Tuina for children with upper respiratory tract infections
A protocol for a systematic review

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Abstract
Background: Upper respiratory tract infections (URTIs) is a common disease in children, which is also known as the common cold. Pediatric Tuina is a common treatment that Traditional Chinese Medicine (TCM) doctors commonly use for URTIs. However, there has no relevant systematic review studied on its effects and safety been reported. We plan to perform a systematic review and analysis of all the clinical evidence on the effectiveness and safety of Tuina for URTIs in children.

Methods: We will conduct the literature searching in the following electronic databases: Pubmed, Embase, Cochrane Library, Web of science, Chinese National Knowledge Infrastructure (CNKI), VIP, Wanfang, China Biomedical Literature Database (CBM), Chinese Clinical Trial Registry System. The time limit for retrieving studies is from establishment to July 2019 for each database. All published randomized controlled trials (RCTs) related to this review will be included. Review Manager (V.5.3.5) will be implemented for the assessment of bias risk and data analyses. Subgroup analysis and sensitivity analysis will be performed based on the conditions of included data.

Results: A high-quality synthesis of current evidence of Tuina for children with URTIs will be provided in this study.

Conclusion: This systematic review will provide evidence of whether Tuina is an effective intervention for children with URTIs.

PROSPERO registration number: CRD42019126963.

Abbreviations: RCTs = randomized controlled trials, TCM = traditional Chinese medicine, URTIs = upper respiratory tract infections.

Keywords: children, protocol, systematic review, Tuina, upper respiratory tract infections.

1. Introduction
Upper respiratory tract infections (URTIs) is a common disease in children whose symptoms include cough, sore throat, nasal stuffiness and discharge, sometimes accompanied with fever, also known as the common cold.[1–3] URTIs is the major cause of pediatric outpatient visits; every child has an average of 6 colds per year.[2,4] Although URTIs is mostly self-limiting, the possibility of developing to lower respiratory tract infections, tympanitis, asthma and febrile seizures is relatively high for children. As the URTIs is mainly caused by a multitude of different virus types with varying pathogenetic mechanisms,[5,6] the effectiveness and safety of current symptomatic interventions are uncertain for children. Wide use of antibiotics in URTIs is highly controversial for unsatisfactory effect on viruses.[7–11] And inappropriate antibiotic prescriptions in children are more likely to lead to drug resistance, and may also increase the risk of diseases such as antibiotic-associated diarrhea, increase diabetes, autoimmune diseases, asthma, obesity, and so on.[9,12–14]

Tuina is a physical therapy derived from Chinese medicine, using a series of manipulation on the human body surface to treat the disease. Pediatric Tuina is more easily accepted by children than drugs, especially for younger children who have difficulties taking medication. Pediatric Tuina is gradually widely used in China. The specific acupoint theory and operation methods are employed in pediatric Tuina to treat the common disease of children such as respiratory infections, anorexia, diarrhea, cerebral palsy, dysplasia, and so on.[15–19] Traditional Chinese medicine (TCM) doctors often apply pediatric Tuina to relieve the symptoms of acute URTIs and reduce the incidence of repeated respiratory infections. Studies have shown that Tuina can regulate the immune system function.[20,21] However, the current clinical efficacy lacks evidence-based medical system evaluation. Therefore, this study conducted a systematic review to objectively evaluate the efficacy of Tuina treatment for respiratory tract infections in children.
2. Method

2.1. Selection criteria

2.1.1. Types of studies. We will include the RCTs that involved Tuina therapy for URTIs in children in the treatment group, and its control group used other kinds of treatment without Tuina therapy. The literature of animal research, case report, review, and meta-analysis will be excluded.

2.1.2. Types of patients. Children (<12 years old) diagnosed with URTIs will be included in the study. There is no limitation on the gender, nation, and duration of the disease. Patients with severe medical conditions will be excluded.

2.1.3. Types of interventions. RCT using Tuina manipulation or Tuina with drugs, other treatments or no treatment (waiting-listed) for comparison will be included. RCT with comparison involved Tuina manipulation will be excluded.

2.1.4. Types of outcomes. The main outcome of this review is the effective rate after treatments. Additional outcomes are reduced symptom scores, recurrence rate and adverse events including hematoma.

2.2. Search strategy

Studies published on the Pubmed, Embase, Cochrane Library, Web of science, Chinese National Knowledge Infrastructure (CNKI), VIP, Wanfang, China Biomedical Literature Database (CBM), Chinese Clinical Trial Registry System will be searched since the establishment to August 2019.

The search keywords used include the following: “upper respiratory infections,” “upper respiratory tract infections,” “common cold,” “acute Coryza,” “Massage,” “Tuina,” “manipulation,” “Massotherapy,” “Child,” “Children,” “Infant,” “pediatric,” and “random” and there will be no restriction on language. More details will be updated on the “PROSPERO” website; the registration number is CRD42019126963. This study is an evidence-based medical research, so the ethical approval is not necessary.

2.3. Data collection and analysis

2.3.1. Selection of studies. Literature screening, study selection, and data extraction were performed by 2 reviewers (Jiayuan Zhang, Liu Cao). The literature searched from the electronic database will be imported EndnoteX9 for further screening of title and abstract, the duplications, and studies not meet the inclusion criteria will be excluded. After reading the full text of the remained literature, discussing within the group, the final included studies will be determined. We will try to contact the corresponding author when full text unavailable. Disagreements were solved by discussion or consulting a third party arbitrator until a consensus was achieved. The entire process of study selection is performed in the PRISMA flow diagram (Fig. 1).

2.3.2. Data extraction. The 2 reviewers will independently extract data by a standard form which includes title (serial number, name of first author, journal source, and published date), participants (age, gender, and number), interventions (method, time, and cycle), main outcomes, additional outcomes, and adverse events. If the data provided in the research are unclear, missing or difficult to extract reliably, the corresponding author will be contacted for clarification.

2.3.3. Assessment of risk of bias in included studies. The quality assessment for each RCT will be conducted independently by 2 reviewers using the Cochrane Collaboration Risk of Bias Tool checklist. Random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias will be assessed as low risk, high risk, or ambiguous risk in each RCT. Third-party experts will be consulted during any disagreement.

2.3.4. Measures of treatment effect. The treatment effect will be analyzed by 2 independent reviewers with Review Manager 5.3 software provided by the Cochrane Collaboration. Risk ratio (RR) with 95% confidence interval (CI) will be adopted for the dichotomous data (e.g., effective rate). For continuous data (e.g., recurrence rate), the mean difference (MD) with 95% CI will be adopted.

2.3.5. Dealing with missing data. The corresponding authors of the included studies with missing data will be contacted by available contact ways. If data are still unattainable, the study will be excluded in the data analysis.

2.3.6. Assessment of heterogeneity. Heterogeneity of the data will be assessed by $Q$ test and $I^2$ statistic. The heterogeneity will be deemed as low when $I^2 < 50\%$, moderate (50%–75%), high ($I^2 > 75\%$). The cause of the heterogeneity will be analyzed and a subgroup analysis will be performed.

2.3.7. Assessment of reporting bias. A funnel plot will be conducted to assess publication bias when the number of sufficient studies included for data analysis is $>10$.

2.3.8. Data synthesis. We will perform the systematic review of the literature with meta-analysis based on measurement methods, intervention methods, and the length of treatment and heterogeneity levels, and so on. Fixed-effect model will be applied when heterogeneity is low. Random-effects model will be applied when heterogeneity is moderate. Although the heterogeneity is significantly high, subgroup analysis or descriptive analysis will be performed.

2.3.9. Subgroup analysis. Subgroup analysis will be performed to assess the high heterogeneity of included studies. We will conduct subgroup analysis based on the data, such as disease duration, intervention time, different acupuncture points for Tuina, and so on.

2.3.10. Sensitivity analysis. After the quality assessment of the included literature, if there are possible low-quality studies, sensitivity analysis will be required. We will observe fluctuation of termination by changing the genre of research (incorporating or excluding a particular study) and reanalysis of simulated missing data.

3. Discussion

URTIs is very common during childhood. Symptomatic treatment in the acute phase does not reduce recurrence, and the use of antibiotics is not necessary in many cases. As a noninvasive external physiotherapy that China has used for thousands of years, TCM doctors believe that Tuina is effective and environmental-friendly with low cost, and especially suitable for children with fever and history of repeated respiratory infections.\textsuperscript{[22]} However, up to now, there has no relevant
Figure 1. Flow of literature screening.

1. Records identified through database searching (n=)
2. Records without duplications (n=)
3. Records screened (n=)
   - Records excluded:
     - reviews (n=)
     - animal mechanism (n=)
     - case reports (n=)
     - other diseases (n=)
     - others (n=)
4. Full-text articles excluded:
   - duplicate data (n=)
   - control group with Tuina (n=)
   - not RCT (n=)
   - inconsistency with outcomes (n=)
   - ongoing clinical trial (n=)
   - others (n=)
5. Full-text articles assessed for eligibility (n=)
6. Studies included in meta-analysis (n=)
systematic review been reported. This review aims to objectively evaluate the effectiveness and safety of pediatric Tuina in the treatment of URTIs in children based on evidence-based medicine, and whether it can effectively relieve acute URTIs and reduce the incidence of repeated URTIs. Due to the particularity of Tuina technology (TCM technology), it is expected that the RCTs retrieved in this review are mostly conducted in China, and the differences in specific treatment regimens and methodological quality in each trial can lead to significant heterogeneity.

Author contributions
Conceptualization: Jiayuan Zhang, Yunhui Chen, Qi Zhang.
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Investigation: Renyan Zhang, Renyuan Ren.
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Supervision: Renyan Zhang.
Visualization: Renyuan Ren.
Writing – original draft: Jiayuan Zhang, Liu Cao.
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