

**EFFECTIVENESS OF TWO STRATEGIES TO REDUCE INAPPROPRIATE ANTIBIOTIC
PRESCRIBING FOR CHILDREN IN PRIMARY CARE**

Marieke B. Lemiengre^{1*}, Jan Y. Verbakel^{2,3}, Roos Colman⁴, Tine De Burghgraeve³, Frank Buntinx^{3,5},
Bert Aertgeerts³, Frans De Baets⁶, An De Sutter¹

¹Department of Family Practice and Primary Health Care, Ghent University, Gent, Belgium

²Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, UK

³Department of Public Health and Primary Care, KU Leuven, Leuven, Belgium

⁴Department of Public Health, Ghent University, Ghent, Belgium

⁵Research Institute Caphri, Maastricht University, Maastricht, The Netherlands

⁶Department of Pediatric Pulmonology, Infection and Immune Deficiencies, Ghent University
Hospital, Ghent, Belgium

***Corresponding author:** Ms. M. B. Lemiengre, Department of Family Practice and Primary Health
Care, Ghent University, De Pintelaan 185 6K3, 9000 Ghent, Belgium, +32 486 61 33 78,
marieke.lemien gre@ugent.be

21 **ABSTRACT**

22 **Background** In primary care, antibiotics are overprescribed for non-severe acute infections in
23 children.

24 **Aim** This study aimed to explore two different interventions that may reduce inappropriate antibiotic
25 prescribing for non-severe acute infections.

26 **Design and Setting** Cluster randomized, factorial controlled trial in primary care.

27 **Method** Family physicians (FPs) included children with non-severe acute infections. FPs performed a
28 Point-of-Care C-reactive protein test (POC CRP) (1), a brief intervention to elicit parental concern
29 combined with safety net advice (BISNA) (2), both (3) or usual care (4). Guidance on the
30 interpretation of CRP was not provided. The main outcome was the immediate antibiotic prescribing
31 rate. A mixed logistic regression analysis was performed.

32 **Results** 2227 non-severe acute infections in children were registered by 131 FPs in Flanders
33 (Belgium). In comparison to usual care, POC CRP did not influence antibiotic prescribing (adjusted
34 odds ratio (aOR) 1.01 (95% Confidence Interval (CI) 0.57 to 1.79)). BISNA increased antibiotic
35 prescribing (aOR 2.04 (95% CI 1.19 to 3.50)). In combination with POC CRP, this increase
36 disappeared.

37 **Conclusion** Systematic POC CRP testing without guidance is not an effective strategy to reduce
38 antibiotic prescribing for non-severe acute infections in children in primary care. Eliciting parental
39 concern and providing a safety net without POC CRP testing conversely increased antibiotic
40 prescribing. FPs possibly need more training in handling parental concern without inappropriately
41 prescribing antibiotics.

42 **Key words** child, inappropriate prescribing, cluster randomized controlled trial, point-of-care testing,
43 physician-patient communication, primary care

44 **Trial registration** ClinicalTrials.gov Identifier: NCT02024282

45

46 **ABBREVIATIONS**

47 FP family physician
48 CDR clinical decision rule
49 POC point-of-care
50 CRP C-reactive protein
51 BISNA brief intervention with safety net advice
52 UC usual care
53 CRCT cluster randomized controlled trial
54 BAPCOC Belgian Antibiotic Policy Coordination Committee
55 SD standard deviation
56 IQR interquartile range
57 ICC intracluster correlation coefficient
58 CI confidence interval
59 OR odds ratio
60 aOR adjusted odds ratio

61

62 **HOW THIS FITS IN**

63 *What is previously known or believed on this topic*

64 Antibiotics are prescribed too often for non-severe acute infections in children in primary care. Point-
65 of-Care CRP testing and promoting shared decision making reduce antibiotic prescribing for acute
66 respiratory tract infections in adults, but the effect of such interventions in children remains unclear.

67 *What this research adds*

68 Systematic point-of-care CRP testing without guidance is not an effective strategy to reduce antibiotic
69 prescribing for non-severe acute infections in children in primary care. Eliciting parental concern and
70 providing a safety net without point-of-care CRP testing conversely increased antibiotic prescribing.
71 FPs possibly need more training in handling parental concern without inappropriately prescribing
72 antibiotics.

73

74

75 **MAIN TEXT**

76 **Introduction**

77 Acute infection in children is a common reason for encounter in family practice. Most children suffer
78 from non-severe conditions, although many of them are unnecessarily treated with antibiotics. This
79 might lead to avoidable adverse effects and costs, and to the emergence of antibiotic resistance.
80 Despite a recent decline, 38% of all Belgian children got at least one antibiotic prescription in
81 outpatient care during 2014¹. This number is more than twice as high as in the Netherlands (18%)
82 and comparable to the annual antibiotic prescription rate in the UK (36%)².

83 Overprescribing can be caused by physicians' diagnostic uncertainty, as distinguishing between viral
84 and bacterial infections is clinically challenging and denying antibiotics to a child with a possible
85 bacterial infection might feel inappropriate³⁻⁶. More diagnostic certainty can be attained by applying
86 clinical prediction rules, intending to rule out serious infection in children⁷⁻⁹. Moreover, new diagnostic
87 tools, such as Point-of-Care C-reactive protein (POC CRP) tests could further reduce uncertainty.
88 Studies suggest that CRP levels lower than 20 mg/L can rule out serious infection in febrile children in
89 a hospital setting, but safe cut-off levels in the primary care setting, in which serious infections are
90 rare, remain unknown¹⁰. By reducing uncertainty, POC CRP could also reduce antibiotic prescribing,
91 as shown in adults with respiratory tract infections¹¹.

92 Overprescribing can also be attributed to physicians' failure to cope with parental concern. When
93 physicians engage in reassuring worried parents too promptly, parents can feel misunderstood and
94 restate their worries to get the physician's attention. Physicians can misinterpret this as parental
95 insistence for antibiotics, which may lead to inappropriate prescribing¹².

96 For the present study, we explored the effect of two interventions on antibiotic prescribing for acute
97 non-severe infections in children: reducing clinicians' uncertainty with an objective inflammatory
98 parameter (POC CRP test) or improving mutual understanding by both actively giving parents the
99 opportunity to express their underlying concerns and providing safety net advice.

100

101 **Methods**

102 *Study design*

103 We performed a cluster randomized, factorial controlled trial (CRCT) in children with an acute non-
104 severe infection, presenting to a family physician (FP). There were four intervention groups: (1)

performing a POC CRP test, (2) applying a brief intervention to elicit parental concern combined with safety net advice (BISNA), (3) performing a POC CRP test plus applying BISNA and (4) usual care (UC). Allocation was performed at practice level to avoid contamination. The allocation ratio was 1:1:1:1. Every cluster consisted of infectious episodes in children included by one physician.

Study population

Participating family physicians. All FPs in Flanders (Belgium) stating that they were able and prepared to consecutively recruit at least 5 ill children during the inclusion period, could participate. Practices were assigned to the four intervention groups using stratified (by practice type) block (block size 4) randomization.

Participating children. Children aged 1 month to 16 years presenting with an acute infection lasting a maximum of 5 days at the initial contact were consecutively included. Episodes at high risk for serious infection were excluded post-hoc as antibiotic prescribing should not be restricted in these cases. We identified these children using a clinical decision rule (CDR) consisting of four clinical criteria: the gut feeling of the physician, presence of dyspnea, temperature $\geq 40^{\circ}\text{C}$ and diarrhea in children aged between 1 and 2.5 years⁷. Children who were referred to a pediatrician were excluded. Other exclusion criteria were episodes caused by merely traumatic or neurological conditions, intoxication, psychiatric or behavioral problems or an exacerbation of a known chronic condition. Written informed consent was solicited from the child's accompanying parent or legal guardian.

Intervention

For the POC CRP test (Afinion AS100 Analyzer, Alere, USA), a finger prick was performed. The result was available within 4 minutes¹³. Guidance on the interpretation of CRP-results was not provided, as safe cut-off levels in primary care are unknown¹⁰. The brief intervention consisted of the following three questions for parents at the start of the consultation: "Are you concerned (about the illness of your child)?", "What exactly concerns you?" and "Why does this concern you?". Apart from these questions, a parent information leaflet containing information about supportive treatment (what to do in case of fever, how to use antipyretics) and when to re-consult was provided as safety net advice.

To avoid contamination between the intervention groups, only FPs in the BISNA-intervention groups (allocation group 2 and 3) were informed about the specific content of the brief intervention.

Data collection

FPs registered child characteristics, clinical parameters, preliminary diagnosis and treatment actions (or referral) on a registration form. Parents completed a diary until they assessed their child as recovered.

End points

The main outcome measure was the immediate antibiotic prescribing rate. An immediate prescription is meant to be delivered and administered immediately after the consultation. Secondly, we looked at the total antibiotic prescribing rate, by adding delayed prescriptions, meant to administer by the parent in certain circumstances (e.g. in case of worsening, persistent fever, ...).

Sample size calculation

To detect an absolute reduction in antibiotic prescribing of 15% (from 40% to 25%), with 80% power at a 5% significance level, an individually randomized study would need 600 patients (150 patients per group, 4 groups)¹⁴. Assuming an ICC of 0.15 (worst case) and a cluster size of 21, the design effect of the study is 4. Twenty-nine FPs (116 FPs in total) per group are thus needed.

Statistical analysis

The analyses were performed with SPSS 24¹⁵. We performed a crude and adjusted mixed logistic regression analysis, considering the hierarchical structure of the data (practice level, FP level, patient level).

At *practice level*, we considered region (urban/rural) and practice type (solo/duo/group).

At *FP level*, we investigated the role of personal characteristics (gender, age (mean), years of experience (mean)), annual antibiotic prescription rate and the FP's risk-avoiding attitude. We used the annual antibiotic prescription rate during 2011 (children and adults, most recent Belgian data available) as a proxy for baseline antibiotic prescribing. National prescribing data only for children were not available. We categorized FPs as high or low prescribers (with the mean rate as cut-off

point). As data from early career FPs and residents were not yet available, we considered them as a separate group. All FPs completed a validated questionnaire measuring their risk-avoiding behavior. Physicians with higher scores 'prefer the certain to the uncertain'¹⁶.

At *child level*, we considered age (infant, preschool child, child/adolescent), fever (no fever, elevation, high fever (39°C or more)) and the presence of an appropriate indication for antibiotics according to the Belgian guidelines (BAPCOC)¹⁷ (Appendix 1), based on age, clinical presentation and the preliminary diagnosis as registered by the FP. The Belgian guidelines follow the international guidelines, but the antibiotic choice and dosages are adapted to the Belgian bacterial resistance patterns. We also considered the perceived parental expectation regarding antibiotics, which was registered by the FPs at the end of the consultation by answering "yes/no" to the question: "Do you think this parent expects a prescription for antibiotics?". The option "I don't know" or missing values were categorized as "unknown".

First, we explored which of these covariates at the univariate level influenced immediate antibiotic prescribing. Secondly, we performed a multivariate analysis. With exception for practice type, which was added because we performed stratification at this level, only covariates with p-values lower than 0.1 were entered. When comparing intervention groups, we found limited imbalances for the child's age and temperature. These were added as covariates to the final adjusted analysis. Episodes with missing data about antibiotic prescribing, were discarded from the analysis.

For more detailed information about the methodology of this trial, we refer to the published protocol ¹⁴

Results

Participant flow, recruitment and numbers analyzed

169 FPs started recruitment. Initially, 3288 acute infectious episodes were included between 15 February 2013 and 28 February 2014. After applying exclusion criteria (Figure 1), 2227 acute infectious episodes registered by 131 FPs (78 practices) were analyzed. 761 episodes (23%) were excluded because the CDR indicated them as higher risk for serious infection. Thirty physicians were excluded because they included less than 5 children. Their baseline characteristics were equal to those of included FPs (appendix 2). 177 episodes were discarded because of missing data on

antibiotic prescribing. These children were of similar age, but had less fever ($p < 0,001$) and fewer indications for antibiotics following the Belgian guidelines ($p < 0,001$) in comparison to children with outcome data on antibiotic prescribing (appendix 3).

Baseline characteristics

Family physicians. Forty-one percent of FPs were men. Their mean age was 39.8 (standard deviation (SD) 10.7) and 17.6% were residents. Fifty-seven percent were practicing in an urban region. The mean risk-avoiding behavior was 17.3 (SD 2.9), and the mean annual antibiotic prescription rate was 41.9% (SD 9.5). There were no differences between the FPs of different intervention arms regarding personal characteristics, risk-avoiding attitude and annual antibiotic prescription rate (appendix 4). The median number of included infectious episodes per FP was 11 (interquartile range (IQR) 6 to 17, range 2 to 304).

Children Fifty-one percent of infectious episodes concerned boys. Their mean age was 5.0 years (SD 4.0, IQR 1.6 to 7.6; 30.6% infant, 37.5% preschool child, 31.9% child/teenager) and mean temperature was 38.2°C (SD 1.1; 25.5% no fever, 43.5% elevation, 29.4% high fever (39°C or more)). The top 3 preliminary diagnoses were: acute respiratory tract infection (34.4%), acute otitis media (15.5%) and other viral disease (11.8%). There were small imbalances in age and temperature across the intervention groups, but there was no difference in appropriate indications for antibiotics (Appendix 5).

For 1017 episodes (45.7%), the parents returned the diary. There were no differences in baseline characteristics of children whose parents did or not returned the diary, except a minor difference in the child's temperature: 4% more parents of children with high fever returned the diary in comparison to those who did not.

Outcomes and estimates

In 593 infectious episodes (26.6%), FPs delivered an antibiotic prescription. In 56.3%, this was an immediate prescription. An appropriate indication to prescribe antibiotics immediately could be found in 13.1% of all episodes. Only in half of these cases, the FPs prescribed an immediate antibiotic course. Conversely, in 73.6% of all infectious episodes there was no appropriate indication, but

antibiotics were prescribed immediately in 125 episodes (7.6%) and a delayed prescription was given in 140 episodes (8.6%). In 298 infectious episodes (13.4%), we could not judge whether there was an appropriate indication for antibiotics because information about clinical parameters or preliminary diagnosis was missing (Table 1).

The intracluster correlation coefficient (ICC) was low (0.09 at practice level and 0.03 at FP level).

The crude mixed logistic regression analysis showed no significant effect of the interventions on antibiotic prescribing. After adjusting for covariates, BISNA increased immediate antibiotic prescribing (adjusted odds ratio (aOR) 2.04; 95% Confidence Interval (CI) 1.19-3.50) and total antibiotic prescribing (aOR 1.95; 95% CI 1.11-3.42) in comparison with usual care. This increase disappeared when BISNA was combined with POC CRP. Performing a POC CRP test as sole intervention did not influence antibiotic prescribing in comparison with usual care (Table 2, complete model in Appendix 6).

Harms

All children recovered. No child was hospitalized for a serious infection. Based on data from the diaries, children were cured on average 4 days (SD 3.8) after the consultation. There were no differences in time to cure across the intervention groups, nor across children with or without antibiotics, whether appropriate or not.

Discussion

Summary

For non-severe infections in children in which inappropriate prescribing could be reduced safely, performing a POC CRP test did not reduce antibiotic prescribing. Improving mutual understanding by eliciting parental concerns and providing safety net advice without POC CRP testing conversely increased antibiotic prescribing.

Strengths and limitations

A cluster randomization was chosen because its design mimics daily practice, where certain tools are either available in the surgery or not. Furthermore, once the content of the communicative intervention is known, it would be difficult (and uncontrollable) for individual physicians to switch randomly

between the interventions. The ICPC-coding of preliminary diagnoses registered by the FP, was executed independently by two investigators to avoid imprecision bias in coding.

The antibiotic prescribing rate was lower than expected. Based on data from a Belgian continuous and integrated computerized morbidity registration network (INTEGO)¹⁸, we expected a prescribing rate of 40%. In this data however, no distinction can be made between severe and non-severe infections. Furthermore, FPs may have been more willing to avoid prescribing antibiotics during the trial because they were eager to perform well.¹⁹ The low prescribing rate in our study cannot be explained by the selection of participating FPs, as their mean annual antibiotic prescription rate was comparable to the national mean. Moreover, 37.4% of the immediate prescriptions could still be considered inappropriate. This highlights the room for improvement.

It can be expected that our results are generalizable to similar children in other Western countries. Results could be different, however, among countries with less accessible health care. Our results are *not* applicable for children at high risk for serious infection.

Comparison with existing literature

A recent Cochrane review²⁰ identified six randomized trials that evaluated the use of POC CRP tests in acute respiratory tract infections in primary care. The pooled result for all trials showed a reduction in antibiotic use (RR 0.90, 95% CI 0.80 to 1.02; $I^2=5\%$ for RCTs and RR 0.68, 95% CI 0.61 to 0.75; $I^2=0\%$ for cluster-RCTs). The most pronounced effect occurred in studies with a restrictive CRP algorithm. In the subgroup of children, no significant reduction in antibiotic prescribing was found (1 trial²¹, N = 139, RR 1.09, 95% CI 0.70 to 1.71). This was in line with the findings of the present study, which collected a much large data sample. Since safe cut-off values for CRP are not available, we could not provide guidance.

A recent Cochrane review²², identifying 10 trials assessing a variety of interventions to promote shared decision making to reduce antibiotic prescribing in acute respiratory infections in primary care, found a reduction of 32 to 45% in antibiotic prescribing compared with usual care in the short term. Five studies recruited children, but no separate analysis assessed the effect of the interventions in this subgroup. Our brief intervention had the advantage of being cheap, reproducible and immediately

applicable in practice without extensive training, but unfortunately failed and even doubled prescribing rates, except when POC CRP testing was at their disposal.

Implications for research and/or practice

Reliable cut-off levels for CRP to distinguish children with self-limiting infections from those who benefit from antibiotic treatment may be needed to make POC CRP a more useful tool to improve antibiotic prescribing. Besides this, a qualitative analysis of the answers on the questions about concerns and in-depth interviews with participating FPs will further help understand why FPs prescribed antibiotics more often when discussing parental worries.

ADDITIONAL INFORMATION

Funding

This study was funded by the National Institute for Health and Disability Insurance (RIZIV, Belgium) under reference CGV n° 2012/235 and the Research Foundation Flanders (FWO) under reference n° G067509N.

Ethical approval

The Ethical Review Board of the University Hospitals/KU Leuven approved the protocol of this study under reference ML8601.

Competing interests

All authors declare: no support from any organization for the submitted work; no financial relationships with any organizations 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

This paper was written on behalf of the ERNIE 2 collaboration. ML, JV, FB, ADS conceived the study. ML drafted this report and JV, RC, TDB, BA, FDB, FB and ADS co-drafted the report and commented on it. All authors have read and approved the final manuscript.

312 The principal ERNIE 2 investigators are: Bert Aertgeerts, Dominique Bullens, Frank Buntinx, Roos
313 Colman, Frans De Baets, Tine De Burghgraeve, Karin Decaestecker, Katrien De Schynkel, An de
314 Sutter, Marieke Lemiengre, Karl Logghe, Jasmine Leus, Luc Pattyn, Marc Raes, Lut Van den Berghe,
315 Christel Van Geet, and Jan Verbakel.

316 We would like to thank all participating FPs and pediatricians at all participating hospitals. We would
317 like to thank Annelien Poppe, Frederick Albert and Greet Delvou for daily follow-up during the study.
318 We would like to thank IKEA, Belgium, for providing little finger puppets that were handed out to
319 participating children as a token of appreciation. And finally, we would like to thank all children and
320 parents who took part in this study.

321

322

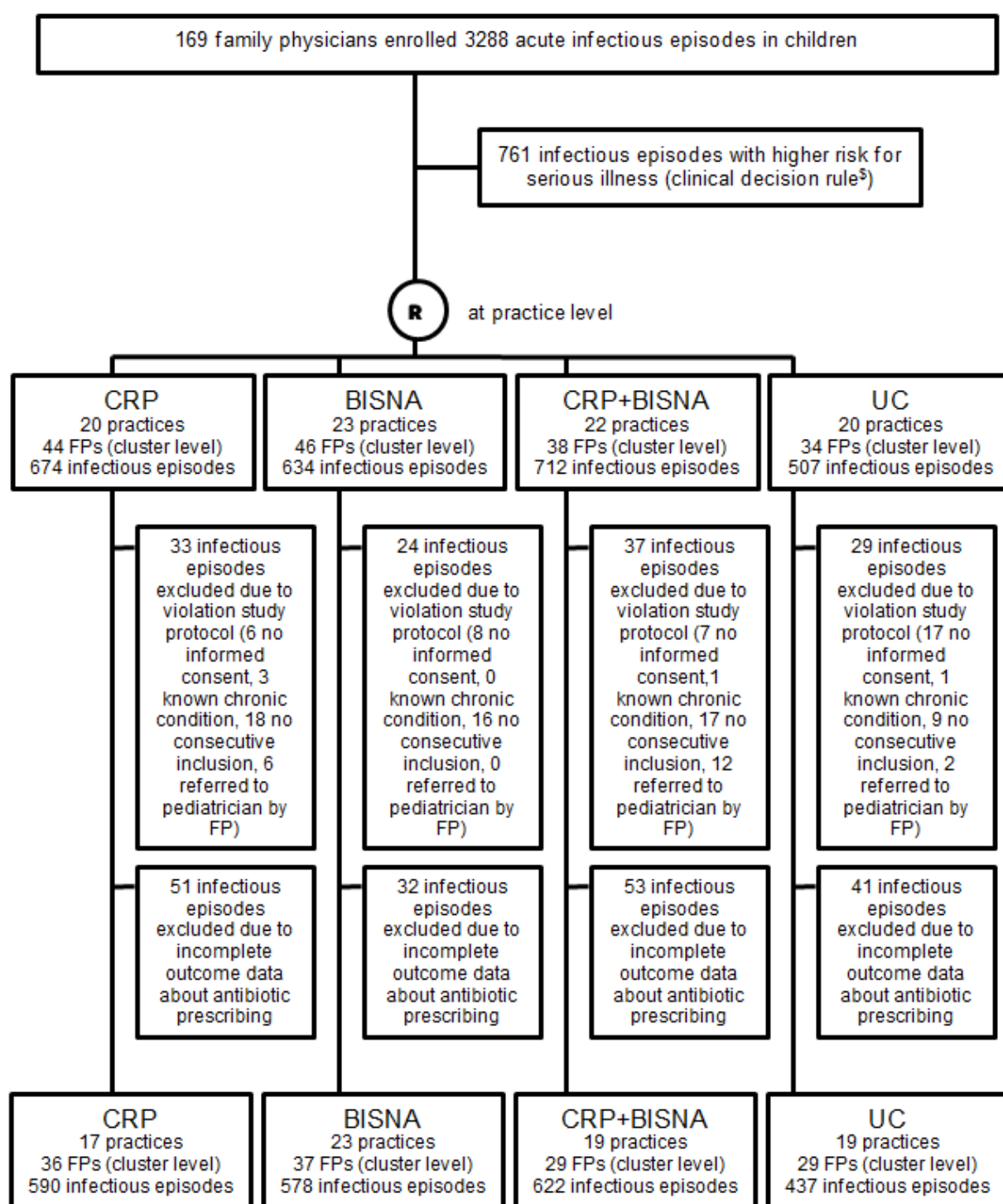
323

324 REFERENCES

- 325 1. Van de Castele M. Cijfers over de terugbetaling van de antibiotica bij het kind in de
326 ambulante zorg. Consensusvergadering RIZIV, 2 juni 2016.
- 327 2. de Bie S, Kaguelidou F, Verhamme KM, et al. Using Prescription Patterns in Primary
328 Care to Derive New Quality Indicators for Childhood Community Antibiotic Prescribing.
329 *Pediatr Infect Dis J* 2016; **35**(12): 1317-23.
- 330 3. Cabral C, Lucas PJ, Ingram J, Hay AD, Horwood J. "It's safer to ..." parent consulting
331 and clinician antibiotic prescribing decisions for children with respiratory tract infections: An
332 analysis across four qualitative studies. *Soc Sci Med (1982)* 2015; **136-137**: 156-64.
- 333 4. Mainous AG, 3rd, Hueston WJ, Love MM. Antibiotics for colds in children: who are
334 the high prescribers? *Arch Pediatr Adolesc Med* 1998; **152**(4): 349-52.
- 335 5. McIsaac WJ, Goel V, To T, Low DE. The validity of a sore throat score in family
336 practice. *CMAJ* 2000; **163**(7): 811-5.
- 337 6. Murray S, Del Mar C, O'Rourke P. Predictors of an antibiotic prescription by GPs for
338 respiratory tract infections: a pilot. *Fam Pract* 2000; **17**(5): 386-8.
- 339 7. Van den Bruel A, Aertgeerts B, Bruyninckx R, Aerts M, Buntinx F. Signs and
340 symptoms for diagnosis of serious infections in children: a prospective study in primary care.
341 *Br J Gen Pract* 2007; **57**(540): 538-46.
- 342 8. Kerkhof E, Lakhanpaul M, Ray S, et al. The predictive value of the NICE "red traffic
343 lights" in acutely ill children. *PloS one* 2014; **9**(3): e90847.
- 344 9. Verbakel JY, Van den Bruel A, Thompson M, et al. How well do clinical prediction
345 rules perform in identifying serious infections in acutely ill children across an international
346 network of ambulatory care datasets? *BMC Med* 2013; **11**: 10.
- 347 10. Van den Bruel A, Jones C, Thompson M, Mant D. C-reactive protein point-of-care
348 testing in acutely ill children: a mixed methods study in primary care. *Arch Dis Child* 2016.
- 349 11. Huang Y, Chen R, Wu T, Wei X, Guo A. Association between point-of-care CRP
350 testing and antibiotic prescribing in respiratory tract infections: a systematic review and
351 meta-analysis of primary care studies. *Br J Gen Pract* 2013; **63**(616): e787-94.
- 352 12. Cabral C, Horwood J, Hay AD, Lucas PJ. How communication affects prescription
353 decisions in consultations for acute illness in children: a systematic review and meta-
354 ethnography. *BMC Fam Pract* 2014; **15**: 63.
- 355 13. Verbakel JY, Aertgeerts B, Lemiengre M, Sutter AD, Bullens DM, Buntinx F.
356 Analytical accuracy and user-friendliness of the Afinion point-of-care CRP test. *J Clin Pathol*
357 2014; **67**(1): 83-6.
- 358 14. Lemiengre MB, Verbakel JY, De Burghgraeve T, et al. Optimizing antibiotic
359 prescribing for acutely ill children in primary care (ERNIE2 study protocol, part B): a cluster
360 randomized, factorial controlled trial evaluating the effect of a point-of-care C-reactive
361 protein test and a brief intervention combined with written safety net advice. *BMC Pediatr*
362 2014; **14**: 246.
- 363 15. Corp I. IBM SPSS Statistics for Windows, Version 24.0. Released 2013 ed. Amonk,
364 NY: IBM Corp.
- 365 16. Grol R, Whitfield M, De Maeseneer J, Mookink H. Attitudes to risk taking in medical
366 decision making among British, Dutch and Belgian general practitioners. *Br J Gen Pract*
367 1990; **40**(333): 134-6.
- 368 17. BAPCOC. Belgische gids voor anti-infectieuze behandeling in de ambulante praktijk.
369 Editie 2012.
- 370 18. Truyers C, Goderis G, Dewitte H, Akker MV, Buntinx F. The Intego database:
371 background, methods and basic results of a Flemish general practice-based continuous
372 morbidity registration project. *BMC Med Inform Decis Mak* 2014; **14**(1): 48.

19. Mangione-Smith R, Elliott MN, McDonald L, McGlynn EA. An observational study of antibiotic prescribing behavior and the Hawthorne effect. *Health Serv Res* 2002; **37**(6): 1603-23.
20. Aabenhus R, Jensen JU, Jorgensen KJ, Hrobjartsson A, Bjerrum L. Biomarkers as point-of-care tests to guide prescription of antibiotics in patients with acute respiratory infections in primary care. *Cochrane Database Syst Rev* 2014; **11**: CD010130.
21. Diederichsen HZ, Skamling M, Diederichsen A, et al. Randomised controlled trial of CRP rapid test as a guide to treatment of respiratory infections in general practice. *Scand Journ Prim Health Care* 2000; **18**(1): 39-43.
22. Coxeter P, Del Mar CB, McGregor L, Beller EM, Hoffmann TC. Interventions to facilitate shared decision making to address antibiotic use for acute respiratory infections in primary care. *Cochrane Database Syst Rev* 2015; **11**: CD010907.

Figure 1: Flow chart representing the number of acute infectious episodes included in the study



FP (family physician)

³ scoring positive at one of the following clinical criteria: (1) FPs gut feeling ('something is wrong'), (2) dyspnea, (3) temperature $\geq 40^{\circ}\text{C}$ and (4) diarrhea in children aged between 1 and 2.5 years

Table 1: Observed antibiotic prescribing rate in comparison to the presence of a rational indication to prescribe

<i>Antibiotic prescription</i>	<i>Indication for antibiotics</i>			
	<i>Present</i>	<i>Absent</i>	<i>Not justifiable</i>	<i>Total</i>
Immediate	143	125	66	334 (14.9%)
Delayed	64	140	55	259 (11.6%)
None	84	1373	177	1634 (73.4%)
Total	291 (13.1%)	1638 (73.6%)	298 (13.4%)	2227 (100%)

Table 2: Mixed logistic regression analysis (crude and adjusted analysis). BISNA significantly increased immediate antibiotic prescribing.

Intervention	Crude analysis				Adjusted analysis ^{§ 2}			
	Immediate prescribing rate		Total prescribing rate		Immediate prescribing rate		Total Prescribing rate	
	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
POC CRP	0.77	0.42-1.44	1.06	0.61-1.86	1.01	0.57-1.79	1.26	0.69-2.30
BISNA	1.36	0.77-2.40	1.47	0.87-2.48	2.04	1.19-3.50	1.95	1.11-3.42
POC CRP+BISNA	0.99	0.54-1.84	1.07	0.61-1.88	1.17	0.66-2.09	1.21	0.66-2.22
Usual care ¹								

¹ Reference category

² 2191 infectious episodes analyzed (36 episodes (1.6%) excluded because missing information about temperature)

OR (odds ratio); CI (confidence interval); POC (point-of-care); CRP (C-reactive protein); BISNA (brief intervention with safety net

[§] Adjusted for region (urban¹); practice type (solo¹), baseline antibiotic prescribing (low¹), the perceived parental expectation for antibiotics (absent¹), clinical presentation (no appropriate indication to prescribe antibiotics¹), child's age (child/adolescent¹), fever (no fever¹)

1 *Appendix 1: Rational indications for antibiotics according to the Belgian guidelines (BAPCOC)¹*

<i>Preliminary diagnosis</i>	<i>Required clinical symptom</i>	<i>Required criteria for rational prescribing</i>
Acute tonsillitis	Pus on tonsils	Appearing seriously ill or less eating/drinking
Acute otitis media	Clinical signs of acute otitis media	1. < 6 months or 2. 6-24 months and appearing seriously ill, fever lasting at least 2 days or bilateral AOM or 3. >24 months and persistent fever lasting at least 3 days or appearing seriously ill or 4. Persistent otorrhea
Acute sinusitis	No clinical symptom required	1. Appearing seriously ill or 2. Fever $\geq 39^{\circ}\text{C}$ or 3. Red swollen face or eyelid (referral)
Pneumonia	No clinical symptom required	No criteria required
Acute bronchitis	No clinical symptom required	1. < 3 months (referral) or 2. < 24 months and insufficient fluid intake or breathing rate $> 70'$ (referral) or 3. Suspected for serious infection (insufficient fluid intake and vomiting, breathing rate $> 50'$, oxygen saturation $\leq 92\%$, sleepy, waking up hard, irritable, drowsy, reduced consciousness, moaning, nasal flaring or chest wall retracting) (referral)
Pertussis	No clinical symptom required	No criteria required
Impetigo	No clinical symptom required	Fever $\geq 38.5^{\circ}\text{C}$, adenopathy or failure local therapy
Erysipelas	No clinical symptom required	No criteria required
Urinary tract infection (cystitis or pyelonephritis)	No clinical symptom required	No criteria required
Gastrointestinal infection with diarrhea	Diarrhea	Fever $\geq 38.5^{\circ}\text{C}$, bloody diarrhea or appearing seriously ill

2 BAPCOC (Belgian Antibiotic Policy Coordination Committee)

3

4 *Appendix 2: Comparison of characteristics of included and excluded FP (after randomization)*

5

Characteristic	Included FP (131) n (%) / mean (SD)	Excluded FP (31) (%) / mean (SD)	p
Gender (man)	54 (41.2%)	12 (38.7%)	0.80 ¹
Age	39.8 (10.7)	38.86 (13.54)	0.68 ²
Region (urban)	74 (56.5%)	22 (75.9%)	0.054 ¹
Graduated (resident)	23 (17.6%)	7 (23.3%)	0.46 ¹
Years of experience	13.3 (10.8)	12.6 (13.1)	0.75 ²
Practice type (exclusive residents) <ul style="list-style-type: none">• Solo• Duo• Group	17 (13.0%) 43 (32.8%) 71 (54.2%)	7 (22.6%) 5 (16.1%) 19 (61.3%)	0.13 ¹

6 ¹Chi-square test
7 ²Student t test
8 FP (family physician); SD (standard deviation)

9
10
11

12

13 *Appendix 3: Comparison of characteristics of infectious episodes with and without outcome data about*
14 *antibiotic prescribing*

Characteristic	Included infectious episode (2227) n (%) / mean (SD)	Excluded infectious episodes (177) (%) / mean (SD)	p
Age			
Infant	681 (30.6%)	52 (30.1%)	0.33
Preschool child	835 (37.5%)	57 (32.9%)	
Child	711 (31.9%)	64 (37.0%)	
Temperature[§]			
no fever	568 (25.9%)	69 (42.6%)	<0.001
elevation	968 (44.2%)	61 (37.7%)	
high fever (39° or more)	655 (29.9%)	32 (19.8%)	
Antibiotics?			
appropriate indication	1638 (73.6%)	124 (70.1%)	<0.001
unjustifiable	298 (13.4%)	48 (27.1%)	
no appropriate indication	291 (13.1%)	5 (2.8%)	

15

16 [§]51 cases no information about temperature (36 included infectious episodes, 15 excluded infectious episodes)
17
18

19 *Appendix 4: Comparison of characteristics of FPs across the intervention groups (after randomization)*
 20

Characteristic	POC CRP (36) n(%) /mean (SD)	BISNA (37) n(%) /mean (SD)	POC CRP+BISNA (29) n(%) /mean (SD)	UC (29) n(%) /mean (SD)	P
Gender (man)	14 (38.9%)	16 (43.2%)	10 (34.5%)	14 (48.3%)	0.73 ²
Age	38.9 (11.0)	38.6 (11.2)	38.5 (10.7)	43.7 (9.3)	0.18 ³
Region (urban)	20 (55.6%)	17 (45.9%)	12 (41.4%)	8 (27.6%)	0.15 ²
Graduated (resident)	7 (19.4%)	8 (21.6%)	6 (20.7%)	2 (6.9%)	0.39 ²
Years of experience	13.0 (10.8)	11.6 (11.2)	12.1 (11.1)	16.8 (9.8)	0.23 ³
Practice type					0.80 ²
Solo	3 (8.3%)	4 (10.8%)	5 (17.2%)	5 (17.2%)	
Duo	10 (27.8%)	14 (37.8%)	10 (34.5%)	9 (31.0%)	
Group	23 (63.9%)	19 (51.4%)	14 (48.3%)	15 (51.7%)	
Risk-avoiding attitude	17.3 (3.2)	17.3 (2.5)	17.5 (2.7)	17.1 (3.2)	0.96 ³
Annual antibiotic prescription rate ¹	40.4% (7.9)	43.8% (8.9)	45.3% (10.4)	39.0% (10.2)	0.08 ³

21 ¹only graduated physicians

22 ²Chi-square test

23 ³One-Way ANOVA

24 FP (family physician); POC (point-of-care); CRP (C-reactive protein); BISNA (brief intervention with safety net advice); UC
 25 (usual care); SD (standard deviation)

26

27

28 Appendix 5: Comparison of characteristics of infectious episodes across the intervention groups (after
 29 randomization)
 30

Characteristic	CRP (590)		BISNA (578)		CRP+BISNA (622)		UC (437)		Total (2227)	
	n	%	n	%	n	%	n	%	n	%
Age										
<i>Infant</i>	169	28,6%	235	40,7%	154	24,8%	123	28,1%	681	30,6%
<i>Preschool child</i>	207	35,1%	224	38,8%	218	35,0%	186	42,6%	835	37,5%
<i>Child</i>	214	36,3%	119	20,6%	250	40,2%	128	29,3%	711	31,9%
Gender										
<i>boy</i>	291	49,3%	285	49,3%	334	53,8%	226	51,7%	1136	51,0%
Temperature										
<i>no fever</i>	178	30,2%	120	20,8%	191	30,7%	79	18,1%	568	25,5%
<i>elevation</i>	228	38,6%	253	43,8%	275	44,2%	212	48,5%	968	43,5%
<i>high fever (39° or more)</i>	174	29,5%	199	34,4%	145	23,3%	137	31,4%	655	29,4%
<i>unknown</i>	10	1,7%	6	1,0%	11	1,8%	9	2,1%	36	1,6%
Antibiotics?										
<i>Not indicated</i>	428	72,5%	430	74,4%	455	73,2%	325	74,4%	1638	73,6%
<i>Unjustifiable</i>	85	14,4%	74	12,8%	87	14,0%	52	11,9%	298	13,4%
<i>Indicated</i>	77	13,1%	74	12,8%	80	12,9%	60	13,7%	291	13,1%
Top preliminary diagnoses										
<i>Upper respiratory tract infection, acute</i>	170	28,8%	209	36,2%	222	35,7%	166	38,0%	767	34,4%
<i>Acute otitis media</i>	80	13,6%	85	14,7%	116	18,6%	64	14,6%	345	15,5%
<i>Viral disease, other (NOS)</i>	112	19,0%	72	12,5%	39	6,3%	39	8,9%	262	11,8%
<i>Gastroenteritis, presumed infection</i>	52	8,8%	44	7,6%	50	8,0%	35	8,0%	181	8,1%
<i>Tonsillitis</i>	45	7,6%	48	8,3%	43	6,9%	36	8,2%	172	7,7%
<i>Bronchitis (no bronchiolitis)</i>	45	7,6%	32	5,5%	46	7,4%	26	5,9%	149	6,7%
<i>Influenza</i>	11	1,9%	19	3,3%	76	12,2%	28	6,4%	134	6,0%
<i>Pneumonia</i>	5	0,8%	7	1,2%	11	1,8%	4	0,9%	27	1,2%
<i>Urinary tract infection</i>	14	2,4%	5	0,9%	8	1,3%	6	1,4%	33	1,5%
<i>Bronchiolitis</i>	3	0,5%	3	0,5%	2	0,3%	5	1,1%	13	0,6%
<i>No preliminary diagnosis</i>	27	4,6%	32	5,5%	27	4,3%	18	4,1%	104	4,7%
Diary return	329	55.8%	232	40.1%	234	37.6%	222	50.8%	1017	45.7%

31

32

Appendix 6: Mixed logistic regression analysis, including all covariates (complete presentation)

Intervention	Adjusted analysis ²			
	Immediate antibiotic prescribing rate		Total antibiotic prescribing rate	
	OR	95% CI	OR	95% CI
intervention				
POC CRP test	1.01	0.57-1.79	1.26	0.69-2.30
BISNA	2.04	1.19-3.50	1.95	1.11-3.42
POC CRP test + BISNA	1.17	0.66-2.09	1.21	0.66-2.22
Usual care ¹				
practice type				
group	1.57	0.93-2.68	1.41	0.81-2.44
duo	1.08	0.62-1.88	0.91	0.51-1.60
solo ¹				
region				
rural	1.30	0.87-1.93	1.41	0.94-2.12
urban ¹				
baseline antibiotic prescribing				
high	2.22	1.43-3.45	2.01	1.32-3.06
early career FP/ resident	1.61	0.96-2.70	1.48	0.92-2.38
low ¹				
the perceived parental expectation regarding antibiotics				
present	16.28	10.89-24.31	33.59	20.88-54.03
unknown	3.34	2.25-4.98	2.67	1.88-3.78
absent ¹				
indication to prescribe antibiotics (based on clinical presentation)				
appropriate indication	11.94	8.29-17.19	12.95	9.16-18.30
unjustifiable	2.88	1.95-4.25	3.69	2.66-5.11
no appropriate indication ¹				
child's age				
infant	0.80	0.53-1.21	1.03	0.73-1.45
preschool	1.07	0.74-1.56	1.40	1.02-1.93
child/adolescent ¹				
temperature				
high fever (39°C or more)	2.67	1.67-4.27	3.86	2.63-5.66
elevation	1.96	1.26-3.06	2.23	1.56-3.19
no fever ¹				

¹Reference category

²2191 infectious episodes analyzed (36 episodes (1.6%) excluded because missing information about temperature)

OR (odds ratio); CI (confidence interval); POC (point-of-care); CRP (C-reactive protein); BISNA (brief intervention with safety net advice); FP (family physician)

1 **CONSORT 2010 checklist of information to include when reporting a cluster**
2 **randomised trial**

Section/Topic	Item No	Standard Checklist item	Extension for cluster designs	Page No *
Title and abstract				
	1a	Identification as a randomised trial in the title	Identification as a cluster randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)		2
Introduction				
Background and objectives	2a	Scientific background and explanation of rationale	Rationale for using a cluster design	4
	2b	Specific objectives or hypotheses	Whether objectives pertain to the cluster level, the individual participant level or both	4
Methods				
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	Definition of cluster and description of how the design features apply to the clusters	5
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons		5
Participants	4a	Eligibility criteria for participants	Eligibility criteria for clusters	5
	4b	Settings and locations where the data were collected		5
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	Whether interventions pertain to the cluster level, the individual participant level or both	5
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and	Whether outcome measures pertain to the cluster level, the individual participant level or both	6

		when they were assessed		
	6b	Any changes to trial outcomes after the trial commenced, with reasons		6
Sample size	7a	How sample size was determined	Method of calculation, number of clusters(s) (and whether equal or unequal cluster sizes are assumed), cluster size, a coefficient of intracluster correlation (ICC or k), and an indication of its uncertainty	6
	7b	When applicable, explanation of any interim analyses and stopping guidelines		not applicable
Randomisation:				
Sequence generation	8a	Method used to generate the random allocation sequence		5
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	Details of stratification or matching if used	5
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Specification that allocation was based on clusters rather than individuals and whether allocation concealment (if any) was at the cluster level, the individual participant level or both	5
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	Replace by 10a, 10b and 10c	
	10a		Who generated the random allocation sequence, who enrolled clusters, and who assigned clusters to interventions	5
	10b		Mechanism by which individual participants were included in clusters for the purposes of the trial (such as complete	5

enumeration, random sampling)			
	10c	From whom consent was sought (representatives of the cluster, or individual cluster members, or both), and whether consent was sought before or after randomisation	5
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	6
	11b	If relevant, description of the similarity of interventions	5
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	How clustering was taken into account 6-7
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	7
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	For each group, the numbers of clusters that were randomly assigned, received intended treatment, and were analysed for the primary outcome 7-8
	13b	For each group, losses and exclusions after randomisation, together with reasons	For each group, losses and exclusions for both clusters and individual cluster members 7-8, figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	7
	14b	Why the trial ended or was stopped	7
Baseline data	15	A table showing baseline demographic and clinical	Baseline characteristics for the individual and cluster levels as Appendix 4-5

		characteristics for each group	applicable for each group	
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	For each group, number of clusters included in each analysis	7, table 2, appendix 6
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Results at the individual or cluster level as applicable and a coefficient of intracluster correlation (ICC or k) for each primary outcome	9
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended		
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory		9
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)		9
Discussion				
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses		10
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	Generalisability to clusters and/or individual participants (as relevant)	10
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence		11
Other information				
Registration	23	Registration number and		2

name of trial registry			
Protocol	24	Where the full trial protocol can be accessed, if available	Supplementary file
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	11

** Note: page numbers optional depending on journal requirements*

3

4