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Khadijeh Ezoji[1,2], Mohsen Yaghoubi[3], Marzieh Nojomi[4], Sussan Mahmoody[5], Seyed Mohsen Zahraie [5], Maziar Moradi-Lakeh [4], Sedigheh R. Tabatabaei [6] and Abdollah Karimi [6]

[1]Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, Islamic Republic of Iran. [2]Department of Community Medicine, Iran University of Medical Sciences, Tehran, Islamic Republic of Iran.

[3] School of Public Health, University of Saskatchewan, Saskatoon, Canada.

[4] Preventive Medicine and Public Health Research Center, Department of Community Medicine, School of Medicine, Iran University of Medical Sciences, Tehran, Islamic Republic of Iran (Correspondence to Maziar Moradi-Lakeh: moradilakeh.m@iums.ac.ir).

[5] Center for Communicable Disease Control, Ministry of Health and Medical Education, Tehran, Islamic Republic of Iran.

[6] Pediatric Infections Research Center, Research Institute for Child Health, Shahid Beheshti University of Medical Sciences, Tehran, Islamic Republic of Iran (Correspondence to Sedigheh R. Tabatabaei: srt.tabatabaei@gmail.com).

Abstract

Background: Pneumococcal disease caused by Streptococcus pneumoniae results in considerable mortality and morbidity. Pneumococcal conjugate vaccines (PCV), such as PCV-13, can prevent invasive pneumococcal disease and avoid disability and death. The cost of introducing PCV-13 in childhood immunization schedules should be assessed against the cost of pneumococcal diseases for each community.

Aims: This study aimed to evaluate the cost–effectiveness of introducing PCV-13 in the

national immunization programme for children under 5 years in the Islamic Republic of Iran.

Methods: The TRIVAC decision support model was used to estimate total costs of introducing PCV-13 and the disability-adjusted life years (DALYs) averted. The main pneumococcal diseases were considered—pneumonia, meningitis, acute otitis media, and non-pneumonia, non-meningitis infections—in terms of hospital admissions, outpatient visits and deaths. Local data were used to estimate costs.

Results: Pneumococcal disease is estimated to affect 18 713 211 children under 5 years (519 412 pneumonia, 18 148 116 acute otitis media, 6884 meningitis, and 38 799 non-pneumonia, non-meningitis) in 10 years (2014–2023) without use of the vaccine. Introduction of PCV-13 would prevent 4 900 084 cases of pneumococcal disease (190 849 pneumonia, 4 692 450 acute otitis media, 2529 meningitis, and 14 256 non-pneumonia, non-meningitis). Pneumococcal infection would cause 287 950 hospital admissions and 29 399 deaths; vaccination could avert 105 802 hospital admissions and 9997 deaths. The incremental cost–effectiveness was estimated to be US$ 1890 and US$ 1538 per averted DALY for the government and society respectively.

Conclusion: According to WHO-recommended thresholds for interpreting cost–effectiveness, introduction of PCV-13 for children under 5 years in the Islamic Republic of Iran would be cost-effective.

Keywords: pneumococcal conjugate vaccine, children, cost–effectiveness, Iran

Citation: Ezoji K; Yaghoubi M; Nojomi M; Mahmoody S; Mohsen-Zahraie S; Moradi-Lakeh M. et al. Cost–effectiveness of introducing the pneumococcal conjugate vaccine for children under 5 years in the Islamic Republic of Iran. East Mediterr Health J. 2019;25(10):686–697. https://doi.org/10.26719/emhj.19.039

Received: 02/09/17; accepted: 19/04/18

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Introduction

Streptococcus pneumoniae is a well-known invasive bacterium. Disease caused by S. pneumoniae (pneumococcal diseases) can result in death, especially in very young children. S pneumoniae causes about 11% (8–12%) of all deaths in children aged 1–59 months (1). The diseases range from non-invasive pneumococcal diseases (e.g. acute otitis media) to invasive pneumococcal diseases (e.g. meningitis and bacteraemia) that can be life-threatening (2–5). Invasive pneumococcal diseases kill over 500 000 children under 5 years old each year (6), and accounted for nearly 9% of deaths in children aged 1–59 months in 2008 in South America (7). Children in low-income and developing countries are particularly at risk of severe disease caused by S. pneumoniae (6). The cost of diseases caused by S. pneumoniae is reported to be one of the highest in terms of the use of health care resources (6,8). However, invasive pneumococcal diseases can be prevented by vaccination (3,6).

Among all serotypes of S. pneumoniae, only a few are invasive and the new pneumococcal conjugate vaccines (PCVs) protect against them (6,9). Of the most preventable serotypes, the PCV vaccines target either 10 serotypes (PCV-10) or 13 serotypes (PCV-13) (9).

The main advantage of a childhood vaccination programme against S. pneumoniae is that it saves lives by preventing S. pneumoniae infection and hence the adverse complications of pneumococcal diseases, and this counterbalances the costs of the programme (5). Vaccination of children under 5 years would also indirectly reduce the incidence of invasive pneumococcal diseases by reducing the rate of nasopharyngeal carriers of S. pneumoniae (10–12).

After running several clinical trials in different regions of the world, PCV-10 and PCV-13 have been introduced in the national vaccination programmes of more than 100 countries, including many low- and middle-income developing countries. These vaccines have been found to be cost-effective, especially in developing countries with limited health care resources (3,8,9), and can be safely administered at the same time as other vaccines without interference (9).

The pneumococcal vaccine is not part of the childhood immunization programme in the Islamic Republic of Iran. However, acute respiratory infection was the fourth leading cause of death in

children under 5 years in the country in 2013 (13%), so there is a need to protect children from the diseases related to S. pneumoniae (13).

When introducing a new vaccine, there are almost always financial and programmatic limitations, and many criteria should be taken into account to make a final decision (14). Analysis of cost–effectiveness is a useful method to provide an overview of health care resources (8). In the case of PCVs, the benefits and costs of introducing the vaccine in the routine schedule should be weighed against the cost of invasive pneumococcal diseases in a particular community.

Therefore, this study aimed to determine the cost–effectiveness of introducing PCV-13 into the Iranian national immunization programme for children under 5 years.

Methods

TRIVAC decision support model

We used the TRIVAC decision support model (version 1.7) developed by the London School of Hygiene and Tropical Medicine in collaboration with the Pan American Health Organization (PAHO) and ProVac Initiative and the World Health Organization. It is a Microsoft Excel based static cohort model designed to facilitate cost–effectiveness analysis of vaccination programmes against Haemophilus influenzae type b, rotavirus or S. pneumoniae in low- and middle-income countries (15). We considered four main disease states resulting from S. pneumoniae infections: pneumonia, meningitis, acute otitis media and non-pneumonia, non-meningitis infections, and other diseases except sepsis) in terms of hospitalization (inpatient admission), outpatient visits and death.

The TRIVAC model requires the following data: demographic data, disease burden, local vaccine serotype distribution, vaccine efficacy, health service utilization, vaccination programme costs and health service costs (6). Based on the data entered, the model calculates the number of cases, deaths and sequelae of S. pneumoniae infection, as well as the associated costs in scenarios with and without vaccination. These data are then used to calculate the health impact [e.g. disability-adjusted life years (DALYs) averted], economic impact (e.g. net costs, incremental programme costs and treatment costs averted), cost–effectiveness (e.g. cost per death averted) and cost utility (e.g. cost per DALY averted) of the vaccination programme (15).

Demographic data

The number of live births was derived from the Iranian national organization for civil registration.

We used estimates of the Institute for Health Metrics and Evaluation for infant, under-5 and neonatal mortality (16). We also used the United Nations Population Division database to extract estimates of current and future life expectancy in the Islamic Republic of Iran (17).

Disease burden

We used data of the Institute for Health Metrics and Evaluation for annual incidence of acute otitis media (Table 1) (16). For pneumococcal pneumonia, we used the incidence and case fatality rate of pneumococcal pneumonia estimated by Rudan et al. for the Islamic Republic of Iran in 2013 (18). The number of new episodes of pneumonia divided by the number of population (0–4 years) was estimated at 830 per 100 000.

No local data were available for pneumococcal meningitis, and non-pneumonia, non-meningitis infections, so data based on the study of O'Brien et al. were used (1).

Given the lack of national published data on meningitis sequelae, we used estimates from a recent global systematic review of the proportion of meningitis survivors with single (20.2%) or multiple (4.5%) major sequelae (19). Major sequelae include hearing loss and multiple impairments. Standard global burden of disease categories (cognitive deficit, bilateral hearing loss, motor deficit, seizures, visual impairment and hydrocephalus) were considered major sequelae (19).

The disability weights due to all-cause acute otitis media, pneumococcal pneumonia and pneumococcal meningitis were taken from the global burden of disease study 2016 (20). For pneumococcal non-pneumonia, non-meningitis infections, we used the disability weights of Griffiths, which were 0.24 for single pneumococcal sequelae and 0.63 for multiple pneumococcal sequelae (21).

The mean duration of disease was considered six days for acute otitis media and non-pneumonia, non-meningitis infections, and 10 days for pneumonia and meningitis based on local expert opinion.

Vaccine coverage and efficacy

The vaccine (PCV-13) is available as a one-dose vial, Prevnar13 (Pfizer, United States of America). A vaccination schedule of three primary doses (at 2, 4 and 6 months) was chosen for

PCV13 based on WHO guideline and an advisory consultation with the Iranian Ministry of Health and Medical Education (Table 2).

Vaccine efficacy data were taken from reports of systematic reviews and meta-analyses from different sources (Table 3). For all-cause acute otitis media, full-dose efficacy data were based on Pavia et al. in 2009 (23). Full-dose vaccine efficacy against vaccine-type pneumococcal pneumonia, meningitis, and non-pneumonia, non-meningitis infection was derived from Lucero 2009 (2).

Serotype coverage

Based on a systematic evaluation of global serotype coverage, we assumed that 70% of pneumococcal acute otitis media, pneumonia, meningitis, and non-pneumonia, non-meningitis infection were covered by the vaccine in the Islamic Republic of Iran (25,26).

Cost estimation

Vaccination programme costs

We used WHO guidelines to calculate the costs of introducing PCV-13 into the current national immunization programme (27). The price of each dose (US$ 20) was obtained from the local representative of the vaccine manufacturer (Pfizer). To estimate the incremental system cost per dose, we included the cost of the distribution system, cold chain, surveillance monitoring, training, maintenance, personnel expenses, and the facilities needed for this vaccination programme. The total annualized capital cost estimate was based on equipment prices and their useful life and an annualizing factor (Table 4).

Health service utilization and costs

It was assumed that 95% of meningitis cases and non-pneumonia, non-meningitis cases are hospitalized based on data of the Iranian Ministry of Health and Medical Education. We asked five paediatricians to help with clinical assumptions; we assumed that 50% of pneumonia cases (that is, severe cases) need inpatient admission, and all non-severe pneumonia cases need outpatient services, similar to all cases of acute otitis media.

Two categories of public and private vaccination providers were considered: clinics and all types of hospital. Distribution between outpatient clinics and hospital admissions was based on the Iranian Ministry of Health and Medical Education as shown in Table 5 . To calculate the distribution between the public and private sector, we used data from the Ministry of Health and Medical Education, which indicated that 32.3% and 67.7% of outpatient services were provided

by the public and private sector respectively, as were 95% and 5% of inpatient services (National Institute of Health Research, Islamic Republic of Iran, 2015, personal communication).

To estimate the average inpatient service cost, we selected a random sample of 20 patients from each of three groups of patients (pneumonia, meningitis, and non-pneumonia, non-meningitis infections) from a public paediatric hospital and we extracted services and costs based on ICD-10-CM diagnostic codes (28). Direct medical costs were estimated as bed costs, medications, diagnostic tests, nursing care, consultations and other costs. We considered mean inpatient costs in a paediatric hospital for all types of hospital in the public sector. We did the same in one general private hospital to estimate the mean cost of inpatient admission in the private sector. Government costs per inpatient admission include mean cost per inpatient day multiplied by the expected length of stay that was covered by the universal public insurance system. Household costs per outpatient visit included direct medical costs (out-of-pocket payments for visit and medicines). Household costs per inpatient admission included out-of-pocket expenditure for direct medical costs of treatment of these diseases. Government costs per outpatient visit included the cost of visit, laboratory tests, X-rays and treatment. Government spending for admission is the daily costs for each inpatient case, which varies according to the type of disease.

For outpatient services, we estimated the pattern of prescribing, diagnostic tests and medications by interviewing 20 professors of paediatric infectious diseases, paediatricians and general physicians. We extracted costs separately for the public and private sector to estimate mean outpatient costs. We considered out-of-pocket payments as household expenditure and the costs covered by the universal public insurance system as government costs.

We estimated average inpatient and outpatient costs for household and government based on different tariffs and distribution of service utilization. All costs were converted from Iranian rials into US$ at a currency exchange rate of US$ 1.00 = 35 000 Iranian rials, which was an average of the official and market rates for 2014 (29).

Sensitivity analysis

We used upper and lower estimates for different inputs to calculate the incremental cost–effectiveness ratio in alternative scenarios.

Results

Estimated health benefits of pneumococcal conjugate vaccine-13

As shown in Table 6 , the introduction of PCV-13 would avert 9998 deaths over the period 2014–2023, or 37.9% of all deaths from pneumococcal disease, and would prevent 105 802 inpatient admissions, 36.7% of all pneumococcal-related hospitalizations.

Estimated economic benefits

From a government perspective, PCV-13 was estimated to avert US$ 45.54 million discounted health service costs over the 10-year period, 2014–2023 (Table 7). From the perspective of society, the saving is about US$ 152.32 million.

The introduction of the PCV13 would be highly cost-effective with an incremental cost–effectiveness threshold of US$ 1890 and US$ 1538 per averted DALY from the perspective of the government and society, respectively. (Table 8).

Sensitivity analysis

In the sensitivity analysis, we ran 19 different scenarios in the model. As part of the analysis (Figure 1), two extreme scenarios were tested.

The most favourable 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 favourable scenario included a high vaccine price, low incidence, low case fatality ratio, low vaccine efficacy, and low inpatient and outpatient treatment costs: The incremental cost–effectiveness threshold was US$ 8857 per DALY averted (still cost-effective).

In all other scenarios, vaccination was highly cost-effective.

Discussion

Our results show that the introduction of PCV-13 would be a highly cost-effective intervention for

the Iranian government and society when compared to no vaccination, based on WHO benchmarks for cost–effectiveness. The WHO Commission on Macroeconomics and Health has recommended that a discounted cost per DALY averted of less than the gross domestic product per capita should be considered highly cost-effective, and a discounted cost per DALY averted of less than three times the gross domestic product per capita should be considered cost-effective (30).

We estimated that vaccination could prevent more than 4.5 million cases of pneumococcal-associated disease over the period 2014–2023. A national immunization programme with PCV-13 was estimated to prevent 38% of all deaths from pneumococcal diseases. The economic burden to society of pneumococcal diseases in children under 5 years in the Islamic Republic of Iran during 2014–2023 was calculated to be US$ 447.78 million; about 34% (US$ 152.32 million) of this cost could be prevented through vaccination. The cost to the government was estimated to be US$ 127.85 million, about 37% (US$ 45.54 million) of which could be prevented with PCV-13.

In developing countries, various studies have shown that PCV-13 is a cost-effective public health intervention. In Egypt, for 10 cohorts, the introduction of PCV-13 would be cost-effective, with an incremental cost–effectiveness ratio of US$ 3916 per DALY averted for the government. The total incremental cost of the PCV-13 vaccination programme would be about US$ 1.09 billion (9). In Peru, for 20 cohorts, net costs of PCV-10 and PCV-13 were estimated to be US$ 363.26 million and US$ 408.26 million respectively. DALYs averted were 226 370 with PCV-10 and 313 119 with PCV-13. The saving on treatment costs was estimated to be US$ 37.39 million with PCV-10 and US$ 47.22 million with PCV-13. Costs per DALY averted were US$ 1605 for PCV-10 and US$ 1304 for PCV-13. Therefore, the PCV-13 would be the preferred option (6). In Croatia, both PCV-10 and PCV-13 were estimated to prevent about 100 hospital admissions and one death each year in children under 5 years. Compared with no vaccine, the discounted cost–effectiveness of either vaccine was estimated to be about US$ 69 000–77 000 per DALY averted (19 cohorts) for the government or society. PCV-10 was more cost-effective than PCV-13, but this would be affected by the price of the vaccine (31).

There are some limitations to our study. First, data from the private sector were not easily available. Second, we did not include some important cost items which indirectly affect the population; for example, opportunity costs such as loss of productivity of parents when taking care of their sick children were not included. However, we believe that if we were to include these indirect cost, the incremental cost–effectiveness ratios would change in favour of vaccination. Finally, our results only took into account children under 5 years. Further analysis should therefore be done to estimate the economic and health burden of pneumococcal disease in older age groups.

Conclusion

Introduction of PCV-13 would be a high-impact public health intervention for the Islamic Republic of Iran and could prevent many cases of pneumococcal disease and 38% of all pneumococcal-related deaths. Evidence-based decision-making for the introduction of new vaccines guide the efficient use of resources in low- and middle-income countries. This study attempted to provide good scientific evidence that can inform decisions about the use of PCV-13 in the Islamic Republic of Iran.

Acknowledgments

We are grateful to the Iranian Ministry of Health and Medical Education, especially the Center for Communicable

Disease Control, and the WHO country office in the Islamic Republic of Iran. We thank all advisers and colleagues, especially Gabriela Felix, for their technical support.

Funding: This work was supported by the ProVac International Working Group, which is funded entirely by a grant from the Bill & Melinda Gates Foundation (grant number: OPP1032888).

Competing interests: None declared.

Rapport coût-efficacité de l’introduction du vaccin antipneumococcique conjugué pour les enfants de moins de cinq ans en République islamique d’Iran

Résumé

Contexte : L’infection à pneumocoque causée par Streptococcus pneumoniae entraîne une mortalité et une morbidité considérables. Les vaccins antipneumococciques conjugués (VPC) comme le VPC-13 permettent de prévenir l’infection invasive à pneumocoque et d’éviter l’incapacité et les décès. Le coût de l’introduction du VPC-13 dans les calendriers de vaccination des enfants devrait être évalué par rapport au coût des infections à pneumocoque pour chaque communauté.

Objectifs : La présente étude visait à évaluer le rapport coût-efficacité de l'introduction du VPC-13 dans le programme national de vaccination des enfants de moins de cinq ans en République islamique d'Iran.

Méthodes : Le modèle TRIVAC pour le processus décisionnel en matière de la vaccination a été utilisé pour estimer le coût total de l'introduction du VPC-13 et les années de vie ajustées sur l'incapacité évitées. Les principales infections à pneumocoque – pneumonie, méningite, otite moyenne aiguë et infections autres que pneumonies et méningites – ont été prises en compte eu égard aux hospitalisations, consultations externes et décès. Des données locales ont été utilisées pour estimer les coûts.

Résultats : Selon les estimations, en l'absence de vaccination, l'infection à pneumocoque touchera 18 713 211 enfants de moins de 5 ans (519 412 cas de pneumonie, 18 148 116 cas d'otite moyenne aiguë, 6884 cas de méningite et 38 799 cas d'infections autres que pneumonies et méningites) sur une période de 10 ans (2014-2023). L'introduction du VPC-13 permettrait de prévenir 4 900 084 cas d'infection à pneumocoque (190 849 cas de pneumonie, 4 692 450 cas d'otite moyenne aiguë, 2529 cas de méningite et 14 256 cas d'infections autres que pneumonies et méningites). L'infection à pneumocoque entraînerait 287 950 hospitalisations et 29 399 décès. La vaccination permettrait d'éviter 105 802 hospitalisations et 9997 décès. Le rapport coût-efficacité cumulatif a été estimé à 1890 USD et 1538 USD par année de vie ajustée sur l'incapacité évitée pour le gouvernement et la société respectivement.

Conclusion : Selon les seuils recommandés par l'OMS pour interpréter le rapport coût-efficacité, l'introduction du VPC-13, pour les enfants de moins de 5 ans en République islamique d'Iran, aurait un bon rapport coût-efficacité.

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WHO EMRO | Cost-effectiveness of introducing the pneumococcal conjugate vaccine for children under

إدراج لقاح 13-PCV في جداول تحصين الأطفال والتي ينبغي تقييمها في ضوء تكلفة أمراض
المكورات الرئوية التي يتكبدها كل مجتمع .

: هدفت هذه الدراسة إلى تقييم فعالية تكلفة إدراج لقاح 13-PCV في برنامجالأهداف
التمنيع الوطني للأطفال دون سن 5 سنوات في جمهورية إيران الإسلامية .

: استُخدم نموذج دعم القرارات المُسمى TRIVAC لتقدير إجمالي تكاليف إدخالطرق البحث
لقاح 13-PCV ، وجُنِّبت سنوات العمر المُعدَّلة حسب الإعاقة (DALYs). ونُظر في أمراض
المكورات الرئوية الرئيسية – الالتهاب الرئوي، والتهاب السحايا، والتهاب الأذن
الوسطى الحاد، والعداوى غير الناجمة عن الالتهاب الرئوي أو التهاب السحايا – من حيث
حالات الحجز في المستشفى وزيارات العيادات الخارجية والوفيات . واستُخدمت بيانات
محلية لتقدير التكاليف .

: أشارت التقديرات إلى أن مرض المكورات الرئوية سيصيب 18 713 211 طفلاً ممن تقلالنتائ ج
سنهم عن 5 سنوات (الالتهاب الرئوي : 519 412 ، والتهاب الأذن الوسطى الحاد : 18 148 116 ،
والتهاب السحايا : 6884 ، العداوى غير الناجمة عن الالتهاب الرئوي أو التهاب السحايا : 38
799) خلال 10 عشر سنوات (من 2014 إلى 2023) من دون استخدام اللقاح . وأن استخدام اللقاح
الالتهاب) الرئوية المكورات بمرض حالة 4 900 084 إصابة دون يحول أن شأنه من PCV-13
الرئوي : 190 849 ، والتهاب الأذن الوسطى الحاد : 4 692 450 ، والتهاب السحايا : 2529 ،
والعداوى غير الناجمة عن الالتهاب الرئوي أو التهاب السحايا : 14 256). وسوف تتسبب عدوى
المكورات الرئوية في دخول 287 950 مريضاً المستشفى، وفي 29 399 حالة وفاة . أما مع
التطعيم، فيمكن تجنب 105 802 من حالات دخول المستشفى و 9997 حالة وفاة . وقُدِّرت فعالية
التكلفة الإضافية للحكومة وللمجتمع بمبلغ 1890 دولاراً أمريكياً، و 1538 دولاراً
أمريكياً لكل سنة مُجنَّبة من سنوات العمر المُعدَّلة حسب الإعاقة، على الترتيب .

: وفقاً للحدود الدنيا التي أوصت بها منظمة الصحة العالمية لتفسير الفعاليةالاستنتا ج
من حيث التكلفة، سيكون إدخال لقاح 13-PCV للأطفال دون سن 5 سنوات في جمهورية إيران
الإسلامية فعالاً من حيث التكلفة .

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