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Cost-effectiveness of strategies for preventing paediatric lower respiratory infections associated with respiratory syncytial virus in eight Chinese cities

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ABSTRACT

Background: New monoclonal antibodies (mAbs) and vaccines against RSV with promising efficacy and protection duration are expected to be available in the near future. We evaluated the cost-effectiveness of the administration of maternal immunisation (MI), infant mAb (IA) and paediatric immunisation (PI) as well as their combinations in eight Chinese cities.

Methods: We used a static model to estimate the impact of these preventive interventions on reducing the burden of RSV-ALRI in twelve monthly birth cohorts from a societal perspective. In addition to year-round administration, we also considered seasonal administration of MI and IA (i.e., administered only to children born in selected months). The primary outcome was threshold strategy cost (TSC), defined as the maximum costs per child for a strategy to be cost-effective.

Results: With a willingness-to-pay threshold of one national GDP per capita per QALY gained for all the cities, TSC of year-round strategies was: (i) US$2.4 (95% CI: 1.9-3.4) to US$14.7 (11.6-21.4) for MI; (ii) US $19.9 (16.9-25.9) to US$144.2 (124.6-184.7) for IA; (iii) US$28.7 (22.0-42.0) to US$201.0 (156.5-298.6) for PI; (iv) US$31.1 (24.0-45.5) to US$220.7 (172.0-327.3) for maternal plus paediatric immunisation (MPI); and (v) US$41.3 (32.6-58.9) to US$306.2 (244.1-441.3) for infant mAb plus paediatric immunisation (AP). In all cities, the top ten seasonal strategies (ranked by TSC) protected infants from 5 or fewer monthly birth cohorts.

Conclusions: Administration of these interventions could be cost-effective if they are suitably priced. Suitably-timed seasonal administration could be more cost-effective than their year-round counterpart. Our results can inform the optimal strategy once these preventive interventions are commercially available.

1. Introduction

Globally, acute lower respiratory infection (ALRI) remains the second leading cause of morbidity and mortality in children under 5 years of age [1,2]. Respiratory syncytial virus (RSV) is the most common viral cause of ALRI in young children and can cause severe complications, resulting in hospitalisations or deaths [3]. In China, ALRI remains the third leading cause of morbidity and mortality among children younger than 5 [1,2]. With an estimated incidence of 31.0 per 1000 persons per year in this age group, China accounted for 7.8% (2.6 million/33.1 million) of the global RSV-associated ALRI (RSV-ALRI) cases among children younger than 5 according to estimates by Shi et al for the year 2015 [4].

The only approved RSV-specific preventive therapy, the monoclonal antibody (mAb) palivizumab, is mainly used among infants at high risk of RSV complications (such as infants with <35 gestational age in weeks, or infants with congenital heart or lung disease) during RSV season with multiple injections in well-resourced settings due to its high costs [5]. New mAbs against RSV are in different stages of development and hold the promise of having lower costs and longer duration of protection [5,6]. The

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Phase IIb trial of an infant mAb nirsevimab has shown promising results in preventing medically-significant RSV-ALRI and hospitalisation through 150 days by a single injection [6]. No licensed RSV vaccine is available, but several maternal and infant vaccine candidates are currently undergoing clinical trials. Although the phase III trial of the first maternal vaccine candidate (ResVax) failed to meet the pre-specified success criterion in preventing medically-significant RSV-ALRI over the first 90 days of life, it did show a promising efficacy against RSV-ALRI hospitalisations (44.4%, 95% confidence interval [CI]: 19.6–61.5%) [7]. The US Food and Drug Administration and European Medicines Agency have recommended an additional phase III trial for ResVax [8].

The guidelines for health technology assessment by the World Health Organisation (WHO) recommend health economic evaluations to inform the inclusion of new technologies into universal health coverage and reimbursement schemes [9]. With these rapid changes in the landscape of RSV preventive interventions, there is a need to conduct an economic evaluation to investigate the optimal use of different strategies for preventing paediatric RSV-ALRI once these new medications are available in the market. The seasonal patterns of RSV transmission vary greatly between the northern and the southern China [10]. In the northern China, the burden of RSV-ALRI illness is concentrated primarily during late autumn to early spring [10,11]. However, in the southern China, the epidemic activities can be observed in summer or early autumn, or even persist nearly year-round [10]. As both maternal vaccines and mAbs aim at providing short-term protection (about 3–5 months), RSV seasonality may influence the administration strategy of these preventive interventions. Hence, we conducted a cost-effectiveness analysis (CEA) of these preventive strategies in eight Chinese cities where severe respiratory acute infection (SARI) surveillance in China was inaugurated (Table 1; Supplementary "Cities included in the analysis").

2. Methods

2.1. Model overview

We evaluated the cost-effectiveness of the following five preventive interventions compared to no preventive interventions: 1) maternal immunisation, which vaccinates pregnant mothers during their antenatal care visits to protect their newborns during their first few months of life; 2) administration of mAbs to newborns at birth which provides protection during their first few months of life; 3) paediatric immunisation, which vaccinates young infants at 3 months old; 4) maternal plus paediatric immunisation; and 5) infant mAb plus paediatric immunisation. For conciseness, we abbreviated the maternal immunisation, infant mAb, paediatric immunisation, maternal plus paediatric immunisation and infant mAb plus paediatric immunisation as MI, IA, PI, MPI and AP, respectively, hereafter. A schedule of single injection was assumed for all these preventive interventions and co-administration with other paediatric vaccines was not considered here.

We used a static model to estimate the burden of paediatric RSV-ALRI (Fig. 1). This model was used to simulate the incidence of RSV-ALRI in twelve hypothetical monthly birth cohorts of Chinese newborns over the first 5 years of their life. Previous cohort studies suggested that although RSV reinfection is common among young children, most children only present medically-attended RSV-ALRI during their first episode of infection [12,13]. As such, we assumed that children would only experience medically-attended RSV-ALRI upon their first episode of infection with three possible clinical outcomes: RSV-ALRI outpatient visit (hereafter referred to as RSV-outpatient), RSV-ALRI inpatient visit (RSV-inpatient) and RSV-ALRI-attributable death (RSV-death). We parameterized the model using data from published studies and publicly available sources (Table 1).

2.2. Disease burden

Previous studies have shown that RSV-ALRI cases, especially severe and fatal cases, are concentrated in young children aged under 6 months [14]. The monthly probability of developing RSV-ALRI depends strongly on not only RSV seasonality (calendar month) but also the age of the children, especially for those aged under 1 year. As such, we estimated the probability of RSV-ALRI with outcome s at age j months for children born in calendar month i, which was denoted by $R_{i,j,s}$. The monthly age distribution assumed for all eight cities and all RSV-ALRI-related outcomes was based on two studies of RSV-ALRI hospitalised infants in Suzhou city (Supplementary Fig. S3) [15,16] for children aged under 12 months and fixed at 1/12 for children aged 12–59 months.

China launched its sentinel surveillance of SARI in different cities in 2009. We used RSV-SARI cases in this surveillance system to estimate RSV-inpatient incidence in our study. Following the WHO guidelines for estimating influenza burden, we estimated $R_{i,j,inpatient}$ as the number of RSV-inpatients residing in the catchment area divided by the size of the catchment population [17]. We defined the catchment area of each sentinel hospital as the administrative district where most SARI patients seeking medical treatments in the sentinel hospital resided. We then estimated $R_{i,j,outpatient}$ by dividing $R_{i,j,inpatient}$ by the proportion of RSV-outpatients who progressed to become RSV-inpatients [4,18]. Similarly, we estimated $R_{i,j,death}$ by multiplying $R_{i,j,inpatient}$ with the hospitalisation-fatality risk among RSV-inpatients [4]. See Supplementary "Disease burden estimation" for details.

2.3. Time-varying preventive efficacy

We assumed that the instantaneous preventive efficacies of all interventions would decay exponentially (Fig. 2). Specifically, we assumed that the efficacy and decay rate of MI and IA, would be similar to that reported in the phase III trial of ResVax [7] and phase IIb trial of nirsevimab [6], respectively. Since no trial data have been published for any RSV infant vaccine candidates yet, we assumed that the efficacy of infant vaccine would be on par with the minimum requirement of WHO's Preferred Product Characteristics for RSV vaccines [19]. For administration of MI or IA plus PI, we assumed that no interference would exist and the monthly preventive efficacy would be the sum of the monthly efficacies of the two interventions when they were administrated alone. See Supplementary "Estimating the preventive efficacies" for details. $R_{i,j,s}$ was then multiplied by the monthly efficacies for disease burden estimation under each preventive intervention programme.

2.4. Year-round and seasonal administration

Given the relatively short protective duration of maternal vaccines and mAbs and the strong seasonality of RSV in many parts of China, we considered both year-round and seasonal administration of these interventions. Under seasonal administration, the intervention would only be delivered to infants born in pre-specified consecutive months of the year. We considered all 132 such seasonal administration strategies for each intervention (Fig. S6).

2.5. Costs and health utility losses

We conducted the CEA from a societal perspective, and included direct medical costs, direct non-medical costs, and indirect costs. We assumed that these costs varied across different cities but

Table 1
Model parameters, distributions and data sources.

Parameters	RSV-outpatient		RSV-inpatient (including RSV-death)	
	Base case (95% CI)	Sensitivity analysis	Base case (95% CI)	Sensitivity analysis
Probability (0–11 months, per 1000 per year) – Dirichlet distribution [4,18,27–30]				
Beijing	24.9 (22.1–27.8)	A multiplier of 0.5 or 1.5	5.7 (4.4–7.2)	A multiplier of 0.5 or 1.5
Changsha	34.7 (19.1–54.8)		5.2 (0.7–14.3)	
Fuzhou	62.5 (28.5–108.5)		14.3 (1.7–39.9)	
Harbin	165.9 (129.7–205.2)		35.8 (19.4–57.1)	
Huzhou	19.3 (13.7–25.8)		4.0 (1.7–7.2)	
Jinan	41.7 (29.3–56.2)		8.6 (3.5–15.9)	
Kunming	23.9 (13.1–38.0)		4.8 (0.9–11.8)	
Zhuhai	37.6 (27.8–48.8)		8.6 (4.3–14.3)	
Probability (12–23 months, per 1000 per year) – Dirichlet distribution [4,18,27–30]				
Beijing	23.1 (20.8–25.5)	A multiplier of 0.5 or 1.5	1.8 (1.2–2.5)	A multiplier of 0.5 or 1.5
Changsha	32.2 (18.3–49.5)		2.6 (0.1–8.7)	
Fuzhou	58.0 (29.5–95.5)		4.5 (0.1–17.6)	
Harbin	153.9 (122.5–188.4)		12.4 (4.5–24.4)	
Huzhou	17.9 (12.9–23.8)		1.5 (0.4–3.5)	
Jinan	38.7 (27.5–51.8)		3.2 (0.7–7.7)	
Kunming	22.2 (12.1–35.2)		1.9 (0.1–6.6)	
Zhuhai	34.9 (26.7–44.1)		2.7 (0.8–5.7)	
Probability (24–59 months, per 1000 per year) – Dirichlet distribution [4,18,27–30]				
Beijing	3.9 (3.4–4.5)	A multiplier of 0.5 or 1.5	1.0 (0.7–1.3)	A multiplier of 0.5 or 1.5
Changsha	5.4 (2.3–9.8)		1.8 (0.3–4.5)	
Fuzhou	9.8 (3.4–19.4)		2.5 (0.2–7.9)	
Harbin	26.1 (18.4–35.1)		6.8 (3.2–11.8)	
Huzhou	3.0 (1.9–4.5)		0.8 (0.3–1.6)	
Jinan	6.6 (3.9–9.8)		1.8 (0.6–3.6)	
Kunming	3.8 (1.5–7.0)		1.1 (0.1–3.0)	
Zhuhai	5.9 (4.0–8.2)		1.5 (0.6–2.7)	
Costs per episode (US$) – Log-normal distribution [31,32]				
Beijing	163.0 (59.9–359.7)	A multiplier of 0.5 or 1.5	1161.3 (764.8–1728.6)	A multiplier of 0.5 or 1.5
Changsha	139.6 (29.9–415.3)		1023.1 (662.7–1538.6)	
Fuzhou	290.7 (75.8–782.1)		1141.1 (725–1736.2)	
Harbin	235.0 (47.1–721.7)		1145.9 (718.8–1756.8)	
Huzhou	258.9 (67.5–696.7)		1039.6 (672.6–1564.6)	
Jinan	284.0 (74.1–764.1)		1124.9 (716.5–1709)	
Kunming	188.6 (40.1–563.1)		1040.7 (662.8–1581.3)	
Zhuhai	163.8 (18·4-642·3)		1133.4 (732.7–1706.6)	
QALY losses due to non-fatal RSV-ALRI per episode ($\times 10^{-2}$) – Gamma distribution [28,33]				
	0.37 (0.02–1.27)	A multiplier of 0.5 or 1.5	1.02 (0.00–5.07)	A multiplier of 0.5 or 1.5
Annual discount rate				
	0.03	0.06	0.03	0.06

Parameters	RSV-outpatient		RSV-inpatient (including RSV-death)	
	Base case (95% CI)	Sensitivity analysis	Base case (95% CI)	Sensitivity analysis
Maternal immunisation intervention – Estimated based on [7]				
Protection duration (months)*	4	3 or 5	3	2 or 4
Efficacy on Day 0 (%)# †	71.6 (16.6–99.0)	69.6 or 70.9	77.2 (26.9–99.3)	74.2 or 77.3
Infant mAb intervention – Estimated based on [6]				
Efficacy on Day 0 (%)* †	100	90	100	90
Efficacy decay rate ($\times 10^{-2}$/day)#	0.5 (0.3–0.9)	0.3	0.5 (0.1–1.7)	0.3
Paediatric immunisation intervention – Assumed based on [19]				
Efficacy on Day 0 (%)* †	100	N/A	100	N/A
Efficacy at age 59 months old (%)*	70	50	70	50
Age of recipient (months)*	3	N/A	3	N/A
Maternal plus paediatric immunisation [7,19]				
Maternal immunisation efficacy	Efficacy on Day 0 and the protection duration were the same as those of single maternal immunisation intervention.			
Age of paediatric immunisation recipient (months)	3	N/A	3	N/A
Paediatric immunisation efficacy	Efficacy on Day 0 and on the last day of age 59 months were the same as those of single paediatric immunisation intervention. The time-varying efficacy was then estimated.			
Infant mAb plus paediatric immunisation [6,19]				
Infant mAb efficacy	Efficacy on Day 0 and decay rate were the same as those of single infant mAb intervention.			
Age of paediatric immunisation recipient (months)	6	N/A	6	N/A
Paediatric immunisation efficacy	Efficacy on Day 0 and on the last day of age 59 months were the same as the single paediatric immunisation intervention. The time-varying efficacy was then estimated.			

*These values were assumed based on available information.
#These parameters were estimated using Bayesian inference with MCMC methods.
N/A: Uncertainty was not considered here.

had no dependence on age. We used quality-adjusted life year (QALY) as the metric for health utility and assumed that QALY losses per non-fatal RSV-ALRI episode were independent of age and city. The QALY losses due to premature deaths were calculated based on the remaining life expectancy in each city. All the costs were inflated to 2019 Chinese Yuan (CNY) using each city's annual

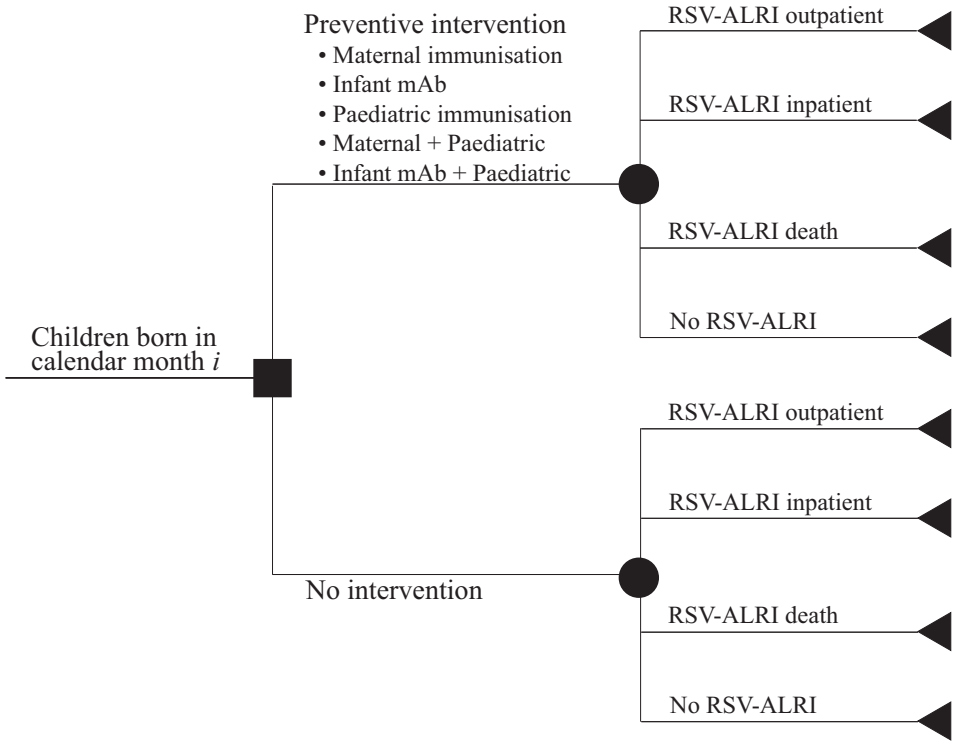

Fig. 1. Model structure. We assumed twelve hypothetical birth cohorts of Chinese newborns, stratified by their month of birth, each of which were followed up at each age of month over the first five years of life. We assumed that children would only experience medically-attended RSV-ALRI upon their first episode of infection. At age *j* months, children who have never experienced medically-attended RSV-ALRI previously could experience one of the three possible clinical outcomes: RSV-outpatient, RSV-inpatient, or RSV-death. The probability of experiencing each possible clinical outcome at age *j* months for children born in calendar month *i* was $R_{i,j,s}$ weighted by the corresponding preventive efficacy ($PE_{j,s}$).

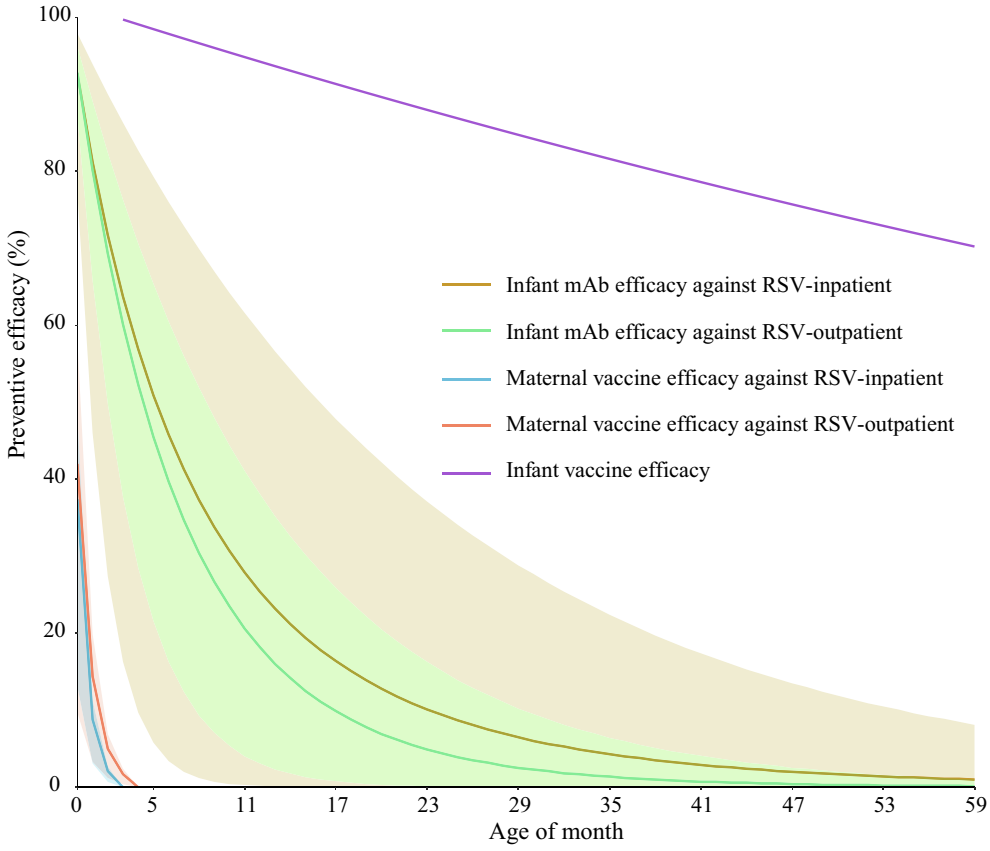

Fig. 2. The time-varying preventive efficacy of maternal vaccine infant mAb and infant vaccine in the base case.

consumer price index (health care) [20] before being converted to 2019 USD (1 US$ = 6.8747 CNY). Costs and QALY losses were discounted at 3% per year in the base case. See Supplementary "Costs and QALY losses" for details.

2.6. Cost-effectiveness evaluation

Given a willingness-to-pay (WTP) threshold with respect to the incremental cost-effectiveness ratio (ICER), we calculated threshold strategy cost (TSC), defined as the maximum cost that can be paid for prevention per newborn for a cost-effective preventive strategy. The equation for TSC was as below:

$$\text{TSC} = \text{WTP threshold} \times \sum_s (\Delta Q_s + \Delta D_s) + \sum_s \Delta C_s$$

where ΔQ_s, ΔD_s and ΔC_s denoted the difference in QALY losses due to non-fatal RSV-ALRI, QALY losses due to premature deaths associated with RSV-ALRI and costs of RSV-ALRI with outcome s of the birth cohort without and with a preventive strategy in the first 5 years. See Supplementary "The model and parameterisation" for details.

In the absence of published consensus for an appropriate WTP threshold in China, we set the WTP threshold based on two sources: one gross domestic product per capita (GDPpc) which was previously recommended by WHO and 63% (47%-88%) of GDPpc proposed by University of York economists [21,22]. We used one national GDPpc (US$10,267 in 2019) as the WTP threshold in the base case and 0.63 times national GDPpc and one and 0.63 times local GDPpc (Table S1) in the sensitivity analysis, respectively.

2.7. Sensitivity analysis

One-way sensitivity analyses were performed to account for uncertainty in the annual discounting rate, WTP threshold, costs per episode of RSV-ALRI at different severity levels, QALY loss per non-fatal RSV-ALRI episode, $R_{i,j,s}$ and time-varying preventive efficacies of the five interventions (Table 1). We also draw 50,000 sample parameter sets using Latin hypercube sampling from predefined distributions to account for parametric uncertainty in our estimates of severity-specific costs and QALY losses per episode and estimates of $R_{i,j,s}$ (Table 1).

3. Results

3.1. Year-round administration

3.1.1. Base case

The TSC of all the year-round strategies were shown in Fig. 3. For each city, TSC ranked in the ascending order of MI, IA, PI, MPI and AP. The maximum cost that can be paid per child for a cost-effective 1) MI ranged from US$2.4 (95% CI: 1.9–3.4; Huzhou) to US$14.7 (95% CI: 11.6–21.4; Harbin); 2) IA ranged from ranged from US$19.9 (95% CI: 16.9–25.9; Huzhou) to US$144.2 (95% CI: 124.6–184.7; Harbin); 3) PI ranged from US$28.7 (95% CI: 22.0–42.0; Huzhou) to US$201.0 (95% CI: 156.5–298.6; Harbin); 4) MPI ranged from US$31.1 (95% CI: 24.0–45.5; Huzhou) to US$ 220.7 (95% CI: 172.0–327.3; Harbin); and 5) AP ranged from US$41.3 (95% CI: 32.6–58.9; Huzhou) to US$306.2 (95% CI: 244.1–441.3; Harbin).

3.1.2. Sensitivity analysis

The results of sensitivity analyses for Beijing are presented in Fig. 4 as an example and for other cities are in Fig. S15-S16. Although RSV-outpatient cases accounted for the majority (82.4–89.9% among all cities and all interventions) of the total difference in the incidence of RSV-ALRI (Fig. S13), the risk of RSV-related death was the more important driving factor of TSC among the three RSV-related outcomes (i.e., RSV-outpatient, RSV-inpatient and RSV-death) because premature death was the most important driver of QALY losses (Fig. S14). Among the total difference in the costs and WTP threshold adjusted QALY losses of RSV-ALRI (i.e., the product of WTP threshold and QALY loss), QALY losses due to RSV-death contributed most to TSC for all five interventions for

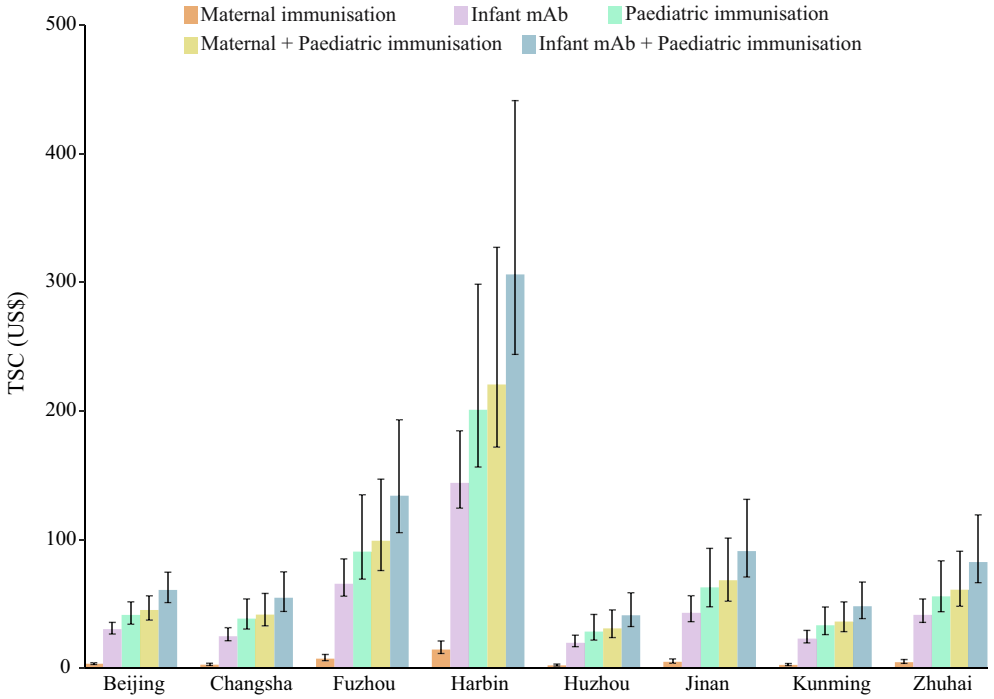

Fig. 3. The TSC of year-round administration of preventive strategies for each city in the base case. The error bars indicate the 95% CIs of the mean TSCs.

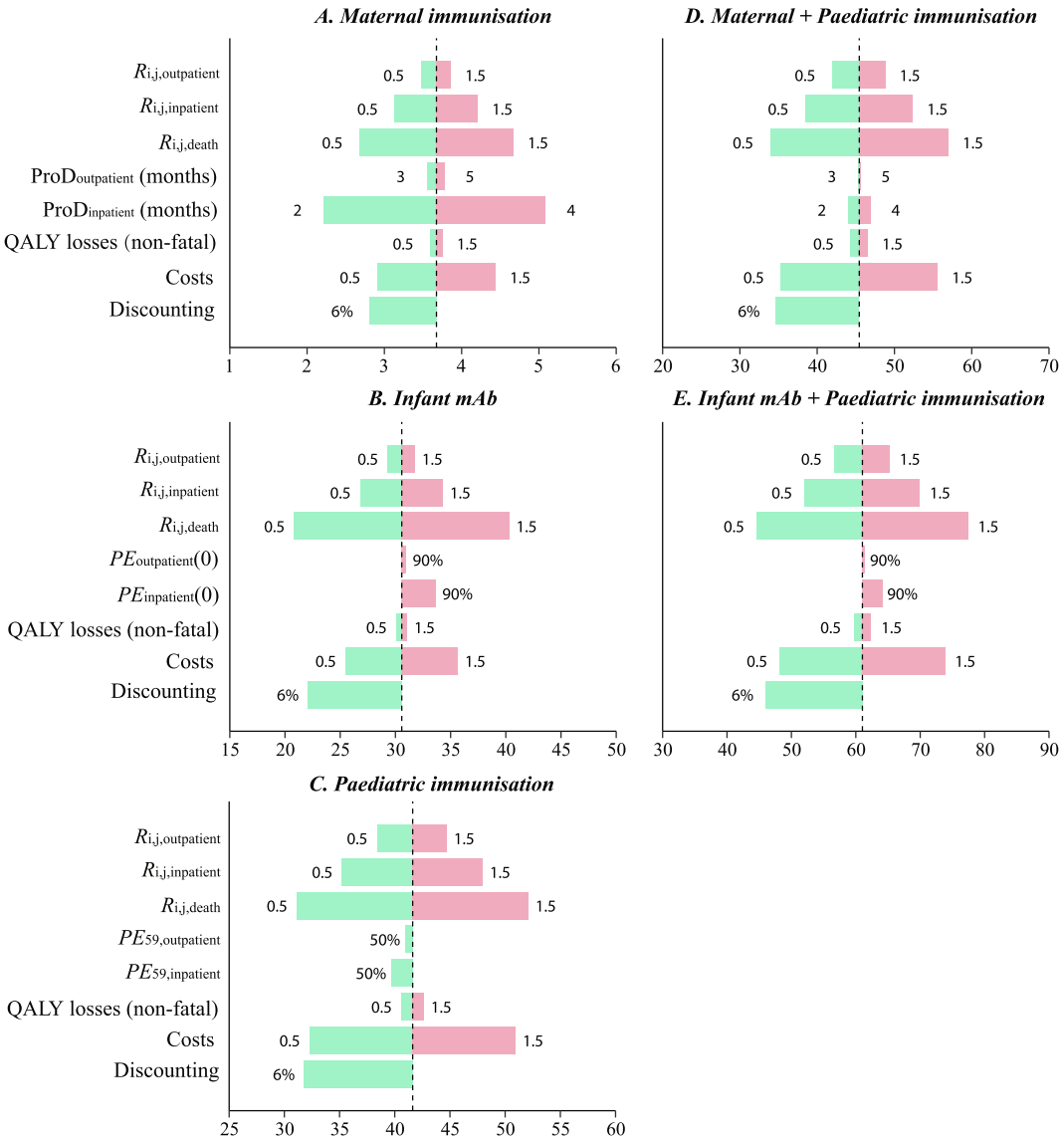

Fig. 4. Tornado plots showing changes of TSC in sensitivity analysis for Beijing as other parameters are varied. The dashed vertical lines indicated TSCs in the base case. **(A) Maternal immunisation strategy. (B) Infant mAb strategy. (C) Paediatric immunisation strategy. (D) Maternal plus paediatric immunisation strategy. (E) Infant mAb plus paediatric immunisation strategy**. Costs per episode for RSV-ALRI of all severity levels were modified together in the sensitivity analysis, as were QALY losses due to non-fatal RSV-ALRI episodes. Some bars were not apparent in the figure because TSC changed little when modifying the corresponding input parameter. $ProD_{outpatient}$ and $ProD_{inpatient}$: Protection duration against RSV-outpatient and RSV-inpatient (including RSV-death) for maternal immunisation; $PE_{outpatient}(0)$ and $PE_{inpatient}(0)$: Preventive efficacy against RSV-outpatient and RSV-inpatient (including RSV-death) of infant mAb on day 0 (i.e., the administration day); $PE_{59,outpatient}$ and $PE_{59,inpatient}$: Preventive efficacy against RSV-outpatient and RSV-inpatient (including RSV-death) for paediatric immunisation on the last day at 59 months old.

all cities (Fig. S14). Additionally, the variation in the protective duration of maternal immunisation is one of the top factors influencing the TSC of MI. In addition, TSC estimated with different WTP thresholds was presented in Fig. S17.

3.2. Seasonal administration

The incidence of RSV-ALRI during the first year of life varied across the 12 monthly cohorts (Fig. S8-S9). The top 10 seasonal MI and IA strategies when ranked in terms of their TSC (written as top 10 seasonal MI and IA hereafter) are shown in Figs. 5 and 6 and all the TSCs of the seasonal strategies are shown in Fig. S11-S12.

The seasonal MI and IA strategies with the highest TSC were always those protecting infants born in only one month of the year, usually the month where RSV incidence peaked in the corresponding city. The top 10 seasonal MI and IA strategies targeted at most 5 monthly birth cohorts, and most (>90%) targeted at most 4 monthly birth cohorts. Given that IA provided stronger and longer protection than MI (Fig. 2), the top 10 seasonal IA strategies generally targeted monthly birth cohorts closer to the RSV season onset month than the top 10 seasonal MI strategies.

4. Discussion

Our study is the first to perform health economic evaluation of different strategies for preventing paediatric RSV-ALRI in eight Chinese cities across different regions. TSC was used instead of ICERs as our primary economic measure because it enabled us to compare different strategies without specifying the price of each intervention. For each city, the TSC of year-round infant mAb plus paediatric immunisation is the highest among all the year-round

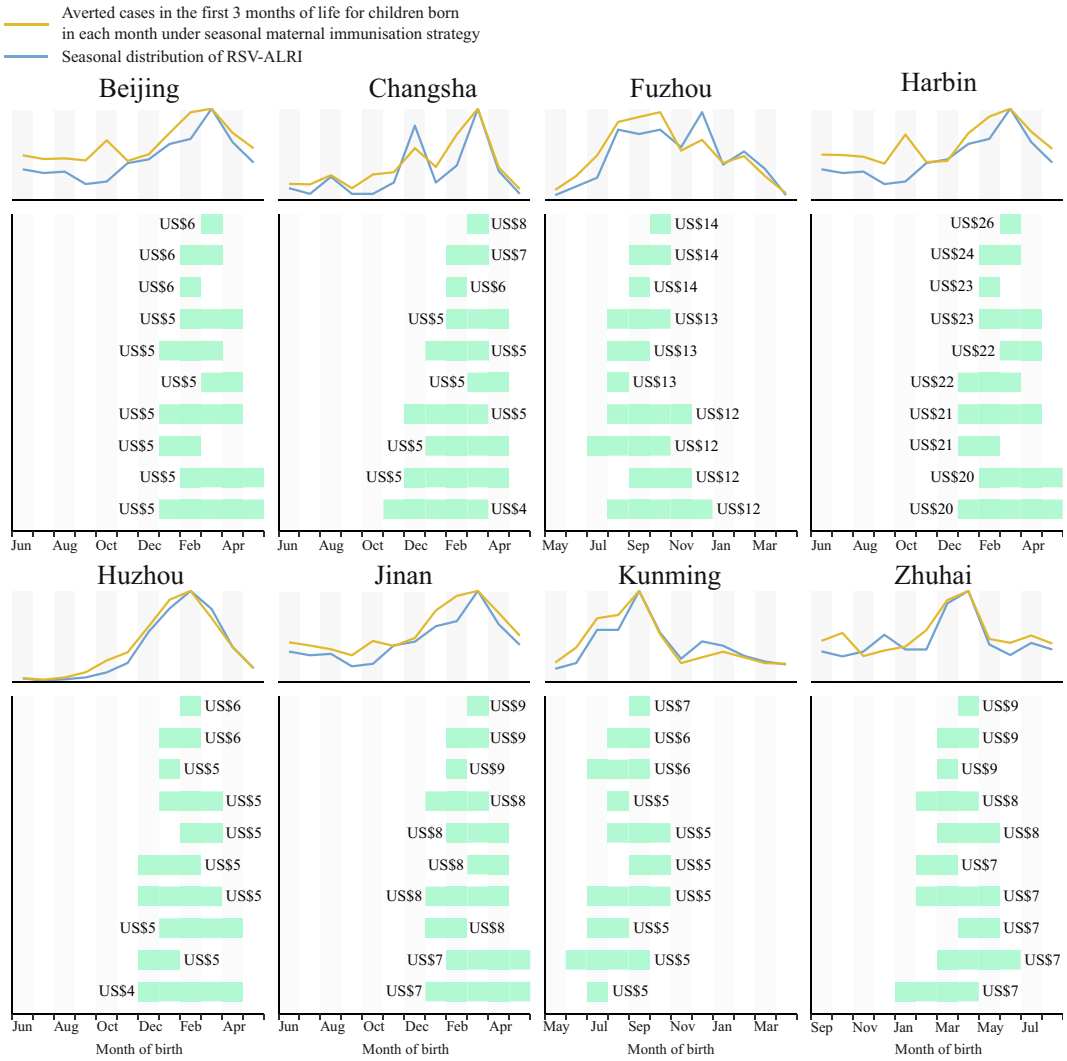

Fig. 5. The top ten seasonal maternal immunisation strategies for each city. The horizontal bars in green indicated the months of birth of infants that are protected for the first few months of life via a maternal immunisation strategy. For example, the top bar of Beijing indicated that only infants born in March were provided the maternal immunisation strategy, while the second top bar of Beijing indicated that only infants born in February and March were provided the maternal immunisation strategy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

strategies, indicating that earlier and longer protection with high efficacy is desirable. Moreover, maternal vaccines would need to be priced very competitively in comparison to paediatric vaccines, in order to offer equivalent value for money. The future market price of infant mAbs was assumed to be more expensive compared to vaccines, but the future price of mAbs would need to be equivalent to that of paediatric vaccines to make mAbs a competitive and cost-effective option.

Our study showed that when RSV seasonality is strong, seasonal administration of the strategy could be more cost-effective than year-round administration. This was in line with an analysis in England by Hodgson et al which also showed that seasonal administration can be more cost-effective than year-round administration when the RSV seasonal pattern can be robustly estimated [23]. In our study, the TSC of seasonal maternal immunisation and infant mAb depended strongly on the seasonality of RSV. Among all the seasonal strategies and their year-round counterparts, the TSC is highest when mAb is administerted to a single monthly birth cohort.

Our results showed that the top 10 seasonal strategies for both maternal immunisation and infant mAb are those that target at 5 or fewer monthly birth cohorts. These results indicate that (1) if a seasonal strategy is administered when the protective duration is unlikely to cover the entire RSV season, the focus should be mainly put on protecting newborns during the months when RSV activity is strongest; (2) if the strategy is administered when protective duration is similar to or even longer than the RSV season, the targeted newborns could be extended to those born near the beginning of the RSV season so that infants can be protected over the entire RSV season and the protection period mainly overlaps with the RSV season; (3) if there are multiple peaks in RSV incidence each year, ideally the protection period should cover all the peaks. If the RSV peak is spread over several months (e.g., Fuzhou's seasonal pattern), a moving-average seasonality curve (average value of several months) may help to inform the month(s) for a more cost-effective seasonal strategy.

Our study has several limitations. First, we used RSV-SARI cases to estimate the risk of becoming an RSV-inpatient case, and then further used them to estimate the risk of developing RSV-outpatient and RSV-death. This may result in underestimation because the definition of SARI requires fever, but a proportion of the hospitalised RSV-infected children, especially young infants, do not present with fever [24]. To account for the potential bias, we conducted sensitivity analysis by increasing or decreasing $R_{i,j,s}$

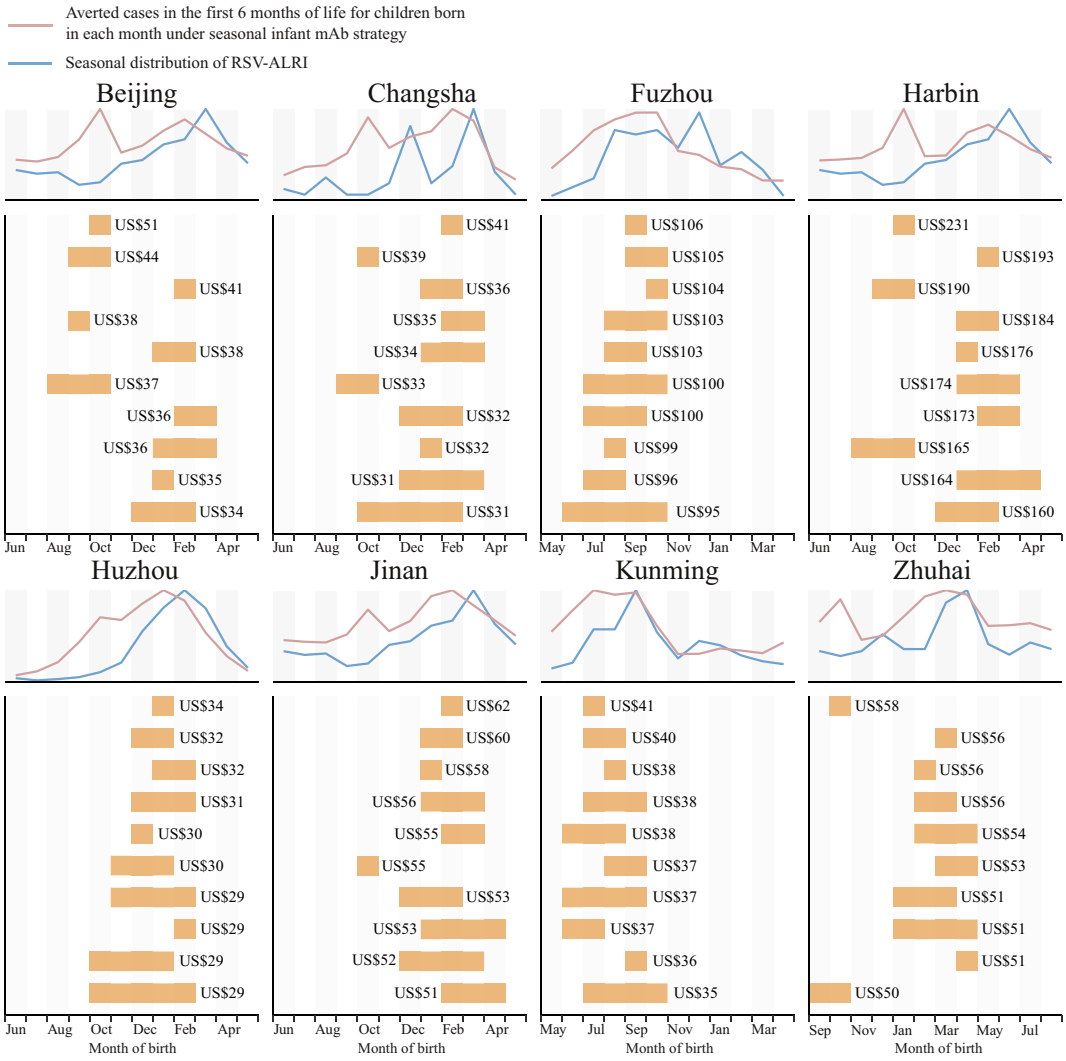

Fig. 6. The top ten seasonal infant mAb strategies for each city. The horizontal bars in orange indicated the months of birth of infants that are protected at birth via an infant mAb strategy. For example, the top bar of Beijing indicated that only infants born in October were provided the infant mAb strategy, while the second top bar of Beijing indicated that only infants born in September and October were provided the infant mAb strategy. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

by 50%. Second, we did not consider potential herd effects in our analysis. One recent study suggested that vaccinating young children (5–10 months old) can provide herd protection to very young children (<6 months old) [25]. Our TSC estimates are thus conservative by underestimating vaccine impact. Third, we only included cities across different regions where the SARI surveillance was inaugurated in China. Previous studies have shown that RSV activity is: (1) highest during winter, correlating with lower temperatures in temperate regions; and (2) continuous throughout the year in tropical regions with a peak between summer to early autumn, mainly driven by the high humidity [26]. However, RSV seasonal patterns can be more diverse in subtropical regions (most regions in southern China) and can vary from year to year even in the same city. And our results show that the cost-effectiveness of a seasonal strategy depends heavily on the RSV seasonal pattern (i.e., the timing and sharpness of the RSV seasonal peak). Since the optimal choice of seasonal strategies depends on correct identification of local RSV seasonality, more active surveillance of RSV is essential for informing the optimal preventive strategy.

Considering the high disease burden of RSV in children, prevention of RSV-associated illness should be a high public health priority in China. Our study showed that vaccines and other immunotherapeutics against RSV can be cost-effective in China with prices below our TSC estimates. Our study also demonstrates the important role of seasonality in the optimal timing of different preventive strategies in China. Our results could help inform the optimal use of future prevention strategies, such as the timing of administration (year-round or seasonal), the target population (mothers, newborns or younger infants) and the subsidy policy (national or municipal programme), for cities in different locations in China once they are available.

Authors' contributions

MJ, JTW and KL designed the study. DL and KL conducted the analysis. DL, KL, JTW and MJ interpreted the results and wrote the manuscript. All authors critically revised the manuscript and approved the final version of the manuscript.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.vaccine.2021.08.057.

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