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2 PRESENCE OF CHRONIC DISEASES AND COMPLIANCE WITH QUÉBEC PROVINCIAL GUIDELINES FOR
3
4 OUTPATIENT ANTIBIOTIC PRESCRIPTION IN CASES OF RESPIRATORY INFECTIONS, AN OPEN COHORT STUDY IN
5
6 QUÉBEC, CANADA, 2010-2017
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Abstract

Objectives. In Québec, antibiotic use is higher in outpatients with chronic diseases, but it is unclear whether it may be improved. We aimed to measure the proportion of prescriptions compliant with provincial guidelines for the treatment of common respiratory infections and measure variations in this proportion with certain chronic diseases.

Methods. Antibiotic dispensing covered by the public drug insurance plan between April 2010 and March 2017, delivered within 2 days of an outpatient consultation for an infection was included. Infections targeted by provincial guidelines were studied: bronchitis in patients with chronic obstructive pulmonary disease, otitis media, pharyngitis, pneumonia and sinusitis. Proportions of prescriptions compliant with guidelines (antibiotic choice for children, and antibiotic choice and dosage for adults) were computed by age (children or adults) and chronic disease (respiratory, cardiovascular, diabetes, mental disorder, none of previous). The impact of chronic diseases on compliance was measured using robust Poisson regression.

Results. Between 14,677 and 198,902 prescriptions were included, for each infection. Compliance was above 87% in children, $\leq 3\%$ lower in children with asthma. In adults, the choice of agent was compliant for at least 73% of prescriptions, except for pharyngitis ($\leq 61\%$). Accounting for dosage lowered compliance (between 31% and 61%). Compliant prescriptions were 2% to 6% less frequent in the presence of chronic diseases.

Conclusions. Non-compliant prescriptions could sometimes be appropriate, but their high frequency suggests room for improvement. Because variations associated with chronic diseases were small, disease-specific guidelines for antibiotic prescriptions are likely to have a limited impact on compliance.

Keywords: surveillance; public health; antimicrobial use; chronic diseases

Introduction

Antimicrobial resistance is of concern to public health authorities worldwide (1–5). As the frequency of multidrug resistant bacteria increases, with very few new antimicrobials developed, therapeutic options become more limited. This has led the World Health Organization to place antimicrobial resistance among its top ten list of global health issues(6). Antimicrobial use, especially inappropriate use, is the main modifiable determinant of resistance, because of how it selects resistant strains. While utilization is more intense in hospitals, most antimicrobial prescriptions arise in the community(7). In Québec, hospitals are expected to have an antimicrobial stewardship program(8,9), however, in the community, the main tools to support adequate use of antimicrobials are the provincial clinical guidelines developed by the Institut national d'excellence en santé et services sociaux (INESSS) for the treatment of the most common infections(10).

Quebec's rates of antimicrobial use in the community are among the lowest in Canada and compare advantageously to those of a majority of European countries(7,11). It is unclear whether this utilization may be further reduced, however, we have observed higher rates of antibiotic use in outpatients with chronic diseases than in patients without these diseases (manuscript currently submitted to CMAJ Open). As this might be an opportunity for intervention, we aimed to measure the proportion of antibiotic prescriptions compliant with provincial guidelines for the treatment of common respiratory infections, and to quantify variations in this proportion in the presence of certain chronic diseases.

Methods

Study design and population

This was a retrospective study of antibiotic prescriptions delivered to individuals covered by the province of Quebec's public drug insurance plan between April 1st, 2010 and March 31st, 2017, and who had consulted a physician in a primary care medical service in the previous two days for a common respiratory infection. We used this very short delay between medical visits and antibiotic delivery to minimize the risk of imputing the wrong treatment indication if antibiotics were actually prescribed for another indication that was not reported.

1 Only antibacterials for systemic use (class J01 of the ATC classification system) were included in the study(12).
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4 Ten open cohorts were created, i.e. one cohort for each age group (children and adults) and infection: otitis
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6 media (only children), chronic obstructive pulmonary disease (COPD) exacerbations and bronchitis (only adults
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8 with COPD), pharyngitis, pneumonia, sinusitis, and upper respiratory tract infections (URTI). Medical visits
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10 occurring less than 90 days after a visit for a similar infection were excluded. URTI were excluded when a
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12 medical visit for a bacterial infection had also occurred in the previous or following week. The 2009 guidelines
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14 were applicable for most of the study period and although many new guidelines were issued in 2016, as we
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16 assumed that the uptake was not immediate, only 2009 guidelines are used as reference in the analysis.
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19 *Data sources and variables*

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22 The Québec Integrated Chronic Disease Surveillance System (QICDSS) links information from five
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24 administrative health databases: the health insurance registry, hospital discharges, vital statistics death registry,
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26 physician claims, and pharmaceutical services(13). We used data from the QICDSS to identify individuals
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28 covered by the public drug insurance plan and their medical visits for respiratory infections (based on the 9th
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30 edition of the International Classification of Diseases, see detailed codes in Table 1), antibiotic prescriptions
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32 delivered to these individuals (antibiotic chosen and, for oral prescriptions delivered to adults, the total dosage),
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34 and individuals with chronic diseases. Chronic diseases were grouped into five categories: chronic respiratory
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36 diseases (asthma or COPD), diabetes, cardiovascular diseases (hypertension, heart failure and ischemic heart
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38 disease), mental disorders (for instance, attention deficit disorder, schizophrenia, anxiety disorders or
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40 Alzheimer's disease) and none of these chronic diseases. Other variables collected were year of prescription
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42 (financial years starting in April and ending in March), patient's age group (1-4, 5-9, 10-17, 18-29, 30-39, 40-49,
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44 50-64, 65-69, 70-79 and 80 years old or over), sex, geographical zone (four category-gradient from urban to
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46 rural) and quintiles of social and material deprivation indexes. The use of QICDSS for surveillance purposes has
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48 been approved by the government bodies, the Public Health Ethics Committee and the *Commission d'accès à*
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50 *l'information du Québec*.
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2 For prescriptions following a visit for a respiratory infection, compliance with INESSS' 2009 clinical guidelines
3 was assessed based on the type of infection, the antibiotic prescribed and, for adults only, the total dosage
4 delivered at the pharmacy(10). The total dosage had to be within the minimal and maximal limits recommended
5 in the guidelines. In the case of URTI, which is usually viral and for which no antibiotic prescription is
6 recommended and therefore no provincial guideline exists, any antibiotic prescription was considered discordant
7 with recommendations; this is why medical visits for URTI were excluded when a visit for a bacterial infection
8 was also reported in the same week, in order to minimize the risk of imputing the wrong treatment indication.
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10 11 12 13 14 15 16 17 18 *Statistical analyses*

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20 The impact of the presence of chronic diseases on the proportion of compliant prescriptions was measured using
21 robust Poisson regression, while adjusting for year, age group, sex, geographical zone and quintiles of
22 deprivation. Generalized estimating equations were used to account for correlation between prescriptions for a
23 given patient or issued by the same prescriber. A separate analysis was performed for each of the ten cohorts.
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30 **Results**

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33 Between April 2010 and March 2017, a total of 424,148 prescriptions were delivered to children covered by the
34 public drug insurance plan for either otitis, pharyngitis, pneumonia, sinusitis or URTI. These prescriptions are
35 described in Table 2. Prescribed antibiotics were usually among the recommended options, as compliance was at
36 least 87% for all infections and categories of chronic diseases. Of note, in the treatment of otitis media,
37 clarithromycin, azithromycin or cefprozil were used in 32% of cases, despite being recommended only in case of
38 an allergy to penicillin. The presence of asthma was always associated with a lower compliance, however, this
39 variation was small (3% less compliant at most, for the treatment of sinusitis in patients with a respiratory
40 disease). A total of 70,064 antibiotic prescriptions delivered for a URTI were identified.
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51 A total of 697,543 prescriptions were delivered to adults covered by the public drug insurance plan for either
52 COPD exacerbation or bronchitis, pharyngitis, pneumonia, sinusitis or URTI (described in Table 3). Throughout
53 the study period, 175,107 prescriptions following a medical visit for a URTI were found. In patients with none of
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1 the studied chronic diseases, the antibiotic choice was compliant with guidelines in 64% of prescriptions for a
2 pharyngitis, 84% of prescriptions for pneumonia and 86% of prescriptions for sinusitis. The lower compliance
3 for pharyngitis was due to the frequent use of amoxicillin, which was not recommended until the 2016
4 guidelines, but was prescribed in 24% of cases nonetheless. Compliance was excellent for patients with COPD
5 exacerbations and bronchitis, at 95%. For all infections, when accounting for the total dose served to patients,
6 compliance decreased markedly, and more importantly in cases of more severe infections (COPD exacerbations
7 [33%] and pneumonia [40%]). In the presence of chronic diseases, compliance was reduced by 6% at most. The
8 majority of non-compliant dosages were higher than what was recommended in the guides (up to 59% of
9 prescriptions against COPD exacerbations and bronchitis for which the chosen antibiotic was compliant), except
10 for the treatment of pneumonia, for which dosages were too low or too high in similar proportions.
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24 **Interpretation**

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27 Between April 2010 and March 2017, antibiotic prescriptions issued to individuals covered by the public drug
28 insurance plan were compliant (recommended antibiotic) with provincial guidelines at least 87% of the time in
29 children, but much less frequently in adults, reaching a low of 53% for the choice of antibiotic for pharyngitis in
30 individuals with diabetes. Compliance was lower when dosage was accounted for, varying between 31% and
31 61% depending on the infection and the presence of certain chronic diseases. Most discordant dosages were
32 higher than recommended. Chronic diseases were systematically associated with lower compliance in both
33 children and adults, but more in adults, for whom dosage was also considered. The lower compliance associated
34 with chronic diseases was however very limited (relative reduction of 6% at most), revealing that the global low
35 compliance levels in adults are not driven by prescribing for patients with chronic diseases.
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48 A higher risk of exposure to inappropriate antibiotic use in the presence of certain chronic diseases has also been
49 observed in a British study(14). In children, a Charlson index of 3 or 4 was associated with more inappropriate
50 use (odds ratio = 1.34), while in adults, the presence of comorbidities increased the odds of inappropriate
51 prescriptions against URTI, lower respiratory tract infections and sinusitis (odds ratios of 1.20, 1.19 and 1.12,
52 respectively). As inappropriate use is relatively frequent, the odds ratios are not equivalent to our proportion
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1 ratios presented in Tables 2 and 3, but the associations remain. Also, the QICDSS uses sensitive algorithms to
2 identify chronic diseases without distinguishing between early and advanced stages, which might lead to lower
3 associations between chronic diseases and antibiotic use. For instance, based on our data, mental disorders
4 appear quite frequent in children, but the definition includes attention deficit disorders, which is very different
5 from adults' Alzheimer's disease in terms of medication and vulnerability. The need to add an antibiotic to
6 regular medication taken for the management of a chronic illness may make the choice of antibiotic more
7 challenging, given the risk of drug interactions; this complexity is likely to increase with the number of
8 diseases(15). Indeed, in another study on the treatment of urinary tract infections, the cumulation of chronic
9 diseases in an individual increased the risk of receiving a non-compliant prescription by up to 12% for patients
10 with four chronic conditions(16). In these cases, not following guidelines can be the appropriate line of conduct
11 to prevent drug interactions, but resources should be available to support primary care physicians.

27 With our methodology, we do not know whether non-compliance was appropriate or justifiable, especially as
28 chronic diseases seem to explain only a small fraction of discordances. We have not looked at the potential
29 impact of obesity, which could explain at least some of the excessive dosages given the high prevalence of
30 obesity in Québec (25% of the adult population in 2018)(17). The absence of a reliable treatment duration in our
31 data sources makes it impossible to identify suboptimal doses for long treatment durations or large doses given
32 over a short period, for example. From an antimicrobial resistance point of view, suboptimal doses and longer
33 treatment durations are more problematic as they could lead more efficiently to selection of resistant
34 strains(18,19). This would have to be investigated with another methodology. Also, non-recommended
35 antibiotics were frequently prescribed (especially in adults), which is less understandable than a non-compliant
36 dosage. The probability of selecting one of the recommended agents was proportional to the number of
37 antibiotics recommended in the guidelines for a given condition (five for pharyngitis treatment versus ten for
38 bronchitis and COPD exacerbations treatment, with sinusitis and pneumonia in the middle(10)). In the specific
39 case of pharyngitis, however, practices might have been influenced by American guidelines, which include
40 amoxicillin since 1997(20,21). Important levels of inappropriate use are reported in the literature, according to
41 different methodologies(22–24). Also, a Québec study similar to ours reported that the proportion of viral

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2 respiratory infections treated with antibiotics varied between 22% and 43% depending on the infection; two
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4 decades later, we still found thousands of antibiotic prescriptions against URTI (24). We thus believe that our
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6 measures, even if imperfect, remain meaningful.
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10 *Limitations*

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12 In addition to measurement issues discussed above, certain limitations must be considered while interpreting our
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14 results. Individuals covered by the public drug insurance plan are older and poorer than the provincial average
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16 due to eligibility criteria(25). It seems unlikely that this would bias the association we found between chronic
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18 diseases and compliant use because recommended antibiotics are basic medication covered regardless of
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20 insurance plans and the province offers universal access to health care to all its citizens. Our regressions
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22 adjusting for age and deprivation indexes gave results rather similar to bivariate regressions, suggesting little
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24 impact on our results. Also, we measured compliance with guidelines when a diagnosis was available, but we
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26 were unable to determine if antibiotics were necessary in the treatment of infections. High proportions of
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28 infections treated with antibiotics are sometimes used as a signal of overuse, however, diagnostic codes are not
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30 mandatory in medical claims and we could not assume that we had all infections, especially as untreated
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32 infections might be coded less frequently. Indeed, a previous study reported good validity of diagnostic codes for
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34 acute respiratory infections in Québec's medical claims database, but a sensitivity below 50%(26). Finally, the
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36 association between chronic diseases and non-compliant use could be overestimated if diagnostic codes related
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38 to chronic diseases were reported preferentially over codes for minor infections. Another study reported less
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40 influenza-like illnesses in patients with chronic diseases, who nonetheless received more antibiotics(27). We did
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42 not observe this trend in our data: data preparation for this project rather showed more infections per patient in
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44 presence of chronic diseases.
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48 *Conclusion*

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50 Individuals with chronic diseases are slightly more exposed to antibiotic prescriptions that are not compliant
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52 with provincial clinical guidelines and they also use more antimicrobials than the rest of the population. It is not
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54 possible with our methodology to determine whether discordance is actually appropriate or not but, the high
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56 frequency of non-compliant prescriptions in general suggests that there is room for improvement. Circumstances
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2 justifying a derogation to guidelines for primary care should be investigated. Further work should focus on
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4 comorbidities that were not studied here and could explain extreme dosages, such as obesity and kidney failure.
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Table 1. Diagnostic codes used to identify infections targeted by provincial clinical guides.

Infection	ICD-9 diagnostic codes
Bronchitis and chronic obstructive pulmonary disease exacerbation	466 466.0 466.1 466.2 466.3 466.4 466.6 466.7 466.9 490 490.0 490.1 490.2 490.6 490.9
Otitis media	382 382.0 382.1 382.2 382.3 382.4 382.7 382.9
Pharyngitis	340 341 462 462.0 462.1 462.4 462.9 463 463.0 463.2 463.8 463.9
Pneumonia	481 481.0 481.1 481.9 482 482.9 485 485.0 485.9 486 486.0 486.4 486.5 486.9
Sinusitis	461 461.0 461.1 461.2 461.3 461.4 461.5 461.6 461.8 461.9
Upper respiratory tract infection	464 464.4 464.9 464.0 464.1 464.2 464.7 465 465.0 465.1 465.2 465.3 465.4 465.5 465.6 465.8 465.9

Table 2. Impact of the presence of chronic diseases on compliance of antibiotic prescriptions with provincial clinical guidelines for the treatment of respiratory infections in children, April 2010 to March 2017.

Infection	Category of chronic disease	Prescriptions*	Recommended antibiotic	Proportion ratio*	
		N	%	[95% confidence interval]	
				Unadjusted	Adjusted
Otitis	None of the following	167,066	97.9	ref.	ref.
	Diabetes	265	97.7	1.003 [0.983 ; 1.023]	1.003 [0.984 ; 1.023]
	Mental health disorder	14,995	97.7	0.999 [0.996 ; 1.001]	0.998 [0.995 ; 1.001]
	Respiratory disease	19,300	97.4	0.996 [0.993 ; 0.999]	0.997 [0.994 ; 1.000]
Pharyngitis	None of the following	86,131	90.6	ref.	ref.
	Diabetes	180	89.4	0.995 [0.947 ; 1.046]	0.992 [0.945 ; 1.043]
	Mental health disorder	9,497	88.7	0.984 [0.976 ; 0.991]	0.986 [0.979 ; 0.994]
	Respiratory disease	14,558	88.4	0.978 [0.972 ; 0.985]	0.978 [0.971 ; 0.985]
Pneumonia	None of the following	25,240	90.1	ref.	ref.
	Diabetes	55	87.3	0.965 [0.871 ; 1.069]	0.966 [0.873 ; 1.069]
	Mental health disorder	2,771	89.8	0.996 [0.983 ; 1.009]	0.994 [0.981 ; 1.007]
	Respiratory disease	5,132	88.9	0.981 [0.971 ; 0.992]	0.978 [0.967 ; 0.989]
Sinusitis	None of the following	10,410	93.6	ref.	ref.
	Diabetes	41	97.6	1.054 [1.004 ; 1.108]	1.056 [1.004 ; 1.110]
	Mental health disorder	1,958	92.5	1.000 [0.986 ; 1.014]	0.999 [0.985 ; 1.014]
	Respiratory disease	2,814	90.2	0.964 [0.951 ; 0.977]	0.970 [0.957 ; 0.984]

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*Categories of chronic diseases are not mutually exclusive, so unadjusted proportion ratios are actually adjusted for the other categories of chronic diseases. The adjusted regressions were also adjusted for year, age group, sex, geographical zone and quintiles of deprivation. The total number of prescriptions is not equal to the sum of prescriptions for each chronic disease category.

Table 3. Impact of the presence of chronic diseases on compliance of antibiotic prescriptions with provincial clinical guidelines for the treatment of respiratory infections in adults, April 2010 to March 2017.

Infection	Category of chronic disease	Prescriptions *		Prescriptions with a dosage		Proportion ratio*	
		N	Recommended antibiotic %	N	Recommended antibiotic and dosage %	Unadjusted	Adjusted [95% confidence interval]
COPD exacerbations and bronchitis	COPD only	24,576	94.5	24,564	33.3	ref.	ref.
	Diabetes	38,398	91.9	38,355	31.4	0.963 [0.944 ; 0.982]	0.951 [0.933 ; 0.970]
	Mental health disorder	31,629	92.1	31,596	32.8	1.017 [0.997 ; 1.037]	1.012 [0.992 ; 1.032]
	Cardiovascular disease	101,208	92.1	101,097	32.2	0.987 [0.968 ; 1.007]	0.987 [0.967 ; 1.008]
Pharyngitis	None of the following	74,188	63.5	74,123	50.6	ref.	ref.
	Diabetes	8,736	53.1	8,725	42.0	0.942 [0.916 ; 0.969]	0.978 [0.951 ; 1.006]
	Mental health disorder	21,273	60.5	21,241	47.0	0.976 [0.960 ; 0.992]	0.976 [0.960 ; 0.991]
	Cardiovascular disease	21,719	52.8	21,699	41.3	0.851 [0.835 ; 0.867]	0.955 [0.934 ; 0.976]

	Respiratory disease	22,563	59.2	22,536	44.7	0.932 [0.917 ; 0.948]	0.939 [0.924 ; 0.955]
Pneumonia	None of the following	23,971	83.9	23,933	40.3	ref.	ref.
	Diabetes	26,245	73.4	26,112	37.6	0.970 [0.952 ; 0.989]	0.963 [0.945 ; 0.982]
	Mental health disorder	26,515	73.4	26,429	36.5	0.935 [0.917 ; 0.953]	0.938 [0.921 ; 0.956]
	Cardiovascular disease	71,019	74.0	70,731	38.5	0.991 [0.975 ; 1.007]	0.960 [0.942 ; 0.977]
	Respiratory disease	51,273	74.2	50,992	37.5	0.938 [0.923 ; 0.953]	0.938 [0.923 ; 0.953]
Sinusitis	None of the following	53,750	86.4	53,728	60.8	ref.	ref.
	Diabetes	15,959	82.4	15,941	52.3	0.960 [0.944 ; 0.977]	0.966 [0.950 ; 0.983]
	Mental health disorder	27,540	83.2	27,522	55.0	0.960 [0.948 ; 0.972]	0.953 [0.941 ; 0.965]
	Cardiovascular disease	50,174	82.7	50,139	52.5	0.895 [0.885 ; 0.905]	0.944 [0.932 ; 0.957]
	Respiratory disease	36,744	83.5	36,716	54.3	0.959 [0.948 ; 0.970]	0.960 [0.949 ; 0.971]

*Categories of chronic diseases are not mutually exclusive, so unadjusted proportion ratios are actually adjusted for the other categories of chronic diseases. The adjusted regressions were also adjusted for year, age group, sex, geographical zone and quintiles of deprivation. The total number of prescriptions is not equal to the sum of prescriptions for each chronic disease category.