Effectiveness of GP online training and an information booklet for parents on antibiotic prescribing for children with RTI in primary care: a cluster randomised controlled trial

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Running title: Improving antibiotic use for children with RTI

ABSTRACT

Objectives: Antibiotics are too often prescribed in childhood respiratory tract infection (RTI), despite limited effectiveness, potential side-effects, and bacterial resistance. We aimed to reduce antibiotic prescribing for children with RTI by online training for general practitioners (GP) and information for parents.

Methods: A pragmatic cluster randomised, controlled trial in primary care. The intervention consisted of an online training for GPs and an information booklet for parents. The primary outcome was the antibiotic prescription rate for children presenting with RTI symptoms, as registered by GPs. Secondary outcomes were number of reconsultations within the same disease episode, consultations for new episodes, hospital referrals and pharmacy dispensed antibiotic courses for children.

Results: After randomisation, GPs of in total 32 general practices registered 1009 consultations. An antibiotic was prescribed in 21% of consultations in the intervention group, compared to 33% in the usual care group, controlled for baseline prescribing (RR 0.65, 95% CI 0.46-0.91). The probability of reconsulting during the same RTI episode did not differ significantly between the intervention and control group, nor did the numbers of consultations for new episodes and hospital referrals. In the intervention group antibiotic dispensing was reduced with 32 courses per 1000 children/year, compared to the control group, and adjusted for baseline prescribing (RR 0.78, 95% CI 0.66-0.92). The numbers and proportion of second choice antibiotics did not differ significantly.

Conclusion: A concise, feasible, online GP training, with an information booklet for parents showed a relevant reduction in antibiotic prescribing for children with RTI.

This trial was registered at the Dutch Trial Register (NTR), registration number: NTR4240

INTRODUCTION

Respiratory tract infections (RTI), including ear-infections, are the most common indication for consulting a general practitioner (GP) during childhood and for prescribing antibiotics.[1,2] Most RTIs are viral and self-limiting, and many high-income countries have guidelines aiming to restrict the use of antibiotics.[3-5] However, even in a low-prescribing country like the Netherlands, one third of antibiotic prescriptions for children are not congruent with guideline recommendations.[6] The main drivers of over-prescription are GPs' interpretation of patient or parent expectations, time pressure, diagnostic and prognostic uncertainty and unfamiliarity with recent guidelines.[7-9] General practice has a major contribution and responsibility towards antibiotic stewardship, since primary care is a driver of antibiotic resistance.[10-12] Efforts to reduce antibiotic prescribing in primary care have been ongoing for decades, most often focusing on antibiotic use in adults, and consisting of a wide range of strategies.[13-16] A different approach might be needed for childhood RTI, because of child-specific indications and risk factors, and communication with parents instead of patients themselves.[17] Multifaceted approaches have been shown to be most effective, however, broad implementation of these interventions is rare because of time and costs.[13,18-20] Online educational programs could be a feasible and cost-effective intervention that could be broadly implemented, updated easily, and ensure a more endurable antibiotic stewardship. Little *et al*. showed that such an intervention was effective in improving antibiotic management of adults with lower RTI.[16] In children, only online instruction on the use of information material was studied in the UK, which was effective.[21] In our study we aimed to assess the effects of an online training for GPs and an information booklet for parents on antibiotic prescribing for children with RTI in general practice.

67 **METHODS**

68 **Trial design**

69 The RAAK (Rational Antibiotic use Kids) study was a pragmatic, cluster randomised, two-arms,
70 controlled trial with measurements before and after the intervention, to allow for adjustment for
71 baseline antibiotic prescribing (baseline audit). GPs within a general practice influence each
72 other and patients within a practice are often managed by different GPs, therefore, the general
73 practice was the unit of randomisation and the unit of analysis to minimize contamination and
74 dilution of the intervention effect. GPs in the control group practised care as usual. We followed
75 the Consolidated Standards of Reporting Trials guidelines, extended for cluster randomised
76 trials.[22]

77 **Ethics approval**

78 This trial was exempted by the Ethics Committee of the University Medical Center Utrecht from
79 obtaining parents' or patients' consent (reference number METC 13-237/C). The trial assigned
80 GPs with the aim to improve their prescribing behaviour according to the national practice
81 guidelines. Children were not the subject of the intervention and were treated according to the
82 guidelines.

83 **General practices and participants**

84 For the baseline audit, GPs were asked to register 40 consecutive consultations of children
85 younger than 18 years with signs and symptoms of RTI (nose, ear, throat and/or lower RTI
86 symptoms), presenting at their general practice during the winter season 2013-2014. GPs
87 registered the following anonymous information on consultation report forms: age, duration of
88 symptoms, fever, most prominent symptoms, findings of physical examination, overall illness
89 severity (1= minimally ill, 5=severely ill), the International Classification of Primary Care code for

90 diagnosis, and whether an antibiotic was prescribed, including which one. General practices
91 were excluded if GPs registered less than ten patients in total per general practice, since low
92 numbers could result in poor estimations of the baseline antibiotic prescription rates. After
93 randomisation and implementation of the intervention, this registration of consultations was
94 repeated in the follow-up audit, during the winter season 2014-2015. In addition, parents were
95 invited to fill in a diary for up to two weeks following the index consultation, and give permission
96 to review the child's medical records after six months to collect secondary outcomes.

97 **Intervention**

98 The intervention consisted of online training for GPs and a written information booklet for
99 parents. These were adapted from an intervention for adults that was: a) theory-based: the
100 educational content was designed to promote positive expectations and self-confidence in GPs
101 and patients to manage the infection without antibiotics, b) person-based: the content was
102 developed with extensive feedback from GPs and patients to ensure that it addressed their
103 concerns and was persuasive.[23-25] The online training consisted of three parts. The first part was
104 a general background about the relevance of prudent antibiotic use and information about
105 antibiotic-related problems. We presented over-prescription by percentages of prescribed
106 antibiotics, not congruent with guideline recommendations, from a recent Dutch study, to make
107 GPs aware of their responsibility in prudent antibiotic use.[6] The second part informed about the
108 child-specific parts of the four national RTI guidelines of the Dutch College of GPs[5], including
109 assessment of disease severity, risk factors, signs and symptoms, when to prescribe antibiotics,
110 and the advised first and second choice antibiotic treatment. This part was summarized in a
111 printable document, which is available as supplementary data at JAC online. The third part
112 focused on training in enhanced communication skills, supported by videos of consultation
113 techniques. The communication skills training was based on the elicit-provide-elicit framework,
114 used in prior antibiotic interventions, adapted to communication with parents.[7,15,26] In summary,

115 the GP first elicits what the parent's main worries and expectations are. Crucially, the GP
116 actively asks how the parent feels about and what he/she expects from antibiotics. Secondly,
117 the GP provides information relevant to the parents individual understanding and interest,
118 including findings from the medical history and physical examination of the child. Then, the GP
119 elicits the parents interpretation about what has been said and done, to reach mutual agreement
120 and concludes with concrete safety netting, explaining specific signs and symptoms when to
121 reconsult.

122 GPs were invited by email to commence the training. If the training was not started or
123 completed, a weekly reminder email was automatically sent with the request to complete the
124 online training.

125 The booklet contained the following information in text and pictograms: epidemiology of RTI,
126 their predominant viral cause, self-limiting prognosis, rationale to withhold antibiotics, and
127 antibiotic related problems, including bacterial resistance. Additionally, self-management
128 strategies for their child and signs and symptoms when to consult the GP were explained.

129 **Outcomes, sample size, and randomisation**

130 The primary outcome was the antibiotic prescription rate per general practice in the follow-up
131 audit, as documented on the consultation report forms filled in by the GPs.[16] The following
132 secondary outcomes were assessed from the patients' medical records: number of
133 reconsultations during the same disease episode, number of consultations for new RTI
134 episodes and the number of hospital referrals during a follow-up of six months. Total and types
135 of dispensed antibiotic courses for all children under 18 years were collected via the Dutch
136 Foundation for Pharmaceutical Statistics.[27] Affiliated pharmacies of the participating general
137 practices (n=68) were asked for permission to collect all dispensed antibiotics that resulted from
138 prescribing by the participating GPs of that practice. Numbers of dispensed systemic antibiotics

139 (ATC-code J01) were collected via an online module for the complete years prior to and after
140 introducing the online training. Total numbers of antibiotics mainly used for RTIs were:
141 tetracyclines (J01AA), amoxicillin (J01CA), pheneticillin (J01CE), amoxicillin/clavulanate
142 (J01CR) and macrolides (J01FA). Amoxicillin (J01CA) and pheneticillin (J01CE) were
143 considered as first choice antibiotics, the others as second choice. The numbers of registered
144 children in the practice for the corresponding year were collected. The median duration of the
145 time being logged-in and the short online evaluation of the GP training were assessed.

146 We calculated that we would need a minimum of 157 consultations per arm, to be able to detect
147 an absolute difference of 15% in prescribing rate (42% and 27%), with 80% power and a 5%
148 significance level. To adjust for clustering of the effect within general practices, we assumed an
149 intra-cluster coefficient of 0.07 and a cluster size of 40, requiring a total of 1171 consultations in
150 both arms.[28] In order to achieve this we set out to ask 30 practices to register 40 consultations
151 each. Simple random allocation was performed by a computer generated list on general practice
152 level.

153 **Data analysis**

154 The primary analysis was according to the principle of intention-to-treat and assessed the
155 intervention effect on antibiotic prescribing to children as registered by the GPs in the follow-up
156 audit. We aggregated the data to the cluster level and used a generalized linear model for
157 Poisson distributed count outcomes, controlled for overdispersion.[29] We calculated Rate Ratios
158 (RR) with corresponding 95% Confidence Intervals (CI) and adjusted for baseline prescription
159 rates per general practice, as assessed in the year before the intervention. We chose not to
160 adjust for signs/symptoms, or diagnosis, because the interpretation, judgment and use of these
161 variables were part of the educational aspect of the online training.[30] The secondary outcomes
162 were also aggregated to the cluster level and analysed similarly as the primary outcome.

Pharmacy antibiotic dispensing data were retrieved per practice. The numbers of total dispensed antibiotics were analysed using a generalized linear model and controlled for the numbers of dispensed antibiotics in the year preceding the intervention, and the numbers of children in the practice. Prescription of second choice antibiotics was analysed related to the total number of children and to the total number of dispensed antibiotics and was controlled for baseline prescribing. Analyses were done in SPSS version 21.

RESULTS

Practice flow

Before randomisation, 38 practices agreed to participate (Figure 1). Preceding the intervention, three practices were excluded, as they did not register any consultation during the baseline audit. Finally, 35 practices were randomised to the control or intervention arm. Three out of 35 randomised practices were excluded during the follow-up audit. They had not registered enough consultations, because of sick leave of participating GPs. Therefore, pharmacy data of these practices could neither be obtained reliably. One single-handed GP was excluded for the pharmacy data, since his practice moved during the study period to another part of the city. Practices of the intervention and control group were comparable with respect to their total list size and numbers of listed children (Table 1).

Registration of consultations

During the baseline audit 1009 consultations of children with symptoms of RTI were registered by 75 GPs from 35 general practices (Figure 1). The mean antibiotic prescription rate from this baseline audit was 29.6% (35.7%, SD 4.8 in the control group versus 24.2%, SD 4.3 in the intervention group). The follow-up audit included 1009 consultations in total, 532 from control and 477 from intervention practices. Consultations were comparable between the intervention and control group with respect to childrens' age, duration of illness before consultation, illness severity and presentation with fever (Table 2). Numbers of registered symptoms appeared to be higher in the intervention group as compared to the control group, especially for earache (37.1% versus 29.3%).

Intervention

The training was completed by all 40 GPs of the intervention group. Their median time logged-in was one hour and 18 minutes. Based on GPs' evaluation, the first and second part of the training, with the general background and information of the four guidelines, were valued highest, with a mean score of 4.5 (1=low value, 5=high value); the third part about communication skills scored a mean of 4.2.

Numbers analysed

Analysis of the primary outcome was performed on 475 consultations in the 15 practices allocated to the intervention, and 531 consultations in 17 practices allocated to usual care. Three consultations lacked the primary outcome and were excluded from analyses. In 535 (53%) consultations of children, the parent gave permission to anonymously collect secondary outcomes after six months from the child's medical record and was willing to fill in a diary. These consultations showed no relevant differences compared to consultations in which parents were not willing to participate in the study (data not shown). Secondary outcomes of 508 children were available for analyses, 27 cases were lost to follow-up.

Outcomes

In 21.4% of consultations an antibiotic was prescribed in intervention practices, compared to 33.2% in the control group. The rate ratio after adjustment for baseline prescription was 0.65 (95% CI 0.46-0.91, Table 3). The intra-cluster coefficient was 0.09. The mean number of reconsultations per 100 children within the same disease episode was lower in the intervention group (42), as compared to the control group (64), but did not differ significantly (RR 0.66, Table 4). The probability of consultation for new RTI within six months did not differ significantly (RR 1.06), nor of hospital referrals (RR 0.66). General practices exposed to the intervention reduced antibiotic dispensing with 32 courses per 1000 children per year, relative to the control group, and based on the full year's pharmacy data (RR 0.78, 95% CI 0.66-0.92, Table 5). Adjusted for

215 the year preceding the intervention, the number of dispensed antibiotics was 114 per 1000
216 children in the intervention group and 146 per 1000 children in the control group. The number of
217 dispensed second choice antibiotics in the intervention group was lower (39.9/1000 children) as
218 compared to the control group (49.2/1000 children), however, this difference was not significant.
219 The percentage of second choice antibiotics neither differed between the control and
220 intervention group (34.1%, versus 34.4%).

DISCUSSION

Online training of GPs and information booklets for parents resulted in less antibiotic prescriptions, measured by GPs' registrations of consultations, as well as by data of total yearly antibiotic dispensing to children with RTIs. The intervention did not result in a significant reduction in second choice antibiotics, reconsultations in the same disease episode, consultations for new RTI episodes, or hospital referrals.

Outcomes of previous studies vary depending on setting, study population, and type of intervention.[13,18-20,31,32] Relatively intensive interventions targeting both parents and clinicians are considered to be most effective, and decrease antibiotic prescribing rates by 6-21%.[19] Focusing on GP-parent communication, supported by written information, also showed to be important.[14,18,19,31-33] In our study, the prescription rates adjusted for baseline prescription differed 11.8%. This effect was striking, particularly as our baseline prescription rates was already low in comparison with other countries. Previous studies often used complex and time consuming interventions, whereas our online training was feasible, concise and without personal (academic) involvement and showed a long-term effect on antibiotic prescribing. Online GP training to reduce antibiotic prescribing for children has not been used yet in primary care, except for one study in the UK.[21] This study primarily focused on consulting behaviour, using an information booklet endorsed by the GP; the online training was about how to use the booklet and did not include guideline education and background of antibiotic-related problems.[21]

Strengths and Limitations

This cluster randomised controlled trial showed a convincing effect on antibiotic prescribing using GPs' registrations and pharmacy dispensing data during a full year after the intervention. In the context of continuously improving RTI treatment in children, our study aimed to make a simple, concise and feasible intervention, which was valued by GPs and parents.[34] The

245 pragmatic study design did not interfere with daily practice and did not require large time
246 investments or organizational adaptations. Our focus on the total childhood population with
247 broad eligibility criteria, and without selection of subgroups, or controlling for patient
248 characteristics, makes our results reliable and generalizable. By measuring both antibiotic
249 prescribing outcomes in the year preceding the intervention, we were able to control for baseline
250 prescribing, making our results more robust, since the number of clusters was not large.[35,36] Our
251 study also has potential limitations. First, the pharmacy data could include GPs in the
252 intervention group who did not receive the online training, since some GPs who were not
253 involved in the trial, for example temporary locums or GPs in training, prescribed antibiotics on
254 behalf of participating GPs. This may have diluted the real, potentially higher, intervention effect.
255 This change of employees in the participating practices was increasing over time, and
256 prevented us from reliably measuring the intervention effect in the second year. Secondly, our
257 study was not powered to study whether severe complications could occur more frequently due
258 to reduced antibiotic prescriptions, nevertheless there was no evidence suggesting an adverse
259 effect of the intervention. Our intervention taught GPs according to the evidence-based
260 guidelines.[5] We therefore expect no risk of inducing under-prescription. Another Dutch
261 intervention, aiming to reduce antibiotic prescribing showed that both over- and
262 underprescribing improved.[27] And, a substantial reduction in antibiotic prescriptions was shown
263 to be safe in a recent population-based study.[37] Finally, there is a non-significant difference in
264 reconsultation in the intervention and control group, with large within group variation. Many
265 parents of registered children were not invited to participate due to time constraints during the
266 consultation and only half of the invited parents were willing to keep a diary and gave
267 permission to assess the medical records of their child.

268 **Conclusion**

The intervention was effective in reducing antibiotic prescribing, and was feasible and acceptable.[34] Given the minimal training time and the clear impact on antibiotic prescriptions it is likely to be cost-effective. To implement this intervention at a national level some aspects could be further developed, e.g. considering presenting the information booklet electronically, stimulating informal learning activities including self-reflection, and potential linkage to a structural antibiotic stewardship program.[34,38]

This trial was registered at the Dutch Trial Register (NTR), registration number: NTR4240

OTHERS

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Registration

This trial was registered at the the Dutch Trial Register (NTR), registration number: NTR4240.

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Transparency declarations

None to declare.

Author contributions

Alike van der Velden, Theo Verheij, Lidewij Broekhuizen, Christopher Butler, Jochen Cals, Nick Francis, Paul Little and Lucy Yardley conceived and designed the study. Anne Dekker organised the trial and collected all data. Anne Dekker, Alike van der Velden, Theo Verheij and Peter Zuithoff analysed and interpreted the data. Anne Dekker, Alike van der Velden and Theo Verheij wrote the first draft of the manuscript, and all coauthors critically revised the manuscript for intellectual content. All authors approved the final version and agreed to serve as guarantors of the work.

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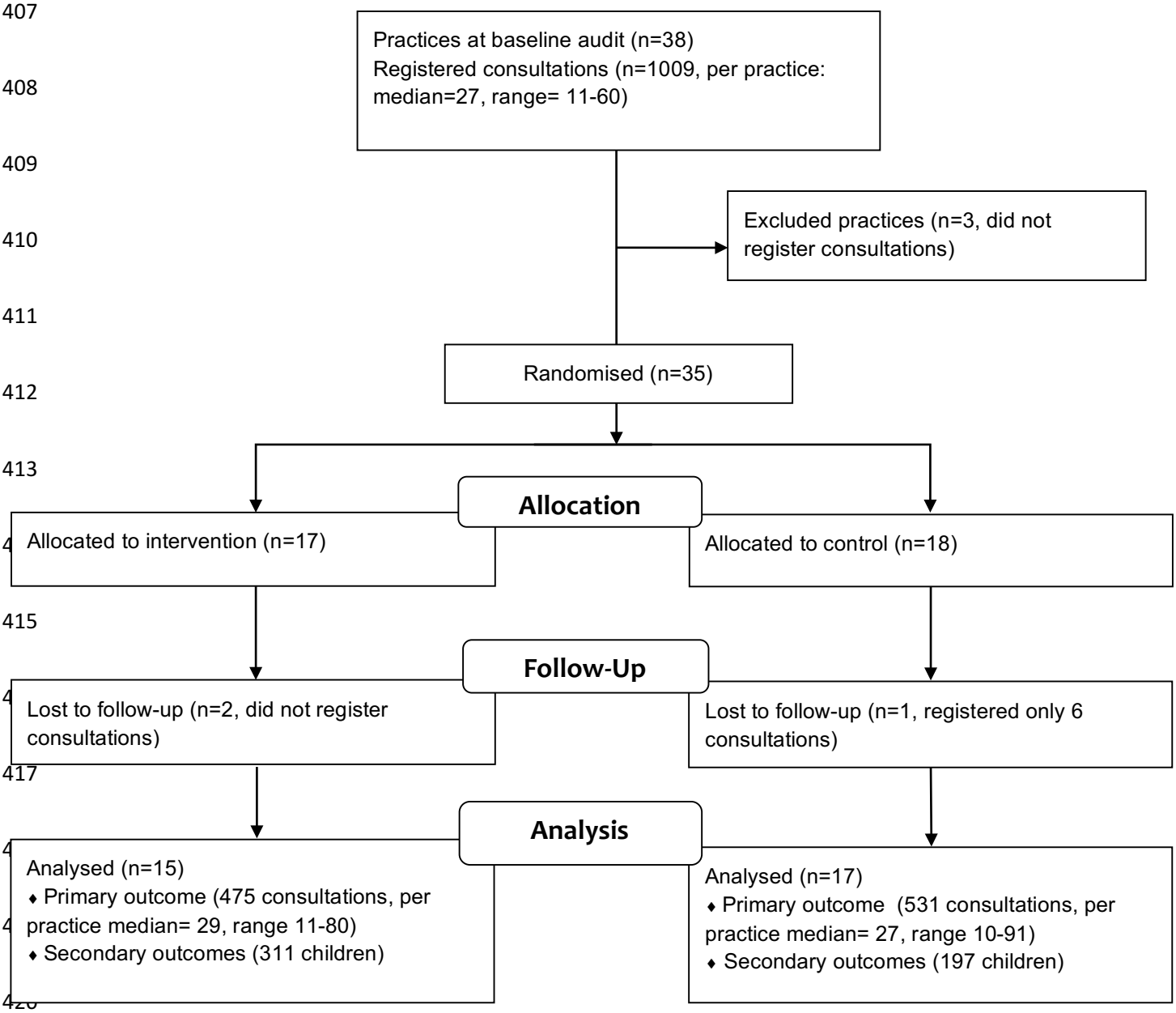
Figure 1 Trial profile, practice flow



424 **Table 1 Characteristics of general practices allocated to the intervention and control**
425 **group**

	Intervention (n=15)	Control (n=17)
Median list size total (IQR)	2980 (2491-4850)	3275 (2589-3589)
Median list size children <18 years (IQR)	604 (518-999)	664 (421-810)
Participating GPs	40	35
Male/female GPs	46%/54%	43%/57%
Mean age GP (SD)	46 (11)	45.3 (9.5)

426 IQR= interquartile range

427 **Table 2 Characteristics of consultations of the follow-up audit after allocation to the**

428 **intervention or control group**

	Intervention (n=477)	Control (n=532)
Mean age, years (SD)	4.7 (4.4)	4.4 (4.1)
Median duration of illness before consultation, days (IQR)	5 (3-14)	5 (3-10)
Mean GPs' perception of illness severity, 1 = not ill, 5 = severely ill (SD)	1.6 (0.8)	1.9 (1.0)
Fever (%)	257 (53.9)	278 (52.3)
Earache (%)	177 (37.1)	156 (29.3)
Runny nose (%)	387 (81.1)	375 (70.5)
Sore throat (%)	128 (26.8)	121 (22.7)
Cough (%)	358 (75.1)	381 (71.6)

429 IQR= interquartile range

430 **Table 3 Effectiveness of the intervention on antibiotic prescription rates**

	Intervention	Control	RR (95% CI)
Crude antibiotic prescription rate (95% CI)	20% (95/475) (15.4-26)	36.9% (196/531) (30.8-44.3)	0.54 (0.4-0.74)*
Adjusted antibiotic prescription rate** (95% CI)	21.4% (16.6-27.6)	33.2% (27-40.8)	0.65 (0.46-0.91)*

431 Data were retrieved from GP-registered consultations. *P<0.05. **Adjusted for baseline

432 prescription.

433 **Table 4 Effectiveness of the intervention on reconsultation, consultations for new RTI**

434 **episodes and hospital referrals**

	Intervention (n=311)	**Control (n=197)**	**RR (95% CI)**
Absolute number of reconsultations	132	126	
Mean number of reconsultations/100 children (95% CI)	42 (29-63)	64 (43-96)	0.66 (0.38-1.16)
Absolute number of new RTI consultations	252	150	
Mean number of new RTI consultations/100 children (95% CI)	81 (64-103)	76 (56-104)	1.06 (0.72-1.58)
Absolute number of hospital referrals	24	23	
Mean number of hospital referrals/100 children (95% CI)	8 (5-13)	12 (7-20)	0.66 (0.31-1.40)

435 Data were retrieved from the child's medical registries.

436 **Table 5 Effectiveness of the intervention on total and second choice yearly dispensed**

437 **antibiotics**

		Intervention	Control	RR (95% CI)
Total antibiotics/1000 children/year (95% CI)	Crude	110 (89.1-136)	161 (137-189)	0.68 (0.52-0.89)*
	Adjusted**	114 (100-129)	146 (132-162)	0.78 (0.66-0.92)*
Number of second choice antibiotics/1000 children/year (95% CI)	Crude	39.3 (29.1-53.1)	54.8 (43.3-69.4)	0.72 (0.49-1.05)
	Adjusted**	39.9 (32.6-48.7)	49.2 (41.7-58.1)	0.81 (0.63-1.05)
Percentage of second choice antibiotics/total antibiotics (95% CI)	Crude	35.7% (29-44)	34% (28.9-40)	1.05 (0.81-1.37)
	Adjusted**	34.1% (29.6-39.3)	34.4% (30.8-38.3)	0.99 (0.83-1.19)

438 Data were retrieved from a full year's pharmacy dispensing data. *P<0.05. ** Adjusted for

439 baseline prescription.