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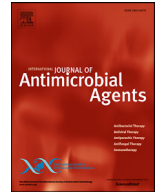
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Outpatient antibiotic use attributable to viral acute lower respiratory tract infections during the cold season in France, 2010–2017[☆]

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ABSTRACT

Antibiotic stewardship requires clear insight into antibiotic overuse and the syndromes that lead to prescription.

The aim of this study was to estimate the proportion of antibiotic prescriptions attributable to acute lower respiratory tract infections (LRTIs) during the cold season.

Using individual data from the French National Health Insurance (NHI) database, weekly time series were constructed of outpatient antibiotic (beta-lactams and macrolides) prescriptions between January 2010 and December 2017. Time series were also constructed of tenth edition of the International Classification of Diseases (ICD-10) discharge diagnoses from a national network of emergency departments (EDs), stratified by specific syndromes (pneumonia, bronchitis, bronchiolitis and influenza-like illness). The number of outpatient antibiotic prescriptions attributable to these syndromes during the cold season in France was modeled and estimated for the entire population, young children (≤ 5 years) and the elderly (≥ 75 years).

LRTIs accounted for 40% (95% confidence interval [95% CI]: 29, 52) of outpatient antibiotic use during the cold season for the entire population, including 23% (95% CI: 13, 33) and 17% (95% CI: 13, 22) for bacterial and viral infections, respectively. In children and the elderly, viral LRTIs were the reason for 38% (95% CI: 31, 46) and 20% (95% CI: 16, 25) of outpatient antibiotic use, respectively (with bronchiolitis accountable for half of use in young children). In the entire population and in children, respectively, outpatient antibiotic overuse attributable to viral LRTIs was estimated to be 289 (95% CI: 221, 374) and 1588 (95% CI: 1295, 1922) prescriptions per 100 000 inhabitants per week.

These results highlight the major role of viral infections in driving antibiotic prescriptions, particularly in young children.

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Abbreviations: AP, Attributable Proportion; 95% CI, 95% Confidence Interval; ED, Emergency Department; ICD-10, tenth edition of the International Classification of Diseases; ILI, Influenza-Like Illness; LRTI, Lower Respiratory Tract Infection; NHI, National Health Insurance; piw, prescriptions per 100 000 inhabitants per week; SD, Standard Deviation; URTI, Upper Respiratory Tract Infection.

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1. Introduction

Antibiotic overuse and misuse are important drivers of the emergence and dissemination of antibiotic resistance [1–3] and have major public health consequences [4]. Antibacterial resistance is a growing concern despite public health policies and international initiatives to combat this problem [5]. In human medicine, antibiotic prescriptions are mostly administered in ambulatory care, often as treatment for acute respiratory tract infections [6,7].

One of the most concerning aspects of antibiotic use in this field is that antibiotics are still commonly used to treat viral respiratory infections [8,9] despite recommendations and evidence that they neither shorten the course of acute illness nor prevent secondary bacterial infections [7,10].

Reducing inappropriate antibiotic use is therefore essential to reduce both antibiotic resistance and adverse events. However, the fraction of antibiotic use that is inappropriate and amenable to reduction is still unknown [11]. Estimates come from surveys focusing on specific age groups or conditions (e.g., ear infections or acute bronchitis) [12]. A recent evaluation of outpatient oral antibiotic prescriptions and potential overuse among US patients across age groups and diagnoses indicated that acute respiratory conditions accounted for an estimated 110 inappropriate antibiotic prescriptions per 1000 inhabitants annually [13]. Another study of antibiotic prescription rates in febrile children presenting to emergency departments (EDs) across Europe showed that one third of all antibiotic prescriptions were of inappropriate or inconclusive indication [14].

As a large part of antibiotic misuse takes place during seasonal outbreaks of viral acute respiratory infections, estimation of the attributable proportion (AP) of antibiotic prescriptions associated with these infections is crucial. For a given epidemic, the AP is defined as the ratio of the number of prescriptions related to the epidemic to the total number of prescriptions over the epidemic period. Taking into account both the characteristics of the epidemic and its associated risk of drug prescriptions, APs may provide useful estimates of the potential impact of interventions at the national level aimed at reducing antibiotic misuse associated with viral epidemics. Tools for the estimation of APs from time series models have been proposed [15].

In 2017, France ranked third highest on the European chart using defined daily doses per 1000 inhabitants per day as a measure of outpatient antibiotic use, with outpatient prescriptions accounting for more than 90% of overall (community and hospital sector) antibiotic consumption [16]. Of these defined daily doses, 68.4% were associated with a diagnosis of (upper and lower) respiratory tract infection and 82% were beta-lactams and macrolides [17].

The aim of this study was to estimate the proportion of outpatient antibiotic use attributable to viral acute lower respiratory tract infections (LRTIs), based on French data and focusing on beta-lactams and macrolides. The study also focused on the two age groups most exposed to antibiotics: young children (≤ 5 years) and elderly patients (≥ 75 years).

2. Material and Methods

2.1. Data sources

2.1.1. Outpatient antibiotic prescriptions

The French National Health Insurance (NHI) program covers all medical care provided by outpatient and private-practice physicians and pharmacies. Individual data were used from the three main NHI agencies that cover salaried workers and self-employed individuals. These agencies cover over 95% of the urban and rural populations of metropolitan France (which excludes overseas French territories, and accounts for 83% of French territory and 96% of its population). Each individual file contains drug-related information, the prescription date, and the patient's sex, year of birth, and region of residence. Given the distribution of antibiotic classes used in the community for LRTIs, the study was restricted to beta-lactams and macrolides (anatomical therapeutic chemical class J01C, J01D, J01F). Aggregate data were used on antibiotics prescribed, filled and reimbursed to outpatients between 2010 and 2017.

To take into account the growth of the French population during the study period, demographic data were obtained from the French National Institute for Statistics and Economic Studies. The results are presented as weekly antibiotic prescription rates for the entire population in metropolitan France.

2.1.2. Oscour® Network

Santé publique France, the French national agency of public health, is responsible for monitoring the welfare of the population and alerting to epidemiological threats through several surveillance systems, epidemiological or behavioral surveys and medico-administrative databases. Oscour® (*organisation de la surveillance coordonnée des urgences*) is one of these systems and is based on a network of hospital EDs that collects daily individual patient data for syndromic surveillance. In August 2014, approximately 600 EDs were included in the network, accounting for more than 80% of national ED attendances, with coverage ranging from 25% to 100% for individual regions [18]. Several reports detail this network, as well as the assessment of the syndromic surveillance system [19,20].

For each visit to a network ED, the patient's demographic (age, sex), administrative (region of residence) and medical variables are recorded, as well as the main and associated medical diagnoses, encoded according to the tenth edition of the International Classification of Diseases (ICD-10). Using ICD-10 codes, indicators for different syndromic groups are built, including details such as the presumed bacterial or viral etiology of infection.

Five syndromic groups were considered for the present study: four specific groups (bronchiolitis, bronchitis, influenza-like illness [ILI] and pneumonia) and one global group (LRTIs), which includes the four specific groups, plus a few other respiratory infections (details in Table S1). For each group, two time series were constructed (depending on whether the infection was bacterial or viral) by aggregating the number of associated visits each week and, because the inclusion of EDs into the Oscour® surveillance network continued to increase during the study period, dividing by the total number of visits to EDs participating to the network each year and expressed in %.

2.1.3. Analysis by age groups

In addition to the entire population, two age groups were studied that are particularly exposed to respiratory infections and antibiotic use: young children (≤ 5 years) and elderly patients (≥ 75 years). The two data sources were therefore filtered to retrieve weekly outpatient antibiotic prescription rates and diagnosis frequencies after visits to EDs for these two age groups.

2.2. Statistical analysis

2.2.1. Descriptive statistics

Sample means and their standard deviations (SDs) were estimated for antibiotic prescription rates and diagnosis frequencies after visits to EDs. To account for autocorrelation in the data sources, the SDs were corrected using heteroscedasticity and autocorrelation consistent estimators [21].

2.2.2. Statistical models

To identify the contributions of LRTIs to antibiotic use, the number of prescriptions associated with LRTIs was modeled using a linear regression with autocorrelated errors [22], distinguishing between viral and non-viral infections. Two models were considered: M1 was for the contribution of the global syndromic group only, and M2 was for the contributions of the four narrower syndromic groups (bronchiolitis, bronchitis, ILI and pneumonia), but only in children aged ≤ 5 years, and elderly people aged ≥ 75 years. For more details, see the Supplementary Text.

Both models were estimated by maximum likelihood using function *arima* from R software version 3.5.1 [23]. For each model, the independence of the residual series and its Gaussian distribution were tested.

2.2.3. Estimation of APs

The fraction of antibiotic prescriptions attributable to each syndromic group included in the model was estimated from the estimates for each model (Supplementary Text). To be able to compare the contributions of the different LRTIs, which have overlapping epidemic periods in winter that do not necessarily coincide, the attributable fractions were calculated over the entire cold season (October to March inclusive).

3. Results

3.1. Descriptive analysis

3.1.1. Outpatient antibiotic prescriptions

Three series of outpatient antibiotic prescriptions were considered between January 2010 and December 2017, one for the entire population and one for each age group selected (Figure 1). All three series displayed a strong seasonality, with higher rates of antibiotic prescriptions during the cold season. For both the entire population and young children, antibiotic use exhibited a seasonal pattern with five peaks per year: in October, December, late January/early February, late March/early April and early June. In the elderly, antibiotic use also exhibited a seasonal pattern, with a single peak repeating every year, in early January.

In the entire population, overall outpatient antibiotic use averaged 1415 prescriptions per 100 000 inhabitants per week (piw) over the 8-year study period; with an average of 1524 piw and 3268 piw in the elderly and young children, respectively. Considering only the data during the cold season, outpatient antibiotic use was estimated at 1701 piw in the entire population, 1822 piw in the elderly and 4178 piw in young children.

3.1.2. Visits to EDs related to LRTIs

According to the ICD-10 codes reported in the surveillance system, bronchitis was deemed viral in 99% of the associated visits during the study period, whereas pneumonia was considered of presumed bacterial etiology in 98% of the associated visits. Consequently, bacterial bronchitis and viral pneumonia were not taken into account in the statistical analysis of specific infections.

The series of diagnosis frequencies after a visit to EDs were considered for the entire population for both viral and non-viral LRTI global indicators. For young children and the elderly, the series were considered for both global indicators, as well as for pneumonia, bronchitis, and ILI, and for bronchiolitis in young children. All these series exhibited seasonality, with higher frequency of visits during the cold season. In young children, the peaks associated with bronchiolitis outbreak preceded those associated with ILI. Of note, the second peak in antibiotic use for young children was strongly associated with the bronchiolitis outbreak, with a correlation coefficient of 0.79 (95% confidence interval [95% CI]: 0.75, 0.82) between the two series, whereas ILI was only weakly associated with the third peak, with a correlation coefficient of 0.36 (95% CI: 0.27, 0.44).

For the entire population, LRTIs represented an average of 4.07% of weekly ED visits during the cold season, with pneumonia accounting for 41% of those, and bronchiolitis, bronchitis, and ILI for 22%, 21%, and 15%, respectively (Table 1). In young children, the ED network reported that viral infections were 3.6 times more frequent than in the general population, with bronchiolitis contributing to 68% of these visits. Conversely, bacterial infections were 3.4 times more frequent in the elderly than in the entire population.

Table 1

Weekly Average Outpatient Antibiotic Prescription Rates (per 100 000 Inhabitants) and Diagnosis Frequency (in Percent) After Visits to Emergency Departments During the Cold Season, Metropolitan France, 2010-2017.

	All ages	≤5 years	≥75 years
Outpatient antibiotic prescriptions, Meanⁱ (SD)			
	1701 (35.8)	4178 (115.4)	1822 (54.2)
Proportion of emergency department visits related to LRTIs, Meanⁱⁱ (SD)			
<u>Non-viral LRTIs</u>			
All infections	1.74 (0.03)	1.54 (0.03)	5.84 (0.14)
Pneumonia	1.66 (0.03)	1.53 (0.03)	5.45 (0.14)
<u>Viral LRTIs</u>			
All infections	2.33 (0.07)	8.37 (0.16)	1.79 (0.10)
Bronchiolitis	0.88 (0.04)	5.71 (0.20)	0.03 (0.00)
Bronchitis	0.86 (0.02)	1.33 (0.03)	1.55 (0.07)
Influenza-like illness	0.60 (0.06)	1.39 (0.15)	0.18 (0.03)

LRTI, lower respiratory tract infection; SD, standard deviation

ⁱ per 100 000 inhabitants per week (NHI data)

ⁱⁱ in percent per week (OSCOUR® network data)

Table 2

Average Contribution (in Percent) [95% Confidence Intervals in Brackets] of Lower Respiratory Tract Infections to Outpatient Antibiotic Use During the Cold Season, Metropolitan France, 2010-2017.

	All ages	≤5 years	≥75 years
<u>Non-viral LRTIs</u>			
All infections	23 [13, 33]	26 [20, 32]	36 [24, 47]
Pneumonia		25 [19, 32]	38 [26, 50]
<u>Viral LRTIs</u>			
All infections	17 [13, 22]	38 [31, 46]	20 [16, 25]
Bronchiolitis		19 [13, 26]	
Bronchitis		14 [07, 21]	17 [10, 24]
Influenza-like illness		07 [05, 09]	02 [01, 03]

LRTI, lower respiratory tract infection

3.2. Statistical models

A model fulfilling goodness-of-fit criteria was obtained for each series (Figures S1 and S2). Parameter estimates are reported in Table S2. The model fit is satisfactory, and almost identical for models M1 and M2 (Figure S3).

3.3. Attributable proportions

The estimated average contribution of bacterial or viral LRTIs to outpatient antibiotic use per 1000 inhabitants during the cold season from 2010 to 2017 is reported in Table 2 for young children and the elderly.

During the cold season, LRTIs accounted for 40% (95% CI: 29, 52) of outpatient antibiotic use in the entire population, with 23% (95% CI: 13, 33) and 17% (95% CI: 13, 22) attributed to bacterial and viral infections, respectively. In young children, the contribution from bacterial infections was comparable (26%), but viral infections accounted for 38% (95% CI: 31, 46), with bronchiolitis as the main cause, associated with 19% (95% CI: 13, 26) attributable antibiotic use. In the elderly, the contribution from viral infections was comparable to that of the entire population, but bacterial infections accounted for 36% (95% CI: 24, 47) of antibiotic use. The difference in the contribution of viral infections between young children and the elderly stems mainly from bronchiolitis affecting young children but not adults.

Over the seven cold seasons from 2010 to 2017, the APs of LRTIs were essentially stable (Figure 2). ILI was the main cause of variation in APs for young children, contributing between 5% and 10% of antibiotic use in this age group, but was negligible at the level of the entire population.

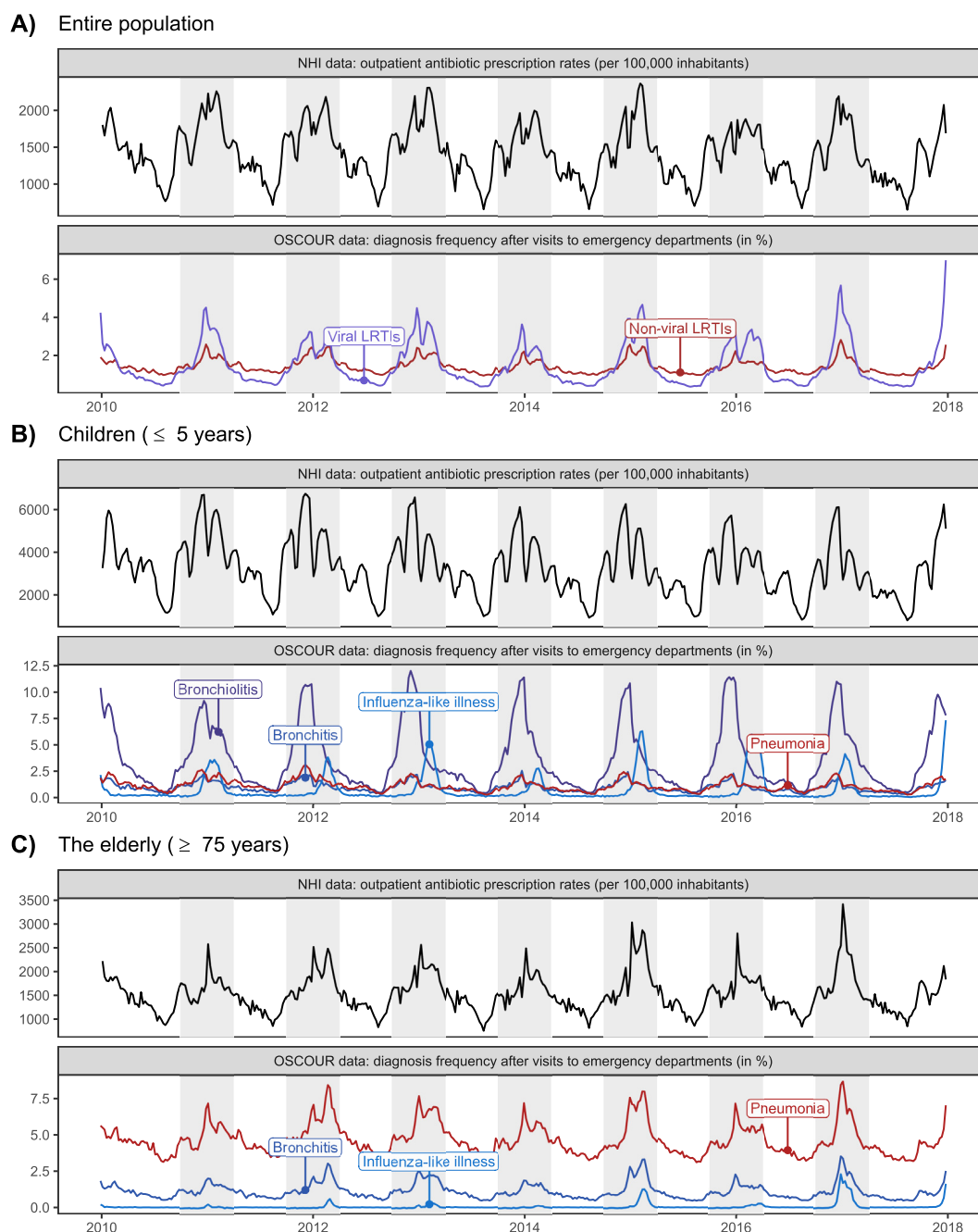


Figure 1. Weekly Outpatient Antibiotic Prescriptions and Visits to Emergency Departments, Metropolitan France, 2010-2017.

Grey intervals correspond to the cold season (October to March). A) For the entire population. B) For young children (≤ 5 years). C) For elderly people (≥ 75 years).

4. Discussion

Antibiotic misuse and overuse are of increasing global concern. Increased understanding about how and why antibiotics are prescribed will help to identify potential methods to reduce their misuse. Estimating the proportion of antibiotic use that can be attributed to misuse is a first step in this process. The results of this study indicate that during the cold season, LRTIs accounted for 40% of overall antibiotic use in the entire population, and up to 56% and 64% for the elderly and young children, respectively. Specifically, viral LRTIs, most notably bronchiolitis, accounted for 38% of antibiotic use in young children.

Estimating the appropriateness of antibiotic prescriptions remains challenging. Although the use of antibiotics in the case

of suspected bacterial pneumonia is accepted by medical professionals, their use is still not clear against viral respiratory infections. Some experts consider antibiotic use to be inappropriate for all viral infections [13]; however, prescription guidelines and expert opinions may suggest their use in some specific cases [24,25], possibly reflecting an ambiguous clinical presentation. Antibiotics may be prescribed in an estimated 10% to 20% of patients without comorbidities presenting with acute respiratory tract infection [24]. In the case of LRTIs, previous studies have shown that overprescription accounted for up to 50% of the prescriptions [9,26], with two of the main reasons cited being the patient was within the active age group (18-65 years) and the physician's perception of high patient expectation for antibiotics [26,27].

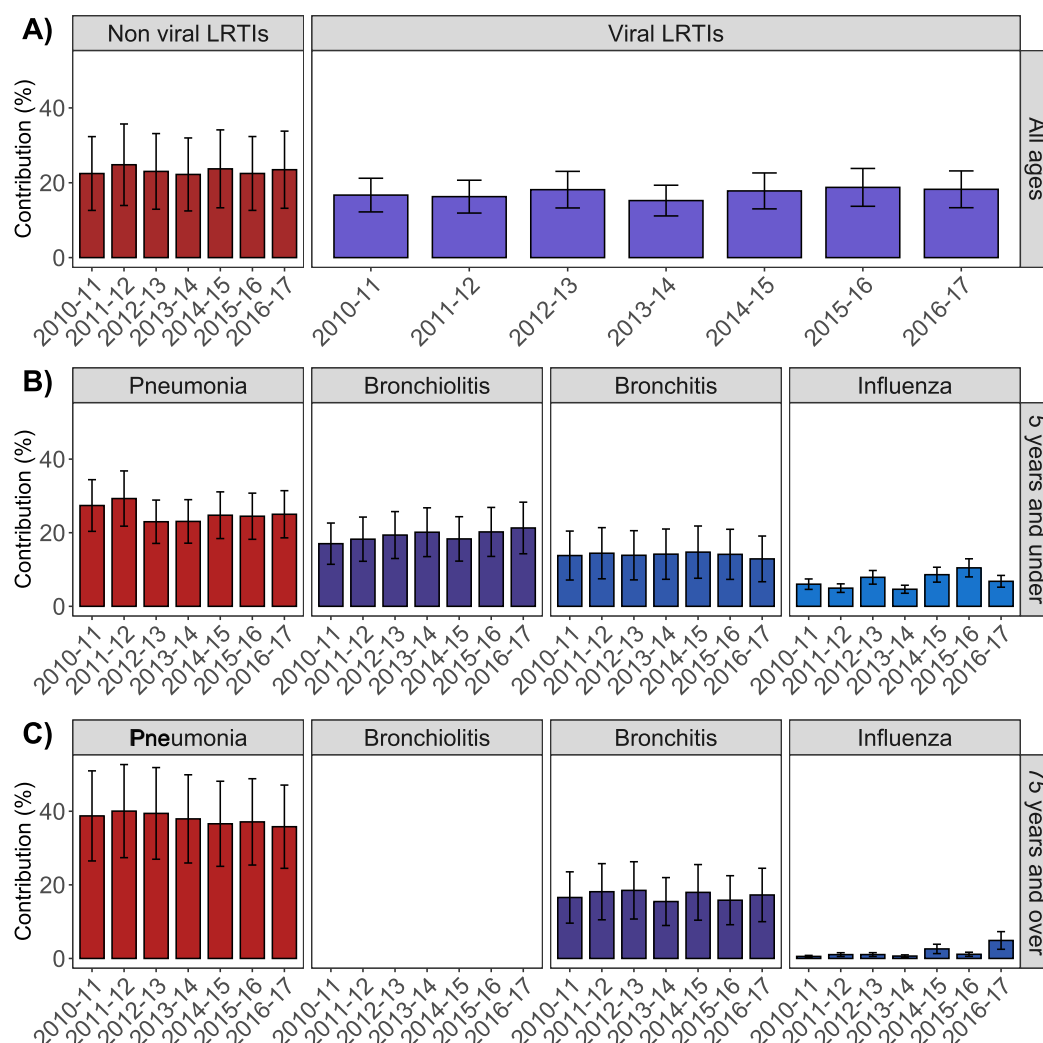


Figure 2. Contribution of Lower Respiratory Tract Infections to Outpatient Antibiotic Prescriptions During the Cold Seasons (in Percent), Metropolitan France, 2010-2017. A) For the entire population. B) For young children (≤ 5 years). C) For elderly people (≥ 75 years).

Two models were used to estimate the AP in each population studied: one used the LRTI global indicator as covariate; the other used the four narrower, but strongly correlated, syndromic groups as covariates. These models yielded similar estimations of the attributable proportions, thereby strengthening the current study results and their interpretation.

Attributable proportions for LRTIs and each LRTI subgroup were estimated over the whole 26-week period of the cold season, which is expected to include the epidemic periods for viral infections. However, some APs may appear underestimated, particularly ILI, the epidemic periods of which vary from 6 to 14 weeks and may overlap with the hot season. Indeed, APs for ILI were estimated to be 10% to 20% during epidemics in the entire population between 2005 and 2010 [15].

Unfortunately, ideal prescription versus overprescription is difficult to compare using nationwide aggregated data, such as those used in this study, as there is no clinical information associated with individual prescriptions. However, in the most conservative case, where only 50% of prescriptions for viral LRTIs are deemed inappropriate [26], overprescription of antibiotics in LRTIs during the cold season would then be estimated at 8.5% of total antibiotic use (145 piw) for the entire population and 19% (794 piw) for young children. In the least conservative case, where all prescrip-

tions given for viral infections are considered inappropriate [13], overprescription for viral LRTIs would reach 17% (289 piw), and 38% (1588 piw) during the cold season in the entire population and in young children, respectively. These results are in line with those of Fleming-Dutra et al. in the US, who reported 110 inappropriate prescriptions per 1000 inhabitants per year attributable to acute respiratory conditions in the entire population, corresponding to 212 piw [13], and concordant with those of Hagedoorn et al. in children across Europe, who found that one third of all antibiotic prescriptions were of inappropriate or inconclusive indication [14].

4.1. Limitations of the study

An important consideration when assessing the appropriateness of an antibiotic prescription for respiratory tract infection is determining both its syndromic group and its bacterial or viral etiology. In this study, this was established according to the ICD-10 code of the main medical diagnosis recorded during a patient's visit to the ED. Henriksen et al. [28] showed that the sensitivity and positive predictive value of ICD-10 discharge diagnoses in a medical ED were moderate for the lower respiratory tract (70.6% and 71.1%, respectively), specifically more so when pneumonia was not pooled with other LRTIs. To our knowledge, no study has assessed the va-

lidity of ICD-10 discharge diagnoses regarding the bacterial or viral etiology of respiratory infections in EDs. However, it is probable that the pneumonia ICD-10 codes do not correctly reflect microbial etiology as there is increasing evidence that an important proportion of pneumonia has viral etiology, particularly in the outpatient setting [29,30], contrasting with Oscour® surveillance data, which indicate 98% were bacterial. On the other hand, there is also evidence that some episodes of acute bronchitis are likely to be of bacterial etiology [31], diverging from 99% of them being classified as viral by EDs.

Another important consideration is whether visits to EDs correctly reflect the epidemiology of infections in the general population. In the current model of the number of outpatient antibiotic prescriptions using ED attendance, the latter was assumed to be a good indicator of the health events in the community. Although the network Oscour® was originally built to answer the need to detect public health threats, studies [19,20,32] show it was sensitive enough to enable evaluation of the health impact of both environmental conditions and infectious diseases, notably by comparing it to data from the sentinel network of general practitioners, which is the reference surveillance system for influenza in France [33].

Although upper respiratory tract infections (URTIs) contribute substantially to outpatient antibiotic use, they were not considered in the current study because they are mostly managed in primary care; therefore, ED attendance seems to accurately reflect outbreaks of LRTIs, but not URTIs, in the community. This exclusion does not change the implications of the current study, as shown by the large amount of inappropriate prescriptions attributable to LRTIs. The figures estimated in this study would be higher if URTIs were taken into account, as previously shown [34].

5. Conclusion

Using nationwide aggregated data from both ED attendance and the NHI database, viral acute LRTIs were shown to be important drivers of outpatient antibiotic overuse. Specifically, they would account for up to 17%, or 289 prescriptions piw, of overall outpatient antibiotic use in the general population during the cold season, and for up to 38%, or 1588 prescriptions piw, in children under 5 years.

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Declarations

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Competing Interests: LW has received consulting fees from IQVIA and Pfizer for works outside the submitted work. LO received research funding from Pfizer through her institution to carry out unrelated research on meningococcus. LO received consulting fees from the World Health Organization. The other authors declare that they have no competing interests.

Ethical Approval: Not required

Authors' contributions. DG and LW designed the study. CCS and IP collected and aggregated the ICD-10 discharge diagnosis datasets from the Oscour® surveillance network. LLF extracted and aggregated the outpatient antibiotic prescription dataset from the National Health Insurance database. FC analysed and interpreted the data and drafted the manuscript. CBB, LO, DG and LW made substantial contributions to the interpretation of the data. FC, CBB and LW substantively revised the manuscript. All authors read and approved the final manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:[10.1016/j.ijantimicag.2021.106339](https://doi.org/10.1016/j.ijantimicag.2021.106339).

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