PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Study protocol for a randomised controlled trial evaluating the clinical effects of antibiotic prophylaxis in children with recurrent respiratory tract infections: the APPROACH study
AUTHORS	Peeters, Daphne; van Geloven, Nan; Visser, Loes; Bogaert, Debby; van Rossum, AM; Driessen, Gertjan; Verhagen, Lilly

VERSION 1 – REVIEW

REVIEWER	van Woensel, Job Amsterdam UMC Locatie AMC, PICU
REVIEW RETURNED	29-Nov-2020

GENERAL COMMENTS	In their manuscript Peeters et al describe a study protocol of a randomised controlled trial that aims to evaluate the clinical effects of antibiotic prophylaxis in otherwise healthy children with recurrent respiratory tract infections. This is an important study that addresses a well known controverse in the prevention of RTI in otherwise healthy children. The protocol is well written and the design of the study is well thought out using relevant endpoints and objectives. The authors include the effect of co-trimoxazole prophylaxis on micorbiotica composition as well as antibiotic resistance. I was wondering why the authors do not also check the presence of viruses in the upper airways on a regular base during the study of the included children. Different types of viruses may influence the symptoms and even be a risk factor for bacterial infections. The introduction is quite long. In particular the detailed information of the effectiveness of antibiotic prophylaxis in children with certain high risk conditions could be shortened. Finally, but inmportantly, the rationale for their study could be worked out more thoroughly. Actually the authors write only one sentence in the introduction: “The high disease burden can lead to failure to thrive and developmental delays in children leading to high costs of the community”. To support this they use a reference that examined RTI of children in a long-care facility. Studies that examined.

REVIEWER	Myers, Angela Children's Mercy Hospitals and Clinics, Pediatrics
REVIEW RETURNED	11-Feb-2021

GENERAL COMMENTS	Introduction: line 21, antibiotic resistance is a concern with

	prophylactic antibiotics, but is not an adverse effect per se. Would change this sentence to say "antibiotic prophylaxis as well as potential adverse effects, such as rash, vomiting, diarrhea, and/or antibiotic resistance development..." The authors provide many examples indicated antibiotic prophylaxis such as children with HIV, sickle cell, and immune deficiencies. However, these populations have nothing to do with this study and thus are less relevant as an argument to study antibiotic prophylaxis in healthy children to prevent RTI. Additionally, the reason TMP/SMX is used in HIV is to prevent PJP, not H. influenzae and pneumococcal infections. Also, azithromycin does prevent CF exacerbations, but is thought to do so from an anti-inflammatory standpoint. Is this the argument for this study? That TMP/SMX provides an anti-inflammatory effect rather than an antibiotic effect? Please explain. There is a high rate of pneumococcal resistance to TMP/SMX in some areas. Is this a problem where this study is being conducted? This is important to know since pneumococcus is the cause in a large portion of bacterial RTIs in children. Methods: It seems like it will be difficult to enroll children between the 6 month and 1 year of age mark based on the requirements for the number of RTIs to be considered recurrent. Was starting at age 1 considered? Page 6 line 59 "..the child will receive antibiotics that conform to national guidelines..."

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Dr. Job van Woensel, Amsterdam UMC Locatie AMC Comments to the Author:
In their manuscript Peeters et al describe a study protocol of a randomised controlled trial that aims to evaluate the clinical effects of antibiotic prophylaxis in otherwise healthy children with recurrent respiratory tract infections.
This is an important study that addresses a well known controverse in the prevention of RTI in otherwise healthy children.
The protocol is well written and the design of the study is well thought out using relevant endpoints and objectives. The authors include the effect of co-trimoxazole prophylaxis on micorbiotica composition as well as antibiotic resistance.
I was wondering why the authors do not also check the presence of viruses in the upper airways on a regular base during the study of the included children. Different types of viruses may influence the symptoms and even be a risk factor for bacterial infections.
Response: The presence of viruses in these children could indeed be interesting. With the type of samples that are collected at 4 different time points, we'll also be able to perform a viral analysis. This option has been added to the manuscript text.
In addition to viral analysis, we've added extra sampling of mucosal lining fluid (MLF) to the protocol because recent results show a potential advantage of MLF sampling over saliva sampling. MLF can be obtained to measure mucosal humoral immunity biomarkers, such as antibody levels, and other immune markers such as cytokines and chemokines. MLF has the potential advantage of better standardisation of collected volumes, reducing the effect of dilution on measurement outcomes. In a recently performed household contact COVID-19 study, MLF was obtained of COVID-19 patients and their household contacts and the results indeed showed precise antibody measurements for different antibody classes (Fröberg et al 2021, https://doi.org/10.1101/2021.02.02.21250910).

The introduction is quite long. In particular the detailed information of the effectiveness of antibiotic prophylaxis in children with certain high risk conditions could be shortened.
Response: We thank the reviewer for this comment and have shortened the introduction accordingly.

Finally, but importantly, the rationale for their study could be worked out more thoroughly. Actually the authors write only one sentence in the introduction: “The high disease burden can lead to failure to thrive and developmental delays in children leading to high costs of the community”. To support this they use a reference that examined RTI of children in a long-care facility.
Response: We agree with the reviewer that the rationale on the burden of children with recurrent respiratory tract infections could be described more thoroughly. We’ve elaborated on this matter in the revised version of our introduction.

Reviewer: 2
Dr. Angela Myers, Children's Mercy Hospitals and Clinics Comments to the Author:
Introduction: line 21, antibiotic resistance is a concern with prophylactic antibiotics, but is not an adverse effect per se. Would change this sentence to say "antibiotic prophylaxis as well as potential adverse effects, such as rash, vomiting, diarrhea, and/or antibiotic resistance development..."
Response: We’ve adjusted the text in order to clarify the distinction between adverse effects and antibiotic resistance.

The authors provide many examples indicated antibiotic prophylaxis such as children with HIV, sickle cell, and immune deficiencies. However, these populations have nothing to do with this study and thus are less relevant as an argument to study antibiotic prophylaxis in healthy children to prevent RTI. Additionally, the reason TMP/SMX is used in HIV is to prevent PJP, not H. influenzae and pneumococcal infections. Also, azithromycin does prevent CF exacerbations, but is thought to do so from an anti-inflammatory standpoint. Is this the argument for this study? That TMP/SMX provides an anti-inflammatory effect rather than an antibiotic effect? Please explain. There is a high rate of pneumococcal resistance to TMP/SMX in some areas. Is this a problem where this study is being conducted? This is important to know since pneumococcus is the cause in a large portion of bacterial RTIs in children.
Response: We thank the reviewer for this helpful comment. We’ve shortened the rationale for antibiotic prophylaxis in high-risk populations. In this study we’ll examine the effect of co-trimoxazol, because this treatment has also been proven to be effective in the prevention of acute and chronic suppurative otitis media (Leach et al 2006, https://doi.org/10.1002/14651858.CD004401.pub2). In addition, in the Netherlands, as in many other countries, it’s the most common antibiotic used (off-label) for children with recurrent RTIs. The combination of the antimicrobial and immunomodulatory properties of co-trimoxazol could indeed provide an additional beneficial effect in the prevention/reduction of RTIs. We’ve added this to the rationale.
The Dutch time trends of resistance numbers for co-trimoxazol are stable. For some bacteria, resistance to co-trimoxazole even tends to decrease in the last 5 years. The co-trimoxazole resistance prevalence observed in diagnostic samples containing S. pneumonia in outpatient and inpatient departments is around 9% (Source: NethMap 2020 by the National Institute for Public Health and the Environment, https://swab.nl/en/abstract-nethmap-2020, Table 4.5.4). It is important to note that the microbiota composition of children with higher rates of t RTIs is different compared to healthy children (Unger and Bogaert 2017, https://doi.org/10.1016/S0163-4453(17)30196-2). Pneumococcus might therefore play a different role in the development of infectious symptoms.

Methods: It seems like it will be difficult to enroll children between the 6 month and 1 year of age mark based on the requirements for the number of RTIs to be considered recurrent. Was starting at age 1 considered?
Response: We agree with the reviewer that it can be challenging for younger children below the age

of 1 year to present with the minimal number of RTIs required to participate in the study. Before initiating this study we've thoroughly discussed the age of our study population with several paediatricians who treat these patients on a regular basis. Also, we've examined the characteristics of a representative sample in two of our main study sites. Based on these findings, we found that some children already suffer from recurrent respiratory tract infections at a very young age and that there was a need to examine this treatment in these younger patients. The burden of these younger children has also been described by Toivonen et al, who showed that children with recurrent RTIs already suffer from a similar number of days with respiratory symptoms at the age of 6-11 months compared to children of 12-23 months (Toivonen et al 2016, doi:10.1097/INF.0000000000001304). During the past 6 months when this protocol was under review, we've also encountered that the maximum age of 5 years might be too young. We've received requests from multiple paediatricians about children who were too old to participate, but would otherwise be eligible. We've therefore taken another representative sample at several outpatient clinics and have discussed this with our research team including our statistician. Based on this information, we've expanded the inclusion criteria up to 10 years. Because our sample size is based on an assumption of the number of symptoms, the older children will also have to comply with the minimal number of RTIs similar to the participants aged 2-5 years. This adjustment was also submitted to and approved by the Medical Research Ethics Committee (MREC).

Page 6 line 59 "..the child will receive antibiotics that conform to national guidelines..."
Response: We've adjusted this accordingly.