Check for updates

STUDY PROTOCOL

Serotypic distribution and antimicrobial resistance of *Streptococcus pneumoniae* in Chinese children under 5 years after the introduction of the 13-valent conjugate pneumococcal vaccine: protocol for a scoping review [version 1; peer review: 2 approved]

Xu Han [1], Niurka Molina Águila [1], Haiyang Yu [1], C. Nivaldo Linares Pérez [2], C. María Eugenia Toledo Romaní[1]

[1]Pedro Kourí National Institute of Tropical Medicine, Havana, Cuba
[2]Finlay Institute of Vaccines, Havana, Cuba

Abstract

The World Health Organization (WHO) recommends that pneumococcal conjugate vaccines (PCVs) be included in immunization programs worldwide. In China, the 7-valent pneumococcal conjugate vaccine (PREVNAR 7®) was authorized in 2008 but was not included in the national immunization programs. In 2016, PREVNAR 13®, a 13-valent pneumococcal conjugate vaccine (PCV13), was licensed for optional use in China. We will conduct a scoping review of the distribution of serotypes and antimicrobial resistance of *Streptococcus pneumoniae* in children aged under 5 years in China since the introduction of PCV13. We will obtain data from PubMed, the China National Knowledge Infrastructure (CNKI), and Wanfang Med Online. We will also review epidemiological data from WHO and the China Antimicrobial Surveillance Network (CHINET). Our analysis will include the condition of interest, the intervention, and the geographical region. All types of studies will be eligible for inclusion in the study database if they meet the inclusion criteria. This scoping review is intended to outline how *S. pneumoniae* serotypes are distributed, and it will map their antimicrobial resistance in children aged under 5 years in China. The results of this study will provide useful information on the impact of PCV13 in China.

Keywords
Streptococcus pneumoniae, serotype, antimicrobial resistance, 13-valent pneumococcal conjugate vaccine, China

Open Peer Review

Reviewer Status ✓ ✓

	Invited Reviewers	
	1	**2**
version 1 31 Mar 2020	✓ report	✓ report

1 **Guanlan Zhao** , University of Alicante, Alicante, Spain

2 **Eric Bonnet** , CEA (French Alternative Energies and Atomic Energy Commission), Evry, France

Any reports and responses or comments on the article can be found at the end of the article.

Corresponding author: C. María Eugenia Toledo Romaní (mariaeugenia@ipk.sld.cu)

Author roles: Han X: Investigation, Project Administration, Writing – Original Draft Preparation; **Molina Águila N**: Methodology, Writing – Original Draft Preparation; **Yu H**: Investigation, Writing – Original Draft Preparation; **Linares Pérez CN**: Methodology, Resources, Validation, Writing – Review & Editing; **Eugenia Toledo Romaní CM**: Conceptualization, Methodology, Project Administration, Resources, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Introduction

Pneumonia accounts for 15% of all deaths of children under 5 years old, killing 808,694 children in 2017; *Streptococcus pneumoniae* is the most common cause of bacterial pneumonia in children[1]. Although the widespread use of PCVs has decreased the burden of invasive pneumococcal disease (IPD)[2], *S. pneumoniae* is still a substantial issue because immunization causes serotype changes, the available PCVs are costly, and widespread antibiotic use during the last decades has resulted in drug-resistant strains of *S. pneumoniae*[3]. The introduction of pneumococcal vaccines has decreased the incidence of drug-resistant strains in some areas[4]. However, because of the widespread abuse of antibiotics and limited use of vaccines in many Asian countries, antibiotic resistance remains a very serious problem in Asia.

In China, pneumococcal disease is a major cause of morbidity and mortality in children[5,6]. Although PCV7 was licensed in China in 2008, it was not included in the national immunization program. The coverage rate of this vaccine is low; only 10% of Chinese children received PCV7 in 2016[7]. An analytical decision model indicated that the use of PCV7 could have prevented more than 16.2 million cases of pneumococcal disease and 709,411 deaths in China during the 10 years after the vaccine's introduction[8]. Similarly, although PCV13 was licensed for optional use in November 2016, it is not widely used because of low awareness and the high price of the vaccine.

China still lacks a systematic surveillance program for pneumococcal diseases. To date, studies analyzing serotypes and antimicrobial resistance of *S. pneumoniae* have not specified the date of introduction or the type of PCV. This study may provide useful information on the impact of PCV13 in China.

Objectives

In this study, we aim to investigate how *S. pneumoniae* serotypes are distributed and to map antimicrobial resistance in children under age 5 years in China since the introduction of PCV13. We formulated our main review question using the SPICE framework (setting, perspective, intervention, comparison, evaluation). The framework and key elements are summarized in Table 1.

Table 1. Overview of the key elements of the review question.

Key Element	Elaboration
Setting	In mainland China, PCV13 has been licensed for optional use since November 2016.
Perspective	Children under the age of 5 years in China may benefit from vaccination.
Intervention	Individual or group interventions that include the PCV13 vaccine.
Comparison	Subgroups with and without the intervention and populations before and after the intervention.
Evaluation	Impact in terms of *S. pneumoniae* serotype distribution and antimicrobial resistance

Methods

Inclusion criteria

All types of studies are eligible for inclusion in our review if they meet all 5 of the following criteria: (1) Analyze serotype distribution or antimicrobial resistance to *S. pneumoniae* in China; (2) contain information on the impact of PCV13 in China; (3) include only subjects less than 5 years of age; (4) be written in English or Chinese; and (5) be published between November 2016 and February 2020.

Two investigators will independently evaluate the titles and abstracts of all articles according to the inclusion criteria. Any disagreement will be resolved through discussion among team members, and if there is difficulty related to the selection of studies, the criteria will be refined.

Information sources

The study will begin in March 2020 and will include searches of PubMed, the China National Knowledge Infrastructure (CNKI), Wanfang Med Online, the WHO database, and the China Antimicrobial surveillance Network (CHINET).

PubMed is the largest database of medical information in the world. Created in 1946 by the National Library of Medicine, it includes the MEDLINE database, which contains information from more than 24 million articles published in 5,600 journals in 30 languages.

CNKI, as the largest, most-used online academic library in China, is a key national information construction project under the lead of Tsinghua University. It is the most comprehensive repository of knowledge in China, with more than 16 million website visits each day. In 2019, the website recorded 2.3 billion full-text downloads.

Wanfang Med Online aims to become a type of bridge that connects medical professionals and researchers in China with medical professionals and researchers around the world. At present, the English version includes about 200 selected Chinese medical journals including the top 115 medical journals published by the Chinese Medical Association, 1 Science Citation Index (SCI) journal, 7 Science Citation Index Expanded (SCIE) journals, and 60 Medline journals.

Search

The search strategy will be based on a combination of three elements: the condition of interest, the specified intervention, and the geographical region (Figure 1). The use of "OR" and "AND" to combine key words is shown in Table 2.

Study records

Data management. Retrieved records will be automatically or manually exported into EndNote.

Selection process. The search and selection process will be documented in a PRISMA flowchart[9]. Screening and selection will be done in duplicate by two members of the review team. Any discrepancies discovered during screening of full-text papers will be discussed with the principal investigator.

Data collection process. Two investigators will independently extract data from the studies that meet the inclusion criteria. Any disagreement will be resolved through discussion, and if they do not agree, the principal investigator will arbitrate. If data are missing or not sufficiently described in the studies, we will contact the corresponding author to obtain the missing information.

Data items. The information technology department will develop two tables for organizing the data: a table that itemizes serotype, and a table that lists antimicrobial resistance to pneumococci. The tables will contain the elements listed in Table 3.
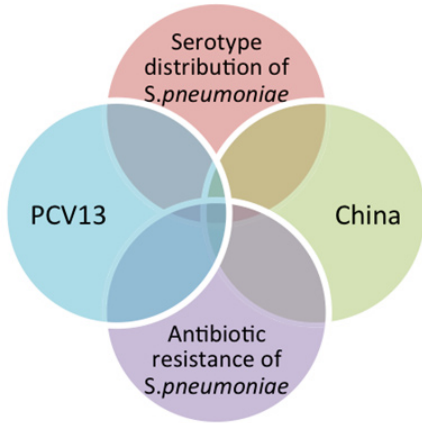
Outcomes and prioritization
Our review will focus on the scope of the available literature about the serotype distribution of and antibiotic resistance to *S. pneumoniae*, and the potential impact of PCV13 in China. We do not foresee outcome prioritization, but the approach will be descriptive.

Risk of bias in individual studies
The risk of bias will be determined independently by two study team members. For nonrandomized studies, we will use the ROBINS-I tool[10], and for randomized trials, or interventions, we plan to use Cochrane Collaboration's risk-of-bias assessment tool[11] .

Data synthesis
A PRISMA flow chart and the methodological process will be described in detail for transparency. It will indicate the evidence identified and whether it was selected for inclusion in the review. If a study is excluded, the reasons will be provided.

The data will be summarized in the form of a figure, diagram, or table. A narrative summary of the findings will also be included. The strategy for synthesizing the data involves the use of analytical methods and will perform a descriptive synthesis of the data to map the distribution of serotypes and antimicrobial resistance of pneumococci in children under 5 years of age in China after the introduction of PCV13.

Review team and roles
The review team is presented in Table 4.

Figure 1. Summary of search strategy.

Table 2. Planned search syntax.

Keyword	Database
((((("serotyping"[MeSH Terms]) OR "drug resistance"[MeSH Terms])) AND "streptococcus pneumoniae"[MeSH Terms]) AND 13-valent pneumococcal conjugate vaccine) AND China	PubMed
((serotype OR antibiotic resistance) AND streptococcus pneumoniae) AND (pneumococcal conjugate vaccine OR 13-valent pneumococcal conjugate vaccine)	CNKI
((serotype OR antibiotic resistance) AND streptococcus pneumoniae) AND (pneumococcal conjugate vaccine OR 13-valent pneumococcal conjugate vaccine)	Wanfang Med Online

Table 3. Type of data to be collected.

Characteristics of extracted data	
Reference	Title, authors, publication type, journal, publication year
Study	Type of study, study period
Setting	Study objective, most frequent isolated serotypes and/or antimicrobial resistance pattern for *S. pneumoniae*
Population	Country where study took place; type and size of population undergoing intervention
Intervention	Description of intervention, and whether it was an individual or group intervention, or both
Study design	Elements needed to assess risk of bias as formulated by the authors
Evaluation	Evaluation of impact (the most predominant serotypes circulating in children, serotype coverage of the available PCVs, whether these serotypes contributed to the distribution of antibiotic-resistant isolates); denominator (children younger than 5 years of age)

Table 4. Review team, affiliations and roles.

Name	Affiliation	Role
Xu Han	Pedro Kourí Institute, Havana, Cuba	Write draft protocol, search & select studies, extract & synthesis data, write draft review
Haiyang Yu	Pedro Kourí Institute, Havana, Cuba	Write draft protocol, search & select studies, extract & synthesis data, write draft review
María Eugenia Toledo Romaní	Pedro Kourí Institute, Havana, Cuba	Write draft protocol, give methodological input, solve discordances in data extraction, write draft review, corresponding author
Niurka Molina Águila	Pedro Kourí Institute, Havana, Cuba	Provide context knowledge, give methodological input
Nivaldo Linares Pérez	Finlay Institute of Vaccine, Havana, Cuba	Provide topic expertise, interpret findings, give feedback on draft texts

Study status

This review is a part of ongoing research in China on the interchangeability of PCV13 with the Cuban vaccine PCV7-TT.

When we complete this scoping review, we will consider conducting a systematic review, and we intend to publish the results in an international journal. While preparing the present protocol, we performed preliminary searches to get an idea of the size of the available literature.

Ethics

Because the scoping review methodology consists of reviewing and synthesizing the data already published, this part of the study is not subject to ethical approval.

Study strengths

- This systematic scoping review will be the first to map antimicrobial resistance to and distribution of pneumo-coccal serotypes in children less than 5 years of age in China after the introduction of PCV13.

- It will present an overview of all studies on serotype distribution and antimicrobial resistance, and the analysis will clarify the characteristics and possible differences between the provinces of China.

- A search of three large databases will enable us to create a comprehensive map of antimicrobial resistance to and distribution of pneumococcal serotypes in China.

Data availability

No data are associated with this article.

References

1. **Pneumonia**. WHO, 2019.
   Reference Source

2. O'Brien KL, Wolfson LJ, Watt JP, *et al.*: **Burden of disease caused by** *Streptococcus pneumoniae* **in children younger than 5 years: global estimates.** *Lancet.* 2009; **374**(9693): 893–902.
   PubMed Abstract | **Publisher Full Text**

3. Balsells E, Guillot L, Nair H, *et al.*: **Serotype distribution of** *Streptococcus pneumoniae* **causing invasive disease in children in the post-PCV era: A systematic review and meta-analysis.** *PLoS One.* 2017; **12**(5): e0177113.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

4. Song JH: **Advances in pneumococcal antibiotic resistance.** *Expert Rev Respir Med.* 2013; **7**(5): 491–8.
   PubMed Abstract | **Publisher Full Text**

5. Chinese Maternal and Child Health Development Report: **Chinese Journal of Women and Children Health**. 2019; **10**(1).
   Reference Source

6. Huang G, Shi Q, Chen H, *et al.*: **Bacteria detection in sputum and analysis of bacterial resistance in childhood pneumonia.** *Journal of HeBeijing Medical University.* 2016; **37**(1): 40–3.
   Reference Source

7. Liu S, Hu HL, Yang YH, *et al.*: **A systematic review about** *Streptococcus Pneumoniae* **serotype distribution in children in mainland of China before the PCV13 was licensed.** *Expert Rev Vaccines.* 2017; **16**(10): 997–1006.
   PubMed Abstract | **Publisher Full Text**

8. Hu S, Shi Q, Chen CI, *et al.*: **Estimated public health impact of nationwide vaccination of infants with 7-valent pneumococcal conjugate vaccine (PCV7) in China.** *Int J Infect Dis.* 2014; **26**: 116–22.
   PubMed Abstract | **Publisher Full Text**

9. Liberati A, Altman DG, Tetzlaff J, *et al.*: **The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration.** *PLoS Med.* 2009; **6**(7): e1000100.
   PubMed Abstract | **Publisher Full Text** | **Free Full Text**

10. Sterne JA, Hernán MA, Reeves BC, *et al.*: **ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions.** *BMJ.* 2016; **355**: i4919.
    PubMed Abstract | **Publisher Full Text** | **Free Full Text**

11. Shuster JJ: **Review: Cochrane handbook for systematic reviews for interventions, Version 5.1.0, published 3/2011. Julian P.T. Higgins and Sally Green, Editors.** *Res Synth Methods.* 2011; **2**(2): 126–30.
    Publisher Full Text

Open Peer Review

Current Peer Review Status: ✔ ✔

Version 1

Reviewer Report 30 July 2020

https://doi.org/10.5256/f1000research.25017.r66175

✔ **Eric Bonnet** [iD]

Institute of Genomics, CEA (French Alternative Energies and Atomic Energy Commission), Evry, France

In this article, the authors describe a protocol for a scoping review of the distribution of serotypes and antimicrobial resistance of *Streptococcus pneumoniae* in children aged under 5 years in China since the introduction of the 13-valent conjugate pneumococcal vaccine (PCV) in China in 2016.

Pneumonia accounts for quite a large number of deaths for children under 5 years old worldwide and *Streptococcus pneumoniae* is the most common cause of the disease. In China, approximately 30,000 children die of pneumonia each year. The introduction of PCV has quite dramatically reduced the impact of the disease in many areas of the world. However, infections by *S. pneumoniae* are still a problem because of the many serotypes for this bacteria and also because immunization triggers serotype changes. In China, PCVs were introduced quite recently (2008), with only 10% of the children that received the vaccine. Furthermore, there is no systematic surveillance program for pneumococcal diseases. Therefore, the main goal of the protocol described in this study is very timely and will be very useful for researchers and epidemiologists.

The article is well written, concise, and with enough precision. The authors focus on the PCV 13-valent which was introduced in China in 2016, and they intend to analyze all the relevant literature published on the subject till February 2020. The criteria defined for the selection of the articles are well described and relevant. The authors intend to use three main databases to conduct their survey, namely PubMed, the China National Knowledge Infrastructure (CNKI) and Wanfang Med Online. Review epidemiological data will also be included from the World Health Organization and the China Antimicrobial Surveillance Network (CHINET).

I only have a few remarks that could help to improve further the quality of the manuscript:

In the methodology section, the authors mention a potential "risk of bias", but do not elaborate much on that topic. I would suggest explaining what this risk is about and if possible give one or two concrete examples.

It seems that a couple of studies have investigated with simulations of the cost-effectiveness of PCV-13

usage in China. See for instance Mo *et al.* Pediatr. Infect. Dis. J. 2016 PMID 27753771, Tyo *et al.* Vaccine 2011 PMID 21745516.[1,2] I would suggest to lookup for more publications of this type and to include a small paragraph summarizing the results in the introduction.

Maybe it would also be useful to include a small paragraph on the serotype distribution in China before the introduction of PCV-13, see Lyu *et al.* Expert Rev. Vaccines PMID 28745918.[3]

References

1. Mo X, Gai Tobe R, Liu X, Mori R: Cost-effectiveness and Health Benefits of Pediatric 23-valent Pneumococcal Polysaccharide Vaccine, 7-valent Pneumococcal Conjugate Vaccine and Forecasting 13-valent Pneumococcal Conjugate Vaccine in China.*Pediatr Infect Dis J*. **35** (11): e353-e361 PubMed Abstract | Publisher Full Text

2. Tyo KR, Rosen MM, Zeng W, Yap M, et al.: Cost-effectiveness of conjugate pneumococcal vaccination in Singapore: comparing estimates for 7-valent, 10-valent, and 13-valent vaccines.*Vaccine*. 2011; **29** (38): 6686-94 PubMed Abstract | Publisher Full Text

3. Lyu S, Hu HL, Yang YH, Yao KH: A systematic review about Streptococcus Pneumoniae serotype distribution in children in mainland of China before the PCV13 was licensed.*Expert Rev Vaccines*. **16** (10): 997-1006 PubMed Abstract | Publisher Full Text

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Not applicable

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: bioinformatics, biology, immunology

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 09 April 2020

https://doi.org/10.5256/f1000research.25017.r62038

Guanlan Zhao iD

Department of Community Nursing, Preventive Medicine and Public Health and History of Science, University of Alicante, Alicante, Spain

The authors describe in details the highlights of this study protocol. Pneumococcal disease is one of the main causes of morbidity and mortality in children under 5 years old. In 2018, the number of newborns in China exceeded 15 million, and there is a huge clinical demand for the vaccine. In China, there are two types of vaccines. The first type of vaccine refers to the vaccine provided by the government to public free of charge, and the public shall be vaccinated in accordance with the government's regulations, mainly with the routine immunization vaccine for children and the second type of vaccine refers to the vaccine that is provided by the public at their own expense and voluntarily, such as Streptococcus pneumoniae vaccine. Due to the huge burden of disease and the acknowledgement of protecting the children's' health about pneumococcal disease, it also shows the importance and feasibility of this study. I think it be useful to create a comprehensive map of this topic in China.

About information sources, the author chooses the China National Knowledge Infrastructure (CNKI), Wanfang Med Online, there are two important Chinese databases. I believe that the integration of these database together with Pubmed will make the future scoping review more complete and perfect.

Possible recommendation of future scoping review: In recent years, China's economy has developed rapidly, but the gap of economic level still exists in different regions of China, and the distribution of medical resources will also be affected. Is there known to be differences in education levels or income levels in selected articles? It might be good to discuss what possible other socioeconomic differences might exist in geographical regions that would account for differences in the vaccination rate in the scoping review.

The authors describe the objective and material and methods of study clearly.

Is the rationale for, and objectives of, the study clearly described?
Yes

Is the study design appropriate for the research question?
Yes

Are sufficient details of the methods provided to allow replication by others?
Yes

Are the datasets clearly presented in a useable and accessible format?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Epidemiology, Occupational Health, Cohort Studies

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Author Response 12 Apr 2020

Xu Han, Pedro Kourí National Institute of Tropical Medicine, Havana, Cuba

Thank you for your comments and suggestions!

We agree with your comments, it is very interesting that you mentioned about these factors affecting immunization coverage level in China, especially the impact caused by the socio-economic differences between the geographic regions.

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias

- You can publish traditional articles, null/negative results, case reports, data notes and more

- The peer review process is transparent and collaborative

- Your article is indexed in PubMed after passing peer review

- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research