Impact of the Pneumococcal Conjugate Vaccine in Hindering Antimicrobial Resistance in China

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Abstract (up to 250 words):

Antimicrobial resistance (AMR) poses a serious threat to global public health. Yet vaccinations have been largely undervalued as a method to hinder AMR progression. This study examined the AMR impact of increasing pneumococcal conjugate vaccine (PCV) coverage in China. China has one of the world's highest rates of antibiotic use and low PCV coverage. We developed an agent-based DREAMR (Dynamic Representation of the Economics of AMR) model to examine the health and economic benefits of slowing AMR against commonly used antibiotics. We simulated PCV coverage, pneumococcal infections, antibiotic use, and AMR accumulation. Four antibiotics to treat pneumococcal diseases (penicillin, amoxicillin, 3rd generation cephalosporins, and meropenem) were modeled with antibiotic utilization, pharmacokinetics, and pharmacodynamics factored into predicting AMR accumulation. Three PCV coverage scenarios were simulated over five years: (1) status quo with no change in coverage, (2) scaled coverage increase to 99% in 5 years, and (3) accelerated coverage increase to 85% over 2 years followed by 3 years to reach 99% coverage. Compared to the status quo, we found that AMR against penicillin, amoxicillin, and 3rd generation cephalosporins was significantly reduced by 1.74%, 19.19%, and 14.87% in the scaled scenario and by 2.87%, 29.97%, and 23.35% in the accelerated scenario. Cumulative costs due to AMR, including direct and indirect costs to patients and caretakers, were reduced by $2.76 billion in the scaled and $4.46 billion in the accelerated scenarios compared to the status quo. AMR benefits of vaccines are essential to quantify in order to drive appropriate investment.

Significance Statement (up to 120 words)

Vaccines are currently undervalued as few studies include vaccines' value in hindering antimicrobial resistance (AMR). Pneumococcal infections pose a major threat to public health, which is preventable by the pneumococcal conjugate vaccine (PCV). China has high antibiotic use and low PCV coverage, making it an important country to assess resource allocations to address AMR. We developed an agent-based model to simulate the impact of increased PCV coverage on AMR accumulation. This study is the first to demonstrate the broader economic value of pneumococcal vaccination in slowing the development of AMR in China. Introducing PCV in China's national immunization program would not only save lives but also bring wider societal benefits by reducing antibiotic utilization and treatment failures due to AMR.

Introduction

The rapid rise in antimicrobial resistance (AMR) is a healthcare emergency (1). It threatens the prevention of infectious diseases and the efficacy of treatment options, leading to worse patient outcomes and resulting deaths. A 2014 study estimates that 700,000 deaths per year are attributable to AMR, which is projected to grow to 10 million deaths by 2050, costing up to US$100 trillion (2). Vaccination is a solution that can contribute to slowing the pace of AMR. Vaccinations can hinder AMR progression by reducing the incidence of sensitive and resistant infections (1). Vaccinations can also decrease disease incidence and the need for antibiotic use, reducing the selection and pressure for resistance to accumulate (3). Resistance to vaccines is unlikely compared to drugs because vaccines are inherently used prophylactically and combat pathogens through multiple pathways (4). Despite a growing recognition that vaccines can deliver AMR benefits, vaccines' AMR-related value is not incorporated in most studies, leading to undervaluation and underinvestment (5).

The pneumococcal conjugate vaccine (PCV), covering up to 13 different serotypes of S*treptococcus pneumoniae* (SP), has demonstrated that AMR benefits are possible. Previous studies in the US, Europe, and Africa have shown that PCV introduction has led to reduction in antibiotic use and decreased resistant invasive disease episodes (6). A 2016 study estimated that universal coverage with PCV could avert 11.4 million days per year of antibiotic use in children under five years of age (7). However, these AMR benefits of PCV have not been shown at the country level related to specific vaccination policies in order to have policy-makers incorporate PCV's AMR-related value in decision making.

China has one of the highest burden of childhood pneumonia cases caused by SP at around 454,000 new episodes per year (8). SP is a major cause of morbidity and mortality in China, especially among children under five (9). The World Health Organization estimates that China accounts for 12% of SP infections and 3.6% of SP deaths worldwide in children under five (10). China's Expanded Program on Immunization (EPI) currently does not include PCV among its mandatory vaccines available for free for registered children (11). The most recent data on PCV coverage among children in China was only at 4.7% in 2014 (12). Antibiotic use and misuse are also widespread in China, both within healthcare and animal agriculture systems (13, 14). In healthcare, Chinese patients often view antibiotics as a panacea, asking for antibiotics from providers even when unwarranted (15). For example, a 2014 Chinese national survey showed that 52.9% of out-patient visits resulted in antibiotic prescriptions, while only 39.4% of patients required them based on their clinical conditions (16). China's high burden of pneumococcal disease, low PCV coverage, and high antibiotic utilization makes it an important country to demonstrate the AMR-related value of pneumococcal vaccination.

This study examined the health and economic impact of increasing PCV coverage in China, focusing on the value of PCV in slowing AMR progression. This research responds to calls for a global coordinated effort to conduct research on AMR-sensitive evaluations and integrated AMR strategies (1, 5, 7). We developed and utilize an agent-based model to simulate PCV coverage, pneumococcal infections, antibiotic use, AMR accumulation, and resulting health and economic

outcomes. To our knowledge, this work is the first to demonstrate the broader economic value of pneumococcal vaccination in slowing the development of AMR in China.

Methods

We developed an agent-based micro-simulation model known as Dynamic Representation of the Economics of Anti-Microbial Resistance (DREAMR) (17). The model has two interactive components, the human and bacteria sub-models (Figure 1). The human sub-model simulates the progression of healthcare seeking and treatment if a child were to become infected by SP. This includes probabilities for whether or not a child seeks care and at what type of health facility, whether a child receives outpatient or inpatient care, and what antibiotics are used for treatment. When antibiotics are utilized, the human sub-model interacts with the bacteria sub-model, where bacteria may die, or survive and replicate, depending on the antibiotic's pharmacokinetics and pharmacodynamics properties and the degree of exposure. The change in ratio between resistant and susceptible bacteria, known as the AMR ratio, subsequently influences pneumococcal disease treatment outcomes in the human sub-model. This model was developed in NetLogo 6.0.2, a free and accessible software with a multi-agent programmable modeling environment (18). All model inputs are presented in Table 1. Details of the model simulations are described below.

Human Sub-model: Vaccination, Care-seeking and Treatment

The DREAMR human sub-model simulated 8,000 agents, where each agent represented ten children, comprising a population of 80,000 children between zero and five years of age. Results were scaled to the pediatric population size in China based on the most current demographic data (19). Each agent in the model was assigned a PCV vaccination status based on coverage data available from the *National Immunization Program Information System* in China (12). Published literature were utilized to simulate PCV vaccine efficacy (20). The model incorporated effects of herd immunity, where immunized individuals provided protection among the unvaccinated population (21, 22). This study assumed herd immunity occurred at 85% PCV vaccination coverage, where decreased age-specific disease incidence rates were applied to simulate the indirect effect of immunization (23, 24).

Modeled child agents faced an incidence of contracting pneumococcal infections, resulting in pneumococcal pneumonia, pneumococcal meningitis, or pneumococcal acute otitis media (AOM). Disease incidence rates for each condition were derived from the China Health Insurance and Research Association (CHIRA) database (25). Care seeking and treatment of pneumococcal disease were modeled separately for rural and urban environments (26). Child agents sought or did not seek care from healthcare facilities based on care-seeking rates from the literature (27, 28). Child agents who sought healthcare received treatment from one of the following levels of health facilities: (1) municipal level, (2) county level, (3) township/village level, or (4) private clinics (29). Child agents who did not seek care either self-medicated or remained untreated based on care-seeking rates from the *Analysis Report of National Health Services Survey in China* (30). Untreated agents faced a greater propensity to develop adverse health outcomes (i.e., disability and death) compared to those who received treatment (31). All children

with acute otitis media were treated as outpatients, while all meningitis cases were treated as inpatients (32). Health facility-level specific hospitalization rates from the literature were applied to pneumococcal pneumonia cases who sought care (29). Antibiotic regimens and treatment durations for each pneumococcal disease were extracted from literature (33-39). Antibiotic utilization was simulated based on recommended doses and intervals (33, 34). The proportion of child agents treated with antibiotics for pneumococcal disease in the human sub-model affected the degree of antibiotic exposure in the bacteria sub-model.

Bacteria Sub-model

The DREAMR bacteria sub-model focused on four antibiotics commonly used to treat pneumococcal diseases in China: penicillin, amoxicillin, 3rd generation cephalosporins, and meropenem. We simulated 120,000 bacteria agents, 30,000 per antibiotic, where each bacteria were classified as either resistant or susceptible. The initial AMR ratios for antibiotics were determined based on the resistance patterns in China (38, 40-43). Bacteria agents were also assigned a minimum inhibitory concentration (MIC) from a gamma distribution based on the antibiotic and resistance status (44, 45). The method of moments approach was used to obtain parameters needed for the gamma distribution to characterize these distributions (46). The susceptibility breakpoint was set to be equal to that of the Clinical Laboratory Standards Institute, at the 90th percentile of the MIC gamma distribution (45).

Pharmacokinetics and pharmacodynamics were used to determine which bacteria agents would die under antibiotic exposure. Pharmacokinetic characteristics, including the volume of distribution, total body clearance, and elimination rate constants were retrieved from literature and the product information for each antibiotic (47-53). The probability that bacteria encountered antibiotic exposure depended both on defined daily doses (DDDs) and the proportion of children colonized with SP (54). DDDs were obtained from the human sub-model, which measured the proportion of child agents using antibiotics for pneumococcal diseases. DDDs were then divided by the percentage of children colonized to estimate the probability that bacterial agents would be exposed to antibiotics. Large DDDs led to a larger probability for antibiotic exposure (55). Since all four antibiotics are time-dependent, we then estimated the percentage of time that exposed antibiotic concentrations were above MIC for each bacterium, which is based on the dose, dosing interval, MIC value, and pharmacokinetics of the antibiotic (56, 57). A bacterium agent would die once the percentage of time it was exposed to antibiotics above its MIC value became greater than the threshold of 50% (56, 58, 59). Susceptible strains of bacteria faced a higher probability of being killed compared to resistant strains due to a lower MIC distribution. Resistant bacteria also faced a fitness cost as they are often less fit to compete for resources and experienced a lowered probability of survival (60). Killed bacteria agents were replaced by replication of susceptible and resistant bacteria agents maintaining the latest AMR ratio.

Human Sub-model: Health and Economic Outcomes

The AMR ratio from the bacteria sub-model subsequently set the proportion of treatment failures in the human sub-model (61). Child agents with treatment failures from first-line antibiotics switched to second-line therapy, and overall treatment durations were prolonged. Child agents who self-medicated and experienced treatment failure sought care from formal health facilities.

Patients either died or recovered from the disease episode based on case-fatality rates from the literature (62). Agents who survived from meningitis and AOM also faced a probability of developing long-term sequelae (35, 63). We simulated the number of cases, deaths, disabilities, average DDD, AMR ratios, cumulative treatments, and treatment failures over time.

Economic outcomes were also assessed by using the cost-of-illness method, estimating related direct medical costs, direct-non-medical costs, productivity losses for caregivers, and productivity losses due to death/disability (29, 64-66). Direct medical and non-medical costs to treat pneumococcal disease at different health facility levels in China were abstracted from the literature (29, 66). Productivity losses were estimated based on China's GDP per capita per day and the duration of lost productivity (67, 68). Caregivers lost income over the duration of illness, and children who died or became disabled lost productivity from age 15 until average age of retirement at 60. Productivity loss for children who lived with a disability due to meningitis was reduced by the relevant disability-adjusted life year (DALY) weight (69, 70). All costs are presented in US dollars (2019).

Scenario and Sensitivity Analyses

Simulations were run over 5 years from 2020 to 2025. Three scenarios of PCV vaccination coverage were modeled. The first scenario simulated the status quo, where PCV coverage remained at current levels (4.74%) over five years. The second "Scaled" scenario linearly increased PCV coverage from status quo to 99% over five years. We scaled PCV coverage to 99% based on China's nationally reported immunization coverage rates for other childhood vaccines. In the third "Accelerated" scenario, PCV coverage increased linearly from status quo to 85% in the first two years, and to 99% over the next three years. This was designed to simulate the adoption of PCV in China's EPI program to quickly reach 85% coverage. Our results compare the scaled and accelerated scenarios to status quo.

Sensitivity analyses were conducted to obtain uncertainty ranges around key outcomes. Uncertainty arising from various procedures in the DREAMR agent-based model were minimized by averaging all results across 5,000 simulations. Moreover, uncertainty in model inputs were incorporated though a probabilistic sensitivity analysis (PSA) where key input values were randomly drawn from underlying distributions based on means and standard errors available from the literature.

Results

The impact of PCV in reducing pneumococcal disease burden are shown in Table 2. Based on current PCV coverage, we estimated that China has 70.8 million cases of pneumococcal pneumonia, 2,800 cases of pneumococcal meningitis, and 62.2 million cases of pneumococcal AOM over 5 years. Compared to the status quo, the scaled scenario reduced the disease burden of pneumococcal pneumonia to 65.1 million cases (8.1% decrease), pneumococcal meningitis to 2,100 cases (25.3% decrease), and pneumococcal AOM to 59.3 million cases (4.7% decrease). The accelerated scenario further reduced the disease burden of pneumococcal pneumonia to 61.4 million cases (13.3% decrease), pneumococcal meningitis to

1,700 cases (38.7% decrease), and pneumococcal AOM to 57.7 million cases (7.2% decrease). While the status quo scenario estimated 1.4 million deaths from pneumococcal diseases over 5 years, the scaled and accelerated scenarios reduced the number of overall deaths to 1.3 million (8.1% decrease) and 1.2 million (13.6% decrease) deaths, respectively.

Increased PCV coverage and decreased disease incidence resulted in reductions in cumulative first-line treatments for pneumococcal diseases by 5.1% in the scaled scenario and 8.3% in the accelerated scenario. At current levels of PCV coverage, direct costs of first-line treatment for pneumococcal diseases in China was estimated at $580,000 in Year 1, increasing yearly to $1.2 million by Year 5. The scaled scenario reduced direct costs of first-line treatment to $570,000 in Year 1 and $960,000 in Year 5 (1.02% to 18.95% reduction). The accelerated scenario further reduced direct costs of first-line treatment to $560,000 in Year 1 and $890,000 in Year 5 (2.19% to 24.60% reduction). Caretaker productivity losses related to first-line treatment reduced by $803 million (6.0% reduction) and $1.3 billion (9.7% reduction) in scaled and accelerated scenarios, respectively. Average annual first-line treatment cost savings per child including care-taker productivity losses reduced by $3.80 (6% decrease) and $6.15 (9.7% decrease) for scaled and accelerated scenarios, respectively.

The AMR-related value of PCV vaccines are presented in Table 3. Based on China's current PCV coverage, we simulated that resistance for penicillin, amoxicillin, and 3rd generation cephalosporins would increase by 10.7%, 26.1%, 11.7%, respectively over 5 years. Compared to the status quo, the scaled scenario significantly reduced resistance for penicillin, amoxicillin, and 3rd generation cephalosporins by 1.7%, 19.2%, and 14.9%, respectively. In the accelerated scenario, resistance for penicillin, amoxicillin, and 3rd generation cephalosporins reduced further by 2.9%, 30.0%, and 23.4%, respectively. In all three scenarios no significant change in AMR ratio was observed for meropenem, likely due to low incidence of pneumococcal meningitis resulting in low utilization of the antibiotic.

PCV vaccinations resulted in fewer first-line antibiotic treatment failures for pneumococcal pneumonia, meningitis, and AOM at 46.4 million treatment failures over 5 years. The scaled and accelerated scenarios decreased treatment failures by 4.1 million (8.8% decrease) and 6.6 million (14.3% decrease) over 5 years, respectively. Under current PCV coverage, wasted direct costs of first-line antibiotics that led to treatment failures were estimated at $4.3 million, growing from $580 million in Year 1 to $1.2 million in Year 5. These wasted costs of ineffective treatment were reduced by 11% ($450 million) in scaled and 17% ($730 million) in accelerated scenarios.

PCV vaccinations brought AMR benefits for second-line treatment cost savings for pneumococcal disease in China. While we estimated direct medical and non-medical costs at $1.79 million in Year 1 increasing to $2.74 million by Year 5 under current PCV coverage, the scaled scenario reduced second-line treatment costs by $200,000 in Year 1 to $450,000 in Year 5 (1.00% to 16.63% reduction). The accelerated scenario further reduced these costs by $400,000 in Year 1 and $57,000 in Year 5 compared to status quo (2.12% to 20.70% reduction). Caretaker productivity losses for second-line treatment reduced by $509 million (8.9% reduction) and $825 million (14.4% reduction) in the scaled and accelerated scenarios,

respectively. Annual cost savings in second-line treatments were also observed at $2.31 (8.9% decrease) and $3.75 (14.4% decrease) per child for scaled and accelerated scenarios, respectively.

Overall AMR-related costs for pediatric pneumococcal treatment in China was estimated at $34.63 billion over 5 years under current PCV coverage. Increase in PCV coverage would reduce AMR-related costs by $2.76 billion (8.0% decrease) and $4.5 billion (12.9% decrease) over 5 years in scaled and accelerated coverage scenarios, respectively. Moreover, this did not include AMR-related productivity losses due to death and disability, which were estimated at $27.7 billion based on current PCV coverage, and reduced by $3.5 billion (12.6% decrease) and $56.9 billion (20.5% decrease) in scaled and accelerated coverage scenarios, respectively.

Discussion

This study is the first to demonstrate the broader economic value of pneumococcal vaccination in slowing the development of AMR in China. We show that increased PCV coverage not only reduces the disease burden, but also provides AMR benefits including lower AMR ratios, reduced treatment failures, averted second-line therapies and cost savings from ineffective or unnecessary treatments. AMR-related costs that could be averted by increased PCV coverage in China ranged in the billions of US dollars over 5 years.

The AMR benefits of vaccines are essential to incorporate in valuation of vaccines to drive appropriate levels of investment. Economic evaluations of vaccinations have not traditionally incorporated the AMR benefits of vaccines, having focused on a narrower set of benefits (1, 5). Our results suggest that the pneumococcal vaccine has been undervalued by not taking this benefit into account, which could affect decision makers' willingness to invest in this newer vaccine. By contributing to slowing the pace of AMR, the pneumococcal vaccine not only saves lives but also adds to global efforts to combat AMR.

Our findings demonstrate that introducing PCV in China's EPI program would not only save lives but also bring wider societal benefits by reducing antibiotic utilization, averting treatment failures, and saving costs due to AMR. Since pneumococcal vaccination is currently not mandated by the Chinese government, it is highly expensive and coverage is very low (4.7%) (12). Interested parents must pay out-of-pocket for their children to receive PCV at select hospitals with prices around $130 per dose (71). As the vaccine is recommended to be given in a series of four doses for children at 2 months, 4 months, 6 months, and 12-15 months of age, this comes to a costly total of $520, deterring parents from vaccinating their children and/or receiving the full course of the vaccine. Including PCV in the EPI schedule would make the vaccine affordable and accessible to the population, allowing China to quickly scale up PCV coverage similar to our accelerated scenario. High PCV coverage can trigger herd immunity, providing protection from pneumococcal diseases even among those who are not vaccinated. Moreover, the large forecasted demand could provide China with the bargaining power to negotiate down the vaccine price or manufacture its own PCV vaccine to curb vaccine costs.

Some Chinese companies are currently conducting research to develop a pneumococcal vaccine, which may contribute to these efforts in the long-run (72).

Vaccination is not the only solution to combatting the threat of AMR. The Chinese government has made gradual improvements in antimicrobial stewardship, including recent revisions to antibiotic use guidelines and enforcement of stricter regulations (73). In 2012, the Chinese government passed a law "Administrative Measures for the Clinical Use of Antibacterial Drugs," which strengthened the management and regulation of clinical uses of antibacterial drugs. A recent study conducted in primary care institutions in Hubei province showed that antimicrobial stewardship interventions can reduce the cost and volume of antibiotic procurement (74).

Our findings are consistent with previous studies on AMR and PCV in China. A 2006 study found that China had a faster growth rate of resistance compared to Kuwait and the United States, with 22% average AMR growth in China between 1994 and 2000 (75). Our study simulated AMR growth by 11% to 26% among 3 commonly used antibiotics over 5 years. A 2016 study estimated that introduction of PCV in China would decrease cases of AOM by 10.0% and cases of pneumococcal pneumonia by 15.3%, which is similar to our results in the accelerated scenario (76).

One of the other benefits of this study is the development of the DREAMR agent-based model to be able to dynamically simulate AMR accumulation. We found that resistance against meropenem decreased in our simulation even in the status quo scenario, which is likely due to the combined effect of low utilization of this antibiotic to treat pneumococcal diseases and high fitness cost of resistant bacteria. As the incidence of pneumococcal meningitis is low, meropenem was rarely utilized in our model. As resistant bacteria are less fit to compete for survival, we observed a reduction in the AMR ratio over time (60). While these results are specific to antibiotic utilization for pediatric pneumococcal diseases in China, the DREAMR model could be used to examine the impact of increased PCV coverage on AMR accumulation across various countries utilizing different antibiotics.

This study has a number of limitations to note. First, model results are limited by the quality and availability of data. Systematic national surveillance data for SP was not available for China, and data on rare cases of pneumococcal meningitis were especially difficult to find. Data were also limited on inpatient distribution of patients at different health facilities. We obtained model inputs from Chinese studies to the greatest extent possible, including literature written in both English and Chinese languages. Second, the model was not able to account for within country heterogeneity, including large disparities across provinces within China. Using available data, we gathered inputs for both urban and rural locations to account for as much variations as possible. Third, this study focused on antibiotic use for pediatric pneumococcal diseases, which is a limited fraction of overall antibiotic utilization. AMR ratios may be different when also considering utilization of antibiotics across other conditions and age groups. Fourth, the current model does not incorporate treatment adherence, serotype replacement, or other rarer diseases associated with SP. Greater data availability in these areas would facilitate model upgrades to examine additional impact. Finally, this study focused on human use of antibiotics, without

incorporating animal agriculture use. Further research should be conducted taking a One Health approach to examine antibiotic utilization across human and animal sectors.

As AMR poses a serious threat to healthcare, the benefit of vaccination in hindering AMR progression needs to be reevaluated. This study illustrates the AMR benefits of pneumococcal vaccination in China, including reduction in treatment failures and large cost savings. Given the sizable pneumococcal disease burden, low PCV coverage, and high antibiotic use, our research reveals the significant AMR-related value of introducing PCV in China's national immunization program. These results are useful for governments, partners such as the Bill and Melinda Gates Foundation, Gavi (the Vaccine Alliance), UNICEF, and the World Health Organization, as well as the vaccine and AMR communities. It contributes to global vaccination and AMR goals in addition to supporting the United Nations Sustainable Development Goals (SGDs) and the Global Health Security Agenda (GHSA) (77). The AMR benefit of vaccines should be further examined to ensure adequate commitments and investments are made for vaccines to not only save lives but also protect the effectiveness of existing medicines.

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Table 1: Vaccine Input Parameters of the DREAMR Model

Parameter variable	Unit	Value	Standard error or uncertainty range	Source
Demographics				
Total population (2015)	Thousands	1397028.6	-	United Nations [(19)]
Population, age 0 - 4 (2015)	Thousands	85884.7	-	United Nations [(19)]
Urban population (2017)	%	58.0	-	United Nations [(26)]
Rural population (2017)	%	42.0	-	United Nations [(26)]
Life expectancy at birth (2017)	USD	76.4	-	United Nations [(70)]
GDP per capita (2016)	Years	8827.0	-	World Bank [(67)]
Epidemiology				
*S. Pneumoniae** colonization rate	%	24.5	19.7-29.4	Wang et al. [(54)]
Pneumonia				
Incidence rate age 0-<2 outpatient	Cases/100000	2165	1624-2706	Shen et al. [(25)]
Incidence rate age 2-<5 outpatient	Cases/100000	2238	1679-2798	Shen et al. [(25)]
Incidence rate age 0-<2 inpatient	Cases/100000	14857	3929-25784	Shen et al. [(25)]
Incidence rate age 2-<5 inpatient	Cases/100000	14059	1743-26375	Shen et al. [(25)]
Case fatality rate	%	4.1	-	Chen et al. [(62)]
Number of cases	Cases	260768	113000–582382	Chen et al. [(62)]
Number of deaths	Cases	10703	4638–23904	Chen et al. [(62)]
Meningitis				
Incidence rate 0-<2	Cases/100000	1.3	0.9-1.6	Shen et al. [(25)]
Incidence rate 2-<5	Cases/100000	0.6	0-0.7	Shen et al. [(25)]
Case fatality rate	%	8.3	-	Chen et al. [(62)]
Number of cases	Cases	902	114-4463	Chen et al. [(62)]
Number of deaths	Cases	75	9-370	Chen et al. [(62)]
Hospitalization rate	%	100.0	-	Assumption
Acute otitis media				
Incidence rate 0-<2 (mild)	Cases/100000	10678	8009-13348	Shen et al. [(25)]
Incidence rate 2-<5 (mild)	Cases/100000	10678	8009-13348	Shen et al. [(25)]
Incidence rate 0-<2 (severe)	Cases/100000	3891	2918-4864	Shen et al. [(25)]
Incidence rate 2-<5 (severe)	Cases/100000	3891	2918-4864	Shen et al. [(25)]
Hospitalization rate	%	0.0%		Assumption
Clinical resolution rate - amoxicillin	%	92.8%		Saux et al. [(32)]
Clinical resolution rate – placebo	%	84.2%		Saux et al. [(32)]
hearing loss	Cases/10000	22.8		Monasta et al. [(63)]
Vaccine characteristics				
Vaccine effectiveness	%			
Pneumonia 0-<2	%	22	-	Shen et al. [(25)]
Pneumonia 2-4	%	17	-	Shen et al. [(25)]
Meningitis 0-<2	%	64	-	Shen et al. [(25)]
Meningitis 2-4	%	64	-	Shen et al. [(25)]
AOM <12 months	%	22	-	Blank et al. [(23)]
AOM 12-23 months	%	27	-	Blank et al. [(23)]
AOM 24-59 months	%	0	-	Blank et al. [(23)]
PCV coverage rate 2014				
2014	%	4.7	-	Yuan et al. [(12)]

Careseeking	%			
Urban	%	84.4	-	Calculated [(27)]
Rural	%	83.1	-	Calculated [(28)]
Self-medicate - urban	%	14.1	-	NHFPC [(30)]
Self-medicate - rural	%	14.4	-	NHFPC [(30)]
Did not seek any care - urban	%	1.4	-	NHFPC [(30)]
Did not seek any care - rural	%	2.4	-	NHFPC [(30)]
Mortality rate odds ratio (non-seeking vs seeking care)	OR	7.6	3.77-15.1	Reyes et al. [(31)]
Health facility				
Outpatient-Urban				
Not reported	%	3.5	-	Li et al. [(29)]
Municipal level	%	89.5	-	Li et al. [(29)]
County level	%	7.0	-	Li et al. [(29)]
Township or village level	%	0	-	Li et al. [(29)]
Private clinic	%	0	-	Li et al. [(29)]
Outpatient-Rural				
Not reported	%	15.6	-	Li et al. [(29)]
Municipal level	%	39.7	-	Li et al. [(29)]
County level	%	10.1	-	Li et al. [(29)]
Township or village level	%	17.1	-	Li et al. [(29)]
Private clinic	%	17.6	-	Li et al. [(29)]
Inpatient-Urban				
Not reported	%	3.5	-	Calculated [(29)]
Municipal level	%	89.5	-	Calculated [(29)]
County level	%	7.0	-	Calculated [(29)]
Township or village level	%	0	-	Calculated [(29)]
Private clinic	%	0	-	Calculated [(29)]
Inpatient-Rural				
Not reported	%	15.6	-	Calculated [(29)]
Municipal level	%	45.6	-	Calculated. [(29)]
County level	%	15.9	-	Calculated [(29)]
Township or village level	%	22.9	-	Calculated [(29)]
Private clinic	%	0	-	Calculated [(29)]
Inpatient treatment				
Not reported	%	1.4%		Calculated [(29)]
Municipal level	%	1.5%		Calculated [(29)]
County level	%	2.0%		Calculated [(29)]
Township or village level	%	1.8%		Calculated [(29)]
Private clinic	%	0.0%		Calculated [(29)]
Treatment length				
Treatment follow-up	Days	3	-	Bradley et al. [(33)]
Pneumonia - inpatient	Days	7.1	4.2-10	Zhang et al. [(39)]
Pneumonia - outpatient	Days	7	-	Assumption
Meningitis	Days	21	-	Li et al. [(38)]
Acute otitis media	Days	7	-	Committee [(37)]
Antibiotics				
Resistance				
Penicillin G	%	53.8	-	Li et al. [(38)]
Amoxicillin	%	8.1	-	Lyu et al. [(42)]

3rd generation cephalosporins	%	20.8	-	Lyu et al. [(42)]
Meropenem	%	36.0	-	Liu et al. [(43)]
Utilization				
Pneumonia				
Penicillin G	%	31.5		Li, Ruimei. [(40)]
Amoxicillin	%	39.4		Adjusted [(40)]
3rd gen cephalosporin	%	29.0		Li, Ruimei. [(40)]
Meningitis				
Meropenem	%	100		Adjusted [(41)]
Acute Otitis Media				
Penicillin G	%	44.4		Calculated [(40)]
Amoxicillin	%	55.6		Calculated [(40)]
Distribution of Costs				
Type of cost				
Direct medical cost - outpatient	%	62.8	-	Li et al. [(29)]
Direct medical cost - inpatient	%	88.3	-	Li et al. [(29)]
Mean medical expenditure by type of health facility				
Outpatient				
Municipal	USD	174.7	-	[(29)] [(66)]
County	USD	126.9	-	[(29)] [(66)]
Township or Village	USD	75.1	-	[(29)] [(66)]
Inpatient				
Municipal	USD	783.3	-	Ma et al. [(66)]
County	USD	568.8	-	Ma et al. [(66)]
Township or Village	USD	336.7	-	Ma et al. [(66)]

S. Pneumoniae; Streptococcus Pneumoniae, AOM; acute otitis media, PCV; pneumococcal conjugate vaccine

Table 2: Health and Economic Outcomes of PCV13

Outcomes	Status Quo (SQ)	Scaled (Difference from SQ)	Percent Change (Scaled vs SQ)	P Value	Accelerated (Difference from SQ)	Percent Change (Accel. vs SQ)	P Value
Cumulative disease cases							
Pneumococcal pneumonia, n	70,790,290	-5,711,125	-8.07%	<0.01	-9,444,681	-13.34%	<0.01
Pneumococcal meningitis, n	2,774	-701	-25.27%	<0.01	-1,074	-38.73%	<0.01
Pneumococcal AOM, n	62,220,967	-2,898,247	-4.66%	<0.01	-4,487,762	-7.21%	<0.01
Cumulative adverse health outcomes							
Overall death, n	1,355,635	-109,733	-8.09%	<0.01	-183,642	-13.55%	<0.01
Disability, n	9,485	-428	-4.51%	<0.01	-725	-7.64%	0.068
Treatment behavior							
Cumulative first line treatments, n	71,640,310	-3,678,303	-5.13%	<0.01	-5,951,186	-8.31%	<0.01
Cumulative second line treatments, n	46,545,018	-4,113,850	-8.84%	<0.01	-6,647,389	-14.28%	<0.01
Average defined daily dose, per 1000 patient days	5.84	-0.40	-6.89%	<0.01	0	0.01%	0.85

AOM; acute otitis media, USD; United States dollar, SQ; status quo. Point estimates were derived from taking averages across 5,000 base case simulations.

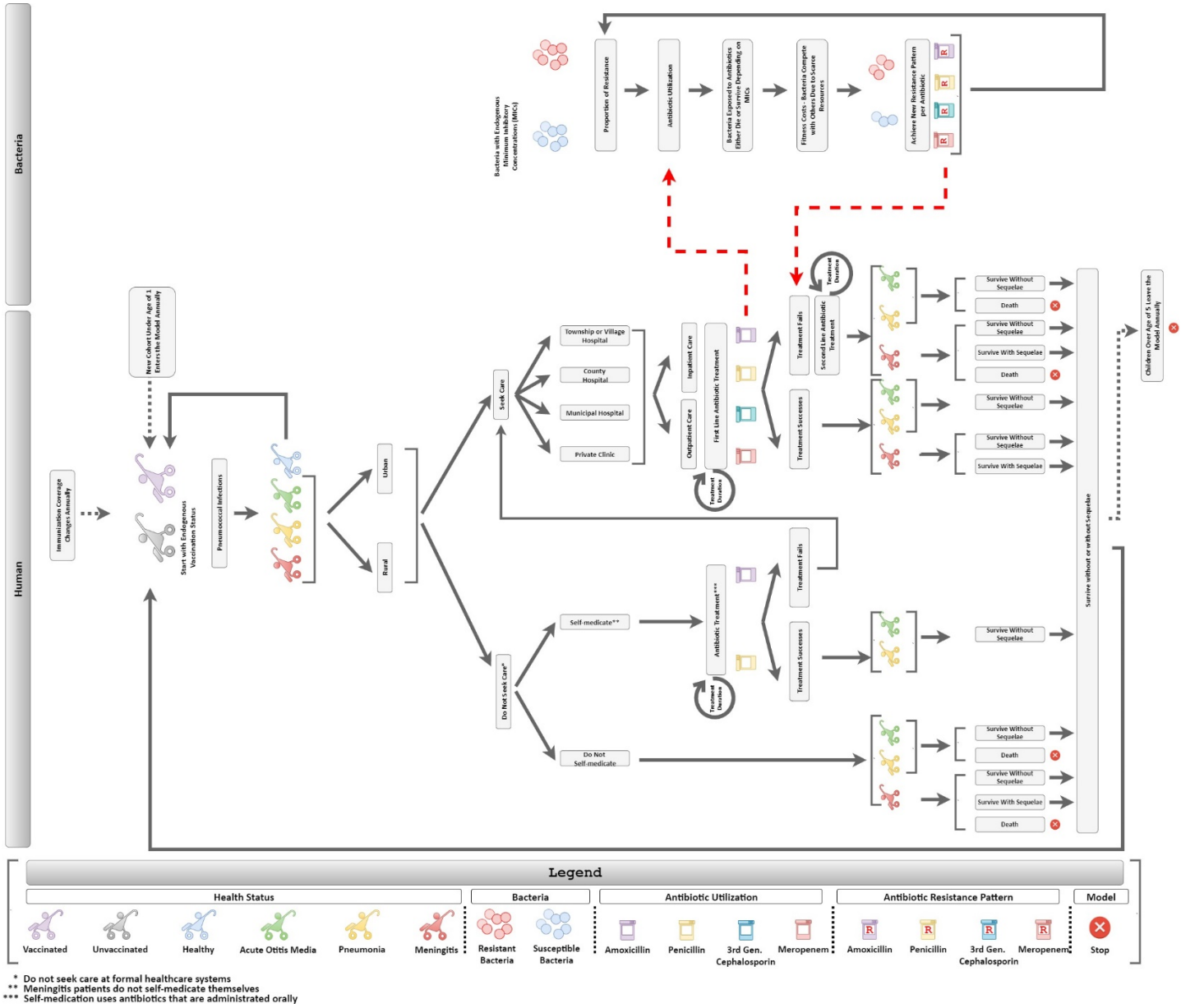
Table 3: AMR Benefits from Increasing Pneumococcal Vaccination in China

Outcomes	Status Quo (SQ)	Scaled (Difference from SQ)	Percent Change (Scaled vs SQ)	P Value	Accelerated (Difference from SQ)	Percent Change (Accel. vs SQ)	P Value
Incremental change in resistance							
Penicillin, %	10.74	-0.19	-1.74%	<0.01	-0.31	-2.87%	<0.01
Amoxicillin, %	26.11	-5.01	-19.19%	<0.01	-7.83	-29.97%	<0.01
3rd generation cephalosporins, %	11.72	-1.74	-14.87%	<0.01	-2.74	-23.35%	<0.01
Meropenem, %	-3.81	0.00	0.01%	0.85	0.00	0.01%	0.94
Treatment failures							
Cumulative treatment failures, n	46,546,169	-4,114,085	-8.84%	<0.01	-0.65	-11.16%	<0.01
Treatment failure (pneumonia), n	24,829,955	-2,624,764	-10.57%	<0.01	-6,647,750	-14.28%	<0.01
Treatment failure (meningitis), n	921	-222	-24.11%	<0.01	-4,269,777	-17.20%	<0.01
Treatment failure (AOM), n	21,806,207	-1,503,290	-6.89%	<0.01	-344	-37.35%	<0.01
Proportion of treatments resulting in failures, %	39.38%	-0.95%	-2.40%	<0.01	-2,401,860	-11.01%	<0.01
Average annual costs per child in first-line treatment due to resistance							
Overall costs, USD	10.25	-1.14	-11.08%	<0.01	-1.83	-17.86%	<0.01
Direct medical costs, USD	3.17	-0.35	-11.13%	<0.01	-0.57	-17.95%	<0.01
Direct non-medical costs, USD	1.81	-0.20	-11.05%	<0.01	-0.32	-17.81%	<0.01
Productivity losses for caretaker, USD	5.27	-0.58	-11.06%	<0.01	-0.94	-17.82%	<0.01
Average annual costs per child in second-line treatment							
Overall costs, USD	26.03	-2.31	-8.89%	<0.01	-3.75	-14.39%	<0.01
Direct medical costs, USD	8.05	-0.72	-8.94%	<0.01	-1.17	-14.48%	<0.01
Direct non-medical costs, USD	4.60	-0.41	-8.86%	<0.01	-0.66	-14.34%	<0.01
Productivity losses for caretaker, USD	13.38	-1.19	-8.87%	<0.01	-1.92	-14.35%	<0.01
Direct costs due to resistance in first line treatment, USD							
Year 1	576,860,426	-5,874,112	-1.02%	<0.01	-12,661,690	-2.19%	<0.01
Year 2	693,525,228	-28,530,502	-4.11%	<0.01	-61,917,227	-8.93%	<0.01
Year 3	823,705,607	-67,170,292	-8.15%	<0.01	-149,617,478	-18.16%	<0.01
Year 4	984,679,043	-126,174,598	-12.81%	<0.01	-213,847,995	-21.72%	<0.01
Year 5	1,180,908,773	-223,778,118	-18.95%	<0.01	-290,540,204	-24.60%	<0.01
Productivity losses for caretaker, USD	5,296,973,655	-435,816,652	-8.23%	<0.01	-705,814,816	-13.32%	<0.01
Direct costs due to resistance in second line treatment, USD							
Year 1	1,788,064,766	-17,666,916	-0.99%	<0.01	-37,819,714	-2.12%	<0.01
Year 2	1,990,245,181	-77,405,255	-3.89%	<0.01	-168,397,355	-8.46%	<0.01
Year 3	2,203,451,649	-164,317,126	-7.46%	<0.01	-369,441,108	-16.77%	<0.01
Year 4	2,452,706,535	-278,205,047	-11.34%	<0.01	-464,963,215	-18.96%	<0.01
Year 5	2,742,489,542	-455,990,189	-16.63%	<0.01	-567,758,255	-20.70%	<0.01

Productivity losses for caretaker, USD	5,745,659,142	-509,482,402	-8.87%	<0.01	-824,540,146	-14.35%	<0.01
Cumulative costs due to resistance, USD	26,479,269,546	-2,390,411,209	-9.03%	<0.01	-3,867,319,202	-14.61%	<0.01
Projected productivity losses from death/disability due to resistance, USD	27,722,050,208	-3,504,994,360	-12.64%	<0.01	-5,692,819,084	-20.54%	<0.01

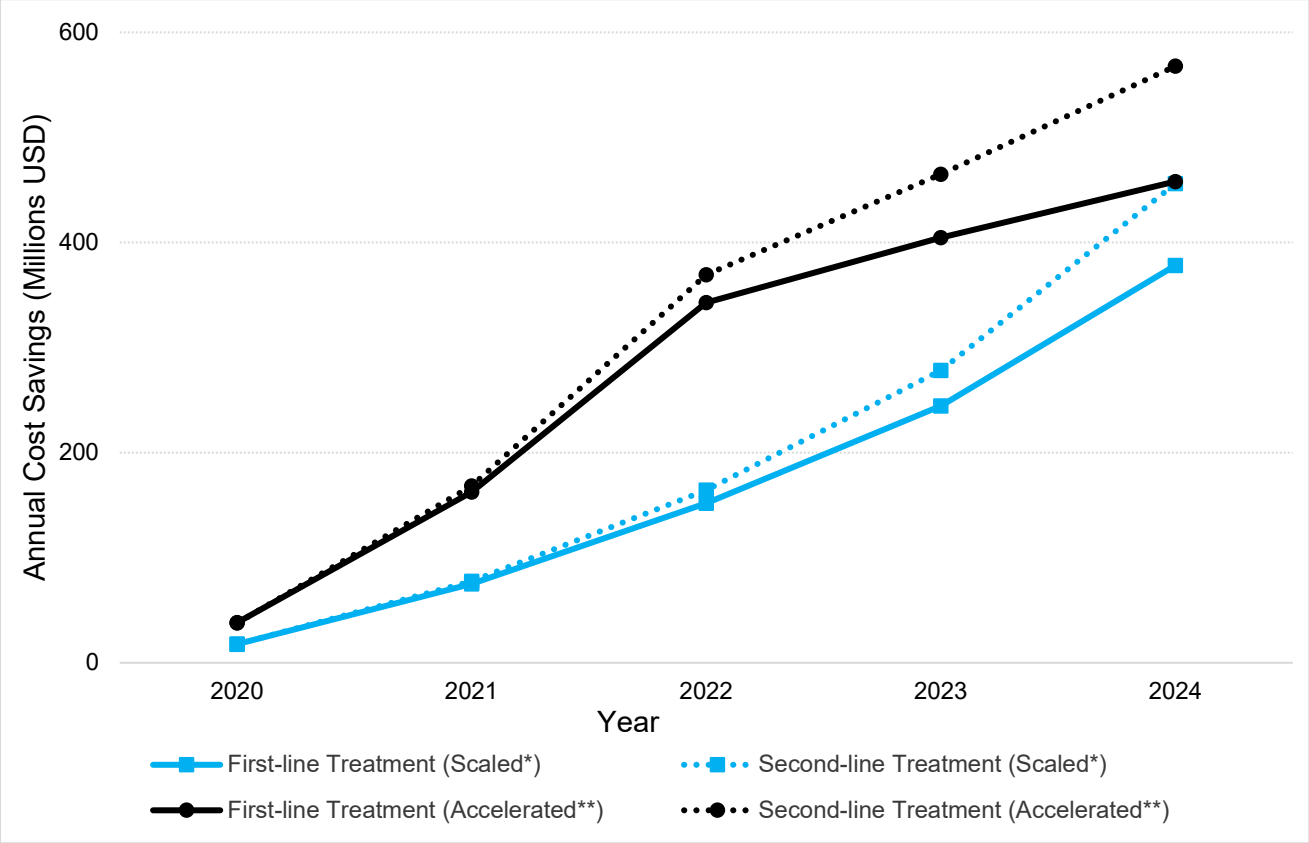
AOM; acute otitis media, USD; United States dollar, SQ; status quo. Point estimates were derived from taking averages across 5,000 base case simulations.
Productivity losses are calculated from 15 years of age until death for all affected individuals (DALY weight of 1 for death and DALY weight of 0.158 for disability)

Figure 1. DREAMR Model Structure



* Do not seek care at formal healthcare systems
** Meningitis patients do not self-medicate themselves
*** Self-medication uses antibiotics that are administrated orally

Figure 2: AMR-related Cost Savings From Increased PCV Coverage in China



AMR: Antimicrobial resistance; PCV: Pneumococcal conjugate vaccine; USD: United States Dollars.

* Scaled scenario linearly increased PCV coverage from 4.7% to 99% over five years.

** Accelerated scenario increased PCV coverage linearly from 4.7% to 85% in the first two years, and to 99% over the next three years.