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# Association of fluoroquinolones with the risk of spontaneous pneumothorax: nationwide case–time–control study

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## ABSTRACT

**Introduction** Fluoroquinolones can cause severe collagen-associated adverse effects, potentially impacting the pulmonary connective tissue. We investigated the association between fluoroquinolones and spontaneous pneumothorax.

**Methods** A case–time–control study was performed using the nationwide French reimbursement healthcare system database (SNDS). Cases were adults ≥18 years admitted for spontaneous pneumothorax between 2017 and 2022. For each case, fluoroquinolone use was compared between the risk period immediately preceding the admission date (days −30 to −1), and three earlier reference periods (days −180 to −151, −150 to −121, −120 to −91), adjusting for time-varying confounders. OR estimates were corrected for potential exposure-trend bias using a reference group without the event (matched on age, sex, chronic obstructive pulmonary disease history, calendar time). Amoxicillin use was studied similarly to control for indication bias.

**Results** Of the 246 pneumothorax cases exposed to fluoroquinolones (63.8% men; mean age, 43.0±18.4 years), 63 were exposed in the 30-day risk period preceding pneumothorax and 128 in the reference periods. Of the 3316 amoxicillin cases (72.9% men; mean age, 39.4±17.6 years), 1210 were exposed in the 30-day risk period and 1603 in the reference ones. OR adjusted for exposure-trend and covariates was 1.59 (95% CI 1.14 to 2.22) for fluoroquinolones and 2.25 (2.07 to 2.45) for amoxicillin.

**Conclusion** An increased risk of spontaneous pneumothorax was associated with both fluoroquinolone and amoxicillin use, with an even higher association for amoxicillin. This strongly suggests the role of the underlying infections rather than a causal effect of the individual antibiotics and can be considered reassuring regarding a potential lung connective toxicity of fluoroquinolones.

### WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Fluoroquinolones can cause severe collagen-associated adverse effects, including tendon rupture, aortic aneurysm or dissection and retinal detachment. The pulmonary connective tissue may also be affected, causing spontaneous pneumothorax.

### WHAT THIS STUDY ADDS

⇒ In this case–time–control study, recent exposure to fluoroquinolones (ie, in the previous 30 days) was significantly associated with the occurrence of spontaneous pneumothorax requiring a hospitalisation compared with former exposure. However, a stronger association was found for the active comparator, amoxicillin, suggesting confounding by indication.

### HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These results are reassuring regarding a potential lung connective toxicity of fluoroquinolones and highlight the need to use an active comparator in self-controlled designs when confounding by indication appears possible.

## INTRODUCTION

A spontaneous pneumothorax refers to the presence of air in the pleural space without any traumatic cause. The annual incidence of hospital admissions for spontaneous pneumothorax is reported to be 11.6 to 22.7 per 100 000 inhabitants in European countries, with variations based on sex (male predominance) and age.[1 2] Primary spontaneous pneumothorax affects patients with no known pre-existing lung conditions, and smoking is a significant risk factor.[3] In addition, it is now surmised that spontaneous pneumothorax might be favoured by the interplay of lung abnormalities such as pre-existing blebs, bullae, emphysema-like changes and perturbations or abnormal levels of matrix metalloproteinases (MMP).[4 5] On the other hand, secondary spontaneous pneumothorax arises as a complication of an established lung pathology; it can also be the consequence of an infectious process (bacterial, viral) occurring in the lung. Besides, spontaneous pneumothorax is a known pulmonary complication of congenital disorders with collagen defects, such as Marfan syndrome, cardinal features of which include aortic aneurysm and dissection, axial myopia leading to retinal detachment, and hyperlaxity.[6–9]

Fluoroquinolones are broad-spectrum antibiotics extensively used for the treatment of various infections, including respiratory or urinary tract infections. Fluoroquinolones can cause serious adverse effects, thought to be due to a direct collagen

toxicity,[10] resulting in tendon rupture,[11 12] aortic aneurysm or dissection[13–17] and, possibly, retinal detachment.[18–20] These antibiotics may decrease collagen synthesis, particularly collagen types I and III, by upregulating the expression of MMP.[12 21 22] Consequently, there is concern about fluoroquinolone-induced collagen toxicity, which might potentially damage connective tissues throughout the body other than those mentioned above. Notably, collagen type I is the most abundant collagen in many interstitial connective tissues; collagen type III is widely distributed in tissues containing collagen type I and is a crucial component of reticular fibres in the interstitial tissue of the lungs.[23] If fluoroquinolone-induced collagen disruption was to involve the pulmonary connective tissue, it is possible that these drugs could lead to spontaneous pneumothorax.

We found almost no publication investigating specifically the potential role of antibiotics. One case report suggested the potential role of antibiotics (among which a fluoroquinolone) in the occurrence of a pneumothorax, the other possible causes discussed were lung metastasis and/or Pneumocystis jirovecii pneumonia).[24] To address this gap, our study aimed to investigate this association between fluoroquinolone use and the risk of spontaneous pneumothorax using real-world data. We performed a case–time–control study using an active comparator (amoxicillin) to assess potential confounding by indication.

## METHODS

### Data source

A nationwide study was conducted from 1 January 2017 through 31 December 2022, using the French Health Insurance (*Système National des Données de Santé*, SNDS nationwide database, linked with the national hospital discharge database (*Programme de Médicalisation des Systèmes d'Information*, PMSI). SNDS contains information on at least 99% of the French population; it consists of an anonymous and exhaustive recording of all reimbursements for outpatients-dispensed healthcare expenditure, including drugs. Indications for prescribing and the results of medical procedures or lab tests are not available in the SNDS. However, the database includes medical diagnosis information relating to long-term chronic diseases and disabilities eligible for full reimbursement of healthcare. On the other hand, the PMSI database provides some medical information (including diagnoses) on all admissions to private and public hospitals in France; information on drugs administered during hospitalisation is not available in the database. Further details on the French medico-administrative databases have been described elsewhere.[25]

The present study focused on the beneficiaries of the main Health Insurance scheme for employees, including salaried workers and their relatives as well as retired salaried workers and their relatives, representing 87% of the French population. The SNDS database has been collecting comprehensive data on this population since 2006.

### Study design

To analyse the association between fluoroquinolone exposure and spontaneous pneumothorax, we used a case–time–control design, which is particularly suitable for investigating acute events and intermittent exposures.[26] Spontaneous pneumothorax is typically characterised by an acute onset of clinical symptoms, and antibiotic therapy is usually of short duration (97% of fluoroquinolone prescriptions in outpatient setting lasted less than 15 days in 2019).[27] The case–time–control design involves two self-controlled case-crossover analyses. In the first one, the distribution of exposure during a risk period (compatible with a causal effect of the drug) is compared with the distribution during one or more earlier reference periods when the exposure cannot be causally related to the outcome. This within-person comparison design allows for self-adjustment over a short period for individual factors not typically recorded in medicoadministrative healthcare databases and that do not vary over time (or vary slowly), such as height and weight, genetic connective-tissue diseases or tobacco smoking habits. However, since reference periods are older than the risk period, the estimated OR for association, determined solely by the exposure of cases at different times, can be biased if there is a trend towards increased or decreased exposure in the population source during the study period. To eliminate this potential exposure-trend bias, the case–time–control design was developed by performing an additional case-crossover analysis using a time-trend control group of exposed subjects free of the event of interest.

Based on previous studies that assessed the risk of adverse events related to collagen-disorders induced by fluoroquinolone use,[13 14] we considered a risk period of 30 days immediately before the outcome (days −30 to −1 before the date of occurrence of the event; index date) and three reference periods of similar duration (days −180 to −151, −150 to −121, −120 to −91). A wash-out window (days −90 to −31) was implemented between the risk and reference periods to minimise any potential carry-over effect of exposure in reference periods on the outcome (figure 1).

The second case-crossover analysis, carried out in order to control for the time-trend in exposure, involved a time-trend control group of non-diseased individuals. Time-trend controls were identified among fluoroquinolone users who remained free of the outcome at the time a case occurred. For each case, we selected up to 10 controls individually matched according to sex, age and history of chronic obstructive pulmonary disease (COPD) among those aged 40 years and over. The patients selected for the time-trend control group were assigned the corresponding case's index date.

The case–time–control design cannot fully eliminate a potential confounding by indication, which could occur if the indication for fluoroquinolone use itself is associated with an increased risk of spontaneous pneumothorax. To assess the potential existence of such a bias, we used an active comparator design with amoxicillin as the comparator. Consequently, we also estimated the association between spontaneous pneumothorax occurrence and amoxicillin use using a similar case–time–control design.[28] Amoxicillin's indication profile overlaps with that of fluoroquinolones, including for respiratory tract infections (although amoxicillin is recommended as the first choice).[29] According to our literature review and Pneumotox data search, it has no known association with pneumothorax. If there was an association between pneumothorax and both fluoroquinolones and amoxicillin, it would be suspected to relate to the risk conveyed by their common indication of use (respiratory tract infection). Conversely, if there were only an association between pneumothorax and fluoroquinolones, it would be considered more likely to relate to the effect of the drug and less likely to constitute a biased consequence of its indication.

### Spontaneous pneumothorax

The study focused on spontaneous pneumothorax as an emergency admission, recorded as the principal reason for the admission (primary diagnosis position), in a non-traumatic context. The International Classification of Diseases 10th revision (ICD-10) code used to identify spontaneous pneumothorax from the

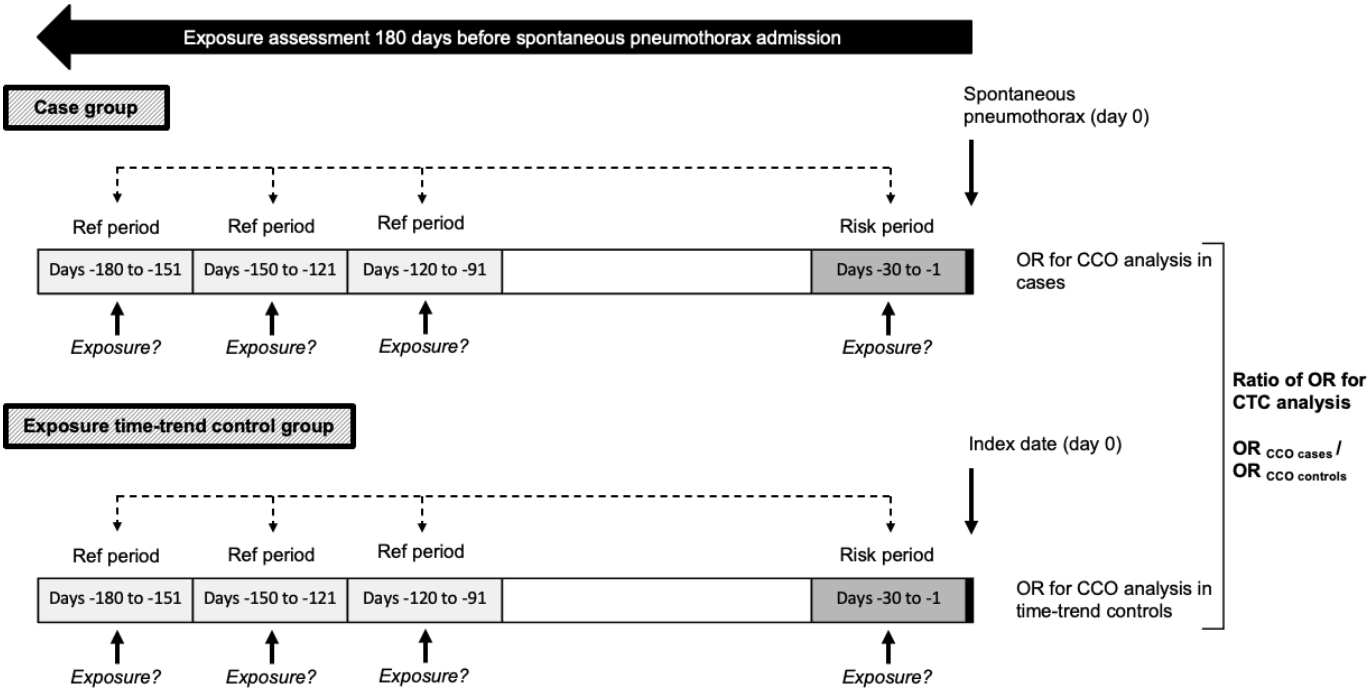


**Figure 1** Diagram of the case–time–control design for studying the association between antibiotic exposure (fluoroquinolone or amoxicillin) and the occurrence of spontaneous pneumothorax. CCO, case-crossover; CTC, case–time–control; Ref period, reference period.

hospital discharge records was ICD-10 J93 as primary diagnosis; records containing additional secondary or subsidiary diagnoses codes indicating traumatic pneumothorax (ICD-10 S27.0-S27.2), or traumatic subcutaneous emphysema (ICD-10 T79.7) were not included. The date of admission for spontaneous pneumothorax was designated as the index date.

There is no distinction between primary and secondary spontaneous pneumothorax in ICD-10 codes. Therefore, in the present study, presumed type of spontaneous pneumothorax relied on risk factors identified either on the same spontaneous pneumothorax record or within the 5 years preceding the event (see online supplemental eTable 1 for codes).

## Exposure to antibiotics

All fluoroquinolones approved for oral or injectable use were considered and identified using the Anatomical Therapeutic Chemical (ATC) classification code J01MA (ciprofloxacin, levofloxacin, lomefloxacin, moxifloxacin, norfloxacin and ofloxacin). Systemic exposure to amoxicillin was considered alone or combined with beta-lactamase inhibitor (ATC codes J01CA04 and J01CR02). In France, systemic antibiotics are not available over-the-counter and their dispensing always leads to reimbursement. Therefore, antibiotic use during the studied periods of interest (risk/reference) was determined based on reimbursements information. Patients were considered exposed if they have been reimbursed for at least one dispensing of an antibiotic during the specified period, and the day of drug dispensing was used as a proxy for drug initiation. Therefore, a treatment contributed only to the period where it started.

## Study populations

Eligible participants were adult patients aged 18 and over admitted through emergency wards with spontaneous pneumothorax as their primary diagnosis (outcome) between 1 January 2017 and 31 December 2022 (index date). Since spontaneous pneumothorax is likely to recur within 1 year, patients with a history of pneumothorax (spontaneous or traumatic) within the year prior to the index date were excluded from the study population to focus on new episodes. Additionally, patients with a history of cystic fibrosis, tuberculosis or lung transplantation during the 5-year period before the index date were excluded because of potential confounding. Patients with a history of cancer were also excluded since lung and pleural cancers, as well as, surgical and radiotherapy procedures performed in oncology, pulmonary metastases and some antineoplastics may enhance the risk of pneumothorax. Finally, due to the lack of information on in-hospital antibiotic exposure in the database, patients hospitalised in the 180-day period before the index date (namely, the 'observation period') were excluded from the study.

In the main analysis, since patients could be exposed to both antibiotic classes, two mutually exclusive populations were identified based on antibiotic exposure: for the fluoroquinolone study population, eligible participants had at least one fluoroquinolone dispensing and no amoxicillin dispensing during the observation period; conversely, for the amoxicillin study population, eligible participants had at least one amoxicillin dispensing and no fluoroquinolone dispensing. Concerning patients who had more than one pneumothorax-related hospital admission during the study period, only the first occurrence of the outcome was analysed.

By agreement of the French Data Protection Supervisory Authority (CNIL), neither ethics committee approval nor informed consent was required for this observational study based on anonymised French medicoadministrative databases.

## Statistical analysis

Descriptive analyses were performed to characterise cases and time-trend controls at baseline. Data for qualitative variables are presented as number and proportion of patients in each group, and continuous variables as median and IQR, mean and SD. As indications for prescribing are not

available on the database, infection site was deduced from medical diagnosis codes, lab tests and medical procedures (online supplemental eTable 2).

We used a conditional logistic model to estimate OR and 95% CIs for both pneumothorax cases and time-trend controls.[30] Age and comorbidities were considered fixed during the short observation period (180 days prior to the index date). Time-varying confounders, such as drugs that enhance the risk of pneumothorax (online supplemental eTable 3), were adjusted for in the model; an individual was considered exposed when a reimbursement for these drugs occurred during risk or reference periods. Case-crossover analyses compared exposure frequencies between the risk period and three reference periods within each pneumothorax case, and within each time-trend control. The case–time–control OR corresponded to the ratio of the respective case-crossover ORs obtained in cases and time-trend controls; it theoretically yields an unbiased estimate of the association between antibiotic use (fluoroquinolones or amoxicillin) and spontaneous pneumothorax accounting for time-trends in antibiotic exposure.

Additionally, we performed a secondary analysis that was not restricted to mutually exclusive populations: all patients exposed to fluoroquinolones and/or amoxicillin in the 180-day period before the index date was included. The analysis yielded OR for the association between spontaneous pneumothorax and fluoroquinolones, adjusted for amoxicillin exposure using an effect modifier approach.[28] This allowed considering patients who could have been exposed to both fluoroquinolones and amoxicillin, a situation that could not be investigated from the main analysis. A further subgroup analysis considering separately primary pneumothorax and secondary pneumothorax was performed.

Data were analysed using SAS Enterprise Guide statistical software (SAS Institute, V.9.4, North Carolina).

## RESULTS

From 2017 to 2022, there were 33 329 emergency hospital admissions for spontaneous pneumothorax as primary diagnosis among 28 077 adults aged ≥18 years covered by the major health insurance scheme (online supplemental eFigure 1). Of these, 23 428 pneumothorax cases met the eligibility criteria, corresponding to 22 423 patients. A total of 3684 patients were found to have been exposed to fluoroquinolones and/or

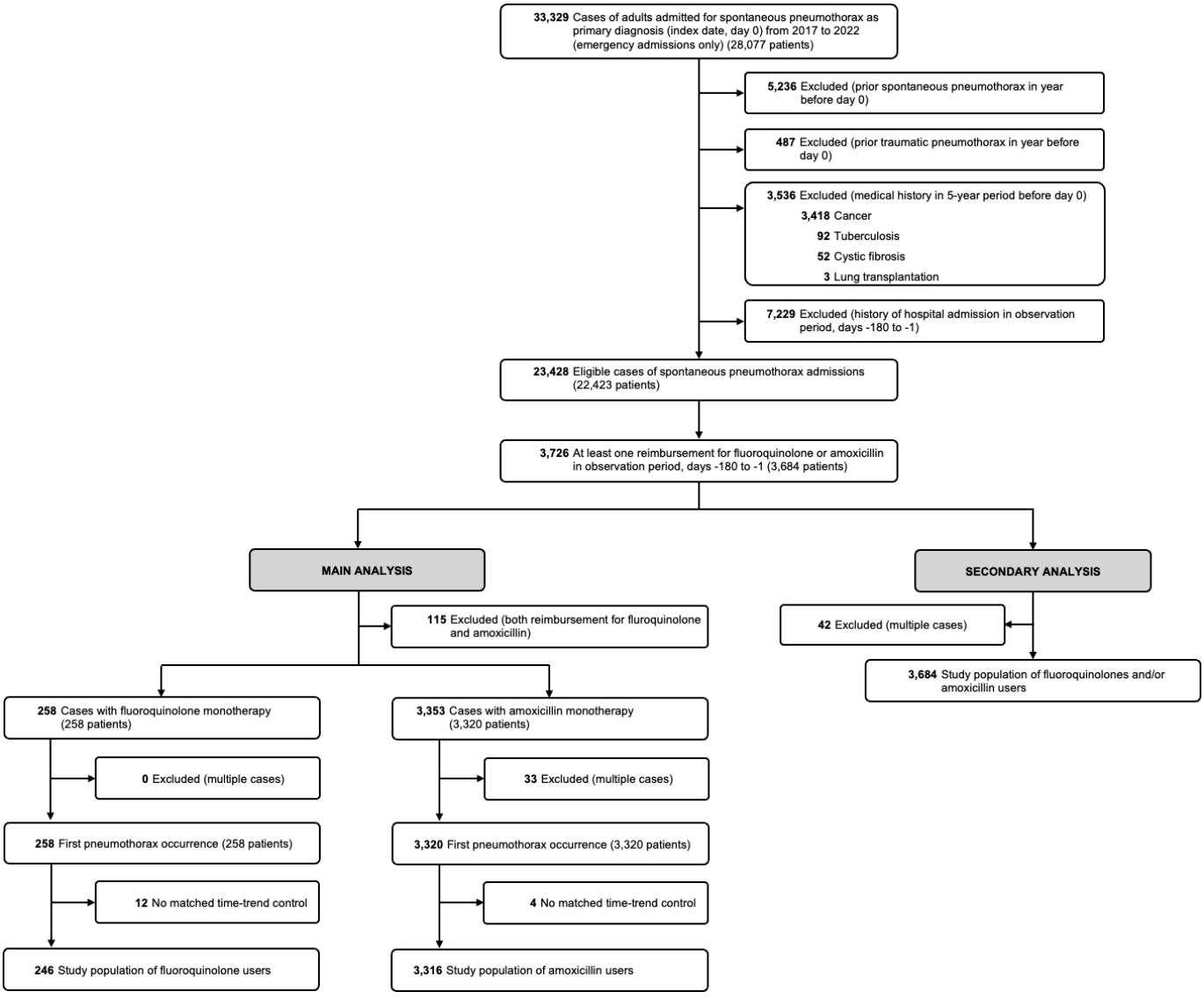


**Figure 2** Flowchart of eligible participants included in study populations (main and secondary analyses).

**Table 1** Main analysis: descriptive characteristics of matched pneumothorax cases, exposed to fluoroquinolones or amoxicillin monotherapy and their time-trend controls

| | Fluoroquinolones users* | | Amoxicillin users* | |
|---|---|---|---|---|
| | Cases N=246 | Controls N=1846 | Cases N=3316 | Controls N=32 494 |
| Male | 157 (63.8) | 1170 (63.4) | 2419 (72.9) | 23 912 (73.6) |
| Age, mean (SD), years | 43.0 (18.4) | 37.3 (15.2) | 39.4 (17.6) | 38.9 (17.1) |
| Age groups, years | | | | |
| <35 | 103 (41.9) | 978 (53.0) | 1676 (50.5) | 16 760 (51.6) |
| 35–54 | 78 (31.7) | 600 (32.5) | 982 (29.6) | 9575 (29.5) |
| ≥ 55 | 65 (26.4) | 268 (14.5) | 658 (19.8) | 6159 (18.9) |
| Season | | | | |
| Winter | 65 (26.4) | 519 (28.1) | 924 (27.9) | 9030 (27.8) |
| Spring | 69 (28.0) | 522 (28.3) | 900 (27.1) | 8848 (27.2) |
| Summer | 54 (21.9) | 410 (22.2) | 716 (21.6) | 7004 (21.5) |
| Autumn | 58 (23.6) | 395 (21.4) | 776 (23.4) | 7612 (23.4) |
| Index year | | | | |
| 2017 | 58 (23.6) | 518 (28.1) | 546 (16.5) | 5388 (16.6) |
| 2018 | 51 (20.7) | 377 (20.4) | 627 (18.9) | 6119 (18.8) |
| 2019 | 43 (17.5) | 312 (16.9) | 626 (18.9) | 6190 (19.0) |
| 2020 | 32 (13.0) | 243 (13.2) | 521 (15.7) | 5105 (15.7) |
| 2021 | 26 (10.6) | 179 (9.7) | 450 (13.6) | 4367 (13.4) |
| 2022 | 36 (14.6) | 217 (11.8) | 546 (16.5) | 5325 (16.4) |
| History of pneumothorax† | 26 (10.6) | 618 (33.5) | 326 (9.8) | 14 147 (43.5) |
| Tobacco addiction treatment | 55 (22.4) | 417 (22.6) | 622 (18.8) | 9677 (29.8) |
| Pneumothorax type | | | | |
| Primary | 167 (67.9) | 1502 (81.4) | 2349 (70.8) | 24 868 (76.5) |
| Secondary | 79 (32.1) | 344 (18.6) | 967 (29.2) | 7626 (23.5) |
| Risk factors for secondary pneumothorax‡ | | | | |
| Airway diseases | 75 (30.5) | 320 (17.3) | 918 (27.7) | 7203 (22.2) |
| History of specific infectious lung diseases§ | 0 (0.0) | 1 (0.1) | 3 (0.1) | 6 (0.0) |
| Interstitial lung diseases | 5 (2.0) | 19 (1.0) | 50 (1.5) | 413 (1.3) |
| Connective-tissue diseases | 2 (0.8) | 28 (1.5) | 35 (1.1) | 375 (1.2) |
| Thoracic endometriosis | 1 (0.4) | 4 (0.2) | 8 (0.2) | 38 (0.1) |
| Infection site | | | | |
| Respiratory tract | 32 (13.0) | 55 (3.0) | 516 (15.6) | 2406 (7.4) |
| Urinary tract | 31 (12.6) | 282 (15.3) | 99 (3.0) | 1032 (3.2) |
| Other identified site | 7 (2.9) | 1 (0.1) | 60 (1.8) | 4 (0.0) |
| Unidentified site | 180 (73.2) | 1519 (82.3) | 2663 (80.3) | 29 225 (89.9) |

*Cases and time-trend controls were matched by sex, age and COPD history. Patient characteristics for matching variables differed between cases and their controls in both groups, depending on the number of controls assigned per case, which could range up to 10, but not necessarily.
†History of spontaneous, or traumatic, pneumothorax identified within 1–5 years prior to the index date.
‡Risk factors identified either in the same spontaneous pneumothorax hospital record or within 5 years prior to the index date.
§Includes Pneumocystis carinii pneumonia and necrotising pneumonias.

amoxicillin during the 180-day observation period before the pneumothorax (median age, 35 years (IQR, 26–50); 71.7% men). Finally, the main analysis was restricted to patients who had only one antibiotic during the observation period, and only the first occurrence of pneumothorax was analysed: 258 patients received fluoroquinolone monotherapy, of whom 246 were matched to at least one time-trend control and included (median age, 37 years (28–55); 63.8% men). Among the 3320 patients receiving amoxicillin monotherapy, 3316 matched cases were considered (median age, 34 years (26–49); 72.9% men) (figure 2).

Additional characteristics of the study populations are summarised in table 1. In seven out of 10 cases, the pneumothorax was idiopathic, with airway diseases, including COPD and other COPDs, being the most frequent risk factor for secondary pneumothorax. Fluoroquinolone cases, compared with amoxicillin cases, were typically older, more often women, and received greater medical support for tobacco dependence. Infection site

**Table 2** Results of the main analysis

| | Number of people | Antibiotic use | | Adjusted OR (95% CI) |
|---|---|---|---|---|
| | | Risk period | Reference period* | |
| Fluoroquinolone | | | | |
| CCO cases | 246 | 63 | 128 | 1.45 (1.06 to 1.97) |
| CCO controls | 1846 | 323 | 1005 | 0.91 (0.80 to 1.03) |
| CTC ratio | | | | 1.59 (1.14 to 2.22) |
| Amoxicillin | | | | |
| CCO cases | 3316 | 1210 | 1603 | 2.32 (2.14 to 2.51) |
| CCO controls | 32 494 | 6562 | 17 739 | 1.03 (1.00 to 1.06) |
| CTC ratio | | | | 2.25 (2.07 to 2.45) |

Adjusted ORs for the risk of pneumothorax according to fluoroquinolones and amoxicillin use.
*Patients who received antibiotics in at least one reference period.
CCO, case-crossover; CTC, case–time–control.

was not identifiable from the database in most patients. In the minority with identified site, respiratory tract infections had a somewhat similar frequency for both groups (fluoroquinolones 13.0%; amoxicillin 15.6%), while urinary tract infections were more frequent among fluoroquinolone users (12.6%) compared with amoxicillin users (3.0%).

Of the 246 cases exposed to fluoroquinolones, 63 were exposed in the risk period (days −30 to −1 before pneumothorax) and 128 in at least one reference period (days −180 to −151, −150 to −121, −120 to −91 before pneumothorax). Of the 3316 cases exposed to amoxicillin, 1210 were exposed in the risk period and 1603 in at least one reference period. OR adjusted for exposure-trend and covariates was 1.59 (95% CI 1.14 to 2.22) for fluoroquinolones and 2.25 (2.07 to 2.45) for amoxicillin (table 2).

ORs were adjusted for drugs that enhance the risk of spontaneous pneumothorax (online supplemental eTable 3). These drugs are primarily antineoplastic agents. Due to the exclusion of patients with a history of cancer from the study population, exposures to drugs at increased risk for pneumothorax were scarce in the observation period. Consequently, crude and adjusted ORs were found to be identical and crude OR are not presented.

The secondary analysis included 3684 patients exposed to fluoroquinolones and/or amoxicillin during the 180-day observation period before the pneumothorax (figure 1): 257 (7.0%) had fluoroquinolone monotherapy, 3315 (90%) amoxicillin monotherapy and 112 (3.0%) received both antibiotics during the observation period. The OR estimate, based on interaction terms, for the association between spontaneous pneumothorax and fluoroquinolones adjusted for amoxicillin exposure was 0.70 (0.54 to 0.91). A further subgroup analysis considering separately primary pneumothorax and secondary pneumothorax provided exactly similar results whatever the outcome type (online supplemental eTable 4).

## DISCUSSION

We identified an association between fluoroquinolone use and spontaneous pneumothorax. To mitigate confounding by indication, we conducted a similar investigation using amoxicillin as an active comparator with a comparable indication profile. This showed a higher association with amoxicillin, which theoretically does not present a pathophysiological rationale for such an adverse effect, and especially does not share the connective tissue toxicity induced by fluoroquinolones. Consequently, we believe that confounding by indication is the more plausible explanation for the association found. These would, therefore, result from the predisposing effect of infections requiring antibiotic prescriptions on the occurrence of pneumothorax, rather than from a causal effect of both fluoroquinolones and amoxicillin. This hypothesis is supported by the higher frequency of prescriptions for respiratory infections identified for cases than for time-controls for both antibiotics (even though most of the indications were unknown).

One major strength of our study is the utilisation of the SNDS, a nationwide database, which provides comprehensive coverage of the French population and exhaustive recording of both all outpatients dispensing reimbursements and all hospitalisation stays. The recorded cases indeed reflect the known epidemiological predominance of the disease in men. The choice to study outcomes through emergency admissions can also be considered as a strength as it avoids the time lag between admission and hospital diagnosis of spontaneous pneumothorax. During this time interval indeed, pneumothorax could have been caused by in-hospital drug exposure or medical procedures not recorded in the database. Another strength of the study lies in the utilisation of a self-controlled design, which allows patients to act as their own controls and takes into account all the time-fixed potential confounders that are not registered in medicoadministrative databases, such as genetic connective-tissue diseases or tobacco smoking habits, both of which are strongly associated with the occurrence of pneumothorax.[6 9] Moreover, we used the case–time–control design developed to address exposure-trend bias. In our study, such a bias relating to a time-trend in exposure could have arisen, especially considering the decline in fluoroquinolone use over the study period due to restrictive measures to promote their correct use[27 31 32] (a 44% decrease in outpatient fluoroquinolones prescriptions in 2019 compared with 2000),[27] and a seasonal trend associated with the recrudescence of respiratory infections in winter. There was, however, limited evidence of such trend in the present study. Finally, we used an active comparator to further mitigate potential within-person confounding in the case–time–control design. However, residual confounding may still exist due to transient risk factors for pneumothorax, such as COPD exacerbations and respiratory infections as well as the severity of those infections.[33 34] These medical conditions often vary over time and are not inherently adjusted for by the self-controlled design. We selected amoxicillin as a comparator because of its similar indication profile and the lack of a mechanistic hypothesis for an increased risk of

pneumothorax. Our results confirm the need for the use of an active comparator in this study, for which confounding by indication was suspected, to avoid incorrectly concluding to a potential causal association with fluoroquinolones.[28 35] Indeed, the stronger association for amoxicillin, consistently found in the secondary analysis, suggests that its use in medical situations that increase the risk of spontaneous pneumothorax could be higher than that of fluoroquinolones; this appears logical, given the first-line ranking of amoxicillin in the prescription guidelines.

## Limitations

Several limitations should be acknowledged. First, the study relies on medicoadministrative data that lack medical information and indication for prescribing. Consequently, identifying infection site or seriousness was challenging, hampering the conduct of subgroup analyses. Second, the study focused on the more severe spontaneous pneumothorax that is, exclusively those managed in hospitals, limiting the generalisability of the results. We could not do otherwise, as patients who may have been managed conservatively (no intervention) without admission cannot be identified in the database. However, ambulatory management of spontaneous pneumothorax is uncommon in France, mainly because the set-up of a dedicated outpatient care system for this condition is currently limited.[36] Finally, as the influence of a time-trend bias appeared very limited for fluoroquinolones and null for amoxicillin, we preferred to adopt a case-crossover approach for the secondary analysis, which could have resulted in a mild underestimation of the association for fluoroquinolones. However, as the association found was much lower than that evidenced for amoxicillin in this analysis, we do not believe that this might have led to ignoring a potential causal increase in the risk of spontaneous pneumothorax induced by fluoroquinolones.

An increased risk of spontaneous pneumothorax was associated with both fluoroquinolone and amoxicillin use, but the association with amoxicillin exceeded that found with fluoroquinolones. As this strongly suggests the role of the underlying infections rather than a direct causal effect of the individual antibiotics, these results are reassuring regarding a potential lung connective-toxicity of fluoroquinolones. These results also highlight the need to use an active comparator in self-controlled designs when confounding by indication appears possible.

**Contributors** The following authors conceived and designed the study: AB-L, J-LF, SK, JB, AP. EP performed data management and conducted statistical analyses. AB-L ensured project and study management. AB-L drafted the manuscript. All authors contributed to interpretation of the data and revised the manuscript. All authors approved the final manuscript. AP is the guarantor. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Competing interests** None declared.

**Patient and public involvement statement** Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

**Patient consent for publication** Not applicable.

**Ethics approval** By agreement of the French Data Protection Supervisory Authority (Commission Nationale de l'Informatique et des Libertés), neither ethics committee approval nor informed consent were required for this observational study based on anonymised French medicoadministrative databases.

**Provenance and peer review** Not commissioned; externally peer-reviewed.

**Data availability statement** No data are available. No additional data available by author (French law to access SNDS www.health-data-hub.fr).

**Author note** Transparency statement: The lead author (AP) affirms that the manuscript is an honest, accurate and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as originally planned (and, if relevant, registered) have been explained.



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## REFERENCES

1 Bobbio A, Dechartres A, Bouam S, *et al*. Epidemiology of spontaneous pneumothorax: gender-related differences. *Thorax* 2015;70:653–8.
2 Hallifax RJ, Goldacre R, Landray MJ, *et al*. Trends in the Incidence and Recurrence of Inpatient-Treated Spontaneous Pneumothorax, 1968-2016. *JAMA* 2018;320:1471–80.
3 Bense L, Eklund G, Wiman LG. Smoking and the increased risk of contracting spontaneous pneumothorax. *Chest* 1987;92:1009–12.
4 Chen C-K, Chen P-R, Huang H-C, *et al*. Overexpression of matrix metalloproteinases in lung tissue of patients with primary spontaneous pneumothorax. *Resp* 2014;88:418–25.
5 Huang Y-F, Chiu W-C, Chou S-H, *et al*. Association of MMP-2 and MMP-9 expression with recurrences in primary spontaneous pneumothorax. *Kaohsiung J Med Sci* 2017;33:17–23.
6 Boone PM, Scott RM, Marciniak SJ, *et al*. The Genetics of Pneumothorax. *Am J Respir Crit Care Med* 2019;199:1344–57.
7 Milewicz DM, Braverman AC, De Backer J, *et al*. Marfan syndrome. *Nat Rev Dis Primers* 2021;7:64.
8 Viveiro C, Rocha P, Carvalho C, *et al*. Spontaneous pneumothorax as manifestation of Marfan syndrome. *BMJ Case Rep* 2013;2013:bcr2013201697.
9 Noppen M. Spontaneous pneumothorax: epidemiology, pathophysiology and cause. *Eur Respir Rev* 2010;19:217–9.
10 Yu X, Jiang D-S, Wang J, *et al*. Fluoroquinolone Use and the Risk of Collagen-Associated Adverse Events: A Systematic Review and Meta-Analysis. *Drug Saf* 2019;42:1025–33.
11 Stephenson AL, Wu W, Cortes D, *et al*. Tendon Injury and Fluoroquinolone Use: A Systematic Review. *Drug Saf* 2013;36:709–21.
12 Tsai W-C, Hsu C-C, Chen CPC, *et al*. Ciprofloxacin up-regulates tendon cells to express matrix metalloproteinase-2 with degradation of type I collagen. *J Orthop Res* 2011;29:67–73.
13 Maumus-Robert S, Bérard X, Mansiaux Y, *et al*. Short-Term Risk of Aortoiliac Aneurysm or Dissection Associated With Fluoroquinolone Use. *J Am Coll Cardiol* 2019;73:875–7.
14 Daneman N, Lu H, Redelmeier DA. Fluoroquinolones and collagen associated severe adverse events: a longitudinal cohort study. *BMJ Open* 2015;5:e010077.
15 Lee C-C, Lee M-T, Hsieh R. Oral Fluoroquinolone and the Risk of Aortic Dissection. *J Am Coll Cardiol* 2018;72:1369–78.
16 Lee CC, Lee MT, Chen YS, *et al*. Risk of Aortic Dissection and Aortic Aneurysm in Patients Taking Oral Fluoroquinolone. *JAMA Intern Med* 2015;175:1839–47.
17 Pasternak B, Inghammar M, Svanström H. Fluoroquinolone use and risk of aortic aneurysm and dissection: nationwide cohort study. *BMJ* 2018;360:k678.
18 Etminan M, Forooghian F, Brophy JM, *et al*. Oral fluoroquinolones and the risk of retinal detachment. *JAMA* 2012;307:1414–9.
19 Kuo S-C, Chen Y-T, Lee Y-T, *et al*. Association between recent use of fluoroquinolones and rhegmatogenous retinal detachment: a population-based cohort study. *Clin Infect Dis* 2014;58:197–203.
20 Raguideau F, Lemaitre M, Dray-Spira R, *et al*. Association Between Oral Fluoroquinolone Use and Retinal Detachment. *JAMA Ophthalmol* 2016;134:415–21.
21 Corps AN, Harrall RL, Curry VA, *et al*. Ciprofloxacin enhances the stimulation of matrix metalloproteinase 3 expression by interleukin-1beta in human tendon-derived cells.

A potential mechanism of fluoroquinolone-induced tendinopathy. *Arthritis Rheum* 2002;46:3034–40.
22 Sharma C, Velpandian T, Baskar Singh S, *et al*. Effect of fluoroquinolones on the expression of matrix metalloproteinase in debrided cornea of rats. *Toxicol Mech Methods* 2011;21:6–12.
23 Gelse K, Poschl E, Aigner T. Collagens--structure, function, and biosynthesis. *Adv Drug Deliv Rev* 2003;55:1531–46.
24 Monti M, Sullo FG, Iamurri AP, *et al*. Recurrent pneumothorax in a patient with liposarcoma as either a complication of lung micrometastasis or a potential adverse event from antibiotic therapy: A case report. *Oncol Lett* 2022;24:202.
25 de Germay S, Conte C, Micallef J, *et al*. Performing pharmacoepidemiological studies using the French health insurance data warehouse (SNDS): How to translate guidelines into practice. *Ther* 2023;78:679–89.
26 Maclure M, Fireman B, Nelson JC, *et al*. When should case-only designs be used for safety monitoring of medical products? *Pharmacoepidemiol Drug Saf* 2012;21 Suppl 1:50–61.
27 Agence Nationale de Sécurité du Médicament et des produits de santé. La consommation des antibiotiques en France de 2000 à 2020 [Juillet]. 2023. Available: https://ansm.sante.fr/actualites/lansm-publie-un-rapport-sur-la-consommation-des-antibiotiques-entre-2000-et-2020
28 Hallas J, Whitaker H, Delaney JA, *et al*. The Use of Active Comparators in Self-Controlled Designs. *Am J Epidemiol* 2021;190:2181–7.
29 Chidiac C. Société de Pathologie Infectieuse de Langue Française, Agence Française de Sécurité Sanitaire des Produits de Santé [Systemic antibiotherapy for the treatment of lower respiratory tract infections. Community acquired pneumonia, acute exacerbation of obstructive chronic bronchitis]. *Med Mal Infect* 2011;41:221–8.
30 Suissa S. The case-time-control design. *Epidemiology* 1995;6:248–53.
31 US Food and Drug Administration. FDA warns about increased risk of ruptures or tears in the aorta blood vessel with fluoroquinolone antibiotics in certain patients. 2019. Available: https://www.fda.gov/drugs/drug-safety-and-availability/fda-warns-about-increased-risk-ruptures-or-tears-aorta-blood-vessel-fluoroquinolone-antibiotics
32 European Medicines Agency. Disabling and potentially permanent side effects lead to suspension or restrictions of quinolone and fluoroquinolone antibiotics. 2019. Available: https://www-ema-europa-eu.docelec.u-bordeaux.fr/en/documents/referral/quinolone-fluoroquinolone-article-31-referral-disabling-potentially-permanent-side-effects-lead_en.pdf
33 Dong Y-H, Chang C-H, Wang J-L, *et al*. Association of Infections and Use of Fluoroquinolones With the Risk of Aortic Aneurysm or Aortic Dissection. *JAMA Intern Med* 2020;180:1587–95.
34 Gopalakrishnan C, Bykov K, Fischer MA, *et al*. Association of Fluoroquinolones With the Risk of Aortic Aneurysm or Aortic Dissection. *JAMA Intern Med* 2020;180:1596–605.
35 D'Arcy M, Stürmer T, Lund JL. The importance and implications of comparator selection in pharmacoepidemiologic research. *Curr Epidemiol Rep* 2018;5:272–83.
36 Jouneau S, Ricard J-D, Seguin-Givelet A, *et al*. Guidelines for management of patients with primary spontaneous pneumothorax. *Rev Mal Respir* 2023;40:265–301.