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Antibiotic use and serious complications following acute otitis media and acute sinusitis

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Abstract

Background

Most people with acute otitis media (AOM) and acute sinusitis (AS) do not benefit from antibiotics, and GPs are under increasing pressure to reduce antibiotic prescribing. Concern about the risk of complications can drive unnecessary prescribing.

Aim

Describe the incidence of serious complications following AOM and AS and determine whether antibiotics are protective.

Design and Setting

Retrospective cohort study. Patients diagnosed in general practice with AOM or AS 1/1/82–31/12/12.

Method

We calculated the incidence of brain abscess and acute mastoiditis following AOM, and of brain abscess and orbital cellulitis following AS, the association between antibiotics and development of these complications, and the numbers needed to treat (NNT).

Results

The incidence of brain abscess and acute mastoiditis following AOM were 0.03 (95% CI:0.01–0.20) and 5.62 (95% CI:4.81–6.56) per 10,000 AOM episodes. The incidence of brain abscess and orbital cellulitis following AS was 0.11 (95% CI:0.05–0.26) and 1.50 (95% CI:1.17–1.90) per 10,000 AS episodes. Antibiotic prescription for AOM was associated with lower odds of developing mastoiditis (OR 0.54; 95% CI:0.37–0.79), NNT 2181 (95% CI:1196–5709). Antibiotic prescribing for AS was associated with lower odds of subsequent brain abscess (OR 0.12; 95% CI:0.02–0.70), NNT 19,988 (95% CI:4951–167,099). We found no significant association between antibiotic prescription and development of orbital cellulitis following AS (OR 0.56; 95% CI:0.2–1.12).

Conclusion

Serious complications following AOM and AS are rare. Antibiotics are associated with lower odds of developing complications but the NNT is large.

Key words

Acute otitis media, acute sinusitis, antibiotics, complications, general practice

How this fits in

Concern about reducing the risk of serious complications can drive antibiotic prescribing for common infections such as acute otitis media and sinusitis; and use of antibiotics is the major driver of antibiotic resistance. The association between use of antibiotics for acute otitis media and acute sinusitis, and the subsequent risk of mastoiditis, brain abscess and orbital cellulitis, has not been adequately explored. We demonstrated that these serious complications are extremely uncommon. Antibiotic use was associated with a lower risk of

mastoiditis following acute otitis media and brain abscess following acute sinusitis, but for both conditions thousands of patients would need to be treated to prevent one complication.

Introduction

Given the current global threat from increasing antimicrobial resistance, judicious use of antibiotics is a major public health challenge. (1, 2) Almost 75% of antibiotic prescribing in England occurs in general practice, (3) and NICE estimate that respiratory tract infections (RTIs) account for 60% of antibiotic prescribing. (4)
Despite antibiotic stewardship activities, antibiotics are prescribed for up to 80% of RTIs in primary care, (5) with prescribing particularly high for acute otitis media (AOM) and rhinosinusitis. (5-7) Experts have suggested that many antibiotic prescriptions are unnecessary and that 'ideal' levels of prescribing for RTIs should be much lower. (7)
AOM is one of the commonest childhood infections, (8) and acute sinusitis (AS) one of the commonest conditions diagnosed in primary care. (9) Most episodes of AOM and AS resolve without antibiotics, and antibiotics offer little benefit in terms of symptom resolution. (8-14) NICE currently recommends most cases of AOM and acute rhinosinusitis are managed without antibiotics or with a back-up antibiotic prescription. (15, 16) AOM and sinusitis can be complicated by serious conditions such as mastoiditis and orbital cellulitis respectively, and both are predisposing factors for brain abscess. (17)

The incidence of mastoiditis following otitis media and protective effect of antibiotics has been examined in two previous UK retrospective cohort studies. (18, 19) One of these studies only included children and both studies used a broad set of codes for otitis media which is likely to have reduced their specificity in relation to the diagnosis of AOM. Risk of orbital abscess following sinusitis has been explored in a previous Swedish cohort study, but this study did not explore whether antibiotics modified this risk, and no other studies exploring the risk of these complications at an individual level have been identified. (20)

Fear of serious complications can drive antibiotic prescribing in RTIs. (21) Therefore understanding the risk of septic complications following AOM or AS, and whether antibiotics are protective, can help allay fears and may lead to more rational prescribing.

We aimed to determine the incidence of acute mastoiditis and brain abscess following AOM, and of orbital cellulitis and brain abscess following AS, and to assess whether antibiotics are protective against development of these complications.

Method

Study design and study population

A retrospective cohort study was undertaken of patients diagnosed in primary care with AOM or AS and recorded in the Clinical Practice Research Datalink (CPRD) database. CPRD contains anonymised primary care records of approximately 7% of the UK population, and its predecessor the GPRD was identified to have high quality data (19, 22).

Defining the population

AOM and AS diagnoses from 1/1/82–31/12/12 in children and adults were identified using pre-specified Read codes. Consultations were included if the diagnosis date occurred on or after the patients' data were defined as 'acceptable' by CPRD. Consultations occurring within 14 days of initial AOM consultation and 28 days of initial AS consultation were

defined as part of the same illness episode. Patients prescribed an antibiotic ≤14 days before AOM/AS diagnosis were excluded. Patients could have >1 illness episode and be included in both AOM and AS cohorts.

Antibiotic Exposure
Antibiotic exposure was defined as prescription of an antibiotic on the same date as initial AOM/AS diagnosis. Antibiotics were defined as all oral antibiotics listed in BNF chapter 5.1. (23)

Outcome measures
Outcomes were identified from primary care Read codes or ICD-10/OPCS codes identified from linked HES data.
Three outcomes were defined:
1. Brain abscess ≤90 days of AOM/AS diagnosis.
2. Acute mastoiditis ≤90 days of AOM diagnosis.
3. Orbital cellulitis ≤90 days of AS diagnosis.

Incidence of complications
We calculated the incidence of acute mastoiditis and brain abscess following AOM, and of orbital cellulitis and brain abscess following AS. Additional stratified analyses were undertaken to calculate incidence of outcomes for those ≤20 years and >20 years. 95% confidence intervals (CIs) were calculated using Wilson method. (24)

Primary Analysis
The association between antibiotics and outcomes was assessed using logistic regression to calculate crude odds ratios (OR). The association between potential confounders (age, smoking history, asplenia, HIV/AIDS, transplanted organ, CSF shunt, diabetes mellitus, and severe chronic kidney disease) and antibiotic exposure and the outcome of interest were examined using logistic regression. Confounders significantly associated with both exposure and outcome (p value <0.05) were included in multivariable logistic regression models. Sequential logistic regression modelling was undertaken to identify the model that provided the best fit of the data and final crude/adjusted OR were obtained.
Additional logistic regression analyses for acute mastoiditis following AOM and for orbital cellulitis/brain abscess following AS were undertaken in those ≤20 and >20 years.

Numbers needed to treat (NNT)
For outcomes significantly associated with antibiotic prescription we calculated the NNT (1/risk difference) and associated 95% CIs using Wilson method. (24)

Statistical analyses were undertaken using SPSS 20.

Results
286,574 episodes of AOM and 441,873 episodes of AS were identified – see figures 1 and 2. 86.9% of AOM patients and 92.1% of AS patients were prescribed antibiotics at initial consultation. Baseline characteristics of both cohorts are shown in Tables 1 and 2.

Incidence of complications
Incidence of brain abscess following AOM was 0.03 per 10,000 AOM episodes (95% CI:0.01-0.20).

Incidence of acute mastoiditis following AOM was 5.62 per 10,000 AOM episodes (95% CI:4.81-6.56).
Incidence of brain abscess following AS was 0.11 per 10,000 AS episodes (95% CI:0.05-0.26).
Incidence of orbital cellulitis following AS was 1.50 per 10,000 AS episodes (95% CI:1.17-1.90).

Incidence of acute mastoiditis following AOM in those ≤20 years was 3.74 per 10,000 AOM consultations (95% CI:3.01-4.65) and 11.41 per 10,000 AOM episodes (95% CI:9.17-14.19) in those >20 years.
All episodes of brain abscess following AS occurred in those >20 years (incidence 0.12 per 10,000 AS episodes (95% CI:0.11-0.13)).
Incidence of orbital cellulitis following AS in those ≤20 years was 4.94 per 10,000 AS episodes (95% CI:2.89-8.46) and 1.28 per 10,000 AS episodes (95% CI:1.17-1.39) in those >20 years.

Primary analysis: Association between antibiotic prescription and outcomes
The incidence of septic complications for those who were and were not prescribed antibiotics at initial consultation and the associated OR and NNT are shown in table 3. The models that best fit the data for the association between antibiotic prescription and acute mastoiditis following AOM and for orbital cellulitis and brain abscess following AS only included age as a confounding variable. There was only one episode of brain abscess following AOM so it was not possible to assess the association with antibiotic prescription.

Antibiotic prescription at initial consultation was protective against development of mastoiditis following AOM and brain abscess following AS – table 3. However, as these are rare complications the NNT to prevent one case lies between 1196 and 5709 for acute mastoiditis following AOM and between 4,951 and 167,099 for brain abscess following AS.
No statistically significant association was identified between antibiotic prescription and development of orbital cellulitis following AS, however the point estimate was in the direction of reduced odds.

Stratified analyses
The association between antibiotic prescription and septic complications stratified by age are shown in table 4. Antibiotics showed a stronger protective benefit against development of acute mastoiditis following AOM in those ≤20 years than in the whole cohort. However, no statistically significant association was seen in those >20 years.
All cases of brain abscess following AS occurred in those >20 years old, and a statistically significant association was seen between antibiotic prescription and odds of developing brain abscess following AS in this age group – table 4.
In those ≤20 years a statistically significant association was demonstrated between antibiotic prescription and development of orbital cellulitis following AS – table 4. However, as it is rare, the NNT to prevent one such case lies between 260 and 2695.

Discussion

Summary
Our findings confirm that the incidence of serious complications following AOM and AS is very low, with only one out of 300,000 patients with AOM developing a brain abscess up to an incidence of 5.62 per 10,000 episodes for acute mastoiditis following AOM. We found

evidence that antibiotic prescription is associated with reduced odds of acute mastoiditis following AOM and brain abscess following AS, with NNT of 2181 and 19,988 respectively. We found a non-significant association between antibiotic prescription and orbital cellulitis following AS. In stratified analyses, antibiotic prescribing was only associated with a reduced odds of acute mastoiditis following AOM, and orbital cellulitis following AS, in those ≤20 years. Cases of brain abscess following AS only occurred in patients >20 years old, and antibiotic prescription was found to significantly reduce the odds of this outcome in this age group.

Strengths and limitations

This is a large study investigating the development of serious complications following common RTIs. Use of the CPRD database facilitated inclusion of a large number of patients from a range of UK general practices, providing a highly representative sample. CPRD is a widely used and well-validated database. (19) The cohort design enabled estimation of the incidence of serious complications following episodes of AOM and AS, the effect of antibiotic prescription on the risk of such complications, and the number of patients that need to be treated with antibiotics in order to prevent one such complication.

The use of routine data meant that we had to rely on the presence and accuracy of Read codes assigned by primary care practitioners to identify patients with AOM and AS as opposed to the use of strictly defined case definitions. Up to a third of antibiotic prescriptions have been shown to have no associated diagnosis or symptom Read code. (25) Therefore, a number of patients with AOM or AS may not have been coded at all and will thus have been missed from this study. However, whilst coding of RTIs in primary care records is not sensitive, it is likely to be specific, and variability in coding related to GP rather than patient characteristics. Therefore, the incidence of consultations for these RTIs is likely to be underestimated from these data. It is, however, unlikely that acute mastoiditis, orbital cellulitis and brain abscess have been misclassified, as such serious diagnoses would usually be made following extensive investigation in secondary care and are usually well coded in HES and/or GP data. Therefore, we believe that our estimates of the incidence of serious complications following AOM or AS, and the changes in risk associated with antibiotic prescribing, are likely to be valid. Routine primary care data only provides information on antibiotic prescribing and not antibiotic consumption, and therefore our estimates reflect the association between being prescribed an antibiotic and developing a complication, as opposed to taking an antibiotic and developing a complication. We were also unable to identify the use of delayed antibiotic prescriptions in this study, but there is no evidence that delayed prescribing was commonly used prior to 2012.

Our study is at risk of indication/selection bias, in that individuals with more severe illness are more likely to have been prescribed antibiotics and more likely to develop complications. As such, the identified beneficial effects of antibiotics may have been diluted and the associated NNTs overestimated.

Whilst a number of potential confounding factors were assessed for their association between antibiotic prescription and the outcomes, and the results adjusted for the effect of age, it is a possibility that unmeasured confounding may have biased the reported associations.

Comparison with existing literature

Several previous studies have examined the risk of serious complications following common RTIs, and attempted to assess whether antibiotics confer a protective effect. Two previous

studies have used CPRD data to explore the risk of mastoiditis following AOM, but neither looked at the risk of brain abscess following AOM or AS, or orbital cellulitis following AS. (18, 19) Petersen at al reported an incidence of mastoiditis within one month of otitis media in adults and children of 2.2 per 10,000 consultations. (18) Thompson et al only assessed the risk in children, and reported an incidence of mastoiditis within three months of otitis media of 2.4 per 10,000 otitis media episodes. (19) Both studies found a lower incidence of mastoiditis than the 5.62 per 10,000 identified in our study, but our findings may be more representative of the actual incidence as our inclusion criteria was more specific and only included codes for *acute* otitis media. We also included a longer follow-up period for detecting acute mastoiditis than that used in the Petersen study, and therefore may have had better ascertainment of the complication outcome. Both of these previous studies also explored the protective effect of prescribing antibiotics for AOM on the risk of mastoiditis, and reported ORs remarkably similar to our study (Petersen OR 0.56 (95% CI:0.37–0.86); Thompson OR 0.56 (95% CI:0.44–0.71); our study OR 0.54 (95% CI:0.37–0.79). (18, 19) However, our results demonstrated a larger absolute difference and therefore a smaller NNT to prevent one complication (Peterson NNT 4064; Thompson NNT 4831; our study NNT 2181). (18, 19) Again, this is likely due to the increased specificity of the diagnostic codes for AOM used in our study.

A Swedish study used both an ecological time-trend analysis and a prospective cohort to explore the risk of serious complications following RTIs, and the association with antibiotic prescribing. (20) They calculated a lower risk of orbital abscess following sinusitis than our study (0.16 per 10,000 for those not prescribed antibiotics and 0.05 per 10,000 for those prescribed antibiotics), but a similar risk of brain abscess following sinusitis (0.16 per 10,000 consultations for those not prescribed antibiotics; 0.10 per 10,000 consultations for those prescribed antibiotics). (20) However, this study did not calculate the relative risk of developing orbital abscess or brain abscess following sinusitis in those prescribed antibiotics compared with those not prescribed antibiotics. In their ecological study they found no association between antibiotic use and incidence of bacterial complications such as mastoiditis and extradural/subdural abscess despite a significant decrease in the volume of antibiotics dispensed between 2006 and 2015.

Gulliford et al explored practice-level associations between antibiotic prescribing for RTIs and incidence of pneumonia, peri-tonsillar abscess, mastoiditis, empyema, meningitis, intracranial abscess and Lemierre's syndrome. (26) They found associations between antibiotic prescribing and both pneumonia and peritonsillar abscess, but not for mastoiditis or brain abscess. (26) They also conducted a cluster RCT in UK General Practice which resulted in an 11% reduction in antibiotic prescribing for RTIs in intervention practices, but found no evidence of an increase in serious bacterial complications such as mastoiditis and intracranial abscess in these practices. (27)

Finally, an American study of hospital admissions where both intracranial abscess and rhinosinusitis had been coded, estimated an incidence of brain abscess following sinusitis of 2.7-4.4 per million child-years, (28) and a systematic review of cases of brain abscess identified that 30% had associated otitis media or mastoiditis. (29) However, we found no other studies examining the association between antibiotic prescribing and brain abscess at the individual level.

Implications for research and/or practice

A key message from our study is that acute mastoiditis following AOM and orbital cellulitis following AS are rare events, and brain abscess is very rare following AOM or AS. Our findings suggest that not prescribing antibiotics for AOM and AS may be associated with

very small increases in the risk of serious complications, but that very large numbers would need to be treated to prevent each complication. Our findings also indicate that antibiotic protection is not complete as even those prescribed antibiotics had a small risk of these complications. Therefore, given the current threat from antibiotic resistance, lack of symptomatic benefit from antibiotic use for these conditions, and risk of adverse effects from antibiotics, our result should not change current recommendations to not prescribe antibiotics for the majority of cases of AOM and AS. However, our findings highlight the importance of ensuring that consultations for AOM and AS include discussion around the natural history of the disease and routinely provide safety netting advice. Our study did not assess whether any specific risk factors were associated with development of these serious complications, so future research focussing on predisposing conditions/clinical features that may increase the risk of such complications would add valuable evidence to current knowledge on this topic.

Conclusion

Our findings provide reassurance that serious complications of AOM and AS are rare. Although we identified that prescription of antibiotics at initial consultation may reduce the risk of acute mastoiditis following AOM and brain abscess following AS, large numbers of patients would need to be treated to prevent one complication, and even those prescribed antibiotics had a very small risk of such complications. We therefore do not advocate changing current recommendations to avoid prescription of antibiotics in the majority of cases of AOM and AS.

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Ethical approval: This study was approved by the Independent Scientific Advisory Committee for MHRA database research on 24th January 2014.

There are no competing interests.

References

1. WHO. The evolving threat of antimicrobial resistance: Options for action. 2012 [accessed 22nd December 2012]. Available from: http://whqlibdoc.who.int/publications/2012/9789241503181_eng.pdf
2. O'Neill, J. Tackling Drug Resistant Infections Globally: Final Report and Recommendations. The Review on Antimicrobial Resistance. 2016 [accessed 29th August 2018]. Available from: https://amr-review.org/sites/default/files/160525_Final%20paper_with%20cover.pdf
3. Public Health England. English Surveillance Programme for Antimicrobial Utilisation and Resistance (ESPAUR) Report 2018. 2018 [accessed 11th October 2019]. Available from: https://webarchive.nationalarchives.gov.uk/20191003132022/https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report
4. NICE. Respiratory Tract Infections – antibiotic prescribing. Prescribing of antibiotics for self-limiting respiratory tract infections in adults and children in primary care. NICE clinical guideline 69. 2008 [accessed 11th October 2019].

Available from: https://www.nice.org.uk/guidance/cg69/evidence/full-guideline-pdf-196853293

5. Gulliford MC, Dregan A, Moore MV, Ashworth M, Van Staa T, McCann G, et al. Continued high rates of antibiotic prescribing to adults with respiratory tract infection: survey of 568 UK general practices. *BMJ Open 2014*; 4:e006245. doi:10.1136/bmjopen-2014-006245 [accessed 11th October 2019]. Available from: https://bmjopen.bmj.com/content/4/10/e006245
6. Hawker JI, Smith S, Smith GE, Morbey R, Johnson AP, Fleming DM et al. Trends in antibiotic prescribing in primary care for clinical syndromes subject to national recommendations to reduce antibiotic resistance, UK 1995-2011: analysis of a large database of primary care consultations. *J Antimicrob Chemother* 2014; 69: 3423–3430 [accessed 11th October 2019]. Available from: https://academic.oup.com/jac/article/69/12/3423/820085
7. Pouwels KB, Dolk FCK, Smith DRM, Robotham JV and Smieszek T. Actual versus 'ideal' antibiotic prescribing for common conditions in English primary care. *J Antimicrob Chemother 2018*; 73 Suppl 2: ii19–ii26 [accessed 11th October 2019]. Available from: https://academic.oup.com/jac/article/73/suppl_2/19/4841820
8. Yates PD and Anari S. Otitis Media. In: Lalwani, A. K. eds. *Current Diagnosis and Treatment in Otolaryngology – Head and Neck Surgery*. 2nd ed. McGraw-Hill Companies; 2008, p. 655–665.
9. Lemiengre MB, Van Driel ML, Merenstein D, Young J and De Sutter AI M. Antibiotics for clinically diagnosed acute rhinosinusitis in adults. *Cochrane Database Syst Rev 2012* Issue 10. Art. No.: CD006089. DOI: 10.1002/14651858.CD006089.pub4
10. Betz CS, Issing W, Matschke J, Kremer A, Uhl E, and Leunig A. Complications of acute frontal sinusitis: a retrospective study. *Eur Arch Otorhinolaryngol 2008;* 265(1): p. 63–72.
11. Shah AR, Salamone FN, and Tami TA. Acute and Chronic Sinusitis. In: Lawani, A. eds. *Current Diagnosis and Treatment in Otolaryngology – Head and Neck Surgery*. 2nd ed. McGraw-Hill Companies; 2008: p. 273–281.
12. Van Buchem FL, Knottnerus JA, Schrijnemaekers VJJ, and Peeters MF. Primary-care-based randomised placebo-controlled trial of antibiotic treatment in acute maxillary sinusitis. *Lancet* 1997; 349: p. 683–687.
13. Venekamp RP, Sanders S, Glasziou PP, Del Mar CB, Rovers MM. 2013. Antibiotics for acute otitis media in children (Review). *Cochrane Database Syst Rev* Issue 1. Art. No.: CD000219. DOI: 10.1002/14651858.CD000219.pub3.
14. Young J, De Sutter A, Merenstein D, Van Essen GA, Kaiser L, Varonen H, et al. Antibiotics for adults with clinically diagnosed acute rhinosinusitis: a meta-analysis of individual patient data. *Lancet* 2008; 371: p. 908–14.
15. NICE. Sinusitis (acute): antimicrobial prescribing. *NICE Clinical Guidelines NG 79*. 2017. [Accessed 31st May 2018]. Available from: https://www.nice.org.uk/guidance/ng79/resources/sinusitis-acute-antimicrobial-prescribing-pdf-1837642625989
16. NICE. Otitis media (acute): antimicrobial prescribing. *NICE Clinical Guidelines NG 91*. 2018. [Accessed 31st May 2018]. Available from: https://www.nice.org.uk/guidance/ng91/resources/otitis-media-acute-antimicrobial-prescribing-pdf-1837750121413
17. Xiao F, Tseng MY, Teng LJ, Tseng HM, and Tsai JC. Brain abscess: clinical experience and analysis of prognostic factors. *Surgical Neurology* 2005; 63: p. 442-450.

18. Petersen I, Johnson AM, Islam A, Duckworth G, Livermore DM, and Hayward AC. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. *BMJ* 2007; 335(982): p. 1–6.
19. Thompson PL, Gilbert RE, Long PF, Saxena S, Sharland M, and Wong I CK. Effect of Antibiotics for Otitis Media on Mastoiditis in Children: A Retrospective Cohort Study Using the United Kingdom General Practice Research Database. *Pediatrics* 2009; 123: p. 424–430.
20. Cars T, Eriksson I, Granath A, Wettermark B, Helman J, Norman C et al. Antibiotic use and bacterial complications following upper respiratory tract infections: a population-based study. *BMJ Open*. 2017; 7(11):e016221. doi: 10.1136/bmjopen-2017-016221 [accessed 11th October 2019]. Available from: https://bmjopen.bmj.com/content/7/11/e016221.long
21. Gonzalez-Gonzalez C, Lopez-Vazquez P, Vazquez-Lago J, Pineiro-Lamas M, Herdeiro MT, Arzamendi AF et al. Effect on Physicians' Attitudes and Knowledge on the Quality of Antibiotic Prescription: A Cohort Study. *PLoS One* 2015; 10(10): e0141820 [accessed 11th October 2019]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4624842/pdf/pone.0141820.pdf
22. Herrett E, Thomas SL, Schoonen WM, Smeeth L, and Hall AJ. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol* 2009; 69(1): p. 4–14.
23. BMJ Group and Pharmaceutical Press 2012. *British National Formulary 64*.
24. Wilson EB. Probable Inference, the Law of Succession, and Statistical Inference. *J Am Stat Assoc* 1927; 22(158): p. 209–212.
25. Dolk FCK, Pouwels KB, Smith DRM, Robotham JV, and Smieszek T. Antibiotics in primary care in England: which antibiotics are prescribed and for which conditions? *J Antimicrob Chemother* 2018; 73 (Suppl 2): p. ii2–ii10 [accessed 19th October 2019]. Available from: https://doi.org/10.1093/jac/dkx504
26. Gulliford MC, Moore MV, Little P, Hay AD, Fox R, Prevost AT et al. Safety of reduced antibiotic prescribing for self limiting respiratory tract infections in primary care: cohort study using electronic health records. *BMJ* 2016; 354:i3410 [accessed 11th October 2019]. Available from: https://www.bmj.com/content/354/bmj.i3410
27. Gulliford MC, Prevost AT, Charlton J, Juszczyk D, Soames J, McDermott L, et al. Effectiveness and safety of electronically delivered prescribing feedback and decision support on antibiotic use for respiratory illness in primary care: REDUCE cluster randomised trial. *BMJ* 2019; 364:l236 [accessed 17th October 2019]. Available from: https://doi.org/10.1136/bmj.l236
28. Piatt JH Jr. Intracranial suppuration complicating sinusitis among children: an epidemiological and clinical study. *J Neurosurg Pediatr* 2011; 7(6): p. 567–574.
29. Brouwer MC, Coutinho JM, van de Beek D. Clinical characteristics and outcome of brain abscess. Systematic review and meta-analysis. *Neurology* 2014; 82(9): p. 806-13.

Figure 1: Consort Flow diagram for Acute otitis media

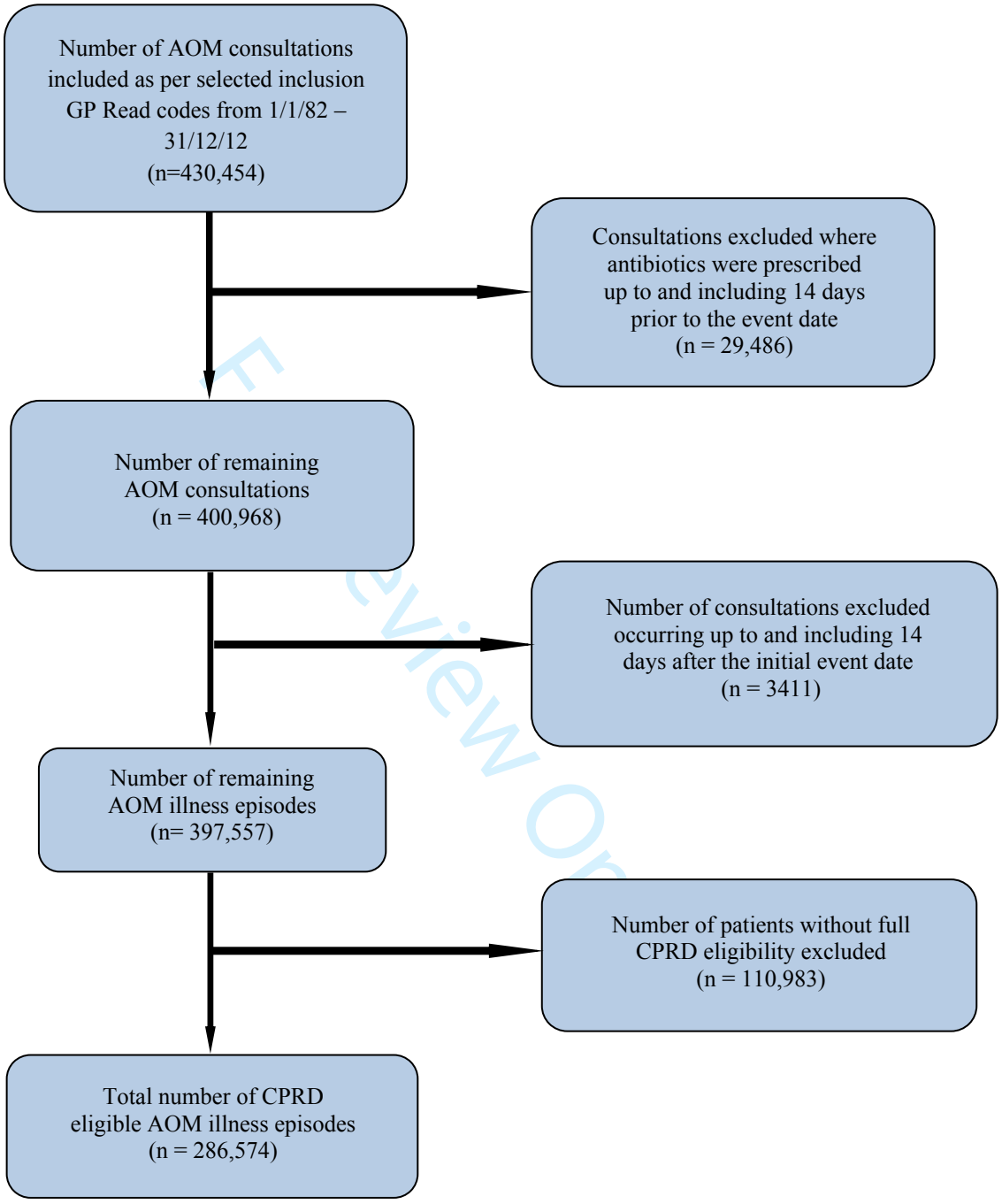

Figure 2: *Consort Flow diagram for Acute sinusitis*

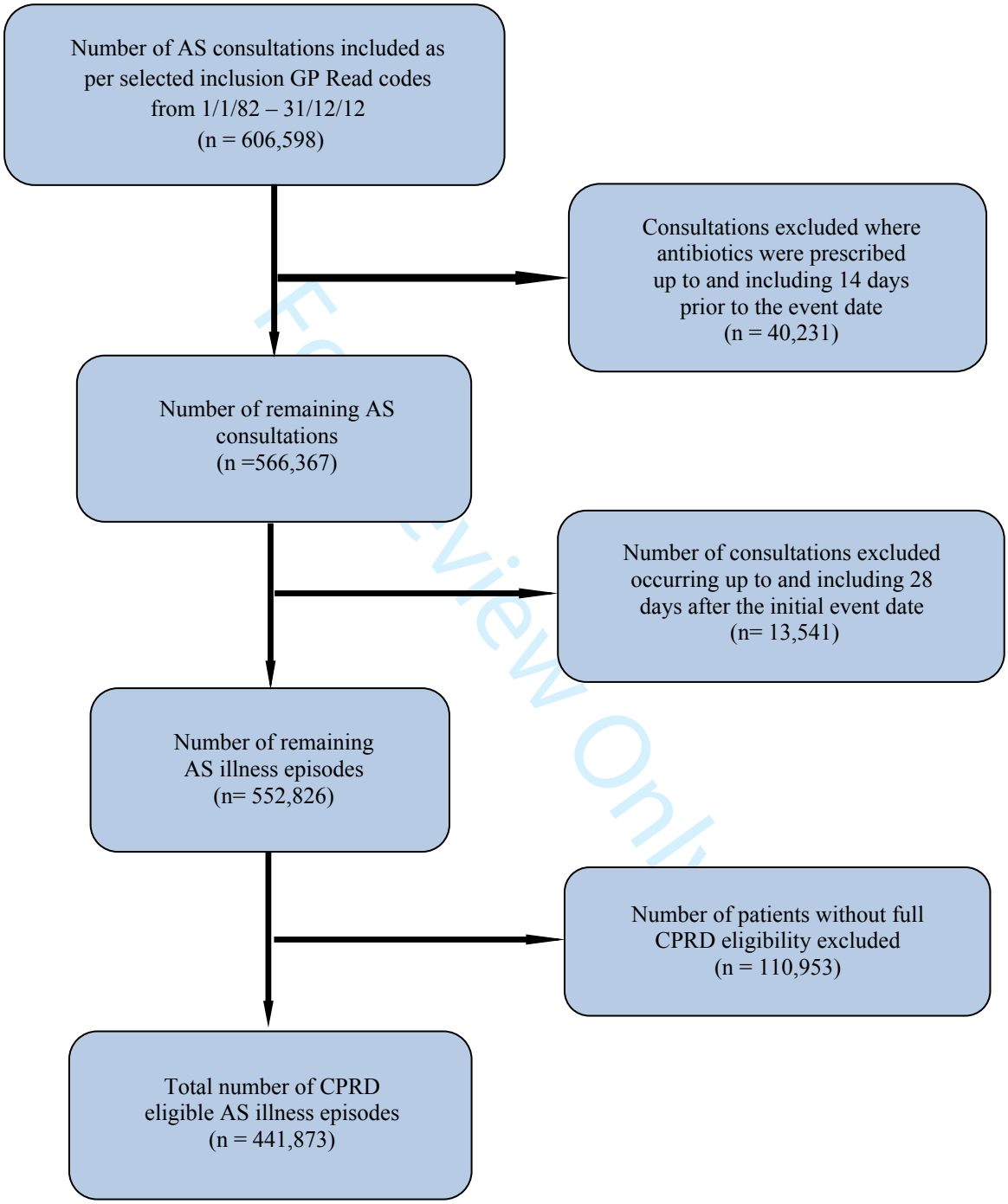

Table 1: Baseline characteristics of the AOM cohort

Characteristic	Whole sample N = 286,574	Prescribed antibiotics N = 249,086 (86.9%)	Not prescribed antibiotics N = 37488 (13.1%)
Gender			
M – N (%)	140787 (49.1%)	122352 (49.1%)	18435 (49.2%)
F – N (%)	145787 (50.9%)	126734 (50.9%)	19053 (50.8%)
Age			
Median*	6 years	6 years	6 years
Interquartile range	3 – 20 years	3 – 19 years	3 – 23 years
Age N (%)			
0 – 2 years	55999 (19.5%)	49262 (19.8%)	6737 (18%)
3 – 5 years	72164 (25.2%)	62704 (25.2%)	9460 (25.2%)
6 – 10 years	55968 (19.5%)	48226 (19.4%)	7742 (20.7%)
11 – 20 years	32318 (11.3%)	28577 (11.5%)	3741 (10%)
21 – 30 years	16050 (5.6%)	13984 (5.6%)	2066 (5.5%)
31 – 40 years	18510 (6.5%)	16029 (6.4%)	2481 (6.6%)
41 – 50 years	14040 (4.9%)	12095 (4.9%)	1945 (5.2%)
51 – 60 years	10427 (3.6%)	8954 (3.6%)	1473 (3.9%)
61 – 70 years	6527 (2.3%)	5543 (2.2%)	984 (2.6%)
71 – 80 years	3334 (1.2%)	2731 (1.1%)	603 (1.6%)
81+ years	1237 (0.4%)	981 (0.4%)	256 (0.7%)
Asplenic			
N (%)	47 (0.02%)	45 (0.02%)	2 (0.0005%)
Chronic kidney disease			
N (%)	95 (0.03%)	81 (0.03%)	14 (0.04%)
CSF shunt			
N (%)	61 (0.02%)	49 (0.02%)	12 (0.03%)
Diabetes mellitus			
N (%)	3485 (1.22%)	2980 (1.20%)	505 (1.35%)
HIV			
N (%)	15 (0.0005%)	14 (0.0006%)	1 (0.0003%)
Immunocompromised			
N (%)	151 (0.05%)	137 (0.06%)	14 (0.04%)
Smoker			
N (%)	14990 (5.23%)	12948 (5.20%)	2042 (5.45%)
Transplanted organ			
N (%)	89 (0.03%)	78 (0.03%)	11 (0.03%)

**Median was used to describe summary of age as the data was skewed to the left*

Table 2: Baseline characteristics of the acute sinusitis cohort

	Whole sample N = 441873	**Prescribed antibiotics** N = 407030 (92.1%)	**Not prescribed antibiotics** N = 34843 (7.9%)
Gender M – number (%) F – number (%)	 124,781 (28.2%) 317,091 (71.8%) (1 – gender unknown)	 113,934 (28%) 293,096 (72%)	 10,847 (31.1%) 23,995 (68.9%) (1 – gender unknown)
Age Mean SD	 45.6 years 16.4	 45.8 years 16.4	 43.8 years 16.4
Age number (%) 0 – 2 years 3 – 5 years 6 – 10 years 11 – 20 years 21 – 30 years 31 – 40 years 41 – 50 years 51 – 60 years 61 – 70 years 71 – 80 years 81+ years	 342 (0.1%) 832 (0.2%) 2835 (0.6%) 22281 (5%) 53078 (12%) 99511 (22.5%) 95828 (21.7%) 81055 (18.3%) 54158 (12.3%) 24418 (5.5%) 7535 (1.7%)	 314 (0.1%) 732 (0.2%) 2479 (0.6%) 19968 (4.9%) 47976 (11.8%) 91277 (22.4%) 89020 (21.9%) 75465 (18.5%) 50442 (12.4%) 22549 (5.5%) 6808 (1.7%)	 28 (0.1%) 100 (0.3%) 356 (1%) 2313 (6.6%) 5102 (14.6%) 8234 (23.6%) 6808 (19.5%) 5590 (16%) 3716 (10.7%) 1869 (5.4%) 727 (2.1%)
Asplenic number (%)	 285 (0.1%)	 266 (0.1%)	 19 (0.1%)
Chronic kidney disease number (%)	 472 (0.1%)	 437 (0.1%)	 35 (0.1%)
CSF shunt number (%)	 102 (0.02%)	 94 (0.02%)	 8 (0.02%)
Diabetes mellitus number (%)	 19477 (4.4%)	 18077 (4.4%)	 1400 (4%)
HIV number (%)	 73 (0.02%)	 67 (0.02%)	 6 (0.02%)
Immunocompromised number (%)	 681 (0.2%)	 631 (0.2%)	 50 (0.1%)
Smoker number (%)	 82188 (18.6%)	 76006 (18.7%)	 6182 (17.7%)
Transplanted organ number (%)	 326 (0.1%)	 301 (0.1%)	 25 (0.1%)

Table 3: Association between antibiotic prescription and complications

Complication	Number of complications			Incidence* (95% CI)			Odds ratio (95% CI)		NNT (95% CI)
	Total	Antibiotics	No antibiotics	Overall incidence	Antibiotics	No antibiotics	Crude	Adjusted**	
Brain abscess following acute otitis media	1	1	0	0.03 (0.01–0.20)	0.04 (0.03-0.05)	N/A	N/A	N/A	N/A
Acute mastoiditis following acute otitis media	161	125	36	5.62 (4.81–6.56)	5.02 (4.21–5.98)	9.60 (6.94–13.29)	0.52 (0.36– 0.76)	0.54 (0.37–0.79)	2181 (1196 to 5709)
Brain abscess following acute sinusitis	5	3	2	0.11 (0.05–0.26)	0.07 (0.03–0.22)	0.57 (0.16–2.10)	0.13 (0.02–0.77)	0.12 (0.02–0.70)	19,988 (4951–167,099)
Orbital cellulitis following acute sinusitis	66	57	9	1.50 (1.17–1.90)	1.40 (1.08–1.81)	2.58 (1.36–4.91)	0.54 (0.27–1.10)	0.56 (0.27–1.12)	N/A

*Per 10,000 AOM/AS primary care consultations
**Adjusted for patient's age at the time of consultation

Table 4: Association between antibiotic prescription and complications in those ≤20 and those > 20 years

Patients aged ≤20 years								
Complication	**Number of complications**			**Incidence*** (95% CI)			**Odds ratio (95% CI)**	**NNT (95% CI)**
	Total	**On antibiotics**	**No antibiotics**	**Overall incidence**	**On antibiotics**	**No antibiotics**		
Acute mastoiditis following acute otitis media	81	61	20	3.74 (3.01-4.65)	3.23 (2.52-4.15)	7.23 (4.68-11.16)	0.45 (0.27-0.74)	2504 (1251-7776)
Brain abscess following acute sinusitis	0	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Orbital cellulitis following acute sinusitis	13	8	5	4.94 (2.89-8.46)	3.41 (1.73-6.72)	17.88 (7.64-41.78)	0.19 (0.06-0.58)	691 (260-2695)
Patients aged >20 years								
Complication	**Number of complications**			**Incidence*** (95% CI)			**Odds ratio (95% CI)**	**NNT (95% CI)**
	Total	**On antibiotics**	**No antibiotics**	**Overall incidence**	**On antibiotics**	**No antibiotics**		
Acute mastoiditis following acute otitis media	80	64	16	11.41 (9.17-14.19)	10.61 (8.31-13.55)	16.31 (10.04-26.48)	0.65 (0.37-1.13)	N/A
Brain abscess following acute sinusitis	5	3	2	0.12 (0.11-0.13)	0.08 (0.07-0.09)	0.62 (0.54-0.72)	0.13 (0.02-0.75)	18,319 (4549-146,666)
Orbital cellulitis following acute sinusitis	53	49	4	1.28 (1.17-1.39)	1.28 (1.17-1.40)	1.25 (1.13-1.38)	1.02 (0.37-2.84)	N/A
*Per 10,000 AOM/AS primary care consultations								