

RESEARCH ARTICLE

High pneumonia lifetime-ever incidence in Beijing children compared with locations in other countries, and implications for national PCV and Hib vaccination

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Abstract

Objectives

To compare the proportion of Beijing children who have ever had pneumonia (%*Pneumonia*) to those in other locations, and to estimate by how much national vaccine coverage with Pneumococcal Conjugate Vaccine (PCV) and Haemophilus Influenzae Type b (Hib) could reduce Beijing %*Pneumonia*.

Methods

%*Pneumonia* was obtained for each age group from 1 to 8 years inclusive from 5,876 responses to a cross-sectional questionnaire. Literature searches were conducted for world-wide reports of %*Pneumonia*. Previous vaccine trials conducted worldwide were used to estimate the pneumococcal (*S. pneumoniae*) and Hib (*H. influenzae*) burdens and % *Pneumonia* as well as the potential for PCV and Hib vaccines to reduce Beijing children's % *Pneumonia*.

Findings

The majority of pneumonia cases occurred by the age of three. The cumulative %*Pneumonia* for 3–8 year-old Beijing children, 26.9%, was only slightly higher than the 25.4% for the discrete 3 year-old age group, similar to trends for Tianjin (China) and Texas (USA). Beijing's %*Pneumonia* is disproportionately high relative to its Gross National Income (GNI) per capita, and markedly higher than %*Pneumonia* in the US and other high GNI per capita countries. Chinese diagnostic guidelines recommend chest X-ray confirmation while most other countries discourage it in favor of clinical diagnosis. Literature review shows that chest X-ray confirmation returns far fewer pneumonia diagnoses than clinical diagnosis. Accordingly, Beijing's %*Pneumonia* is likely higher than indicated by raw numbers. Vaccine trials

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suggest that national PCV and Hib vaccination could reduce Beijing's %*Pneumonia* from 26.9% to 19.7% and 24.9% respectively.

Conclusion

National PCV and Hib vaccination programs would substantially reduce Beijing children's pneumonia incidence.

Introduction

By 2012, Beijing had achieved a remarkable decrease in her mortality rate for children under 5 years old (U5MR) to 3.6 per thousand (3.6‰) [1] compared to 7.1‰ for the United States [2,3]. However, the Beijing pneumonia U5MR of 0.25‰ in 2012 [1], was still higher absolutely and more especially as a fraction of the total U5MR than the 0.20‰ in 2012 for the United States [2]. Pneumonia, the world's largest killer of children from 1 to 59 months, persists as a severe public health problem in Beijing [4].

Although pneumonia is said to be a major public health problem in China [5], pneumonia incidence data for China have been scarce [5–7]. Total pneumonia incidence cannot be deduced from hospitalization and/or mortality rates. The present study, part of the China, Children, Homes, Health (CCHH) multi-city project, used a questionnaire that asked parents of kindergarten children (1 to 8 years old) whether their child had ever had doctor-diagnosed pneumonia [8]. Thus, our study returned total incidence as well as the proportion of children in each age group from 1 to 8 who had ever had pneumonia. We will use %*Pneumonia* to designate the proportion of Beijing children who have ever had pneumonia. To our knowledge, these are the first such estimates for Beijing children. Of great interest is how Beijing children's %*Pneumonia* compares with others around the world. We note that such comparisons require accounting for diagnostic methods because diagnosis using chest X-ray confirmation returns many fewer pneumonia diagnoses than clinical judgment [4,9].

Developed countries are widely acknowledged to have much lower pneumonia incidence than developing countries [3,4]. The World Bank defines “developed” as having Gross National Income (GNI) per capita equal to or above the “high income” threshold. In 2014, while China's overall GNI per capita was 60% of the World Bank's \$12,736 threshold for high income [10], the provincial level municipality of Beijing had achieved near developed status with a GNI per capita calculated at 98% that of the high income threshold [10,11] (calculated below in the section “Relative GNI”) [11,12].

Viral, bacterial and other micro-organisms cause pneumonia [4]. There are vaccines for two of the bacterial pathogens, “Haemophilus Influenzae Type b” (Hib) for *H. influenzae* type B [4,13] and “Pneumococcal Conjugated Vaccine” (PCV) for 13 serotypes of *S. pneumoniae* (also called “SP” or “pneumococcus”) [4,13,14]. To avoid confusion about terminology, we note that both the *H. influenzae* type B pathogen and the vaccine are commonly called Hib. The Hib vaccine was first introduced in a national vaccine program by Iceland in 1989 [15], and PCV7 and PCV13 vaccines by the United States in 2000 [15] and 2010 respectively [16]. Hib is presently included in the national vaccination programs of 185 countries, and PCV7 or PCV13 in 103 countries, but as of January 2016 neither PCV or Hib was part of China's national vaccination program [15].

Accordingly, the objectives of the present study are (1) to compare %*Pneumonia* for Beijing children to those in other regions and countries, and analyze these comparisons in the context

of different diagnostic criteria, national vaccination status and GNI per capita and (2) to estimate by how much Beijing children's %Pneumonia could be reduced by national coverage with PCV and Hib.

Methods

Acquisition of Beijing, Tianjin and Texas data

The Beijing CCHH cross-sectional survey was conducted in 2010–2011. Its methods are described in Qu et al. 2013 [17] and the full CCHH questionnaire is published in Zhang et al. 2013 [8]. The Texas and Tianjin studies used the same methods. The question for pneumonia is: *Has your child been diagnosed with pneumonia by a doctor? (Yes/No)*. We will use %Pneumonia to represent the proportion of children, at a given age, who have ever had pneumonia.

Worldwide lifetime-ever pneumonia incidence (%Pneumonia)

We conducted a literature search for %Pneumonia in other regions and countries. Inclusion criteria required (1) age-specific %Pneumonia and (2) total doctor-diagnosed %Pneumonia, regardless of whether hospitalization was required and (3) data for any group of children 3 years old and older. Nine studies, with data for 23 different locations, met these criteria (Table 1, Results and Discussion).

Age groups

For a specific age group, %Pneumonia is given by:

$$\%Pneumonia = \frac{n_{lifetime}}{N} \times 100 \tag{1}$$

where $n_{lifetime}$ is the number of children in that age group who have ever had pneumonia, that is, the number of children who have had at least one episode of pneumonia, and N is the total number of children in that age group. Because a child can have more than one case of pneumonia, the total number of pneumonia cases for a population is greater than %Pneumonia.

Pneumonia incidence, defined as the number of cases in a population of children, is highest in the first 2–3 years (S1 Table). We hypothesized that %Pneumonia, defined as the proportion of children who have ever had pneumonia, increases from 0 to 3 years-old and then plateaus. If so, %Pneumonia can be compared among any samples of children between 3 and 8 years-old, with the understanding that there are slight %Pneumonia increases for successive ages. For samples of children <3 years-old, %Pneumonia can be compared only among identical age groups. That is, for age i where $3 \leq i \leq 8$, %Pneumonia can be approximated as:

$$\%Pneumonia = \frac{n_3 + \dots + n_i}{N_3 + \dots + N_i} \times 100 \tag{2}$$

We test this hypothesis in the Results and Discussion section (%Pneumonia related to age).

Diagnostic criteria

Pneumonia is diagnosed predominantly by chest X-ray confirmation of clinically suspected pneumonia, or by clinical signs and symptoms alone. We used the country's national diagnostic guidelines as default if a study did not report diagnostic criteria.

Table 1. Lifetime-ever pneumonia (%Pneumonia) reported for children ≥ 3 years old.

Location	Age (Years)	N	%Pneumonia (%)	Diagnostic criteria	Vaccination ^a	Reference
Changsha, China	3–6	2,622	38.3	Chest X-ray	Unknown (very low)	Lu 2014 [20]
Shanghai, China		14,084 ^b [21]	33.2		11.4% PCV, 41% Hib [18]	Zhang 2013 [8]
Chongqing, China		5,092	31.3		Unknown (very low)	
6 CCHH cities ^c , China		~19,000	31.1		Unknown (very low)	
Tianjin, China		4,616	29.1		5.3% PCV, 41% Hib [18]	Present Study
Romania	7–11	3,470	27.9	Unknown	No	Leonardi 2002 [22]
Beijing, China	3–6	5,331	26.9	Chest X-ray	1.2% PCV, 41% Hib [18]	Present Study
Bulgaria	7–11	3,631	24.7	Unknown	No	Leonardi 2002 [22]
Hungary		3,479	24.6			
Poland		2,932	21.5			
Slovak Republic		3,038	16.3			
Czech Republic		3,479	16.2			
Germany	6	2,234	13.5	Clinical	Hib	Schnabel 2009 [23]
Texas, USA^d	3–6	1,523	13.1		53% PCV, >90% Hib [24]	Present Study
Germany ^e	3	~2,100	8.8		>90% Hib	Schnabel 2009 [23]
Tucson AZ, USA	3	788	7.4	Chest X-ray	No	Castro-Rodriguez 1999 [25]
Germany ^f	7	~74,000	6.9	Clinical	>90% Hib	Weigl 2003 [26]
West Sydney, Australia	5–15	2,020	6.8	Chest X-ray	>90% Hib	MacIntyre 2003 [27]
Spain	5	654	3.0	Clinical	No	Garcés-Sánchez 2005 [28]

^a Shanghai, with GNI equal to 1.02 times the World Bank high income index, was reported to have 11.4% PCV and 41% Hib coverage in 2012. Given the high purchase price for these vaccines [18], we estimated that Beijing and Tianjin with relative GNI equal to 0.98 and 0.85 of the high income index had similar coverage (corrected for vaccine availability), but that Chinese cities with lower GNI had very little coverage.

^b Calculated from Liu 2014 [21].

^c Harbin, Nanjing, Taiyuan, Urumqi, Xi'an, Wuhan.

^d Vaccination coverage for Texas sample estimated from Center for Disease Control [24].

^e Munich, Leipzig, Wesel, Bad Honnef.

^f Schleswig-Holstein.

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Vaccination status

National vaccination status for PCV and Hib was obtained from the International Vaccine Information Center [15]. We assumed full coverage if a national vaccination program had been established at least one year before the birth year of the oldest children. In China, PCV and Hib became available for private purchase in October 2008 and 2000 respectively [18]. We estimated Beijing children's private vaccination rates using data compiled by Wagner et al. for Shanghai children [18]. We reasoned that the two cities' similar GNIs per capita, estimated using data from the World Bank [10,11], the China National Bureau of Statistics [12] and the International Money Fund (IMF) [12] means that similar proportions of parents would be willing and able to incur the high cost of these vaccinations. Of Shanghai children born between 2005 and 2010, 11.4% received PCV7 and 41% received Hib vaccination. For Beijing children in the present study, only 10.4% of the 3 to 8 year-old Beijing children were born late enough to have had timely PCV vaccination, so PCV coverage is estimated at 1.2% (that is, 10.4% × 11.4%), leaving 98.8% of Beijing children not PCV vaccinated. All of the Beijing children were born after 2000 when Hib was available, so we estimate 41% were Hib vaccinated and 59% were not. For Tianjin children, 47% were born when PCV7 was available, so we estimate that 5.3% coverage (that is, 47% × 11.4%). All Tianjin children were born when Hib was established, so we estimate 41% Hib coverage.

Relative GNI

Every year, the World Bank sets GNI per capita index numbers for low, lower middle, upper middle and high income [10]. A country whose GNI is equal to or more than the high income index is classified as “developed.” Accordingly, we calculated a relative GNI as the ratio of a country’s average GNI per capita for the children’s birth years to the average high income index for those years [10], so that a country’s whose relative GNI per capita ≥ 1.0 can be considered as “developed” [10]. GNIs were not directly available for the province-level municipalities Beijing, Tianjin, Chongqing and Shanghai, so we estimated these GNIs from their GDPs [12] multiplied by China’s GNI/GDP ratio [10,12]:

$$GNI_m = \left(\frac{GNI_C}{GDP_C} \right) (GDP_m) \quad (3)$$

where the subscript “m” denotes municipalities and the subscript “C” denotes China. These estimates assume that the municipality’s GNI/GDP ratio scales linearly with that of China.

Results and discussion

The Beijing cross-sectional survey yielded 5,876 completed questionnaires, a 65% response rate. The 5,440 Beijing children aged 3 to 8 had an average %Pneumonia of 26.9%, with diagnoses most likely confirmed by chest X-ray, as per China’s national guidelines [7,19].

Table 1 shows that the %Pneumonia for the Chinese cities in recent years is the highest, followed by those of Central European countries (Bulgaria, Czechoslovakia, Hungary, Poland, Romania and Slovakia), whose %Pneumonia in the 1980s were only slightly lower than for China cities. The lowest %Pneumonias are for locations in the US, Germany, Australia and Spain in various years.

%Pneumonia related to age

Is it valid to compare %Pneumonia for any age group ≥ 3 as we have done in Table 1? We plotted %Pneumonia for age groups 1–8 years from Beijing, Tianjin and Texas in Fig 1, the data for which are shown in S2 Table. Fig 1 shows that %Pneumonia climbs steeply in the first two to three years, plateauing at about 36 months (3 years), or approximately 25% for Beijing, 10% for Texas, and 28% for Tianjin. Published data from the CCHH cities Xi’an [29] and Changsha [20] also show %Pneumonia increasing until age three, and then plateauing. These data are, to the best of our knowledge, the total of available %Pneumonia data for each age group.

For incidence, abundant data are available (S1 Table), and an example of incidence versus age for half-year age groups is shown in S1 Fig. In this scatterplot, the incidence of Lower Respiratory Tract Infection rises steeply until 3 years old and then plateaus, similarly to that of %Pneumonia. We conclude that %Pneumonia can be compared for any two years between 3 and 8 inclusive, recognizing that each subsequent year (or added year) will increase %Pneumonia slightly. %Pneumonia comparisons between groups younger than 3 years-old can only be made between same-age groups.

No diagnostic “gold standard”

Table 1 specifies whether %Pneumonia was obtained using clinical judgment of signs and symptoms or chest X-ray confirmation of clinical suspicion. The national guidelines for pneumonia diagnosis in China require chest X-ray confirmation and at least one of four clinical signs or laboratory findings [5,19]. By contrast, most countries represented in Table 1, and in

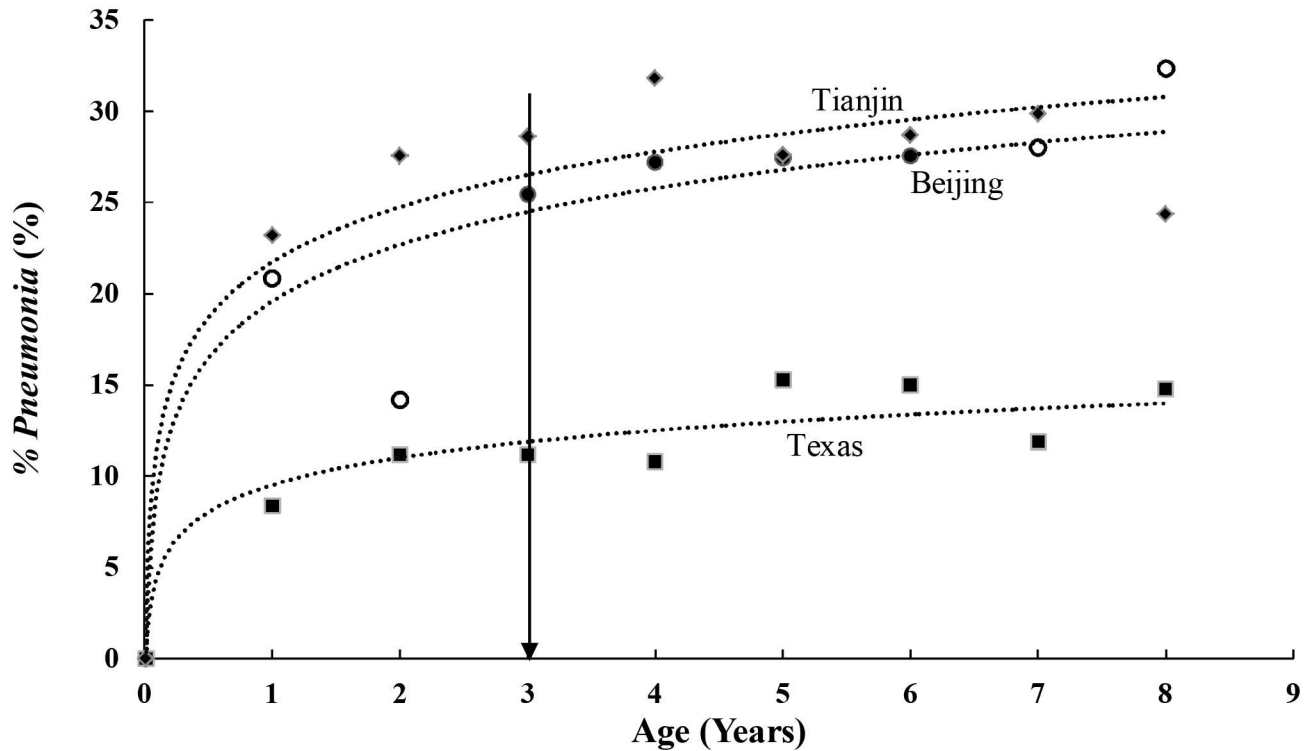


Fig 1. Lifetime-ever pneumonia (%Pneumonia) for each discrete age group from 1 to 8 years old in Beijing, Tianjin (China) and Texas (USA). Data for this figure is shown in [S2 Table](#). The open circles for Beijing indicate small sample sizes.

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particular the UK [30] and US [31], recommend pneumonia diagnosis solely by clinical criteria, except in the case of severe pneumonia, where serial chest X-rays are recommended to track improvement.

There is no diagnostic “gold standard” for pneumonia [4,32,33]. We surveyed literature studies in which each subject was diagnosed separately by clinical signs/symptoms and chest X-ray (Table 2). The ratios for clinical to chest X-ray diagnoses range from 1.1 to 7.7, clustering between 2 and 3. In other words, just 1/3 to 1/2 those diagnosed with pneumonia using clinical signs had their pneumonia confirmed by chest X-ray. Accordingly, differences between % Pneumonia in Chinese cities (diagnosis by X-ray) and locations where diagnosis was by clinical signs are even greater than those indicated by the raw numbers of Table 1. S1 Text (Pneumonia diagnosis) further explores the difficulties associated with diagnosing pneumonia.

%Pneumonia using chest X-ray: Beijing, Tianjin and Tucson (USA)

Table 3 shows %Pneumonia generated by chest X-ray (CXR) diagnoses for Beijing, Tianjin, and Tucson AZ, USA [25]. We compared 3 year-olds only so as to minimize uncertainty inherent in comparing different age groups. The %Pneumonias for the Chinese cities are substantially higher than that for the USA city. Table 3 does not include the 11.2%Pneumonia from a study in northeast Texas USA of 384 three-year-olds born in 2004 [57], because diagnosis was primarily by clinical criteria. Since %Pneumonia by clinical diagnosis is reliably higher than by chest X-ray confirmation, the Texas %Pneumonia is consistent with the Tucson data.

Table 2. Ratio of clinical to chest X-ray diagnoses in various samples of children.

N	Age	Location	Ratio of diagnoses: clinical/chest X-Ray	Comments	Reference
222	0-60M ^a	Sevagram Wardha, central India	1.05	Chest X-ray criteria were more sensitive than the WHO-EPC introduced in 2001.	Gupta 1996 [34]
2,071	<21Y ^b	Boston MA, USA	1.2	1,501 < 5 years old. Ratio is for physician rated probability of pneumonia >75%. Study conducted at Children's Hospital of Boston.	Neuman 2010 [35]
155	≤19Y	Baltimore MD and Columbus OH, USA	1.4	62% < 2 years old.	Grossman 1988 [36]
314	<60M	Hong Kong	1.8	Hospitalized. Clinical diagnosis: bacterial, pneumonia, chest X-ray criterion: consolidation.	Chiu 2014 [37]
191	<60M	Orlando FL, USA	1.9		Rothrock 2001 [38]
420	2-59M	Gambia (rural)	1.9		Kuti 2014 [39]
651	<24M	Mozambique (rural)	2.3		Roca 2010 [40]
4,093	1-35M	Bogotá, Colombia	2.4		Benavides 2012 [41]
125,983 ^c	<60M	Washington, USA	2.4		Nelson 2008 [9]
100	<16Y	Unugu, Nigeria	2.7	Clinical diagnostic criteria were not specified.	Njeze 2011 [42]
13,026	1-35M	Goiana, Brazil	2.8	Goiana, Brazil, children who presented at hospital, but were not necessarily hospitalized.	Andrade 2012 [43]
1,068	<36M	Northern California	2.8	"High suspicion" of pneumonia from clinical exam. (See Black [44] below for "low suspicion" pneumonia.)	Black 2002 [44]
570	12M-16Y	Ontario or Quebec, Canada	2.8	Study includes all who presented to hospital; 97% were not admitted.	Lynch 2004 [45]
30,397 ^d 30,444 ^e	0-17M	Guatemala (rural)	2.8	Parents excluded some clinically diagnosed children from X-ray, so ratio may be artifactually large.	Smith 2011 [46]
525	1M-16Y	Tel Aviv, Israel	2.9	68% <6 years old.	Ayalon 2013 [47]
351	≤18M	Guatemala (rural)	3.0	Children with WHO criteria for pneumonia referred to MD by field health worker for diagnosis and X-ray read by same MD.	Bruce 2007 [48]
NR ^f	<24M	Refugee camp, Thailand	3.3	Cohort was 955 children. Incidence reported as cases/(child-year).	Turner 2013 [49]
1,608	1-36M	San Jose, Costa Rica	3.5	Prospective Surveillance of children presenting to health centers for invasive pneumococcal disease only.	Arguedas 2012 [50]
413	36-60M	Hong Kong	4.1		Ho 2007 [51]
1,698	<36M	Northern California	4.5	"Lower suspicion" pneumonia (See Black [44] above for "high suspicion" of pneumonia).	Black 2002 [44]
477	<24M	Hong Kong	4.9		Ho 2007 [51]
711	0-15Y	Northern England	5.0	80% < 5 years old.	Clark 2007 [52]
1,519	<60M	Pakistan (urban)	5.8	Clinical impression was "suspicion" of pneumonia.	Hazir 2006 [53]
1,622	<60M	Boston MA, USA	5.9	Clinical diagnosis based on WHO tachypnea.	Shah 2010 [54]
200	<60M	Beer Shiva, Israel	6.1	Clinical impression was "suspicion" of pneumonia.	Ben Shimon 2012 [55]
1,918	4-23M	Ukraine (urban)	7.7		Plishvili 2013 [56]

^a Months.

^b Years.

^c Child-years of observation.

^d Child weeks of observation, clinical diagnoses.

^e Child weeks of observation, chest X-ray diagnoses.

^f Not reported, but 488/955 (51.1%) had at least one episode.

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Table 3. Comparison of chest X-ray (CXR) generated %Pneumonia for 3 year-old children in two Chinese cities and one US location.

Location	Children's birth years	N	Vaccination ^a		%Pneumonia (%) (Chest X-ray)	Reference
			Hib (%)	PCV (%)		
Beijing, China	2007–2008	1,336	41 ^b	1.2 ^b	25.4	Present Study
Tianjin, China	2009	528	41 ^b	5.3 ^b	28.6	Present Study
Tucson AZ, USA	1980–1984	888	No ^c	No ^c	7.4	Castro-Rodriguez 1999 [25]

^a Vaccine coverage is assumed if a national program was initiated one or more years before children's birth.

^b Vaccination rates estimated from Shanghai voluntary vaccination rates [18], as explained in Methods.

^c Study completed before vaccines were available.

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Estimating by how much national PCV and Hib coverage can reduce Beijing children's pneumonia

Pathogens other than *S. Pneumoniae* and *H. Influenzae*, for example viruses, can cause pneumonia—especially Respiratory Syncytial Virus (RSV) but also influenza virus, various bacteria and other organisms [4]. The etiological causative agent is usually very difficult to identify [4] so that the “etiological fraction” (the proportion of pneumonia attributable to any given pathogen [58]) cannot be determined directly. Nonetheless, vaccine trials, both Randomized Controlled Trials (RCTs) and observational studies of vaccination, measure the proportional reduction of pneumonia [13,58–61]. Such a trial, termed “Vaccine Probe” [13,58–62] estimates Vaccine Efficacy (VE) as well as the lower bound of etiological fraction. For any given Vaccine A that targets Pathogen A,

$$VE_A = \frac{I_u - I_{v,A}}{I_u} \leq \text{Pathogen A etiological fraction} \tag{4}$$

where I_u is the incidence in the unvaccinated “control” sample and I_v is the incidence in the vaccinated “test” sample [58,59]. Re-arranging yields the incidence in a vaccinated population:

$$I_{v,A} = I_u(1 - VE_A) \tag{5}$$

While Vaccine Probe studies of PCV and Hib have not yet been conducted in China, they have been conducted in countries that differ from each other demographically and climatically, and have yielded remarkably tight ranges for both *S. Pneumoniae* and *H. Influenzae* etiological fractions, with chest X-ray confirmed pneumonia as the endpoint. Table 4 shows VEs calculated via meta-analysis of PCV and Hib studies. Information on the individual studies used for these meta-analyses is given in S3 Table (S3A and S3B Table). These VEs are

Table 4. VEs obtained by meta-analyses for PCV and Hib.

Study	Vaccine	Number of studies included	Countries	VE (%) (95% Confidence Interval, CI)
Lucero 2009 [63]	PCV	6	South Africa (2), USA (2), Finland (1), Philippines (1)	27 (15, 36)
O'Brien 2009 [14]	PCV ^a	4	Gambia, USA, Philippines, South Africa	36 (16, 52) ^b
Theodoratou 2009 [13]	PCV9	3	Gambia, South Africa, Philippines	26 (12, 37)
Theodoratou 2009 [13]	Hib	6	Bangladesh, Brazil, Chile, Colombia, Gambia, Indonesia	18 (-2, 33)

^a Adjusted for PCV Valence.

^b Confidence Interval (CI) estimated from O'Brien 2009, Fig 1.

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Table 5. Impact of PCV and Hib vaccination on a birth cohort of 122,747, the number of babies born in Beijing in 2012 [1], assuming %Pneumonia to be 26.9% at age 3. We used the Lucero value for VE_{PCV} , 27% (15%, 36%) [63] and the Theodoratou value for VE_{Hib} , 18% (-2%, 33%) [13]. Potential pneumonia reductions are given for both wholly unvaccinated and vaccinated populations as we have estimated for Beijing.

Vaccine	% Vaccinated	$N_{T,u}$	Vaccination reduces to %Pneumonia from 26.9% this %. ^a (95% CI)	This many fewer children get pneumonia (95% CI)
PCV	0	122,747	19.6 (22.9, 17.2)	8915 (4953, 11887)
Hib	0	122,747	22.1 (26.9, 21.7)	5943 (0, 10896)
PCV+Hib	0	122,747	14.8 (22.9, 12.1)	14,858 (4953, 22783)
PCV ^b	1.2	121,274	19.7 (22.9, 17.3)	8808 (4893, 11744)
Hib ^b	41	72,421	24.9 (26.9, 21.7)	3507 (0, 6429)
PCV+Hib	-	-	16.9 (22.9, 12.1)	12,315 (4893,18173)

^a $I_{v,PCV} = I_u (1 - VE_{PCV})$. $I_{v,Hib} = I_u (1 - VE_{Hib})$. $I_{v,PCV + Hib} = (n_{T,u} - n_{T,v})/N_T$. VE_{PCV} : 27% (95%CI: 15%, 36%) [63]. VE_{Hib} : 18% (95%CI: -2%, 33%) [13].

^b Estimated using data from Shanghai [18], and assuming that Beijing voluntary vaccination rates are approximately the same as those in Shanghai.

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sufficiently robust to estimate by how much PCV and Hib vaccination could reduce Beijing children's %Pneumonia.

In Table 5, we have estimated I_v for PCV ($I_{v,PCV}$) and Hib ($I_{v,Hib}$) using Eq (5) and the Lucero value for VE_{PCV} , 27% (15%, 36%) [63] and the Theodoratou value for VE_{Hib} , 18% (-2%, 33%) [13]. $I_u = \%Pneumonia = 26.9\%$. For a population in which there has been no vaccination, %Pneumonia would decrease from 26.9% to 19.6% for PCV or to 22.1% for Hib. Among Beijing's 122,747 children born in 2012, 8,915 (PCV) or 5,943 (Hib) fewer children would get pneumonia. Based on Shanghai data [18], we estimate 1.2% and 41% of Beijing's children have been vaccinated with PCV and Hib respectively. Since these children are already protected, we subtract these subsets from the total and so obtain a smaller reduction in %Pneumonia, from 26.9% to 19.7% for PCV or to 24.9% for Hib. Among the Beijing 2012 birth cohort, 8,808 (PCV) or 3,507 (Hib) fewer children would get pneumonia.

Of great interest is the impact of introducing both PCV and Hib. There are no studies to guide a prediction of this impact. However, we can propose a Confidence Interval (CI): the lower limit of %Pneumonia reduction is equal to or slightly greater than that of PCV alone and the upper limit is the sum of PCV and Hib reductions. Table 5 shows that for a population with no vaccination, the maximum reduction by PCV + Hib in %Pneumonia would be to 14.8% from 26.9%. For Beijing's 122,747 children born in 2012, 14,900 fewer children would get pneumonia. For a population that had 1.2% PCV and 41% Hib vaccination rates, the maximum reduction in %Pneumonia would be to 16.9% from 26.9%. For Beijing's 122,747 children born in 2012, 12,300 fewer children would get pneumonia.

%Pneumonia related to GNI per capita

Fig 2 is a scatterplot of %Pneumonia in children three years old and older versus relative GNI for the studies listed in Table 4. The data for Fig 2 are shown in Table 6. Consistent with smaller pneumonia incidence in developed than developing countries [3,4], the trend is of %Pneumonia decreasing with increasing GNI per capita. However, Beijing, Tianjin and Shanghai, with relative GNIs at 0.98, 0.85 and 1.02 respectively, depart markedly from this trend as shown in Fig 2. These cities have %Pneumonia as high as or higher than countries with relative GNIs only half as great.

Beijing has developed towards being a high GNI per capita city with unprecedented speed [64]. Although increasing GNI per capita is accompanied by changes that ameliorate risk factors for infectious diseases [65], it is possible that Beijing's modernization and development

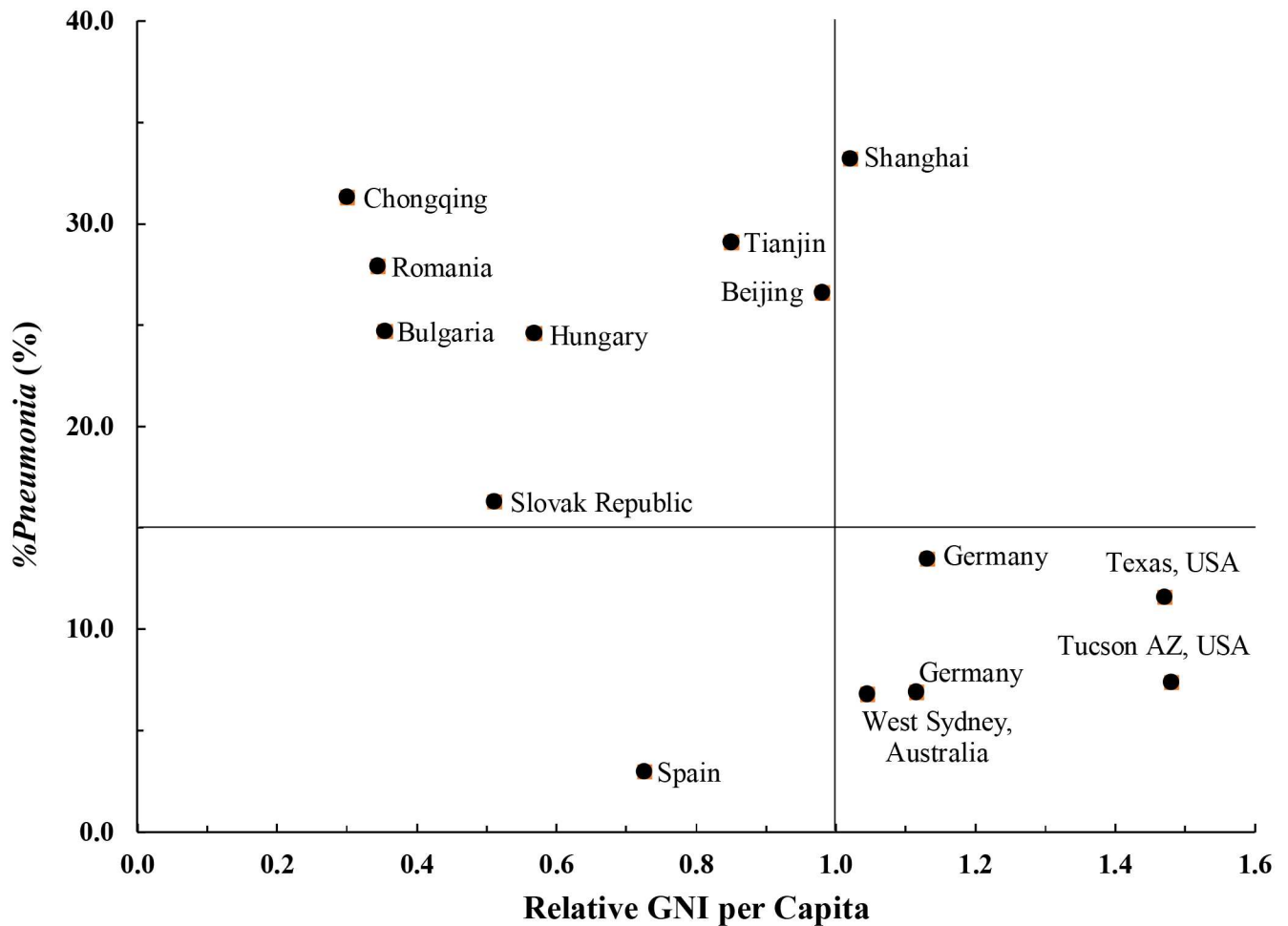


Fig 2. Lifetime-ever pneumonia (%Pneumonia) as related to relative GNI per capita. Relative GNI per capita is the ratio of a country's GNI to the World Bank High GNI Index for the children's birth years.

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has been so rapid that the positive effects have not yet had enough time to take root. Moreover, when a certain proportion of a population has been vaccinated, the reduced density of pathogens results in decreased incidence in the unvaccinated, or a “herd effect,” which further decreases the overall incidence [66].

Limitations

This study is subject to the limitations of survey questionnaires, including recall bias and memory errors. In addition, reported “incidences” are an underestimate if medical attention was not sought for a sick child with pneumonia, but an overestimate if there was incentive, as there has been in China, for physicians to prescribe antibiotics [67]. The literature estimates of *VE* are for children ≤ 2 years old and not for older children; however, we have shown that for children aged 1 to 8, most pneumonia happens before age 3 (Fig 1 and S1 Fig). Literature *VEs* were derived from incidence rather than %Pneumonia data, and it is not known whether they can be applied to %Pneumonia. Our data do not include mortality statistics. However, we can estimate from the U5MR mortality rate of 0.25‰ in 2012 [1] that the pneumonia deaths in this sample of approximately 6,000 would have been 1.5, a mathematically negligible quantity.

Table 6. %Pneumonia as related to relative GNI per capita, the ratio of a country's GNI to the World Bank high income GNI for the children's birth years.

Location	Relative GNI ^a	%Pneumonia (%)	Children's birth years	Reference
Texas, USA	1.48	13.1	2002–2006	Present Study
Tucson AZ, USA	1.48	7.4	1980–1984	Castro-Rodriguez 1999 [25]
Germany ^b	1.13	13.5	1997–2005	Schnabel 2009 [23]
Germany ^c	1.11	6.9	1992–1996	Weigl 2003 [26]
Shanghai	1.02	33.2	2005–2008	Zhang 2013 [8]
Beijing	0.98	26.9	2005–2008	Present Study
Tianjin	0.85	29.1	2007–2010	Present Study
Spain	0.82	3.0	1995–1996	Garcés-Sánchez 2005 [28]
Hungary	0.57	24.6	1984–1989	Leonardi 2002 [22]
Slovak Republic	0.51	16.3		
Bulgaria	0.35	24.7		
Romania	0.34	27.9		
Chongqing	0.30	31.3	2005–2008	Zhang 2013 [8]

^a Relative GNI = GNI/High Income GNI.

^b Munich, Leipzig, Wesel, Bad Honnef.

^c Schleswig-Holstein.

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We also do not know the severity of pneumonia cases (whether the pneumonia required hospitalization or was invasive) or the number of cases per child. Finally, fluctuations in the severity of yearly influenza, a risk factor for pneumonia [68] and likely to increase pneumonia incidence especially in children 0–3 years-old, have been neglected.

Conclusions

The proportion of Beijing children who have had pneumonia at least once by age 8, 26.9%, is similar to that of Tianjin. Because the Beijing %Pneumonia is mostly chest X-ray derived, it likely represents true pneumonia cases, but also may underestimate %Pneumonia for Beijing children. Beijing, Tianjin and Shanghai all have higher %Pneumonia than those of other comparably high GNI regions and countries. There is potential for reducing Beijing's %Pneumonia. China, unlike other country locations with lower %Pneumonia, lacks both PCV and Hib national vaccination programs. Based on vaccine efficacies, it is estimated that national PCV and Hib vaccination would reduce Beijing's %Pneumonia from 26.9% to 19.7% and 24.9% respectively.

However, Beijing would still have greater %Pneumonia than consistent with high GNI per capita. It is likely that Beijing's severe air pollution [64], a known risk factor for pneumonia [69–71] must be addressed to achieve further reduction.

Supporting information

S1 Fig. Cumulative Lower Respiratory Tract Infection (LRTI) incidence as a function of age.

(TIF)

S1 Table. Ratio of pneumonia incidence in first 12, 24 and 36 months (M) of life to subsequent months.

(DOCX)

S2 Table. The proportion of children in each age group who have ever had pneumonia (% Pneumonia), Beijing, Tianjin and Texas.

(DOCX)

S3 Table. VEs of PCV and Hib by meta-analyses. S3A Table. Studies used in meta-analyses of PCV VE. S3B Table. Studies used in Theodoratou et al.'s meta-analysis of Hib VE.

(DOCX)

S1 Text. Pneumonia diagnosis: clinical judgment versus chest X-ray confirmation.

(DOCX)

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