Aims: To systematically review the effectiveness of preventative and therapeutic interventions for respiratory tract infections (RTIs) in people with Down’s syndrome.

Methods: Databases were searched for any published and ongoing studies of respiratory tract diseases in children and adults with Down’s syndrome. These databases were searched for controlled trials, cohort studies and controlled before–after studies. Trial registries were searched for ongoing studies. Initially, all study types were included to provide a broad overview of the existing evidence base. However, those with a critical risk of bias were excluded using the Cochrane Risk of Bias tool.

Results: A total of 13,575 records were identified from which 5 studies fulfilled the eligibility criteria and 3 fulfilled our criteria for data extraction. One randomized controlled trial of moderate risk of bias compared zinc therapy with placebo. Outcome data were only reported for 50 (78%) children who presented with extreme symptoms; no benefit of zinc therapy was found. One non-randomized controlled trial with serious risk of bias included 26 children and compared pidotimod (an immunostimulant) with no treatment; pidotimod was associated with fewer upper RTI recurrences compared with no treatment (1.43 vs. 3.82). A prospective cohort study with moderate risk of bias compared 352 palivizumab treated children with 233 untreated children and found that children treated with palivizumab had fewer respiratory syncytial virus-related hospitalization (23 untreated and 8 treated), but the same number of overall RTI-related hospitalizations (73 untreated and 74 treated) in the first 2 years of life.

Conclusions: The evidence base for the management of RTIs in people with Down’s syndrome is incomplete; current studies included children only and carry a moderate to serious risk of bias. Methodological rigorous studies are warranted to guide clinicians in how best to prevent and treat RTIs in children with Down’s syndrome.

Key Words: Down’s syndrome, respiratory tract infection, prevention (Pediatr Infect Dis J 2016;35:1075–1079)

Disease of Down’s syndrome, also known as trisomy 21, is amongst the commonest genetic conditions worldwide, with an incidence of 1 in 1000 live births in the United Kingdom. Despite advances in antenatal screening since the 1990s, the number of children born with Down’s syndrome in the United Kingdom has remained stable.

Discrete immune deficiencies, morphologic variations of the airways, generalized hypotonia and swallowing dysfunction predispose children with Down’s syndrome to frequent and more severe respiratory tract infections (RTIs). In one of 3 of all hospitalization of children with Down’s syndrome less than 3 years of age are caused by RTIs, with 80% occurring before 2 years of age.

Children with Down’s syndrome on average spend 2–3 times more time in hospital than those without Down’s syndrome. In children with Down’s syndrome, up to the age of 18, RTIs are the second leading cause of death. It is therefore important that effective interventions to prevent and treat these infections are developed. A number of preventive interventions are commonly practiced and believed to be of benefit including use of prophylactic antibiotics, respiratory syncytial virus (RSV) prophylaxis for subgroups (eg, those with cardiac disease), additional immunizations and longer treatment courses. However, no previous systematic review has been undertaken to ascertain the evidence base.

The aim of this study is to systematically review the literature on the management of RTIs in this vulnerable group to identify which strategies work best.

METHODS

Search Strategy

We developed a broad search strategy combining the terms "Down’s Syndrome, Respiratory Tract Infections" and relevant synonyms. To increase the yield of potential relevant articles, management
options for Down’s syndrome-related comorbidities such as sleep-disordered breathing, chronic lung disease and congenital heart disease were also included in the syntax. To obtain a broad overview of the existing evidence base, we did not limit our search strategy to specific study types, language or publication date (Appendix 1).

**Information Sources**

We searched the following electronic databases from their inception up to February 2015: PubMed, EMBASE, CINAHL and Cochrane Library. Trial registries such as WHO ICTRP and ClinicalTrials.gov were also searched for completed or ongoing studies. To identify any additional studies, reference lists of all included articles and relevant systematic reviews were screened.

We searched gray literature through web searches via Google Scholar, SIGLE and relevant research websites [including National Institute for Health Research (NIHR), Wellcome Trust and Medical Research Council]. Contact with research networks and charities were also made (including Trisomy 21 Research Society, Down’s Syndrome Association, Down’s Syndrome International, Down’s Heart Group and Down’s Syndrome Medical Interest Group United Kingdom and Ireland).

**Eligibility Criteria**

We included studies of individuals with Down’s syndrome irrespective of age and covering any intervention (ie, medical and/or surgical) for the prevention or treatment of RTIs including watchful waiting and supportive care. We anticipated that the number of randomized controlled trials (RCTs) for this topic would be limited because of the specific study population. Therefore, we included all study types except for case series and case reports.

**Study Selection and Inclusion**

Two review authors (L.M. and K.R.) independently screened titles and abstracts retrieved from the database searches along with the reference lists of the included studies and relevant systematic reviews. The same authors independently reviewed the full text of potentially relevant studies against the predefined eligibility criteria. A third author (R.V) reviewed the discrepancies, and differences were resolved by consensus. Data extraction was performed by 1 reviewer (K.R.) and was independently checked by 2 reviewers (L.M. and R.V). Two reviewers (L.M. and R.V) independently performed the quality assessment of included studies.

**Outcomes of Interest**

As our systematic review aimed to identify interventions to either prevent or treat RTIs, identified papers were likely to encompass a broad range of outcome measures. As a consequence, we did not pre-specify any detailed outcome measures. We looked specifically at impact on frequency and recurrence of RTIs and any documented adverse effects.

**Data Extraction**

Data were extracted using a standardized form including information on study characteristics, setting, design, randomization, inclusion and exclusion criteria, data-analysis methods, interventions, outcomes and results.

**Risk of Bias Assessment**

We measured risk of bias in RCTs and non-randomized studies using the relevant “Risk of Bias” tools developed by Cochrane. We excluded studies with a critical risk of bias from our analyses.

**FIGURE 1.** Flow diagram of search results and selecting studies for inclusion.
Assessment of Heterogeneity

We assessed clinical heterogeneity across the included studies by reviewing differences in populations, interventions, and outcomes measured. In view of the marked differences in the interventions used in the individual studies, we did not perform a meta-analysis.

Role of the Funding Source

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RESULTS

Study Selection

Our searches identified 13,575 articles. After screening of titles and abstracts, 157 potentially relevant published articles were identified. After reviewing the full texts, 5 published studies were deemed suitable for inclusion (Fig. 1). An additional unpublished ongoing study was identified through our searches.

Study Characteristics

The main characteristics of the 5 published studies are presented in Table 1. All studies evaluated preventative interventions against RTI in children with Down’s syndrome: 2 studies assessed the effectiveness of passive immunotherapy, with palivizumab and pidotimod, respectively; 2 studies looked at prophylactic treatment with oral zinc supplements and 1 study at the effects of a school-based infection-control program.

All studies exclusively studied children with Down’s syndrome. The studies varied in terms of design (1 RCT, 1 non-RCT, 1 cohort study and 2 controlled before-after studies), age range of included children and duration of follow-up (Table 1). Two studies were conducted in Italy, 1 in Canada, 1 in Canada and the Netherlands and 1 in the United States.

We identified 1 postmarketing observational study ongoing in Japan, looking at the effects of palivizumab in preventing lower RTIs caused by RSV in children under the age of 2 who are either immunocompromised or who have Down’s syndrome.

Risk of Bias Across Studies

The overall risk of bias of the RCT was moderate. The overall risk of bias of the non-randomized studies was moderate for the cohort study (although high quality, there was no controlled comparator arm) and serious for the non-RCT. For the 2 controlled before-after studies, risk of bias was noted to be critical, and they were therefore excluded from analyses (Table 3).

TABLE 1. Characteristics of Included Published Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design</th>
<th>Number of Participants (%) Down’s Syndrome</th>
<th>Age (yr)</th>
<th>Domain</th>
<th>Intervention</th>
<th>Control</th>
<th>Outcome Measures</th>
<th>Risk of Bias*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lockitch et al19</td>
<td>RCT</td>
<td>64</td>
<td>1-19</td>
<td>Children with Down’s syndrome</td>
<td>Placebo (identical lactose pills)</td>
<td>No treatment</td>
<td>Number of children with URTI (days and episodes), doctor visits, antibiotic use and school absence</td>
<td>Moderate</td>
</tr>
<tr>
<td>Yi et al18</td>
<td>Prospective cohort study</td>
<td>765</td>
<td>2-18 months</td>
<td>Children with Down’s syndrome</td>
<td>Palivizumab</td>
<td>No treatment</td>
<td>RSV-related hospitalization, respiratory infection-related hospitalization</td>
<td>Moderate</td>
</tr>
<tr>
<td>La Mantia et al19</td>
<td>Non-RCT</td>
<td>26</td>
<td>3-13</td>
<td>Children with Down’s syndrome who had at least 6 URTIs in preceding 6 mo</td>
<td>Pidotimod 400 mg/d for 3 mo</td>
<td>No treatment</td>
<td>Number of URTI episodes (“relapses”) and days with fever</td>
<td>Serious</td>
</tr>
<tr>
<td>Kilfoil et al21</td>
<td>CBA</td>
<td>71</td>
<td>0-5</td>
<td>Children with Down’s syndrome</td>
<td>Infection Control Program</td>
<td>n/a</td>
<td>Respiratory illness rate, doctor visits, antibiotic use and school absence</td>
<td>Critical</td>
</tr>
<tr>
<td>Licastro et al22</td>
<td>CBA</td>
<td>21</td>
<td>7-15</td>
<td>Children with Down’s syndrome</td>
<td>Zinc sulfate supplements</td>
<td>n/a</td>
<td>Infection rate (mainly upper respiratory tract infection) and days with fever</td>
<td>Critical</td>
</tr>
</tbody>
</table>

*Risk of Bias was assessed using the Cochrane Risk of Bias Tools for Non-Randomized Studies (ACROBAT-NSRI).

TABLE 2. Risk of Bias Assessment for Lockitch et al20

<table>
<thead>
<tr>
<th>Domain</th>
<th>Judgment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
</tr>
<tr>
<td>Incomplete outcome data addressed (attrition bias)</td>
<td>High risk</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Other bias</td>
<td>Unclear risk</td>
</tr>
<tr>
<td>Overall</td>
<td>Moderate risk</td>
</tr>
</tbody>
</table>
Results of Individual Studies

Zinc Therapy

Lockitch et al randomized 64 children with Down’s syndrome to oral zinc therapy for 6 months or placebo, but reported only on the 50 children (23 treated with zinc and 27 with placebo) who had extreme numbers (ie, exceeding the 90th percentile value for siblings and age-matched unrelated children). In this subset of children with Down’s syndrome, during 6 months of treatment, no significant differences in terms of upper RTI episodes, doctor consultations and antibiotic use were found between children receiving zinc and children receiving placebo.19

Palivizumab

In a non-RCT, La Mantia et al followed 26 children with Down’s syndrome who had experienced at least 6 upper RTIs in the preceding 6 months and who received either the immunostimulant palivizumab for 3 months (14 children) or no treatment (12 children). While on palivizumab treatment, children with Down’s syndrome had fewer parent-reported upper RTI recurrences [mean 2.9, standard deviation (SD) 1.1 vs. mean 6.8, SD 1.3] and days with fever (mean 4.5, SD 3.5 vs. mean 16.9, SD 6.7) compared with those not receiving this treatment.19

APPENDIX 1. DOWN’S SYNDROME TERMS

MeSH: “Down Syndrome” OR TiAB: Down* syndrome* OR mongoloid OR trisomy 21 OR mongolism OR trisomy 21 OR aneuploidy OR down* disease* OR mongoloid idiocy OR Trisomy G AND

INFECTION TERMS

MeSH: Respiratory tract diseases OR Otitis media OR Respiratory syncytial virus, human OR Empyema OR TiAB: respiratory tract infection* OR upper respiratory infection* OR lower respiratory infection* OR RTI OR URTI OR LRTI OR rhinitis OR common cold* OR head cold* OR sinusitis OR rhinosinusitis OR pharyngitis OR laryngitis OR tracheitis OR tonsillitis OR sore throat* OR group OR epiglottitis OR otitis media OR AOM OR OME OR glue ear OR ear discharge OR otitis media OR middle ear disease* OR lung disease* OR cardiovascular disease* or obstructive sleep apnea* OR pleural cyst* OR congenital heart disease* OR atrioventricular canal defect* OR aortic valve disease* OR mitral valve disease* OR Fallot* tetralogy OR cyanotic heart* OR trisomy 21 OR aneuploidy OR Trisomy G OR tetralogy OR cleft palate OR oral cleft* OR mongoloid OR trisomy 21 OR aneuploidy OR down* disease* OR mongoloid OR trisomy 21 OR aneuploidy OR down* disease*

ASSOCIATED CONDITION TERMS

MeSH: cardiovascular diseases OR TiAB: respiratory tract disease* OR lung disease* OR cardiovascular disease* OR obstructive sleep apnea* OR pleural cyst* OR congestive heart disease* OR atrioventricular canal defect* OR aortic valve disease* OR mitral valve disease* OR Fallot* tetralogy OR cyanotic heart* OR trisomy 21 OR aneuploidy OR Trisomy G OR tetralogy OR cleft palate OR oral cleft* OR mongoloid OR trisomy 21 OR aneuploidy OR down* disease*

REFERENCES


