare data for all Stockholm County residents (around 2.3 million people, approximately 23% of the population of Sweden). Virtually all healthcare contacts financed by the Stockholm County Council are documented in VAL. From VAL we obtained the following information: demographic data (patient age and sex), diagnoses in primary care, outpatient specialist- and inpatient care (diagnoses are coded using the International Classification of Diseases [ICD-10] codes), consultation dates (for both in-person and

phone consultations), hospital admission and discharge dates, as well as migration and death records. From the Swedish Prescribed Drug Register we obtained data on dispensed antibiotics (drugs are coded using the Anatomical Therapeutic Chemical [ATC] codes).

Ecological time-trend analysis

For the ecological time-trend analysis we used aggregate level antibiotic utilization data (exposure) and data on the incidence of bacterial complications (outcome) between 1 January, 2006, and 31 December, 2015. We also assessed data on the incidence of URTIs during this period. We matched the exposure and outcomes data based on the year in which they were recorded. The list of antibiotics classified as those used to treat URTIs is provided in Supplement 1. The utilization of antibiotics was expressed as the defined daily dose (DDD) per 1000 inhabitants per day(18).

We studied the following bacterial complications: mastoiditis, meningitis, retropharyngeal and parapharyngeal abscess, invasive group A streptococcal disease, acute pansinusitis, acute ethmoidal sinusitis, orbital abscess, extradural abscess- and subdural abscess documented in inpatient care. For peritonsillar abscess, diagnoses recorded both in outpatient and in inpatient setting were included. The lists of ICD-10 codes used to define bacterial complications and primary URTIs are provided in Supplement 2 and Supplement 3, respectively.

Prospective cohort study

Inclusion and exclusion criteria

In the prospective cohort study we included all patients with a diagnosis of acute otitis media, tonsillitis, sinusitis or acute upper respiratory tract infections of multiple and unspecified sites diagnosed in the outpatient setting (primary care or outpatient specialist care) from 1 January, 2006, to 31 December, 2015 (see Supplement 3 for ICD-10 codes used to define the cohorts). The selected population was stratified into four sub-cohorts to study the incidence of bacterial complications in the antibiotic-exposed and non-exposed individuals: 1) acute otitis media cohort to study the incidence of mastoiditis and meningitis; 2) tonsillitis cohort to study the incidence of peritonsillar abscess, retropharyngeal and parapharyngeal abscess and invasive group A streptococcal disease; 3) acute sinusitis cohort to study the incidence of acute pansinusitis, orbital abscess and extra- and subdural abscess; 4) a combined cohort of patients with sinusitis and acute upper respiratory tract infections (corresponding to the ICD10-code: J06) to study the incidence of orbital cellulitis (without formation of abscess). This last combination cohort allowed identifying complications to acute rhinosinusitis, mainly of ethmoidal origin not included in the acute sinusitis cohort (the majority of this combination cohort are children). In the widespread Swedish clinical practice children displaying symptoms and signs of an orbital complication in relation to an URTI (often of viral origin) are designated as cases of acute ethmoidal sinusitis (or other types of acute sinusitis) based on the clinical findings(19). In this paper and internationally, these complications are referred to as orbital cellulitis. The cohort selection flow chart can be found in Supplement 4.

Episode definition

As more than one diagnosis of an URTI can be recorded for the same patient, an episode was created to combine data on diagnoses and treatment attributed to the same URTI and the start and the end dates were defined for each episode (Figure 1).

The episode start date (index date) was defined as the date of the first recorded diagnosis within the episode. If there was more than a month (30 day period used in all calculations) between diagnoses, the later diagnosis was attributed to a new URTI episode. The 30 day period was based on the Swedish guidelines on URTIs (sinusitis, acute otitis media, tonsillitis) stating that new symptoms within 30 days are a relapse and not a new episode. If a dispensation of antibiotic occurred within 3 days after the latest recorded diagnosis attributed to an episode (reflecting the strategy of watchful waiting), the date of antibiotic dispensation constituted the episode end date. If a bacterial complication occurred, the date of complication diagnosis constituted the episode end date.

If a bacterial complication occurred on the same date as the episode start date this episode was excluded from our analyses. Furthermore, episodes with less than one month of follow-up were also excluded.

For all bacterial complications, if more than 6 months passed between recorded diagnoses it was defined as an incident bacterial complication. The 6 month period was chosen in order to not miss any late bacterial complications. If more than 6 months passed since the primary URTI it is highly unlikely that any new signs and symptoms would be due to the primary URTI.

Exposure groups

Patients were considered exposed to respiratory tract antibiotics if a prescription was dispensed within the episode. An episode was not considered exposed to antibiotic if the first antibiotic prescription was dispensed on the same day as the suspected bacterial complication.

Outcomes

The follow-up of patients for study outcomes started at the episode start date and continued for a one month period (30 days) after the episode end date.

The study outcomes included: 1) mastoiditis and meningitis diagnosed in inpatient setting (acute otitis media cohort); 2) peritonsillar abscess diagnosed in either outpatient or inpatient setting, retropharyngeal and parapharyngeal abscess and invasive group A streptococcal disease diagnosed in inpatient setting (tonsillitis cohort); 3) pansinusitis, orbital abscess and extra- and subdural abscess diagnosed in inpatient setting (sinusitis cohort); 4) orbital cellulitis diagnosed in inpatient setting (sinusitis and acute upper respiratory tract infections (corresponding to ICD10-code: J06) in combination cohort). ICD-10 codes used to define bacterial complications are provided in Supplement 2. We included as outcomes in the study those bacterial complications that have an established or plausible association to various URTIs.

Statistical analyses

For the time-trend analysis, aggregate level of respiratory antibiotic utilization data (DDD per 1000 inhabitants per day, DID), number of bacterial complications per year as well as number of primary URTI episodes per year were plotted over time.

Trends for bacterial complications and respiratory antibiotic utilization (using DDD as the measure of utilization) were investigated using negative binomial regression models with annual Stockholm County population counts (as of December 31 each year) as the offset variable.

For the prospective cohort study, we calculated the number of patients experiencing episodes of URTIs and stratified these patients by age and antibiotic treatment (no antibiotic treatment group and treated with antibiotics group). We then calculated the number of bacterial complications occurring in these patients and risk of bacterial complications per 10 000 patients.

Data management and analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC).

Results

The volumes of dispensed respiratory tract antibiotics in Stockholm County declined by 22% from 2006 to 2015 (Figure 2). The number of acute otitis media and sinusitis episodes declined and the number of tonsillitis episodes was increasing from 2006 to 2012 and then sharply declined and remained stable from 2013 to 2015 (Table 1). The proportion of patients treated with antibiotics declined in the cohorts of acute otitis media (from 88% in 2006 to 81% in 2015), sinusitis (from 86% in 2006 to 71% in 2015) and sinusitis/acute URTI unspecified (from 36% in 2006 to 18% in 2015), and remained stable for tonsillitis (73% in 2006 and 73% in 2015).

In the ecological time-trend analysis we observed a significant decrease in the volumes of dispensed antibiotics from 2006 to 2015 ($p<0.0001$). During the same time period there was no significant trend in the number of the following bacterial complications: mastoiditis ($p=0.0933$), peritonsillar abscess ($p=0.0544$), invasive group A streptococcal disease ($p=0.3991$), orbital abscess ($p=0.9637$), extra- and subdural abscess ($p=0.4790$) and pansinusitis ($p=0.3971$). For meningitis and acute ethmoidal sinusitis, a decrease in the numbers of infections from 2006 to 2015 was observed ($p=0.0038$ and $p=0.0003$, respectively) and for retropharyngeal and parapharyngeal abscess an increase was observed ($p=0.0214$). Data are presented in Figure 3.

Using individual patient level data we identified 515 156 acute otitis media, 866 378 tonsillitis, 269 215 sinusitis, and 2 015 595 sinusitis/acute upper respiratory tract infections of multiple and unspecified sites episodes (see Supplement 4 for cohort selection flow charts). Table 2 provides information on the number of bacterial complications, stratified by age and antibiotic treatment. Our data showed that all bacterial complications in URTI patients were infrequent (less than 1.5 per 10 000 episodes) with the exception of peritonsillar abscess after tonsillitis (risk per 10 000 tonsillitis episodes: 32.4 and 41.1 in patients with no antibiotic treatment and patients treated with antibiotics, respectively). Peritonsillar abscess was most common in adults aged 15 to 64 years old (risk per 10 000 tonsillitis patients aged 15 to 64: 42.2 and 67.4 in patients with no antibiotic treatment and patients treated with antibiotics, respectively).

Discussion

The volumes of dispensed URTI antibiotics in Stockholm County decreased by 22% over a ten-year period from 2006 to 2015. Our ecological time-trend analysis covering the entire population in a large region showed that restricted use of antibiotics was not associated with an increase in bacterial complications of mastoiditis, meningitis, peritonsillar abscess, invasive group A streptococcal disease, acute pansinusitis, acute ethmoidal sinusitis, orbital abscess and extradural abscess and subdural abscess. Moreover, the number of meningitis and acute ethmoidal sinusitis complications decreased over the study period. For retropharyngeal and parapharyngeal abscess an increase was observed.

The analyses of individual level data revealed that the incidence of bacterial complications following primary URTIs was very low: the risk per 10 000 URTI episodes was less than 1.5 (average for all age groups) for all analyzed bacterial complications (with the exception of peritonsillar abscess) for both patients with no antibiotic treatment and patients treated with antibiotics. We observed a slightly higher risk of bacterial complications in the antibiotic treated group in 3 out of 9 bacterial complications studied. This can possibly be explained by the presence of confounding by indication: patients prescribed antibiotics likely had a more severe primary URTI thus were at a higher risk of both being prescribed an antibiotic and progressing to bacterial complications.

Our findings of no association between more restricted antibiotic use and the incidence of bacterial complications are in line with previous studies(10, 20-22). A previous Swedish study(23) showed that there was no increase in acute mastoiditis since 2000, when new guidelines recommending restrictive use of antibiotics for AOM were introduced. In 2010 new revised guidelines with an even more restrictive recommendation were issued(24). Our study includes data on mastoiditis in Stockholm County before and after these most restrictive recommendations, thus providing a first update on the impact of further restriction of antibiotic use in treatment of AOM. Of interest also is that while the proportion of patients with tonsillitis, sinusitis and other URTI receiving antibiotics in our study was comparable with that of Norway(25) the doctors in Stockholm prescribed antibiotics to a larger proportion of AOM patients than the doctors in Norway did. This may possibly be explained by different frameworks for coding AOM (ICD-10 vs. ICPC) and different definitions for exposure to antibiotic. Our definition of the antibiotic-exposed group included patients receiving an antibiotic anytime during their URTI episode thus likely resulting in a more complete capture of patients treated with antibiotics. Differences in definitions used can also explain discrepancies with other observational studies(20, 26). Our definition of bacterial complication only included bacterial complications recorded in inpatient care and therefore was stricter than those used in other studies (for example in comparison to analyses by Petersen et al.).

We found that a large proportion of diagnosed bacterial complications analyzed in this study were not preceded by patients seeking care for URTIs. A short duration from the onset of primary URTI to progression to bacterial complication could be an explanation for this as patient would have already developed a bacterial complication by the time of the first contact with healthcare professionals. In children, for example, the onset of symptoms and signs of mastoiditis is often very quick (within 24 hours). In this case a rapid progress of the disease is likely related to the virulence of pathogenic airway

bacteria. It has also been noted that peritonsillar abscess, the most common bacterial complication among adults in our study, often occurs without a preceding typical tonsillitis(27). Alternate routes of infection, for example oral pathogenic bacteria, may play a role in etiology of peritonsillar abscess.

The decline in meningitis and acute ethmoidal sinusitis observed in our analyses is in line with previous studies demonstrating a similar decrease in these infections after the introduction of conjugated anti-pneumococcal vaccine in the general vaccine schedule in Stockholm in 2007(28). Retropharyngeal and parapharyngeal abscesses are uncommon diseases and it was outside of scope of this study to investigate what may have contributed to the discreet increase in these complications observed during the study period. Risk factors for these heterogeneous infections are local trauma, immunosuppression, and dental infections(29).

All data used in our study are population-based and include information on diagnoses in primary, outpatient specialist and inpatient care as long as they were recorded by healthcare professionals, as well as on all dispensations of antibiotics in ambulatory care. These data are updated on a monthly basis thus enabling a real-time patient follow up. Using administrative data in general carries a number of known limitations, including reliance on the accuracy and completeness of recorded diagnoses, lack of information on antibiotics administered in the inpatient setting and inability to assert whether the patient completed the prescribed course of antibiotic treatment.

Our study demonstrated that routinely collected administrative healthcare data can provide valuable information on the number of URTIs, antibiotic use, and bacterial complications to patients, prescribers and policymakers. We found that bacterial complications were rare both in patients with no antibiotic treatment and in patients treated with antibiotics. While over the past decade the utilization of respiratory tract antibiotics decreased by 22% bacterial complications following URTIs remained uncommon.

Contributorship statement

TC, IE, AG, BW, JH, CN, AT contributed to the design of the study. TC extracted the data, wrote statistical programs and led statistical analyses. TC, IE, AG, BW, JH, CN, AT participated in the interpretation of data. TC had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. TC and IE drafted the paper. TC, IE, AG, BW, JH, CN, AT critically revised the paper for important intellectual content and approved the final version to be published.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

Additional data are available by emailing the corresponding author.

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Tables

Table 1. Number of episodes and antibiotic treatment for acute otitis media (cohort 1), tonsillitis (cohort 2), sinusitis (cohort 3) and sinusitis/acute upper respiratory tract infections of multiple and unspecified sites in combination (cohort 4) in Stockholm County from 2006 to 2015

	Acute otitis media		Tonsillitis		Sinusitis		Sinusitis/acute URTI unspecified	
	No antibiotic treatment	Treated with antibiotics	No antibiotic treatment	Treated with antibiotics	No antibiotic treatment	Treated with antibiotics	No antibiotic treatment	Treated with antibiotics
	n, %	n, %	n, %	n, %	n, %	n, %	n, %	n, %
2006	6 414(12)	47 657(88)	20 496(27)	54 998(73)	3 744(14)	23 586(86)	108 735(64)	61 658(36)
2007	6 971(12)	53 050(88)	23 262(26)	66 098(74)	4 364(14)	26 703(86)	123 484(64)	68 564(36)
2008	8 374(13)	55 350(87)	25 857(27)	71 041(73)	5 065(17)	25 057(83)	138 906(69)	62 195(31)
2009	8 260(15)	47 543(85)	27 007(29)	67 040(71)	5 942(22)	21 440(78)	149 417(74)	51 323(26)
2010	10 266(18)	47 248(82)	27 024(28)	68 774(72)	7 361(26)	20 737(74)	160 610(76)	52 044(24)
2011	8 773(18)	41 111(82)	23 635(25)	70 060(75)	7 531(28)	19 497(72)	167 915(77)	50 351(23)
2012	9 464(19)	39 697(81)	24 299(24)	78 428(76)	8 377(30)	19 988(70)	172 164(78)	49 398(22)
2013	7 933(19)	33 613(81)	20 069(27)	54 321(73)	7 150(29)	17 245(71)	160 925(80)	39 023(20)
2014	8 271(19)	35 656(81)	20 794(28)	53 111(72)	6 453(28)	16 376(72)	161 070(81)	38 395(19)
2015	7 858(19)	34 437(81)	19 956(27)	53 786(73)	6 949(29)	16 771(71)	172 759(82)	38 556(18)
2006-2015	**82 584(16)**	**435 362(84)**	**232 399(27)**	**637 657(73)**	**62 936(23)**	**207 400(77)**	**1 515 985(75)**	**511 507(25)**

Table 2. Risk of bacterial complications in the month after diagnosis of upper respiratory tract infections

	No antibiotic treatment			Treated with antibiotics		
	No of patients	No of complications	Risk per 10000	No of patients	No of complications	Risk per 10000
Mastoiditis after acute otitis media						
0-4	45 473	6	1.32	243 141	23	0.95
5-14	21 294	3	1.41	88 741	13	1.46
15-64	12 676	1	0.79	93 582	9	0.96
65+	2 412	0	-	7 809	1	1.28
Total[1]	**81 864**	**10**	**1.22**	**433 273**	**46**	**1.06**
Meningitis after acute otitis media						
0-4	45 476	2	0.44	243 151	1	0.04
5-14	21 292	1	0.47	88 746	0	-
15-64	12 676	1	0.79	93 581	13	1.39
65+	2 412	0	-	7 808	4	5.13
Total[1]	**81 865**	**4**	**0.49**	**433 286**	**18**	**0.42**
Peritonsillits after pharyngotonsillitis						
0-4	20 772	4	1.93	116 785	15	1.28
5-14	44 609	57	12.8	156 170	183	11.7
15-64	157 178	663	42.2	347 424	2 340	67.4
65+	9 167	27	29.5	12 552	61	48.6
Total[2]	**231 749**	**751**	**32.4**	**632 933**	**2 599**	**41.1**
Retropharyngeal and parapharyngeal abscess after pharyngotonsillitis						
0-4	20 772	0	-	116 811	2	0.17
5-14	44 585	0	-	156 332	3	0.19
15-64	156 805	24	1.53	349 240	76	2.18
65+	9 154	4	4.37	12 627	9	7.13
Total[2]	**231 339**	**28**	**1.21**	**635 012**	**90**	**1.42**
Invasive group A streptococcal disease after pharyngotonsillitis						
0-4	20 772	0	-	116 811	0	-
5-14	44 585	0	-	156 333	2	0.13
15-64	156 806	4	0.26	349 255	8	0.23
65+	9 155	3	3.28	12 632	1	0.79
Total[2]	**231 341**	**7**	**0.30**	**635 033**	**11**	**0.17**
Orbital abscess after sinusitis						
0-4	199	0	-	679	0	-
5-14	1 791	1	5.58	4 333	0	-
15-64	54 811	0	-	181 930	1	0.05
65+	5 637	0	-	19 832	0	-
Total[3]	**62 441**	**1**	**0.16**	**206 774**	**1**	**0.05**

	No antibiotic treatment			Treated with antibiotics		
	No of patients	**No of complications**	**Risk per 10000**	**No of patients**	**No of complications**	**Risk per 10000**
Extra- and subdural abscess after sinusitis						
0-4	199	0	-	679	0	-
5-14	1 791	0	-	4 333	1	2.31
15-64	54 811	1	0.18	181 930	1	0.05
65+	5 637	0	-	19 832	0	-
Total[3]	**62 441**	**1**	**0.16**	**206 774**	**2**	**0.10**
Acute pansinusitis after sinusitis						
0-4	198	0	-	679	0	-
5-14	1 790	0	-	4 330	1	2.31
15-64	54 812	7	1.28	181 923	15	0.82
65+	5 637	0	-	19 832	2	1.01
Total[3]	**62 440**	**7**	**1.12**	**206 764**	**18**	**0.87**
Acute ethmoidal sinusitis after sinusitis / acute upper respiratory tract infections of multiple and unspecified sites						
0-4	419 540	39	0.93	70 887	15	2.12
5-14	208 157	21	1.01	34 173	13	3.80
15-64	778 900	4	0.05	347 041	6	0.17
65+	100 201	1	0.10	56 669	0	-
Total[4]	**1 506 825**	**65**	**0.43**	**508 770**	**34**	**0.67**

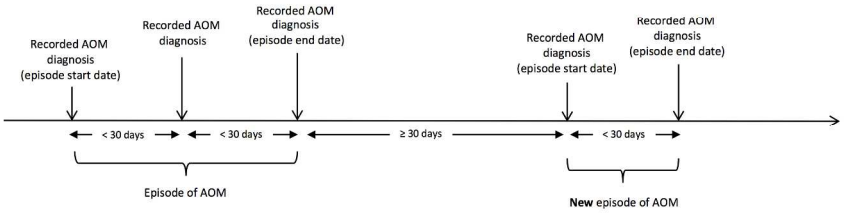
1. Missing information on age for 9 episodes of acute otitis media
2. Missing information on age for 25 episodes of tonsillitis
3. Missing information on age for 3 episodes of sinusitis
4. Missing information on age for 27 episodes of sinusitis

Figure legends

Figure 1. Definition of an episode of upper respiratory tract infection (here exemplified with acute otitis media (AOM) and mastoiditis)

Figure 2. Trend for respiratory tract antibiotic utilization in Stockholm County from 2006 to 2015

Figure 3. Trend for bacterial complications in Stockholm County from 2006 to 2015.



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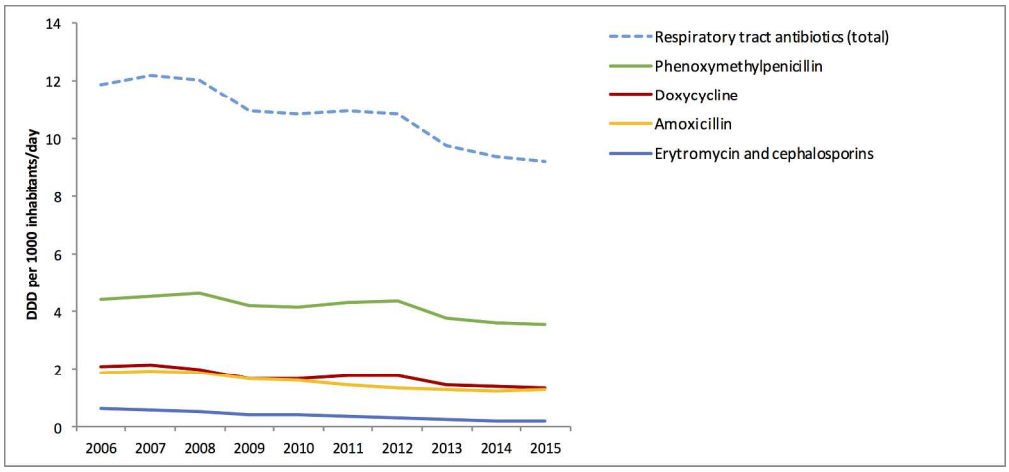

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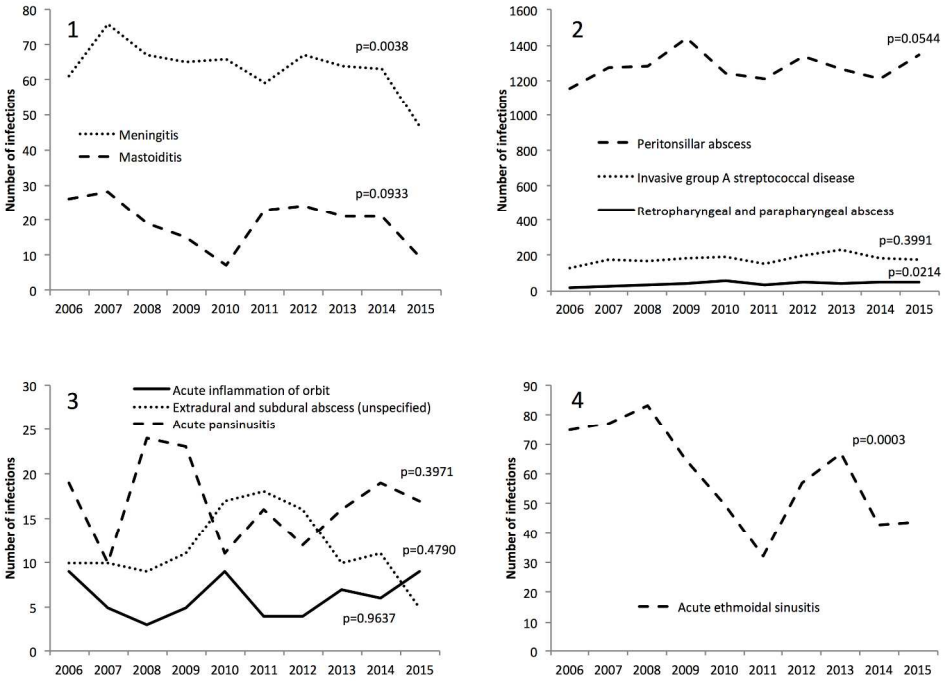


Figure 3 presents trends for bacterial complications in Stockholm County from 2006 to 2015. The four panels (1-4) corresponds to the complications we also assess in the four cohorts of the prospective cohort study ((1) acute otitis media cohort, (2) tonsillitis cohort, (3) sinusitis cohort and (4) sinusitis and acute upper respiratory tract infections of multiple and unspecified sites cohort. P-values present test for trend.

254x190mm (300 x 300 DPI)

Supplements

Supplement 1. Antibiotics used to treat upper respiratory tract infections

ATC code	Name of substance	ATC code	Name of substance
J01AA01	demeclocycline	**J01DD01**	cefotaxime
J01AA02	doxycycline	**J01DD04**	ceftriaxone
J01AA04	lymecycline	**J01DD08**	cefixime
J01AA06	oxytetracycline	**J01DD13**	cefpodoxime
J01AA07	tetracycline	**J01DD54**	ceftriaxone, combinations
J01AA08	minocycline	**J01DE01**	cefepime
J01AA12	tigecycline	**J01DE02**	cefpirome
J01BA01	chloramphenicol	**J01DH02**	meropenem
J01CA01	ampicillin	**J01DH03**	ertapenem
J01CA02	pivampicillin	**J01DH04**	doripenem
J01CA04	amoxicillin	**J01DH51**	imipenem and enzyme inhibitor
J01CA06	bacampicillin	**J01DI02**	ceftaroline fosamil
J01CA12	piperacillin	**J01EE01**	sulfamethoxazole and trimethoprim
J01CE01	benzylpenicillin	**J01FA01**	erythromycin
J01CE02	phenoxymethylpenicillin	**J01FA06**	roxithromycin
J01CE08	benzathine benzylpenicillin	**J01FA09**	clarithromycin
J01CR02	amoxicillin and enzyme inhibitor	**J01FA10**	azithromycin
J01CR05	piperacillin and enzyme inhibitor	**J01FA15**	telithromycin
J01CR50	combinations of penicillins	**J01FF01**	clindamycin
J01DA10	cefotaxime	**J01FF02**	lincomycin
J01DB01	cefalexin	**J01FG01**	pristinamycin
J01DB03	cefalotin	**J01FG02**	quinupristin/dalfopristin
J01DB04	cefazolin	**J01MA02**	ciprofloxacin
J01DB05	cefadroxil	**J01MA12**	levofloxacin
J01DC01	cefoxitin	**J01MA14**	moxifloxacin
J01DC02	cefuroxime	**J01RA01**	penicillins, combinations with other antibacterials
J01DC04	cefaclor	**J01XA01**	vancomycin
J01DC06	cefonicid	**J01XA02**	teicoplanin
J01DC08	loracarbef	**J01XX08**	linezolid
		J01XX09	daptomycin

Supplement 2. ICD-10 codes used to identify bacterial complications

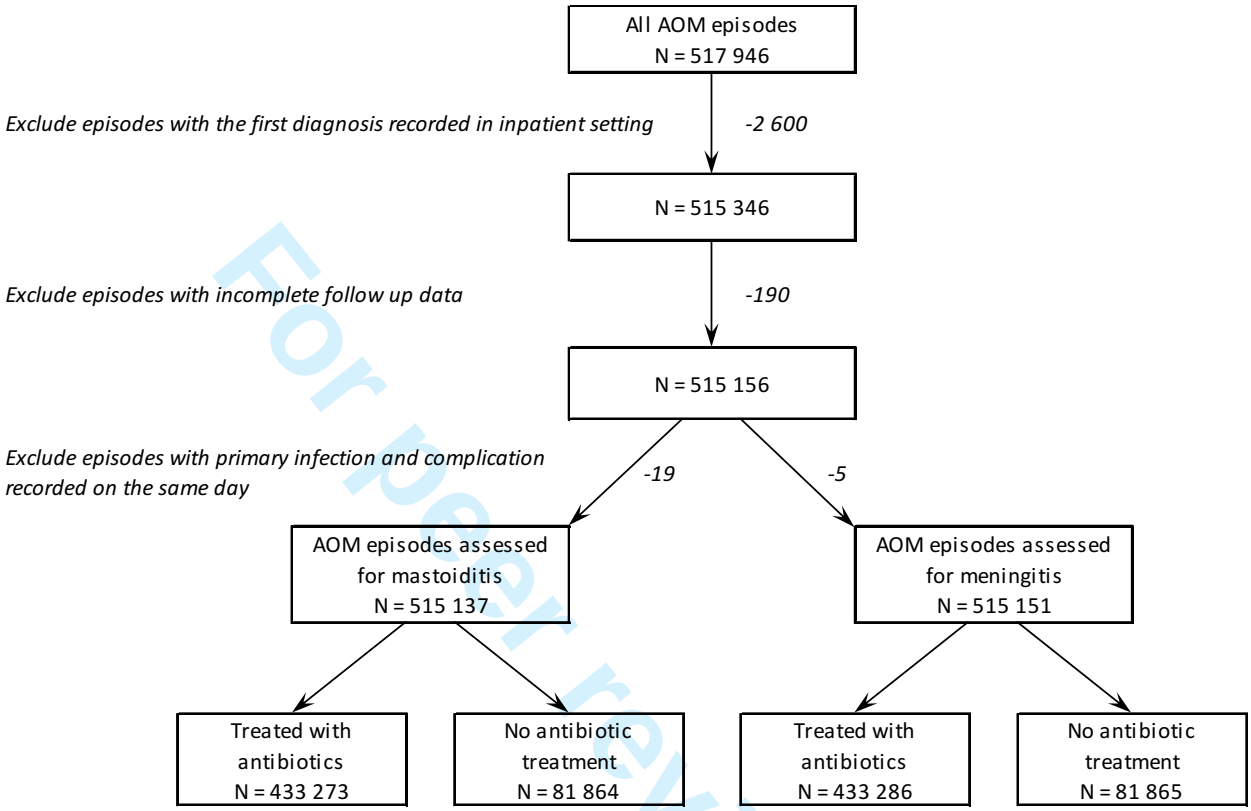
Bacterial complication	ICD-10 code	ICD-10 text
Mastoiditis	H70.0	Acute mastoiditis
	H70.2	Petrositis
	H70.9	Mastoiditis, unspecified
Meningitis	G00.0	Haemophilus meningitis
	G00.1	Pneumococcal meningitis
	G00.2	Streptococcal meningitis
	G00.3	Staphylococcal meningitis
	G00.9	Bacterial meningitis, unspecified
Peritonsillar abscess	J36	Peritonsillar abscess
Retropharyngeal and parapharyngeal abscess	J39.0	Retropharyngeal and parapharyngeal abscess
Invasive group A streptococcal disease	A40.0	Sepsis due to streptococcus, group A
	A40.9	Streptococcal sepsis, unspecified
	M72.6	Necrotizing fasciitis
Pansinusitis	J01.4	Acute pansinusitis
Orbital abscess	H05.0	Acute inflammation of orbit
Extra- and subdural abscess	G06.2	Extradural and subdural abscess, unspecified
Acute ethmoidal sinusitis	J01.2	Acute ethmoidal sinusitis

Supplement 3. ICD-10 codes used to identify primary URTIs

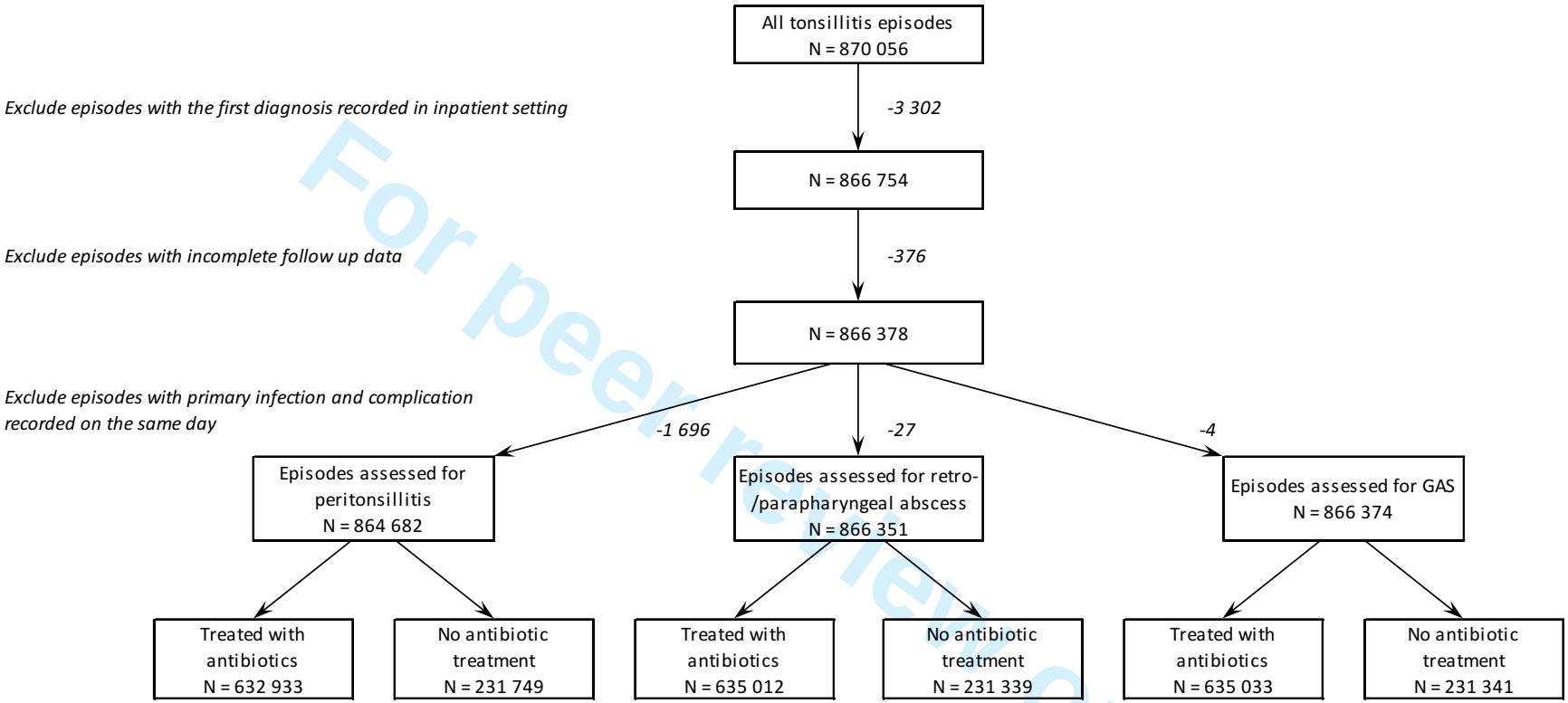
Primary URTIs	ICD-10 code	ICD-10 text
Acute otitis media	H66.0	Acute suppurative otitis media
	H66.9	Otitis media, unspecified
Tonsillitis	J02	Acute pharyngitis
	J03	Acute tonsillitis
Sinusitis	J01.0	Acute maxillary sinusitis
	J01.9	Acute sinusitis, unspecified
	J01	Acute sinusitis (for primary care records only)
Sinusitis and acute upper respiratory tract infections of multiple and unspecified sites	J01.0	Acute maxillary sinusitis
	J01.9	Acute sinusitis, unspecified
	J01	Acute sinusitis (for primary care records only)
	J06.0	Acute laryngopharyngitis
	J06.9	Acute upper respiratory infection, unspecified
	J06	Acute upper respiratory infections of multiple and unspecified sites (for primary care records only)

Supplement 4. Cohort selection flow-chart

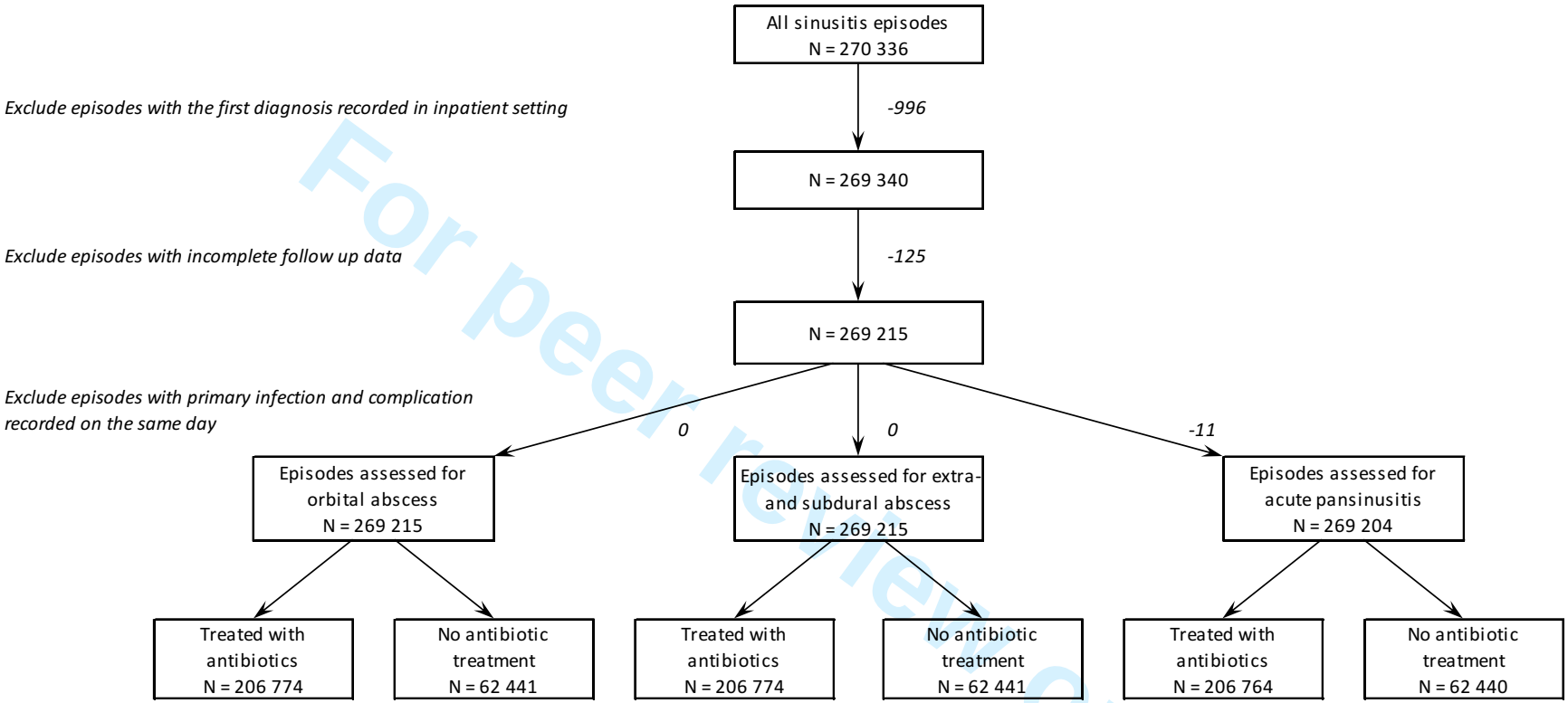
1. Acute otitis media (AOM) cohort



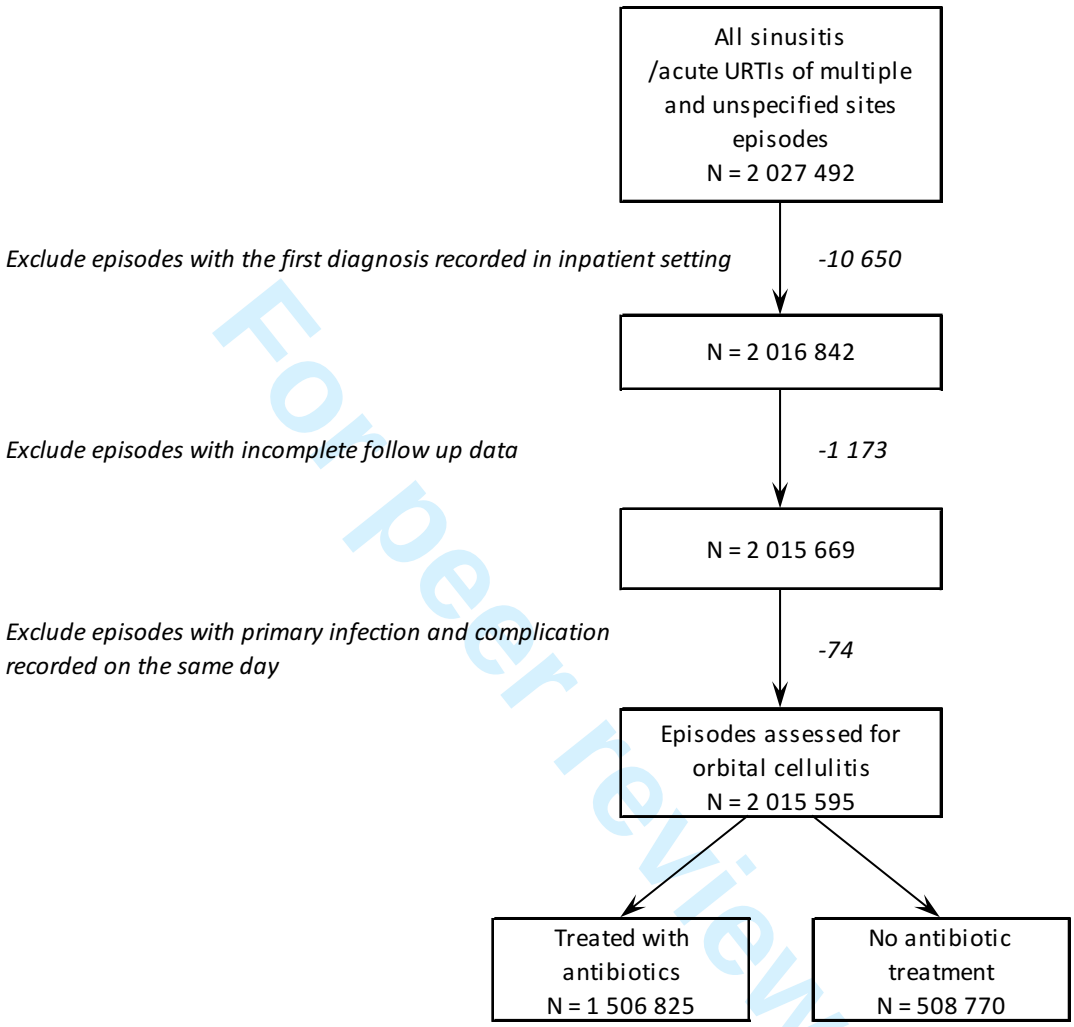
2. Tonsillitis cohort



3. Acute sinusitis cohort



4. Acute sinusitis / acute upper respiratory tract infections of multiple and unspecified sites cohort



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Antibiotic use and bacterial complications following upper respiratory tract infections: a population based study

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Antibiotic use and bacterial complications following upper respiratory tract infections: a population based study

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Patients were not directly involved in this study. General practitioners, specialists in infection diseases as well as representatives from health authorities were involved in the study design and the development of the outcome measure. There was no direct consumer involvement in this study. All data used in this study were anonymized, thus we do not know who the patients included in our analyses are. Therefore, the study results cannot be directly disseminated to the patients. We will however communicate the findings to the general practitioners and specialists in infection diseases involved in care of patients with upper respiratory tract infections.

Abstract

Objectives

To investigate if use of antibiotics was associated with bacterial complications following upper respiratory tract infections (URTIs).

Design

Ecological time-trend analysis and a prospective cohort study.

Setting

Primary, outpatient specialist and inpatient care in Stockholm County, Sweden. All analyses were based on administrative healthcare data on consultations, diagnoses and dispensed antibiotics from January, 2006, to January, 2016.

Main outcome measures

Ecological time-trend analysis: 10-year trend analyses of the incidence of URTIs, bacterial infections/complications and respiratory antibiotic use.
Prospective cohort study: Incidence of bacterial complications following URTIs in antibiotic-exposed and non-exposed patients.

Results

The utilization of respiratory tract antibiotics decreased by 22% from 2006 to 2015 but no increased trend for mastoiditis (p=0.0933), peritonsillar abscess (p=0.0544), invasive group A streptococcal disease (p=0.3991), orbital abscess (p=0.9637), extra- and subdural abscess (p=0.4790) and pansinusitis (p=0.3971) were observed. For meningitis and acute ethmoidal sinusitis, a decrease in the numbers of infections from 2006 to 2015 was observed (p=0.0038 and p=0.0003, respectively) and for retropharyngeal and parapharyngeal abscess an increase was observed (p=0.0214). Bacterial complications following URTIs were uncommon both in antibiotic-exposed (less than 1.5 per 10 000 episodes) and non-exposed patients (less than 1.3 per 10 000 episodes) with the exception of peritonsillar abscess after tonsillitis (risk per 10 000 tonsillitis episodes: 32.4 and 41.1 in patients with no antibiotic treatment and patients treated with antibiotics, respectively).

Conclusions

Bacterial complications following URTIs are rare and antibiotics may lack protective effect in preventing bacterial complications. Analyses of routinely collected administrative healthcare data can provide valuable information on the number of URTIs, antibiotic use, and bacterial complications to patients, prescribers and policymakers.

Strengths and limitations of this study

Data used in this study are population based and include information from primary, outpatient specialist and inpatient care as well as data on all drugs dispensed in ambulatory care

Data are continuously updated and loss to follow-up is minimal (only when an individual moves out of the region)

Antibiotic exposure assessment is based on the information from a drug dispensation database; no information on antibiotics administered in hospitals was available for these analyses

Outcome definitions are based on recorded diagnoses thus this study relies on the accuracy and completeness of diagnoses data

It is unknown whether the individual completed the prescribed course of antibiotic treatment

Introduction

The use of antibiotics contributes to the emergence and spread of drug-resistant bacteria(1-3). Curbing antibiotic resistance requires coordinated action at the global, national and regional levels(4). In Sweden, a comparatively low level of antibiotic utilization has been achieved through years of strategic work at the national and regional level that has included surveillance of antibiotic utilization(5, 6) and resistance trends, development and implementation of treatment guidelines as well as educational activities targeted at healthcare professionals, patients and the general public(7).

Most antibiotics prescribed in the Swedish primary care are used for treatment of respiratory tract infections(8). Over the past 20 years such use in Sweden has gradually declined(9). Most of this decline has been attributed to limiting the inappropriate antibiotic use in viral respiratory tract infections or mild self-healing bacterial infections(10) by the implementation of stricter guidelines, for example for pharyngotonsillitis and acute otitis media(11-13). However, we know that a substantial number of antibiotic prescriptions are still issued by doctors “just in case” in fear of complications(14, 15). There is therefore a need for large studies on rare complications of upper respiratory tract infections (URTIs) in order to quantify these risks and hopefully to reduce some of the uncertainty for primary care physicians and their patients.

The objective of this study was to investigate if use of antibiotics was associated with bacterial complications following URTIs. First, we present results from an ecological time-trend analysis assessing whether the reduction in antibiotic use in URTIs was associated with a change in the incidence of bacterial complications in a large geographically defined population. Second, we present findings from a prospective cohort study based on individual patient level data describing the incidence of bacterial complications in antibiotic-exposed and non-exposed patients with URTIs.

Methods

Setting

We conducted both an ecological time-trend analysis and a prospective cohort study in Stockholm County, Sweden, using administrative healthcare data from 1 January, 2006, to 31 January, 2016. Because this study used only anonymized administrative healthcare data, informed consent was not required. The study was approved by the regional ethics committee in Stockholm, Sweden (Ref. no. 2015/158-31).

Data sources

We used data from the regional healthcare data warehouse of Stockholm County (VAL) (16)and the Swedish Prescribed Drug Register(17). VAL contains comprehensive administrative healthcare data for all Stockholm County residents (around 2.3 million people, approximately 23% of the population of Sweden). Virtually all healthcare contacts financed by the Stockholm County Council are documented in VAL. From VAL we obtained the following information: demographic data (patient age and sex), diagnoses in primary care, outpatient specialist- and inpatient care (diagnoses are coded using the International Classification of Diseases [ICD-10] codes), consultation dates (for both in-person and

phone consultations), hospital admission and discharge dates, as well as migration and death records. From the Swedish Prescribed Drug Register we obtained data on dispensed antibiotics (drugs are coded using the Anatomical Therapeutic Chemical [ATC] codes).

Ecological time-trend analysis

For the ecological time-trend analysis we used aggregate level antibiotic utilization data (exposure) and data on the incidence of bacterial complications (outcome) between 1 January, 2006, and 31 December, 2015. We also assessed data on the incidence of URTIs during this period. We matched the exposure and outcomes data based on the year in which they were recorded. The list of antibiotics classified as those used to treat URTIs is provided in Supplement 1. The utilization of antibiotics was expressed as the defined daily dose (DDD) per 1000 inhabitants per day(18).

We studied the following bacterial complications: mastoiditis, meningitis, retropharyngeal and parapharyngeal abscess, invasive group A streptococcal disease, acute pansinusitis, acute ethmoidal sinusitis, orbital abscess, extradural abscess- and subdural abscess documented in inpatient care. For peritonsillar abscess, diagnoses recorded both in outpatient and in inpatient setting were included. The lists of ICD-10 codes used to define bacterial complications and primary URTIs are provided in Supplement 2 and Supplement 3, respectively.

Prospective cohort study

Inclusion and exclusion criteria

In the prospective cohort study we included all patients with a diagnosis of acute otitis media, tonsillitis, sinusitis or acute upper respiratory tract infections of multiple and unspecified sites diagnosed in the outpatient setting (primary care or outpatient specialist care) from 1 January, 2006, to 31 December, 2015 (see Supplement 3 for ICD-10 codes used to define the cohorts). The selected population was stratified into four sub-cohorts to study the incidence of bacterial complications in the antibiotic-exposed and non-exposed individuals: 1) acute otitis media cohort to study the incidence of mastoiditis and meningitis; 2) tonsillitis cohort to study the incidence of peritonsillar abscess, retropharyngeal and parapharyngeal abscess and invasive group A streptococcal disease; 3) acute sinusitis cohort to study the incidence of acute pansinusitis, orbital abscess and extra- and subdural abscess; 4) a combined cohort of patients with sinusitis and acute upper respiratory tract infections (corresponding to the ICD10-code: J06) to study the incidence of orbital cellulitis (without formation of abscess). This last combination cohort allowed identifying complications to acute rhinosinusitis, mainly of ethmoidal origin not included in the acute sinusitis cohort (the majority of this combination cohort are children). In the widespread Swedish clinical practice children displaying symptoms and signs of an orbital complication in relation to an URTI (often of viral origin) are designated as cases of acute ethmoidal sinusitis (or other types of acute sinusitis) based on the clinical findings(19). In this paper and internationally, these complications are referred to as orbital cellulitis. The cohort selection flow chart can be found in Supplement 4.

Episode definition

As more than one diagnosis of an URTI can be recorded for the same patient, an episode was created to combine data on diagnoses and treatment attributed to the same URTI and the start and the end dates were defined for each episode (Figure 1).

The episode start date (index date) was defined as the date of the first recorded diagnosis within the episode. If there was more than a month (30 day period used in all calculations) between diagnoses, the later diagnosis was attributed to a new URTI episode. The 30 day period was based on the Swedish guidelines on URTIs (sinusitis, acute otitis media, tonsillitis) stating that new symptoms within 30 days are a relapse and not a new episode. If a dispensation of antibiotic occurred within 3 days after the latest recorded diagnosis attributed to an episode (reflecting the strategy of watchful waiting), the date of antibiotic dispensation constituted the episode end date. If a bacterial complication occurred, the date of complication diagnosis constituted the episode end date.

If a bacterial complication occurred on the same date as the episode start date this episode was excluded from our analyses. Furthermore, episodes with less than one month of follow-up were also excluded.

For all bacterial complications, if more than 6 months passed between recorded diagnoses it was defined as an incident bacterial complication. The 6 month period was chosen in order to not miss any late bacterial complications. If more than 6 months passed since the primary URTI it is highly unlikely that any new signs and symptoms would be due to the primary URTI.

Exposure groups

Patients were considered exposed to respiratory tract antibiotics if a prescription was dispensed within the episode. An episode was not considered exposed to antibiotic if the first antibiotic prescription was dispensed on the same day as the suspected bacterial complication.

Outcomes

The follow-up of patients for study outcomes started at the episode start date and continued for a one month period (30 days) after the episode end date.

The study outcomes included: 1) mastoiditis and meningitis diagnosed in inpatient setting (acute otitis media cohort); 2) peritonsillar abscess diagnosed in either outpatient or inpatient setting, retropharyngeal and parapharyngeal abscess and invasive group A streptococcal disease diagnosed in inpatient setting (tonsillitis cohort); 3) pansinusitis, orbital abscess and extra- and subdural abscess diagnosed in inpatient setting (sinusitis cohort); 4) orbital cellulitis diagnosed in inpatient setting (sinusitis and acute upper respiratory tract infections (corresponding to ICD10-code: J06) in combination cohort). ICD-10 codes used to define bacterial complications are provided in Supplement 2. We included as outcomes in the study those bacterial complications that have an established or plausible association to various URTIs.

Statistical analyses

For the time-trend analysis, aggregate level of respiratory antibiotic utilization data (DDD per 1000 inhabitants per day, DID), number of bacterial complications per year as well as number of primary URTI episodes per year were plotted over time.

Trends for bacterial complications and respiratory antibiotic utilization (using DDD as the measure of utilization) were investigated using negative binomial regression models with annual Stockholm County population counts (as of December 31 each year) as the offset variable.

For the prospective cohort study, we calculated the number of patients experiencing episodes of URTIs and stratified these patients by age and antibiotic treatment (no antibiotic treatment group and treated with antibiotics group). We then calculated the number of bacterial complications occurring in these patients and risk of bacterial complications per 10 000 patients.

Data management and analyses were carried out using SAS 9.4 (SAS Institute, Cary, NC).

Results

The volumes of dispensed respiratory tract antibiotics in Stockholm County declined by 22% from 2006 to 2015 (Figure 2). The number of acute otitis media and sinusitis episodes declined and the number of tonsillitis episodes was increasing from 2006 to 2012 and then sharply declined and remained stable from 2013 to 2015 (Table 1). The proportion of patients treated with antibiotics declined in the cohorts of acute otitis media (from 88% in 2006 to 81% in 2015), sinusitis (from 86% in 2006 to 71% in 2015) and sinusitis/acute URTI unspecified (from 36% in 2006 to 18% in 2015), and remained stable for tonsillitis (73% in 2006 and 73% in 2015).

In the ecological time-trend analysis we observed a significant decrease in the volumes of dispensed antibiotics from 2006 to 2015 ($p<0.0001$). During the same time period there was no significant trend in the number of the following bacterial complications: mastoiditis ($p=0.0933$), peritonsillar abscess ($p=0.0544$), invasive group A streptococcal disease ($p=0.3991$), orbital abscess ($p=0.9637$), extra- and subdural abscess ($p=0.4790$) and pansinusitis ($p=0.3971$). For meningitis and acute ethmoidal sinusitis, a decrease in the numbers of infections from 2006 to 2015 was observed ($p=0.0038$ and $p=0.0003$, respectively) and for retropharyngeal and parapharyngeal abscess an increase was observed ($p=0.0214$). Data are presented in Figure 3.

Using individual patient level data we identified 515 156 acute otitis media, 866 378 tonsillitis, 269 215 sinusitis, and 2 015 595 sinusitis/acute upper respiratory tract infections of multiple and unspecified sites episodes (see Supplement 4 for cohort selection flow charts). Table 2 provides information on the number of bacterial complications, stratified by age and antibiotic treatment. Our data showed that all bacterial complications in URTI patients were infrequent (less than 1.5 per 10 000 episodes) with the exception of peritonsillar abscess after tonsillitis (risk per 10 000 tonsillitis episodes: 32.4 and 41.1 in patients with no antibiotic treatment and patients treated with antibiotics, respectively). Peritonsillar abscess was most common in adults aged 15 to 64 years old (risk per 10 000 tonsillitis patients aged 15 to 64: 42.2 and 67.4 in patients with no antibiotic treatment and patients treated with antibiotics, respectively).

Discussion

The volumes of dispensed URTI antibiotics in Stockholm County decreased by 22% over a ten-year period from 2006 to 2015. Our ecological time-trend analysis covering the entire population in a large region showed that restricted use of antibiotics was not associated with an increase in bacterial complications of mastoiditis, meningitis, peritonsillar abscess, invasive group A streptococcal disease, acute pansinusitis, acute ethmoidal sinusitis, orbital abscess and extradural abscess and subdural abscess. Moreover, the number of meningitis and acute ethmoidal sinusitis complications decreased over the study period. For retropharyngeal and parapharyngeal abscess an increase was observed.

The analyses of individual level data revealed that the incidence of bacterial complications following primary URTIs was very low: the risk per 10 000 URTI episodes was less than 1.5 (average for all age groups) for all analyzed bacterial complications (with the exception of peritonsillar abscess) for both patients with no antibiotic treatment and patients treated with antibiotics. We observed a slightly higher risk of bacterial complications in the antibiotic treated group in 3 out of 9 bacterial complications studied. This can possibly be explained by the presence of confounding by indication: patients prescribed antibiotics likely had a more severe primary URTI thus were at a higher risk of both being prescribed an antibiotic and progressing to bacterial complications.

Our findings of no association between more restricted antibiotic use and the incidence of bacterial complications are in line with previous studies(10, 20-22). A previous Swedish study(23) showed that there was no increase in acute mastoiditis since 2000, when new guidelines recommending restrictive use of antibiotics for AOM were introduced. In 2010 new revised guidelines with an even more restrictive recommendation were issued(24). Our study includes data on mastoiditis in Stockholm County before and after these most restrictive recommendations, thus providing a first update on the impact of further restriction of antibiotic use in treatment of AOM. Of interest also is that while the proportion of patients with tonsillitis, sinusitis and other URTI receiving antibiotics in our study was comparable with that of Norway(25) the doctors in Stockholm prescribed antibiotics to a larger proportion of AOM patients than the doctors in Norway did. This may possibly be explained by different frameworks for coding AOM (ICD-10 vs. ICPC) and different definitions for exposure to antibiotic. Our definition of the antibiotic-exposed group included patients receiving an antibiotic anytime during their URTI episode thus likely resulting in a more complete capture of patients treated with antibiotics. Differences in definitions used can also explain discrepancies with other observational studies(20, 26). Our definition of bacterial complication only included bacterial complications recorded in inpatient care and therefore was stricter than those used in other studies (for example in comparison to analyses by Petersen et al.).

We found that a large proportion of diagnosed bacterial complications analyzed in this study were not preceded by patients seeking care for URTIs. A short duration from the onset of primary URTI to progression to bacterial complication could be an explanation for this as patient would have already developed a bacterial complication by the time of the first contact with healthcare professionals. In children, for example, the onset of symptoms and signs of mastoiditis is often very quick (within 24 hours). In this case a rapid progress of the disease is likely related to the virulence of pathogenic airway

bacteria. It has also been noted that peritonsillar abscess, the most common bacterial complication among adults in our study, often occurs without a preceding typical tonsillitis(27). Alternate routes of infection, for example oral pathogenic bacteria, may play a role in etiology of peritonsillar abscess.

The decline in meningitis and acute ethmoidal sinusitis observed in our analyses is in line with previous studies demonstrating a similar decrease in these infections after the introduction of conjugated anti-pneumococcal vaccine in the general vaccine schedule in Stockholm in 2007(28). Retropharyngeal and parapharyngeal abscesses are uncommon diseases and it was outside of scope of this study to investigate what may have contributed to the discreet increase in these complications observed during the study period. Risk factors for these heterogeneous infections are local trauma, immunosuppression, and dental infections(29).

All data used in our study are population-based and include information on diagnoses in primary, outpatient specialist and inpatient care as long as they were recorded by healthcare professionals, as well as on all dispensations of antibiotics in ambulatory care. These data are updated on a monthly basis thus enabling a real-time patient follow up. We based our selection of bacterial complications on those that we perceived have an established association to various URTIs. There could be other bacterial complications such as pneumonia that we have missed by narrowing the number of complications we looked for. Using administrative data in general carries a number of known limitations, including reliance on the accuracy and completeness of recorded diagnoses, lack of information on antibiotics administered in the inpatient setting and inability to assert whether the patient completed the prescribed course of antibiotic treatment.

Our study demonstrated that routinely collected administrative healthcare data can provide valuable information on the number of URTIs, antibiotic use, and bacterial complications to patients, prescribers and policymakers. We found that bacterial complications were rare both in patients with no antibiotic treatment and in patients treated with antibiotics. While over the past decade the utilization of respiratory tract antibiotics decreased by 22% bacterial complications following URTIs remained uncommon.

Contributorship statement

TC, IE, AG, BW, JH, CN, AT contributed to the design of the study. TC extracted the data, wrote statistical programs and led statistical analyses. TC, IE, AG, BW, JH, CN, AT participated in the interpretation of data. TC had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. TC and IE drafted the paper. TC, IE, AG, BW, JH, CN, AT critically revised the paper for important intellectual content and approved the final version to be published.

Competing interests

All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the

submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Data sharing statement

Additional data are available by emailing the corresponding author.

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Tables

Table 1. Number of episodes and antibiotic treatment for acute otitis media (cohort 1), tonsillitis (cohort 2), sinusitis (cohort 3) and sinusitis/acute upper respiratory tract infections of multiple and unspecified sites in combination (cohort 4) in Stockholm County from 2006 to 2015

	Acute otitis media		**Tonsillitis**		**Sinusitis**		**Sinusitis/acute URTI unspecified**	
	No antibiotic treatment	Treated with antibiotics	No antibiotic treatment	Treated with antibiotics	No antibiotic treatment	Treated with antibiotics	No antibiotic treatment	Treated with antibiotics
	n, %	n, %	n, %	n, %	n, %	n, %	n, %	n, %
2006	6 414(12)	47 657(88)	20 496(27)	54 998(73)	3 744(14)	23 586(86)	108 735(64)	61 658(36)
2007	6 971(12)	53 050(88)	23 262(26)	66 098(74)	4 364(14)	26 703(86)	123 484(64)	68 564(36)
2008	8 374(13)	55 350(87)	25 857(27)	71 041(73)	5 065(17)	25 057(83)	138 906(69)	62 195(31)
2009	8 260(15)	47 543(85)	27 007(29)	67 040(71)	5 942(22)	21 440(78)	149 417(74)	51 323(26)
2010	10 266(18)	47 248(82)	27 024(28)	68 774(72)	7 361(26)	20 737(74)	160 610(76)	52 044(24)
2011	8 773(18)	41 111(82)	23 635(25)	70 060(75)	7 531(28)	19 497(72)	167 915(77)	50 351(23)
2012	9 464(19)	39 697(81)	24 299(24)	78 428(76)	8 377(30)	19 988(70)	172 164(78)	49 398(22)
2013	7 933(19)	33 613(81)	20 069(27)	54 321(73)	7 150(29)	17 245(71)	160 925(80)	39 023(20)
2014	8 271(19)	35 656(81)	20 794(28)	53 111(72)	6 453(28)	16 376(72)	161 070(81)	38 395(19)
2015	7 858(19)	34 437(81)	19 956(27)	53 786(73)	6 949(29)	16 771(71)	172 759(82)	38 556(18)
2006-2015	**82 584(16)**	**435 362(84)**	**232 399(27)**	**637 657(73)**	**62 936(23)**	**207 400(77)**	**1 515 985(75)**	**511 507(25)**

Table 2. Risk of bacterial complications in the month after diagnosis of upper respiratory tract infections

	No antibiotic treatment			Treated with antibiotics		
	No of patients	No of complications	Risk per 10000	No of patients	No of complications	Risk per 10000
Mastoiditis after acute otitis media						
0-4	45 473	6	1.32	243 141	23	0.95
5-14	21 294	3	1.41	88 741	13	1.46
15-64	12 676	1	0.79	93 582	9	0.96
65+	2 412	0	-	7 809	1	1.28
Total[1]	**81 864**	**10**	**1.22**	**433 273**	**46**	**1.06**
Meningitis after acute otitis media						
0-4	45 476	2	0.44	243 151	1	0.04
5-14	21 292	1	0.47	88 746	0	-
15-64	12 676	1	0.79	93 581	13	1.39
65+	2 412	0	-	7 808	4	5.13
Total[1]	**81 865**	**4**	**0.49**	**433 286**	**18**	**0.42**
Peritonsillits after pharyngotonsillitis						
0-4	20 772	4	1.93	116 785	15	1.28
5-14	44 609	57	12.8	156 170	183	11.7
15-64	157 178	663	42.2	347 424	2 340	67.4
65+	9 167	27	29.5	12 552	61	48.6
Total[2]	**231 749**	**751**	**32.4**	**632 933**	**2 599**	**41.1**
Retropharyngeal and parapharyngeal abscess after pharyngotonsillitis						
0-4	20 772	0	-	116 811	2	0.17
5-14	44 585	0	-	156 332	3	0.19
15-64	156 805	24	1.53	349 240	76	2.18
65+	9 154	4	4.37	12 627	9	7.13
Total[2]	**231 339**	**28**	**1.21**	**635 012**	**90**	**1.42**
Invasive group A streptococcal disease after pharyngotonsillitis						
0-4	20 772	0	-	116 811	0	-
5-14	44 585	0	-	156 333	2	0.13
15-64	156 806	4	0.26	349 255	8	0.23
65+	9 155	3	3.28	12 632	1	0.79
Total[2]	**231 341**	**7**	**0.30**	**635 033**	**11**	**0.17**
Orbital abscess after sinusitis						
0-4	199	0	-	679	0	-
5-14	1 791	1	5.58	4 333	0	-
15-64	54 811	0	-	181 930	1	0.05
65+	5 637	0	-	19 832	0	-
Total[3]	**62 441**	**1**	**0.16**	**206 774**	**1**	**0.05**

	No antibiotic treatment			Treated with antibiotics		
	No of patients	**No of complications**	**Risk per 10000**	**No of patients**	**No of complications**	**Risk per 10000**
Extra- and subdural abscess after sinusitis						
0-4	199	0	-	679	0	-
5-14	1 791	0	-	4 333	1	2.31
15-64	54 811	1	0.18	181 930	1	0.05
65+	5 637	0	-	19 832	0	-
Total[3]	**62 441**	**1**	**0.16**	**206 774**	**2**	**0.10**
Acute pansinusitis after sinusitis						
0-4	198	0	-	679	0	-
5-14	1 790	0	-	4 330	1	2.31
15-64	54 812	7	1.28	181 923	15	0.82
65+	5 637	0	-	19 832	2	1.01
Total[3]	**62 440**	**7**	**1.12**	**206 764**	**18**	**0.87**
Acute ethmoidal sinusitis after sinusitis / acute upper respiratory tract infections of multiple and unspecified sites						
0-4	419 540	39	0.93	70 887	15	2.12
5-14	208 157	21	1.01	34 173	13	3.80
15-64	778 900	4	0.05	347 041	6	0.17
65+	100 201	1	0.10	56 669	0	-
Total[4]	**1 506 825**	**65**	**0.43**	**508 770**	**34**	**0.67**

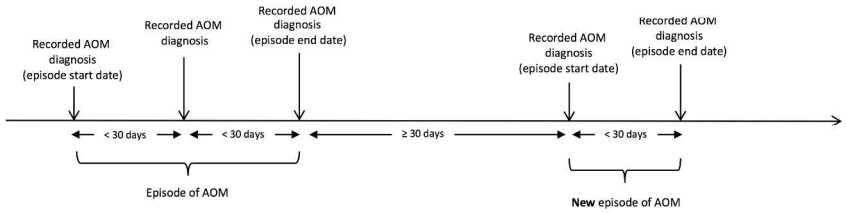
1. Missing information on age for 9 episodes of acute otitis media
2. Missing information on age for 25 episodes of tonsillitis
3. Missing information on age for 3 episodes of sinusitis
4. Missing information on age for 27 episodes of sinusitis

Figure legends

Figure 1. Definition of an episode of upper respiratory tract infection (here exemplified with acute otitis media (AOM) and mastoiditis)

Figure 2. Trend for respiratory tract antibiotic utilization in Stockholm County from 2006 to 2015

Figure 3. Trend for bacterial complications in Stockholm County from 2006 to 2015.



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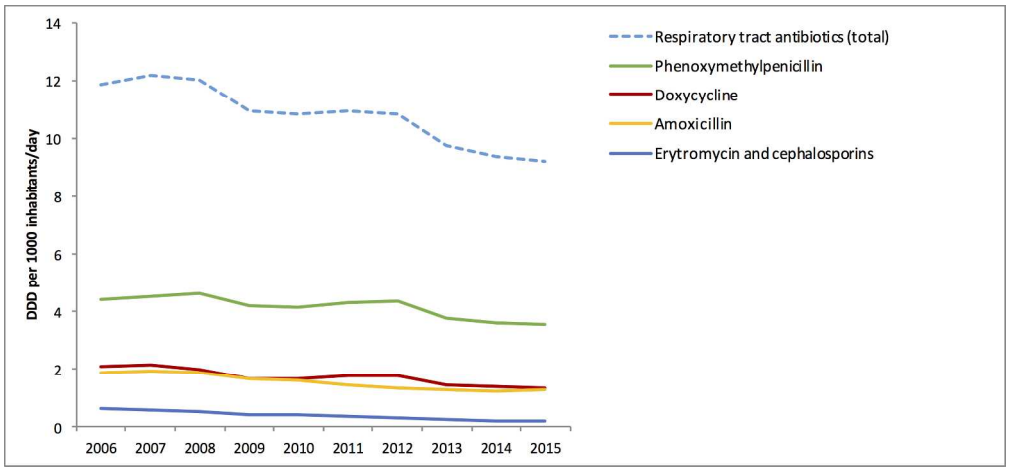

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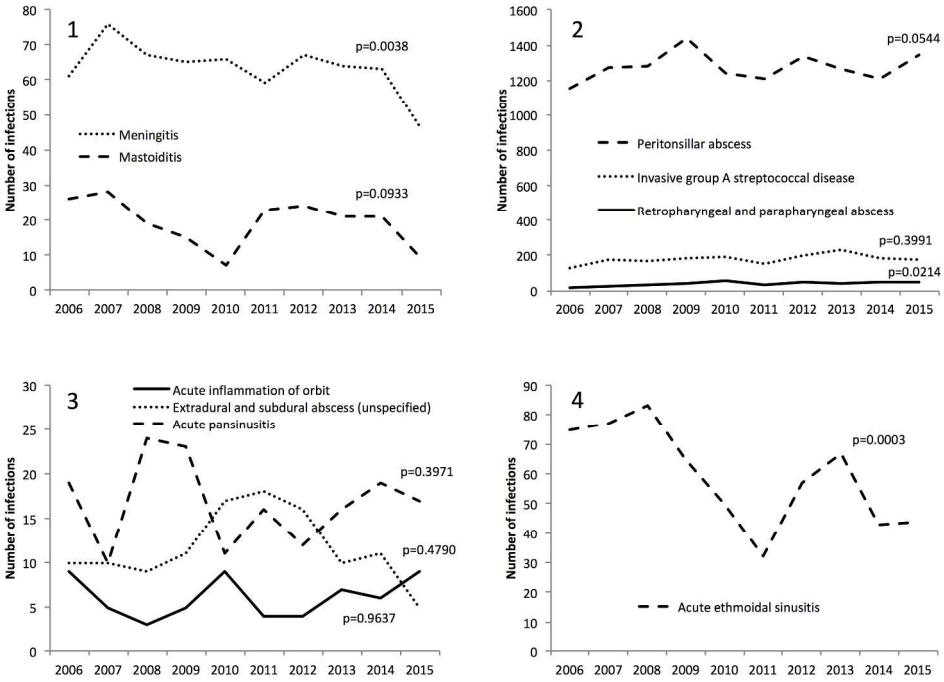


Figure 3 presents trends for bacterial complications in Stockholm County from 2006 to 2015. The four panels (1-4) corresponds to the complications we also assess in the four cohorts of the prospective cohort study ((1) acute otitis media cohort, (2) tonsillitis cohort, (3) sinusitis cohort and (4) sinusitis and acute upper respiratory tract infections of multiple and unspecified sites cohort. P-values present test for trend.

254x190mm (300 x 300 DPI)

Supplements

Supplement 1. Antibiotics used to treat upper respiratory tract infections

ATC code	Name of substance	ATC code	Name of substance
J01AA01	demeclocycline	**J01DD01**	cefotaxime
J01AA02	doxycycline	**J01DD04**	ceftriaxone
J01AA04	lymecycline	**J01DD08**	cefixime
J01AA06	oxytetracycline	**J01DD13**	cefpodoxime
J01AA07	tetracycline	**J01DD54**	ceftriaxone, combinations
J01AA08	minocycline	**J01DE01**	cefepime
J01AA12	tigecycline	**J01DE02**	cefpirome
J01BA01	chloramphenicol	**J01DH02**	meropenem
J01CA01	ampicillin	**J01DH03**	ertapenem
J01CA02	pivampicillin	**J01DH04**	doripenem
J01CA04	amoxicillin	**J01DH51**	imipenem and enzyme inhibitor
J01CA06	bacampicillin	**J01DI02**	ceftaroline fosamil
J01CA12	piperacillin	**J01EE01**	sulfamethoxazole and trimethoprim
J01CE01	benzylpenicillin	**J01FA01**	erythromycin
J01CE02	phenoxymethylpenicillin	**J01FA06**	roxithromycin
J01CE08	benzathine benzylpenicillin	**J01FA09**	clarithromycin
J01CR02	amoxicillin and enzyme inhibitor	**J01FA10**	azithromycin
J01CR05	piperacillin and enzyme inhibitor	**J01FA15**	telithromycin
J01CR50	combinations of penicillins	**J01FF01**	clindamycin
J01DA10	cefotaxime	**J01FF02**	lincomycin
J01DB01	cefalexin	**J01FG01**	pristinamycin
J01DB03	cefalotin	**J01FG02**	quinupristin/dalfopristin
J01DB04	cefazolin	**J01MA02**	ciprofloxacin
J01DB05	cefadroxil	**J01MA12**	levofloxacin
J01DC01	cefoxitin	**J01MA14**	moxifloxacin
J01DC02	cefuroxime	**J01RA01**	penicillins, combinations with other antibacterials
J01DC04	cefaclor	**J01XA01**	vancomycin
J01DC06	cefonicid	**J01XA02**	teicoplanin
J01DC08	loracarbef	**J01XX08**	linezolid
		J01XX09	daptomycin

Supplement 2. ICD-10 codes used to identify bacterial complications

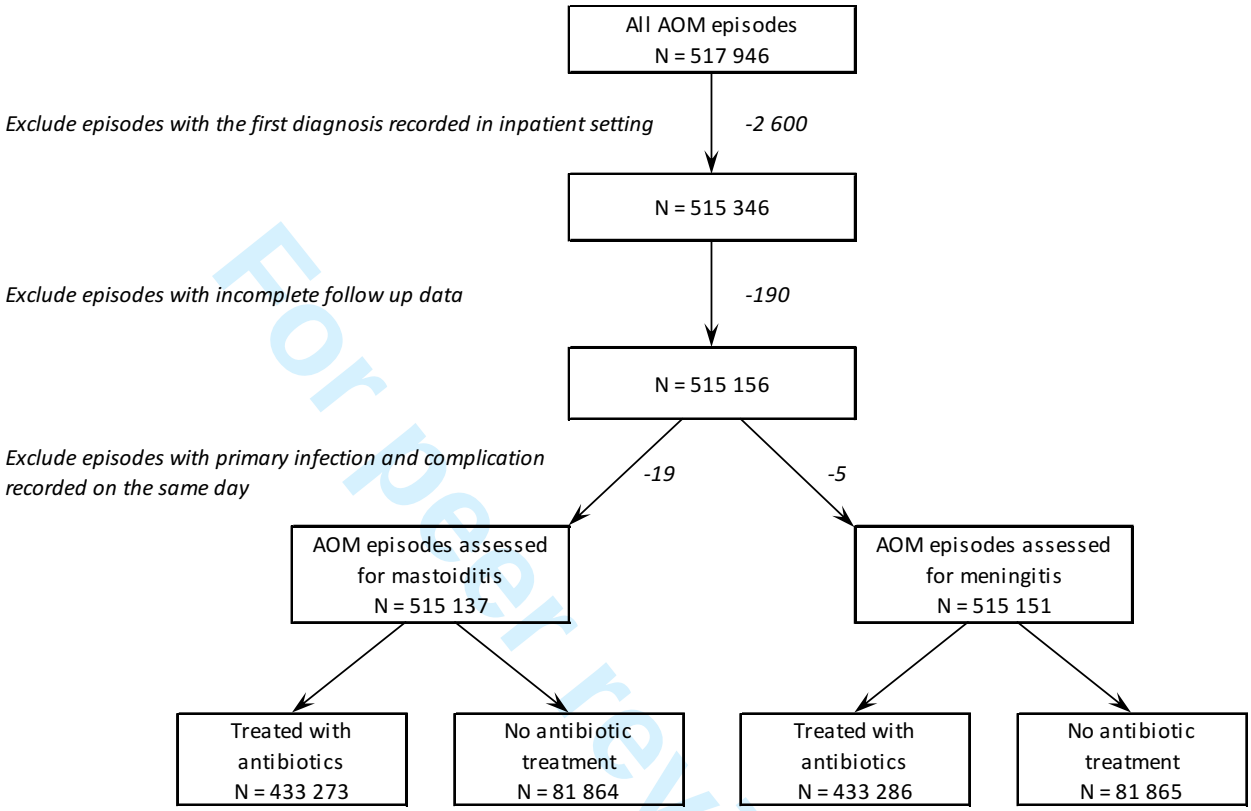
Bacterial complication	ICD-10 code	ICD-10 text
Mastoiditis	H70.0	Acute mastoiditis
	H70.2	Petrositis
	H70.9	Mastoiditis, unspecified
Meningitis	G00.0	Haemophilus meningitis
	G00.1	Pneumococcal meningitis
	G00.2	Streptococcal meningitis
	G00.3	Staphylococcal meningitis
	G00.9	Bacterial meningitis, unspecified
Peritonsillar abscess	J36	Peritonsillar abscess
Retropharyngeal and parapharyngeal abscess	J39.0	Retropharyngeal and parapharyngeal abscess
Invasive group A streptococcal disease	A40.0	Sepsis due to streptococcus, group A
	A40.9	Streptococcal sepsis, unspecified
	M72.6	Necrotizing fasciitis
Pansinusitis	J01.4	Acute pansinusitis
Orbital abscess	H05.0	Acute inflammation of orbit
Extra- and subdural abscess	G06.2	Extradural and subdural abscess, unspecified
Acute ethmoidal sinusitis	J01.2	Acute ethmoidal sinusitis

Supplement 3. ICD-10 codes used to identify primary URTIs

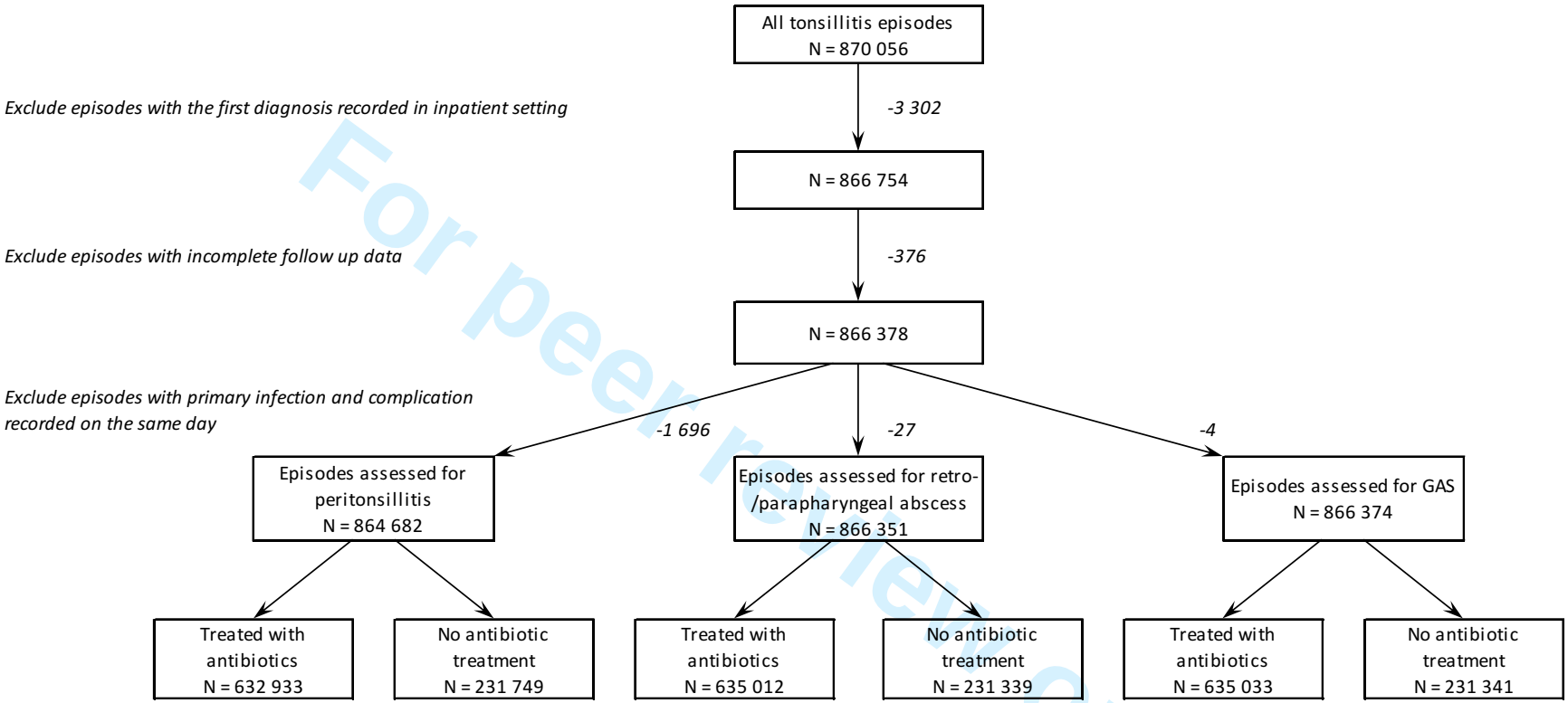
Primary URTIs	ICD-10 code	ICD-10 text
Acute otitis media	H66.0	Acute suppurative otitis media
	H66.9	Otitis media, unspecified
Tonsillitis	J02	Acute pharyngitis
	J03	Acute tonsillitis
Sinusitis	J01.0	Acute maxillary sinusitis
	J01.9	Acute sinusitis, unspecified
	J01	Acute sinusitis (for primary care records only)
Sinusitis and acute upper respiratory tract infections of multiple and unspecified sites	J01.0	Acute maxillary sinusitis
	J01.9	Acute sinusitis, unspecified
	J01	Acute sinusitis (for primary care records only)
	J06.0	Acute laryngopharyngitis
	J06.9	Acute upper respiratory infection, unspecified
	J06	Acute upper respiratory infections of multiple and unspecified sites (for primary care records only)

Supplement 4. Cohort selection flow-chart

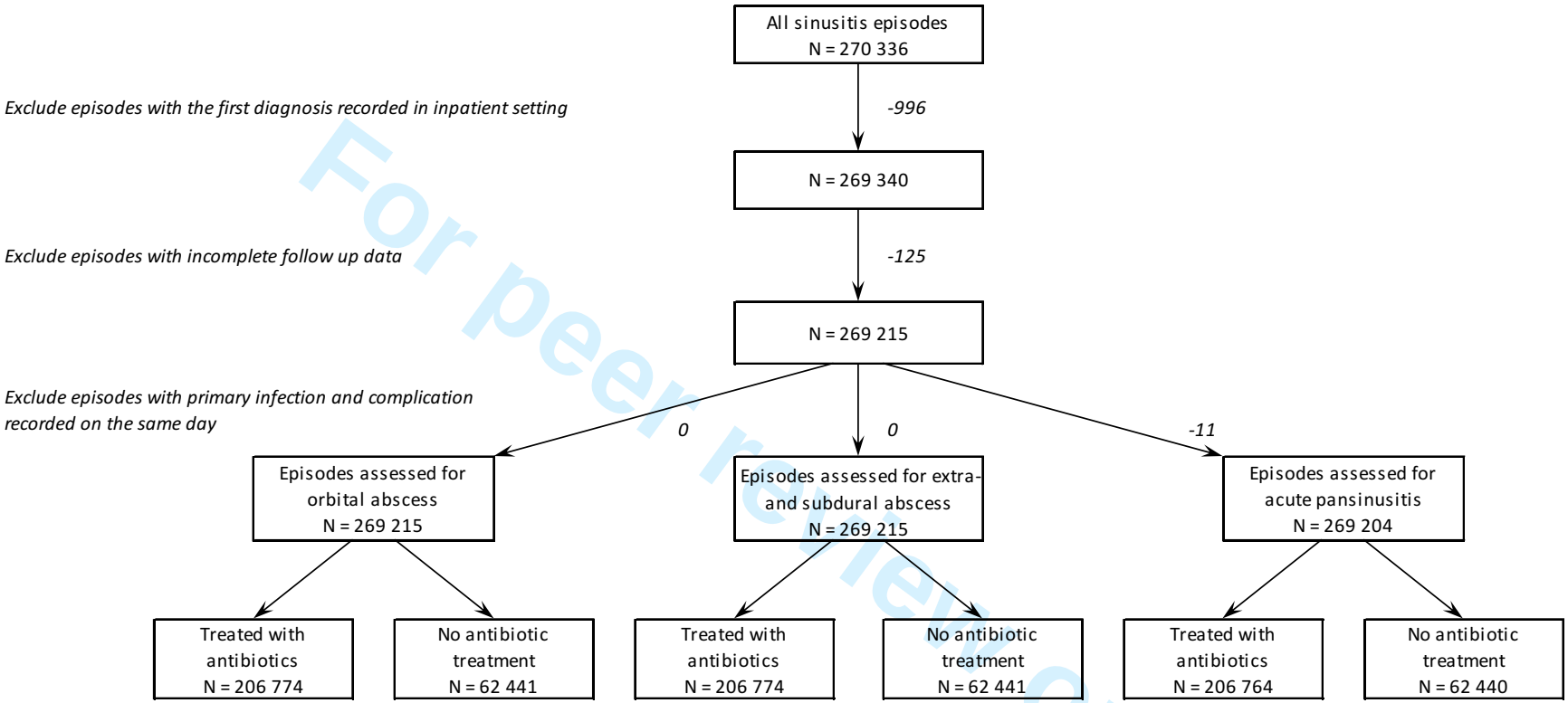
1. Acute otitis media (AOM) cohort



2. Tonsillitis cohort



3. Acute sinusitis cohort



4. Acute sinusitis / acute upper respiratory tract infections of multiple and unspecified sites cohort