LISBOA
UNIVERSIDADE DE LISBOA

FACULDADE DE MEDICINA LISBOA

TRABALHO FINAL
MESTRADO INTEGRADO EM MEDICINA

Laboratório de Farmacologia Clínica e Terapêutica

A systematic review of the criteria reported in parent-delivered as-needed intermittent pharmacological treatment strategies in preschool wheezing

Carolina Ribeiro Rodrigues

Orientado por:

Ricardo Miguel Ribeiro Marques Fernandes, MD, PhD

Maio'2023

Abstract

Keywords: preschool; wheezing; strategies; treatment; asthma.

Background: Episodic wheezing and asthma are among the most frequent conditions in preschool children. Wheezing illnesses are frequent at this age and are mainly related to viral infections or other triggers, such as exercise, smoke or allergens. However, their management remains challenging, with a key role for parent-led tailored interventions that require adequate treatment plans. **Objectives:** To evaluate the completeness and quality of the reporting of parent-delivered as-needed intermittent pharmacological treatment strategies in preschool wheezing across published studies. **Search method:** MEDLINE, CENTRAL databases and ClinicalTrials.gov up until December 1st, 2022. **Selection Criteria:** Randomized controlled trials (RCTs) of preschool children (up to 6 years old) diagnosed with recurrent wheezing or asthma. **Data collection:** One reviewer extracted data on general study characteristics and on wheezing interventions according to an adapted version of the Template for Intervention Description and Replication (TIDieR) checklist, with data verification by a second reviewer. We selected a priori a set of core TIDieR items (items 3 - What Materials, 4 - What Procedures, 8 - When and How much and 9 - Tailoring). **Data analysis:** We performed a descriptive synthesis and assessed the completeness and quality of the reporting of the wheezing interventions. **Results:** Fourteen RCTs (5 875 participants) were included. Seven studies (50%) reported completely more than 50% of the core items and no studies reported completely or incompletely all of items. The item 3 (What materials) was the only one that was not correctly reported by any study. **Conclusion:** The reporting of wheezing interventions is still insufficient because the absence of core information to replicate the therapeutic strategy persists. Improving the reporting and comparability of these interventions in future studies will allow better optimization of care for children with episodic wheezing.

Resumo

Palavras-chave: pré-escolar; sibilância; estratégias; tratamento; asma.

Introdução: As patologias que causam sibilância são frequentes em crianças em idade pré-escolar, causando elevada morbilidade, bem como custos económicos e sociais importantes. Estima-se que um terço das crianças tenha tido um episódio de sibilância até aos 3 anos de idade e que quase 50% tenha um episódio de sibilância até aos 6 anos. As patologias subjacentes a um episódio de sibilância são múltiplas e quanto mais jovem for a criança, maior é o leque de diagnósticos diferenciais. Ainda assim, a sibilância recorrente está principalmente relacionada com infeções virais, mas também a múltiplos estímulos, como o exercício e a exposição ao fumo, alergénios ou ar frio. Apesar dos episódios serem separados por períodos assintomáticos, as crianças têm exacerbações graves, com uma morbilidade significativa. Consequentemente, tem havido um esforço para se definirem novas estratégias e diretrizes, de forma a se conseguir gerir melhor a sibilância episódica. Porém, os resultados são heterogéneos nos vários ensaios clínicos analisados. Assim, este trabalho é desenvolvido com o intuito de descrever as diferentes estratégias e a qualidade da sua descrição, pois um relato completo permite que as estratégias adotadas sejam replicadas e utilizadas na prática clínica.

Objetivos: Avaliar a qualidade da descrição das estratégias terapêuticas farmacológicas intermitentes administradas pelos pais na sibilância pré-escolar em estudos publicados.

Pesquisa: pesquisa sistemática na MEDLINE, CENTRAL e ClinicalTrials.gov até 1 de dezembro de 2022.

Critérios de seleção: Ensaios clínicos aleatorizados de crianças em idade pré-escolar (até 6 anos de idade) diagnosticadas com sibilância recorrente ou asma, independentemente do fenótipo.

Colheita de dados: A seleção de estudos a incluir envolveu uma fase de *screenning* e outra de *eligibility*. Um revisor extraiu as características conforme a versão adaptada da *TIDieR Checklist,* com verificação dos dados pelo segundo revisor.

Análise de dados: Realizamos uma síntese descritiva, avaliando a descrição e a qualidade do relato das intervenções em sibilância. Devido à diversidade metodológica dos estudos incluídos, não foi efetuada uma meta-análise. Os itens gerais e subitens de 1.) a 12.) foram classificados como completos, incompletos ou ausentes. Para os subitens dos itens 3.), 4.), 8.) e 9.), os dados extraídos correspondentes a cada subitem foram analisados e pontuados como completos, incompletos, ausentes ou não aplicável. Esta classificação foi realizada por um autor e depois verificada por um segundo autor. Após o anterior, de forma a calibrar a classificação, analisou-se o mesmo item/subitem dos 14 artigos ao mesmo tempo e reajustou-se. Os resultados foram depois apresentados graficamente para resumir a extensão de descrição da intervenção.

Resultados: Quatorze ensaios foram incluídos (total de 5.875 participantes). Treze estudos (92.9%) incluíram crianças que apresentavam sibilância recorrente e sintomas de asma durante infeções anteriores do trato respiratório superior e infeções das vias aéreas e um estudo (7.1%) concentrou-se apenas em episódios de sibilância moderada a grave. Sete estudos (50%) relataram corretamente mais de 50% dos itens principais e nenhum estudo relatou corretamente ou incorretamente todos esses itens. O item 3 (*What materials*) foi o único que não foi relatado corretamente em nenhum dos estudos.

Discussão: Teoricamente não existem critérios que nos permitem classificar um artigo relativamente à qualidade do seu *reporting.* Assim, essa avaliação recaiu sobre a nossa análise pessoal e, observando a tabela 3, e considerando os 14 estudos incluídos, apenas um estudo (Chinedu N. et al (2015)) teve proporção superior a 70% duma descrição completa dos vários itens da *TIDieR checklist*.

Relativamente ao item 1 (*Brief Name*) e item 2 (*Why)*, a maioria dos estudos relatou completamente, 92.9% e 100% respetivamente. No item 3 (*What materials*), 50% dos estudos não nos forneceu a marca do fármaco e/ou dispositivo. Relativamente aos dispositivos, 14.3% não referiram o tipo de dispositivo utilizado para a administração do medicamento. Quanto ao item 4 (*What procedures)*, todos os estudos referiram o fármaco específico utilizado e respetivas co-intervenções. Sobre o item 5 (*Who provided)*, consideramos incompletos os artigos Ebisawa, M. et al (2015) e Valovirta E. et al (2011) porque, comparativamente aos outros, não mencionaram diretamente que a medicação era administrada pelos pais/responsáveis, apesar de aquando da leitura

dos artigos se conseguir presumir que era realizada por eles. Sobre o item 6 (*How)*, por comparação, consideramos que a descrição nos artigos Ebisawa, M. et al (2015), Bisgaard H. et al (2006), Valovirta E. et al (2011), Kotaniemi-Syrjänen A. et al (2022) não era tão clara, ainda assim em todos eles descreveram quais indivíduos estavam envolvidos e como o tratamento foi administrado. Em relação ao item 7 (*Where)*, em todos os artigos, ao ler e interpretar a metodologia, foi possível entender que seria um tratamento administrado em ambulatório; mas, isso nem sempre foi descrito no texto completo do artigo, o que nos levou a classificar como ausente em 2 artigos (Valovirta E. et al (2011) e Kotaniemi-Syrjänen A. et al (2022)) e incompleto em 5 outros (Oommen A. et al (2003), Li L. et al (2022), Francine M. et al (2009), Svedmyr J. et al (1999) e Papi A. et al (2009)). Sobre o item 8 (*When and How much)*, a maioria dos estudos falhou em descrever adequadamente o momento em que os pais/responsáveis devem iniciar o tratamento (85.7%), ou seja, mencionaram que se deveria começar no "início dos sintomas ou sinais de uma doença das vias respiratórias" mas, considerando que seria administrado em ambulatório pelos pais/responsáveis, seria importante aprimorar a descrição com uma lista de sinais/sintomas para facilitar a objetivação do início da terapêutica, algo presente no estudo Ebisawa, M. et al (2015). Quanto à dosagem da intervenção principal, todos os estudos a mencionaram; no entanto, isso nem sempre aconteceu para as co-intervenções. No item 9.), os resultados foram muito heterogéneos. Sobre o método de administração, 71.4% dos artigos não descreveram o método, algo que é essencial para garantir uma boa qualidade da administração. Todos os artigos mencionaram a duração do tratamento ativo. O item 10 (*Modification)* é o item mais frequentemente ausente (35.7%) ou incompleto (50%), pois a maioria dos artigos não mencionaram o protocolo de forma alguma, nem referiram se se tinham desviado dele ou se tinham cumprido integralmente o protocolo. No item 11 (*How well planned*) classificámos como completo se os seguintes critérios fossem cumpridos: critérios e método utilizados pelos pais/responsáveis para relatar os sintomas, complicações e medicamentos utilizados; menção da explicação dada ao responsável/pai sobre a técnica/método utilizado para administrar determinado medicamento e respetiva revisão; e check-ups periódicos das crianças e familiares por meio de consultas ou telefonemas. Assim, apesar de ser um item importante, a maioria dos estudos não correspondeu (78.6%). Por fim, relativamente ao item 12 (*How well*

current), todos os artigos investigaram a adesão à terapêutica e respetiva fase em que deixaram o ensaio. A presentação dos dados realizou-se sob a forma de diagrama ou no texto integral.

Conclusão: Como pudemos verificar nos artigos incluídos no nosso projeto, tem havido um grande esforço para estabelecer certas diretrizes e descrever algumas estratégias que permitam aos pais controlar melhor a doença. Ainda assim, a maioria dos autores não descreveu completamente todos os itens adaptados da *TIDieR Checklist*, algo que permitiria a outros replicar o mesmo tratamento e métodos utilizados aquando da administração. O relato das intervenções é ainda insuficiente por persistir a ausência de dados essenciais para replicar a estratégia terapêutica. Reforçamos que, ao melhorar o relato dessas intervenções em estudos futuros, teremos evidência de melhor qualidade e, portanto, uma maior otimização do controlo de sibilância episódica em pré-escolares.

Table of Contents

Introduction

Background

Wheezing illnesses are frequent occurrences in preschool children and cause high morbidity and important socioeconomic costs. It is estimated that one-third of children experience a wheezing episode by 3 years of age, and almost 50% experience a wheezing episode by the age of 6 (P. L. P. Brand et al., 2008; Valovirta et al., 2011). This high prevalence is due to several characteristics of this age group, namely the small caliber of the airways and their high complacency, as well as the size of the lymphoid tissue (Waldeyer's lymphatic ring). Pathologies underlying a wheezing episode are multiple and the younger the child, the greater the range of differential diagnosis (Celedón et al., 2002). Even so, recurrent wheezing is mainly related to viral infections and to multiple triggers such as exercise and exposure to smoke, allergens or cold air (Bacharier et al., 2008; P. L. Brand et al., 1999; P. L. P. Brand et al., 2008; Kuehni et al., 2007; Papi et al., 2009; Saglani et al., 2007). Recurrent wheezing is a heterogeneous entity whose long-term prognosis ranges from apparent complete recovery, in most cases, to diagnosis of asthma or irreversible impairment of lung function (Ferreira C. et al., 2020).

According to the literature, several phenotypes of preschool wheezing illnesses have been described, which are associated with different prognoses. However, there is no consensus regarding their definition, since they may overlap and change over time, thus having little clinical application. This makes diagnosis, assessment and management more difficult (P. L. P. Brand et al., 2008; Papi et al., 2009; Valovirta et al., 2011).

There are a variety of terms used to describe this intermittent condition, such as “infrequent episodic asthma,” “transient wheeze,” and “viral wheeze.” For the purposes of this review, the phenotype is referred to as “episodic wheezing.” Episodic wheezing is the most frequent phenotype in preschool children since it is related mostly to lower respiratory tract illnesses. Even though these episodes are intermittent and separated by extended asymptomatic periods, the exacerbations are severe and with high morbidity (Bacharier et al., 2008; Silverman, 1993). Rates for wheezing-related emergency department visits and hospitalizations are the highest in children younger than 5 years old, evidencing the difficulty in treating wheezing illness to prevent the

occurrence of these episodes. (Bacharier et al., 2008; Bloomberg et al., 2003; Getahun et al., 2005; Moorman JE, Akinbami LJ, Bailey CM, 2010).

There has been a great effort over the years to try and establish strategies and guidelines to manage episodic wheezing in preschool children. Meta-analyses in pediatric asthma have not shown consistent benefits of medication traditionally effective in persistent asthma, including inhaled corticosteroids (Everard et al., 2005; McKean & Ducharme, 2000; Vuillermin et al., 2007). In some studies, the use of regular inhaled glucocorticoids has shown a reduction of symptoms (Hans Bisgaard et al., 1999; De Blic et al., 1996; Guilbert et al., 2004), but this has not been the case in other studies (Barrueto et al., 2002; Hofhuis et al., 2005). Currently, intermittent high-dose of inhaled glucocorticoids in association with short-acting β2-agonists as-needed is the recommended therapy for episodic wheezing (Expert Panel Working Group of the National Heart, Lung et al., 2020; Global Initiative for Asthma, 2022). And, if needed, it can be escalated to regular therapy with inhaled or oral glucocorticoids for moderate to severe exacerbations ("And Prevention Program Expert Panel Report 3 : Guidelines for the Diagnosis and Management of Asthma Full Report 2007," 2007; P. L. P. Brand et al., 2008; Pedersen et al., 2011).

An alternative medication frequently used in the management of asthma is montelukast, which has been suggested in three studies as being effective in the management of intermittent wheezing in children when given daily (H Bisgaard et al., 2005) or on an episode-driven basis (Bacharier et al., 2008; Robertson et al., 2007). However, in another study, neither regimen was able to reduce the number of asthma episodes culminating in attacks in children with episodic wheezing, although both regimens had some positive effects on symptoms (Valovirta et al., 2011).

Some trials have also been carried out in order to evaluate the effectiveness of anticholinergics. While with Ipratropium Bromide the results have been inconclusive (Memon et al., 2016; Xu et al., 2021), the same did not happen with Tiotropium Bromide. With the latter, a trial was carried out last year that showed promise, however, more research is needed (Kotaniemi-Syrjänen et al., 2022).

A further proposed intervention was the use of antibiotics to improve symptoms (Stokholm et al., 2016), considering that the airway bacteria and respiratory viruses are equally closely associated with episodes of asthma-like symptoms in the first 3 years of

life (Hans Bisgaard et al., 2010), questioning the previous idea that asthma-like symptoms in this age group are largely virally induced (Bardin et al., 1992; Khetsuriani et al., 2007; Kusel et al., 2006). However, the results have been heterogeneous and, overall, the data collected so far have not confirmed the safety of antibiotics in the treatment of preschool wheezing exacerbations (Mandhane et al., 2017; Schwerk et al., 2011; Valovirta et al., 2009).

An additional issue complicates the diversity in the evidence base for these different medications and treatment approaches. Management of episodic wheezing depends on selecting specific triggers to initiate, adjust, and terminate treatment, which are reflected in treatment action plans. Differences between details of these plans may influence study results, and hamper the applicability of these plans, particularly when deployed by parents. We committed to writing the present review to describe the different strategies and the quality of their reporting. It is essential that the reporting is complete in order to be replicated and used in clinical practice. The validated framework and checklist Template for Interventions Description and Replication (TIDieR) allows the assessment of the completeness of reporting of interventions in published studies (Hoffmann et al., 2014). So far, no studies have evaluated the quality of the reporting of intermittent wheezing interventions in preschool children using the TIDieR checklist.

Objectives

The main purposes of this methodological review of randomized controlled trials on preschool wheezing were:

- To identify and describe the reported criteria used to add/increase the parent-delivered as-needed intermittent pharmacological treatment strategies;
- To evaluate the completeness and quality of the reporting of intermittent pharmacological treatment strategies.

Methods

Methodology was designed based on previous studies focused on assessing the quality of the reporting of different interventions,by adapting our objectives (Akers; J, 2009; Hoffmann et al., 2015; Tew et al., 2016; Yamato et al., 2016). The manuscript is reported according to the PRISMA guidance (Akers; J, 2009; Hoffmann et al., 2014).

Eligibility Criteria

The studies considered in our work were selected according to the following criteria:

Study Design

We included randomized controlled trials (RCTs). Observational studies, including cohort studies, case-control and case series, cross-sectional studies, and case reports were not included.

Participants

We included studies recruiting exclusively preschool children (up to 6 years old) diagnosed with recurrent wheezing or asthma, regardless of the phenotype. Studies addressing older age groups and adults were excluded unless data on preschool children was reported separately. Additionally, we also excluded studies on bronchiolitis as first wheezing episode.

Interventions and Comparators

We included comparative randomized controlled trials testing parent-delivered as-needed intermittent pharmacological treatment strategies, except for SABA-only on-demand treatment. We excluded studies in which children were on long-term maintenance therapy at enrollment. Included trials needed to have at least one comparator group, regardless of the type of comparator.

Outcomes

In this review we considered the technical features of wheezing interventions, the completeness of their reporting in each study and associated triggers. Therefore, the outcomes considered were:

1) A description of the wheezing interventions in selected published studies, according to the checklist Template for Intervention Description and Replication, and its completion (TIDieR) (Bush et al., 2014);

2) The quality of the reporting of wheezing interventions.

Setting

We focused on studies whose patients were followed in primary care and specialty care and initiated treatment in outpatient care. We excluded hospitalized patients as well as in the intensive care unit.

Language and timing of publication

We included studies published until December 1st 2022, which were written in English or Portuguese. No restrictions in length of treatment or follow-up were applied.

Information sources

We developed a search strategy using medical subject headings (MeSH) and text words related to Pediatrics, target age group, wheezing, wheezing therapy and strategies. We searched in electronic databases, including MEDLINE (through Pubmed interface), ClinicalTrials.gov (through API interface) and Cochrane Central Register of Controlled Trials (through Wiley interface).

Whenever possible, our research was complemented by consulting the reference lists, study protocols, and study authors to determine whether additional information about the intervention had been published in other databases. The search was limited to human subjects.

Search Strategy

We performed a systematic search in MEDLINE, CENTRAL databases and ClinicalTrials.gov up to December 1st 2022, according to the search strategy previously mentioned. This was performed by one researcher (CR) with the Health Sciences Librarian's support. Our MEDLINE and CENTRAL search strategies are reported in Appendix 1 and Appendix 2. Regarding ClinicalTrials.gov, it was only used to keep up with the clinical trials that were occurring.

Study Records

Data management before screening

After the literature search was made, on both MEDLINE and CENTRAL, we downloaded all the papers using the CSV format. The files were then transferred to Mendeley, where we could access all the titles and abstracts. This data was also uploaded to a Google Sheets.

Piloting

Before the formal screening process and data extraction, RM and CR performed a pilot study (n=50) in order to refine the implementation of eligibility criteria, extraction form, and their processes.

Selection Process (Screening)

The screening process was divided in two phases. RM and CR proceeded to the First Screening, where they analyzed the titles and abstracts separately. All studies were classified as “Included”, “Excluded” or “Unclear”. This was followed by a full-text analysis of the “Unclear” and “Included” citations. The goal was to decide on their final eligibility (Second Screening).

At the end of each stage, both researchers discussed their results and resolved their discrepancies, considering the eligibility criteria, through oral consensus. Additionally, we noted the reasons why each study was excluded on both stages. Review authors were not blinded to the study titles, authors or institutions.

Collection Process (Data extraction)

The following extraction process was carried out by CR into a specific Google Sheets, with another (RF) verification according to the items of TIDieR checklist, listed below in “Data items”. This checklist was previously developed by both researchers and adapted for wheezing.

Data Items

First, we extracted general paper and study characteristics from the included articles, including the article title, authors, journal/magazine where it was first published, year of publication, language, study design, setting, aim of study, number of arms, the randomization method if applicable, blinding if applicable, inclusion and exclusion criteria, definition of the clinical condition studied, number of patients included, active and control interventions and co-interventions.

We then extracted the data according to the TIDieR items. TIDieR (Template for Intervention Description and Replication) consists of a 12 items checklist that evaluates the completeness of intervention reporting. Items 1 and 2 cover the name and the rationale of the intervention. Items 3 to 9 pose several questions - what (materials and procedures), who (provided), how, where, when and how much and tailoring. The answers to these questions so far allow researchers and clinicians to access detailed information about the procedures and the context, since it allows its replicability. Items 10 to 12 cover the modifications along the study and the fidelity (actual and to the planned intervention).

Considering that our research focused on intervention strategies to parents and preschool children for adding/increasing wheezing medication and its respective triggers, we chose to adapt TIDieR, which subdivides items 3 (What Materials), 4 (What Procedures), 8 (When and How much) and 9 (Tailoring) into subitems.

- **Item 3 (What Materials)** was subdivided in:
    - 3.a) **Brand(s) of the device(s) and drug(s)** used to provide the medication;
    - 3.b) **Device(s)** (used to provide medication, specifying the model as complete as possible);
    - 3.c) **Physical, informational materials or training** provided to parents or patients;
    - 3.d) **The recommended source of information** used to clarify doubts about the intervention.

- **Item 4 (What - Procedures)** was subdivided in:
    - 4.a) **Main Intervention performed** (reporting the medication used);
    - 4.b) **Co-interventions performed** (if any therapeutic co-interventions was performed, including pharmacological and non-pharmacological interventions and intravenous hydration).

- **Item 8 (When and How Much)** was subdivided in:
    - 8.a) **When was the medication added/increased?** (clinical and/or analytical criteria that determined the beginning of the intervention);
    - 8.b) **What was the dosage of the medication introduced/added?;**
    - 8.c) **Co-interventions** (scheduling and doses of the therapeutic co-interventions, the latter in case of pharmacological co-interventions, hydration or feeding).

- **Item 9 (Tailoring)** was subdivided in:
    - 9.a) **Criteria used to start/add medication** (clinical and/or analytical criteria used to start medication);
    - 9.b) **Medication administration method** (process and method for adding or increasing medication);
    - 9.c) **Duration of the treatment** (how long was the patient submitted to the treatment (active and control)).

These subitems were intended to assess in detail the main components of the intervention strategies to parents and preschool children for adding/increasing wheezing medication.

The general items from 1.) to 12.) were classified as complete, incomplete, or absent. For subitems within items 3.), 4.), 8.) and 9.), the extracted data corresponding to each subitem was analyzed and scored as complete, incomplete, or absent. If all the subitems of an item were reported as "complete", then the general item was considered: complete. If some but not all the subitems of an item were reported as "complete", then the general item was considered: incomplete. If all the subitems of an item were absent, then the general item was considered: absent.

The process of scoring each subitem and item as complete, incomplete, or absent was performed by one author (CR) and then checked by a second author (RF). Disagreements were resolved through oral discussion.

Having finished ranking all of the items and sub-items, further calibration of the ranking was done by choosing an example of each item considered complete . The examples are listed in Table 1.

Outcomes

The outcomes of this systematic review were:

1) A description of the wheezing interventions and its criteria to add/increase the medication in the included studies, according to the checklist Template for Intervention Description and Replication (TIDieR) (Bush et al., 2014);

2) The quality of the reporting of wheezing interventions.

We assessed:

1) The proportion of interventions with complete reporting of each of the twelve TIDieR items, in primary papers, available study protocols and references with readily available details about the interventions;

2) The proportion of studies that completely reported all the items 3.) to 9.), which were considered core items for study replicability;

3) The proportion of interventions with complete reporting of each of the sub-items of items 3.), 4.), 8.) and 9.);

4) The TIDieR items (3.) to 9.)) more often completely described in the reporting of intervention strategies to parents and preschool children;

5) The TIDieR items (3.) to 9.)) more often absent/incompletely described in the reporting of intervention strategies to parents and preschool children;

6) The quality of the reporting of intervention strategies to parents and preschool children for wheezing medication.

Risk of Bias

We did not consider our own studies' outcomes, but rather the descriptive intervention strategies reported as being provided to parents and preschool children for adding/increasing wheezing medication and the results obtained on their reporting. Therefore, we did not perform any risk of bias assessment .

Data Synthesis

We performed a descriptive synthesis of all included studies (Table 2) and a quantitative analysis of the review's outcomes, using descriptive statistics methods.

The initial synthesis consisted of a descriptive summary of the included studies using tables. In these tables, the last column mentioned the intervention descriptive completeness of each study, as a percentage of TIDieR items that were completely described.

Results were presented graphically to summarize the completeness of the intervention's description, according to TIDieR checklist. Each TIDieR item was rated as "complete" or "incomplete/absent" and then perform a summary for each item across included studies as a percentage of studies with a "complete" description of that item.

Results

With our search strategy, we were able to select 914 reports which, after eliminating the duplicates, ended up being 652 papers.

During the first screening, we came across 11 clinical reports from ClinicalTrials.gov and CENTRAL. Six of these were excluded because the publications associated with the reports had already been included at this stage. Four of them had publications associated that were not present in our database, therefore we added those sixteen papers manually to our second screening. One of the reports had no connected publications. The previous was performed by CR.

Figure 1 presents our study's flow diagram through the different stages of our systematic review. (Moher et al., 2009) The full list of the included studies is presented in Table 2.

Description of included studies

A detailed description of the most relevant characteristics of our included studies is presented in Table 2. On our study analysis we included 14 studies, with a total of 5 875 participants.

Considering the criteria of inclusion, 13 studies (92.9%) included children who had recurrent wheezing and asthma symptoms during previous upper respiratory tract infections and airway infections. One study (7.1%) focused only on moderate-to-severe wheezing episodes, and so children were required to have experienced urgent/emergent department visits, need for oral corticosteroids and/or hospitalization.

In terms of intervention, there were 8 studies (57.1%) in which the active group was only administered with glucocorticoids (GCs), 3 studies (21.4%) with leukotriene receptor antagonists (LTRAs) only, 1 with both GCs and LTRAs (7.1%), 1 study with Long-acting-muscarinic antagonists (LAMA) and GCs (7.1%) and 1 study with only antibiotics (ATBs) (7.1%). Among the included RCTs, 12 studies (85.7%) used a placebo as a control. Considering concomitant medication, in both active/control groups, 13 of all studies (92.9%) had a bronchodilator as needed prescribed.

Studies were restricted to an outpatient setting (100%), even though this was not always clear in the paper.

Description of reporting TIDieR items across included studies

Among the 14 papers, 7 studies (50%) reported correctly more than 50% of the items 3.) to 9.). No studies reported correctly or incorrectly all of those items.

The items that were more consistently reported were items 1 (Brief name) (92.9%), 2 (Why) (100%), 4 (What procedures) (100%), item 5 (Who provided) (85.7%) and 12 (How well) (85.7%). However, if we only consider the items 3.) to 9.), the items 4 (What procedures), 5 (Who provided) and 6 (How) stand out for having respectively 100%, 85.7% and 71.4% of complete reporting. The remaining items 3.), 7.), 8.) and 9.) were completely reported in proportions that varied between 0% for item 3 (What materials) and 50% for item 7 (Where). All of the previous is presented in figure 2.

Core items 3.), 4.), 8.) and 9.), which were adapted from the TIDieR checklist, are presented in figures 3, 4, 5 and 6 respectively.

For item 3 (What materials), the subitem more frequently absent or incorrectly reported was 3.d) (The recommended source of information) in 85.7% of studies. On the other hand, the sub-item more often correctly reported was 3.b) (Device(s)) in 57.1% of all papers. About 3.a) (Brand(s)), it is important to mention that it was only provided in half of the studies and that the training to the parents/guardians (3.c)) was poorly described (incompletely reported – 28.6% and absent – 50%) (figure 3).

Concerning item 4 (What procedures), most studies were quite complete in this regard. All studies fully reported sub-item 4.a) (Main intervention performed) and sub-item 4.b) (Co-interventions performed) (100%) (figure 4).

Item 8 (When and how much), the sub-item 8.a) (When was the medication added/increased) was poorly reported, with only 2 studies with complete information (14.3%). However, the sub-item 8.b) (What was the dosage of the medication introduced/increased) was completely reported in all studies (100%). Finally, half of the studies (50%) completely reported the sub-item 8.c) (Co-interventions) (figure 5).

Regarding item 9 (Tailoring), the most correctly reported sub-item was 9.c) (Duration of the active treatment), in 100% of the studies. The most frequently absent or incomplete was 9.b) (Medication administration method), reported in 12 studies

(85.7%). For sub-item 9.a) (Criteria used to start/add medication), 10 studies (71.4%) reported completely (figure 6).

The reporting of all items and sub-items for each included study is presented in table 3 with a color code, in order to facilitate the assessment of the results.

Discussion

In this systematic review we aimed to identify and describe the reported criteria used for initiating/stepping up the treatment and evaluate the completeness and quality of the reporting of intermittent pharmacological treatment strategies. We used a validated framework, the TIDieR checklist, in order to evaluate the completeness of the reporting of the interventions and adapted some core items (3.) to 9.)) so that they would better meet the objective of our project. While there is clear cut-off to consider if a certain paper has a good reporting quality of the intervention's description, only one study had a proportion superior to 70% of complete item's reporting. Therefore, although most studies described the main interventions, the description of the methodology of this intervention in certain items/sub-items was inadequate in most papers.

A more detailed analysis and discussion of the results obtained from the classification of the various papers on their items/sub-items follows. Regarding item 1 (Brief Name), almost all papers were classified as complete given that the population, intervention and context were mostly reported. As for item 2 (Why), all studies described the current context regarding the management of wheezing in the age group in question, and the rationale behind conducting the study considered. On item 5 (Who provided), two papers, Ebisawa, M. et al (2015) and Valovirta E. et al (2011), were considered incomplete as they did not mention directly in the full text that the treatment was administered by the parents. Regarding item 6 (How) the reporting in 4 papers was incomplete because the description was not as clear as the others (Ebisawa, M. et al (2015), Bisgaard H. et al (2006), Valovirta E. et al (2011), Kotaniemi-Syrjänen A. et al (2022)). However, all described which individuals were involved and how the treatment was administered. Regarding item 7 (Where), in every paper, when reading and interpreting the methodology, it was possible to understand that it would be a treatment administered in an outpatient setting; but, this was not always described in the full text of the paper. Item 10 (Modification) is the item most frequently missing (35.7%) or incomplete (50%). Most papers did not mention the protocol at all, nor to say that they had deviated from it nor to mention they had fully complied with the protocol. In item 11 (How well planned) was only considered complete if the following criteria were met: criteria and method used by the parents/guardian to report the symptoms, complications and medication used; mention of the explanation given to the

guardian/parent about the technique/method used to administer a specific medication and respective review; and periodic check-ups on the children and family through consultations or phone calls. Thus, despite being a very important item, most of the studies did not meet the needs and 78.6% of the papers included did not mention these. The last general item 12 (How well current), all the papers investigated adherence to therapy and up to what stage of the study the individual was involved. This data was described either in the full text or in the form of a diagram.

Adapted items from the TIDieR checklist, 3.) to 9.) are most relevant for the replication of the described interventions and results. For item 3 (What materials), we would have expected that the brand of the devices and drugs in the various studies, as well as the model of the respective devices, would be provided, since these are essential elements for therapeutic administration; however, they were not fully reported. In terms of brands, 50% of the studies did not provide the brand of the drug and/or device. Regarding devices, 14.3% failed to mention the type of device used for the administration of the drug. On the other two sub-items, although not essential to implement the therapy, they would still be relevant to increase the fidelity of the results, either by training parents/guardians on how to administer the therapy or by providing them with available and reliable literature that they could access at home.

On item 4.) (What procedures), as anticipated, every study referred the specific drug used as the main intervention and respective co-interventions performed.

Considering the item 8 (When and how much), most studies failed to adequately describe the moment when parents/guardians should start the treatment (85.7%). Most of them mentioned it should start at the “onset of symptoms or signs of a respiratory tract illness” but, considering this is in an outpatient environment, it I would be important to better describe on the paper if a list of signs and symptoms were provided to the parents/guardians and which were they, in order for them to objectively detect and use it to know the exact moment. As an example provided in one study: "(...) when the participating children had symptoms of a common cold (runny nose, cough, and/or wheezing)" present in Ebisawa, M. et al (2015). In terms of dosage of the main intervention, every study mentioned it. About the co-interventions, which medication was given was always referred, but half of the studies failed to mention its dosage, which could affect the improvement and control of wheezing.

Finally, on item 9.), the 3 sub-items were very heterogeneous. In terms of the criteria used to start/add medication, most papers completely reported this sub-item. The four papers that failed to completely report this sub-item included children who had episodes of wheezing, but did not correctly specify how many previous episodes, hospitalizations, previous medications, among others. About the medication administration method, almost every paper (71.4%) did not describe the method. This may have been explained in consultation to the parents/guardians, however, how this was performed is not reported in the full text. It is important to mention that an inadequate administration method is one of the main reasons why the medication does not always lead to the wanted effect, so it is essential to explain to the parents, practice with them and review the method in periodic consultations (Amirav & Newhouse, 2001; El Rifai & Rizk, 2019; Lavorini & Usmani, 2013). Every paper mentioned the duration of the active treatment.

For the purpose of reproducing, aggregation, and implementation of clinical results as well as in the ethics of research development, it becomes essential to report adequately and completely the specific interventions, something considered a core issue in medical research (Hoffmann et al., 2014). Therefore, in recent years there has been an effort to develop checklists and guidelines that would allow a good quality reporting of various types of interventions across study reports. These included the Consolidated Standards of Reporting Trials 2010 statement (CONSORT 2010) (Warde, 2010), Standard Protocol Items: Recommendations for Interventional Trials 2013 (SPIRIT 2013)(Chan et al., 2016) and more recently the Template for Interventions Description and Replication checklist (TIDieR)(Hoffmann et al., 2014). Before the development of the latter checklist, there was evidence that the reporting of the interventions was related to the lack of awareness of the researchers to the core elements needed to replicate and that this lack of reporting was only detected and fixed by peer reviewers and editor after publication (Hoffmann et al., 2014; Schroter et al., 2012). Even though there has been an effort to create good quality checklists and to provide guidance to the researchers, the reporting still does not reach the required standards, as shown in the present project as well as in others (Duff et al., 2010; Schroter et al., 2012; Yu et al., 2018). We believe this may relate to publication-related limitations, such as

unawareness or lack of implementation by editors and peer reviewers (Schroter et al., 2012) or restrictions in word counts (Abell et al., 2015; Conn et al., 2008).

As mentioned, in order to replicate certain interventions, it becomes essential to correctly describe every aspect tested. However, a detailed reporting of the properties and certain interventions may be difficult, even with the TIDieR framework and adaptation of its core items/sub-items. This might explain the absence and incompletion of certain item/sub-items. However, it is important to highlight that there is some information that is essential and that was not reported in any paper, such as brands of medication/device; more specifically when to start/add medication; dosage of co-interventions and administration method.

Study limitations

When establishing the inclusion and exclusion criteria for the population to be considered in our project, we established that the children should be "up to 6 years old". Some studies included 5-year-old children or less and others with 6 years old or less. Therefore, we consider this grey area of 5-6 years old as a limitation of our study.

Additionally, we did not request the protocols via e-mail to the researchers of each paper. Hence, some of the information that was incomplete/absent might have been present in these documents.

The main limitation of our study is related to our adapted version of the TIDieR checklist. As already mentioned, in order to capture que complexity and analyze every aspect of this intervention, we had to adapt some items/sub-items. This adaptation was made by the review authors, without consultation of a larger panel of experts. Thus, we might have made some mistakes in the core elements, such as being too strict or too flexible, which might have influenced the results.

Conclusions

It is essential to study the different strategies and types of treatment in order to decrease the number of exacerbations and progression to persistent wheezing. As we could see from the papers included in our project, there has been a great effort to establish certain guidelines and describe some strategies that would allow parents to better control the disease. Nevertheless, most authors did not describe completely all the adapted items from the TIDieR Checklist, which would allow others to replicate the exact same treatment and the methods used to administer it.

Considering the main intervention and co-interventions, all of the papers described the medications used and most of the dosages. The data that lacked the most, and whose absence has the greatest impact on the replication of the studies conducted and its results, are the description of specific training to the guardians, the criteria used to start/add the medication and how to administer the inhaled or oral medication. Other data such as other sources of information for the guardians and device/medication's brands were also frequently missing, however, its absence, presumably, would not have such a bit impact.

In order for the reporting to be more complete, it is essential to encourage researchers, peer reviewers, and editors to get involved and make sure all requirements, items and sub-items are described by using the validated TIDieR framework correctly and completely. By having stronger and better-quality evidence in this field, this may allow the establishment of specific guidelines and strategies to approach wheezing in preschool children.

Contribution of authors

(RF: Ricardo Fernandes; CR: Carolina Rodrigues; SH: Susana Henriques)

RM is the guarantor. Both RM and CR contributed to the conception and design of the study and developed its search strategy. SH provided support with the design and application of the search strategy on the various platforms. RM and CR contributed to the analysis and interpretation of the data. Then, RM and CR performed a critical revision and RM gave the final approval of the version to be presented.

Reference List

Abell, B., Glasziou, P., & Hoffmann, T. (2015). Reporting and Replicating Trials of Exercise-Based Cardiac Rehabilitation: Do We Know What the Researchers Actually Did? *Circulation: Cardiovascular Quality and Outcomes*, *8*(2), 187–194. https://doi.org/10.1161/CIRCOUTCOMES.114.001381

Akers; J. (2009). Systematic reviews. In *Systematic reviews* (3rd ed.). University of York.

Amirav, I., & Newhouse, M. T. (2001). Aerosol therapy with valved holding chambers in young children: Importance of the facemask seal. *Pediatrics*, *108*(2 II), 389–394. https://doi.org/10.1542/peds.108.2.389

and Prevention Program Expert Panel Report 3 : Guidelines for the Diagnosis and Management of Asthma Full Report 2007. (2007). *Children*.

Bacharier, L. B., Phillips, B. R., Zeiger, R. S., Szefler, S. J., Martinez, F. D., Lemanske, R. F., Sorkness, C. A., Bloomberg, G. R., Morgan, W. J., Paul, I. M., & al., et. (2008). Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. *Journal of Allergy and Clinical Immunology*, *122*(6 CC-Airways), 1127-1135.e8. https://doi.org/10.1016/j.jaci.2008.09.029

Bardin, P. G., Johnston, S. L., & Pattemore, P. K. (1992). Viruses as precipitants of asthma symptoms. II. Physiology and mechanisms. *Clinical and Experimental Allergy*, *22*(9), 809–822. https://doi.org/10.1111/j.1365-2222.1992.tb02825.x

Barrueto, L., Mallol, J., & Figueroa, L. (2002). Beclomethasone dipropionate and salbutamol by metered dose inhaler in infants and small children with recurrent wheezing. *Pediatric Pulmonology*, *34*(1), 52–57. https://doi.org/10.1002/ppul.10115

Bisgaard, H, Hermansen, M. N., Loland, L., Halkjaer, L. B., & Buchvald, F. (2006). Intermittent inhaled corticosteroids in infants with episodic wheezing. *New England Journal of Medicine*, *354*(19 CC-Airways CC-Musculoskeletal), 1998-2005. https://doi.org/10.1056/NEJMoa054692

Bisgaard, H, Zielen, S., Garcia-Garcia, M. L., Johnston, S. L., Gilles, L., Menten, J., Tozzi, C. A., & Polos, P. (2005). Montelukast reduces asthma exacerbations in 2- to 5-year-old children with intermittent asthma. *American Journal of Respiratory and Critical Care Medicine*, *171*(4 CC-Airways CC-Child Health), 315-322. https://doi.org/10.1164/rccm.200407-894OC

Bisgaard, Hans, Gillies, J., Groenewald, M., & Maden, C. (1999). The effect of inhaled fluticasone propionate in the treatment of young asthmatic children: A dose comparison study. *American Journal of Respiratory and Critical Care Medicine*, *160*(1), 126–131. https://doi.org/10.1164/ajrccm.160.1.9811024

Bisgaard, Hans, Hermansen, M. N., Bønnelykke, K., Stokholm, J., Baty, F., Skytt, N. L., Aniscenko, J., Kebadze, T., & Johnston, S. L. (2010). Association of bacteria and viruses with wheezy episodes in young children: Prospective birth cohort study. *BMJ (Online)*, *341*(7776), 770. https://doi.org/10.1136/bmj.c4978

Bloomberg, G. R., Trinkaus, K. M., Fisher, E. B., Musick, J. R., & Strunk, R. C. (2003). Hospital readmissions for childhood asthma: A 10-year metropolitan study. *American Journal of Respiratory and Critical Care Medicine*, *167*(8), 1068–1076. https://doi.org/10.1164/rccm.2201015

Brand, P. L., Duiverman, E. J., Waalkens, H. J., van Essen-Zandvliet, E. E., & Kerrebijn, K. F. (1999). Peak flow variation in childhood asthma: correlation with symptoms, airways obstruction, and hyperresponsiveness during long-term treatment with inhaled corticosteroids. Dutch CNSLD Study Group. *Thorax*, *54*(2 CC-HS-HANDSRCH CC-Airways CC-Child Health), 103-107. https://doi.org/10.1136/thx.54.2.103

Brand, P. L. P., Baraldi, E., Bisgaard, H., Boner, A. L., Castro-Rodriguez, J. A., Custovic, A., De Blic, J., De Jongste, J. C., Eber, E., Everard, M. L., Frey, U., Gappa, M., Garcia-Marcos, L., Grigg, J., Lenney, W., Le Souëf, P., McKenzie, S., Merkus, P. J. F. M., Midulla, F., … Bush, A. (2008). Definition, assessment and treatment of wheezing disorders in preschool children: An evidence-based approach. *European Respiratory*

Journal, *32*(4), 1096–1110. https://doi.org/10.1183/09031936.00002108
Bush, A., Grigg, J., & Saglani, S. (2014). Managing wheeze in preschool children. *BMJ (Online)*, *348*(February), 1–7. https://doi.org/10.1136/bmj.g15
Celedón, J. C., Litonjua, A. A., Ryan, L., Weiss, S. T., & Gold, D. R. (2002). Bottle feeding in the bed or crib before sleep time and wheezing in early childhood. *Pediatrics*, *110*(6). https://doi.org/10.1542/peds.110.6.e77
Chan, A., Tetzlaff, J. M., & Altman, D. G. (2016). SPIRIT 2013 Statement : Defining Standard Protocol Items for Clinical Trials. *Ann Intern Med*, *158*(3), 200–207. https://doi.org/10.7326/0003-4819-158-3-201302050-00583.Requests
ChiCTR2000031893. (2020). Efficacy of three Different Budesonide Treatments in Chinese Preschool Children with Recurrent Wheezing. *Http://Www.Who.Int/Trialsearch/Trial2.Aspx?TrialID=ChiCTR2000031893*. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-02447114/full
Conn, V. S., Cooper, P. S., Ruppar, T. M., & Russell, C. L. (2008). Searching for the intervention in intervention research reports. *Journal of Nursing Scholarship*, *40*(1), 52–59. https://doi.org/10.1111/j.1547-5069.2007.00206.x
De Blic, J., Delacourt, C., Le Bourgeois, M., Mahut, B., Ostinelli, J., Caswell, C., & Scheinmann, P. (1996). Efficacy of nebulized budesonide in treatment of severe infantile asthma: A double-blind study. *Journal of Allergy and Clinical Immunology*, *98*(1), 14–20. https://doi.org/10.1016/S0091-6749(96)70221-X
Duff, J. M., Leather, H., Walden, E. O., Laplant, K. D., & George, T. J. (2010). Adequacy of published oncology randomized controlled trials to provide therapeutic details needed for clinical application. *Journal of the National Cancer Institute*, *102*(10), 702–705. https://doi.org/10.1093/jnci/djq117
Ebisawa, M., Terada, A., Sato, K., Kurosaka, F., Kondo, N., Sugizaki, C., Morikawa, A., Nishima, S., & Urashima, M. (2015). Intermittent and episode-driven use of pranlukast to reduce the frequency of wheezing in atopic children: a randomized, double-blind, placebo-controlled trial. *World Allergy Organization Journal*, *8*(1 CC-Airways). https://doi.org/10.1186/s40413-015-0062-3
El Rifai, N., & Rizk, H. (2019). Effect of health education about proper inhaler technique among asthmatic children/caregivers. *Alexandria Journal of Pediatrics*, *32*(1), 6. https://doi.org/10.4103/ajop.ajop_9_19
Everard, M., Bara, A., Kurian, M., N'Diaye, T., Ducharme, F., & Mayowe, V. (2005). Anticholinergic drugs for wheeze in children under the age of two years. *Cochrane Database of Systematic Reviews*. https://doi.org/10.1002/14651858.cd001279.pub2
Expert Panel Working Group of the National Heart, Lung, and B. I. (NHLBI), Program, administered and coordinated N. A. E. and P., & (NAEPPCC), C. C. (2020). *2020 Focused Updates to the Asthma Management Guidelines: A Report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group*. *146*(6), 1217–1270. https://doi.org/10.1016/j.jaci.2020.10.003.2020
Ferreira, C., & Guilherme, M. (2020). Sibilância recorrente em idade pré-escolar: Abordagem terapêutica. *Revista Portuguesa de Imunoalergologia*, *28*(4), 217–229. https://doi.org/10.32932/rpia.2020.12.045
Getahun, D., Demissie, K., & Rhoads, G. G. (2005). Recent trends in asthma hospitalization and mortality in the United States. *Journal of Asthma*, *42*(5), 373–378. https://doi.org/10.1081/JAS-62995
Global Initiative for Asthma. (2022). Global Strategy for Asthma Management and Prevention 2022 Update. In *Global Initiative for Asthma* (pp. 1–225). http://www.ginasthma.org
Guilbert, T. W., Morgan, W. J., Krawiec, M., Lemanske, R. F., Sorkness, C., Szefler, S. J., Larsen, G., Spahn, J. D., Zeiger, R. S., Heldt, G., & al., et. (2004). The Prevention of Early Asthma in Kids study: design, rationale and methods for the Childhood Asthma Research and Education network. *Controlled Clinical Trials*, *25*(3 CC-Airways CC-Child Health), 286-310. https://doi.org/10.1016/j.cct.2004.03.002
Hoffmann, T. C., Glasziou, P. P., Boutron, I., Milne, R., Perera, R., Moher, D., Altman, D. G., Barbour, V., Macdonald, H., Johnston, M., Kadoorie, S. E. L., Dixon-Woods, M.,

McCulloch, P., Wyatt, J. C., Phelan, A. W. C., & Michie, S. (2014). Better reporting of interventions: Template for intervention description and replication (TIDieR) checklist and guide. *BMJ (Online)*, *348*(March), 1–12. https://doi.org/10.1136/bmj.g1687

Hoffmann, T. C., Walker, M. F., Langhorne, P., Eames, S., Thomas, E., & Glasziou, P. (2015). What's in a name? The challenge of describing interventions in systematic reviews: Analysis of a random sample of reviews of non-pharmacological stroke interventions. *BMJ Open*, *5*(11). https://doi.org/10.1136/bmjopen-2015-009051

Hofhuis, W., Van Der Wiel, E. C., Nieuwhof, E. M., Hop, W. C. J., Affourtit, M. J., Smit, F. J., Vaessen-Verberne, A. A. P. H., Versteegh, F. G. A., De Jongste, J. C., & Merkus, P. J. F. M. (2005). Efficacy of fluticasone propionate on lung function and symptoms in wheezy infants. *American Journal of Respiratory and Critical Care Medicine*, *171*(4), 328–333. https://doi.org/10.1164/rccm.200402-227OC

Khetsuriani, N., Kazerouni, N. N., Erdman, D. D., Lu, X., Redd, S. C., Anderson, L. J., & Teague, W. G. (2007). Prevalence of viral respiratory tract infections in children with asthma. *Journal of Allergy and Clinical Immunology*, *119*(2), 314–321. https://doi.org/10.1016/j.jaci.2006.08.041

Kotaniemi-Syrjänen, A., Klemola, T., Koponen, P., Jauhola, O., Aito, H., Malmström, K., Malmberg, L. P., Rahiala, E., Sarna, S., Pelkonen, A. S., & Mäkelä, M. J. (2022). Intermittent Tiotropium Bromide for Episodic Wheezing: A Randomized Trial. *Pediatrics*, *150*(3). https://doi.org/10.1542/peds.2021-055860

Kuehni, C. E., Strippoli, M. P. F., Low, N., Brooke, A. M., & Silverman, M. (2007). Wheeze and asthma prevalence and related health-service use in white and south Asian pre-schoolchildren in the United Kingdom. *Clinical and Experimental Allergy*, *37*(12), 1738–1746. https://doi.org/10.1111/j.1365-2222.2007.02784.x

Kusel, M. M. H., De Klerk, N. H., Holt, P. G., Kebadze, T., Johnston, S. L., & Sly, P. D. (2006). Role of respiratory viruses in acute upper and lower respiratory tract illness in the first year of life: A birth cohort study. *Pediatric Infectious Disease Journal*, *25*(8), 680–686. https://doi.org/10.1097/01.inf.0000226912.88900.a3

Lavorini, F., & Usmani, O. S. (2013). Correct inhalation technique is critical in achieving good asthma control. *Primary Care Respiratory Journal*, *22*(4), 385–386. https://doi.org/10.4104/pcrj.2013.00097

Mandhane, P. J., Paredes Zambrano De Silbernagel, P., Nwe Aung, Y., Williamson, J., Lee, B. E., Spier, S., Noseworthy, M., Craig, W. R., & Johnson, D. W. (2017). Treatment of preschool children presenting to the emergency department with wheeze with azithromycin: A placebo-controlled randomized trial. *PLoS ONE*, *12*(8), 1–15. https://doi.org/10.1371/journal.pone.0182411

McKean, M. C., & Ducharme, F. (2000). Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database of Systematic Reviews*, *2010*(1). https://doi.org/10.1002/14651858.CD001107

Memon, B. N., Parkash, A., Khan, K. M. A., Gowa, M. A., & Bai, C. (2016). Response to nebulized salbutamol versus combination with ipratropium bromide in children with acute severe asthma. *Journal of the Pakistan Medical Association*, *66*(3), 243–246.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Altman, D., Antes, G., Atkins, D., Barbour, V., Barrowman, N., Berlin, J. A., Clark, J., Clarke, M., Cook, D., D'Amico, R., Deeks, J. J., Devereaux, P. J., Dickersin, K., Egger, M., Ernst, E., … Tugwell, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7). https://doi.org/10.1371/journal.pmed.1000097

Moorman JE, Akinbami LJ, Bailey CM, et al. (2010). *National Surveillance of Asthma : United States* ,.

Nwokoro, C., Pandya, H., Turner, S., Eldridge, S., Griffiths, C. J., Vulliamy, T., Price, D., Sanak, M., Holloway, J. W., Brugha, R., Koh, L., Dickson, I., Rutterford, C., & Grigg, J. (2015). Parent-determined oral montelukast therapy for preschool wheeze with stratification for arachidonate 5-lipoxygenase (ALOX5) promoter genotype: a multicentre, randomised, placebo-controlled trial. *Efficacy and Mechanism Evaluation*, *2*(6), 1–126. https://doi.org/10.3310/eme02060

Papi, A., Nicolini, G., Baraldi, E., Boner, A. L., Cutrera, R., Rossi, G. A., & Fabbri, L. M. (2009). Regular vs prn nebulized treatment in wheeze preschool children. *Allergy*, *64*(10 CC-Airways), 1463-1471. https://doi.org/10.1111/j.1398-9995.2009.02134.x

Pedersen, S. E., Hurd, S. S., Lemanske, R. F., Becker, A., Zar, H. J., Sly, P. D., Soto-Quiroz, M., Wong, G., & Bateman, E. D. (2011). Global strategy for the diagnosis and management of asthma in children 5 years and younger. *Pediatric Pulmonology*, *46*(1), 1–17. https://doi.org/10.1002/ppul.21321

Robertson, C. F., Price, D., Henry, R., Mellis, C., Glasgow, N., Fitzgerald, D., Lee, A. J., Turner, J., & Sant, M. (2007). Short-course montelukast for intermittent asthma in children: a randomized controlled trial. *American Journal of Respiratory and Critical Care Medicine*, *175*(4 CC-Airways), 323-329. https://doi.org/10.1164/rccm.200510-1546OC

Saglani, S., Wilson, N., & Bush, A. (2007). Should preschool wheezers ever be treated with inhaled corticosteroids? *Seminars in Respiratory and Critical Care Medicine*, *28*(3), 272–285. https://doi.org/10.1055/s-2007-981648

Schroter, S., Glasziou, P., & Heneghan, C. (2012). Quality of descriptions of treatments: A review of published randomised controlled trials. *BMJ Open*, *2*(6), 1–7. https://doi.org/10.1136/bmjopen-2012-001978

Schwerk, N., Brinkmann, F., Soudah, B., Kabesch, M., & Hansen, G. (2011). Wheeze in preschool age is associated with pulmonary bacterial infection and resolves after antibiotic therapy. *PLoS ONE*, *6*(11), 1–7. https://doi.org/10.1371/journal.pone.0027913

Smart, B. A. (2009). Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. *Pediatrics*, *124*(SUPPL. 2). https://doi.org/10.1542/peds.2009-1870RRR

Stokholm, J., Chawes, B. L., Vissing, N. H., Bjarnadottir, E., Pedersen, T. M., Vinding, R. K., Schoos, A.-M., Wolsk, H. M., Thorsteinsdottir, S., Hallas, H. W., & al., et. (2016). Azithromycin for episodes with asthma-like symptoms in young children aged 1-3 years: a randomised, double-blind, placebo-controlled trial. *Lancet Respiratory Medicine*, *4*(1 CC-Airways), 19-26. https://doi.org/10.1016/S2213-2600%2815%2900500-7

Tew, G. A., Brabyn, S., Cook, L., & Peckham, E. (2016). The completeness of intervention descriptions in randomised trials of supervised exercise training in peripheral arterial disease. *PLoS ONE*, *11*(3), 1–14. https://doi.org/10.1371/journal.pone.0150869

Valovirta, E., Boza, M. L., Robertson, C. F., Verbruggen, N., Smugar, S. S., Nelsen, L. M., Knorr, B. A., Reiss, T. F., Philip, G., & Gurner, D. M. (2011). Intermittent or daily montelukast versus placebo for episodic asthma in children. *Annals of Allergy, Asthma & Immunology*, *106*(6 CC-Airways), 518-526. https://doi.org/10.1016/j.anai.2011.01.017

Valovirta, E., Boza, M. L., Robertson, C. F., Verbruggen, N., Smugar, S. S., Nelsen, L. M., Knorr, B. A., Reiss, T. F., Philip, G., Gurner, D. M., Papi, A., Nicolini, G., Baraldi, E., Boner, A. L., Cutrera, R., Rossi, G. A., Fabbri, L. M., Oommen, A., Lambert, P. C., … Hedlin, G. (2009). Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children With a History of Such Illnesses: a Randomized Clinical Trial. *Pediatrics*, *12*(6 CC-Airways), 17043. https://doi.org/10.1080/08035259950170583

Vuillermin, P. J., Robertson, C. F., & South, M. (2007). Parent-initiated oral corticosteroid therapy for intermittent wheezing illnesses in children: Systematic review. *Journal of Paediatrics and Child Health*, *43*(6), 438–442. https://doi.org/10.1111/j.1440-1754.2007.01107.x

Warde, R. C. (2010). CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. *Notes and Queries*, *s1-XI*(274), 64. https://doi.org/10.1093/nq/s1-XI.274.64-d

Xu, H., Tong, L., Gao, P., Hu, Y., Wang, H., Chen, Z., & Fang, L. (2021). Combination of ipratropium bromide and salbutamol in children and adolescents with asthma: A meta-analysis. *PLoS ONE*, *16*(2 February), 1–15. https://doi.org/10.1371/journal.pone.0237620

Yamato, T. P., Maher, C. G., Saragiotto, B. T., Hoffmann, T. C., & Moseley, A. M. (2016). How completely are physiotherapy interventions described in reports of randomised trials? *Physiotherapy (United Kingdom)*, *102*(2), 121–126.

https://doi.org/10.1016/j.physio.2016.03.001
Yu, A. M., Balasubramanaiam, B., Offringa, M., & Kelly, L. E. (2018). Reporting of interventions and “standard of care” control arms in pediatric clinical trials: a quantitative analysis. *Pediatric Research*, *84*(3), 393–398. https://doi.org/10.1038/s41390-018-0019-7
Zeiger, R. S., Mauger, D., Bacharier, L. B., Guilbert, T. W., Martinez, F. D., Lemanske, R. F., Strunk, R. C., Covar, R., Szefler, S. J., Boehmer, S., & al., et. (2011). Daily or intermittent budesonide in preschool children with recurrent wheezing. *New England Journal of Medicine*, *365*(21 CC-Airways), 1990-2001. https://doi.org/10.1056/NEJMoa1104647

Figures

Figure 1

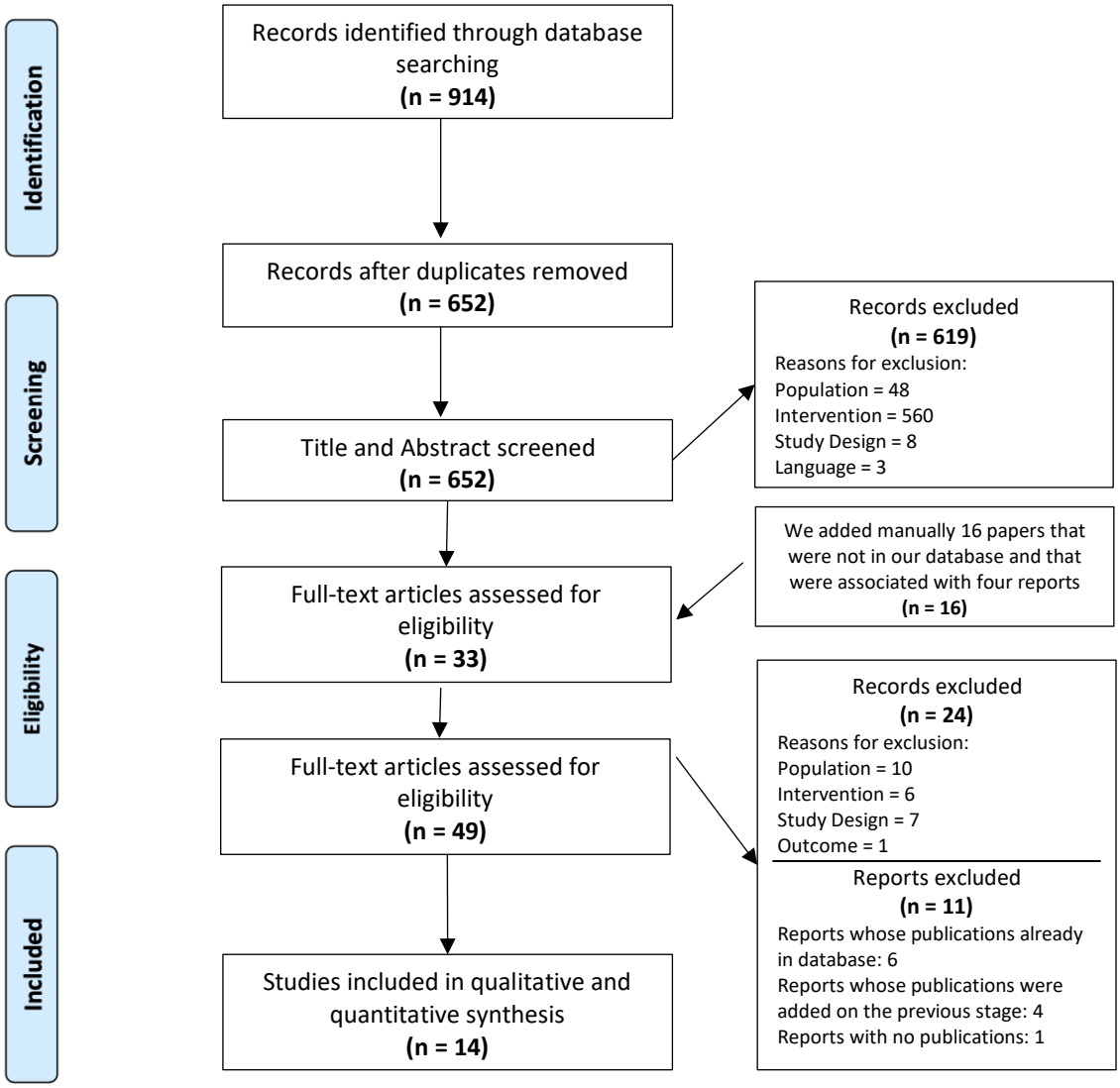

Figure 1 Study flow chart according to PRISMA flow diagram (Moher et al., 2009).

Figure 2

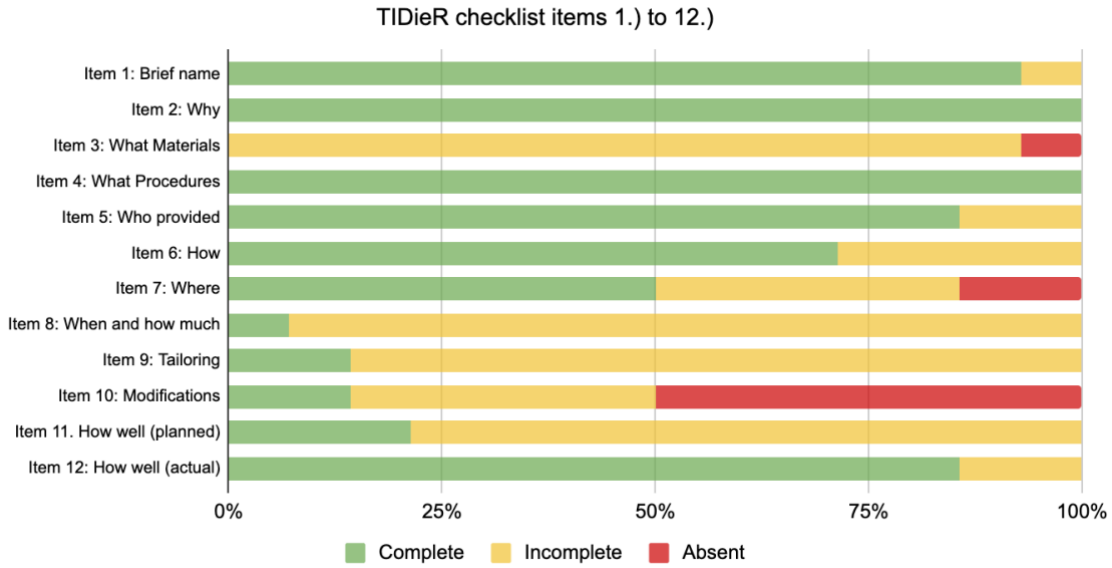

Figure 2 The proportion of studies with complete, incomplete and absent reporting of each of the items 1.) to 12.) of the TIDieR checklist.

Figure 3

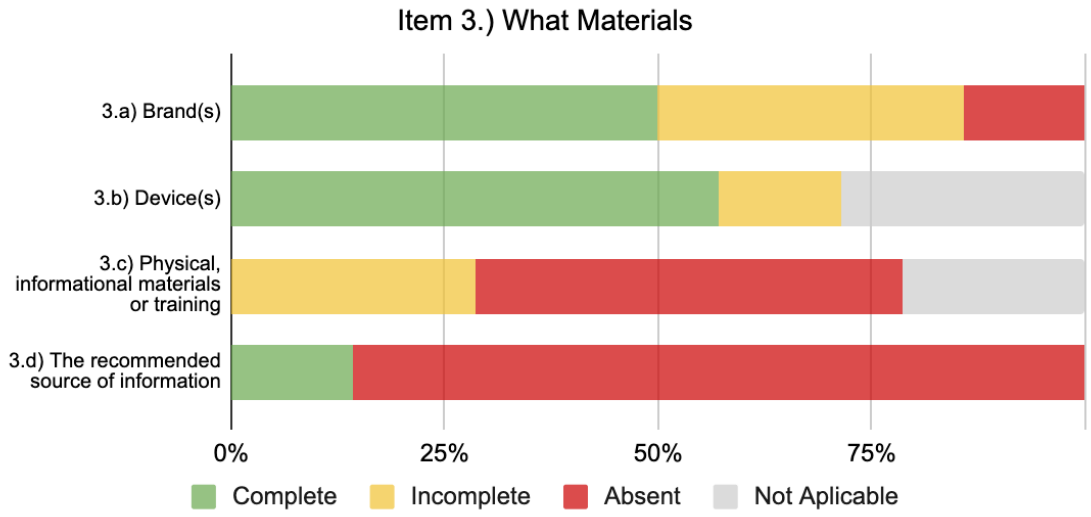

Figure 3 The proportion of studies with complete, incomplete and absent reporting of each of the subitems 3.a) to 3.d) of our model of the TIDieR checklist adapted to wheezing interventions.

Figure 4

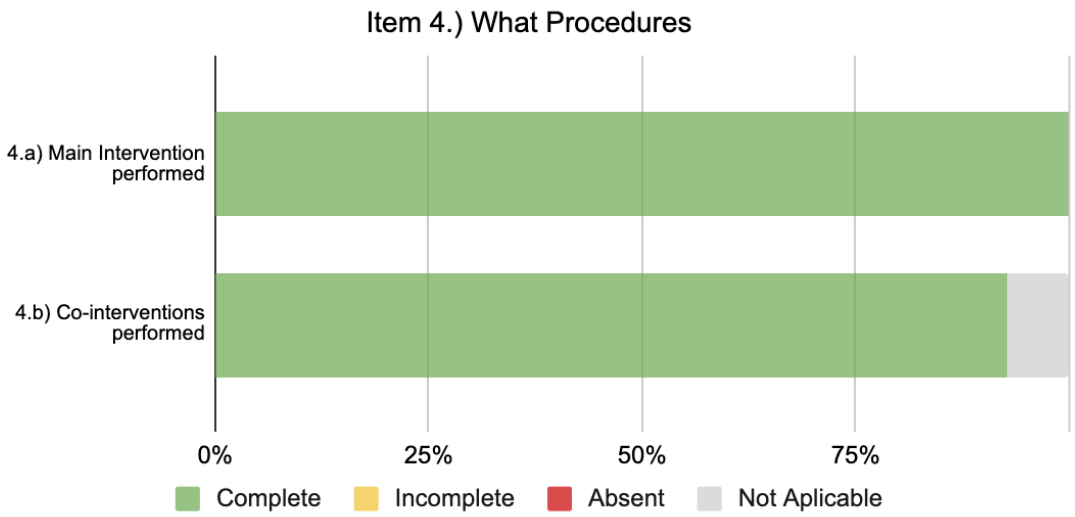

Figure 4 The proportion of studies with complete, incomplete and absent reporting of each of the subitems 4.a) to 4.b) of our model of the TIDieR checklist adapted to wheezing interventions.

Figure 5

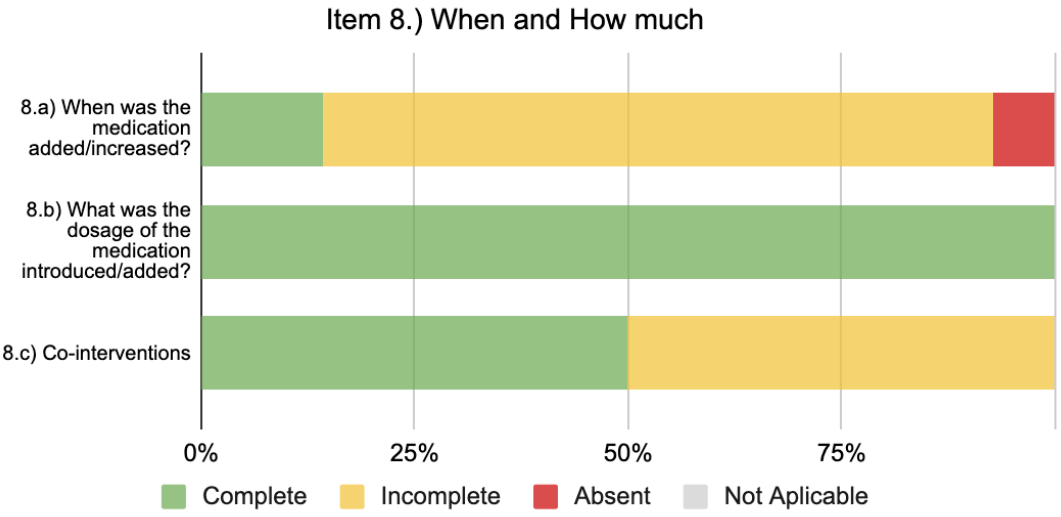

Figure 5 The proportion of studies with complete, incomplete and absent reporting of each of the subitems 8.a) to 8.c) of our model of the TIDieR checklist adapted to wheezing interventions.

Figure 6

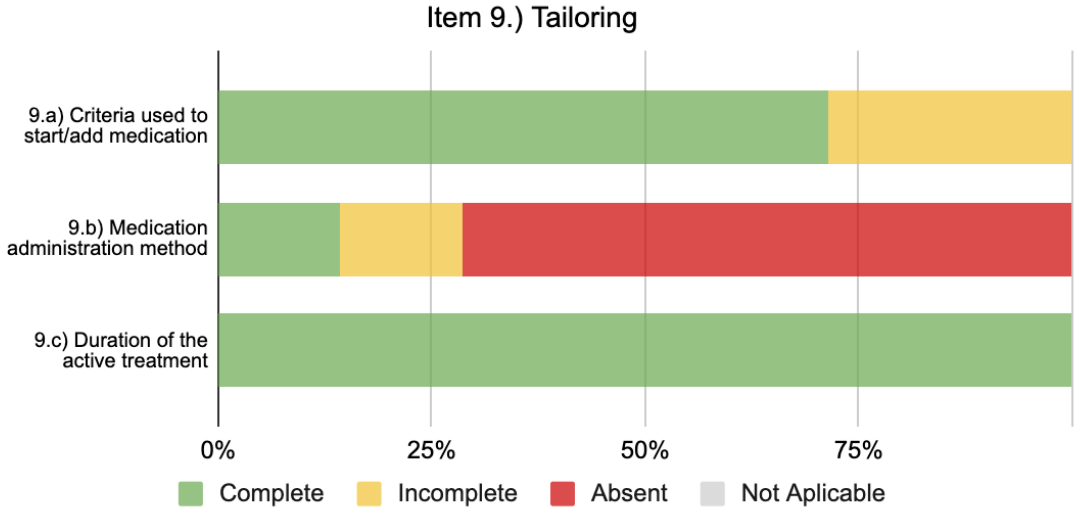

Figure 6 The proportion of studies with complete, incomplete and absent reporting of each of the subitems 9.a) to 9.c) of our model of the TIDieR checklist adapted to wheezing interventions.

Tables

Table 1

TIDieR items		Example to classify the various papers on the same item/sub-item
Item 1 (Brief Name)		“Daily or intermittent budesonide in preschool children with recurrent wheezing” (Zeiger et al., 2011)
Item 2 (Why, Rational)		"Children infected with respiratory syncytial virus in early life are at increased risk of developing asthma during the school years. Upper respiratory viral infections are also associated with 80-85% of asthma exacerbations in school-age children. Of interest, virus-induced asthma attacks occurred less in children on inhaled corticosteroid and/or leukotriene receptor antagonist (LTRA) therapy in a case–control study. In addition, montelukast, one of the LTRAs, was shown to reduce asthma exacerbations in children with intermittent asthma, which is sometimes very difficult to differentiate from viral infections, especially in preschool children, with over 12 months of treatment in the PREVIA study (2- to 5-year-olds) and the PRE-EMPT study (2- to 14-year-olds). On the other hand, atopic children have been shown to experience more colds and asthma exacerbations than non-atopic children. However, whether early intervention using an LTRA in atopic smaller children aged 1 to 2 years who had experienced episodic wheezing but were not yet diagnosed as having asthma can reduce the frequency of wheezing episodes was unclear. Therefore, a randomized, double-blind, placebo-controlled trial was conducted to determine whether intermittent and episode-driven use of pranlukast, one of the LTRAs, could improve control of wheezing symptoms in small children aged 1 to 2 years with atopic sensitization and two episodes of wheezing prior to entry." (Ebisawa et al., 2015)
Item 3 (What, Materials)	3.a) Brand(s)	“Merck & Co, Inc, West Point, Pa, donated montelukast (Singulair) tablets and granules and placebo; AstraZeneca, Wilmington, Del, donated Pulmicort Respules and placebo; Schering-Plough Corporation, Kenilworth, NJ, donated Proventil MDIs and Proventil nebules.” (Bacharier et al., 2008)
	3.b) Device(s)	"Study medications were administered with the use of a Pari Ultra II compressor with a Pari LC Sprint reusable nebulizer and a mask (Bubbles the Fish II or Pari Baby mask), if needed, or a mouthpiece, depending on the age of the child. (...) AeroChamber Z-STAT Plus with FlowSIGnal Whistle with ComfortSeal Mask (Monaghan Medical)(...).” (Zeiger et al., 2011)
	3.c) Physical, informational materials or training	**On this sub-item, no paper was complete. Therefore, we had to use the next citation, considered incomplete, to calibrate.** “We reviewed the inhalation technique with the parents and provided an age-appropriate spacer with mask or mouthpiece for the children (AeroChamber, Trudell Medical Internationall). Clearing of nasal passages with salty water was recommended to minimize post-nasal drip." (Smart, 2009)
	3.d) Recommended source of information	“A dedicated book on asthma-like symptoms and treatment in young children was given to the parents (and is available at www.copsac.com).” (H Bisgaard et al., 2006)
Item 4 (What, Procedures)	4.a)Main Intervention performed	“The children in the daily group were initially given inhaled BUD 1 mg once a day." (ChiCTR2000031893, 2020)
	4.b) Co-intervention performed	“During RTIs, all participants received albuterol inhalation treatments 4 times daily while awake for the first 48 hours as well as whenever needed at any time during the RTI.” (Valovirta et al., 2009)
Item 5 (Who provided)		“The IMP was administered unsupervised by the patients’ carers in their usual place of residence.” (Nwokoro et al., 2015)
Item 6 (How)		“The IMP was presented as white granules administered either directly into the child’s mouth, or mixed with a spoonful of cold or room-temperature soft food(…)”(Nwokoro et al., 2015)
Item 7 (Where)		“The IMP was administered unsupervised by the patients’ carers in their usual place of residence.” (Nwokoro et al., 2015)

Item 8 (When and How much)	8.a) When was the medication added?	"(…) when the participating children had symptoms of a common cold (runny nose, cough, and/or wheezing)." (Ebisawa et al., 2015)
	8.b) What was the dosage of the medication introduced/added?	"(…) 4 mg of montelukast sodium (...) One sachet to be given once a day." or "(...) once daily tiotropium bromide 5 mg, ie, 2 puffs of 2.5 mg once daily as an intermittent treatment." (Nwokoro et al., 2015)
	8.c) Co-interventions	"(…) as-needed albuterol sulfate 0.2 mg, ie, 2 puffs of 0.1 mg as-needed (4–6 times daily)." (Kotaniemi-Syrjänen et al., 2022)
Item 9 (Tailoring)	9.a) Criteria used to start/add medication	"Children between the ages of 12 and 53 months who (...) during the previous year, they had at least four episodes of wheezing (or three episodes of wheezing and controller use for ≥3 months), positive values on the modified API,[reference] and at least one exacerbation requiring the use of systemic glucocorticoids, urgent or emergency care, or hospitalization, and during a 2-week run-in period, they had fewer than 3 days per week of albuterol use and fewer than 2 nights with awakening." (Zeiger et al., 2011)
	9.b) Medication administration method	"(...) administered either directly into the child's mouth, or mixed with a spoonful of cold or room-temperature soft food (e.g. apple sauce, ice cream, carrots and rice). (...) After opening the sachet, the full dose of granules was administered within 15 minutes." (Nwokoro et al., 2015) or "Parents instructed to activate two puffs into the spacer, and the child inhale for 30seg." (Valovirta et al., 2009)
	9.c) Duration of the treatment	"(...) with moderate-to-severe intermittent wheezing received 7 days of either budesonide inhalation suspension (1 mg twice daily), montelukast (4 mg daily), or placebo (...)." (Bacharier et al., 2008)
Item 10 (Changes in Protocol)		"There were 31 reported protocol deviations throughout the study. Very few necessitated withdrawal from the trial, no deviations from protocol exposed a participant to risk of harm, or appeared systematic or particular to an individual site, or had the potential to compromise study validity. Most protocol deviations were addressed by a gentle reminder of the study requirements to the parent or carer." (Nwokoro et al., 2015)
Item 11 (What strategies were use to maintain or improve fidelity?)		We considered this item complete if the paper mentioned the criteria and method used by the parents/guardian to report the symptoms, complications and medication used; mentioned they had explained the technique/method used to administer a specific medication and respective review; and they made periodic check-ups on the children and family through consultations or phone calls. **As an example:** "Parents received extensive education at all study visits (…) Clinic visits were scheduled 4 weeks after randomization and then every 8 weeks, whereas telephone calls were scheduled 2 weeks after randomization, followed by calls 4 weeks after each scheduled clinic visit. (…) during which parents completed diary cards twice daily. Diary cards incorporated the validated Pediatric Asthma Caregiver Diary[reference] and included 5 symptom categories (nocturnal cough, daytime cough, wheezing, difficulty breathing, and symptoms interfering with activities), each scored on a 0- through 5-point scale (…)" (Bacharier et al., 2008)
Item 12 (If intervention adherence was assessed, describe the extent the intervention was delivered as planned)		"Full documentation was made of any withdrawals that occurred during the study in the case report form (CRF). The investigator documented the date and time of the withdrawal and results of any assessments made at this time.(…) A total of 1366 patients gave consent and were genotyped. Of these, 8 withdrew prior to randomisation and 12 were subsequently excluded from the analysis owing to parental withdrawal of permission to use data. (…) For the primary outcome phonecall data, at the time of writing (prior to unblinding) we have: Full 12 months data on 1134/1347(84%) 29/1347 (2%) participants withdrew before the first 2 month phonecall and have no data collected as expected 12/1347 (0.9%) do not have any follow up data and this is being queried with the sites. Partial follow up data is available for 172 (13%). 44 of these participants did not formally withdraw from follow up." (Nwokoro et al., 2015)

Table 1 Citations used as an example to score the various items/sub-items of the included papers.

Table 2

Title	Author, Year	Journal	Study Design	Population	Intervention	Control / Comparator	Concomitant med. in active and control group	Setting	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	No of items 3-9 correctly reported (%)
Daily or intermittent budesonide in preschool children with recurrent wheezing	Zeiger RS. et al (2011)	N. Engl. J. Med.	RCT	12-53 M (N = 278)	Budesonide (daily low-dose) Budenoside (Prn high-dose)	MP	Albuterol Prn	Outpatient	I	C	C	C	C	I	I	4 (57%)
Early Administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses a randomized clinical trial	Bacharier, LB. et al (2015)	JAMA	RCT	12-71 M (N = 607)	Azithromycin (Prn)	MP	Albuterol Prn	Outpatient	A	C	C	C	C	I	I	4 (57%)
Efficacy of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1-5 years: randomised controlled trial	Oommen A. et al (2003)	Lancet	RCT, DB	1-5 Y (N = 217)	Prednisolone (Prn)	MP	Salbutamol Prn	Outpatient	I	C	C	C	I	I	I	3 (43%)
Efficacy of three different budesonide treatments in Chinese preschool children with recurrent wheezing	Li L. et al (2022)	Sci Rep.	RCT, prospective	12-59 M (N = 476)	Budenoside (Daily) Budenoside (Prn high-dose) Budenoside (Prn medium-dose)	NA	NA	Outpatient	I	C	C	C	I	I	I	3 (43%)
Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing	Bacharier LB. et al (2008)	J. Allergy Clin. Immunol.	RCT	12-59 M (N = 238)	Budesonide (Prn) Montelukast (Prn)	MP	Albuterol per treatment or Proventil Prn	Outpatient	I	C	C	C	C	I	I	4 (57%)
Intermittent and episode-driven use of pranlukast to reduce the frequency of wheezing in atopic children: a randomized, double-blind, placebo-controlled trial	Ebisawa, M. et al (2015)	World Allergy Organization journal	RCT, DB, PC, multicenter	1-2 Y (N = 77)	Pranlukast (Prn)	MP	β2 agonist and antitussives/expectorants Prn	Outpatient	I	C	I	I	C	I	I	2 (29%)
Intermittent inhaled corticosteroids in infants with episodic wheezing	Bisgaard H. et al (2006)	N. Engl. J. Med.	RCT, DB	1 M - 3 Y (N = 301)	Budesonide (Prn)	MP	Terbutaline Prn	Outpatient	I	C	C	I	C	I	I	3 (43%)

Intermittent or daily montelukast versus placebo for episodic asthma in children	Valovirta E. et al (2011)	Ann Allergy Asthma Immunol	RCT, DBDD, multicenter and parallel group	6 M - 5 Y (N = 1771)	Montelukast (Daily) + Placebo (Prn) Montelukast (Prn) + Placebo (daily)	MP	Short-acting-agonists Prn	Outpatient	I	C	I	I	A	I	I	1 (14%)
Intermittent Tiotropium Bromide for Episodic Wheezing: A Randomized Trial	Kotaniemi-Syrjänen A. et al (2022)	Pediatrics	RCT, open-label and parallel-group	6-35 M (N = 80)	Tiotropium bromide group (Prn) Fluticasone propionate group (Prn)	Albuterol group (Prn)	Albuterol sulfate Prn	Outpatient	I	C	C	I	A	I	I	2 (29%)
Parent-determined oral montelukast therapy for preschool wheeze with stratification for arachidonate 5-lipoxygenase (ALOX5) promoter genotype: a multicentre, randomised, placebo-controlled trial	Chinedu N. et al (2015)	NIHR J. Library	RCT, PC multicentre	6 M - 5 Y (N = 1346)	Montelukast sodium (Prn)	MP	Salbutamol Prn	Outpatient	I	C	C	C	C	I	C	5 (71%)
Preemptive use of high-dose fluticasone for virus-induced wheezing in young children	Francine M. et al (2009)	N. Engl. J. Med.	RCT, TB, PC, parallel-group	1 - 6 Y (N = 129)	Fluticasone propionate (Prn)	MP	Albuterol hydrofluoroalkane Prn	Outpatient	I	C	C	C	I	C	I	4 (57%)
Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers	Svedmyr J. et al (1999)	Acta Paediatrica	RCT, DB, parallel group	1-3 Y (N = 55)	Budesonide (Prn)	MP	Beta2-agonists and/or Theophylline Prn	Outpatient	I	C	C	C	I	I	C	4 (57%)
Regular vs prn nebulized treatment in wheeze preschool children	Papi A. et al (2009)	Allergy	RCT, DBDD, PC, multicenter and three parallel-group	1-4 Y (N = 276)	Regular beclomethasone group (Beclomethasone daily + Salbutamol Prn) Prn combination group (Placebo Daily + Beclomethasone/Salbutamol Prn)	Prn salbutamol group (Placebo Daily + Salbutamol Prn)	Salbutamol Prn	Outpatient	I	C	C	C	I	I	I	3 (43%)
Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home	Wilson, NM. (1990)	Archives of disease in childhood	RCT, DB	1-5 Y (N = 24)	Beclomethasone dipropionate (Prn high dose)	MP	Bronchodilators Prn	Outpatient	I	C	C	C	C	I	I	4 (57%)

Table 2 Details and completeness of reporting of included studies.

***C = an item correctly reported**; **I = an item only partially/incompletely reported**; **A = an absent item**.; DB = Double-blind; DBDD = Double-blind double-dummy; TB = Triple-Blind; M = months of age; MP = matching placebo; NA = Not aplicable; PC = Placebo-Controlled; Prn = "Pro re nata"; RCT = Randomized Controlled Trial; Y = Years of age.*

Table 3

Article's Number	Author/Year	Item 1) Brief Name	Item 2) Why	Item 3) What (Materials)					Item 4) What (Procedures)			Item 5) Who Provided	Item 6) How	Item 7) Where	Item 8) When and How Much				Item 9) Tailoring				Item 10) Modification	Item 11) How Well (Planned)	Item 12) How Well (Actual)
		1) General Item	2) General Item	3.a)	3.b)	3.c)	3.d)	3) General Item	4.a)	4.b)	4) General Item	5) General Item	6) General Item	7) General Item	8.a)	8.b)	8.c)	8) General Item	9.a)	9.b)	9.c)	9) General Item	10) General Item	11) General Item	12) General Item
1	Zeiger RS. et al (2011)	C	C	C	C	A	A	I	C	C	C	C	C	C	I	C	C	I	C	A	C	I	A	I	C
2	Bacharier, LB. et al (2015)	C	C	A	NA	A	A	A	C	C	C	C	C	C	I	C	I	I	C	A	C	I	A	I	C
3	Oommen A. et al (2003)	C	C	I	C	A	A	I	C	C	C	C	C	I	I	C	C	I	I	A	C	I	A	I	C
4	Li L. et al (2022)	C	C	C	I	A	A	I	C	NA	C	C	C	I	I	C	I	I	C	A	C	I	I	I	C
5	Bacharier LB. et al (2008)	C	C	C	C	A	A	I	C	C	C	C	C	C	I	C	C	I	C	I	C	I	I	C	C
6	Ebisawa, M. et al (2015)	C	C	C	NA	NA	A	I	C	C	C	I	I	C	C	C	I	I	I	A	C	I	I	I	I
7	Bisgaard H. et al (2006)	C	C	I	C	A	C	I	C	C	C	C	I	C	I	C	I	I	I	A	C	I	I	C	I
8	Valovirta E. et al (2011)	C	C	A	NA	NA	A	I	C	C	C	I	I	A	I	C	I	I	C	I	C	I	A	C	C
9	Kotaniemi-Syrjänen A. et al (2022)	C	C	C	C	A	A	I	C	C	C	C	I	A	I	C	C	I	I	A	C	I	A	I	C
10	Chinedu N. et al (2015)	C	C	C	NA	NA	C	I	C	C	C	C	C	C	I	C	I	I	C	C	C	C	C	I	C
11	Francine M. et al (2009)	C	C	I	C	I	A	I	C	C	C	C	C	I	C	C	C	C	C	A	C	I	A	I	C
12	Svedmyr J. et al (1999)	C	C	I	C	I	A	I	C	C	C	C	C	I	I	C	I	I	C	C	C	C	C	I	C
13	Papi A. et al (2009)	I	C	C	C	I	A	I	C	C	C	C	C	I	A	C	C	I	C	A	C	I	I	I	C
14	Wilson, NM. (1990)	C	C	I	I	I	A	I	C	C	C	C	C	C	I	C	C	I	C	A	C	I	A	I	C

Table 3 *Scoring of all items and subitems of our adapted checklist of wheezing interventions across included studies.*

Appendices

Appendix 1: MEDLINE (Pubmed) search strategy

((((((((((((((((((((child*[Title/Abstract]) OR ("child s"[Title/Abstract])) OR ("children s"[Title/Abstract])) OR ("pre-school"[Title/Abstract])) OR ("pre school"[Title/Abstract])) OR (preschool*[Title/Abstract])) OR ("preschool child"[Title/Abstract])) OR ("preschooler s"[Title/Abstract])) OR (Infant*[Title/Abstract])) OR ("infant s"[Title/Abstract])) OR (newborn*[Title/Abstract])) OR ("newborn infant"[Title/Abstract])) OR ("newborn s"[Title/Abstract])) OR ("pro re nata"[Title/Abstract])) OR (prn[Title/Abstract])) OR (child[MeSH Terms])) OR (infant[MeSH Terms])) OR (infant, newborn[MeSH Terms])) OR (child,preschool[MeSH Terms])) AND ((((((((((((((((asthma[MeSH Terms]) OR (bronchiolitis[MeSH Terms])) OR (bronchitis[MeSH Terms])) OR ("respiratory sounds"[MeSH Terms])) OR (asthm*[Title/Abstract])) OR ("asthma s"[Title/Abstract])) OR (bronchiolitis[Title/Abstract])) OR (bronchiolitides[Title/Abstract])) OR (bronchitis[Title/Abstract])) OR (bronchitides[Title/Abstract])) OR (wheez*[Title/Abstract])) OR ("respiratory sounds"[Title/Abstract])) OR ("respiratory sounds"[Title/Abstract])) OR ("obstructive airway"[Title/Abstract])) OR ("obstructive airway disease"[Title/Abstract])) OR ("obstructive airway diseases"[Title/Abstract])) OR ("obstructive lung"[Title/Abstract])) OR ("obstructive lung disease"[Title/Abstract])) OR ("obstructive lung diseases"[Title/Abstract]))) AND ((((((((((((((((((steroid*[Title/Abstract]) OR (corticosteroid*[Title/Abstract])) OR ("adrenal cortex hormones"[Title/Abstract])) OR (leucotrien*[Title/Abstract])) OR (leukotrien*[Title/Abstract])) OR (antileucotrien*[Title/Abstract])) OR (antileukotriene*[Title/Abstract])) OR (anti-leucotrien*[Title/Abstract])) OR (anti-leukotrien*[Title/Abstract])) OR ("leukotriene antagonists"[Title/Abstract])) OR (montelukast[Title/Abstract])) OR ("short-acting beta-agonist"[Title/Abstract])) OR ("short-acting beta-agonists"[Title/Abstract])) OR ("long-acting beta-agonist"[Title/Abstract])) OR ("long-acting beta-agonists"[Title/Abstract])) OR (beta-agonist*[Title/Abstract])) OR ("acting beta-agonist"[Title/Abstract])) OR ("acting beta-agonists"[Title/Abstract])) OR (steroid[MeSH Terms])) OR ("adrenal cortex hormones"[MeSH Terms])) OR ("leukotriene antagonists"[MeSH Terms]))) AND ((((((((((guideline*[Title/Abstract]) OR ("health planning"[Title/Abstract])) OR (recommend*[Title/Abstract])) OR ("care pathway"[Title/Abstract])) OR (intermitt*[Title/Abstract])) OR (strateg*[Title/Abstract])) OR ("strategy s"[Title/Abstract])) OR ("management strategies"[Title/Abstract])) OR ("management strategy"[Title/Abstract])) OR ("guidelines as topic"[MeSH Terms]))) AND ((randomizedcontrolledtrial[Filter]))) NOT ((animals[mh] NOT humans[mh]))

Appendix 2: CENTRAL database search strategy

#1 (child* or "child s" or "children s" or "pre-school" or "pre school" or preschool* or "preschool child" or "preschooler s" or Infant* or "infant s" or newborn* or "newborn infant" or "newborn s" or "pro re nata" or prn):ti,ab,kw (Word variations have been searched)

#2 MeSH descriptor: [Child] explode all trees

#3 MeSH descriptor: [Infant] explode all trees

#4 MeSH descriptor: [Infant, Newborn] explode all trees

#5 #1 OR #2 OR #3 OR #4

#6 (asthm* or "asthma s" or bronchiolitis or bronchiolitides or bronchitis or bronchitides or wheez* or "respiratory sounds" or "respiratory sounds" or "obstructive airway" or "obstructive airway disease" or "obstructive airway diseases" or "obstructive lung" or "obstructive lung disease" or "obstructive lung diseases"):ti,ab,kw (Word variations have been searched)

#7 MeSH descriptor: [Asthma] explode all trees

#8 MeSH descriptor: [Bronchiolitis] explode all trees

#9 MeSH descriptor: [Bronchitis] explode all trees

#10 #6 OR #7 OR #8 OR #9

#11 (steroid* or corticosteroid* or "adrenal cortex hormones" or leucotrien* or leukotrien* or antileucotrien* or antileukotriene* or anti-leucotrien* or anti-leukotrien* or "leukotriene antagonists" or montelukast or "short-acting beta-agonist" or "short-acting beta-agonists" or "long-acting beta-agonist" or "long-acting beta-agonists" or beta-agonist* or "acting beta-agonist" or "acting beta-agonists"):ti,ab,kw (Word variations have been searched)

#12 MeSH descriptor: [Steroids] explode all trees

#13 #11 OR #12

#14 (guideline* or "health planning" or recommend* or "care pathway" or intermitt* or strateg* or "strategy s" or "management strategies" or "management strategy"):ti,ab,kw (Word variations have been searched)

#15 #5 AND #10 AND #13 AND #14 in Trials

#16 [mh animals] NOT [mh humans]

#17 #15 NOT #16

Appendix 3: Full reference list of included studies

1. *Zeiger, R. S., Mauger, D., Bacharier, L. B., Guilbert, T. W., Martinez, F. D., Lemanske, R. F., Strunk, R. C., Covar, R., Szefler, S. J., Boehmer, S., & al., et. (2011). Daily or intermittent budesonide in preschool children with recurrent wheezing. New England Journal of Medicine, 365(21 CC-Airways), 1990-2001. https://doi.org/10.1056/NEJMoa1104647*
2. *Bacharier, L. B., Guilbert, T. W., Mauger, D. T., Boehmer, S., Beigelman, A., Fitzpatrick, A. M., Jackson, D. J., Baxi, S. N., Benson, M., Burnham, C.-A., & al., et. (2015). Early Administration of azithromycin and prevention of severe lower respiratory tract illnesses in preschool children with a history of such illnesses a randomized clinical trial. JAMA - Journal of the American Medical Association, 314(19), 2034-2044. https://doi.org/10.1001/jama.2015.13896*
3. *Oommen, A., Lambert, P. C., & Grigg, J. (2003). Efficacy of a short course of parent-initiated oral prednisolone for viral wheeze in children aged 1-5 years: randomised controlled trial. Lancet (London, England), 362(9394 CC-Airways CC-Acute Respiratory Infections CC-Child Health), 1433-1438. https://doi.org/10.1016/S0140-6736(03)14685-5*
4. *Li, L., Zhang, F., Sun, P., Zheng, J., Chen, T., Huang, T., Wang, F., & Li, K. (2022). Efficacy of three different budesonide treatments in Chinese preschool children with recurrent wheezing. Scientific Reports, 12(1), 17043. https://doi.org/10.1038/s41598-022-21505-9*
5. *Bacharier, L. B., Phillips, B. R., Zeiger, R. S., Szefler, S. J., Martinez, F. D., Lemanske, R. F., Sorkness, C. A., Bloomberg, G. R., Morgan, W. J., Paul, I. M., & al., et. (2008). Episodic use of an inhaled corticosteroid or leukotriene receptor antagonist in preschool children with moderate-to-severe intermittent wheezing. Journal of Allergy and Clinical Immunology, 122(6 CC-Airways), 1127-1135.e8. https://doi.org/10.1016/j.jaci.2008.09.029*
6. *Ebisawa, M., Terada, A., Sato, K., Kurosaka, F., Kondo, N., Sugizaki, C., Morikawa, A., Nishima, S., & Urashima, M. (2015). Intermittent and episode-driven use of pranlukast to reduce the frequency of wheezing in atopic children: a randomized, double-blind, placebo-controlled trial. World Allergy Organization Journal, 8(1 CC-Airways). https://doi.org/10.1186/s40413-015-0062-3*
7. *Bisgaard, H, Hermansen, M. N., Loland, L., Halkjaer, L. B., & Buchvald, F. (2006). Intermittent inhaled corticosteroids in infants with episodic wheezing. New England Journal of Medicine, 354(19 CC-Airways CC-Musculoskeletal), 1998-2005. https://doi.org/10.1056/NEJMoa054692*
8. *Valovirta, E., Boza, M. L., Robertson, C. F., Verbruggen, N., Smugar, S. S., Nelsen, L. M., Knorr, B. A., Reiss, T. F., Philip, G., & Gurner, D. M. (2011). Intermittent or daily montelukast versus*

placebo for episodic asthma in children. Annals of Allergy, Asthma & Immunology, 106(6 CC-Airways), 518-526. https://doi.org/10.1016/j.anai.2011.01.017

9. *Kotaniemi-Syrjänen, A., Klemola, T., Koponen, P., Jauhola, O., Aito, H., Malmström, K., Malmberg, L. P., Rahiala, E., Sarna, S., Pelkonen, A. S., & Mäkelä, M. J. (2022). Intermittent Tiotropium Bromide for Episodic Wheezing: A Randomized Trial. Pediatrics, 150(3). https://doi.org/10.1542/peds.2021-055860*
10. *EUCTR2009-015626-11-GB. (2010). Parent-determined oral montelukast therapy for preschool wheeze with stratification for arachidonate-5-lipoxygenase (ALOX5) promoter genotype. - Wheeze And Intermittent Treatment; WAIT. Https://Trialsearch.Who.Int/Trial2.Aspx?TrialID=EUCTR2009-015626-11-GB. https://www.cochranelibrary.com/central/doi/10.1002/central/CN-01877693/full*
11. *Smart, B. A. (2009). Preemptive use of high-dose fluticasone for virus-induced wheezing in young children. Pediatrics, 124(SUPPL. 2). https://doi.org/10.1542/peds.2009-1870RRR*
12. *Svedmyr, J., Nyberg, E., Thunqvist, P., Asbrink-Nilsson, E., & Hedlin, G. (1999). Prophylactic intermittent treatment with inhaled corticosteroids of asthma exacerbations due to airway infections in toddlers. Acta Paediatrica, 88(1 CC-Airways CC-ENT), 42-47. https://doi.org/10.1080/08035259950170583*
13. *Papi, A., Nicolini, G., Baraldi, E., Boner, A. L., Cutrera, R., Rossi, G. A., & Fabbri, L. M. (2009). Regular vs prn nebulized treatment in wheeze preschool children. Allergy, 64(10 CC-Airways), 1463-1471. https://doi.org/10.1111/j.1398-9995.2009.02134.x*
14. *Wilson, N. M., & Silverman, M. (1990). Treatment of acute, episodic asthma in preschool children using intermittent high dose inhaled steroids at home. Archives of Disease in Childhood, 65(4 CC-Airways CC-Child Health), 407-410. https://doi.org/10.1136/adc.65.4.407*