Report of Health Technology Assessment.

Pneumococcal Conjugate Vaccine to prevent mortality and morbidity of pneumococcal disease in Indian Adults

Conducted by

RRC-HTA; SCTIMST, Trivandrum

In collaboration with

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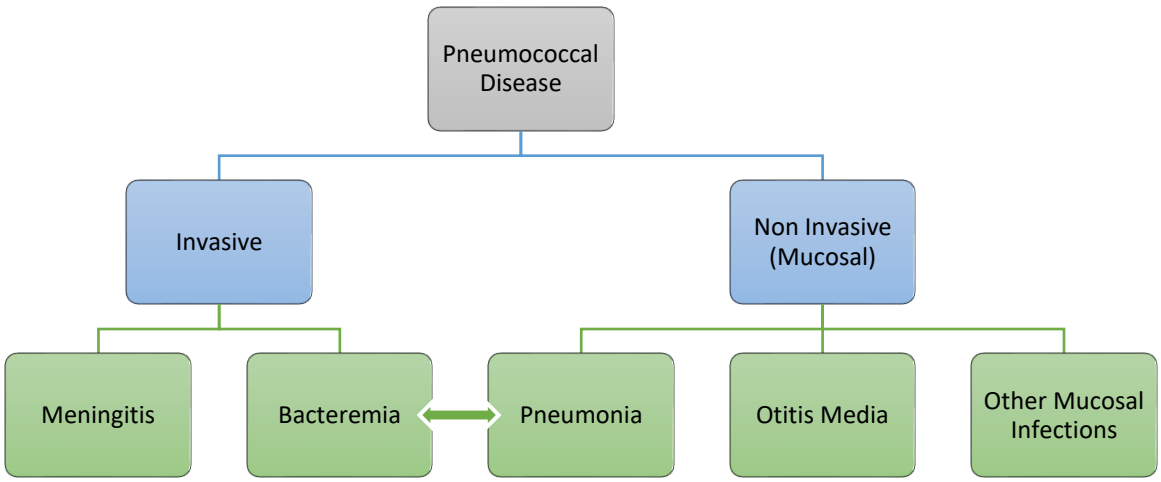
Background and rationale

Streptococcus pneumonia is a gram-positive facultative anaerobic bacteria that is pathogenic to humans.[1] More than 100 capsular serotypes of *S. pneumoniae* have been identified, out of which most are infectious, although only a minority of serotypes cause most cases of invasive diseases.[1,2] Pneumococci are transmitted by direct contact with respiratory secretions from patients and healthy carriers.[3]

Pneumococcal disease is the collective term for a range of conditions caused by *S. pneumoniae* infection and is classified as invasive and non-invasive. The invasive ones refer to infections where the bacteria are isolated from normally sterile body fluids such as blood, CSF, and pericardial fluid; examples of such infections include meningitis, bacteremia, etc. The non-invasive ones include mucosal infections such as sinusitis, otitis media, and community-acquired pneumonia(CAP). The non-invasive infections could be termed invasive when coupled with bacteremia[1,4,5]. According to WHO, invasive pneumococcal diseases(IPD) result in the deaths of 6 lakh- 8 lakh adults every year.[6] Incidence of IPD is highest in people >65 years of age, followed by infants 0-23 months.[7]

Figure 1: Pneumococcal Disease



As per Indian studies, the most common clinical manifestation of *S.pnemococcus* is pneumonia, accounting for 39% of total IPD cases due to the organism, followed by meningitis at 24.3%.[8] Historically, *S. pneumonia* has been the most common pathogen causing community-acquired pneumonia, accounting for more than 90% of cases in the pre-antibiotic era. In the antibiotic era (1990-2010), the proportion of CAP cases where pneumococcus is detected has ranged from 15% to 75% in North America and Europe. After introducing pneumococcal conjugate vaccines, pneumococcus is identified in these regions in as few as 9% to 35% of pneumonia cases.[9,10] Pneumococcal pneumonia can result in complications, including empyema, pericarditis, septicaemia, and respiratory failure.[4] Uncomplicated pneumonia is treated with penicillin, cephalosporins, and macrolides and sometimes with higher antibiotics as per antibiotic sensitivity testing.[11]

Pneumococci are the most common causative organism of bacterial meningitis, with a share of infections ranging from 50-90% across geographical regions.[12,13] Bacterial meningitis is a devastating disease that kills around 1 in 10 people and leaves 1 in 5 with severe complications.[14] Case fatality rate of pneumococcal meningitis can be as high as 30-50%.[15] Major complications of bacterial meningitis include loss of hearing, epilepsy, loss of vision, and problems with memory, coordination, and balance.[16] Acute cases of bacterial meningitis are treated with broad-spectrum antibiotics. Individuals living with meningitis sequelae often have healthcare needs requiring long-term medical treatments.[14] Acute otitis media is a non-invasive manifestation of *S. pneumonia,* primarily seen in children but less common in adults. Otitis media can result in complications including hearing loss, Tympanic Membrare™ perforation, mastoiditis, labyrinthitis, and facial paralysis.[17]

Most common serotypes identified from pneumococcal diseases in India are 1, 5, 19F, 14, 23F(covered by PCV10); 3, 19A, 6A, 6B(PCV13); 8, 12F, 9N, 11A, 17F(PCV23).[8,18]

High-Risk Populations for Pneumococcal Disease.[4]

Children under two years and adults 65 years or older are at increased risk for pneumococcal disease. Immuno-senescence, or the deterioration in the immune system seen in older adults, makes them more susceptible to infectious diseases, including IPDs. Current smokers have a two-times higher risk for IPD compared to non-smokers. Adults of all ages are at increased risk for pneumococcal disease if they are suffering from

- Alcoholism
- Chronic heart, lung, kidney, or liver disease
- Cochlear implant
- Cerebro-spinal Fluid (CSF) leak
- Diabetes
- HIV infection, cancer, solid organ transplant, or another condition or taking medicine that weakens the immune system
- Nephrotic syndrome
- Sickle cell disease, a damaged spleen, or no spleen

Besides susceptibility to infection, the risk of mortality from infections is also higher in old-age individuals and those with comorbidities.[19]

Pneumococcal Vaccines.

Pneumococcal Conjugate Vaccines

These vaccines have pneumococcal capsular polysaccharide conjugated to diphtheria toxin. PCVs generate a T-cell-dependent antibody response, producing a longer immunity duration than PPSV, and have a boosting effect at revaccination.[18,20] Conjugate vaccines also reduce carriage rate and have a protective herd effect, unlike polysaccharide vaccines.[20]

Table 1: Conjugate Vaccine Serotypes

Vaccine	Serotypes
PCV7[20]	4, 6B, 9V, 14, 18C, 19F, 23F
PCV10[21]	1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F, 23F
PCV13[18]	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F
PCV15[22]	1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F,22F, 23F, 33F
PCV20[23]	1, 3, 4, 5, 6A, 6B, 7F, 8, 9V, 10A, 11A, 12F, 15B, 14, 18C, 19A, 19F,22F, 23F, 33F

Pneumosil: A 10 valent PCV targeting serotypes 1, 5, 6A, 6B, 7F, 9V, 14, 19A, 19F, 23F developed by Serum Institute of India in collaboration with PATH and Bill and Melinda Gates Foundation. Pneumosil is WHO pre-qualified for its procurement by United Nations Agencies and GAVI. The manufacturers claim that Pneumosil is designed to provide the same degree

of protection as current vaccines at roughly 30% of the GAVI-supported price for LICS and substantially lower pricing than current vaccines for other LMICS.[24]

Pneumococcal Polysaccharide Vaccine (PPSV)-PPSV23**:** Polysaccharide vaccine introduced in 1983 consists of unconjugated capsular polysaccharide antigens and is active against 23 serotypes of Streptococcus pneumonia: 1, 2, 3, 4, 5, 6B, 7F, 8, 9N, 9V, 10A, 11A, 12F, 14, 15B, 17F, 18C, 19F, 19A, 20, 22F, 23F, and 33F.[18,20] PPSV produces a T-cell independent immune response and has proven efficacy of 50-70% against invasive pneumococcal diseases in immunocompetent elderly individuals. CAP patients previously vaccinated with PPSV 23 have a 40% lower risk for mortality and ICU admission compared to non-vaccinated individuals.[18] Vaccine is administered as a 0.5ml dose, IM/SC.[25] Side effects are relatively mild and include local reaction, tiredness, fever, and myalgia, which subside in about two days.[26]

Adult Pneumococcal Vaccination Recommendations

Adults who have never received a pneumococcal conjugate vaccine should receive PCV15 or PCV20 if they are 65 years and older; or are 19 through 64 years old and have certain medical conditions or other risk factors. CDC recommends that all children younger than two years receive PCV13, and children of 2-18 years old with certain medical conditions should receive PCV13 and PPSV23. If PCV15 is used, it should be followed by a dose of PPSV23.[26]. Detailed age-wise recommendations by CDC, Atlanta, are shown in Table 1.

Table 2: CDC Vaccination Recommendation

Age	Vaccine	Schedule	Recommendation
<2years	PCV13	2m, 4m, 6m, 12-15m	
2-5 years with medical conditions	PCV13 + PPSV23	Two doses at 8-week intervals One dose eight weeks after completion of PCV13	One dose if already received three doses before 12m
6-18 years with medical conditions	PCV13 +	One dose	If not previously immunised

	PPSV23	One dose	
19-64 years with medical conditions	PCV15+PPSV23	Single doses at 1-year interval	If previously immunized with PPSV, one dose of PCV15/PCV20
>65 Years	OR PCV20	Single Dose	

Indian Guidelines & Recommendations.[27]

The Association of Physicians in India (API) recommends PCV13 and PPSV23 vaccinations for individuals over 65 years and those over 18 years with comorbidities. The Geriatric Society of India (GSI) recommends vaccination for adults >65 years of age. Detailed recommendations by API and GSI are given in Tables 2 and 3, respectively.

Table 3: API recommendation

Age and Immune Status	**Vaccination History**	**Recommendations**
>19years	No prior vaccination	PCV13 followed by PPSV 23 8 weeks later
With predisposing conditions	Prior vaccination with PPSV23	PCV13 1 year after PPSV23
<65 years with predisposing conditions		One dose of PPSV23 Repeat dose after 1 year for nephrotic syndrome, chronic renal failure, immunosuppression
>65 years		One dose of PPSV23

Geriatric Society of India Recommendation

Table 4: GSI Recommendation

Age	**Vaccination History**	**Recommendations**
Adults>65 years	No known vaccination history	• Initial dose of PCV 13; PPSV23 6-12 months after

	Prior vaccination with PPSV23	• PCV 12 months after PPSV23
Hajj pilgrims		• PCV administration 4 weeks prior • PPSV23 on return

The rationale of the study.

Respiratory diseases are the third most common cause of death globally and India's second most common cause. Streptococcal pneumonia is primarily responsible for respiratory diseases such as pneumonia, apart from other invasive diseases, such as septicaemia and meningitis. The adult population over 65 years and those with comorbidities are at the highest risk of being infected by *S. pneumonia* and suffer long-term sequelae/mortality from it. As India is in a stage of demographic transition, the number of individuals requiring protection from invasive pneumococcal diseases is bound to rise. In this regard, it is necessary to analyse the clinical effectiveness of pneumococcal vaccinations in the elderly and other high-risk groups against IPDs and to determine their cost-effectiveness and budget impact. The effectiveness of pneumococcal vaccinations in bringing down readmission rates and the costs associated with readmissions is another pertinent issue in an insurance-based system.

Aim

This HTA study aims to evaluate the clinical and cost-effectiveness of the Pneumococcal Conjugate Vaccine, and serial administration of Pneumococcal Conjugate Vaccine and Pneumococcal Polysaccharide Vaccine in reducing mortality, morbidity, and hospital readmissions caused by pneumococcal disease in Indian adults compared to usual care scenarios without vaccination.

Objectives

1. Determine the cost-effectiveness of PCV vaccine alone and serial administration of PCV/PPSV in the adult population in India to reduce pneumococcal disease morbidity and mortality.

2. Perform subgroup analysis for adults aged 18-49 years, 50-64 years, 65-74 years, and >74 years to identify subgroups best served by adult pneumococcal vaccination.
3. Estimate the budget impact of PCV administration in the eligible subgroups among the beneficiaries of hospitals empanelled in the AB-PMJAY scheme.

Research Methods

Economic Evaluation Framework

A cost-utility analysis was performed to evaluate the effectiveness of PCV alone and in combination with PPSV23 in reducing mortality, morbidity, and hospital admissions caused by pneumonia and invasive pneumococcal diseases.

PICO

Population

The study population of Indian adults was classified into four age bands for the analysis. i)18-49 years ii) 50-64 years iii) 65-74 years and iv) 75 years.

Each age group was classified into low-risk, moderate-risk, and high-risk groups depending upon existing health conditions that influenced the risk of incidence of pneumonia/invasive pneumococcal disease. The high-risk group included patients with splenic dysfunction/post-splenectomy status, hematologic malignancies, chronic renal diseases, HIV infections, and high-dose corticosteroid use. Moderate-risk groups included those with diabetes mellitus, chronic liver disease, chronic pulmonary diseases, and cardiovascular diseases.

Intervention.

Adult pneumococcal vaccination using the following vaccines.

i. Pneumococcal conjugate vaccine (PCV13)

Single dose of PCV13 vaccine administered intramuscularly at adult immunization clinics in Community Health Centres (CHCs) & tertiary care hospitals.

ii. Serial administration of PCV 13 and Pneumococcal Polysaccharide Vaccine(PPSV23).

Single dose each of PCV13 and PPSV23 administered intramuscularly with a gap of 8 weeks.

Comparator

Usual care for Pneumococcal disease in the no-vaccination scenario, including in-patient care for Pneumonia and invasive pneumococcal diseases.

Outcomes.

i. Mortality from pneumococcal diseases – pneumonia, meningitis, sepsis, and complications
ii. Morbidity from pneumococcal disease in terms of the number and duration of hospital admissions, and the incidence of complications
iii. Hospital readmissions due to pneumococcal diseases.
iv. Cost of management of pneumonia and invasive pneumococcal diseases.

Study Perspective

Analysis was carried out from a health-system perspective. Costs incurred by the health system in vaccine administration and management of pneumonia/IPDs were included in the analysis.

Time Horizon & Discounting.

A time horizon of 15 years, which is the estimated duration of effectiveness of PCV, was adopted for the analysis for those in the age band of 18-74. For the age group of 75+, a time horizon of 10 years was used.

A uniform discounting of 3% was applied to all costs and consequences included in the analysis.

Model Overview

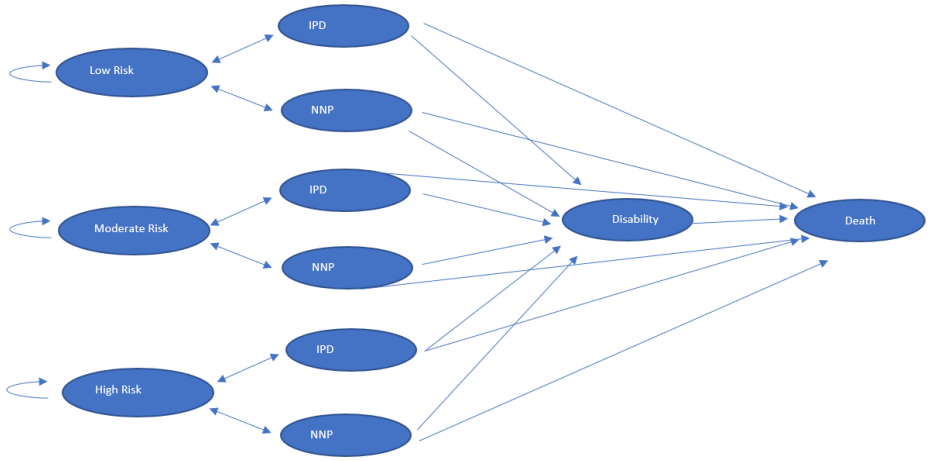
Markov models were created to compare the vaccination scenario with the usual care scenario for each of the four age bands and the two vaccination strategies.

The cohort enters the Markov model in three risk groups- low risk, moderate risk, and high risk. From each of these three initial stages, the cohort moves into Non-bacteraemic Pneumococcal Pneumonia(NPP) or Invasive Pneumococcal Disease (IPD) stages as per the respective incidence risks. From NPP and IPD stages, the cohort can move into Disability stage based on the incidence risk of multiple complications or the absorbing stage of Death based on disease-related mortality. Age-related mortality risks are also applied to all stages in the Markov cycle(Figure 2).

The stages in the Markov model and the initial probabilities of the stages are identical for both vaccination and no-vaccination arms. In the vaccination arm, the incidence risk for IPD and NPP are multiplied by the proportion of the population susceptible after vaccination to incorporate change in transition probability due to vaccination.

The actual models created using Tree Age Pro software are given as Supplementary Materials 1-4

Figure 2: Markov Model



Input parameters

The input parameters for the models were obtained from a targeted literature review and expert consultations. The input parameters included in the model are shown in Table 5. Parameters derived from primary input parameters along with the equations used are shown in table 6.

Table 5: Input Parameters

Parameters	**18-49**	**50-64**	**65-74**	**75+**	**References**
Costs					
Cost_pcv13	3955	3955	3955	3955	K.I.I.
Cost_PPSV23	2279	2279	2279	2279	K.I.I.
Cost_vaccineadministration	116	116	116	116	
Cost_ip day	1076	1076	1076	1076	National Health System Cost Database
Utilities					
Low Risk Group	.972	.948	.913	.85	

Moderate Risk Group	.972	.948	.913	.85	Heo et al[28]
High Risk Group	.843	.792	.682	.68	
IPD Low Risk Group	.0416	.048	.0436	.0338	
IPD Moderate Risk Group	.0335	.0388	.0416	.0416	
IPD High Risk Group	.0482	.0476	.0379	.0425	
NPP Low Risk Group	.0197	.0197	.0263	.0285	
NPP Moderate Risk Group	.0285	.0285	.0395	.0416	
NPP High Risk Group	.0395	.0395	.0526	.057	
In-patient days					
IPD, High Risk group	22	21.7	17.3	19.4	Heo et al[28] Koul et al[18]
IPD, Moderate Risk Group	15.3	17.7	19	19	
IPD, Low Risk Group	19	21.9	19.9	15.4	
NPP, High Risk Group	18	19	24	26	
NPP, Moderate Risk Group	13	13	18	19	
NPP, Low Risk Group	9	9	12	13	
Initial Probabilities					
Low Risk	.865	.706	.546	.56	Heo et al[28]
Moderate Risk	.1	.246	.382	.373	
High Risk	0.035	.048	.072	.067	
Transition Probabilities					
Low Risk to NPP	0.000049	.000305	0.002138	0.007105	Heo et al[28] Jayaraman et al[13] Koulet al[18]
Low Risk to IPD	0.0000090	0.000043	0.000176	0.000643	
Moderate Risk to NPP	0.000123	0.000768	0.002379	0.005784	
Moderate Risk to IPD	0.000022	0.000109	0.000194	0.000528	
High Risk to NPP	0.000233	0.001457	0.005399	0.011129	
High Risk to IPD	0.000041	0.000205	0.000441	0.001009	
NPP to Disabled	.0163	.0066	.0064	.0064	
IPD to Disabled	.0326	.0132	.0128	.0128	
Low Risk NPP mortality	0.045	0.072	0.116	0.141	
Low Risk IPD mortality	0.136	0.224	0.292	0.377	
Moderate Risk NPP mortality	0.068	0.108	0.174	0.212	
Moderate Risk IPD mortality	0.216	0.257	0.292	0.377	
High Risk NPP mortality	0.09	0.144	0.232	0.282	
High Risk IPD mortality	0.259	0.308	0.4	0.72	
Vaccine effectiveness: Base Year					
Low Risk to NPP	0.535	0.535	0.535	0.535	Ngampra sertchai et al[29] Daniel et al[20] Stacey et al[22]
Low Risk to IPD	0.75	0.75	0.75	0.75	
Moderate Risk to NPP	0.535	0.535	0.535	0.535	
Moderate Risk to IPD	0.75	0.75	0.75	0.75	
High Risk to NPP	0.15	0.15	0.15	0.15	
High Risk to IPD	0.25	0.25	0.25	0.25	
Vaccine effectiveness: Serial Vaccination	Estimated to be 10% more than PCV alone				
WTP Threshold					
India GDP Per Capita	1,87,530 INR				

(Refer Supplementary material 5 for complete list of input parameters with high and low values used for sensitivity analysis).

Cost and QALY Estimation

Estimation of Cost

A one-time cost of vaccination was assigned to the initial stages of Low Risk, Intermediate Risk, and High risk at the beginning of the Markov cohort. The cost of vaccination included the price of the vaccine and the cost of administration of one unit of vaccine for the health system(Table 6). The treatment cost of each condition was calculated by multiplying the estimated in-patient days for the condition multiplied by the per-day cost of inpatient management in secondary-level health centres in Kerala. To estimate the cost of each stage in each cycle, the treatment cost was multiplied by the probability of being in that stage.

Estimation of Effectiveness.

QALYs generated by Low Risk, Moderate Risk, and High-Risk groups were estimated by multiplying the utility value of the state by 1 year. For the calculation of QALY estimation of IPD/NPP stages, the utility value of IPD/NPP was multiplied by the fraction of the year spent in in-patient treatment, and the utility value of the parent stage was multiplied by the remaining fraction(Table 6).

Table 6: Derived parameters

Category	Parameters
Cost of vaccination- PCV 13	Cost PCV 13+ Cost of Vaccine Administration
Cost of vaccination- PPSV23	Cost of PPSV23+ Cost of Vaccine Administration
Cost of vaccination- serial	Cost of vaccination-PCV13 + Cost of vaccination-PPSV23
Cost Health System(IPD/NPP)	Hospital days(IPD/NPP)* Cost IP day
Transition probability-Vaccination arm	Transition probability non-vaccination arm* (1- vaccine effectiveness)
QALY- IPD Low Risk	Utility_IPD Lowrisk*(IPdays_IPD Lowrisk/365)+ Utility_Lowrisk*(1-IPdays_IPDLowrisk/365)

ICER estimation.

The Incremental Cost-Effectiveness Ratio (ICER) was calculated as follows.

Incremental cost = Total Cost of Vaccination Arm- Total Cost of Usual Care Arm.

Incremental Effectiveness = Total QALYs generated by Vaccination Arm- Total QALYs of Usual Care Arm.

ICER= Incremental Cost/Incremental Effectiveness.

Independent analyses were done for the four age bands(18-49, 50-64, 65-74, 75+) and the two vaccination scenarios (PCV 13 alone, PCV13 and PPSV23 serial administration).

Sensitivity Analysis

To assess the robustness of the ICERs estimated, a one-way- sensitivity analysis was done for each of the 8 base-case scenarios by varying the value of input parameters by 20% on either side. Tornado diagrams were constructed for each analysis, plotting the value of ICER obtained against the high and low values of input parameters with maximum impact on ICER value.

Results

Deterministic Results

Vaccination with PCV13.

The cost-effectiveness of vaccination with PCV 13 was analysed for the four age bands of 18-49, 50-64, 65-74, and 75+.

i. 18-49 Age Group

The discounted incremental cost for vaccinating a patient in the 18-49 age group is 4166 INR, which yields an incremental QALY of 0.0003, resulting in an ICER of 1,41,37,000 INR per QALY. PCV13 vaccination for all adults in this age group is not cost-effective at a threshold of 1GDP per capita of India of 1.87Lakhs INR. (Table 7)

Table 7: ICER: PCV Vaccination, 18-49 age group.

Strategy	Costs (INR)	QALYs	Incremental Costs	Incremental QALYS
Usual Care	14.06	14.51165		
PCV13 Vaccination	4180.39	14.51195	4166.34	0.000295
ICER	**1,41,37,187 INR/QALY**			

ii. 50-64 Age Group

The discounted incremental cost for vaccinating a patient in the 50-64 age group is 4140 INR, which yields an incremental QALY of 0.003, resulting in an ICER of 13,97,318 INR per QALY. PCV13 vaccination for all adults in this age group is not cost-effective at a threshold of 1GDP per capita of India. (Table 8)

Table 8: ICER:PCV Vaccination, 50-64

Strategy	Costs (INR)	QALYs	Incremental Costs	Incremental QALYS
Usual Care	88.30	11.38972		
PCV13 Vaccination	4229.03	11.39268	4140.73	0.002963
ICER	**13,97,318 INR/QALY**			

iii. 65-74 age group

The discounted incremental cost for vaccinating a patient in the 65-74 age group is 3995 INR, which yields an incremental QALY of 0.025, resulting in an ICER of 1,59,418INR per QALY. PCV13 vaccination for all adults in this age group is cost-effective at a threshold of 1GDP per capita of India of 1.83lakhs INR. (Table 9)

Table 9:ICER: PCV Vaccination, 65-74 age group

Strategy	Costs (INR)	QALYs	Incremental Costs	Incremental QALYS
Usual Care	539.65	10.80456		
PCV13 Vaccination	4535.57	10.82963	3995.92	0.025066
ICER	**1,59,418 INR/QALY**			

iv. 75+ Age Group

The discounted incremental cost for vaccinating a patient in the 65-74 age group is 3732 INR, which yields an incremental QALY of 0.054, resulting in an ICER of 69,363 INR per QALY. PCV13 vaccination for all adults in this age group is cost-effective at a threshold of 1GDP per capita of India. (Table 10)

Table 10:ICER: PCV Vaccination, 75+ age group

Strategy	Costs (INR)	QALYs	Incremental Costs	Incremental QALYS
Usual Care	1057.36	7.15799		
PCV13 Vaccination	4790.019	7.21180	3732.66	0.05381
ICER	**69,363 INR/QALY**			

Serial Vaccination with PCV 13 and PPSV23

The cost-effectiveness of vaccination with PPSV23 was analysed for the four age bands of 18-49, 50-64, 65-74, and 75+.

i. 18-49 Age Group

The discounted incremental cost for vaccinating a patient in the 18-49 age group is 6660 INR, which yields an incremental QALY of 0.0003 resulting in an ICER of 2,05,46,677 INR per QALY. Serial vaccination with PCV13 and PPSV23 for all adults in this age group is not cost-effective at a threshold of 1GDP per capita of India. (Table 11)

Table 11: ICER: Serial Vaccination, 18-49 age group.

Strategy	Costs (INR)	QALYs	Incremental Costs	Incremental QALYS
Usual Care	14.06	14.51165		
Serial Vaccination	6674.88	14.51198	6660.82	0.000324
ICER	**2,05,46,677 INR/QALY**			

ii. 50-64 Age Group

The discounted incremental cost for vaccinating a patient in the 50-64 age group is 6632 INR, which yields an incremental QALY of 0.003, resulting in an ICER of 20,34,608 INR per QALY. Serial vaccination for all adults with PCV 13 and PPSV23 in this age group is not cost-effective at a threshold of 1GDP per capita of India. (Table 12)

Table 12:ICER: Serial Vaccination, 50-64 age group.

Strategy	Costs (INR)	QALYs	Incremental Costs	Incremental QALYS
Usual Care	88.30	11.38972		
Serial Vaccination	6720.76	11.39298	6632.46	0.00326
ICER	**20,34,608 INR/QALY**			

iii. 65-74 age group

The discounted incremental cost for vaccinating a patient in the 65-74 age group is 6472 INR, which yields an incremental QALY of 0.027, resulting in an ICER of 2,34,672 INR per QALY. Serial vaccination for all adults with PCV13 and PPSV23 in this age group is not cost-effective at a threshold of 1GDP per capita of India. (Table 13)

Table 13:ICER: Serial Vaccination, 65-74 age group.

Strategy	Costs (INR)	QALYs	Incremental Costs	Incremental QALYS
Usual Care	539.65	10.80456		
Serial Vaccination	7011.53	10.83214	6471.88	0.02758
ICER	**2,34,672 INR/QALY**			

iv. 75+ Age Group

The discounted incremental cost for vaccinating a patient in the 65-74 age group is 6178INR, which yields an incremental QALY of 0.059, resulting in an ICER of 1,04,355INR per QALY. Serial vaccination for all adults with PCV13 and PPSV23 in this age group is cost-effective at a threshold of 1GDP per capita of India. (Table 14)

Table 14:ICER: Serial Vaccination, 75+ age group

Strategy	Costs (INR)	QALYs	Incremental Costs	Incremental QALYS
Usual Care	1057.359185	7.15799		
Serial Vaccination	7235.980004	7.21719	6178.62	0.05921
ICER	**1,04,355 INR/QALY**			

One-way Sensitivity Analysis

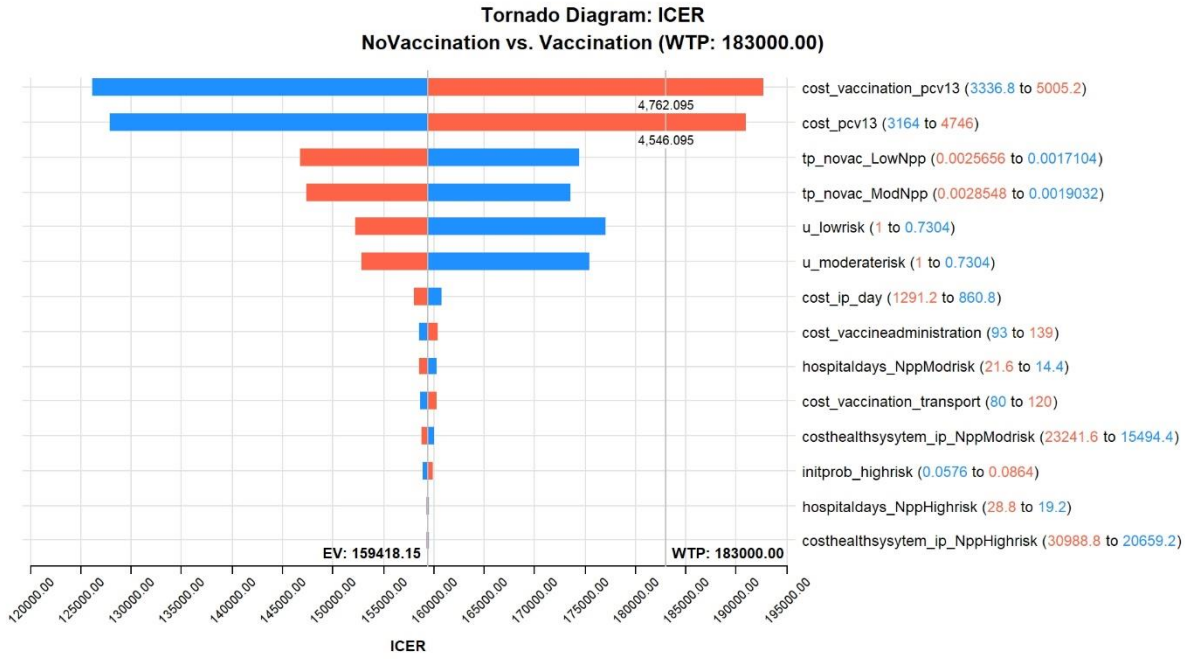
One-way sensitivity analysis was carried out for all age groups for both vaccination scenarios by varying the input parameters by 20% in both directions. The sensitivity analyses for cost-effective scenarios are presented below. Text reports of Tornado diagrams are given as Supplementary material(6).

Vaccination with PCV 13

i. 65-74 age group

Input parameters that caused maximum variations in ICER estimations are Cost of vaccination, transition probabilities form low risk and moderate risk states to NPP, and utility value of low-risk and moderate-risk states. ICER ranged from 1,26,317 to 1,92,698 INR per QALY with change in the value of the parameter Cost of Vaccination. ICER crosses WTP of 1 GDP per capita of India with high value of cost of vaccination. (Figure 3)

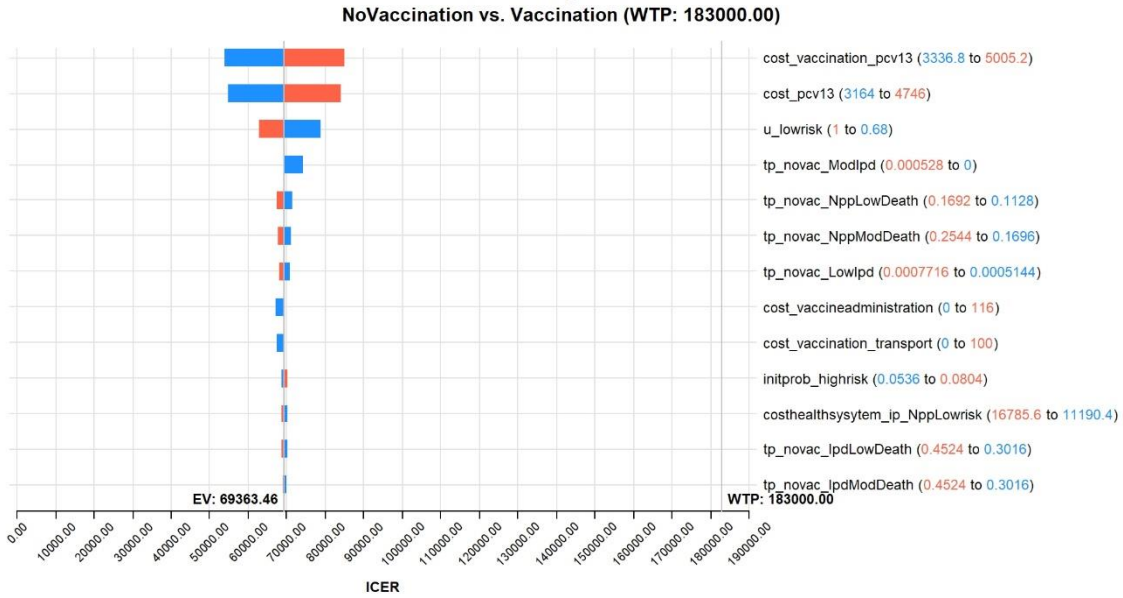
Figure 3:Tornado diagram, 65-74 age group, PCV13



ii. 75+ Age group

Input parameters that caused maximum variations in ICER estimations are Cost of vaccination, utility value of the low-risk state, transition probability from Moderate risk stage to IPD, and mortality risk in the Low-risk NPP stage. ICER ranged from 53,861 to 84,865 INR per QALY with change in the value of the parameter Cost of Vaccination. ICER did not cross with WTP of 1 GDP per capita of India with change in the value of any parameter.(Figure 4)

Figure 4: Tornado Diagram, 75+ Age group, PCV13

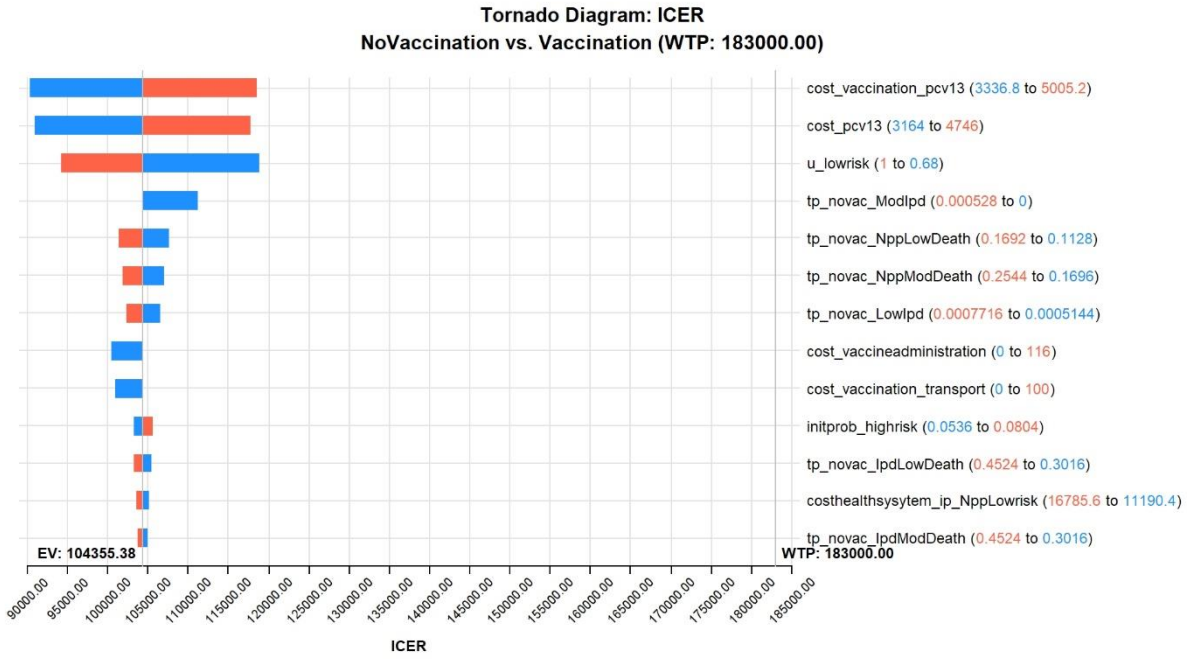


Serial Vaccination with PCV13 and PPSV23

i. 74+ Age group

Input parameters that caused maximum variations in ICER estimations are Cost of vaccination, utility value of the low-risk state, transition probability from Moderate risk stage to IPD, and mortality risk in the Low-risk NPP stage. ICER ranged from 90,265 to 1,18,444 INR per QALY with change in the value of the parameter Cost of Vaccination. ICER did not cross with WTP of 1 GDP per capita of India with change in the value of any parameter. (Figure 5)

Figure 5:Tornado diagram,74+ age group, serial vaccination



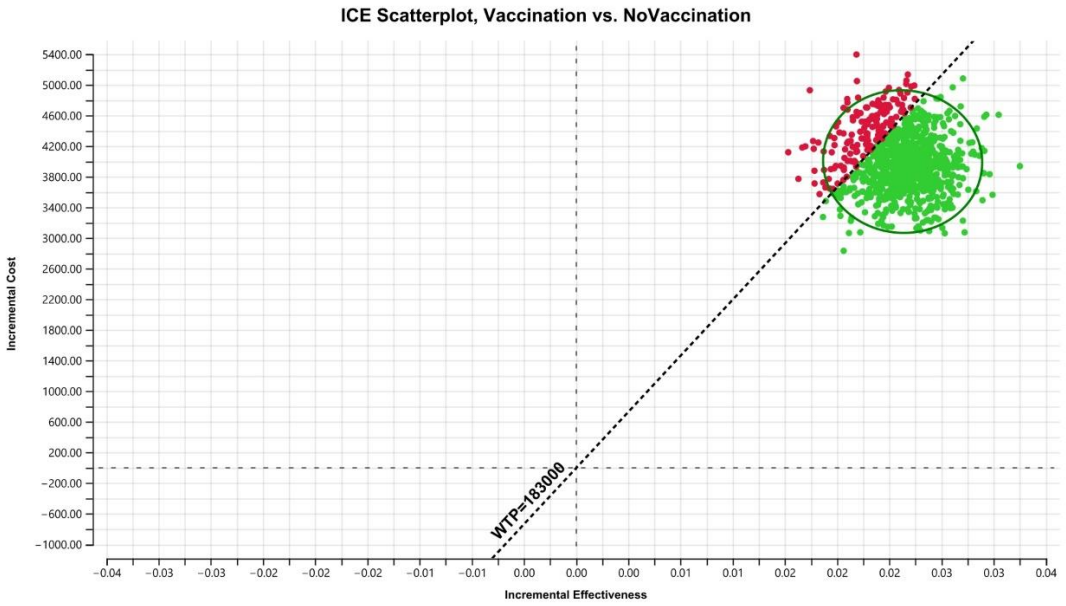
Proabilistic Sensitivity Analysis

Probabilistic Sensitivity Analysis was done for PCV 13 vaccination in 65-74 and 75+ age groups by assigning probabilistic distributions to the input parameters and running 1000 Monte-carlo simulations randomly selecting input values from the assigned distributions.

i. 65-74 age group.

In the 65-74 age group, all iterations were in the North East quadrant which corresponds to higher cost and higher effectiveness of the intervention compared to the no-vaccination scenario. Out of this, 84.2% were below the willingness to pay threshold of 1 GDP per caita for India. (Figure 6)

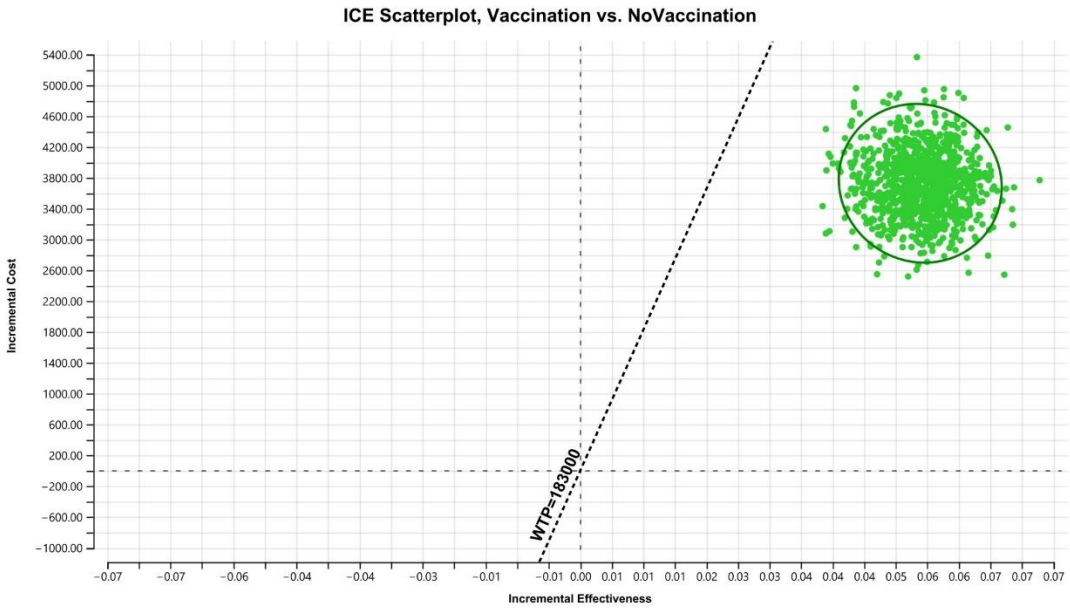
Figure 6: ICER cloud, PCV 13, 65-74 age group



ii. 75+ age group

In the 75+ age group, all iterations of ICER were in the North East quadrant and below the willingness to pay threshold of 1 GDP per capita for India.

Figure 7: ICER Cloud, PCV 13, 75+ age group



Budget Impact Analysis

A budget impact analysis was done to estimate the burden on the exchequer for implementing cost-effective vaccination scenarios for the eligible population. (Table 15). Analysis was done for the two age groups where PCV13 alone/serial vaccination with PCV13 and PPSVS23 was cost-effective. The budget was estimated for,

i. All populations in eligible age groups and

ii. High-Risk population in the eligible age group.

Table 15: Budget Impact Analysis

Age Group	Population*[30]	HRG-proportion	PCV 13- all (INR)*	Serial vaccination-all (INR)*	PCV-HRG (INR)*	Serial-HRG (INR)*
75+	2.05	0.0670	8,354	13,269	560	889
65-74	4.57	0.0720	18,585	29,519	1,338	2,125
Total	6.61		26,939	42,787	1897	3014

*Value in crores

The budget requirement to vaccinate all high-risk populations of age 75 years and above with a single dose of PCV13 is estimated to be 560 Crores INR.

According to NITI Aayog's Multidimensional Poverty Index (MPI) report, 2023, 14.96% of Indian population is multidimensionally poor[31]. The cost of vaccinating those who are multidimensionally poor in the eligible age groups and in high-risk groups within the eligible age groups is presented in table 16.

Table 16: Budget Impact: Multidimensionally Poor

Age Group	PCV 13- all (INR)*	Serial vaccination-all (INR)*	PCV-HRG (INR)*	Serial-HRG (INR)*
75+	1250	1985	84	133
65-74	2780	4416	200	318
Total	4030	6401	284	451

Discussion

This study yielded ICER values of 1,59,418 and 69,363 INR per QALY for the age groups 65-74, and 75+, respectively, for single-dose vaccination with PCV 13, demonstrating that

vaccination with Pneumococcal Conjugate Vaccine is cost-effective considering the prevalence of intermediate and high-risk conditions in the population at the threshold willingness to pay of 1 GDP per capita per QALY. Serial vaccination with PCV 13 and PPSV was found to be cost-effective in the age group 75+ with an ICER value of 1,04,355INR/QALY.

At a proposed lower threshold (~1.2lakh INR) for preventive programs, vaccination is cost effective only in the 75+ age group for both PCV alone and serial vaccination strategies.

For both PCV13 alone and serial vaccinations, the lowest ICER was observed in the age group 75+, suggesting that initiating vaccination in this age band will be most beneficial from an economic perspective. While vaccination with PCV13 alone was cost-effective in deterministic analysis in the 65-74 age group, the ICER value is high at around 1.6 lakhs INR against the WTP of 1.83 lakhs. This raises the question of the appropriateness of willingness to pay thresholds in analysing the cost-effectiveness of preventive programs.

Neither PCV 13 alone nor serial vaccination with PCV 13 and PPSV23 was found to be cost-effective in the 18-49 or 50-64 age group at the current WTP, due to lower incidence of Invasive Pneumococcal Diseases and Non-bacteraemic Pneumococcal Diseases, and a relatively lower proportion of moderate and low-risk groups.

Tornado diagrams constructed through one-way sensitivity analysis point to the robustness of ICER estimations. The parameters Cost of vaccination, Utility values of low/moderate risk states, Transition probability from low risk to NPP, and Initial probability of high-risk states were found to have maximum influence on ICER values. ICER values crossed the willingness to pay threshold of 1GDP per capita of India in the 65-74 age group with a high cost of vaccination.

While vaccination was found to be cost-effective in both age group above 65, the estimated budget impact of rolling out vaccination to the whole of this population is huge, even with conservative estimation of vaccine costs. Vaccination of the current cohort of 65+ with PCV13 will add an approximate burden of INR 27000 crores to the exchequer. To vaccinate the 75+ age group which yielded the lowest ICER, the total cost will be over INR 8000 Crores, and to vaccinate the high-risk group alone, INR 560 Crores.

Recommendations.

1. Vaccination of high risk population in 75+ age group with a single dose of PCV13 is most beneficial, considering the ICER value and budget impact.
2. We should promote the development and manufacture of indigenous pneumococcal vaccines; the cost of vaccines has the maximum impact on cost-effectiveness. Vaccination in other age bands and low-risk groups may be considered with the availability of cheaper vaccines.

Limitations of the study

1. The cost of vaccination has not considered the potential additional cost of setting up new vaccination centres/enhancing existing centres and cold chains.
2. The cost of management of permanent sequelae/long-term complications of invasive pneumococcal diseases is not included due to the complexity of calculation.
3. Where Indian data was not available, studies from similar settings from other countries were used as sources of input parameters.
4. Vaccine wastage is an important consideration in the estimation of vaccination cost. The current model has not incorporated vaccine wastage.
5. Appropriateness of using Willingness to Pay Threshold as a decision-making tool in preventive health care programs like vaccinations is disputed.

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List of Annexures

1. **Abbreviations**

Abbreviated form	Full form
API	Association of Physicians in India
CAP	Community Acquired Pneumonia
CDC	Centre for Disease Control
CSF	Cerebro Spinal Fluid
GDP	Gross Domestic Product
GRADE	Grading of Recommendation Assessment, Development and Evaluation
GSI	Geriatric Society of India
HIV	Human Immunodeficiency Virus
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ICU	Intensive Care Unit
IM	Intramuscular
IP	In Patient
IPD	Invasive Pneumococcal Disease
LICS	Low Income Countries
LMICS	Low- and Middle-Income Countries
NPP	Non-bacteremic Pneumococcal Pneumonia
OPD	Outpatient Department
PCV	Pneumococcal Conjugate Vaccine
PICO	Population Intervention Comparator Outcome
PPSV	Pneumococcal Polysaccharide Vaccine
QALY	Quality Adjusted Life Years
SC	Subcutaneous
WHO	World Health Organisation

2. Excel sheet: Input parameters ;Tree Age Pro Software
3. Markov Models, Tree age pro.
    a. 18-49
    b. 50-64
    c. 65-74
    d. 75+
4. Excel sheet: Tornado Diagram Text Reports; Tree Age Pro Software

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