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Cost-Effectiveness Analysis of Pneumococcal Conjugate Vaccine in Taiwan: A Transmission Dynamic Modeling Approach

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A B S T R A C T

Objectives: *Streptococcus pneumoniae* causes significant morbidity and mortality worldwide. Static pharmacoeconomic models have been used to conduct pharmacoeconomic analyses of pediatric pneumococcal conjugate vaccination programs. The objective of this study was to develop a transmission dynamic model to evaluate the cost-effectiveness of a 13-valent pneumococcal conjugate vaccine (PCV13) in Taiwan. **Methods:** An age-structured transmission dynamic model was populated with parameters from the Taiwanese National Health Insurance Research Database and publicly available sources to evaluate the clinical and economic impact of PCV13. Sensitivity analyses were performed to explore model uncertainties. **Results:** In the base-case analysis, four-dose scheduled universal infant PCV13 vaccination will prevent 5112 cases of invasive pneumococcal diseases, 535,607 cases of all-cause hospitalized pneumonia, 726,986 cases of acute otitis media, and 420 deaths over a 10-year time horizon since 2009. The four-dose vaccination program is estimated to yield an incremental cost-effectiveness ratioof US$38,045 and US$18,299 from payer and societal perspectives. One-way sensitivity analyses indicated that the incremental cost-effectiveness ratio is most sensitive to vaccine price. The 95% confidence interval of the incremental cost-effectiveness ratio was US$10,186 to US$34,563 by multivariate probabilistic sensitivity analyses in the societal perspective. **Conclusions:** With a World Health Organization–recommended cost-effectiveness threshold, the PCV13 vaccination program would be cost-effective in Taiwan. To circumvent the lack of long-term real data, a transmission dynamic model is informative to decision makers on evaluating the long-term cost-effectiveness of PCV13.

Keywords: cost-effectiveness, herd effect, *Streptococcus pneumoniae*, transmission dynamic model, 13-valent pneumococcal conjugate vaccine (PCV13).

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Introduction

Infectious disease is one of the major causes of morbidity and mortality among children younger than 5 years [1]. The World Health Organization reported that five of the top seven diseases in developing countries were caused by infectious pathogens [2]. *Streptococcus pneumoniae* (SP) causes invasive pneumococcal diseases (IPDs; meningitis and bacteremia) and non-IPDs (pneumonia and acute otitis media [AOM]). In Taiwan, pneumococcal diseases constitute a considerable proportion of the overall disease burden among high-risk groups: namely, children younger than 2 years and those older than 65 years [3,4]. A recent study found that 80.7% of *SP* isolates from Taiwanese children younger than 14 years were penicillin resistant. Despite the implementation of stringent antibiotic-prescribing protocols, Taiwan has one of the highest rates of antibiotic-resistant *SP* in the world [5].

Seven-, 10-, and 13-valent pneumococcal conjugate vaccines (PCV7, PCV10, and PCV13) have been introduced to prevent *SP* infection in children. PCV7 is included as the routine national immunization schedule in many countries [6]. PCV13 was developed owing to epidemiological changes of pneumococcal diseases. Compared with PCV7, PCV13 targets six additional serotypes of the same carrier protein (CRM197) [7].

Surveillance data indicated that mass vaccination protects children from acquiring pneumococcal diseases and reduces overall incidence [8-11]. This is known as the *herd effect*, a reduction in disease transmission from the vaccinated to the unvaccinated with which its inclusion would increase the cost-effectiveness of a vaccine [12,13]. Many pharmacoeconomic studies have utilized the decision analytic or Markov model [14] (collectively termed the static model) to evaluate the cost-effectiveness of PCV7 [15-17]. A recent cost-effectiveness analysis (CEA) of PCV7 in Hong Kong [18] incorporated the herd effect into the model by using observational data from the United States [8]. One of the major limitations with static models is that the force of infection (FOI), defined as the per-capita rate of infection, is assumed to be unaffected by a vaccination program [19]. Instead, a transmission dynamic model (TDM) treats FOI as dependent on the number of infected persons over time [20]. Much empha-

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sis has been placed on the use of the TDM to evaluate the cost-effectiveness of a vaccination program as more appropriate than the static model because the TDM treats FOI as time dependent [21,22]. To our knowledge, there are only three studies that used the TDM to explore the transmission dynamics of *SP* [23-25].

Methods

Transmission dynamic model

An age-stratified TDM was developed to simulate the clinical and economic outcomes over 10 years. Age groups were chosen according to demographic and epidemiological data to account for various incidences of pneumococcal diseases. The model comprised seven major compartments: susceptible, $S(t)$; vaccinated, $V(t)$; *SP* infection without vaccination, $I_V{}^C(t)$; *SP* infection with vaccination, $I_V(t)$; *SP*-induced death without vaccination, $D_V{}^C(t)$; *SP*-induced death with vaccination, $D_V(t)$; and recovery from pneumococcal diseases, $R(t)$ (see Fig. 1 in Supplemental Materials found at doi:10.1016/j.jval.2011.11.013). Each represented the number of individuals at a certain time point t. These compartments were further divided into six age groups: $i = 1, 2, \ldots, 6$, i.e., ≤2, 3–4, 5–17, 18–49, 50–64, and ≥65, where N represents the overall Taiwanese population in 2009. Newborns were assumed to be susceptible and entered into $S_1(t)$ at the annual birth rate ì, with the current birth cohort moving into the next higher age group $S_2(t)$, and so on, until the last age group, which was assigned an aging rate A_i, the reciprocal of the length of age group i. These aging rates were also applied to other age-specific compartments. $\dot{\eta}$ denoted the non-*SP*–induced mortality rates for individuals of age group i in susceptible and vaccinated compartments. Susceptible individuals of age group i were vaccinated with vaccine coverage Ψ and entered into the vaccinated compartment, and vaccinated individuals became susceptible again at vaccine-waning rate Ω, which was the mean rate at which vaccinated individuals lost their immunity (equivalently, $1/\Omega$ was the mean duration of vaccine-derived immunity). Susceptible individuals of age group i acquired one of the jth pneumococcal diseases ($j = 1, 2, 3$ for IPD, all-cause hospitalized pneumonia, and all-cause AOM) with FOI, $\lambda_{ij}(t)$, and entered into one of the three infectious compartments without vaccination ($I_{i1,V}{}^C(t)$, $I_{i2,V}{}^C(t)$, $I_{i3,V}{}^C(t)$). Vaccinated individuals of age group i infected with one of the pneumococcal diseases moved into one of the three infectious compartments with vaccination ($I_{i1,V}(t)$, $I_{i2,V}(t)$, $I_{i3,V}(t)$) with a smaller FOI, $(1 - p_j)\lambda(t)$, where p_j represented vaccine efficacy against the jth pneumococcal disease. Infectious individuals with the jth pneumococcal disease recovered at a rate of $\tilde{a}_{ij}$ and moved back to the susceptible compartment. Individuals with the jth pneumococcal disease died from the disease with the case fatality rate (CFR) ρ_j. The dynamic structure is represented in a set of differential equations as follows:

$$\frac{dS_i(t)}{dt} = \mu N - \left(\varphi_i + \sum_j \lambda_{ij}(t) + \eta_i + A_i\right)S_i(t) + \omega V_i(t) + A_{i-1}S_{i-1}(t)$$

$$\frac{dV_i(t)}{dt} = \varphi_i S_i(t) - \left(\sum_j \lambda_{ij}(t)(1-p_j) + \eta_i + \omega + A_i\right)V_i(t) + A_{i-1}V_{i-1}(t)$$

$$\frac{dI_{ij,V^C}(t)}{dt} = \lambda_{ij}(t)S_i(t) - (\rho_{ij} + \gamma_{ij} + A_i)I_{ij,V^C}(t) + A_{i-1}I_{ij-1,V^C}(t)$$

$$\frac{dI_{ij,V}(t)}{dt} = \lambda_{ij}(t)(1-p_j)V_i(t) - (\rho_{ij} + \gamma_{ij} + A_i)I_{ij,V}(t) + A_{i-1}I_{ij-1,V^C}(t)$$

$$\frac{dD_{ij,V^C}(t)}{dt} = \rho_{ij}I_{ij,V^C}(t)$$

$$\frac{dD_{ij,V}(t)}{dt} = \rho_{ij}I_{ij,V}(t)$$

$$\frac{dR_i(t)}{dt} = \sum_j \gamma_{ij}\left(I_{ij,V^C}(t) + I_{ij,V}(t)\right) - \eta_i R_i(t) - A_i R_i(t) + A_{i-1}R_{i-1}(t)$$

The initial conditions are described as below; e.g., 60 in $I_{1,V}{}^C(0)$ is the prevaccination number of IPD in the first age group (≤2 years of age) at time 0 and all other column vectors are similarly defined.

$$\mathbf{S}(0) = [393014\ 414771\ 4060519\ 11794340\ 3972167\ 2402220]'$$

$$\mathbf{V}(0) = [0\ 0\ 0\ 0\ 0\ 0]'$$

$$\mathbf{I}_{1,V^C}(0) = [60\ 73\ 57\ 106\ 167\ 291]'$$

$$\mathbf{I}_{2,V^C}(0) = [19703\ 9016\ 9234\ 12832\ 6308\ 52015]'$$

$$\mathbf{I}_{3,V^C}(0) = [79156\ 52989\ 115351\ 0\ 0\ 0]'$$

$$\mathbf{I}_{1,V}(0) = [0\ 0\ 0\ 0\ 0\ 0]'$$

$$\mathbf{I}_{2,V}(0) = [0\ 0\ 0\ 0\ 0\ 0]'$$

$$\mathbf{I}_{3,V}(0) = [0\ 0\ 0\ 0\ 0\ 0]'$$

$$\mathbf{D}_V(0) = [0\ 0\ 0\ 0\ 0\ 0]'$$

$$\mathbf{D}_{V^C}(0) = [0\ 0\ 0\ 0\ 0\ 0]'$$

$$\mathbf{R}(0) = [0\ 0\ 0\ 0\ 0\ 0]'$$

FOI was estimated by using prevaccination prevalence data [20]. It can then be expressed as the product of the who-acquire-infection-from-whom matrix $\boldsymbol{\beta}_{n\times n}$ [20] and $\mathbf{I}_{n\times 1}(t)$ as follows:

$$\alpha_{n\times 1}(t) = \beta_{n\times n}\mathbf{I}_{n\times 1}(t) \quad (1)$$

where $\boldsymbol{\beta}_{n\times n}$ contained n^2 parameters, in which $\hat{a}_{ij}$ ($1 \le i, j \le n$) was the transmission rate of effective infectious contacts from an infectious person of age group j to a susceptible person of age group i. Nevertheless, the number of parameters to be estimated in the who-acquire-infection-from-whom matrix would exceed the number of equations in (1); i.e., it is an identifiability problem. Therefore, an assumed structure of contact patterns among different age groups allowed us to estimate n unknown parameters of the who-acquire-infection-from-whom matrix, where n was maximally equal to the number of known FOIs in (1) [20]. Because of the complexity of the system, the differential equations were solved numerically.

Model parameters

Demographic data

The age-specific population structure and non-*SP*–related mortality were derived from government data [26]. Life-years lost owing to *SP*-induced death for individuals in different age groups were also estimated [26] (see Table 1 in Supplemental Materials found at doi:10.1016/j.jval.2011.11.013).

Epidemiological parameters. The average annual disease burden caused by *SP* was estimated from 2002 to 2004 by using the National Health Insurance Research Database (NHIRD) to reflect prevaccination disease burden because PCV7 was first introduced in Taiwan in October 2005 (see Table 1 in Supplemental Materials found at doi:10.1016/j.jval.2011.11.013). Because IPD was included as a notifiable disease by the Taiwanese Centers for Disease Control (CDC) on October 15, 2007, the CFR of microbiologically confirmed IPD could be estimated accurately [27]. The CFRs of those hospitalized with all-cause pneumonia and AOM were derived

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