Author’s response to reviews

Title: The Landscape of Vaccines in China: History, Classification, Supply, and Price

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Author’s response to reviews:

Dear Editor,

Thank you having our manuscript reviewed for consideration of publication in BMC ID. We appreciate the constructive reviews and suggestions. We took the reviewers’ comments seriously and have done our best to satisfy reviewer suggestions, revising the manuscript accordingly.

In the response letter, the reviewers’ comments are in bold font and are followed, comment-by-comment, with our response in regular font. When we changed the manuscript, we quote the new wording in the response.

Thank you for the opportunity to address reviewers’ comments and to revise and resubmit our manuscript. We continue to believe that it will be of interest to readers of BMC ID, and that it will be cited as a description of the vaccine landscape in China.

On behalf of the authors,

Hongjie YU,

Corresponding author
Reviewer #1: The paper "The Landscape of Vaccines in China: History, Classification, Supply, and Price" depicts China's situation with respect to vaccination, providing interesting insights into the Chinese landscape. Anyway, the paper might be of limited interest for the international reader. This is my major concern. The paper is rather fluid and accountable with respect to sources used, even though there are some aspects that could be implemented and are as follows.

Response: Thank you very much for this perspective and valuable advice. This manuscript is focused on the development of Chinese vaccines and their use in China. As a developing country, China has several notable achievements in vaccine development and immunization—such as the development of EV71 and hepatitis E vaccines, and control of Japanese encephalitis with a novel, live, attenuated vaccine. China is a large vaccine-producing country, and the Chinese vaccines are emerging into international use through the Gavi/UNICEF market for WHO-prequalified vaccine; 3 are currently prequalified. We believe that for these 2 reasons, the international reader will be interested in the manuscript. We also believe that Chinese experience in vaccine and immunization in the last few decades could be of use in low- and middle-income countries.

1. General organization of the paper: in my opinion the paper should take into account the different items (vaccination history and immunization policies, classification, supply and prices of vaccines) in the same order both in methods and in results.

Response: Thank you for the careful reading and helpful recommendation. We revised the manuscript and placed these items in the same order in the Methods and Results sections.

Introduction

2. Authors should provide references for the EPI and the assessment by WHO in 2010 and 2014.

Response: We have added references for these 3 items – references.
Methods

3. High- and middle-income countries considered for comparison are not explicated. Several times Authors referred to selected European but, eventually, they considered United States, United Kingdom and BRICS countries. Furthermore, in some parts of the paper, Authors refer to WHO recommendation for all countries.

Response: Thanks for the advice; we added a sentence to clarify which countries are included in the comparative analysis. The Methods section now says, “We compared the list of vaccine of China with high-income countries including UK, US and middle-income countries including Brazil, Russia, India and South Africa. We obtained lists of vaccines available in the United States (US) and the United Kingdom (UK) from US CDC [6] and Public Health England. [7] Lists of vaccines and diseases prevented through routine immunization for China, US, UK, Brazil, Russia, India, and South Africa were obtained from China CDC, UNICEF, and WHO. [8]”

4. The specification of vaccines belonging to categories 1 and 2 should be addressed earlier in the paper, in the paragraph "History, vaccine categories and vaccines".

Response: Thank you for the advice. We have the full list of vaccines with categorization in table S1 in an appendix. Because of the restriction on number of figure and table, we put the full list of vaccine in the appendix.

5. The study period should be justified (2007-2015).

Response: Thank you for the advice. The study periods for each part had different purposes: 1930s-2016 for history, 2007-2015 for supply, and 2013-2015 for price. We now define the study periods in the Methods section, specifying “Vaccine supplied, expanded program of immunization and categorization. We obtained names and types of vaccines released in China between 1930s and 2015 from Applied Vaccination Handbook, the Biologicals Lot Release program of the National Institutes for Food and Drug Control (NIFDC), China Food and Drug Administration (CFDA)”

“Vaccine supply
We obtained the numbers of doses of vaccines released in China between 2007 and 2015 from NIFDC.

Prices

Costs data were collected between 2013 and 2015.

Results

6. Authors quoted "In China, 25 diseases are preventable by 50 vaccines". I would encourage Authors to add some details about the number of VPDs that may be actually prevented in China as compared to the rest of the world.

Response: Thank you for the advice. We listed all VPDs for each vaccine supplied in China in table s1, but have placed this list in an appendix because of the restriction on number of figures/tables. We list the set of VPDs in Figure 3, which provides a comparison between China and other countries.

7. Authors quoted "Procurement prices of EPI-substitute vaccines (Category 2 vaccines against diseases preventable by Category 1 vaccines) were higher than for their EPI equivalents". This sentence is not clear in my opinion. Were not category 1 vaccines free of charge?

Response: Thank you for the question; this is a good point. Although the category 1 vaccine were free for the vaccinated, the government had to pay the vaccine in the procurement process. We revised the manuscript in the Results section to: "Both Category 1 and Category 2 vaccines are contracted for and procured by government, even though Category 2 vaccines are paid for by families or vaccinees, while Category 1 vaccines are provided at no cost."

Discussion

8. Authors quoted "Especially notable is the lack Hib, ORV, PCV, influenza, and HPV vaccines, which are recommended by WHO for all countries' national immunization programs". This sentence should be further elaborated as these vaccines are not lacking in China but they are not included in the EPI.
Response: This is a good point. We revised the sentence to “Especially notable is that, despite availability in China as Category 2 vaccines, Hib, ORV, PCV, influenza and HPV vaccines, which are recommended by WHO for all countries’ national immunization programs, are not in China’s EPI system.”

9. Authors quoted "tetanus was verified to be eliminated in 2012”. Did the Authors refer to maternal/neonatal tetanus? Furthermore, no references were provided.

Response: Yes, we meant maternal/neonatal tetanus. We have included a reference to the WHO declaration that China eliminated MNT.

Figures

10. In figure 5 Authors refer to European countries and UNICEF. As told before, Authors did not specify which European countries they took into account. The caption reports "(6.2 Chinese Renminbi per USD)"; what does it mean? Furthermore, Authors should report details in methods about extraction (and conversion/correction, if any) of vaccines cost data from the different sources used.

Response: In response to the previous comment (Comment 3), we clarified which countries are being compared. We have rewritten the sentence on the exchange rate between Chinese currency and U.S. currency, which is used for making country-to-country comparisons. The exchange rate sentence now reads, “We used US dollars for country comparisons; the exchange rate for US dollars to Chinese Yuan was 6.2 dollars per Yuan.”

We revised the description to add more detail about how the prices were extracted in the methods. The description now states, “We obtained vaccine prices from the Chinese Central Government Procurement (CCGP) office and from vaccine contracts published in the E-procured system by departments of health or CDCs in central, provincial, autonomous regions, municipal, city, and county-level governments. We used “NIP vaccine” and “Category 2 vaccine” as separate keywords to search for vaccine prices. For analyses, we used the lowest price for each vaccine, consistent with procurement practices. We compared government procurement prices in China with those of US, Europe and low-income countries. Prices of US vaccines were obtained from US CDC’s Vaccine Price List. Prices for European countries vaccines were obtained from “Review of Vaccine Price Data, 2013” by the WHO European Region. A total of 24 European
countries reported their procurement prices for 41 vaccines. The median price for each vaccine was used in country comparison. Many low-income countries obtain low-priced vaccines from UNICEF. We therefore used vaccine price data published by UNICEF as representative of low-income country vaccine prices. We used US dollars for country comparisons; the exchange rate for US dollars to Chinese Yuan was 6.2 dollars per Yuan. Vaccine price data were collected between 2013 and 2015.”

Reviewer #2: This article delivered the information on vaccination situations, vaccine manufacturing and marketing status in China between 2007 to 2015. The authors were able to point out the improvement of vaccination related matters in China throughout these years and the deficiencies in comparison with other developing and also developed countries in detail.

However, there're several problems with this article that should be fixed or improved. The rationale of this study was confusing without a clear definition of purpose. Problematic expressions were also found in the results. In Figure 3 and S Figure 1, several diseases data are prevented by national programs in the UK, US, Russia, or Brazil's NIP but not China, which deserves an explanation. Vaccination situation comparisons between China and other countries are made without enough detail aspects.

Response: Thank you very much for the advice. We have clarified the rationale in the Introduction so that the second paragraph of the Introduction now states, “China is an emerging producer of vaccines for global use and has had several notable immunization achievements. China’s vaccine industry and its immunization program have some differences compared with other countries’ industries and programs, but an overview of the Chinese vaccine industry and immunization effort has not been published in the international scientific literature. To describe the development of China’s vaccine industry and immunization program, we analyzed selected aspects of vaccines and immunization in China and report the history, immunization policies, classification, supply, and price of vaccines in comparison with selected high- and middle-income countries.”

We have also added more comparative data between China and the comparison countries. The modified description is: “Figure 3 depicted the national immunization program in high-income counties such as US and UK, middle income countries such as Russia, Brazil, India and South Africa. National immunization program in China had more VPD prevented by EPI than Russia, India and South Africa, but less VPD prevented than US, UK and Brazil. Hib vaccine,
pneumococcal conjugate vaccine (PCV) and Rotavirus vaccine are included in the US, UK, Brazil and South Africa’ national immunization programs, while China’s EPI includes neither vaccine (Figure 3). Hib vaccine, PCV13, oral rotavirus vaccine (ORV), varicella vaccine (Var), and seasonal influenza vaccine (InfV) are available only as Category 2 vaccines, while meningococcal group B (MenB) vaccine is not available in China.”

For the discussions, the authors mentioned that vaccination work in China has implications for other countries, however without specifications.

Response: To address this comment, we added to the Discussion to indicate that provision of vaccine and vaccination strategy may be useful contributions, stating, “We believe that China’s immunization program experience can help other countries achieve similar results with effective and affordable vaccines. In addition to contributing to UNICEF’s global supply of WHO-prequalified vaccines, China’s experience achieving high vaccination coverage levels in challenging situations, such as the program for administering a timely birth dose of hepatitis B vaccine, can provide good examples of program strategy.”

Although this article provides meaningful information about vaccination related situations in China in the recent years, the authors fail to provide in depth review or discussion on the numbers and figures. The discussions were mostly simple comparisons or fact expressions. Suggestions made at the end of the article were dogmatic and superficial.

Response: To address this comment, we added more information to the Discussion and removed the suggestions made at the end of the manuscript. We now mention that the change in population policy will increase the demand for vaccine domestically, stating, “The fluctuation of vaccine supply in 2007-2015 has shown that vaccine demand depends on both the birth cohort size and the use of catch-up campaigns. In 2015, the central government changed the one-child policy to become a two-child policy. This change will lead to an increase in the birth cohort size, and therefore will lead a greater domestic demand for vaccine.”

We have removed the suggestions at the end of the manuscript, substituting the paragraph with a shorter paragraph: “In Summary, China is a well-regulated producer of globally-important vaccines, some of which are uniquely made in China. However, some vaccines that are important
globally are available in China but are not included in China’s EPI system. Sustained and coordinated effort will be required to bring China’s vaccine industry and EPI into an era of global leadership.”

I also suggest more discussions on the impact of category 2 vaccine prices on the prevention and control of diseases; the measures and related analysis for expanding the vaccination program (EPI) coverage area; benefit analysis on rabies vaccination considering the increasing threat of rabies occurrence and death rate, etc.

Response: Thank you for the advice. We added the following discussion on the impact of regulation revision and discussion on price: “From a short- to medium-term public health perspective, lower-cost vaccines are preferable because more children can be vaccinated for a given budget. Low pricing can be achieved in part through large demands in an economy of scale. Prices for Category 2 vaccines may be high because their demand volumes are not large enough to achieve an economy of scale. Manufacturers of Category 2 vaccines profit from high prices, which provides an incentive to stay in the market and fund innovations in research and development of novel vaccines. Finding a balance between manufacturers’ profit needs and public health’s needs is challenging. The 2-category system in China is one approach to finding a balance, with traditional vaccines in the program and newer vaccines available in China, but not provided by the program.”

We also added a reference to the link between vaccine category and coverage and a reference to the link between price and disease. However, we think that a detailed discussion on the link between vaccine cost and disease is too big of a topic for the scope of this manuscript and would prefer not to go into more detail.