Future strategic plan for national immunisation program in Iran: cost effectiveness of acellular pertussis versus whole-cell

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Abstract: We investigated the new strategic plan of immunisation against whooping cough by conducting cost effectiveness analysis of acellular whooping cough vaccination compared with whole-cell vaccination, a current strategy used in the Iranian national immunisation program. We used a decision tree model together with sensitivity analysis to find the results. The findings of this study suggest that the implementation of acellular immunisation program for children and acellular immunisation program for high-risk groups are the most cost-effective strategies in Iran by US$12,691 incremental cost per disability adjusted life years averted. The results also suggest that acellular vaccine for children is cost-effective scenario in Iran when resulting from whole-cell vaccine associated side-effects is accounted. This study contributes to the literature on the factors that decrease healthcare sector costs. The study also provides critical policy recommendations for the decision makers in the healthcare sector. The findings may be useful for decision makers in the healthcare sectors and the government of Iran.

Keywords: strategic plan; whooping cough; acellular; whole-cell; cost effectiveness; children; Iran.


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1 Introduction

National immunisation program in Iran has been developed in recent decade and this program plays a pivotal role in reducing burden of infection disease among children. This program, however, faces many challenges and changing the vaccination plan against whooping cough is one of them. The whooping cough is an acute bacterial respiratory disease which may be transmitted easily and its attack rate is between 80% and 100%. Considering prolonged use of whooping cough vaccines, this disease continues to be a preventable disease with vaccine; however, its control is considered to be undesirable (Murray et al., 2005; Guiso et al., 2009).

The whooping cough is not just a childhood illness and adults may also become infected. Today, in fact, due to routine immunisation of children, most disease incidences in countries with a vaccination program occur among older children and adults (Schellekens et al., 2005). In recent years, the evidence suggests epidemiological changes in this disease and increase of its incidence among adults. Given that the accurate diagnosis of whooping cough by tests is difficult, it is the probable common cause of many unknown coughs which last for several weeks and also occur among people who appear to be healthy after every cough (Gidengil and Sandora, 2008).

Whooping cough has been considered as one of the 10 main cause of death in children under 1 year old around the world. Global incidence of this disease is estimated around 10 million cases along with more than 400,000 deaths annually and more than 90% of them occurred in developing countries (Crowcroft et al., 2003; Tan et al., 2005).

Accordingly, in 2004, the burden of whooping cough in 0–14 years old age group in high-income, middle-income, and low-income countries was estimated to be 44,000, 674,000, and 9,154,000 the disability-adjusted life year (DALY), respectively (Mathers, 2008). In Iran, despite implementing vaccination program with coverage of over 90%, the evidence suggests an increase in incidence of this disease in some years; one of the reasons is lack of controlling this disease in adults (Nikbin et al., 2013).

Today, there are two types of whooping cough vaccine: the vaccines which are made from whole-cell including all contents of whooping cough bacteria which are killed by chemical operations and the non-cellular vaccines which are recently provided by some industrialised countries. The whooping cough vaccines are made from killed bacteria and
may cause severe neurological complications such as seizure, encephalopathy, and hypothalamus and other complications such as anorexia, drowsiness, fever, irritability, prolonged crying, vomiting, pain, redness, and swelling at injection site (Nikbin et al., 2013). Due to increasing concerns about neurological disorders which are associated with whole-cell vaccine, the no cell vaccines were produced and tested in 1970 and used in Japan in 1980 (Gidengil and Sandora, 2008; Marzouqi et al., 2010; Hitchcock, 2006). The used vaccine in Iran is whole-cell vaccine which is injected as triple vaccine (anti diphtheria, tetanus, and whooping cough) in infants 2, 4, 6 months old and as booster dose at 18 months old and 4-6 years old (Zahraei et al., 2010).

Considering the recommendations of World Health Organization on necessity of providing documentation to change the vaccination program of countries from whole-cells to acellular and also the necessity of conducting cost-effectiveness studies to prioritise and strengthen executive strategic plan for implementing prevention programs, this study performed the cost-effectiveness of implementing acellular vaccination instead of whole-cell vaccination in one year time horizon with societal prospective. So, the documents on accurate evaluation of this prevention program would be provided and health policymakers would be helped to make optimal decisions and policies in this area.

2 Material and methods

2.1 Model structure

Using decision tree model, the cost effectiveness of acellular vaccination was investigated in four scenarios: (1) acellular Vaccine to children (under 5 years old), (2) whole-cell vaccine in current way, as well as acellular vaccine to high-risk groups, (3) acellular vaccine to children, as well as acellular vaccine to high-risk groups, (4) whole-cell vaccine in current way, as well as acellular vaccine to high risk groups and a 10-year booster dose. Three outcomes including outpatient visit, inpatient care, and death were defined for each scenario. Based on calculated incidence rate in base state, the cost of implementing vaccination program, the cost of whooping cough disease, medical cost averted after vaccination, and the disability-adjusted life years (DALYs) averted in each scenario were estimated for corresponding population groups. After incorporating all epidemiological, effectiveness, and cost data to model, the cost effectiveness was obtained by calculating cost per DALYs averted and cost per case averted in each scenario. Figure 1 shows the structure of acellular vaccination implementation decision-making model in four scenarios compared with current state (whole-cell vaccination).

2.2 Epidemiological parameters

The incidence rate of whooping cough in each group of children and high-risk groups (healthcare system employees and pregnant mothers) was obtained from the surveillance system of the Ministry of Health and Medical Education (MoHME), centre for communicable disease control. Then, the calculated rates of disease such as incidence, mortality, and duration were entered into R software (DALYs Package) to calculate the burden of whooping cough in all scenarios. The disability which is associated with whooping cough disease, time discount rate, and different age values were also applied in calculation of disease burden.
The whole-cell and acellular vaccines efficacy and safety data were extracted from systematic review and meta-analysis of trial studies (Mansour-Ghanaei et al., 2016). Seizure incidence rate and its mortality rate were considered as most common side effect after injecting whole-cell and acellular vaccine, based on systematic review and meta-analysis (Mansour-Ghanaei et al., 2016). We used literature to extract the probability of disease incidence in people who do not receive booster dose and people in high risk group in the absence of vaccination or failure in immune according to decision tree model.

Since Pertussis is highly communicable, by secondary attack rates of 80% among susceptible household contacts (Tiwari et al., 2005), we considered indirect impact of vaccination on not vaccinated population (Herd effect) in target population in this analysis. Epidemiological parameters in target population are shown in Table 1.

2.3 Vaccine cost

The major costs which were associated with implementation of vaccination program such as cost of vaccine supply, cost of transportation, and cost of cold chains were estimated based on models which based on previous vaccinations data and World Health Organization (WHO) guidelines (World Health Organization, 2002). Due to coincidence
of injection with other routine vaccines, the staff costs were ignored. The cost data were extracted in collaboration with the MoHME. In order to estimate the acellular and whole-cell vaccines supplied costs, we consider the cohort population in reference year, vaccine price per dose, coverage rate, and number of required doses and wastage factor in a full immunisation period for each of four scenarios. Vaccine price per dose was taken from the local representative of the vaccine’s manufacturer that would be US$10 per dose for acellular vaccine, also 5% wastage rate was assumed. We extracted data on incidence of complications for whole-cell vaccines, the cost of vaccine complications is also calculated for seizure after vaccine injection and its treatment costs and is added to total cost of vaccination (see Table 2).

Table 1  Epidemiological parameters in different target population

<table>
<thead>
<tr>
<th>Incidence 100,000</th>
<th>Mortality 100,000</th>
<th>DALYs</th>
<th>YLDs</th>
<th>YLL</th>
<th>Cases</th>
<th>Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children</td>
<td>14.03</td>
<td>0.42</td>
<td>1976</td>
<td>2</td>
<td>1974</td>
<td>873</td>
</tr>
<tr>
<td>High Risk</td>
<td>2.6</td>
<td>0.01</td>
<td>550</td>
<td>4</td>
<td>170</td>
<td>491</td>
</tr>
<tr>
<td>Adults</td>
<td>1.68</td>
<td>0.04</td>
<td>290</td>
<td>0</td>
<td>289</td>
<td>181</td>
</tr>
</tbody>
</table>

2.4 Health service cost

The direct and indirect costs of treating whooping cough in inpatient and outpatient sections were calculated by sampling from among children with whooping cough who had received outpatient and inpatient services in Mofid Children’s Specialised Hospital. Also, to estimate inpatient and outpatient services costs among high-risk groups, the average cost of inpatient and outpatient services were estimated by experts. The inpatient and outpatient cost rates in hospital and health centres were extracted from MoHME statistics and applied to calculation. The average cost of admission, hospital hoteling, diagnostic tests, medication, nursing services, physician visits, and counselling were estimated among children who were admitted to Mofid hospital. To calculate cost of outpatient services, we used tariffs for costs of drugs, diagnostic tests, and outpatient visit. The average cost of inpatient and outpatient services for those who received booster doses of acellular vaccine was calculated based on cost of treatment in children. Also, the indirect cost of treatment including cost of losing productivity in high risk group was calculated using human capital method. In this method, the number of lost days due to illness is 5.98 days (Lee and Pichichero, 2000). The cost of providing informal care services to children was calculated using opportunity cost method and considering duration of diseases and average daily income of family. After calculating the average cost and considering the incidence rate in each population, the total cost of treating whooping cough was estimated for children, adults, and high risk groups in the base year. The total costs and people use of inpatient and outpatient service in each of the four scenarios are provided in (see Table 3 and Table 4).

2.5 Cost effectiveness analysis

The cost effectiveness analysis of acellular vaccination in each of the four scenarios was conducted compared with base state (injection of whole-cell vaccine in current way). It should be noted that in order to coordinate the cohort of second, third, and fourth
scenarios with base scenario, we assumed the likelihood of incidence (if vaccination program is not implemented or failure of immunisation) in high risk individuals and those who do not receive booster dose were considered. Also, we estimated the impact of natural immunity (%herd effect) and YLDs associated with whole-cell vaccine related adverse events were considered in cost-effectiveness analysis. A one-way sensitivity analysis has been conducted on each scenario and we were considered GBD 2105 estimation of incidence and disability – adjusted life years in this regard.

The following formula was used to estimate the Incremental cost-effectiveness ratio (ICER). Also, the World Health Organization (Iran’s GDP per capita in reference year) threshold rate was used to interpret ICER.

\[
\text{ICER} = \frac{\text{Total vaccination cost} - \text{Cost savings}}{\text{DALYs without vaccine} - \text{DALY with vaccine}}
\]

3 Result

The incidence of whooping cough in children, high risk groups, and those who need booster dose is estimated to be 14.03, 2.6, and 1.68 per 100,000 individuals, respectively. The incidence rate in high risk group is calculated considering 1.3 relative risk of whooping cough incidence in this group and also epidemiological estimates of high risk group from literature (Sandora, 2008; Gabotti, 2012). Also, according to MoH statistics in 2012, the inpatient and outpatient rate of patients with whooping cough has been 84% and 16%, respectively. The patients with mild whooping cough who did not go to hospitals or health centres to receive inpatient or outpatient services were not considered in study. According to MoH report, the mortality rate in each of three studied groups was estimated to be 0.04, 0.01, and 0.42 per 100,000 people. The DALYs rate of whooping cough disease in children group, high risk group, and those who should receive booster dose was estimated to be 550, 1976, and 290 DALYs, respectively. Also, the disease burden of seizure in children was calculated considering the mortality rate due to seizure complication for acellular vaccine (0.002) and whole-cell vaccine (0.006) and was estimated to be 219 and 656 DALYs, respectively. Moreover, according to literature, vaccination with whole-cell carries an increased risk of adverse event while acellular vaccine is not associated with serious complication and incidence of febrile seizures after whole-cell vaccination is 57.14 per 100,000 (Mansour-Ghanaei et al., 2016).

To compare strategies for using acellular vaccine in national vaccination program and compare it with current state (i.e., injection of whole-cell vaccine for children), the probability of disease incidence in people who do not receive booster dose and people in high risk group in the absence of vaccination was extracted from previous studies. This rate is estimated to be 49% and 35% for high risk group (Greer and Fisman, 2009) and those who do not receive booster dose (Rodriguez, 2008), respectively. Regarding herd effect, vaccination against pertussis will reduce the number of infected children in the not-immune population by 30%, this amount is estimated 25% for adults and also the indirect effect of booster dose vaccination is about 20% (Caro, 2005).

The result of vaccine efficacy shows that the efficacy of whole-cell and acellular vaccines in children is 73% and 71%, respectively (Mansour-Ghanaei et al., 2016). Although the whole-cell vaccine is slightly more effective, the complications of both
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Vaccines show that the incidence of seizure after injection of whole-cell and acellular vaccines is 57.14 per 100,000 people and 26.80 per 100,000 people, respectively; this shows that the acellular vaccine has less complications compared with whole-cell vaccine. Also, the efficacy of acellular vaccine for high-risk groups and booster dose group was estimated to be 76% and 85%, respectively (Mansour-Ghanaei et al., 2016).

To estimate incremental system cost of adding a new vaccine to national immunisation system, the factors which are listed in WHO guidelines were calculated and estimated (WHO, 2002). This cost for implementing existing scenario (injection of whole-cell vaccine in current state) was considered to be zero. It was calculated for other strategies including acellular immunisation. The total system costs, regardless of cost of vaccine supplied, were estimated to be US$343,373.

To calculate the exact cost of vaccination program, the cost of complications incidence after whole-cell vaccine should also be added to scenario that include whole-cell vaccine. For this purpose, considering the seizure complication and estimating the epidemiological data for this complication in the case of injecting whole-cell vaccine in children (incidence of complications in booster dose and high risk groups is not considered due to low incidence rate), the treatment cost of this complication was estimated by extracting cost data related to hospitalisation due to seizure following vaccine injection in Mofid hospital; it was calculated to be US$484 per patient. The total cost of implementing vaccination program, considering the cost of vaccine complications, is equivalent to US$5,026,616 for whole-cell vaccine and US$72,765,000 for acellular vaccine for children. The total cost of vaccination program in three other scenarios of acellular-based vaccination is shown in Table 2.

Table 2  Cost of vaccination and medical cost saved in four different scenarios

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Total number of dose required</th>
<th>Total vaccination cost US$*</th>
<th>Total medical cost saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTwP</td>
<td>7,276,500</td>
<td>5,026,616</td>
<td>38,250</td>
</tr>
<tr>
<td>DTaP</td>
<td>7,276,500</td>
<td>72,765,000</td>
<td>39,328</td>
</tr>
<tr>
<td>DTwP+DTaP High risk</td>
<td>9,230,760</td>
<td>24,569,216</td>
<td>40,217</td>
</tr>
<tr>
<td>DTaP +DTaP High risk</td>
<td>9,230,760</td>
<td>92,307,600</td>
<td>40,971</td>
</tr>
<tr>
<td>DTwP +DTaP Booster+ DTaP High risk</td>
<td>10,686,060</td>
<td>39,122,216</td>
<td>51,285</td>
</tr>
</tbody>
</table>

Note: *Include cost of whole-cell related adverse effect.

Considering the efficacy of vaccine, the saved medical and social costs of acellular and whole-cell vaccines in children population were estimated to be US$39,328 and US$938,250, respectively. The saved social and medical costs of acellular vaccination in high-risk and booster dose groups were US$1643 and US$12,091, respectively. Also, implementing acellular vaccination program for children with effectiveness level of 71% and considering incidence rate of 14.08 per 100,000, 120 hospitalisations, 22.9 outpatient admissions, and 4.3 deaths will be averted among children. In whole-cell vaccination, this rate would be 117, 22.3, and 4.2, respectively; further details are shown in Table 3.
Table 3  Summery of cost-effectiveness result of all scenario of acelluar vaccination compare to whole-cell vaccination for children

<table>
<thead>
<tr>
<th>Scenario</th>
<th>Admission averted</th>
<th>Outpatient averted</th>
<th>Death averted</th>
<th>DALYs averted*</th>
<th>ICER (US$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DTaP</td>
<td>120</td>
<td>22.9</td>
<td>4.3</td>
<td>3942</td>
<td>13,441</td>
</tr>
<tr>
<td>DTwp + DTaP High risk</td>
<td>125</td>
<td>52</td>
<td>4.3</td>
<td>1849</td>
<td>19,846</td>
</tr>
<tr>
<td>DTaP + DTaP High risk</td>
<td>128</td>
<td>53</td>
<td>4.4</td>
<td>4377</td>
<td>12,691</td>
</tr>
<tr>
<td>DTwp + DTaP Booster + DTaP High risk</td>
<td>165</td>
<td>59</td>
<td>5.4</td>
<td>2124</td>
<td>21,984</td>
</tr>
</tbody>
</table>

Note:  *DALY averted include YLDs associated with whole-cell related adverse events.

The final results of cost-effectiveness analysis are presented separately for each of four scenarios as follows:

1. **Acellular vaccine for children**: The comparison of implementing the scenario of whooping cough acellular vaccine with current scenario (whole-cell vaccine for children) shows that the incremental cost of DALYs averted by acellular vaccine compared with whole-cell vaccine is US$13,441. Although the implementation of this scenario is costlier, the DALYs averted in this scenario is 5040 DALYs more than existing scenario. Considering three times of Iran’s gross domestic product (US$13,576), this intervention is cost effective. In one way sensitivity analysis ICER in this scenario changed to US$13,516 and remain cost-effective.

2. **Whole-cell vaccine for children and acellular vaccine for high-risk groups**: The comparison of this scenario with current scenario (whole-cell vaccine for children) shows that the incremental cost of DALYs averted compared with whole-cell vaccine is US$19,846. The implementation of this scenario is costlier and DALYs averted in this scenario is 985 more than existing scenario. This shows that this scenario is not cost effective. In one way sensitivity analysis ICER in this scenario changed to US$54,576 and remain not cost-effective.

3. **Acellular vaccine for children along with high-risk groups**: The comparison of this scenario with current scenario (whole-cell vaccine for children) shows that the incremental cost of DALYs averted compared with whole-cell vaccine is US$12,691. Although the implementation of this scenario is costlier, the DALYs averted in this scenario is 6877 DALYs more than existing scenario. This shows that this scenario is cost effective. In one way sensitivity analysis ICER in this scenario changed to US$15,629 and is not cost-effective.

4. **Whole-cell vaccine for children and acellular vaccine for high-risk group along with booster dose**: The comparison of this scenario with current scenario (whole-cell vaccine for children) shows that the incremental cost of DALYs averted compared with whole-cell vaccine is US$21,984. The implementation of this scenario is costlier and DALYs averted in this scenario is 1550 DALYs more than existing scenario. This shows that this scenario is not cost effective. In one way sensitivity analysis ICER in this scenario changed to US$23,095 and remain not cost-effective.
4 Discussion and conclusion

The findings of this study suggest that the implementation of acellular immunisation program for children and high-risk groups prevent totally from 4,377 the disability-adjusted life years. Although the cost of implementing this program is more than existing scenario due to adding acellular vaccine, it is cost effective considering there times of GDP per capita in Iran (US$13,576). Using acellular vaccination for children is also the superior alternative compared with current scenario when considering DALYs due to whole-cell vaccine related adverse events.

The second scenario (using whole-cell vaccine for children and acellular vaccine for high-risk groups) was not cost-effective scenario with the high incremental cost-effectiveness ratio (US$19,846). The whole-cell vaccine for children and acellular for high-risk group along with booster dose scenario averted most medical cost among exiting scenario, but it prevented less DALYs and was not cost-effective. These two scenarios are not cost effective because of adverse event of whole-cell vaccination.

The results of Lee et al. (2005) study on cost-effectiveness of whooping cough vaccine in adults show that considering two strategies for whooping cough vaccination including adult at the age of 20–60 and booster dose vaccination in every 10 years, will be cost-effective if the incidence of whooping cough in this age group is more than 120 per 100,000. This researcher conducted another study on cost-effectiveness of three strategies for whooping cough vaccination in adults between 20–64 years old in German. The findings showed that compared with non-vaccination, the incremental cost of whooping cough case averted is €160 for adult vaccine and €200 for vaccination in every 10 years. The incremental cost for quality-adjusted life year (QALY) gained is €5800 for a single vaccine and €7200 for vaccination in every 10 years. Also, the authors found that this scenario is cost-effective and cast-saving if the incidence rate will be more than 200 per 100,000 (Lee et al., 2008).

On the other hand, Rodriguez et al. (2008) conducted a systematic review study and showed that due to insufficient evidence, no accurate comment may be provided (Rodriguez et al., 2008). Recently, Itatani (2013) in Japan conducted a study on cost effectiveness of acellular vaccination considering intergeneric infection level and showed that the implementation of acellular vaccination plus booster dose is not cost effective in Japan (Itatani, 2013).

A recent study about Use of acellular pertussis vaccines in the United States focused optimum vaccination time of pertussis in this country. Authors maintained that, an alternative vaccination plan would be to take advantage of the epidemiologic cyclical of pertussis outbreaks and recommended that ‘timed’ Tdap vaccination should be taking into account. This alternative scenario considers susceptible adolescents and young adults during periods when there is a greater risk of being exposed to pertussis (Klein and Zerbo, 2017).

Another recent study in United State, found that efficacy of vaccine have strong linear association with health outcome and economic gain so an increase in the efficacy of the first dose of pertussis vaccine from 0.55 to 0.75 would provide an average gain of 900 QALYs annually during the first 10 years following implementation along with averting US$5.7 million in health expenditures annually (Fitzpatrick et al., 2017).

In conclusion, considering the evidence of vaccine efficacy for reducing the risk of severe forms of disease, its safety, high burden of disease, and economic situation given the standards of World Health Organization, current program of whole cell vaccination
against Pertussis could be replaced by acellular vaccination in Iran and it should be considered as a priority in decision-making process of MoHME. Among four different scenarios for adding acellular vaccination, using acellular vaccination only for children and also in combination of children and high risk groups should be considered as priority.

5 Limitations and future research

Since some of complications of disease were not measurable due to lack of access to reliable epidemiological data in Iran, only epidemiological burden and economic burden of seizure was estimated as the most important complication after vaccine injection; other complications of vaccine were ignored. Future research should investigate generalisations of the findings beyond the Iran.

References


