Original Research

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Cost-effectiveness analysis of the 13-valent pneumococcal conjugate vaccine administered to children under 5 years of age in the Republic of Moldova

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Abstract

Background. The Moldovan health authorities introduced the 13 valent pneumococcal conjugate vaccine into the national immunization schedule for children in 2013. This study aimed to evaluate the cost-effectiveness of the pneumococcal conjugate vaccine compared to a no-vaccination strategy in children under 5 Years of age in the Republic of Moldova.

Methods. We used UNIVAC (version 1.7), a static decision model, to evaluate the health and economic outcomes of vaccination in a single-cohort of children under five years. We modeled vaccine introduction over 10 birth cohorts starting in 2013. We assumed a 2+1 (two doses + booster) schedule and a vaccination price of US$ 16.34 per dose. We used locally-specific data for pneumonia incidence, mortality, treatment, and costs. Model outcomes included pneumonia cases, hospitalizations, deaths, disability-adjusted life years, and costs presented in USD. Cost-effectiveness was reported as Incremental Cost Effectiveness Ratio. The Incremental Cost Effectiveness Ratio was calculated to estimate the additional cost to save an additional life year.

Results. From the governmental health sector the Incremental Cost Effectiveness Ratio was $5939 and from society perspective, $7272, respectively. Withal cost per disability-adjusted life years (DALY) averted was US$ 6311. PCV-13 was projected to prevent 2310 hospitalizations due to pneumococcal disease, including 118 deaths. Vaccination could potentially reduce the highest treatment cost from the payer perspective at $ 4 081 412 for the 13 valent pneumococcal conjugate vaccine.

Conclusion. This study evidenced that cost per DALY averted is US$ 6311, which is between one and three times Gross Domestic Product (GDP) per capita, these findings extrapolate PCV-13 as a cost-effective intervention. Considering the scenario of Republic of Moldova the PCV program is a cost effective intervention and justifies the introduction of PCV into routine immunization schedule throughout the country in order to reduce morbidity and mortality among the under-five-year-old children.

Keywords: pneumococcal, pneumococcal vaccines, cost-effectiveness, immunization programs

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Introduction

Streptococcus pneumoniae (*S. Pneumoniae)* is one of the most widespread causes of morbidity and mortality, leading to about 1.6 million deaths annually [1,2]. Pneumococcal diseases (PD) are a wide range of infections, which can be categorized as non-invasive, such as pneumonia, bronchitis, rhinitis, otitis media and sinusitis, as well as invasive infections, such as bacteremia, meningitis, bacteremic pneumonia and septicemia [3]. Prior research has thoroughly investigated serotyping of *S. Pneumoniae*, the data extrapolate over 100 pneumococcal serogroups, though most PD cases are caused by a particular subset [4,5]. It should be noted that pneumococcal vaccines are available in two formulations for clinical use: pneumococcal polysaccharide vaccine (PPSV) and pneumococcal conjugate vaccine (PCV) which is responsible for a more vital and prolonged immune response [6]. Until recently, PCV-10 and PCV-13 were two principal types of PCV currently in use in European countries, except for Estonia, which is among the last countries in Europe where the pneumococcus vaccine is not already included on the national immunization schedule [7]. In 2022, the European Medicine Agency licensed PCV-15 for adults and children and PCV20 for adults with anticipated licensing for children. These vaccines expand on PCV-13, adding two and seven serotypes, respectively [8].

According to international data [4,6,9] there have been significant reductions in mortality attributed to invasive pneumococcal disease over the past 2 decades on account of improved vaccination rates and improved serotype coverage with PCV-13 and PPSV-23.

The full benefits of a vaccination program could be explored through an epidemiological and health economics research which will study vaccine effectiveness (VE) and cost effectiveness at a national level. These investigations are able to bring vital evidence for public health decision makers. According to national data, the Moldovan health authorities introduced the pneumococcal conjugate vaccine (PCV-13) into the national immunization schedule for children in 2013. This study provides cost-effectiveness analyses, original national data on the cost per unit of effect for health-related interventions (PCV-13 vaccination).

Aim

This study aimed to evaluate the cost-effectiveness of the PCV-13 compared to a no-vaccination strategy in children under 5 Years of age in the Republic of Moldova.

Method

Methodological assumptions follow the WHO guidelines for the standardization of economic evaluations of immunization programs [10]. The authors declare that all the procedures and experiments of this study observe the ethical standards in the Helsinki Declaration of 1975, revised in 2008 [5], as well as the national law.

We used UNIVAC (version 1.7), a static decision model, to evaluate the health and economic outcomes of single-cohort vaccination among children under five years. As a static model, it takes no account of indirect effects, such as herd immunity. UNIVAC is a Microsoft Excel spreadsheet software developed by Pan American Health Organization (PAHO) Provac initiative, PATH and Centre for Disease Control and Prevention (CDC). This model was designed for low and middle income countries to calculate the Incremental Cost Effectiveness Ratio (ICER) and other relevant indicators [11]. This model has simulated the natural history of different diseases – severe and non-severe pneumonia, acute otitis media, meningitis, meningitis sequel and NPNM = non-pneumonia, non-meningitis, and other diseases except sepsis known to be caused by S. pneumoniae in terms of hospital admissions, outpatient visits and deaths.

We modeled vaccine introduction over 10 birth cohorts up to age 5 years from 2013 to 2023. We assumed a 2+1 (two doses + booster) schedule and a vaccination price of US$ 16.34 per dose.

The primary outcome measure of the analysis is the discounted cost per disability adjusted life year (DALY) averted. Other outcomes include the incremental cost of the vaccine program, as well as the number of averted cases, visits, hospitalizations, treatment costs, and deaths. Technically healthcare costs saved by the pneumococcal prevention strategy are subtracted from intervention program costs to estimate incremental net costs. Incremental net costs are then divided by the number of DALYs averted to calculate the cost per DALY averted [12].

UNIVAC calculates total healthcare costs by multiplying the number of clinic visits and hospital admissions by the respective average cost per visit or hospital admission. Average costs of visits/admissions per disease episode can be calculated outside the model by calculating the cost per visit or admission for different types of healthcare providers and the share of total visits/admissions provided by each.

The results were analyzed from the government and societal perspectives. A government perspective includes bed-day costs (buildings, nurse salaries, etc.) and disease-specific costs (e.g. drugs, tests) incurred by providers in the public health sector. A societal perspective includes all costs included in the government perspective plus direct out-of-pocket costs borne by patients and their families (e.g. travel, drugs, and fees for using private healthcare) [12].

While there are many pathways to pneumococcal death and many healthcare measures (clinic visits and/or hospital admissions) are possible (Figure 1), for simplicity only one rate of pneumococcal mortality is required; moreover all this activity was captured within a single rate of pneumococcal hospital admissions, and two rates of pneumococcal clinic visits (one for severe pneumococcal and one for non-severe pneumococcal). The model does not include a separate category for emergency room visits.

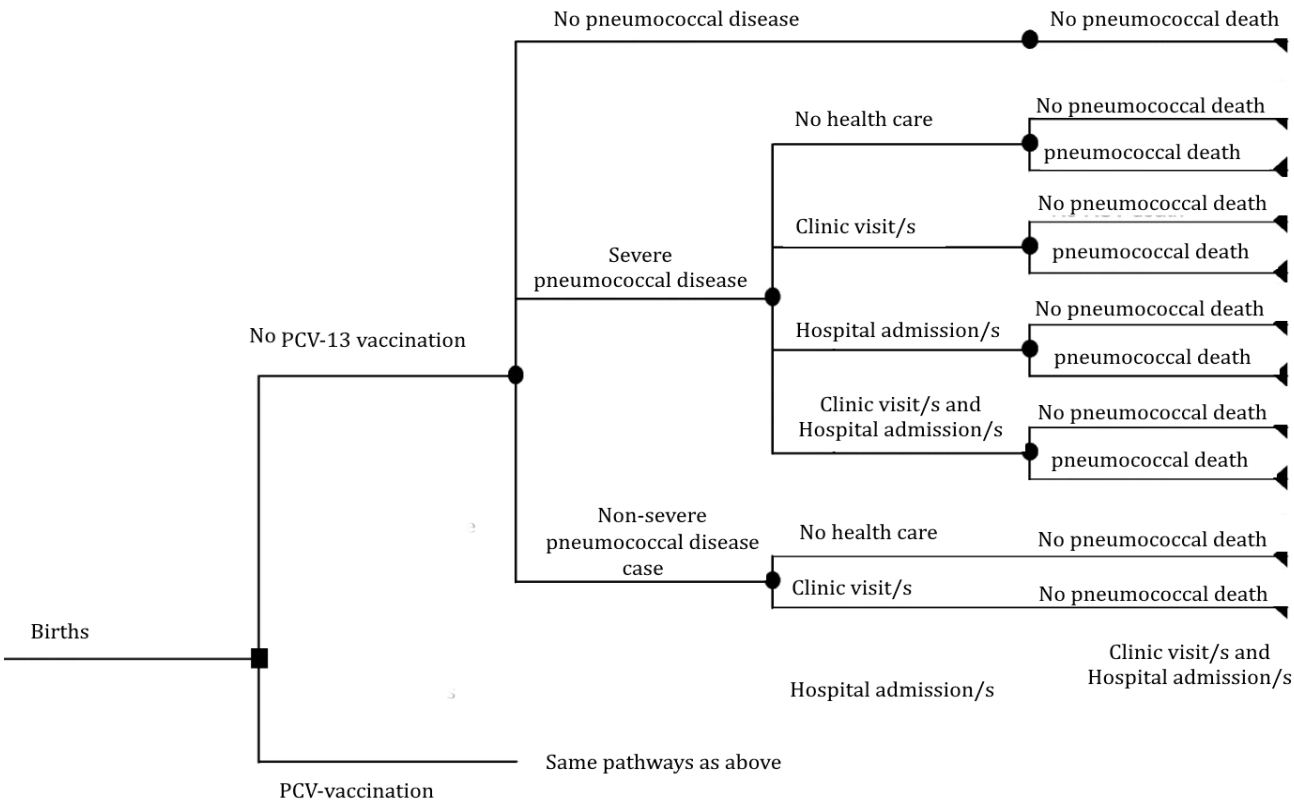

Figure 1. Cost-effectiveness of pharmaceutical strategies to prevent pneumococcal disease in young children: a decision-support model for use in low-income and middle-income countries.

Results

In consonance with generated date from UNIVAC static model (Figure 2), pneumococcal disease is estimated to affect 256,343 children under 5 years (6.222 pneumonia, 249,603 acute otitis media (AOM), 58 meningitis, and 396 non-pneumonia, non-meningitis (NPNM), 26 meningitis sequelae) in a time span of 10 years (2013–2023) without use of the vaccine. Introduction of PCV-13 would prevent 115.726 cases of pneumococcal disease (2.810 pneumonia, 112.683 AOM, 43 meningitis, and 179 NPNM, 12 meningitis sequelae).

Estimated health benefits of pneumococcal conjugate vaccine-13

As shown in table I, the introduction of PCV-13 would avert 118 deaths over the period 2013–2023, while PCV-13 was projected to prevent 2310 hospitalizations, 90,287 visits, leading to 119,113 total cases averted due to pneumococcal disease.

Estimated economic benefits

Generated data (Table I) extrapolate that from a government perspective, PCV-13 was estimated to avert US$ 4 081 412 discounted health service costs over the 10-year period, 2013–2023. From the governmental health sector the ICER was $5939 and from society perspective, $7972, respectively. Overall, the cost per DALY averted was US$ 6219.

In global health, for many years, cost-effectiveness thresholds of one and three times GDP per capita per DALY averted have been frequently cited. The World Health Organization's (WHO's) Choosing Interventions that are Cost-Effective (CHOICE) program defines interventions for which the cost per DALY averted is less than GDP per capita as very cost-effective, between one and three times GDP per capita as cost-effective, and greater than three times GDP per capita as not cost-effective [13,14]. Conforming to World Bank national accounts data, national GDP per capita in Republic of Moldova is about US$ 5562 [15]. Data from our study evidence cost per DALY averted as US$ 6219, which between one and three times GDP per capita, these findings extrapolate PCV-13 as a cost-effective intervention.

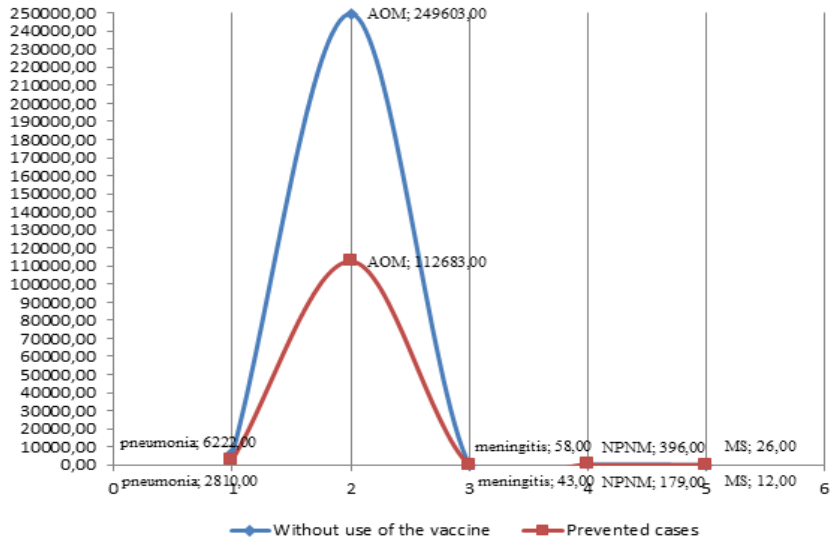

Figure 2. UNIVAC generated data - total disease events. AOM - Acute otitis media; NPNM - Non-Pneumonia, Non-Meningitis; MS - meningitis sequelae.

Table I. Estimated discounted cost – effectiveness.

	Government perspective			Societal perspective		
Results for all runs	**Treat costs saved**	**ICER**	**DALY averted**	**Treat costs saved**	**ICER**	**DALY averted**
Median	**4,081,412**	**5,939**	**3,130**	**4,121,544**	**7,272**	**3,130**
Lower 95%	2,608,022	4,126	2,084	2,304,023	5,198	2,084
Upper 95%	5,655,789	9,369	4,421	5,158,785	10,703	4,421

Abbreviations used in table: ICER- Incremental Cost Effectiveness Ratio is the difference in costs divided by the difference in outcomes; DALY - Disability adjusted life year, DALY burden for a particular condition is the sum of YLL (years of life lost due to premature mortality) and YLD (years lost to disability). Health interventions seek to avert DALYs, and in doing so, to increase the number of years that a person lives in good health.

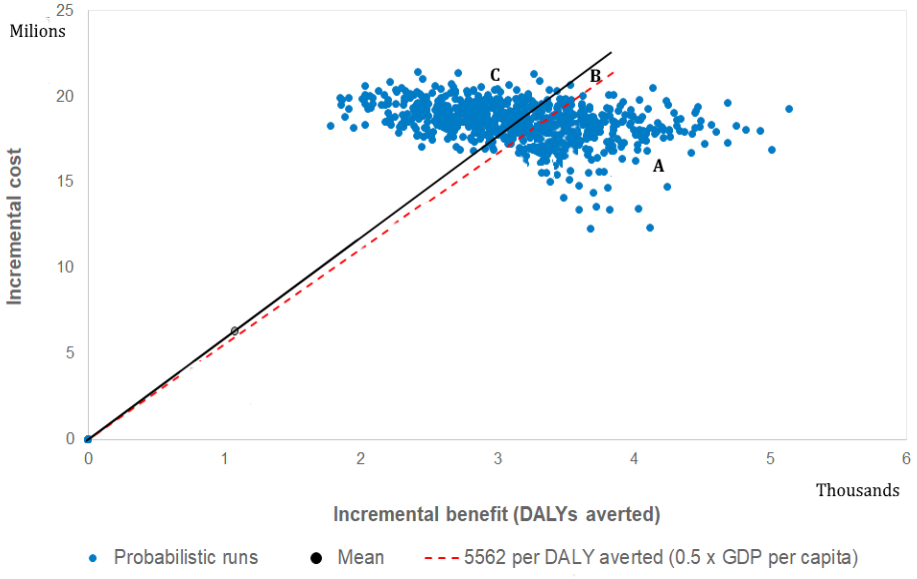

Figure 3. ICER scatter plot. DALY averted - Disability adjusted life year averted; GDP - Gross Domestic Product per capita.

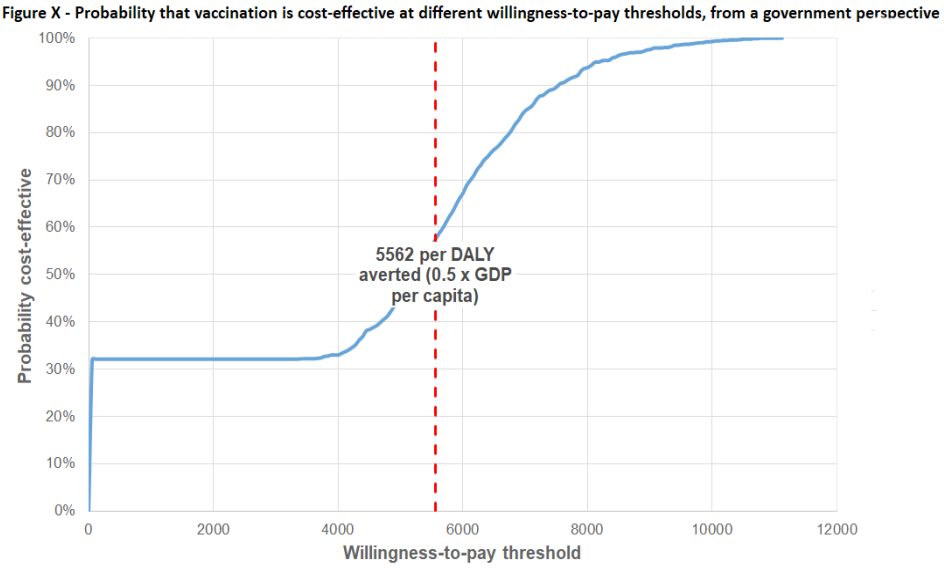

Figure 4. Cost-effectiveness acceptability curve. GDP - Gross Domestic Product per capita.

Probabilistic sensitivity analysis

In the probabilistic sensitivity analysis (PSA), we ran 1000 different scenarios in the model. As part of the analysis two extreme scenarios were tested. The most favorable scenario included a low vaccine price, high incidence, high case fatality ratio, high vaccine efficacy, and high inpatient and outpatient treatment costs. With these conditions, vaccination was cost saving, which means it averted DALYs at a lower cost compared with the no vaccination. The least favorable scenario included a high vaccine price, low incidence, low case fatality ratio, low vaccine efficacy, and low inpatient and outpatient treatment costs.

Examination of ICER scatter plot (Figure 3) shows that the solid line represents willingness-to-pay thresholds for costs per DALY averted of three times the GDP per capita of Moldova and the dashed line is the GDP per capita of Moldova. The ICER classifications are as follows: "cost-effective" shows those simulations in which the ICER was lower than three times the GDP per capita (B), "extremely cost-effective" shows those simulations in which the ICER was lower than the GDP per capita (A), "dominated" designates that the intervention (in this case C) was both more expensive and less effective in those simulations (B).

According to these data (Figure 4) at a Willingness–to–pay (WTP) of 5562 US$ per Daly, probability of the intervention (PCV-13 vaccination) to be cost-effective is about 60%.

Discussion

The health *impact assessment* of *vaccination* programs aims to investigate the potential epidemiological impact and cost-effectiveness. Regarding the health impact assessment of vaccination programs, according to preliminary data from a recent national research [16] VE of PCV-13 was 63% in the Republic of Moldova, meaning that vaccination with PCV-13 has a positive impact by reducing the frequency of hospitalizations due to community-acquired pneumonia in children younger than 5 years of age, as compared with those who are not vaccinated.

To the best of our knowledge, this is the first study to evaluate the cost-effectiveness and health benefits of the PCV-13 vaccine in the Republic of Moldova. Cost-effectiveness analysis provides a unifying framework for the evaluation of population health. This economic assessment explores benefits, harms, and costs inherent in alternative options [17,18]. There are different metrics such as DALYS or quality-adjusted life years QALYs to estimate health benefits on these economic evaluations [19]. However, it is essential to point out that DALYs and QALYs differ in concept and application. The DALY is a measure of lost healthy life years and is more commonly used in global health and preferred in LMICs [20,21]. Prior research clarifies valuable data for the national government and society that evidences the introduction of PCV-13 as a cost-effective intervention when compared to no vaccination, based on WHO criteria for cost-effectiveness. Over the time, an increasing number of studies have investigated PCV-13 cost-effectiveness worldwide. These results were in line with latest studies, which advocated that vaccination with PCV 13 valent is a cost-effective strategy [22-24]. Wang et al. [22] found that with a willingness-to-pay (WTP) threshold of three-times Chinese per-capita gross domestic product (GDP) all vaccination programs were cost-effective compared to no vaccination

and children aged 2 to 5 years received 1 dose of new PCV-13 would incur the lowest additional cost of US$2417 per quality-adjusted-life-years (QALYs) compare with other vaccination programs. According to other recent study from Philippines [25] PCV-13 was found not only cost-effective but also cost-saving vaccine programme being compared with PCV -10, therefore it was estimated to avert 375,831 more cases, save 53,189 additional lives, and gain 153,349 QALYs compared with PCV-10. This equates to cost-savings of PHP (philippine peso) 12.27 billion. The vaccination strategy with PCV-13 was estimated to be cost-effective not only among the pediatric population; according to the results of a study conducted in Portugal among the adult population PCV-13 vaccination strategy was cost-effective and associated with a reduction of the pneumococcal disease burden, avoiding up to 5,712 deaths [23].

This analysis demonstrates that the PCV program is projected to avert a substantial health and economic burden of disease in Republic of Moldova. The country is projected to experience reduced disease burden (2310 hospitalizations, 90,287 visits and 119,113 cases).

Our analysis showed that PCV vaccination is a cost-effective intervention in our country. The cost-effectiveness analysis is based on a number of assumptions, some of which may not be accurate, introducing uncertainty. Sensitivity analysis formalizes ways to measure and evaluate this uncertainty. In the context of cost-effectiveness analysis, PSA is the probability that a given strategy is cost-effective, defined as achieving the maximum health benefit at a cost per unit benefit gained less than a defined maximum WTP per unit benefit. The cost-effective strategy is equivalently defined as the strategy that maximizes the net monetary benefit (NMB) calculated as WTP. This research estimates that the PCV program has >60% chance of being cost-effective at a WTP threshold of US$5562 as long as the country pays approximately US$16.34 per dose.

These findings have implications for PCV-13 vaccination policy in Republic of Moldova and other low-income and middle-income countries settings with comparable demographic and PCV-13 epidemiological profiles moreover this study contributes to the growing body of literature on the health impact and cost-effectiveness of PCV-13 vaccine.

Discussions regarding the extension of the PCV-13 vaccination in conjunction with PPSV23 in high risk adults have dominated research in recent years [26-28]. Thus further analysis should therefore be implemented to estimate the economic and health burden of pneumococcal disease in older age groups.

A drawback of this framework is the fact that results are dependent on model assumptions and input parameters, as is the case with all modelling studies.

This study had some limitations. UNIVAC is a static model that is unable to capture indirect effects, such as herd immunity. For this reason, static cohort models are likely to underestimate the benefit and cost-effectiveness of PCV prevention strategies. This limitation should be carefully communicated to decision-makers when sharing results. A large body of local epidemiologic evidence was unavailable, where information was missing or uncertain, we have had to make assumptions. Some of the parameters were based on global estimates or assumptions.

This research was done without patient or public involvement. It was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination of our research as the study focused on assessing cost and cost-effectiveness of an intervention provided by the Ministry of Health.

Conclusion

This study evidences that cost per DALY averted is US$ 6311, which is between one and three times GDP per capita, these findings extrapolate PCV-13 as a cost-effective intervention. Considering the scenario of Republic of Moldova, the PCV program is a cost effective intervention and justifies the introduction of PCV into routine immunization schedule throughout the country in order to reduce morbidity and mortality among the under five-year-old children.

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