

BMJ Open Study protocol for a randomised controlled trial evaluating the clinical effect of antibiotic prophylaxis in children with recurrent respiratory tract infections: the Approach study

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ABSTRACT

Introduction Respiratory tract infections (RTIs) affect children all over the world and are associated with significant morbidity and mortality. In particular, recurrent RTIs cause a high burden of disease and lead to frequent doctor visits. Children with recurrent RTIs generally have no significant alterations or deficits in systemic immunity. In an attempt to treat the assumed bacterial component involved, they are often treated with prolonged courses of prophylactic antibiotics taken on a daily basis. Despite its common use, there is no evidence that this is beneficial. Studies assessing the clinical effectiveness of antibiotic prophylaxis as well as potential adverse effects and antibiotic resistance development, are therefore urgently needed.

Methods and analysis We present a protocol for a randomised double-blind placebo-controlled trial comparing co-trimoxazole with placebo treatment in children with recurrent RTIs. A total of 158 children (aged 6 months–10 years) with recurrent RTIs without significant comorbidity will be enrolled from a minimum of 10 Dutch hospitals. One group receives co-trimoxazole 18 mg/kg two times per day (36 mg/kg/day) and the other group receives a placebo two times per day for a period of 3 months. The main objective is to determine whether antibiotic prophylaxis is more effective than placebo to prevent/reduce respiratory symptoms in children with recurrent RTIs. Respiratory symptoms will be scored by parents on a daily basis in both study arms by the use of a mobile phone application. Our primary outcome will be the number of days with at least two respiratory symptoms during the treatment.

Ethics and dissemination Ethics approval was obtained from the Medical Ethics Research Committee Zuidwest Holland/LDD. A manuscript with the study results will be submitted to a peer-reviewed journal. All participants will be informed about the study results. The results of the study will inform clinical guidelines regarding the prophylactic treatment of children with recurrent RTIs.

Trial registration number NL7044.

Strengths and limitations of this study

- Apart from studies focusing exclusively on otitis media, this is the first randomised controlled trial that examines whether co-trimoxazole prophylaxis is effective to prevent/reduce symptoms in children with recurrent respiratory tract infections (RTIs).
- We will examine the clinical response to prophylactic antibiotic treatment both during the period in which treatment is taken and also in the 3 months following that period, because of an extended follow-up duration of 6 months in total.
- We will examine predictors of treatment effect, such as clinical characteristics, microbiota parameters and immunological characteristics.
- All children receive the same dose per kg body-weight of co-trimoxazole and this study does not measure pharmacokinetic parameters. Therefore, we will not be able to determine the most optimal dosage of co-trimoxazole when prescribed for a prophylactic indication in children with recurrent RTIs.
- We will not enrol children with underlying chronic illnesses, such as cardiorespiratory or neuromuscular conditions, immune deficiency and congenital abnormalities, so the results of our study cannot be extrapolated to these patient groups.

INTRODUCTION

Lack of evidence-based guidelines for a common clinical problem

Young children (up to 2 years of age) experience symptoms of a respiratory tract infection (RTI) for a median of 44 days per year. The median number of infectious episodes is almost double in children with recurrent RTIs when compared with healthy peers.¹ Even in the absence of high-risk conditions such as major immune deficiencies or congenital malformations, some children develop many more RTIs than their peers.² Recurrent RTIs in children are among the leading reasons for



primary care consultations and for referral to paediatricians and ear, nose and throat (ENT) specialists.³ In developed countries, recurrent RTIs, defined as a minimum of six to eight episodes per year, affect 15%–20% of children under 5 years of age.⁴ Most children suffer from recurrent RTIs of the upper airways, but in approximately 10%–30%, the lower respiratory tract is also affected.⁵ Compared with their healthy peers, children with recurrent RTIs visit the outpatient clinic more often and they frequently need hospitalisation. In addition, these children are treated more frequently with medication, for example, inhaled bronchodilators and corticosteroids, as well as antibiotics.¹ The high disease burden can also lead to failure to thrive and developmental delays in children, as well as parental productivity losses associated with children's illness and absenteeism from work, leading to high costs for the community.^{1 6 7} Lower RTIs in childhood can also lead to pulmonary sequelae such as bronchiectasis and irreversible lung damage,^{8–10} putting children with recurrent RTIs even more at risk for long-term damage. In our experience, children who visit the outpatient clinics because of recurrent RTIs are generally ≤ 10 years of age and most are treated on a 'trial and error' base because there is no international consensus about the best (prophylactic) treatment for children with recurrent RTIs. Previous studies suggest that antibiotic prophylaxis, treatment with the immunomodulator OM-85, active immunisation and/or parental education on risk factors (passive smoking) may be at least of some benefit.^{4 11–14} In general, antibiotics are frequently used for the treatment of acute RTIs in children. In an attempt to treat the assumed bacterial component involved in recurrent RTIs, prolonged antibiotic regimens are often prescribed. Previous studies in children with recurrent acute otitis media showed that antibiotic prophylaxis prevented one and a half episode for every 12 months of treatment per child.¹⁵ Studies examining the clinical effectiveness of antibiotic prophylaxis in children suffering from recurrent RTIs are scarce and mainly focus on high risk groups with recurrent lower RTIs.^{11 16–21} No studies have been performed on the clinical effectiveness of antibiotic prophylaxis in otherwise healthy children who suffer from recurrent RTIs.

The antibiotic regimen that is commonly prescribed in children with recurrent RTIs is trimethoprim/sulfamethoxazole (co-trimoxazole). Both trimethoprim and sulfamethoxazole are bacteriostatic if used alone. Combining trimethoprim and sulfamethoxazole elicits a synergistic effect and makes the antibiotic regimen bactericidal. Co-trimoxazole is a fixed antibiotic combination of trimethoprim and sulfamethoxazole (1:5) which covers most Gram-positive and Gram-negative potential pathogens as well as *Pneumocystis jirovecii*. In addition, several studies suggest that co-trimoxazole has an immunomodulatory effect.^{22–25} The combination of antimicrobial and immunomodulatory properties could provide an additional beneficial effect in the prevention or reduction of RTIs.

In this study, we will compare the clinical effectiveness of co-trimoxazole prophylaxis with placebo in children with recurrent RTIs.

Role of microbiota in respiratory infection and disease

Prolonged antibiotic treatment is of major concern, since antimicrobial resistance (AMR) development increases with duration of the antimicrobial course.²⁶ Probably, the most important route of AMR gene selection in humans is antibiotic-induced changes to our protective microbial communities, also called the microbiota.²⁷ Whereas microbial disturbances elicited by antibiotic treatment in adults are mostly temporary, exposure to antibiotic treatment early in life may have a lasting impact on the composition of the microbiota leading to permanent replacement by resistant organisms.^{28 29} While the microbiota of the gastrointestinal tract has been studied most extensively,^{30 31} the human nasopharynx is considered the niche from which both upper and lower RTIs originate and resistance can also emerge in commensals or pathogens colonising this body site.³² During the past decade, high-throughput pipelines have become available to also characterise the complete nasopharyngeal microbiota.³³

In this study, we will examine short-term and long-term effects of co-trimoxazole prophylaxis on the microbiota composition and antibiotic resistance in children who suffer from recurrent RTIs.

METHODS AND ANALYSIS

Objectives and study parameters

Primarily, we aim to investigate the clinical efficacy of co-trimoxazole prophylaxis in Dutch children (aged 6 months up to 10 years) with recurrent RTIs. Children will be randomised to co-trimoxazole or placebo for a treatment period of 3 months, since this is the treatment period after which a beneficial effect was achieved in children with recurrent acute or chronic suppurative otitis media.¹⁵

Primary objective

To determine whether 3 months of prophylactic treatment with co-trimoxazole causes a reduction in the number of days a child experiences at least two RTI symptoms in children aged 6 months to ≤ 10 years with recurrent RTIs, when compared with placebo.

Secondary objectives

- To determine whether co-trimoxazole prophylactic therapy reduces:
 - Time to resolution of symptoms.
 - The severity of symptoms defined by the number and type of different symptoms.
 - Use of analgesics/antipyretics.
 - Use of antibiotic treatment courses.
 - Absenteeism from day care or school and/or parental absenteeism from work.
 - Alterations in nutritional status.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	<ul style="list-style-type: none"> ▶ Presenting to one of the participating clinics. ▶ Age 6 months–10 years. ▶ Suffering from recurrent respiratory tract infections (RTIs).* ▶ Informed consent from parent(s)/caregiver(s) with legal custody.
Exclusion criteria	<ul style="list-style-type: none"> ▶ Current prophylactic antibiotic use or prophylactic antibiotic use during the previous month. ▶ Underlying immune deficiency other than for IgA or IgG subclasses. ▶ Congenital abnormalities (including but not limited to cleft palate, neuromuscular or cardiac disorders and syndromes). ▶ Suffering from chronic respiratory disease, such as cystic fibrosis, primary ciliary dyskinesia or anatomical abnormalities. ▶ Only experiencing recurrent AOM or chronic suppurative otitis media without other recurrent RTIs. ▶ Known allergy to co-trimoxazole. ▶ Known contraindication for co-trimoxazole, for example, liver failure or impaired kidney function and/or haematologic disorders.

*Recurrent upper RTIs: for children aged <2 years yearly at least 11 and for children aged 2–10 years yearly at least 8 parental-reported upper RTIs possibly including, but not limited to, otitis media. Recurrent lower RTIs (ie, pneumonia, bronchopneumonia or acute bronchitis) are defined as at least two episodes per year or three or more episodes during the child's life regardless of age.^{34 35} AOM, acute otitis media.

2. To examine predictors (eg, demographic, environmental, family history, mucosal, microbiological and immunological characteristics) for the (absence of) prophylactic treatment effect.
3. To examine whether cessation of antibiotic prophylactic treatment affects the presence of RTI symptoms and how this correlates with clinical, microbiological and immunological characteristics of the patients.
4. To record and evaluate adverse events.
 - The occurrence of mild adverse effects as described in the Summary of Product Characteristics, such as skin rash, gastrointestinal complaints, pruritus or mild headache.
 - The occurrence of severe adverse reactions
5. To examine short-term and long-term effects of co-trimoxazole prophylaxis on microbiota deviation, AMR and (mucosal and systemic) immunological outcomes.

Study design

We will conduct a randomised placebo-controlled double-blind clinical trial in which we compare co-trimoxazole with a placebo in 158 children with recurrent upper and/or lower RTIs. The inclusion and exclusion criteria are listed in [table 1](#). We will enrol children aged 6 months up to 10 years. Children younger than 6 months will not participate in this study, because at this age, the presence of recurrent RTIs cannot be established yet. For age-specific definitions of recurrent RTIs, we took the twofold SD of the mean number of upper RTIs per year in a cohort of 1314 German children, except for children aged 5–10 years, in whom we used the same definition as younger children (2–5 years). This means that we define recurrent RTIs as at least 11 parental-reported upper RTIs per year for children younger than 2 years and eight parental-reported upper RTIs per year for children aged 2–10 years.³⁴ Recurrent lower RTIs (ie, pneumonia,

bronchopneumonia or acute bronchitis) are defined as at least two episodes per year or three or more episodes during the child's life regardless of age. These definitions of recurrent upper and lower RTIs were also used in the Dutch guideline for diagnostic strategies in children with recurrent RTIs.³⁵ If an underlying immune deficiency or contraindication for co-trimoxazole³⁶ has not been ruled out yet, these will be tested in the blood sample taken in all participants before randomisation. Children will be randomised to one of two oral suspension regimens for 3 months: co-trimoxazole 36 mg/kg/day (2×18 mg/kg) or placebo two times per day. The dose of co-trimoxazole is in accordance with the therapeutic dose (for acute infections) as described in the Dutch paediatric drug formulary. Doses and duration of treatment are also based on studies of antibiotic prophylaxis in paediatric populations with recurrent acute or chronic suppurative otitis media.¹⁵ In case of a new RTI episode occurring during follow-up for which the child has a clinical indication to receive (additional) antibiotic treatment, the child will receive antibiotics according to national guidelines and the study medication will be discontinued for the duration of this antibiotic course. Medication compliance will be measured in two ways. During the T3 visit to the hospital, parents will be asked to bring the bottles of trial medication and to answer questions about compliance. By doing so, we will be able to compare the self-reported compliance with the number of empty and (partly) full bottles that are returned.

Randomisation

The randomisation procedures are performed by a member of the trial pharmacy. Randomisation is computer-generated and subjects will be allocated in a 1:1 ratio with random block sizes of two, four or six subjects to prevent predictability of the allocation. Study medication

would be $(42/76) \times 31 = 17$ days per 100 = 14 days per 81 days. Following, we took the average of the Finnish study and our own study to end up with an estimated median number of symptomatic days of $(14+34)/2 = 24$ days per 81 days in the placebo group.

The IQR in the Finnish study was 104–136, translating into a SD of 23.7, which was comparable to the SD in our pilot study (20.5); as such we took the SD of our study for our sample size calculation since the period in which symptoms were measured in the pilot study (mean 115 days) better reflected the follow-up period of the trial (90 days) than the period in which symptoms were measured in the Toivonen study (at least 1 year).

Assuming 24 days with at least two RTI symptoms in the placebo group and taking our aim to detect a clinically meaningful 40% reduction (ie, a reduction of $0.40 \times 24 = 10$ days with RTI symptoms) in the antibiotic treatment arm, we need to include 71 children per arm, so a total number of $71 \times 2 = 142$ children, according to the Wilcoxon-Mann-Whitney test for two groups (two-tailed) with α 0.05 and power 80%. Including a dropout rate of 10%, this brings us to a number of $71/0.9 = 79$ children per arm, so a total number of 158 children.

Outcomes and data analysis

Table 2 summarises the assessment and sampling schedule.

Assessment of RTI symptoms

Descriptive statistics for demographic and clinical characteristics for both treatment allocation groups will be described. These include but are not limited to age, height, weight, ethnicity, co-morbidity, previous ENT-interventions, use of medication, the number of RTI episodes before inclusion, the severity of the infections (eg, hospital admissions) and type of RTI (eg, bronchiolitis, otitis, pneumonia). Also, we will examine the frequency distribution of risk factors for the development of RTIs, which include for example smoking in the household, number of siblings and daycare attendance.

Analyses will be performed on the basis of the ‘intention-to-treat principle’, comparing the treatment arm with the placebo arm, defining the treatment group based on the treatment allocation. In the intention-to-treat analysis, every randomised subject will be included according to treatment assignment, thus ignoring potential non-adherence, protocol deviations, withdrawal and anything that happens after randomisation, therefore maintaining prognostic balance generated from the original random treatment allocation. The analyses will only include subjects of whom at least 80% of the symptom diary data is available. An inventory of missing data will be made and if over 5% of 142 subjects have less available data than 80% of the symptom diary days, an imputation strategy will be used. We will also conduct a ‘per-protocol analysis’ in which we will only include the days that patients adhered to the protocolled treatment allocation. R and IBM SPSS Statistics will be used for statistical analyses.³⁸

For our primary objective, we will compare the number of days with at least two RTI symptoms during 90 days of receiving antibiotic treatment/placebo. Since the actual number of monitored days may vary per patient, we will analyse the incidence rate (number of days with at least two RTI symptoms divided by the total number of days monitored). We will use a negative binomial regression analysis with the number of days with at least two respiratory symptoms as outcome and the number of days monitored as offset. Our target parameter is the incidence rate ratio for treatment. We will include main effects of strong predictors of RTI symptoms in the model.

To determine which set of available determinants predicts heterogeneity of treatment effect, we will first develop a prediction model including well-known risk factors for the development of RTI complaints in children. These include, for example, age of the child, smoke exposure in the household, day-care attendance and number of siblings. In this prediction model, we will adjust for treatment allocation.³⁹ From this model, a summary score will be derived that is used as a risk score in the final model. The interaction between this risk score and the treatment allocation will be added as a covariate in a model for the primary outcome to investigate to what extent these host factors affect the effect of treatment on our primary outcome.

As a secondary analysis, we will also perform a negative binomial regression analysis with number of days with at least two RTI symptoms as the dependent variable and number of monitored days as offset, during the total 0–6 months period in order to assess the outcome both during and after cessation of co-trimoxazole versus placebo. In addition, we will also apply a mixed-effect model to estimate whether the pattern of RTI symptoms over time changes according to treatment allocation.

Respiratory and gut microbiota

For the secondary objective to detect shifts in microbiota composition in the group that received antibiotic prophylaxis compared with the placebo group, we will collect nasopharyngeal swabs (paediatric Copan e-swab with flocced nylon tip) and faecal samples from which bacterial DNA will be extracted according to previously validated methods. Swabs and faecal samples are frozen at -80°C until further analyses. Metagenomic sequencing will be conducted in order to identify the microbiota composition and AMR genes of the faecal samples, in addition to antimicrobial resistance analyses of specific bacteria. For nasopharyngeal samples, 16S-based sequencing will be used to examine the microbiota composition and follow-up analyses for AMR genes or resistance analyses for specific bacteria may take place.^{30 40}

Saliva, blood and mucosal lining fluid samples

Blood samples (peripheral blood mononuclear cells and plasma), saliva samples and mucosal lining fluid will be collected at predetermined intervals (**table 2**) for immunological analyses aimed at the identification of markers

associated with clinical outcome and treatment effect, and further exploration of the immune response against RTIs/pathogens and microbiota-immune interactions. Techniques include, but are not limited to, flow cytometry, proteomics, proliferative studies, cytokine release assays and RNA expression profiling. Saliva samples will also be used for the determination of antimicrobial peptides, inflammatory cytokines, proteomics and mucosal antibodies. Mucosal lining fluid will be used to measure (protein) immune markers such as antibodies, chemokines and cytokines. Finally, saliva/MLF/nasopharyngeal swab samples can be used for viral analyses.

Data management

Clinical data will be collected from the Electronic Medical Record by the research staff. All research data will be stored in the data management programme Castor Electronic Data Capture (EDC). The handling of personal data will comply with the Dutch General Data Protection Regulation (in Dutch: Algemene Verordening Gegevensbescherming). Data will be handled confidentially. The research team has access to coded data. To be able to trace data to an individual subject, a subject identification code list will be used to link the research data to the subject, which will be safeguarded by the local investigators and the trial pharmacy. This trial is monitored in accordance with the Good Clinical Practice guidelines.

PATIENT AND PUBLIC INVOLVEMENT

Because we are supported by two patient involvement groups, we feel confident that both physicians and also patients will be open to our study results. The patient involvement groups were actively involved in the development of our study protocol. During the yearly conference day of the Foundation for Primary Immune Deficiencies ('Stichting voor Afweerstoornissen'), one of our group members (LMV) has discussed the use of antibiotic prophylactic treatment for mild immune deficiencies in children with patients and parents. Many patients and parents expressed their worries about prolonged antibiotic use, mainly related to its adverse effects and the possibility of future infections with resistant bacteria that can no longer be treated with antibiotics. Following this discussion, we started discussion sessions with parents of children visiting the airway clinic in the Wilhelmina Children's Hospital, UMC Utrecht, at several time points. The results showed that parents felt that more research was needed to determine whether antibiotic prophylaxis is an effective treatment. The involvement of both patient groups facilitates acceptance and implementation of our study results in the patient community. We will provide these patient support groups with our study results by publication of the outcomes in 'Paraplu', the monthly journal of the Foundation for Primary Immune Deficiencies, and by discussion of the results during meetings of the patient support groups. Also, we will send a half-yearly

newsletter and an information bulletin containing the final results to the study participants.

ETHICS AND DISSEMINATION

This study will be conducted according to the principles of the Declaration of Helsinki (2013, Brazil, version 64) and in accordance with the *Research Involving Human Subjects Act (WMO)*. The Medical Research Ethics committee Zuidwest Holland/LDD (The Hague/Leiden, The Netherlands) has approved the study protocol. Approval of the local board of each trial site will be obtained before enrolment of the first subject in that specific hospital. This study is registered in The Netherlands National Trial Register (NTR) as Trial NL7044. After completion of this study, results will be submitted to a peer-reviewed journal.

CURRENT TRIAL STATUS

The first subject was enrolled in January 2019. All the local boards of the first 10 trial sites have given their approval to start enrolling patients in this study, the latest approval was obtained in February 2020. If enrolment is slower than expected, a request for the addition of extra trial sites will be submitted to the Medical Research Ethics committee.

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Contributors All authors helped with the design of this study and approved the final manuscript. DP, LMV and GJAD wrote the first draft of the study protocol and manuscript. NvG was consulted for the statistical analysis plan for this study. LEV helped in preparing the trial medication and advised on improving safety measures in relation to the trial medication. DB was consulted for the secondary outcomes on microbiota composition and AMR genes. AMvR was consulted for the design of the study.

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REFERENCES

- Toivonen L, Karppinen S, Schuez-Havupalo L, *et al*. Burden of recurrent respiratory tract infections in children: a prospective cohort study. *Pediatr Infect Dis J* 2016;35:e362–9.
- Ball TM, Holberg CJ, Aldous MB, *et al*. Influence of attendance at day care on the common cold from birth through 13 years of age. *Arch Pediatr Adolesc Med* 2002;156:121–6.
- Otters HBM, van der Wouden JC, Schellevis FG, *et al*. Changing morbidity patterns in children in Dutch general practice: 1987–2001. *Eur J Gen Pract* 2005;11:17–22.
- Schaad UB, Esposito S, Razi CH. Diagnosis and management of recurrent respiratory tract infections in children: a practical guide. *Arch Pediatr Infect Dis* 2016;4:e31039.
- Couriel J. Assessment of the child with recurrent chest infections. *Br Med Bull* 2002;61:115–32.
- Murray MT, Heitkemper E, Jackson O, *et al*. Direct costs of acute respiratory infections in a pediatric long-term care facility. *Influenza Other Respir Viruses* 2016;10:34–6.
- Enserink R, Lugnér A, Suijkerbuijk A, *et al*. Gastrointestinal and respiratory illness in children that do and do not attend child day care centers: a cost-of-illness study. *PLoS One* 2014;9:e104940.
- Edmond K, Scott S, Korczak V, *et al*. Long term sequelae from childhood pneumonia; systematic review and meta-analysis. *PLoS One* 2012;7:e31239.
- Brower KS, Del Vecchio MT, Aronoff SC. The etiologies of non-CF bronchiectasis in childhood: a systematic review of 989 subjects. *BMC Pediatr* 2014;14:4.
- Thomson M, Myer L, Zar HJ. The impact of pneumonia on development of chronic respiratory illness in childhood. *Pediatr Allergy Immunol Pulmonol* 2010;23:279–90.
- Onakpoya IJ, Hayward G, Heneghan CJ. Antibiotics for preventing lower respiratory tract infections in high-risk children aged 12 years and under. *Cochrane Database Syst Rev* 2015;9:CD011530.
- Esposito S, Bianchini S, Bosis S, *et al*. A randomized, placebo-controlled, double-blinded, single-centre, phase IV trial to assess the efficacy and safety of OM-85 in children suffering from recurrent respiratory tract infections. *J Transl Med* 2019;17:284.
- Esposito S, Marchisio P, Cavagna R, *et al*. Effectiveness of influenza vaccination of children with recurrent respiratory tract infections in reducing respiratory-related morbidity within the households. *Vaccine* 2003;21:3162–8.
- Bugova G, Janickova M, Uhliarova B, *et al*. The effect of passive smoking on bacterial colonisation of the upper airways and selected laboratory parameters in children. *Acta Otorhinolaryngol Ital* 2018;38:431–8.
- Leach AJ, Morris PS. Antibiotics for the prevention of acute and chronic suppurative otitis media in children. *Cochrane Database Syst Rev* 2006;4:CD004401.
- Chintu C, Bhat GJ, Walker AS, *et al*. Co-trimoxazole as prophylaxis against opportunistic infections in HIV-infected Zambian children (CHAP): a double-blind randomised placebo-controlled trial. *Lancet* 2004;364:1865–71.
- Hughes WT, Kuhn S, Chaudhary S, *et al*. Successful chemoprophylaxis for Pneumocystis carinii pneumonitis. *N Engl J Med* 1977;297:1419–26.
- Genel F, Kutukculer N, Prospective KN. Prospective, randomized comparison of OM-85 bv and a prophylactic antibiotic in children with recurrent infections and immunoglobulin A and/or G subclass deficiency. *Curr Ther Res Clin Exp* 2003;64:600–15.
- Rankine-Mullings AE, Owusu-Ofori S. Prophylactic antibiotics for preventing pneumococcal infection in children with sickle cell disease. *Cochrane Database Syst Rev* 2017;10:CD003427.
- Saiman L, Anstead M, Mayer-Hamblett N, *et al*. Effect of azithromycin on pulmonary function in patients with cystic fibrosis uninfected with Pseudomonas aeruginosa: a randomized controlled trial. *JAMA* 2010;303:1707–15.
- Clement A, Tamalet A, Leroux E, *et al*. Long term effects of azithromycin in patients with cystic fibrosis: a double blind, placebo controlled trial. *Thorax* 2006;61:895–902.
- Church JA, Fitzgerald F, Walker AS, *et al*. The expanding role of co-trimoxazole in developing countries. *Lancet Infect Dis* 2015;15:327–39.
- Ghilchik MW, Morris AS, Reeves DS. Immunosuppressive powers of the antibacterial agent trimethoprim. *Nature* 1970;227:393–4.
- Rozin A, Schapira D, Braun-Moscovici Y, *et al*. Cotrimoxazole treatment for rheumatoid arthritis. *Semin Arthritis Rheum* 2001;31:133–41.
- Emmanouilides CE, Lianou PE, Bassaris HP, *et al*. Trimethoprim, sulphamethoxazole, bacterial adhesion and polymorphonuclear leucocyte function. *J Antimicrob Chemother* 1990;26:803–12.
- Wolf J. Antibiotic resistance threatens the efficacy of prophylaxis. *Lancet Infect Dis* 2015;15:1368–9.
- Pettigrew MM, Johnson JK, Harris AD. The human microbiota: novel targets for hospital-acquired infections and antibiotic resistance. *Ann Epidemiol* 2016;26:342–7.
- Bedford Russell AR, Murch SH. Could peripartum antibiotics have delayed health consequences for the infant? *BJOG* 2006;113:758–65.
- Moore AM, Patel S, Forsberg KJ, *et al*. Pediatric fecal microbiota harbor diverse and novel antibiotic resistance genes. *PLoS One* 2013;8:e78822.
- Reyman M, van Houten MA, van Baarle D, *et al*. Impact of delivery mode-associated gut microbiota dynamics on health in the first year of life. *Nat Commun* 2019;10:4997.
- Sommer MOA, Dantas G. Antibiotics and the resistant microbiome. *Curr Opin Microbiol* 2011;14:556–63.
- Bogaert D, De Groot R, Hermans PWM. Streptococcus pneumoniae colonisation: the key to pneumococcal disease. *Lancet Infect Dis* 2004;4:144–54.
- Biesbroek G, Sanders EAM, Roeselers G, *et al*. Deep sequencing analyses of low density microbial communities: working at the boundary of accurate microbiota detection. *PLoS One* 2012;7:e32942.
- Grüber C, Keil T, Kulig M, *et al*. History of respiratory infections in the first 12 yr among children from a birth cohort. *Pediatr Allergy Immunol* 2008;19:505–12.
- ErasmusMC-Sophia in collaboration with the pulmonary, infectious diseases and immunology section of the Dutch Paediatric Society, Dutch College of General Practitioners (NHG) and 'Stichting kind en ziekenhuis'. (2016). Evidence-based richtlijn diagnostiek naar onderliggende aandoeningen bij kinderen met recidiverende luchtweginfecties. Available: [https://www.kinderinfectieziekten.nl/Summary of product characteristics \(SMPC\) CO-TRIMOXAZOL, medicines evaluation board \(MEB\) the Netherlands, RVG 10550 SPC 0817.23v.RS](https://www.kinderinfectieziekten.nl/Summary of product characteristics (SMPC) CO-TRIMOXAZOL, medicines evaluation board (MEB) the Netherlands, RVG 10550 SPC 0817.23v.RS).
- Prins-van Ginke AC, de Hoog MLA, Uiterwaal C, *et al*. Detecting acute otitis media symptom episodes using a mobile APP: cohort study. *JMIR Mhealth Uhealth* 2017;5:e181.
- R Core Team. *R: a language and environment for statistical computing*. Vienna, Austria: R Foundation for Statistical Computing, 2019. <https://www.R-project.org/>
- Kent DM, Paulus JK, van Klaveren D, *et al*. The predictive approaches to treatment effect heterogeneity (path) statement. *Ann Intern Med* 2020;172:35–45.
- Man WH, van Houten MA, Mérelle ME, *et al*. Bacterial and viral respiratory tract microbiota and host characteristics in children with lower respiratory tract infections: a matched case-control study. *Lancet Respir Med* 2019;7:417–26.