An illness-focussed interactive booklet to optimize management and medication for childhood fever and infections in out-of-hours primary care: a cluster randomized controlled trial

Eefje GPM de Bont, MD, MSc¹
Geert-Jan Dinant, MD, PhD¹
Gijs Elshout, MD, PhD²
Gijs van Well, MD, PhD³
Nick A Francis, MD, PhD⁴
Bjorn Winkens, PhD⁵
Jochen WL Cals, MD, PhD¹

¹ Department of Family Medicine, Care and Public Health Research Institute (CAPHRI), Maastricht University, eefje.debont@maastrichtuniversity.nl, geertjan.dinant@maastrichtuniversity.nl, j.cals@maastrichtuniversity.nl
² Department of General Practice, Erasmus MC, University Medical Center Rotterdam, g.elshout@erasasmusmc.nl
³ Department of Pediatrics, Maastricht University Medical Center (MUMC+), g.vanwell@mumc.nl
⁴ Division of Population Medicine, School of Medicine, Cardiff University, francisna@cf.ac.uk
⁵ Department of Methodology and Statistics, Research School CAPHRI, Maastricht University, bjorn.winkens@maastrichtuniversity.nl

Correspondence to: Eefje GPM de Bont Maastricht University, Department of Family Medicine, PO Box 616, 6200 MD Maastricht, The Netherlands eefje.debont@maastrichtuniversity.nl Tel: 0031-433882094 Fax: 0031-433619344

Support and funding: The Netherlands Organization for Health Research and Development (ZonMW grant 836-021022) funded this study. The funders had no role in study design, data collection, data analysis, data interpretation, or writing the report.

Word count: 3430
Number of tables: 4, 3 supplementary tables
Number of figures: 1
ABSTRACT

Purpose

Fever is the most common reason for a child to be taken to a physician, yet unwarranted antibiotic prescriptions remain high. We aimed to determine the effect on antibiotic prescribing of providing an illness-focussed interactive booklet on fever in children to out-of-hours primary care providers.

Methods

A two armed cluster randomized trial, at 20 out-of-hours general practice centres in the Netherlands. Children <12 years with fever were included. Family Physicians (FPs) at 10 intervention sites had access to an illness-focussed interactive booklet between Nov 2015 and June 2016. Primary outcome was antibiotic prescribing during index consultations. Analysis was performed by fitting two level random intercept logistic regressions models using MLwiN and complier average causal effect analysis.

Results

25355 children were included by 3518 FPs. The booklet was used in 28.5% (3407/11945) of consultations. Access to the booklet did not result in a significant difference in antibiotic prescribing (OR 0.90, 95%CI 0.79 to 1.02, 25.2% and 23.5% ICC 0.005). FP use of the booklet significantly reduced antibiotic prescribing during index consultation (OR 0.83, 95% CI 0.74 to 0.94, reduction of 25.2% to 21.9%, ICC 0.002). Children managed by FPs with access to the booklet were less likely to receive any drug prescription. Parents showed a reduced intention to reconsult for similar illnesses.

Conclusions

We did not find sufficient evidence that providing access to an illness-focussed interactive booklet on childhood fever in out-of-hours primary care reduces antibiotic prescribing. However, use of the booklet
led to reduced antibiotic and overall medication prescriptions, and parents were less inclined to consult for future similar illnesses.

Keywords
Children, antibiotics, fever, infections, family practice, out-of-hours

Abbreviations
FP – Family Physician
RCT – Randomized Controlled Trial
CHILI study - CHILdhood Infections study
ICPC - International Classification of Primary Care
INTRODUCTION

Fever is the most common reason for a child to be taken to a doctor and most consultations take place in general practice.\textsuperscript{1} Since many parents work during the day, and fever typically rises in the early evening, these rates are even higher during out-of-hours care.\textsuperscript{1,2} In most cases, fever is caused by benign (viral) infections, and general recommendations given by a Family Physician (FP) are sufficient.\textsuperscript{3} However, one in three to four children who visit FP out-of-hours care with a fever receive an antibiotic prescription.\textsuperscript{4,5} These prescription rates are nearly twice as high as prescription rates during routine office hours.\textsuperscript{6}

Consultations are generally driven by parental concerns about harmful consequences of fever, and these concerns can be more prominent when needing to consult a FP on call who is not their personal FP.\textsuperscript{7}

Previous studies have demonstrated that antibiotic prescribing is strongly influenced by patients’ expectations and that FPs experience pressure from patients to prescribe antibiotics.\textsuperscript{8} Most parents of a febrile child in fact do not expect antibiotics, but seek reassurance and consistent, reliable information about fever, specific symptoms and self-management strategies.\textsuperscript{7,9,10} Nevertheless, conveying evidence-based information to parents is challenging for FPs. Even more so in time-pressured consultations in the evening and night.\textsuperscript{11} A systematic review showed that information leaflets during Family Physicians consultations for common infections are promising tools to provide parents with a safety net and to reduce antibiotic prescriptions. However, there were no studies performed during out-of-hours care or in childhood fever consultations.\textsuperscript{12}

The CHILdhood Infections (CHILI) study therefore aimed to develop, and determine the effectiveness of an illness-focussed interactive fever booklet for parents on the management of children presenting with fever at FP out-of-hours care.
METHODS

Study design and participants

We performed a cluster randomized controlled trial with randomization on the level of FP out-of-hours centres. Recruited FP out-of-hours centres were randomized to one of two arms; FP access to the illness-focussed interactive booklet or care as usual. FPs working at the intervention centres were given access to the booklet and were free to use them during childhood fever consultations at their own discretion (FP use of booklet). A full detailed description of the development of the intervention and the methods that were used has been previously published.13

20 FP out-of-hours centres across the Netherlands providing care for 3 557 206 residents participated in this trial from Nov 2015 to June 2016. FP out-of-hours care is defined as primary care provided beyond office hours every day between 5 p.m. to 8 a.m. and the entire weekend.14 Since the year 2000, FP out-of-hours care in The Netherlands is provided by approximately 120-130 large-scale FP centres. Per FP centre, 50 to 200 FPs rotate shifts, providing out of hours care to residents of one specific region in which their daytime practice is located.14 Hence, in most out-of-hours consultations patients will not consult with their own FP. FP out-of-hours centres are essentially intended for urgent help requests that cannot wait until the next day. Furthermore, Dutch FPs function as gatekeepers for secondary care. Only those children who need treatment from a paediatrician will be referred in case the FP decides this is medically indicated.

Inclusion criteria for patients were: age between three months and twelve years, and the FP recording the consultation as a fever-related consultation. This study was approved by the ethical committee of Zuyderland-Zuyd (METC Z) in Heerlen, the Netherlands (Ref 14-N-171).
Procedures and outcomes

The content of the illness-focussed interactive booklet was developed in a multistage process using a nationwide survey among parents, focus group sessions and semi-structured interviews with parents, FPs and triage nurses working or consulting during out-of-hours FP care, extensive literature research and expert discussions.7,15 The booklet contained the following sections:

- A traffic light system for childhood fever in general with advice on when to consult a FP (red symptoms) and information on self-management strategies, as well as specific traffic lights for infections of the upper respiratory tract (cough, cold and sore throat), acute otitis media (earache) and gastrointestinal symptoms (abdominal pain, vomiting and diarrhoea)
- Information on the benefits and harms of antibiotic treatment
- An overview of natural duration of common infections in children
- A table with weight-banded paracetamol dosage schemes
- Advice and information on febrile convulsions and skin rash

The booklet was designed to be used in the final part of a clinical consultation facilitating an interactive discussion between parents and FPs, by which we mean that FPs had the possibility to highlight and mark specific signs, symptoms and questions which were relevant for that specific child and provide parents with a tailored advice and safety net for that specific clinical problem. Thereby not only making sure that the advice FPs gave was tailored to parents their specific questions, but also facilitating communication and solving misconceptions between parents and FPs’ about their expectations of the consultation.

The primary outcome (antibiotic prescriptions during the index consultation yes/no), and secondary outcomes based on the complete sample ((re-)consultations during out-of-hours care yes/no, antibiotic prescriptions during re-consultations at the FP out-of-hours centre yes/no, overall medication
prescriptions during index consultation and two weeks follow-up yes/no, and referral to secondary care
yes/no) data was collected in a coded, automatic manner from the FP out-of-hours centre databases,
and was supplied by an independent party that is responsible for the electronic patient files software
(Labelsoft Clinical IT B.V., CompuGroup Medical AG, Phoenix, AZ, USA). Every time the FP closed the
patient file of a child aged <12 years a pop-up screen occurred: Did this child have a fever (at home or
during the consultation)? This pop-up occurred after the parents had already left the consultation room.
Children for whom the FP selected yes were included in the study. FPs working at intervention sites had
an additional question: Did you hand out the booklet? The International Classification of Primary Care
(ICPC) coding system was used to map reasons for consultation.
In addition to the automatic registration in the complete study sample, data on secondary outcomes
was collected among a subsample of parents using telephone surveys during three two-week periods
during month 2, 4 and 6. A triage nurse provided parents with information about the study during their
visit in these weeks. If parents in this subsample gave written informed consent, they were asked to
participate in a telephone survey two weeks after the index consultation. Telephone surveys were used
to question parents about intention to re-consult in the same fever episode and in the future (yes/no), if
they received and used antibiotics at re-consultation (yes/no), parental satisfaction (VAS scale), parental
reassurance (reassured/not reassured and VAS scale), self-reported complications, consultations with
their own FP, and their opinion about the booklet (VAS scale, intention to use again, most important
section).

Randomization and masking
We chose cluster randomization to reduce the risk of contamination. We stratified participating FP out-
of-hours centres by size (10 smallest vs. 10 largest centres, with a cut-off point of fewer or more than
20500 consultations/year), to ensure equal distribution of size between the intervention and control
group. A blinded, independent researcher performed a computer based randomization with random permuted blocks of two. Allocation for each centre was provided only after the centre agreed to participate.

**Statistical analysis**

The primary outcome was antibiotic prescribing rate during the index consultation (dichotomous). The required number of clusters and participants was based on the following assumptions: (1) Intra-cluster coefficient (ICC) of 0.01, (2) alpha of 0.05, power of 0.80, (3) proportion of antibiotic prescriptions in control group of 25% and a proportion of 19% in the intervention group, (4) 10% loss to follow-up and 10% efficiency loss based on unequal cluster sizes. This resulted in a need for 20 clusters to acquire the same power as an individual randomized controlled trial (with an effective sample size of 737 patients in both groups (1474 in total) for an individual RCT based on chi-square test). Taking the cluster effect into account, the total recruitment target for this cluster randomized trial was 20 000 children, recruited at 20 FP out-of-hours centres (10 control, 10 intervention).

To inform the required sample size, we performed a retrospective cohort study. We identified an average of 15 consultations per day for children with fever, and fever-related conditions. Based on this cohort study and a pilot study, we assumed that 1,000 children per centre could be included in 6 months.

Initial descriptive statistics and frequencies were generated to summarize the data using IBM SPSS Statistics for Windows version 21.0. Statistical analyses were then performed based on intention-to-treat principle by fitting two level (FP out-of-hours centre and patient) random intercept logistic regressions models using MLwiN software version 2.22. Fixed parameters were group (intervention vs. control), and size (small vs. large centre). The clustering in the data was accounted for by a random
intercept at the FP centre level. We also checked whether the results changed after including gender, age and socioeconomic status (SES) of the patients to this model. We expected compliance (use of the booklet) to be lower than 100% due to the nature and pragmatic design of the trial. Unfortunately, there were no previous comparable trials or studies that provided us with an indication of how high this level compliance would be. We therefore chose to perform pre-specified additional secondary analyses adjusting for compliance (control vs actual use of booklet instead of control vs. access to booklet) using complier average causal effect (CACE) analysis. Randomization ensures that, on average, the proportion of compliers in the control group would have been the same as that in the access to booklet group. Hereby, we estimated the proportion of unobserved (would-be) compliers in the control group from the proportion observed in the treatment group. This analysis was based on the assumption that there could only be compliers and never-takers, since FPs in the control arm had no access to the booklet. We also assumed that there would be no effect of randomization on the outcome (exclusion restriction). We then calculated the OR adjusted for compliers and corrected for stratification during randomization based on centre size (small vs. large centre). During outcome data analysis, researchers were blinded to the group assignment.
RESULTS

A total of 106,014 contacts for children took place at the 20 participating centres during the trial period. Of these contacts, 36.1% were fever related, and 77.3% of these fever related telephone contacts resulted into a face to face consultation with a FP. 3518 FPs (range per centre 73 FPs to 273 FPs) recruited 25355 children (11945 in intervention and in 13410 control group, varying from 366 children to 2756 children per centre, equally divided across groups) into the trial by (Figure 1). Baseline patient characteristics of the study population are shown in table 1. The distribution of age, gender, socioeconomic status and ICPC diagnosis were similar over the intervention and control groups and between clusters.

In the intervention group, the booklet was used in 3407 (28.5%) encounters (range over centres 23.1% to 38.5%). Antibiotic prescribing was not significantly different at centres with FP access to the booklet and control centres (OR 0.90, 95%CI 0.79 to1.02, ICC 0.005, Table 2). There were no significant differences in reconsultation rates at the out-of-hours centres within two weeks of the index consultation for the same illness episode. We found no significant differences in out-of-hours reconsultation rates within six months following randomization or referral rates to secondary care at index consultation (Table 2).

Children in the access to booklet group, were less likely to receive a prescription for any medication, including non-antibiotic medication, (OR 0.87, 95% CI 0.77 to 0.97, ICC 0.004). Most commonly prescribed non-antibiotic medications were xylomethazoline, salbutamol and ibuprofen, see supplementary table 5. Adjusting for gender, age and socioeconomic status had no effect on any of the outcomes. Mean antibiotic prescription rates varied between the three most common ICPC codes, as is shown in table 3. Amoxicillin was the most commonly prescribed antibiotic, accounting for 76.1% of all antibiotic prescriptions in the trial.
When correcting for compliance, there was a significant reduction in antibiotic prescribing in those children managed by a FP using the booklet during the consultation (n=3407) compared to children managed by FPs in the control group (OR 0.83, 95% CI 0.74 to 0.94, ICC 0.002, Table 2). This significant effect on antibiotic prescribing for FP use of booklet maintained during two week follow-up (including the index consultation) (OR 0.84, 95%CI 0.75 to 0.95, ICC 0.002). After correcting for compliance we also found no significant differences in out-of-hours reconsultation rates within six months following randomization or referral rates to secondary care at index consultation (Table 2). Children for whom the booklet was actually used, were also less likely to receive a prescription for any medication, including non-antibiotic medication, (OR 0.77, 95% CI 0.70 to 0.86, ICC 0.001).

The OR for antibiotic prescriptions during index consultations based on the complier adjusted average causal effect (CACE) analysis was 0.71 (95% CI 0.63 to 0.79). The OR for any prescription during index consultations based on the complier adjusted analysis was 0.62 (95% CI 0.57 to 0.69). The ICC for compliance was 0.09. Table 6 in the supplementary materials shows the patient characteristics for the groups access to booklet vs. use of booklet and no use of booklet in the intervention group, in supplementary table 7 the same is shown for parents participating in the telephone survey.

Parents and children in the subsample (telephone interview), were comparable to parents in the main study (supplementary table 7). Of the 553 participating parents in the telephone survey, 36.0% indicated they received the booklet. In the control group 2.8% of parents reported receiving written patient information or referral to a website with patient information. 23.5% of parents (130/553) reported having visited their own FP before consulting during out-of-hours care, with no significant difference between intervention and control. We observed a significant reduction in intention to reconsult for similar illnesses among parents in the access to booklet group (OR 0.55, 95% CI 0.35 to 0.85, reduction from 84.4% to 75.6%, ICC < 0.001, Table 4).
DISCUSSION

FPs having access to an illness-focussed interactive booklet on childhood fever and common infections in fever-related consultations used the booklet in one in three fever related consultations in out-of-hours general practice. FP access to the booklet did not significantly reduce antibiotic prescriptions at index consultations. However, our pre-specified analysis correcting for actual use of the booklet found a reduction in antibiotic prescriptions at index consultation, overall medication prescriptions and intention to reconsult for future similar illnesses.

This is one of the largest cluster RCTs ever performed in general practice and the first one assessing the effectiveness of a booklet for one of the most common reasons for childhood consultations and antibiotic prescriptions. We chose a cluster randomized design because individual randomization would have led to a high risk of contamination. Specific considerations for choosing a cluster RCT design are described elsewhere.\textsuperscript{13}

FPs believe that interventions for use during out-of-hours need to be readily available in every consultation room.\textsuperscript{15} Widespread availability means that they can act as a reminder to use them. This was also the reason a paper booklet was used in an era of internet and smartphone applications. The cluster design enabled us to provide every consultation room at intervention centres with the necessary material making it more pragmatic. However, a cluster RCT has important limitations. By the cluster randomization and pragmatic nature of the trial we aimed to get as close as possible to actual practice and to the considerations of FPs’ prescribing decisions in childhood fever consultations. As in everyday practice, we anticipated that not every child in the intervention group would receive a booklet. Moreover, FPs were only provided with brief email instructions about use of the intervention. We specifically decided not to provide a special more intensive training or meeting as this would make the intervention more costly, and would be unlikely to happen in actual daily practice. A recent
Cochrane Review on this subject backed up such an approach.\textsuperscript{20} We chose to perform a pragmatic study, allowing for variation and facilitating possible implementation into daily practice.

Since we expected compliance (use of the booklet) to be lower than 100%, but had no comparable data informing us what actual compliance would likely be we had to consider and pre-specify additional analyses correcting for compliance during the design of this study.\textsuperscript{13} The chosen complier CACE analysis enabled us to evaluate the effect of actually receiving the booklet on antibiotic prescriptions in a more robust way than simply undertaking a per-protocol analysis alongside the intention-to-treat analysis. Estimation of CACE is however dependent upon potentially challengeable assumptions that cannot be tested, which means that a risk of post-randomization recruitment bias cannot be completely excluded.\textsuperscript{18,21} However, as is shown in table 6 (supplementary material) characteristics of those children where the booklet was used were comparable to those in which the booklet was not used. The only difference noticeable difference was the percentage of children with ICPC code A03.00 for Fever and R74.00 for Acute upper respiratory tract infection between use and no use of booklet groups. This could suggest FPs were more likely to use the booklet in cases of fever without a specific diagnosis.

Furthermore, best available statistical models and software do not allow for correction of the cluster effect in a CACE analysis with a dichotomous outcome. Nevertheless, an increasing number of studies have shown that a CACE analysis is much closer to the real world intention-to-treat estimates of treatment effects.\textsuperscript{8,21,22}

Our trial shows that handing out patient information leaflets about childhood fever during routine out-of-hours care is very uncommon, as only 2.8% of parents consulting at control centres reported receiving such information. This shows that even in the bread-and-butter condition of childhood fever, uptake and hand-out of available patient information materials (either written or online) is very low in routine care, yet crucial for parents to learn about self-management strategies and alarm symptoms. However, provision of patient information materials is largely a clinician behaviour, and could be
influenced by relatively light-touch interventions such as desk or computer prompts, or even dissemination of the results of this and other similar studies.

Blinding of the participating FPs for the intervention was not possible, but to minimize the risk of bias we blinded FPs to the outcome in both groups, and blinded outcome assessors. In terms of generalisability, more than one in three active FPs in The Netherlands took part in the study, and we believe that this population is representative of the wider FP population in The Netherlands. In addition, The Netherlands has one of the lowest antibiotic prescribing rates in the world. One could expect the effect of the booklet to be larger in countries with higher antibiotic prescribing rates.

We found a statistical significant reduction in antibiotic prescriptions from 25.2% in the care as usual group to 21.9% in the actual use of booklet group. This was lower than the 6%-points (25% versus 19%) which was chosen for the sample size calculation. Our findings are in keeping with a previous UK study that found a significant reduction in antibiotic prescribing from use of an interactive booklet about childhood respiratory tract infections during in-hours general practice. The previous study reported a larger reduction in antibiotic prescribing than was found in our study, but only in those who agreed to participate. Our study included all fever-related consultations and therefore provides results which are more likely to be indicative of real world effects. Other studies examining the effect of information leaflets on antibiotic prescriptions in primary care have mainly been undertaken among adults and focused on specific symptoms, such as acute cough.

Ideally, these behavioural interventions should be combined with other interventions aimed at reducing unwarranted antibiotic prescriptions, such as improved diagnostics, point-of-care tests, interactive workshops, and peer comparison.
Conclusions

This low-cost and light-touch intervention focused on the illness experience of parents, and would be easy to implement into routine care. We found insufficient evidence to conclude that simply providing access to a booklet on childhood fever during out-of-hours care results in reduced antibiotic prescriptions. However, correcting for actual use of the booklet, we found a reduction in antibiotic prescriptions. The reduction in antibiotic prescribing found in this implementation study of all children seen at out of hours care with fever seems modest. However, it provides evidence of the likely ‘real world’ benefits of this intervention, and it is likely that evidence of its efficacy in those that use it could increase use. It is therefore highly relevant to the aims of reducing antimicrobial resistance.
FOOTNOTES

ACKNOWLEDGEMENTS

We would like to thank Mascha Twellaar and Paddy Hinssen for their data support in this study. We would also like to acknowledge all the participating FPs, parents and out-of-hours centres in this study.

CONFLICT OF INTEREST

All authors declare that they have no financial relationships with any organizations that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work. All authors declare that they have no competing interests.

AUTHORS CONTRIBUTIONS

JC and EB conceived the idea for this study. EB is the principal investigator and wrote the first version of the manuscript. JC, GE, GW, NF, BW and GD were involved in the development of the protocol and all authors commented on the first draft and all further revisions of this manuscript.

TRIAL REGISTRATION

This trial was registered at ClinicalTrials.gov, NCT02594553.

CONSORT STATEMENT

This study is reported in accordance with the Consolidated Standards of Reporting Trials (CONSORT) and extension statement for cluster RCTs.
FUNDING SUPPORT

The Netherlands Organization for Health Research and Development (ZonMW grant 836-021022) funded this study. Jochen Cals is supported by a Veni-grant (91614078) of the Netherlands Organisation for Health Research and Development (ZonMw). The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.
REFERENCES


TABLES

Table 1. Patient characteristics of children recruited in control and intervention group (FP access to booklet)

<table>
<thead>
<tr>
<th></th>
<th>Control n= 13410</th>
<th>FP access to booklet n= 11945</th>
<th>Total N=25355</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years - Mean (SD)</td>
<td>3.2 (2.7)</td>
<td>3.3 (2.7)</td>
<td>3.2 (2.7)</td>
</tr>
<tr>
<td>Male sex- n= (%)</td>
<td>7100 (52.9%)</td>
<td>6313 (52.9%)</td>
<td>13413 (52.9%)</td>
</tr>
<tr>
<td>Socioeconomic status parents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>2261 (16.9%)</td>
<td>1826 (15.4%)</td>
<td>4087 (16.2%)</td>
</tr>
<tr>
<td>Middle</td>
<td>9055 (67.8%)</td>
<td>8459 (71.5%)</td>
<td>17514 (69.5%)</td>
</tr>
<tr>
<td>High</td>
<td>2032 (15.2%)</td>
<td>1550 (13.1%)</td>
<td>3582 (14.2%)</td>
</tr>
<tr>
<td>ICPC top 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A03.00 Fever</td>
<td>2471 (18.5%)</td>
<td>2174 (18.2%)</td>
<td>4645 (18.4%)</td>
</tr>
<tr>
<td>R74.00 Acute upper respiratory tract infection</td>
<td>2653 (19.8%)</td>
<td>2357 (19.9%)</td>
<td>5010 (19.8%)</td>
</tr>
<tr>
<td>H71.00 Acute otitis media acuta/myringitis</td>
<td>1872 (14.0%)</td>
<td>1604 (13.5%)</td>
<td>3476 (13.8%)</td>
</tr>
</tbody>
</table>

SD = standard deviation, ICPC = International Classification of Primary Care, Socioeconomic status numbers do not add up to totals in column due to missing data
Table 2. FP access and use of booklet - Primary outcome and secondary outcome measures based on the complete sample

<table>
<thead>
<tr>
<th></th>
<th>Control n= 13410</th>
<th>Access to booklet n= 11945</th>
<th>OR access to booklet [95%CI]</th>
<th>Use of booklet n= 3407</th>
<th>OR use of booklet [95%CI]</th>
<th>Adjusted OR use of booklet (age,gender,SES) [95%CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antibiotic prescription during index consultation</td>
<td>3375 (25.2%)</td>
<td>2809 (23.5%)</td>
<td>0.90 [0.79 to 1.02]</td>
<td>746 (21.9%)</td>
<td>0.83 [0.74 to 0.94]*</td>
<td>0.85 [0.75 to 0.97]*^</td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reconsultation OOH within two weeks</td>
<td>861 (5.5%)</td>
<td>741 (5.4%)</td>
<td>0.95 [0.83 to 1.09]</td>
<td>165 (4.3%)</td>
<td>0.97 [0.80 to 1.16]</td>
<td>0.95 [0.79 to 1.15]</td>
</tr>
<tr>
<td>Antibiotic prescription OOH during index consultation and two weeks follow-up</td>
<td>3570 (26.6%)</td>
<td>2975 (24.9%)</td>
<td>0.90 [0.79 to 1.02]</td>
<td>797 (23.4%)</td>
<td>0.84 [0.75 to 0.95]*</td>
<td>0.86 [0.76 to 0.96]*^</td>
</tr>
<tr>
<td>Reconsultations OOH within 6 months study period</td>
<td>1262 (8.1%)</td>
<td>1145 (8.3%)</td>
<td>0.99 [0.84 to 1.18]</td>
<td>283 (7.3%)</td>
<td>0.97 [0.74 to 1.29]</td>
<td>0.94 [0.71 to 1.25]</td>
</tr>
<tr>
<td>Referral to secondary care at index consultation</td>
<td>1066 (7.9%)</td>
<td>893 (7.5%)</td>
<td>1.03 [0.87 to 1.21]</td>
<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Prescription of any kind</td>
<td>5162 (38.5%)</td>
<td>4245 (35.5%)</td>
<td>0.87 [0.77 to 0.97]*</td>
<td>1114 (32.7%)</td>
<td>0.77 [0.70 to 0.86]*</td>
<td>0.79 [0.71 to 0.87]*^</td>
</tr>
</tbody>
</table>

**OOH = out-of-hours care; N/A = Not applicable since parents of children who were referred did not receive the booklet; SES = socio-economic status; Unadjusted ORs were corrected for centre size; 187 (5.5%) children in FP use of booklet were referred; * indicates statistically significant effect compared to control group with p<0.05, ^ OR antibiotic prescription during index consultation (95%CI) complier adjusted causal effect (CACE) analysis 0.71 (0.63 to 0.79), OR antibiotic prescription during index consultation and two weeks follow-up CACE analysis 0.83 (0.75 to 0.93), OR prescription of any kind CACE analysis 0.62 (0.57 to 0.69)**
### Table 3. Antibiotic prescribing rates for different ICPC codes

<table>
<thead>
<tr>
<th>ICPC Code</th>
<th>Description</th>
<th>Control n= (% within ICPC)</th>
<th>Access to booklet n= (% within ICPC)</th>
<th>Use of booklet n= (% within ICPC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A03.00</td>
<td>Fever</td>
<td>191/2471 (7.7%)</td>
<td>144/2174 (6.6%)</td>
<td>51/835 (6.1%)</td>
</tr>
<tr>
<td>R74.00</td>
<td>Acute upper respiratory tract infection</td>
<td>486/2653 (18.3%)</td>
<td>359/2357 (15.2%)</td>
<td>102/789 (12.9%)</td>
</tr>
<tr>
<td>H71.00</td>
<td>Acute otitis media/myringitis</td>
<td>1246/1872 (66.6%)</td>
<td>1034/1604 (64.5%)</td>
<td>289/449 (64.4%)</td>
</tr>
</tbody>
</table>

### Table 4. Effects of intervention on parental reported secondary outcome measures based on telephone survey

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Control (n=250)</th>
<th>Access to booklet (n=303)</th>
<th>Use of booklet (n=109)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reconsultation with own FP within two weeks - n= (%)</td>
<td>73 (29.2%)</td>
<td>104 (34.3%)</td>
<td>37 (33.9%)</td>
</tr>
<tr>
<td>Antibiotic prescription by own FP during reconsultations within two weeks - n= (%)</td>
<td>26/73 (35.6%)</td>
<td>27/104 (26.0%)</td>
<td>12 (32.4%)</td>
</tr>
<tr>
<td>Hospital admission within two weeks - n= (%)</td>
<td>17 (6.8%)</td>
<td>21 (6.9%)</td>
<td>6 (5.5%)</td>
</tr>
<tr>
<td>Satisfaction with care</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- Satisfaction VAS score (1-10) - Median (IQR)</td>
<td>8.0 (7.0 to 8.0)</td>
<td>8.0 (7.0 to 9.0)</td>
<td>8.0 (7.0 to 9.0)</td>
</tr>
<tr>
<td>- Reassurance VAS score (1-10) - Median (IQR)</td>
<td>8.0 (7.0 to 8.0)</td>
<td>8.0 (7.0 to 8.0)</td>
<td>8.0 (8.0 to 9.0)</td>
</tr>
<tr>
<td>- VAS score booklet (1-10) - Median (IQR)</td>
<td>-</td>
<td>-</td>
<td>8.0 (8.0 to 9.0)</td>
</tr>
<tr>
<td>Intention to reconsult for similar illness - n= (%)</td>
<td>211 (84.4%)</td>
<td>229 (75.6%)*</td>
<td>78 (71.6%)*</td>
</tr>
</tbody>
</table>

* VAS score: 1 is most negative, 10 most positive answer; * indicates statistically significant effect compared to control group with p<0.05
Figure 1. Study profile and inclusion; FP = Family Physician