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## Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database

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### ABSTRACT

**Objective** To determine the extent to which antibiotics reduce the risk of serious complications after common respiratory tract infections.

**Design** Retrospective cohort study.

**Setting** UK primary care practices contributing to the general practice research database.

**Data source** 3.36 million episodes of respiratory tract infection.

**Main outcome measures** Risk of serious complications in treated and untreated patients in the month after diagnosis: mastoiditis after otitis media, quinsy after sore throat, and pneumonia after upper respiratory tract infection and chest infection. Number of patients needed to treat to prevent one complication.

**Results** Serious complications were rare after upper respiratory tract infections, sore throat, and otitis media, and the number needed to treat was over 4000. The risk of pneumonia after chest infection was high, particularly in elderly people, and was substantially reduced by antibiotic use, with a number needed to treat of 39 for those aged  $\geq 65$  and 96-119 in younger age groups.

**Conclusion** Antibiotics are not justified to reduce the risk of serious complications for upper respiratory tract infection, sore throat, or otitis media. Antibiotics substantially reduce the risk of pneumonia after chest infection, particularly in elderly people in whom the risk is highest.

### INTRODUCTION

Most antibiotic prescribing is in primary care, and most of it is for respiratory tract infections.<sup>1</sup> Clinical guidelines advise against the routine use of antibiotics in patients with upper respiratory tract infection,<sup>2,3</sup> sore throat,<sup>2</sup> and otitis media.<sup>2</sup> Guidelines divide chest infection into acute bronchitis, for which antibiotics are not recommended, and pneumonia, for which they are recommended.<sup>2,4</sup> Recommendations not to prescribe are based on concerns about the development of antimicrobial resistance and evidence from meta-analyses of randomised controlled trials that have shown minimal benefits.<sup>5-8</sup>

A national campaign in the United Kingdom targeting doctors and the public aimed to reduce unnecessary antibiotic prescribing.<sup>9</sup> Whether in response to these campaigns or to a declining incidence of disease, rates of antibiotic prescribing for acute respiratory infections in UK general practice declined by 45% between 1994 and 2000.<sup>10</sup> Despite this, in 2000 antibiotics were still prescribed to 67% of patients presenting to general practice with respiratory infection, including over 90% of those with chest infection, 80% with ear infections, 60% with sore throat, and 47% with upper respiratory tract infections.<sup>10</sup> The decisions to prescribe antibiotics are complex but on the basis of this evidence there seems to be a substantial gap between evidence based guidance and general practitioners' prescribing behaviour.

Continuing high rates of prescribing may relate to patients' expectations and to fears about serious complications of infection.<sup>11</sup> Research has suggested that low rates of antibiotic prescribing in primary care might be associated with higher rates of complications of infection,<sup>12</sup> and decreases in prescribing might have led to increases in mastoiditis<sup>13</sup> and increased hospital admissions for respiratory infection in the UK<sup>14</sup> and the United States.<sup>15</sup> These studies cannot determine whether adverse events are occurring less frequently in those people who received antibiotics for minor infections than in those who did not. Meanwhile, randomised controlled trials generally have insufficient power to examine the effect of interventions on rare outcomes, and the patients included might not be representative of those seen in routine clinical practice.

We used a large primary care database to describe the effect of antibiotics in routine practice on the risk of serious complications after common respiratory tract infections.

### METHODS

We used data from 162 practices that contributed to the UK General Practice Research Database from 1 July 1991 to 30 June 2001. In patients with common respiratory infections, we examined the risk of developing serious complications in the month after

diagnosis of infection, excluding those that were recorded on the day of diagnosis. We calculated and compared this risk in those who were treated with antibiotics and those who were not. Patients were considered to have been prescribed an antibiotic for a respiratory tract infection if the prescription was issued on the day of the consultation. We included consultations for chest infection (excluding those in patients with a diagnosis of pneumonia at baseline), upper respiratory tract infection, sore throat, and acute otitis media based on OXMIS<sup>16</sup> and Read<sup>17</sup> codes (tables 1 and 2). Potentially serious complications were mastoiditis for otitis media, quinsy for sore throat, and pneumonia for chest infection and upper respiratory tract infection. In addition to these severe complications we examined the effect of antibiotics given for upper respiratory tract infection on the risk of chest infection in the subsequent month.

We used logistic regression, adjusted for age, sex, and social deprivation, to calculate odds ratios for the potential protective effect of antibiotics. Social deprivation was area based on Carstairs' scores<sup>18</sup> for all electoral wards in England, Wales, and Scotland.

**Table 1** | Read and OXMIS codes used to define adverse outcomes

Disease and Read/OXMIS codes	Description
<b>Mastoiditis</b>	
3831	MASTOIDITIS CHRONIC
3839	MASTOIDITIS
3879AM	MASTOID DISEASE
F53..00	Mastoiditis and related conditions
F531.00	Chronic mastoiditis
F531z00	Chronic mastoiditis NOS
F53z.00	Mastoiditis NOS
F55yz00	Other middle ear or mastoid disorder NOS
F55z.00	Middle ear or mastoid disorder NOS
<b>Pneumonia</b>	
481 A	PNEUMONIA PNEUMOCOCCAL
481 B	LOBAR PNEUMONIA
481 BA	PNEUMONIA BASAL
485	BRONCHOPNEUMONIA
486	PNEUMONIA
H2...00	Pneumonia and influenza
H21..00	Lobar (pneumococcal) pneumonia
H22..00	Other bacterial pneumonia
H22z.00	Bacterial pneumonia NOS
H25..00	Bronchopneumonia due to unspecified organism
H25..11	Chest infection—unspecified bronchopneumonia
H26..00	Pneumonia due to unspecified organism
H260.00	Lobar pneumonia due to unspecified organism
H261.00	Basal pneumonia due to unspecified organism
<b>Quinsy</b>	
501 N	QUINSY
501 PB	ABSCESS PERITONSILLAR
501 PC	PERITONSILLAR ABSCESS
501 TA	ABSCESS TONSIL
2DB5.11	O/E—quinsy present
H15..00	Peritonsillar abscess—quinsy
H15..11	Quinsy

Practices were assigned to fifths of social deprivation based on the electoral wards in which they were located. The analyses were further stratified on age if there was a significant interaction between age and antibiotic prescription. When there was a significant protective effect of antibiotics between treated and untreated patients we calculated the number needed to treat with antibiotics to prevent one patient from developing complications as 1/(absolute risk difference). We also performed separate analyses of the impact of smoking and underlying chronic respiratory disease on the risk of pneumonia after chest infection and the number needed to treat. These were performed with a different set of practices selected according to the level of completeness of recording of smoking status.

## RESULTS

The study included 1 081 000 episodes of upper respiratory tract infection, 1 065 088 cases of sore throat, and 459 876 cases of otitis media. The risk of serious complications in the month after diagnosis of these conditions was low (table 3) and was significantly reduced with the use of antibiotics, but the number needed to treat to prevent one serious complication was over 4000 for all of these conditions (table 4). The protective effect of antibiotics did not vary significantly by age. We also attempted to examine acute rheumatic fever and acute glomerulonephritis as potential complications of sore throat but found that it was difficult to distinguish between acute and chronic events and that there were virtually no cases after sore throat. Therefore, we did not continue this analysis. The risk of a consultation for chest infection in the month after upper respiratory tract infection was 17 per 1000 in those not treated with antibiotics and 11 per 1000 in those who were treated (adjusted odds ratio 0.64, 95% confidence interval 0.58 to 0.71, number needed to treat =161).

There were 749 389 episodes of chest infection. The risk of pneumonia in the month after diagnosis was high and was substantially reduced by antibiotics (tables 3 and 4). This effect varied significantly with age, such that the greatest protective effect was in those aged 65 and over. Without an antibiotic prescription 4% of those aged 65 and over were diagnosed with pneumonia in the month after diagnosis of a chest infection compared with 1.5% of those who were treated with an antibiotic (table 3). The number needed to treat to prevent one patient subsequently consulting with pneumonia was 39 (36 to 42) in this age group and between 96 and 119 in younger age groups (table 4). Analyses stratified by smoking status and by underlying chronic respiratory disease found no evidence that these factors affected the risk of complications or the protective effect of antibiotics.

## DISCUSSION

### Principal findings of the study

The risk of serious complications after sore throat, otitis media, and upper respiratory tract infection is

**Table 2** | Read and OXMIS codes used to define sore throat, upper respiratory tract infection, chest infections, and otitis media

Disease and Read/OXMIS codes	Description
<b>Sore throat</b>	
0340	SORE THROAT STREPTOCOCCAL
0340A	B-HAEMOLYTIC STREPTOCOCCAL PHARYNGIT
0340B	SORE THROAT STREPTOCOCCAL PROVEN
0340BP	PHARYNGITIS STREPTOCOCCAL PROVEN
0340BT	STREPTOCOCCAL TONSILLITIS PROVEN
0340P	PHARYNGITIS STREPTOCOCCAL
0340PN	PHARYNGITIS SEPTIC
0340T	STREPTOCOCCAL TONSILLITIS
0799B	THROAT VIRUS
460 AN	ACUTE FEBRILE NASOPHARYNGITIS
460 DN	NASOPHARYNGITIS
460 RN	RHINOPHARYNGITIS
462 AB	PHARYNGITIS
462 AC	SCRATCHY THROAT
462 AR	SORE THROAT
462 AV	PHARYNGITIS VIRAL
462 C	ACUTE PHARYNGITIS
462 CT	SORE THROAT ACUTE
462 F	PHARYNGITIS FEBRILE
463	ACUTE TONSILLITIS
463 A	TONSILLITIS
463 AP	PHARYNGO TONSILLITIS
463 B	FOLLICULAR TONSILLITIS
463 BC	TONSILLITIS BACTERIAL
463 MP	TONSILS SYMPTOMS OF
463 NF	INFLAMMATION TONSIL
508 E	INFECTION THROAT
508 EA	ACUTE THROAT INFECTION
508 LD	DISCOMFORT LARYNGEAL
1C9..00	Sore throat symptom
1C9..11	Throat soreness
1C92.00	Has a sore throat
1C92.00	Sore throat symptom NOS
A340.00	Streptococcal sore throat
A340200	Streptococcal pharyngitis
A340300	Streptococcal tonsillitis
H00..00	Acute nasopharyngitis
H02..00	Acute pharyngitis
H02..11	Sore throat NOS
H02..12	Viral sore throat NOS
H02..13	Throat infection - pharyngitis
H024.00	Acute viral pharyngitis
H02z.00	Acute pharyngitis NOS
H03..00	Acute tonsillitis
H03..11	Throat infection - tonsillitis
H03..12	Tonsillitis
H031.00	Acute follicular tonsillitis
H035.00	Acute bacterial tonsillitis
H03z.00	Acute tonsillitis NOS
<b>Upper respiratory tract infection</b>	
460 A	COMMON COLD FEBRILE
460 AB	COLD FEBRILE
460 B	COMMON COLD NONFEBRILE
460 BA	COLD NONFEBRILE
460 D	COLD (CORYZA)
465	INFECTION UPPER RESPIRATORY (TRACT)
465 A	UPPER RESPIRATORY INFECTION ACUTE

low and the number of courses of antibiotic needed to prevent one serious complication is high (over 4000). Antibiotics for upper respiratory tract infection reduced the risk of consultation for chest infection but even without treatment less than 2% of patients consulted with a chest infection in the following month.

We found a substantial risk of pneumonia after chest infection, which was greatly reduced by antibiotic use, with a relatively low number of courses of antibiotic needed to prevent one diagnosis of pneumonia (39 in those aged 65 and over and between 96 and 119 in younger age groups). The risks of pneumonia after chest infection and the number of antibiotic courses needed to prevent one case of pneumonia were not appreciably different in smokers, those with chronic respiratory disease, or those with cardiac disease.

#### Strengths and weaknesses of the study

This was a large study of complications after common respiratory tract infections. The patients included in the study are probably highly representative of those seen in primary care. The cohort design allowed us to estimate the absolute risk of rare outcomes, the effect of antibiotics on this risk, and the number of antibiotic courses needed to prevent one complication.

The non-randomised design means that it is likely that patients with more severe disease will be treated with antibiotics. If those with severe disease have a higher risk of complications then this would tend to lead to an underestimation of the protective effect of antibiotics. For upper respiratory tract infection, sore throat, and otitis media the number needed to treat would be lowered but would remain high, while for chest infection this further emphasises the benefit of antibiotic prescribing.

Studies that use routine primary care databases need to rely on the Read and OXMIS codes that general practitioners have assigned to conditions. In routine practice doctors are unlikely to apply strict case definitions when allocating diagnostic codes. For example, the term “chest infection” potentially includes both acute bronchitis and pneumonia. We excluded those with a code for pneumonia at the initial consultation for chest infection but some patients probably already had undiagnosed pneumonia.

The more specific term of “acute bronchitis” was rarely coded, precluding separate analysis of this entity. In reality the only way to distinguish reliably between acute bronchitis and early pneumonia is with chest radiography. As chest radiography is not readily available in primary care there may be some misclassification of chest infection and pneumonia. This misclassification could lead to an overestimation of the risk of pneumonia after chest infection. When patients return with an unresolved chest infection there may be more pressure to prescribe and some doctors who know that guidance advises against prescription in chest infection may label the condition as pneumonia to justify their prescribing decision. This may have led to overestimation of the apparent risk of pneumonia after chest infection and the protective

465 AA	U R I (UPPER RESPIRATORY INFECTION)
465 B	UPPER RESPIRATORY INFECTION ACUTE VI
H00..11	Common cold
H00..13	Febrile cold
H05..00	Other acute upper respiratory infections
H051.00	Acute upper respiratory tract infection
H05z.00	Upper respiratory infect.NOS
H05z.11	Upper respiratory tract infection NOS
H05z.12	Viral upper respiratory tract infection NOS
<b>Chest infection</b>	
466 BC	BRONCHITIS SUBACUTE
466 C	ACUTE BRONCHITIS
466 D	BRONCHITIS PURULENT
490 C	CHEST COLD
5199E	CHEST INFECTION
H060.00	Acute bronchitis
H060.11	Acute wheezy bronchitis
H060300	Acute purulent bronchitis
H062.00	Acute lower respiratory tract infection
H06z000	Chest infection NOS
H06z011	Chest infection
H06z100	Lower resp tract infection
H07..00	Chest cold
<b>Otitis media</b>	
3810	ACUTE OTITIS MEDIA
3810ML	A L O M (ACUTE LEFT OTITIS MEDIA)
3810MR	A R O M (ACUTE RIGHT OTITIS MEDIA)
3810TP	OTITIS ACUTE SUPPURATIVE
3811AR	OTITIS MEDIA RECURRENT
3811E	BSOM (BILATERAL SUPPURATIVE OTITIS M
3819	OTITIS MEDIA
3819E	BILATERAL OTITIS MEDIA
3819MP	SUPPURATIVE OTITIS MEDIA
3819N	OTITIS
3819 <sup>TH</sup>	HAEMOTYMPANUM
F510.00	Acute non suppurative otitis media
F510000	Acute otitis media with effusion
F510011	Acute secretory otitis media
F510100	Acute serous otitis media
F510300	Acute sanguinous otitis media
F510z00	Acute nonsuppurative otitis media NOS
F52..00	Suppurative otitis media
F520.00	Acute suppurative otitis media
F520000	Acute suppurative otitis media tympanic membrane intact
F520100	Acute suppurative otitis media tympanic membrane ruptured
F520z00	Acute suppurative otitis media NOS
F524.00	Purulent otitis media NOS
F524000	Bilateral supp otitis media
F526.00	Acute left otitis media
F527.00	Acute right otitis media
F528.00	Acute bilateral otitis media
F52z.00	Otitis media NOS

effect of antibiotics. Anecdotal evidence, however, suggests that general practitioners are unlikely to use the term pneumonia lightly as it is a serious condition.

Other biases may have led to underestimation of the risk of pneumonia. For example, pneumonia may be more likely to be treated in secondary care or during out of hours home visits and therefore under-recording may have occurred. General practitioners contributing

to the database are, however, asked to record events that occur outside the surgery when they become aware of them. Several biases working in different directions may have influenced the findings, though they would need to be extreme to alter our main conclusions substantially. For sore throat, otitis media, and upper respiratory tract infection the number of antibiotic courses needed to prevent serious complications is high. For chest infection, however, the number needed to prevent one case of pneumonia is relatively modest, especially in elderly patients. Antibiotics for chest infection might also reduce the risk of other serious complications of chest infection, such as admissions to hospital for reasons other than pneumonia, but we did not assess this.

#### Strengths and weaknesses in relation to other studies

Observational studies using large datasets of routinely collected primary care data are the only practicable way to examine the effect of antibiotic prescribing on rare complications of common infection. Randomised controlled trials could theoretically overcome some of the biases discussed but have insufficient power and are highly selective about the patients involved. Meta-analyses have had insufficient power to examine the protective effect of antibiotics for pneumonia after upper respiratory tract infection<sup>7</sup> or for mastoiditis after otitis media.<sup>5</sup> With sample sizes of more than a million patients with upper respiratory tract infection (compared with 1495 participants in the meta-analysis)<sup>7</sup> and nearly half a million with otitis media (compared with 1669 participants in the meta-analysis),<sup>8</sup> we were able to show that, while antibiotics have a protective effect in these conditions, the number needed to treat to prevent complications is high.

Meta-analyses have shown that antibiotics can reduce the risk of quinsy after sore throat,<sup>6</sup> but this conclusion is primarily related to one large study in the 1950s, when the population incidence of quinsy was much higher than today.<sup>19</sup> We included over a million cases of sore throat treated in the 1990s (compared with 10 101 participants included in the meta-analysis)<sup>6</sup> and showed that antibiotics do indeed reduce the risk of quinsy. As with upper respiratory tract infections and otitis media, however, the number needed to treat to prevent one serious complication is high.

Our analysis focuses on the main serious complications of common respiratory infections, particularly those complications that are rare and therefore difficult to assess through randomised controlled trials or meta-analyses. We did not include length of illness, cough, days off work, or fever for this reason and also because the database includes consultations and therefore has virtually no information on these outcomes. Similarly, we have not included need for steroids in patients with asthma because this is likely to involve them taking additional doses of a previously prescribed medication that they already have at home. We have no way of assessing such use.



**Table 3** | Risk of complications in the month after diagnosis of common respiratory infections (per 10 000)

Complication after infection by age (years)	Without prescription		With prescription	
	Risk per 10 000	No of patients	Risk per 10 000	No of patients
<b>Pneumonia after upper respiratory tract infection</b>				
0-4	10.74	216 863	6.69	165 802
5-15	4.45	98 852	4.04	103 866
16-64	6.73	145 596	5.40	263 044
≥65	53.67	26 646	33.15	60 331
<b>Quinsy after sore throat</b>				
0-4	1.57	25 518	0.42	95 045
5-15	5.99	73 429	5.34	226 588
16-64	21.26	148 601	18.37	449 646
≥65	9.46	14 794	6.04	31 467
<b>Mastoiditis after otitis media</b>				
0-4	1.33	30 178	0.53	186 931
5-15	2.39	16 765	1.79	123 032
16-64	11.92	16 780	6.77	76 763
≥65	13.00	2 307	5.62	7 120
<b>Pneumonia after chest infection</b>				
0-4	125.92	14 613	27.15	75 512
5-15	127.31	5 027	22.74	46 612
16-64	116.10	38 588	31.80	322 932
≥65	402.68	45 470	146.14	200 635

Many of these less serious outcomes have previously been examined by randomised controlled trials and meta-analyses that have emphasised the minimal benefits of prescribing for upper respiratory tract infection, sore throat, and otitis media.<sup>5-7</sup> Antibiotics for upper respiratory tract infection did reduce the risk of consultations for chest infection in the following month but the number needed to treat (161) to prevent such a consultation was relatively high considering that chest infection is not a particularly serious condition. This reduction in consultation needs to be balanced against other research that has shown that prescribing for minor infections may make patients more likely to consult the next time they have such an infection.<sup>20</sup>

We identified a higher risk of pneumonia after chest infection than observed in randomised control trials for treatment of acute bronchitis.<sup>8</sup> In such trials great care is taken to exclude pneumonia through use of

chest radiography either for all patients or all those with focal chest signs. These procedures are likely to be less stringent in routine practice. This is one of the factors likely to account for the considerably higher risk of pneumonia in our study compared with the risk in randomised control trials. Given that chest radiography is not routinely available in primary care outside the context of trials it is arguable that our findings are more pertinent to general practitioners' treatment decisions than the results of randomised control trials.

#### Implications of the study

There are legitimate concerns about the overuse of antibiotics in primary care and the development of resistance. For example, a recent randomised controlled trial has clearly shown increased carriage in resistant organisms after macrolide administration but not after placebo.<sup>21</sup> General practitioners should not base their prescribing for sore throat, otitis media, or upper respiratory tract infections on a fear of serious complications. There is also broad consensus that the benefit in terms of more minor outcomes such as duration and severity of illness does not justify antibiotic use for these conditions.<sup>2-7</sup> Nevertheless, many general practitioners continue to prescribe for these conditions.<sup>10</sup>

In contrast, antibiotics substantially reduce the risk of a diagnosis of pneumonia after chest infection. Prescribing guidance from the UK<sup>2</sup> and the US<sup>4</sup> recognises the difficulty in distinguishing between acute bronchitis, where doctors are advised not to prescribe antibiotics, and early pneumonia, where they are advised to prescribe. The guidance notes that in otherwise healthy, non-elderly adult patients who present with cough, pneumonia is unlikely if there are no new focal chest signs and all vital signs are normal<sup>2,4</sup> and emphasises the importance of a thorough clinical examination before the decision to withhold antibiotics from patients with chest infection. Community acquired pneumonia is a serious condition with mortality ranging from 5% in ambulatory and hospitalised patients to 37% among those in intensive care.<sup>22</sup> General practitioners already prescribe antibiotics to nearly all patients with chest infection<sup>10</sup> but are often criticised for doing so. We have shown that antibiotic prescribing to reduce the risk of pneumonia after chest infection is justifiable, particularly in elderly patients.

#### Unanswered questions and future research

We could not evaluate the effect of antibiotics on resolution of symptoms. Randomised controlled trials have consistently found these benefits to be small,<sup>5-8</sup> and they need to be balanced against the risk of side effects and the development of antibiotic resistance. It is now unlikely that randomised controlled trials that are sufficiently large to accurately measure the protective effect of antibiotics on serious complications of common respiratory tract infection will ever be conducted. For upper respiratory tract infection, sore

**Table 4** | Protective effect of antibiotics for common respiratory tract infections and number needed to treat to prevent one complication

Infection/adverse outcome (age group)	Adjusted odds ratio* (95% CI)	Number needed to treat (95% CI)	P value
URTI/pneumonia (all ages)	0.68 (0.58 to 0.79)	4407 (2905 to 9126)	<0.001
Otitis media/mastoiditis (all ages)	0.56 (0.37 to 0.86)	4064 (2393 to 13 456)	0.008
Sore throat/quinsy (all ages)	0.84 (0.73 to 0.97)	4300 (2522 to 14 586)	0.021
Chest infection/pneumonia (significant interaction between prescribing and age):			
0-4 years	0.22 (0.17 to 0.27)	101 (85 to 125)	<0.001
5-15 years	0.18 (0.13 to 0.24)	96 (73 to 137)	<0.001
16-64 years	0.27 (0.23 to 0.32)	119 (105 to 136)	<0.001
≥65 years	0.35 (0.33 to 0.38)	39 (36 to 42)	<0.001

URTI=upper respiratory tract infection.

\*Adjusted for age, sex, and social deprivation.

**WHAT IS ALREADY KNOWN ON THIS TOPIC**

Guidelines based on randomised controlled trials recommend that antibiotics should not be prescribed for upper respiratory tract infection, sore throat, or otitis media  
Chest infections are divided into acute bronchitis (antibiotics not recommended) and pneumonia (antibiotics recommended)

**WHAT THIS STUDY ADDS**

Antibiotics reduce the risk of mastoiditis after otitis media, quinsy after sore throat, and pneumonia after upper respiratory tract infection but over 4000 courses of antibiotics are needed to prevent one complication

Conversely, the risk of pneumonia in those presenting with chest infection is high, particularly in elderly patients, and can be substantially reduced by the use of antibiotics

throat, and otitis media research should focus on effective interventions to reduce prescribing. For chest infection research should focus on developing clinical algorithms and diagnostic technology that can be easily applied in primary care to enable confident distinction between acute bronchitis and early pneumonia and to identify those who are most likely to develop pneumonia.

**Contributors:** ACH was chief investigator, had the original idea for the study, and developed the analytical strategy with IP. The study plan was refined with input from all authors. IP analysed the data. AI extracted the relevant data from the database. IP and ACH drafted the paper, incorporating comments from the other authors. ACH is guarantor.

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