Post-consultation acute respiratory tract infection recovery: a latent class informed analysis of individual patient data from randomised controlled trials and observational studies

Abstract

Background

There is a lack of evidence regarding post-consultation symptom trajectories for patients with respiratory tract infections (RTIs) and whether patient characteristics can be used to predict illness duration.

Aim

To describe symptom trajectories in patients with RTIs, assess baseline characteristics and adverse events associated with trajectories.

Design and setting

9103 adults and children from 12 primary care studies

Method

Individual patient data latent class-informed regression analysis of randomised controlled trials and observational cohort studies. Post-consultation symptom trajectory (severity and duration), re-consultation with same or worsening illness and hospitalisation were assessed.

Results

90% of participants recovered from all symptoms by 28 days, regardless of antibiotic prescribing strategy (none, immediate and delayed antibiotics). For studies of RTI with cough as a dominant symptom (n=5314), four trajectories were identified: 'rapid[6 days]' (90% of participants recovered within 6 days)' in 52.0%; 'intermediate[10 days]' (28.9%); 'slow progressive improvement[27 days]' (12.5%); and 'slow initial high symptom burden[27 days]' (6.6%). Older age (OR: (95% CI): 2.57 (1.72-3.85), higher presenting illness baseline severity (OR) (95% CIs): 1.51 (1.12-2.03)); presence of lung disease (OR (95% CI): 1.78 (1.44-2.21)); above median illness duration prior to consultation (>7 days) (OR (95% CI): 1.99 (1.68-2.37)) were associated with slower recovery (>10 days) compared to faster

recovery (≤10 days). Re-consultations and hospitalisations were respectively higher in those with slower recovery (ORs: 2.15 (1.78-2.60) and 7.42 (3.49-15.78)).

Conclusion

Older patients presenting with more severe, longer pre-consultation symptoms, and chronic lung disease should be advised they are more likely to experience longer post-consultation illness durations, and that recovery rates are similar with and without antibiotics.

Study registration: PROSPERO CRD42018079400

Keywords: general practice, respiratory tract infections, antibiotics, latent class analysis

How this fits in

- There is a lack of evidence regarding post-presentation symptom trajectories for patients with RTIs and whether patient characteristics can be used to predict illness duration.
- For patients with RTI with cough, 1 in 2 patients will recover within 6 days of presentation, with the rest taking up to one month.
- Four trajectory groups were identified, two 'faster' and two 'slower'. For clinical utility, these could be grouped into 'faster' and 'slower' recovery. Slower recovery was associated with older age, higher baseline severity, prior illness duration longer than 7 days, presence of lung disease.
- These characteristics can be easily assessed in primary care and could be used to provide more accurate prognostic information with patients and parents and manage expectations.

Introduction

Respiratory tract infections (RTIs) are one of the most common acute conditions managed in primary care and account for approximately 60% of antibiotic prescribing in primary care in UK and Europe

(1,2,3). Antibiotic prescribing remains widespread (1), despite studies showing antibiotic treatment has little effect on symptom duration (4-7).

Studies have identified the importance of good clinician-patient communication in reducing inappropriate use of antibiotics (8,9). Patients often do not expect antibiotics for acute RTI, but instead seek reassurance and information on what to expect (10,11,12). Similarly, physicians often face uncertainty about the natural course of RTIs, and who is more likely to experience complications (13). There is relatively little data on the severity and duration of key symptoms for patients, and specifically adults (14,15). To our knowledge, only one study has previously described post-consultation symptom trajectories, and it was unable to identify baseline factors predictive of subsequent trajectory, other than prior severity of symptoms (16). A more complete understanding the symptoms trajectories associated with clinically identifiable patient and disease characteristics could guide patient assessment, help facilitate more personalised advice in consultations, and help reduce clinician uncertainty (17).

This study aimed to describe patterns of change in severity and duration of symptoms in patients with acute and uncomplicated RTIs. We explored which baseline characteristics predict different trajectories of symptoms and whether adverse outcomes vary across trajectories.

Methods

Participants

Participants were from an individual patient data (IPD) database on antibiotic prescribing for RTIs [acute sore throat, acute cough, otitis media] in a community setting (Box 1). Full details of the IPD database have been reported elsewhere (18,19). For the present study, we included participants in the IPD database who completed symptom diaries (n=9,103). Study and patient-level characteristics are presented in Supplementary Table 1 (20-31).

Diary data

For most studies, patients (or parents/caregivers of children <16 years of age) were asked to complete daily symptom diaries for the first 10 to 28 days (depending on the study) following their consultation or until symptoms returned to normal. Diary designs were based on previous validated formats (24, 32). Symptom severity was rated from 0 to 6 (0=no problem at all, 1=very little problem, 2=slight problem, 3=moderate problem, 4=bad problem, 5=very bad problem, 6= as bad as can be). Symptoms recorded ranged across studies (depending on type of infection).

Antibiotic group

Data on antibiotic consumption was available in some diaries (n=4243). For diaries that did not collect this information, we assumed participants who were not prescribed antibiotics did not take antibiotics for the duration of the study period, and those who were prescribed immediate antibiotics were assumed to have taken antibiotics (28). Those prescribed delayed antibiotics were excluded from the longitudinal latent class analyses (LLCA) described below.

Baseline characteristics

Baseline data on sociodemographic variables included age (<16, 16-64, >64) and sex. Clinical variables were fever at baseline consultation (≥/<37.5 C for each study), duration of illness prior to index consultation (≥/<median), baseline severity of symptoms (average severity across all symptoms being ≥/< median), presence of any lung disease (including asthma, chronic obstructive pulmonary disease or any other lung disease).

Outcomes

The primary outcomes of interest were symptom duration (both any symptom and individual symptoms) and change in symptom severity from index consultation. We examined duration of cough, sleep disturbance, feeling generally unwell and interference with normal activities, as these were the symptoms for which data was collected in most studies. Change in severity of all symptoms collected in each study was examined. For incomplete diaries where the last observation was a value of 0 ('no problem at all'), it was assumed symptoms had resolved on that day and a value of 0 was assigned for all following days.

Secondary outcomes were re-consultation, defined as a consultation with same or worsening illness (within 28 days following the index consultation) and hospitalisation.

Data analysis

Study characteristics were described for all studies included in the analysis. Baseline characteristics of participants who provided symptom diary data were compared to those who did not. Data on the proportion of participants who were symptom-free at each of the first 28 days post-consultation were plotted against time. Separate plots were produced for individual symptoms and for those who took and those who did not take antibiotics during the study period.

Trajectories of symptom severity (based on the most severe symptom on each day as previously defined) (14,28) were modelled for participants. Separate trajectories were modelled for each initial diagnosis (i.e., prevailing symptom at time of consultation). LLCA was used to identify classes of participants with distinct trajectories of symptom severity (33) using Mplus 8. LLCA is a type of mixture model that models patterns of states across time. Patients are assigned to classes/groups according to the probability of being in that class based on their symptom severity score at each time point (Box 2). Recovery time was defined for 90% rather than 50% of patients as this is thought to be more clinically useful and helpful to patients.

Baseline characteristics of the different classes were compared using descriptive statistics (ANOVA for continuous variables and chi-square tests for categorical variables). Multinomial logistic regression models assessed which baseline characteristics predicted class membership, adjusting for confounders (age, sex, baseline severity, duration of illness prior to index consultation, fever at baseline, any lung disease, and antibiotic treatment group), and study ID variable. Multivariable logistic regression analysis assessed the association with class membership and outcomes of interest, accounting for clustering by study and confounders in observational studies. Multi-level multivariable logistic regression models assessed associations between recovery within 10 days

(yes/no) with baseline characteristics and outcomes of interest. Analyses were repeated separately for adults (>18) and children.

Results

Symptom duration

67.9%, 24.4%, and 7.8% of participants had cough (as a dominant symptom), sore throat and otitis media, respectively.

Data on time to symptom resolution was available for 11 studies, (n=8,607). A flowchart showing inclusion and exclusion is available in the Supplementary files. Median time to complete symptom resolution for these patients was 9 days (IQR: 4-27 days), with 90% of participants recovering within 28 days. Median time (IQR) to complete symptom resolution was 15 (7-28) days for cough (90% recovered within 28 days), 4 (3-7) days for sore throat (90% recovered within 11 days), and 4 (2-8) days for otitis media studies (90% recovered within 10 days).

Participants who took antibiotics (48.3%) had shorter median illness duration compared to those who did not take antibiotics (median: 9 (4-28) days vs 11 (5-28) days). However, 90% recovery was the same for those who took antibiotics and those who did not (28 days). A similar pattern was observed for those who took antibiotics during the study period (64.5% symptom free at 15 days) and those who did not take antibiotics (65.9% symptom free at 15 days) (Figure 1). Over the first 28 days post-consultation, a larger percentage of people still had cough symptoms compared to other symptoms such as sleep disturbance, feeling generally unwell, interference with normal activities (Figure 1).

Overall, the proportion of people who recovered within 1 week, 2 weeks, 3 weeks and 4 weeks was 30.7%, 65.4%, 80.5% and 87.2%, respectively. For adults, the proportion of people who recovered within 1 week, 2 weeks, 3 weeks and 4 weeks was 26.1%, 58.8%, 76.5% and 84.4%, respectively. For children, the proportion of people who recovered within 1 week, 2 weeks, 3 weeks and 4 weeks was 40.7%, 77.8%, 87.2% and 91.3%, respectively. Among those without any lung disease, the proportion of people who recovered within 1 week, 2 weeks, 3 weeks and 4 weeks was 30.3%, 64.1%, 79.6%

and 86.9%, respectively. Among those with lung disease, the proportion of people who recovered within 1 week, 2 weeks, 3 weeks and 4 weeks was 25.6%, 56.2%, 69.7% and 76.9%, respectively.

Symptom trajectories

Data on symptom severity was available for 6,436 participants (from 7 studies). Three of these studies focused on children and four on a general population. Five of the 7 studies were on cough (n=5,314), one was on sore throat (n=914), and one was on otitis media (n=208).

LLCA trajectories

LLCA for cough identified 4 trajectories with distinct patterns of change in symptom severity over time (Supplementary Table 3). These trajectories and their distribution within the population were: 'rapid recovery (52.0%), 'intermediate recovery' (28.9%), 'slow progressive improvement' (12.5%), 'slow improvement with initial high symptom burden' (6.6%) (Figure 2). Time to symptom resolution to below moderate level for 90% of participants was 6 days for the 'rapid recovery' trajectory, 10 days for the 'intermediate recovery' trajectory, 27 days for the 'slow progressive improvement' and 'slow improvement with initial high symptom burden' trajectories.

Baseline characteristics of the symptom trajectories are presented in Table 1. Participants with 'rapid recovery' were generally younger and had slightly shorter duration of illness prior to the index consultation than participants in the remaining trajectory groups. A higher proportion of participants with 'rapid recovery' trajectory had lower baseline severity compared to the remaining trajectories. A lower proportion of participants with 'rapid recovery' were female or had any lung disease compared to the remaining trajectories.

Similar results were obtained for adults and children. Similar, although faster, trajectories were observed for sore throat and otitis media (Supplementary material 1).

Faster vs slower recovery

Post-consultation acute respiratory tract infection recovery

To increase clinical usefulness, individuals were re-grouped into two groups each for cough and sore throat: 'faster recovery (symptom recovery to below moderate levels within 10 days)' and 'slower recovery (symptom recovery to below moderate levels >10 days)'.

Associations with baseline characteristics

Older age (16-64 and >64 compared to <16 years) was associated with higher odds of slower recovery (Odds Ratios (95% CI): 2.57 (1.72-3.85) and 3.17 (2.05-4.90), respectively). Median and above baseline severity was associated with 'slower recovery' compared to 'faster recovery': (OR (95% CI): 1.51 (1.12-2.03)) (Table 2). Presence of lung disease (OR (95% CI): 1.78 (1.44-2.21)) was also associated with 'slower recovery' compared with 'faster recovery'. Median and above prior duration of illness (i.e., more than 7 days) (OR (95% CI): 1.99 (1.68-2.37)) were also associated with 'slower recovery' compared with 'faster recovery' (Table 2). Compared to no antibiotic prescribing, immediate antibiotic prescribing was associated with lower odds of slower recovery (OR: 0.82 (0.68-0.98)) (Table 2).

Associations with re-consultation and hospitalisation

Re-consultation data were available for 5,239 out of 6,179 (84.8%) participants with symptom diary data. Of these, 1,538 (29.4%) re-consulted. Rates of re-consultation were 25.9% (1,015/3,915) and 48.8% (516/1057) in the 'faster' and 'slower' recovery group, respectively. Compared to the 'faster recovery' group, those in the 'slower recovery' group had increased odds of re-consultation (OR: 2.15 (1.78-2.60)). Hospitalisation data were available for 5,367 participants (86.9%). Hospitalisation rates were 0.7% (29/4021) and 2.5% (27/1079) in the 'faster' and 'slower' recovery group, respectively. Compared to the 'faster recovery' group, those in the 'slower recovery' group had increased odds of hospitalisation (OR: 7.42 (3.49-15.78)).

Associations with the LLCA trajectories and baseline characteristics, re-consultation and hospitalisation are available in Supplementary Tables 4-7).

Discussion

Summary

This study found that older age, greater baseline severity, longer prior duration of illness and presence of lung disease predicted membership to trajectories with slower symptom recovery. Immediate antibiotic prescribing was associated with lower odds of slower recovery (i.e., those prescribed immediate antibiotics were more likely to recover faster). Trajectories with slower recovery had higher odds of re-consultation and hospitalisation.

Strengths and Limitations

Strengths of the study include the large sample size, broad age group and use of symptom diaries. The study brings together data from both observational cohort studies and RCTs, allowing greater confidence in the study findings (34).

A limitation of the study was that not all studies collected data on symptom severity (resulting in 70.7% (6436/9103) of participants being included in this analysis), although this is comparable to other studies (16). It is possible that those who did not provide data on symptom severity had different trajectories of change in severity and duration of symptoms. Similarly, patient confirmation of antibiotic consumption was available for 46.6% of participants. We assigned antibiotic group where possible based on prescribing strategy, however some participants may have been misclassified, for example if they obtained antibiotics through other sources or after the index consultation and some people who were prescribed immediate antibiotics may not have taken it (35,36). However, evidence from trial data indicates that most people who are prescribed immediate antibiotics consume antibiotics (28).

Missing data on symptom severity, antibiotic consumption and outcomes resulted in a smaller sample size and limited statistical power for some of the analyses. Our study is consistent with previous studies that have reported little benefit with immediate antibiotics for RTIs. However, some associations may be confounded by patients in the slower recovery groups being more unwell or being more likely to have a bacterial infection. Additionally, self-report symptom data may be prone to bias and individual differences in perception. Furthermore, we were not able to examine whether repeat antibiotic prescriptions influenced illness duration and trajectories as this data was

not available in most studies. Similarly, we did not have data on previous admissions due to RTI. Furthermore, we only analysed data on symptom severity during the first 15 days following consultation. Although symptoms may last longer, most symptoms are resolved within the first 15 days as shown here and elsewhere (16). Finally, studies were conducted in high income countries high-income countries, and may not be generalisable to low- and middle-income countries or areas where there is higher prevalence of severe RTI (e.g.: TB).

Comparison with existing literature

This study contributes to knowledge on the duration and severity of symptoms in patients with acute uncomplicated RTIs by describing trajectories of symptom recovery in a broad age group. The study findings are consistent with a previous study that identified 5 trajectories of cough severity and duration in children, which was predicted by prior severity of symptoms (16). We add to these findings by identifying trajectories based on all symptoms and identifying patient characteristics associated with these trajectories. This present study extends this literature by illustrating slightly longer duration of symptoms (90% recovery time) and different patterns of symptom recovery in patients. This information is important given a recent study has suggested many patients are not aware of the natural history of RTIs and want to know when their symptoms are likely to improve (37). Our study of this general population also found longer duration of symptoms for cough, sore throat and otitis media compared to that reported by a systematic review of symptom duration in children (15).

Implications for practice and research

Table 1 indicated a similar antibiotic prescribing rate across the different groups, highlighting clinician uncertainty and a need for a better guide on which patients should be prescribed antibiotics. Many key characteristics identified here such as illness severity, prior duration of illness, and presence of lung disease can easily be assessed in primary care and can be used by clinicians to reassure patients and appropriately manage those at risk. Clinicians can advise patients with severe baseline severity, prior illness duration lasting longer than 7 days, cough, or lung disease that they

are likely to experience longer duration of symptoms (>10 days, and up to 28 days) and should be alerted to the higher risk of hospitalisation.

We found similar 90% recovery time and relatively small differences in odds of slower recovery for patients managed with and without antibiotics. These findings support a "no" or "watchful waiting" approach to antibiotic prescribing and may help achieve current national targets to reduce antibiotic usage (38).

The present study can be used to update the UK Health Security Agency guidance on RTI illness duration, which reports that most people will recover within 21 days for cough, 7-8 days for sore throat, 14 days for colds, and 8 days for otitis media (39). Characteristics of patients who are more likely to experience slower recovery or persistent symptoms may be additionally included in patient educational materials (e.g., leaflets, videos, etc.) to help personalise prognosis (39). This could serve to modify patient expectations regarding illness duration and could reduce re-consultations. Further research that more fully captures data on antibiotic consumption would allow more accurate estimates on the natural duration of symptoms. Our study may also inform risk prediction modelling, by highlighting which predictors may be included in models used to predict longer symptom duration or poorer outcomes for acute RTIs.

Conclusions

Patients presenting with more severe and longer pre-consultation symptoms, and chronic lung disease should be advised they are more likely to experience longer post-consultation illness durations, which can last up to 28 days, and that overall recovery rates are similar with and without antibiotics. This information can be included in educational resources that are provided to parents/patients and patients with these characteristics should be alerted to the higher risk of hospitalisation.

Acknowledgements: We would like to thank the following collaborators which assisted us by allowing us to use the data from their studies: Professor Ngaire Kerse, Ms Jacqueline Nuttall.

Author contributions: BS is the guarantor. BS conceived the original study concept and design. BS, PL, MM, SZ, GY, and JB wrote the grant application and obtained funding from the *NIHR* Research for Patient Benefit (*RfPB*) Programme. HH, BS, PA and AH contributed to the data analysis. HH, BS, PA and AH wrote the first draft of the manuscript. All listed authors contributed to the concept and design of the study, the interpretation of the results and manuscript editing. All authors read, provided feedback and approved the final manuscript.

Funding: This work was funded by the *NIHR* Research for Patient Benefit (*RfPB*) Programme, grant number: PB-PG-0416-20005. This funding supported the collation of the individual participant data, data management and analyses. The NIHR RfPB was not involved in any other aspect of the project, such as the design of the project's protocol and analysis plan, the collection and analyses. The funder had no input on the interpretation or publication of the study results.

Data sharing statement: The IPD database can be shared subject to the approval of the study collaborators.

Conflicts of interest: none declared.

References

1. Public Health England. English surveillance programme for antimicrobial utilisation and resistance report. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/843129/English_Surveillance_Programme_for_Antimicrobial_Utilisation_and_Resistance_2019.pdf (accessed 22 Feb 2022).
2. Gulliford MC, Dregan A, Moore MV, 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.
3. Cassini A, Hogberg LD, Plachouras D, et al. Burden of AMR Collaborative Group. Attributable deaths and disability-adjusted life-years caused by infections with antibiotic-resistant bacteria in the EU and the European Economic Area in 2015: a population-level modelling analysis. *Lancet Infect Dis* 2019;19:56-66. doi:10.1016/S1473-3099(18)30605-4.

4. Little P, Stuart B, Hobbs FDR, et al. Antibiotic prescription strategies for acute sore throat: A prospective observational cohort study. *Lancet Infect Dis* 2014;**14**:213–9. doi:10.1016/S1473-3099(13)70294-9
5. Spinks A, Glasziou PP, Del Mar CB. Antibiotics for sore throat. *Cochrane Database Syst Rev* 2013**;**. doi:10.1002/14651858.CD000023.pub4
6. Kenealy T, Arroll B. Antibiotics for the common cold and acute purulent rhinitis. *Cochrane Database Syst Rev* 2013. doi:10.1002/14651858.CD000247.pub3
7. Spurling GKP, Del Mar CB, Dooley L, et al. Delayed antibiotic prescriptions for respiratory infections. *Cochrane Database Syst Rev* 2017. doi:10.1002/14651858.CD004417.pub5
8. EPM L, Page K, Whitty JA, et al. Antibiotic prescribing in primary healthcare: dominant factors and trade-offs in decision-making. *Infect Dis Health* 2018;23:74–86.
9. Mustafa M, Wood F, Butler CC, et al. Managing expectations of antibiotics for upper respiratory tract infections: a qualitative study. *Ann Fam Med* 2014;12:29–36.
10. O'Connor R, O'Doherty J, O'Regan A, et al. Medical management of acute upper respiratory infections in an urban primary care out-of-hours facility: cross-sectional study of patient presentations and expectations. *BMJ Open* 2019;9**:**e025396. doi: 10.1136/bmjopen-2018-025396
11. Perera AI, Thomas MG, Petrie KJ, et al. Reducing expectations for antibiotics in patients with upper respiratory tract infections: a primary care randomized controlled trial. *Ann Fam Med* 2021;19(3):232-239. doi:10.1370/afm.2672
12. Mortazhejri S, Patey AM, Stacey D et al. Understanding determinants of patients' decisions to attend their family physician and to take antibiotics for upper respiratory tract infections: a qualitative descriptive study. *BMC Fam Pract* 2020; 21**:** 119. https://doi.org/10.1186/s12875-020-01196-9
13. Harris AM, Hicks LA, Qaseem A, et al. Appropriate antibiotic use for acute respiratory tract infection in adults: advice for high-value care from the American College of Physicians and the Centers for Disease Control and Prevention. *Ann Intern Med* 2016;164:425.

14. Moore M, Little P, Rumsby K, et al. Predicting the duration of symptoms in lower respiratory tract infection. *Br J Gen Pract* 2008;58(547):88-92. doi:10.3399/bjgp08X264045
15. Thompson M, Vodicka TA, Blair PS et al. Duration of symptoms of respiratory tract infections in children: systematic review. *BMJ* 2013; 347: f7027.
16. Knut-Arne Wensaas K-A, Heron J, Redmond N, et al. Post-consultation illness trajectories in children with acute cough and respiratory tract infection: prospective cohort study. *Family Pract* 2018, 35(6):676–683. https://doi.org/10.1093/fampra/cmy021
17. Boiko O, Burgess C, Fox R, et al. Risks of use and non-use of antibiotics in primary care: qualitative study of prescribers' views. *BMJ Open* 2020;10:e038851. doi:10.1136/ bmjopen-2020-038851
18. Stuart B, Hounkpatin H, Becque T, et al. Delayed antibiotic prescribing for respiratory tract infections: individual patient data meta-analysis. *BMJ* 2021;373:n808. doi: 10.1136/bmj.n808.
19. Stuart B, Hounkpatin H, Becque T, et al.Delayed antibiotic prescribing for respiratory tract infections: protocol of an individual patient data meta-analysis. BMJ Open2019;9:e026925. doi:10.1136/bmjopen-2018-026925
20. Little P, Williamson I, Warner G, et al. Open randomised trial of prescribing strategies in managing sore throat. *BMJ* 1997;314:722–7.
21. Little P, Gould C, Williamson I, et al. Pragmatic randomised controlled trial of two prescribing strategies for childhood acute otitis media. *BMJ* 2001;322:336–42.
22. Arroll B, Kenealy T, Kerse N. Do delayed prescriptions reduce the use of antibiotics for the common cold? A single-blind controlled trial. *J Fam Pr* 2002;51:324–8.
23. McCormick DP, Chonmaitree T, Pittman C, et al*.* Nonsevere acute otitis media: a clinical trial comparing outcomes of watchful waiting versus immediate antibiotic treatment. *Pediatrics* 2005;115:1455–65. doi:10.1542/peds.2004-1665
24. Little P, Rumsby K, Kelly J,, et al. Information leaflet and antibiotic prescribing strategies for acute lower respiratory tract infection: a randomised controlled trial. *JAMA* 2005;293:3029-35

25. Chao JH, Kunkov S, Reyes LB, et al. Comparison of two approaches to observation therapy for acute otitis media in the emergency department. *Pediatrics* 2008;121:e1352-6. doi:10.1542/peds.2007-2278
26. Francis NA, Gillespie D, Nuttall J, et al. Delayed antibiotic prescribing and associated antibiotic consumption in adults with acute cough. *Br J Gen Pr* 2012;62:e639-46. doi:10.3399/bjgp12X653561
27. Little P, Stuart B, Hobbs FDR, et al. Predictors of suppurative complications for acute sore throat in primary care: Prospective clinical cohort study. *BMJ* 2013;347. doi:10.1136/bmj.f6867
28. Little P, Moore M, Kelly J, et al. Delayed antibiotic prescribing strategies for respiratory tract infections in primary care: pragmatic, factorial, randomised controlled trial. *BMJ* 2014;348:g1606. doi:10.1136/bmj.g1606
29. Hay AD, Redmond NM, Turnbull S, et al*.* Development and internal validation of a clinical rule to improve antibiotic use in children presenting to primary care with acute respiratory tract infection and cough: a prognostic cohort study. *Lancet Respir Med* 2016;4:902–10. doi:10.1016/S2213-2600(16)30223-5
30. de la Poza Abad M, Mas Dalmau G, Moreno Bakedano M, et al.. Prescription strategies in acute uncomplicated respiratory infections: a randomized clinical trial. *JAMA Intern Med* 2016 ;176(1):21-9. doi: 10.1001/jamainternmed.2015.7088
31. Mas-Dalmau G, Villanueva López C, Gorrotxategi Gorrotxategi P,et al. Delayed antibiotic prescription for children with respiratory infections: a randomized trial. *Pediatrics* 2021;147(3): e20201323. doi: 10.1542/peds.2020-1323.
32. Watson L, Little P, Williamson I, et al. Validation study of a diary for use in acute lower respiratory tract infection. *Fam Pract* 2001;18:553-4
33. Feldman BJ, Masyn KE, Conger RD. New approaches to studying problem behaviors: a comparison of methods for modeling longitudinal, categorical adolescent drinking data. *Dev Psychol* 2009;45(3):652-676. doi:10.1037/a0014851

34. Faraoni D, Schaefer ST. Randomized controlled trials vs. observational studies: Why not just live together? *BMC Anesthesiol* 2016;16. doi:10.1186/s12871-016-0265-3
35. Gillespie D, Farewell D, Brookes-Howell L, et al. Determinants of initiation, implementation, and discontinuation of amoxicillin by adults with acute cough in primary care. *Patient Prefer Adherence* 2017;11:561-569. doi:10.2147/PPA.S119256
36. Francis NA, Gillespie D, Nuttall J, et al. Antibiotics for acute cough: an international observational study of patient adherence in primary care. *Br J Gen Pract* 2012;62(599):e429-e437. doi:10.3399/bjgp12X649124
37. McDermott L, Leydon GM, Halls A, et al. Qualitative interview study of antibiotics and self-management strategies for respiratory infections in primary care. *BMJ Open* 2017;7:e016903. doi: 10.1136/bmjopen-2017-016903
38. Department of Health. Tackling antimicrobial resistance 2019–2024. The UK's five-year national action plan. London: Department of Health, 2019.
39. Public Health England. Treating your infection. London: Public Health England, 2015.

Box 1. IPD database on antibiotic prescribing for RTIs

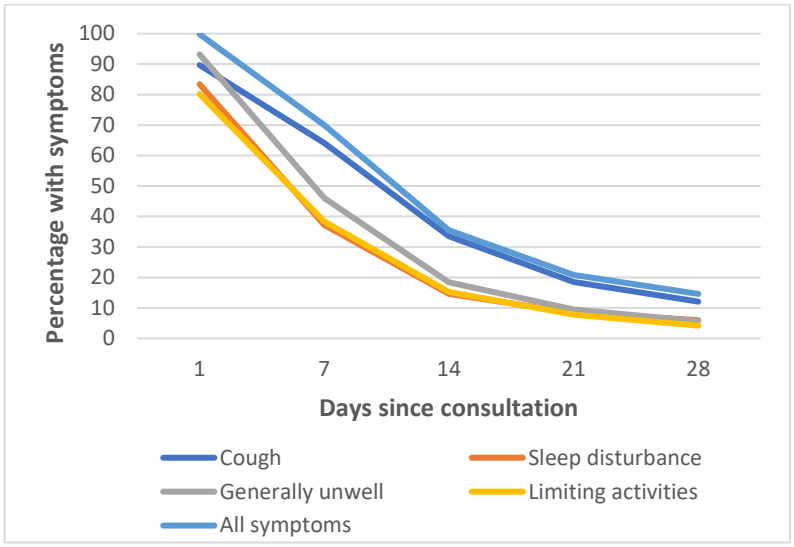
The IPD database included 13 studies (9 randomised controlled studies (RCTs) and 4 observational cohort studies) on antibiotic prescribing for RTIs [acute sore throat, acute cough, otitis media] in a community setting. Studies were included in the IPD database if they compared delayed antibiotic prescribing to either immediate or no antibiotic prescribing. Studies were conducted in the United Kingdom, United States, New Zealand and 13 European countries and included 55,682 participants. Studies were conducted between 1997 and 2016. Six of the 13 studies assessed all age groups, 4 studies assessed adult populations and 3 studies focused on paediatric populations. Eleven studies were conducted in a primary care setting, 1 study each was conducted in a paediatric emergency department and paediatric clinic. Symptom severity data were not collected for all studies or were only collected for

Box 2. LLCA method and assumptions

A series of models were fitted to determine the optimal number of classes. Model selection was based on the Bayesian Information Criterion, high entropy (≥0.80), good posterior probabilities (>0.8), and clinically relevant difference between classes. Full-information maximum likelihood estimation accounted for missing data, allowing us to use all available data and retain a larger sample size.
For the LLCA, three restrictions were made to reduce the data and allow model convergence (16). First, data from the first 15 days post-consultation were included in the analyses. Second, data from alternate days (days 1, 3,5, etc) were used to reduce the number of measures. Third, symptom severity was re-grouped into three categories: 0- mild (severity scores 0-2), 1- moderate (scores 3-4), or 2- severe (scores 5-6). Symptom recovery time for each trajectory group was therefore described as time to symptom resolution to below moderate level.

Figure 1. Symptom resolution over the first 28 days after index consultation: (a) for those who took antibiotics and (b) those who did not take antibiotics

(a)



(b)

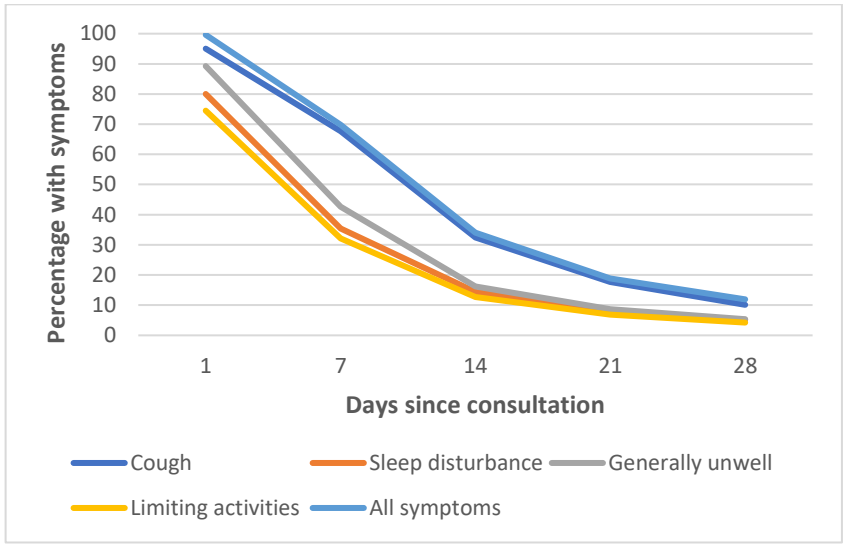
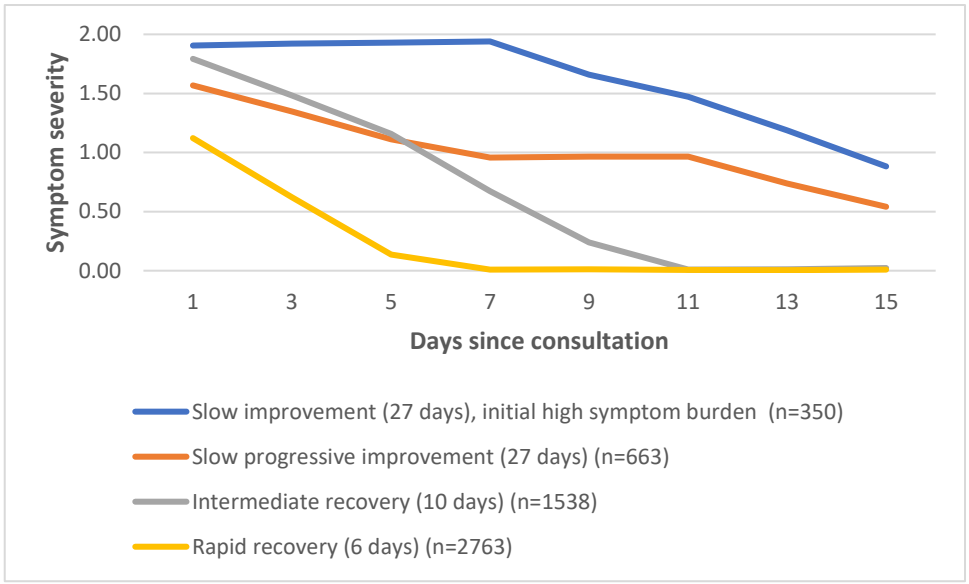
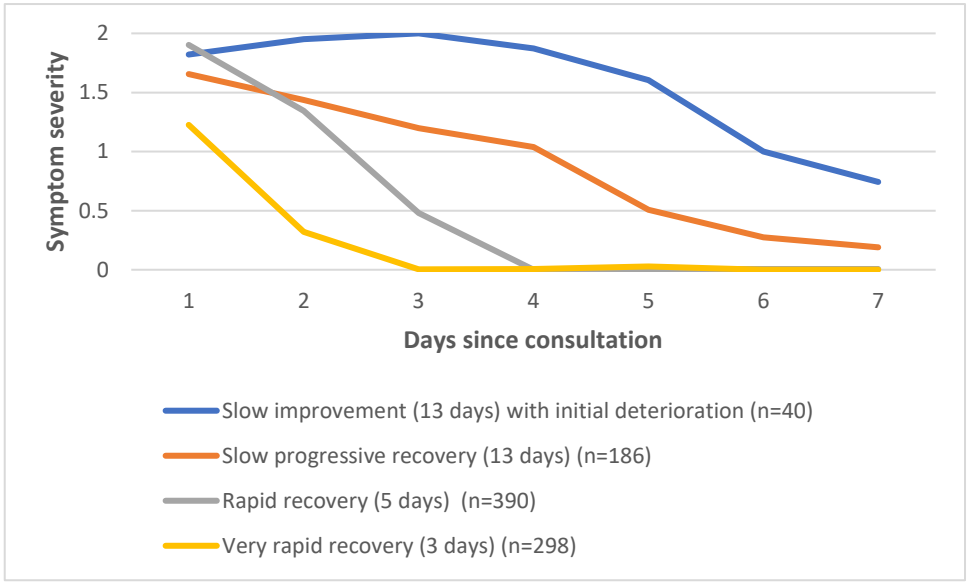


Figure 2. Symptom trajectories based on LLCA for (a) cough, (b) sore throat and (c) acute otitis media

(a)



(b)



Post-consultation acute respiratory tract infection recovery

(c)

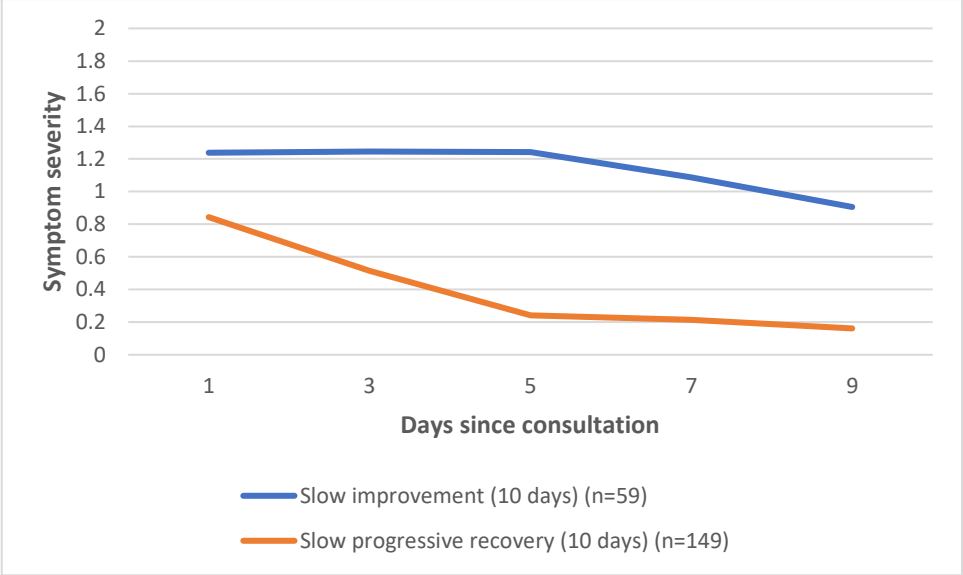


Table 1. Baseline characteristics of all participants (adults and children) according to symptom trajectories for cough studies

	Rapid recovery [6 days] (n=2763, 52.0%)		Intermediate recovery [10 days] (n=1538, 28.9%)		Slow progressive improvement [27 days] (n=663, 12.5%)		Slow improvement with initial high symptom burden [27 days] (n=350, 6.6%)		p-value
	Mean (SD)*	**Number of participants (% overall)**	**Mean (SD)***	**Number of participants (% overall)**	**Mean (SD)***	**Number of participants (% overall)**	**Mean (SD)***	**Number of participants (% overall)**	
Age (yrs)	25.3 (24.4)		36.4 (22.8)		39.6 (24.2)		39.3 (22.7)		<0.001
Sex									
Female		1361 (54.3)		820 (60.9)		349 (60.1)		212 (67.5)	<0.001
Mean baseline severity score	1.5 (0.6)		1.8 (0.7)		1.5 (0.6)		1.8 (0.6)		<0.001
Mean prior duration illness (days)	8.2 (7.0)		9.1 (7.2)		10.5 (7.3)		8.7 (5.9)		0.025
Fever at baseline		1269 (46.2)		745 (48.7)		293 (44.6)		152 (43.7)	0.163
Any lung disease		263 (14.2)		218 (17.1)		115 (21.6)		63 (21.1)	<0.001
Treatment group									
No Antibiotics		1321 (47.8)		683 (44.4)		329 (49.6)		164 (46.9)	0.021
Immediate		1031 (37.3)		647 (42.1)		260 (39.2)		136 (38.9)	
Delayed		411 (14.9)		208 (13.5)		74 (11.2)		50 (14.3)	

*p-value <0.05 indicates statistically significant difference across groups. Data on sex and mean prior duration of illness were based on 4 studies

Table 2. Logistic regression analysis determining associations with slower (>10 days) vs faster recovery (≤10 days) for cough

	Cough		
	Slower recovery (>10 days) (n=1172, 20.3%)		
	OR	**95% CI**	
Age			
<16 (reference)	1.00		
16-64	**2.57**	**1.72**	**3.85**
>64	**3.17**	**2.05**	**4.90**
Female	1.05	0.88	1.25
Baseline severity			
Below median	1.00		
Median and above	**1.51**	**1.12**	**2.03**
Prior duration illness			
Below median (<7 days)	1.00		
Median and above (≥ 7 days)	**1.99**	**1.68**	**2.37**
Fever at baseline			
Below 37.5	1.00		
Above 37.5	1.01	0.84	1.20
Any lung disease			
No	1.00		
Yes	**1.78**	**1.44**	**2.21**
Antibiotics			
No antibiotics (reference)	1.00		
Immediate	**0.82**	**0.68**	**0.98**
Delayed	0.99	0.72	1.37

*Regression additionally adjusted for study ID variable as a random effect