Accepted Manuscript

British Journal of General Practice

Predicting illness progression for children with lower respiratory infections (LRTI) presenting to primary care

Little, Paul; Becque, Taeko; Hay, Alastair; Francis, Nick; Stuart, Beth; O'Reilly, Gilly; Thompson, Natalie; Hood, Kerry; Moore, Michael; Verheij, Theo

DOI: https://doi.org/10.3399/BJGP.2022.0493

To access the most recent version of this article, please click the DOI URL in the line above.

Received 06 October 2022
Revised 06 May 2023
Accepted 12 May 2023

Predicting illness progression for children with lower respiratory infections (LRTI) presenting to primary care

Paul Little[1], Taeko Becque[1] Alastair D Hay[2],Nick A. Francis[1],Beth Stuart[1], Gilly O'Reilly[1], Natalie Thompson[1], Kerenza Hood[3], Michael Moore[1],Theo Verheij[4].

[1] Primary Care Population Sciences and Medical Education Unit, University of Southampton

[2] Centre for Academic Primary Care, Bristol Medical School: Population Health Sciences, University of Bristol

[3]Centre for Trials Research, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK.

[4]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands.

Correspondence to Professor Little p.little@soton.ac.uk Tel +44 2380 241050; fax +44 2380 701125

This project is funded by the Health Technology Assessment (HTA) Programme (study reference **13/34/64**) of the NIHR.

Word count 2722. 5 tables; 1 Figure; 1 Appendix

Key words: primary care; lower respiratory tract infection; prognosis; children

P Little Professor of Primary Care Research (ORCID: 0000-0003-3664-1873), FRCGP; **T Becque Senior Clinical Trials Statistician**(ORCID: 0000-0002-0362-3794), PhD; **NA Francis Clinical Professor of Primary Care Research** (ORCID: 0000-0001-8939-7312), PhD; **B Stuart Professor of Medical Statistics** (ORCID: 0000-0001-5432-7437), PhD; **Dr G O'Reilly Senior Trial manager** (ORCID: 0000-0001-6141-4360), PhD; **Ms N Thompson trial manager** (ORCID: 0000-0002-1880-6438), MSc; **M Moore Professor of Primary Care Researc** (ORCID: 0000-0002-5127-4509), FRCGP, Primary Care Population Sciences and Medical Education Unit, University of Southampton, Southampton, UK. **AD Hay Professor of Primary Care** (ORCID: 0000-0003-3012-375X), PhD, Centre for Academic Primary Care, Bristol Medical School: Population Health Sciences, University of Bristol, Bristol, UK. **K Hood Professor of Trials** (ORCID: 0000-0002-5268-8631), PhD, Centre for Trials Research, College of Biomedical and Life Sciences, Cardiff University, Cardiff, UK. **T Verheij Professor of General Practice** (ORCID: 0000-0002-0166-1498), PhD, Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands.

Abstract.

Background

Antibiotics are commonly prescribed for children with LRTI, fuelling antibiotic resistance, and there are few prognostic tools available to inform management.

Aim. To externally validate an existing prognostic model (STARWAVe) to identify children at low risk of illness progression, and if model performance was limited to develop a new internally validated prognostic model.

Design and Setting Prospective cohort study with nested trial in primary care setting

Method. Children aged one to twelve presenting with uncomplicated LRTI were included in the cohort. Children were randomised to receive Amoxicillin 50mg/kg/day/7 days or placebo, or if not randomised participated in a parallel observational study to maximise generalisability. Baseline clinical data was used to predict adverse outcome (illness progression requiring hospital assessment).

Results. 758 children participated (432 trial, 326 observational). For predicting illness progression the STARWAVe prognostic model had moderate performance (AUROC 0.66;0.50, 0.77), but a new, internally validated model (7 items: baseline severity/respiratory rate/duration of prior illness/oxygen-saturation/sputum-rattly chest/passing urine less often/diarrhoea) had good discrimination (bootstrapped AUROC 0.83) and calibration. A 3 item model (respiratory rate; oxygen saturation; sputum-rattly chest) also performed well (AUROC 0.81), as did a score (ranging from 19 to 102) derived from coefficients of the model (AUROC was 0.78; 0.68, 0.88): a score of less than 70 classified 89% (600/674) of children having a low risk (<5%) of progression of illness.

Conclusion.

A simple 3 item prognostic score could be useful as a tool to identify children with LRTI who are at low risk of adverse outcome and guide clinical management.

Key words: antibiotic resistance; antibiotics; LRTI; children; primary care

How this fits in

- Antibiotics are commonly prescribed for children with LRTI, fuelling antibiotic resistance, and there are few prognostic tools available to inform management.
- In a cohort of unwell children presenting with uncomplicated LRTI an existing rule (the STARWAVe prognostic model) had limited performance in predicting illness progression.
- A new internally validated prognostic score (using respiratory rate, oxygen saturation and having sputum or a rattly chest) performed well and could be useful in identifying children at low risk of adverse outcomes and guiding management.

Introduction

Lower respiratory tract infection (LRTI) is a frequent trigger for attendance in primary care - where nearly all children are managed, most still receiving antibiotics[1-4]. Antibiotics probably have limited benefit for LRTI in children [5], and individuals using antibiotics are likely to have more antibiotic-resistant organisms subsequently [6] and prolonged infections[7]. Outpatient antibiotic prescribing is strongly related to Anti-microbial-resistance (AMR)[8]. AMR is a global public-health threat[9](Chief-Medical-Officer(CMO)-Annual-Report-Vol-2-2011) since much of modern medicine (e.g. complicated infections, cancer care, surgery) relies on antibiotics.

Judicious and targeted use of antibiotics is likely to be key to both efficient clinical care and to minimise the risk of antibiotic resistance. Clinicians are risk averse to a child developing a complication when a prescription has not been issued[10], and so commonly prescribe antibiotics 'in case'[11 12 13]. A key problem is the absence of evidence to assist clinicians in the consultation to assess risk - in order to help tailor patient information, inform monitoring of disease, or help the targeting of treatment - particularly to minimise the use of antibiotics[14-18]. The CRB-65 rule was developed in hospital settings to predict 30 day mortality, but is not well validated even among adults in primary care settings and is not suitable for use in children[19]. There is one evidence-based internally validated prognostic tool for children with LRTI developed in primary care - the STARWAVe model: this was developed in children presenting in primary care in the UK to predict hospital admissions for respiratory infection in the following 30 days[20]. The independently predictive variables included in the model were age <2 years, current asthma, illness duration of 3 days or less, parent-reported moderate or severe vomiting in the previous 24 h, parent-reported severe fever in the previous 24 h or a body temperature of 37.8°C or more at presentation, clinician-reported intercostal or subcostal recession, and clinician-reported wheeze on auscultation. The area under the receiver operating characteristic (AUROC) was 0.81 (the internally validated bootstrapped estimate). Although the model was internally validated, the spectrum of illness among children was milder than recent studies [5 20], and STARWAVe was not able to use oxygen saturation data which is likely to be an important independent predictor of outcome.[15 16]

Trial data alone can be less useful in generating prognostic models due to the inevitable selection bias (where more unwell children tend to be excluded), but nesting trial data within observational studies increases external validity of analyses and facilitates the generation of more robust clinical prediction models. We report the data on the progression of illness from a cohort of children which combined trial and observational data. We report both the external validation of an existing prognostic model, and since the performance of the existing model was limited in this cohort of more unwell children, the development of a new internally validated model.

Methods

Study Design. Cohort study including both children from a trial and parallel observational study

Overview of methods. Full details of all data collection methods have been previously published [5]. Children with were recruited between 6 months and twelve years old presenting to primary care in UK general practices with acute uncomplicated LRTI, i.e. where the clinician does not suspect pneumonia on clinical grounds. Parents and children were consented for participation by the responsible clinicians (usually general practitioners). The protocol was approved by the South West - Central Bristol Research Ethics Committee, reference 15/SW/0300.

Acute LRTI was defined syndromically in several previous cohorts and trials as an acute cough as the predominant symptom, judged by the GP to be infective in origin, lasting <21 days (which will exclude children with protracted bacterial bronchitis[21 22]), and with other symptoms or signs localising to the lower respiratory tract (shortness of breath, sputum, pain)[23-29]. Exclusion criteria included acute illness requiring immediate referral to hospital (e.g. pneumonia, sepsis), non infective causes of cough (e.g. hay fever), immune deficiency and inability to provide consent.

Where parents and clinicians were willing for children to be randomised, they were randomised to receive Amoxicillin 50mg/kg/day in divided doses for 7 days, or placebo, using pre-prepared packs randomised using computer generate random number by an independent statistician[5]. Children not randomised (because ineligible or due to clinician or parent choice) were invited to participate in an observational study where the baseline clinical data and all outcome data as for the trial were collected by the same methods [5]. In the observational study the choice of treatment was at the physician's discretion and could involve antibiotic prescription or no prescription. Most practices that recruited children to the trial also recruited to the observational study but some sites could only recruit to the observational study.

Outcomes. Progression of illness, the focus of this paper, was defined as illness requiring hospital assessment and/or admission, within one month of the index consultation. It was documented from a medical record review[29].

Sample size. The standard rules used by statisticians suggest that the number of variables that can be assessed robustly in a prognostic model is 1 variable per 10 cases– so with 29 children experiencing adverse outcomes the three variable model should be adequately powered[30]. However the traditional rule of thumb has been questioned[30] – and making the recommended assumptions[30] (a margin of error of <=0.05, a mean absolute prediction error of <=0.05, and shrinkage factor of <10%, and expected optimism factor of 0.05) with an expected outcome event rate of 5% suggests that 566 participants were required.

Statistical analysis.

We used logistic regression models to assess the prediction of illness. We assessed the external validity of the STARWAVe score using the three STARWAVe classifications of low, normal or high risk[20]. The performance of STARWAVe limited in this population, so we then developed a new model, using a backwards fitting approach to model the predictors of progression of illness in the current data set. Backward elimination is preferred among automatic predictor selection techniques because the correlations between predictors are accounted for in the multivariable model[31]. Simulation studies suggest that p-values larger than 0.05 should be considered, particularly in small data sets[32]. For the first, most inclusive, model we retained in the multivariable model variables with $p<0.20$. Given the danger of over-fitting we also assessed a model for the variables that were significant at $p<0.05$ in multivariate analysis in the first model resulting in a 4 item model, and finally generated a model including the 3 most significant variables. Developing a model with only a few major predictors can increase applicability in clinical practice. We explored whether progression of illness could be predicted from the following baseline characteristics: age, the severity of symptoms, heart rate, respiratory rate, temperature, duration of illness prior to consultation, gender, comorbid conditions, history of asthma, chest signs, feeling generally unwell, oxygen saturation, sputum/rattly chest, vomiting, dry cough, chills, diarrhoea, disturbed sleep, passing urine less often.

We present the discrimination of the model in the Area Under the Receiver Operator Curve (AUROC), using bootstrapping to limit overly optimistic estimates due to overfitting - and a recommended and more efficient approach to internal validation rather than using split samples [33]. Model calibration was assessed with a Hosmer Lemeshow (HL) test.

Results

326 patients were recruited to the observational study (see Figure 1), 312 with antibiotic prescription data: 157 received no antibiotic, 141 immediate and 14 delayed. Since the numbers with a delayed prescription were so small, these have been combined with immediate for the purposes of analysis. Combined with the trial data, there were 744 participants in total, of whom 368 received no antibiotic and 376 were given or were prescribed an antibiotic. In the observational cohort, 52/312 (16.7%) were recruited via A&E/paediatric assessment vs 260/312 via GP practices. In the trial, 5/432 (1.1%) were recruited via A&E/paediatric vs 427/432 via practices.

Clinical characteristics. As expected, the number of children in the observational cohort with more severe clinical features (Table1) was greater in the antibiotic group compared with the no antibiotic group – with more severe average baseline symptom scores (1.8 score and 1.5 score respectively), and more with abnormal chest signs (81%, 24%), sputum production (87%, 70%), history of fever (91%,64%), feeling unwell (81%,51%), shortness of breath (70%,36%) and low oxygen saturation (21%,7%).

Progression of illness was recorded for 705 participants (94.8%). 29 children (4%) in the cohort had illness progression requiring attendance or admission to hospital (for details of the illnesses, see Appendix, Table S1).

Prognostic model. We tested the STARWAVe score using the three classifications. The calibration was excellent with a HL test p-value of 0.9847, but the AUROC was modest 0.66 (95% CI 0.50, 0.77). Since STARWAVe was developed to predict progression of illness requiring overnight hospital admission (11 of the children in the current data set) we separately tested test performance for this outcome, the AUROC for STARWAVe in predicting the need for overnight hospital admission was 0.70 (0.56, 0.84; HL p-value 1.00).

Given the modest discrimination of the STARWAVe model in this population we developed a new model. The predictors of the progression of illness are shown in Table 2. The variables that were retained in the model were baseline severity; difference in respiratory rate from normal for age; low oxygen saturation; sputum/rattly chest (Y/N), passing urine less often or drier nappies than normal (Y/N); diarrhoea (Y/N); and duration of illness prior to consultation. The model had an AUROC of 0.83 (95% CI 0.74, 0.92) and model calibration was good with a Hosmer Lemeshow (HL) test p-value of 0.22. A four item model including significant variables (at the 5% level) from the 7 item model (difference in respiratory rate from normal for age, presence of sputum/rattly chest, low oxygen saturation (<95%)and passing urine less frequently or drier nappies than normal), had an AUROC of 0.83 (95% CI 0.73 to 0.92) for progression of illness, with a HL p-value of 0.51. A reduced model using only the three significant predictors from the four item model (difference in respiratory rate

from normal for age, sputum/rattly chest and low oxygen saturation) had an AUROC of 0.81 (95% CI 0.71, 0.91), HL statistic p-value 0.86 (Table 3). We did not include antibiotic prescription in the primary predictive model due to the observed inverse association between antibiotic prescribing and the progression of illness (very likely due to confounding by indication), nevertheless we also assessed the model after including antibiotic prescription and the same variables were still included. We also looked at the discrimination the four item model for the 11 children requiring overnight admissions: the AUROC was 0.89 (0.80, 0.97; HL p-value 0.88). The AUCROC for the three item model was 0.86 (0.74, 0.98), but an HL p-value of 0.004 indicates a poor model fit for overnight admission.

We converted the three-item model (respiratory rate (breaths/min), oxygen sat<95%, sputum) to a score by multiplying the beta coefficients by 10 and rounding to nearest integer (score = 46 + difference in respiratory rate from normal for age + 14*low oxygen saturation + 18*sputum, where low oxygen saturation = 1 if oxygen saturation<95% (0 otherwise), and sputum =1 for presence of sputum or rattly chest (0 otherwise). Scores range from 19 to 102, and the AUROC was 0.78 (95% CI 0.68, 0.88) for progression of illness, and 0.86 (95% CI 0.72, 1.00) for hospital admission. The performance of the score for different cut points is shown in Tables 4 and 5, and it is clear that the risk of progression of illness remains low (<5%) until a score of 70, as does the risk of overnight admission.

Discussion

Summary

A simple 3 item prognostic score using clinical variables that are all readily available in the consultation could be useful as a tool to identify children with acute LRTI who are at low risk of significant illness progression in order to guide clinical management.

Strengths and Limitations.

The differences in clinical characteristics between observational and trial data participants was expected, but cannot be attributed just to clinical decision making in deciding who to recruit to the trial or the observational study since some observational patients came from less typical sites that were not able to recruit to the trial (e.g. Emergency Departments). The prognostic model was limited by the relatively few children where illness progressed (potentially limiting detection of relevant variables due to lower power), but both using traditional rules of thumb and more recent guidance the study should have had sufficient power, at least for the three item model[30]. The discrimination of the model was good, but we may have underestimated the discriminatory ability, since more significant variables would increase the discriminatory power. Bootstrapping limited the problem of over-fitting and provided internal validation which is the recommended, most efficient approach to internal validation rather than using split samples [33]. The reduced model with fewer variables also provided reasonable estimates of discrimination, but external validation will preferably be needed. 23(6.1%) of the study population had the label of asthma by clinicians, which will have some error, but this was a pragmatic study using information readily available to clinicians. The presence of clinician diagnosed asthma was also not a predictor of outcome, and the number of children with the diagnostic label of asthma was very few (<10%).

Comparison with existing literature.

Children given antibiotics in the observational study had much more severe clinical presentations than children not given antibiotics – matching the trends in STARWAVe [20 34]. The children in both the trial and observational cohorts were more severely affected than STARWAVe – among children given antibiotics very high percentages had sputum production (87% in the observational cohort compared with 63% in STARWAVe) fever (91%, 75% respectively) shortness of breath (70%, 46%).

We provide some evidence of external validation in that STARWAVe is able to distinguish different levels of prognostic risk in this dataset, albeit with lower levels of prognostic accuracy than in the derivation dataset[20], which could be explained by the different populations studied. The new prognostic model to predict the progression or illness included seven variables and demonstrated good

discrimination (AUROC 0.83) and calibration. However it included rather different variables to the STARWAVe model[20 34] - only age and prior illness duration being in common (STARWAVe included age <2 years, current asthma, illness duration of 3 days or less, parent-reported moderate or severe vomiting in the previous 24 h, parent-reported severe fever in the previous 24 h or a body temperature of 37·8°C or more at presentation, clinician-reported intercostal or subcostal recession, and clinician-reported wheeze on auscultation). Thus it is perhaps not surprising that the STARWAVe model had lower discrimination in the current population (AUROC 0.65), and the differences probably reflects the more severely affected group of children recruited for the current study. Other differences with STARWAVe are: that pulse oximetry was only available in <50% of children for the STARWAVe cohort, and if saturation had been more available it might have been included in STARWAVe; intercostal recession was also not measured in the current study, so it is possible the estimates of discrimination might be improved further. If the outcome was 'illness progression sufficient to require overnight hospital admission', then the discrimination of both the new model and STARWAVe improved further.

Implications for clinical practice.

A simple, internally validated, clinical score for use in more unwell children with uncomplicated acute LRTI uses variables that are easily documented in routine consultations, and shows promise in enabling clinicians to identify the minority of children whose illness is more likely to progresses sufficiently to require hospital assessment, and those where the illness is very unlikely to progress – potentially helping guiding management decisions to minimise antibiotic use for children at low risk, and/or for closer follow-up for children at high risk[16]. The clinical score preferably also requires external validation, and only applies to children with acute LRTI; children with protracted bacterial bronchitis (a wet cough lasting more than 4 weeks, commonly recurrent), are likely to benefit from a longer course of antibiotics[21 22]. The simplicity of the rule, using variables that do not require extensive medical training, means that there is potential for the use of the clinical score in settings such as pharmacies – but this would require careful assessment of feasibility and safety. Although the data comes from a UK setting, the clinical score is also likely to valid for children presenting with LRTI in other high income countries, but may not be valid in low and middle income countries, even assuming oxygen saturation monitors were available.

Ethics. The trial protocol; was approved by the South West - Central Bristol Research Ethics Committee reference 15/SW/0300

Competing Interests. All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). Dr. Verheij reports grants from EU and The Netherlands Organization of Health Research and Development, during the conduct of the study; grants from Abbott, Becton Dickinson and Bio-Merieux, grants from Janssen Pharmaceuticals, outside the submitted work; .
Other authors declare (other than the grant support from the NIHR for the submitted work), no support from other organisations for the submitted work ; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Acknowledgements. The views expressed in this publication are those of the author(s) and not necessarily those of the HTA, NHS, NIHR or the Department of Health We are very grateful to both the TSC (Chair Elaine Hay) and the DMSC (Chair Sally Kerry) for their support and advice.

Contributorship. PL and TV developed the original idea. PL led the funding applications with input from all coauthors, and the protocol was developed and modified by all authors. The study progress was supervised on a day to day basis by GOR and NT with input at regular study management meetings from all authors. BS,KH, TB,TV and PL developed the statistical analysis plan and interpreted the analyses, with input from all the authors; TB performed the statistical analysis supervised by BS. PL led the writing of the paper and all authors contributed to interpretation of the analyses and to revisions of the paper. BLS, NT and TB accessed and verified the data, and PL and TV were responsible for the decision to submit the manuscript.

Data sharing. De-identified participant data is available for further analyses. Request for data, with justification, should be made to PL or TV.[35]

References.

1. Okkes IM, Oskam SK, Lamberts H. The probability of specific diagnoses for patients presenting with common symptoms to Dutch family physicians. *J Fam Pract* 2002;51(1):31-6. [published Online First: 2002/04/03]
2. Hay AD, Heron J, Ness A. The prevalence of symptoms and consultations in pre-school children in the Avon Longitudinal Study of Parents and Children (ALSPAC): a prospective cohort study. *Fam Pract* 2005;22(4):367-74. doi: 10.1093/fampra/cmi035 [published Online First: 2005/05/18]
3. Hersh AL, Shapiro DJ, Pavia AT, et al. Antibiotic prescribing in ambulatory pediatrics in the United States. *Pediatrics* 2011;128(6):1053-61. doi: 10.1542/peds.2011-1337 [published Online First: 2011/11/09]
4. Petersen I, Johnson A, Islam A, et al. 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 (10 November), doi:10.1136/bmj.39345.405243.BE.
5. Little P, Francis NA, Stuart B, et al. Antibiotics for lower respiratory tract infection in children presenting in primary care in England (ARTIC PC): a double-blind, randomised, placebo-controlled trial. *Lancet* 2021 doi: 10.1016/s0140-6736(21)01431-8 [published Online First: 2021/09/26]
6. Costelloe C, Metcalfe C, Lovering A, et al. Effect of antibiotic prescribing in primary care on antimicrobial resistance in individual patients: systematic review and meta-analysis. *BMJ* 2010;340:doi: http://dx.doi.org/10.1136/bmj.c2096.
7. Little P, Turner S, Rumsby K, et al. Urinary tract infection: development and validation, randomised trial, economic analysis, observational cohort and qualitative study. *Health Technol Assess* 2009;13: No 19
8. Goossens H, Ferech M, Vander Stichele R, et al. Outpatient antibiotic use in Europe and association with resistance: a cross-national database study. *Lancet* 2005;365:579-87.
9. Carlet J, Jarlier V, Harbarth S, et al. Ready for a world without antibiotics? The Pensières Antibiotic Resistance Call to Action. *Antimicrob Resist Infect Control 2012 Feb 14;1(1):11* 2012;1:11.
10. Cabral C, Lucas PJ, Ingram J, et al. "It's safer to …" parent consulting and clinician antibiotic prescribing decisions for children with respiratory tract infections: An analysis across four qualitative studies. *Soc Sci Med* 2015;136-137:156-64. doi: 10.1016/j.socscimed.2015.05.027 [published Online First: 2015/05/26]
11. Lucas PJ, Cabral C, Hay AD, et al. A systematic review of parent and clinician views and perceptions that influence prescribing decisions in relation to acute childhood infections in primary care. *Scand J Prim Health Care* 2015;33(1):11-20. doi: 10.3109/02813432.2015.1001942 [published Online First: 2015/02/27]
12. Kumar S, Little P, Britten N. Why do Gps prescribe antibiotics for sore throat? A grounded theory interview study of general practitioners. *BMJ* 2003;326:(18 January):138.
13. Horwood J, Cabral C, Hay AD, et al. Primary care clinician antibiotic prescribing decisions in consultations for children with RTIs: a qualitative interview study. *Br J Gen Pract* 2016;66(644):e207-13. doi: 10.3399/bjgp16X683821 [published Online First: 2016/02/09]
14. Little P, Stuart B, Smith S, et al. Antibiotic prescription strategies and adverse outcome for uncomplicated lower respiratory tract infections: prospective cough complication cohort (3C) study. *Bmj* 2017;357:https://www.bmj.com/content/357/bmj.j2148. doi: 10.1136/bmj.j2148 [published Online First: 2017/05/24]
15. Moore M, Stuart B, Little P, et al. Predictors of pneumonia in lower respiratory tract infections: 3C prospective cough complication cohort study. *Eur Respir J* 2017;50(5):https://erj.ersjournals.com/content/50/5/1700434. doi: 10.1183/13993003.00434-2017 [published Online First: 2017/11/24]

16. Moore M, Stuart B, Lown M, et al. Predictors of Adverse Outcomes in Uncomplicated Lower Respiratory Tract Infections. *Ann Fam Med* 2019;17(3):231-38. doi: 10.1370/afm.2386 [published Online First: 2019/05/16]
17. Stuart B, Hounkpatin H, Becque T, et al. Delayed antibiotic prescribing for respiratory tract infections: individual patient data meta-analysis. *BMJ (Clinical research ed)* 2021;373:n808-n08. doi: 10.1136/bmj.n808
18. Little P, Hobbs FD, Moore M, et al. Clinical score and rapid antigen detection test to guide antibiotic use for sore throats: randomised controlled trial of PRISM (primary care streptococcal management). *Bmj* 2013;347:f5806. doi: 10.1136/bmj.f5806 [published Online First: 2013/10/12]
19. McNally M, Curtain J, O'Brien KK, et al. Validity of British Thoracic Society guidance (the CRB-65 rule) for predicting the severity of pneumonia in general practice: systematic review and meta-analysis. *Br J Gen Pract* 2010;60(579):e423-33. doi: 10.3399/bjgp10X532422 [published Online First: 2010/10/05]
20. 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(11):902-10. doi: 10.1016/s2213-2600(16)30223-5 [published Online First: 2016/11/02]
21. Kantar A, Chang AB, Shields MD, et al. ERS statement on protracted bacterial bronchitis in children. *Eur Respir J* 2017;50(2) doi: 10.1183/13993003.02139-2016 [published Online First: 2017/08/26]
22. Bush A. Persistent Bacterial Bronchitis: Time to Venture beyond the Umbrella. *Front Pediatr* 2017;5:264. doi: 10.3389/fped.2017.00264 [published Online First: 2018/01/13]
23. MacFarlane J, Holmes W, Gard P, et al. Prospective study of the incidence, aetiology and outcome of adult lower respiratory tract illness in the community. *Thorax* 2001;56:109-14.
24. MacFarlane J, Holmes W, Gard P, et al. Reducing antibiotic use for acute bronchitis in primary care: blinded, randomised controlled trial of patient information leaflet. *BMJ* 2002;324:91-94.
25. MacFarlane J, Macfarlane RM, Rose D, et al. How common is pneumonia and other radiographic features in previously well adults who present in the community with acute lower respiratory tract illness? *E R J* 1999;14:16s.
26. Bruyndonckx R, Stuart B, Little P, et al. Amoxicillin for acute lower respiratory tract infection in primary care: subgroup analysis by bacterial and viral aetiology. Clin. Microbiol. Infect. 2018;24(8):871-76. doi: 10.1016/j.cmi.2017.10.032 [published Online First: 2017/11/08]
27. 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.
28. Little P, Francis NA, Stuart B, et al. Antibiotics for lower respiratory tract infection in children presenting in primary care in England (ARTIC PC): a double-blind, randomised, placebo-controlled trial. *Lancet* 2021;398(10309):1417-26. doi: 10.1016/s0140-6736(21)01431-8 [published Online First: 2021/09/26]
29. Little P, Stuart B, Moore M, et al. Amoxicillin for acute lower respiratory tract infection where pneumonia is not suspected clinically : a 12 country randomised placebo controlled trial in primary care. *Lancet Infect.Dis.* 2013;Feb;13(2):123-9. doi: 10.1016/S1473-3099(12)70300-6.
30. Riley RD, Ensor J, Snell KIE, et al. Calculating the sample size required for developing a clinical prediction model. *Bmj* 2020;368:m441. doi: 10.1136/bmj.m441 [published Online First: 2020/03/20]
31. Mantel N. Why stepdown procedures in variable selection? . *Technometrics* 1970;12:621-25.
32. Steyerberg EW, Eijkemans MJ, Harrell FE, Jr., et al. Prognostic modeling with logistic regression analysis: in search of a sensible strategy in small data sets. *Med Decis Making* 2001;21(1):45-56. doi: 10.1177/0272989x0102100106 [published Online First: 2001/02/24]

33. Steyerberg E, Harrel FE, Borsboom G, et al. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. *J Clin Epidemiol* 2001;54:774-81.
34. Redmond NM, Turnbull S, Stuart B, et al. Impact of antibiotics for children presenting to general practice with cough on adverse outcomes: secondary analysis from a multicentre prospective cohort study. *Br J Gen Pract* 2018;68(675):e682-e93. doi: 10.3399/bjgp18X698873 [published Online First: 2018/09/12]
35. Bergmann M, Haasenritter J, Beidatsch D, et al. Coughing children in family practice and primary care: a systematic review of prevalence, aetiology and prognosis. *BMC Pediatr* 2021;21(1):260. doi: 10.1186/s12887-021-02739-4 [published Online First: 2021/06/06]
36. Fleming S, Thompson M, Stevens R, et al. Normal ranges of heart rate and respiratory rate in children from birth to 18 years of age: a systematic review of observational studies. *Lancet* 2011;377(9770):1011-8. doi: 10.1016/s0140-6736(10)62226-x [published Online First: 2011/03/18]

Figure 1. Flow of patients through observational study and trial

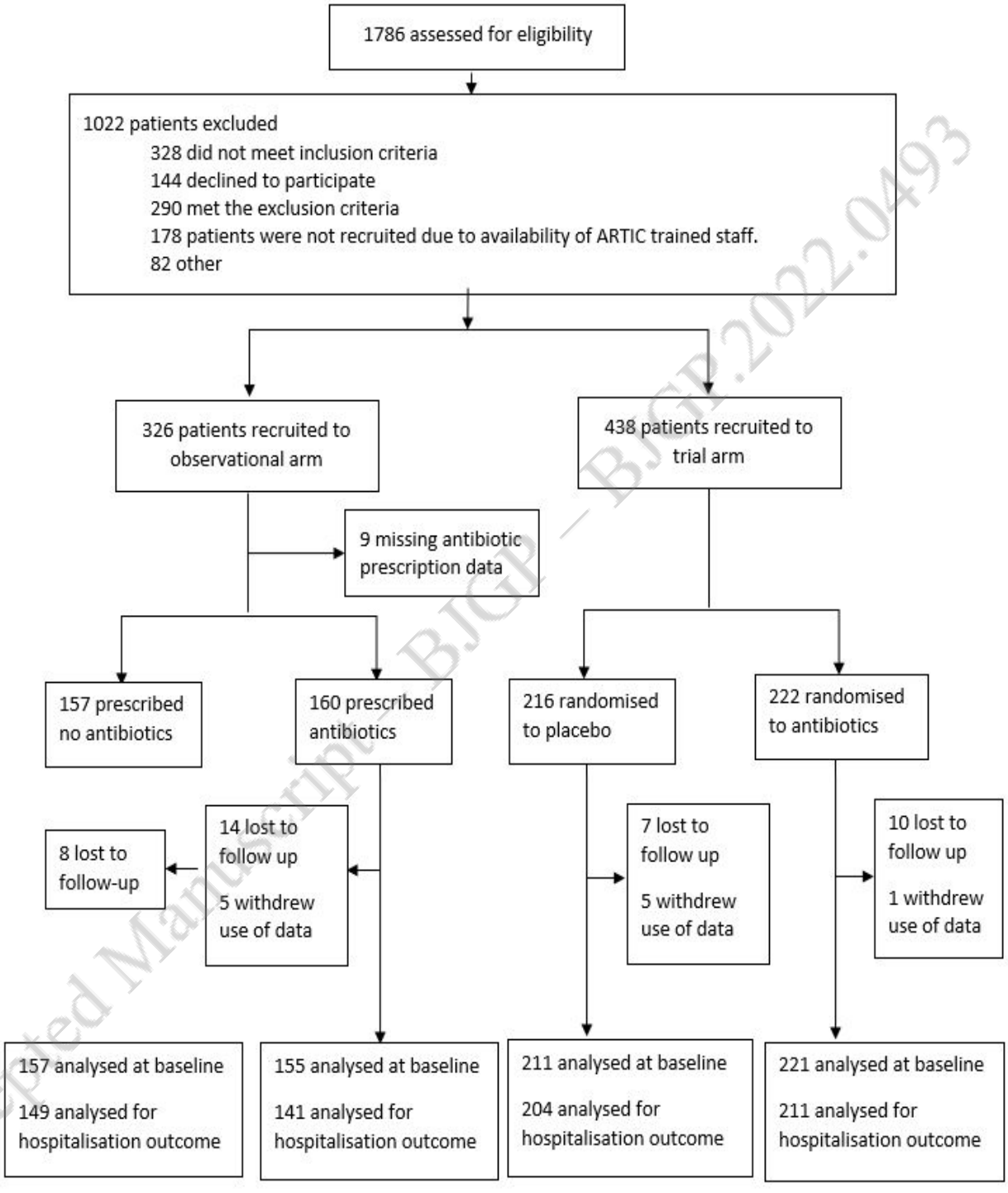

Table 1. Baseline characteristics of observational participants and combined dataset

	Observational study		Trial only		Combined	
	No Antibiotics (n=157)	Antibiotics (n=155)	Placebo (N = 211)	Antibiotics (N = 221)	No Antibiotics[1] (n=368)	Antibiotics (n=376)
Male (n, %)	82 (52.2)	86 (55.5)	112 (53.1)	121 (54.8)	194 (52.7)	207 (55.1)
Age in years (median, IQR)	3.0 (1.4, 4.9)	3.1 (1.8, 5.2)	3.1 (1.4, 5.6)	3.2 (1.7, 5.8)	3.1 (1.4, 5.4)	3.2 (1.7, 5.5)
Comorbidity[2] (n, %)	17 (10.8)	18 (11.6)	31 (14.7)	24 (10.9)	48 (13.0)	42 (11.2)
Asthma (n, %)	9 (5.7)	10 (6.5)	19 (9.0)	13 (5.9)	28 (7.6)	23 (6.1)
Long term illness[2] (n, %)	12 (11.8)	7 (7.5)	7 (6.3)	13 (10.7)	19 (8.9)	20 (9.3)
Baseline severity* (mean, SD)	1.5 (0.3)	1.8 (0.4)	1.6 (0.3)	1.6 (0.3)	1.6 (0.3)	1.7 (0.3)
Duration of illness in days (median, IQR)	5 (3,7)	4 (2,7)	6 (3, 10)	5 (3, 10)	6 (3, 10)	5 (3, 8)
Abnormal chest signs** (n, %)	38 (24.2)	126 (81.3)	72 (34.1)	78 (35.3)	110 (29.9)	204 (54.3)
Sputum/Rattly chest (n, %)	108 (69.7)	135 (87.1)	155 (73.8)	170 (77.6)	263 (71.5)	305 (81.6)
Fever during illness (n, %)	100 (63.7)	141 (91.0)	161 (76.3)	177 (80.1)	261 (70.9)	318 (84.6)
Unwell (n, %)	79 (51.0)	125 (80.7)	141 (66.8)	143 (64.7)	220 (60.1)	268 (71.3)
Shortness of breath (n, %)	57 (36.3)	109 (70.3)	95 (45.0)	104 (47.1)	152 (41.3)	213 (56.7)
Oxygen saturation low (n, %)	7 (6.6)	28 (21.2)	9 (5.4)	13 (7.7)	16 (5.9)	41 (13.6)
STARWAVe* (n, %)						
Very low risk	94 (59.9)	60 (38.7)	110 (52.1)	123 (55.7)	204 (55.4)	183 (48.7)
Normal risk	60 (38.2)	77 (49.7)	95 (45.0)	94 (42.5)	155 (42.1)	171 (45.5)
High risk	3 (1.9)	18 (11.6)	6 (2.8)	4 (1.8)	9 (2.5)	22 (5.9)
Physician rating unwell* (mean, SD)	4.9 (1.9)	6.3 (1.6)	5.5 (1.7)	5.5 (1.6)	5.3 (1.8)	5.9 (1.7)
Parent rating of unwell* (mean, SD)	3.3 (1.6)	5.3 (1.7)	3.8 (1.7)	3.7 (1.7)	3.6 (1.7)	4.3 (1.8)
Temperature (mean, SD)	37.1 (0.7)	37.5 (0.9)	37.3 (0.8)	37.2 (0.8)	37.2 (0.8)	37.3 (0.8)
Oxygen saturation (mean, SD)	97.6 (1.5)	96.1 (2.3)	97.3 (1.6)	97.3 (1.6)	97.4 (1.6)	96.8 (2.0)

Heart rate (beats per min) (mean, SD)	110.8 (19.0)	124.5 (21.3)	112.0 (20.3)	111.8 (17.9)	111.6 (19.8)	117.1 (20.3)
Respiratory rate (breaths per min) (mean, SD)	24.0 (7.4)	30.7 (10.3)	24.8 (6.8)	25.4 (7.1)	24.4 (7.0)	27.6 (8.9)
Capillary refill >3 seconds (n, %)	1 (0.7)	3 (2.0)	3 (1.5)	2 (0.9)	4 (1.1)	5 (1.4)
Consciousness (n, %)						
Normal	154 (98.7)	138 (90.2)	203 (96.2)	214 (97.3)	357 (97.3)	352 (94.4)
Irritable	1 (0.6)	11 (7.2)	8 (3.8)	5 (2.3)	9 (2.5)	16 (4.3)
Drowsy	1 (0.6)	4 (2.6)	0 (0.0)	1 (0.5)	1 (0.3)	5 (1.3)
Ill appearance (n, %)	17 (10.8)	71 (45.8)	48 (22.9)	47 (21.3)	65 (17.7)	118 (31.4)

*Average baseline severity score for all symptoms: dry cough, wet cough, barking cough, wheezy cough, rattly chest, runny/blocked nose, breathing faster than normal, wheeze/whistling chest, fever, chills/shivering, diarrhoea, vomiting, fewer fluids than usual, disturbed sleep, passing urine less often, headache, muscle aches, confusion, sore throat (each on a scale 1 to 4: 1=none, 2=mild, 3=moderate, 4=severe).

**Abnormal chest signs include wheeze, stridor, grunting, nasal flaring, inter/subcostal recession, crackles/crepitations, bronchial breathing; STARWAVe prediction rule for hospital admission (short illness, temperature, age, recession, wheeze, asthma, vomiting); Physician and parent rating of unwell on a scale 0 to 10

[1] No antibiotics for the combined data set comprises no antibiotics for the observational data and placebo for the trial data

[2] Comorbidity includes asthma, heart disease, renal disease, diabetes, and other chronic disease. Longer term illness was a self report item in the diary to the question 'Does he/she have any long-term illness, health problem, or illness/disease which limits his/her daily activities'

Table 2. Predictor of progression of illness (requiring hospital attendance or admission) using the combined trial and observational data sets

	No Progression of illness	Progression of illness	Univariable RR (95% CI)	Multivariable RR (95% CI)
Female	316/676 (46.8%)	10/29 (34.5%)	0.57 (0.27, 1.24)	
Age (mean, SD)	3.79 (4.89)	3.59 (2.75)	1.00 (0.93, 1.06)	
Baseline severity (mean, SD)	1.64 (0.33)	1.73 (0.38)	2.29 (0.96, 6.13)	0.34 (0.09, 1.35)
Longer duration of illness in days prior to consultation (n, %)	419/676 (62.0%)	13/29 (44.8%)	0.57 (0.27, 1.17)	0.43 (0.17, 1.07)
At least one comorbid condition (n%)	83/676 (12.3%)	4/29 (13.8%)	1.03 (0.35, 3.00)	
Asthma	66/676 (9.8%)	3/29 (10.3%)	0.98 (0.29, 3.30)	
Abnormal chest signs (n, %)	271/676 (40.1%)	20/29 (69.0%)	3.72 (1.67, 8.29)	
Sputum/Rattly chest (n, %)	404/670 (60.3%)	23/28 (82.1%)	2.62 (1.05, 6.50)	3.79 (1.36, 10.56)
Unwell (n, %)	442/676 (65.5%)	24/29 (82.8%)	1.89 (0.77, 4.61)	
Oxygen saturation<95%(n, %)	43/509 (8.5%)	10/28 (35.7%)	5.87 (2.64, 13.09)	2.51 (0.98, 6.45)
Dry cough (n, %)	368/676 (54.4%)	12/29 (41.4%)	0.64 (0.31, 1.31)	
Runny nose (n, %)	550/676 (81.4%)	24/29 (82.8%)	1.17 (0.44, 3.11)	
Diarrhoea (n, %)	89/676 (13.2%)	5/29 (17.2%)	1.28 (0.48, 3.42)	2.26 (0.80, 6.44)
Chills (n, %)	165/676 (24.4%)	7/29 (24.1%)	1.02 (0.44, 2.40)	
Vomiting (n,%)	217/676 (32.1%)	14/29 (48.3%)	2.22 (1.07, 4.61)	
Taking less fluid (n, %)	284/676 (42.0%)	16/29 (55.2%)	1.72 (0.83, 3.56)	
Disturbed sleep (n, %)	575/676 (85.1%)	27/29 (93.1%)	2.10 (0.50, 8.71)	
Passing urine less often, or drier nappies than normal (n, %)	165/676 (24.4%)	15/29 (53.3%)	3.71 (1.79, 7.72)	2.68 (1.01, 7.10)
Temperature (mean, SD)	37.26 (0.78)	37.5 (1.08)	1.35 (0.90, 2.03)	
Heart rate (beats per min) (mean, SD)	113.5 (19.69)	125.8 (22.96)	1.03 (1.01, 1.05)	
Difference between respiratory rate and normal respiratory rate for age* in breaths/min (mean, SD)	-1.8 (7.8)	6.0 (11.1)	1.07 (1.05, 1.10)	1.06 (1.02, 1.11)
Antibiotics (n, %)	331/676 (49.0%)	20/29 (69.0%)	2.64 (1.20, 5.81)	N/A
STARWAVe (n, %)				
• Very low risk	363/676 (53.3%)	8/29 (27.6%)	Reference	N/A
• Normal risk	292/676 (42.9%)	17/29 (58.6%)	2.70 (1.16, 6.28)	
• High risk	26/676 (3.9%)	4/29 (13.8%)	7.60 (2.34, 24.59)	

*'Normal' respiratory rate for age (breath per minute) taken as the midpoint from Fleming at al [36] 12-<18months: 37; 18-<24month: 33; 2->3yrs:28; 3-<4: 24; 4-<6: 24; 6-<8: 21;8-12: 20

Table 3. Predictors of progression of illness using the combined trial and observational data sets with reduced models

	No Progression of illness	Progression of illness	Four item model RR (95% CI)	Three item model RR (95% CI)
Difference between respiratory rate and normal respiratory rate for age in breaths/min (mean, SD)	-1.8 (7.8)	6.0 (11.1)	1.05 (1.01, 1.09)	1.06 (1.03, 1.10)
Sputum/Rattly chest (n, %)	404/670 (60.3%)	23/28 (82.1%)	3.63 (1.32, 9.98)	3.11 (1.32, 7.37)
Oxygen saturation <95% (n, %)	43/509 (8.5%)	10/28 (35.7%)	2.53 (1.05, 6.12)	4.29 (1.58, 11.62)
Passing urine less often (n, %)	165/676 (24.4%)	15/29 (53.3%)	2.20 (0.93, 5.21)	
Diarrhoea (n, %)	89/676 (13.2%)	5/29 (17.2%)		
Baseline severity* (mean, SD)	1.64 (0.33)	1.73 (0.38)		
Longer duration of illness in days prior to consultation (n, %)	419/676 (62.0%)	13/29 (44.8%)		

Table 4. Progression of illness and overnight admission for different cut-offs of the 3-item prognostic score.

Score	No progression of illness	Progression of illness	Risk of progression	No overnight admission	Overnight admission	Risk of admission
<40	53 (8.2%)	1 (3.6%)	1.9%	54 (6.7%)	0 (0.0%)	0.0%
40-49	179 (27.7%)	2 (7.1%)	1.1%	180 (24.7%)	1 (9.1%)	0.6%
50-59	152 (23.5%)	3 (10.7%)	1.9%	155 (31.7%)	0 (0.0%)	0.0%
60-69	202 (31.3%)	8 (28.6%)	3.8%	208 (25.6%)	2 (18.2%)	1.0%
70-79	41 (6.4%)	3 (10.7%)	6.8%	42 (8.0%)	2 (18.2%)	4.5%
80-89	14 (2.2%)	6 (21.4%)	30.0%	16 (1.7%)	4 (36.5%)	20.0%
>=90	5 (0.8%)	5 (17.9%)	50.0%	8 (1.4%)	2 (18.2%)	20.0%

Table 5. Sensitivity and Specificity for different cut-offs of the 3-item prognostic score.

	Progression of illness				Overnight admission			
Score cut-off	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
>=40	96.4%	8.2%	4.4%	98.2%	100%	8.1%	1.8%	100%
>=50	89.3%	35.9%	5.7%	98.7%	90.9%	35.3%	2.3%	99.6%
>=60	78.6%	59.4%	7.8%	98.5%	90.9%	58.7%	3.5%	99.7%
>=70	50.0%	90.7%	18.9%	97.7%	72.7%	90.1%	10.8%	99.5%
>=80	39.3%	97.1%	36.7%	97.4%	54.6%	96.4%	20.0%	99.2%
>=90	17.9%	99.2%	50.0%	96.5%	18.2%	98.8%	20.0%	98.6%