Asian Journal of Pharmaceutical and Clinical Research

Innovare Academic Sciences
Knowledge to Innovation

Vol 9, Issue 1, 2016

ISSN - 0974-2441

Research Article

VACCINATION EXTERNALITIES: THE CONCEPT AND APPLICATION IN PHARMACOECONOMIC STUDIES

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Received: 19 October 2015, Revised and Accepted: 10 November 2015

ABSTRACT

Objective: Externalities, could be positive or negative effects, occur in almost all daily life including vaccination activities. This paper aimed to presents a literature review of the concept of vaccination externalities and its application in pharmacoeconomic/economic evaluation studies.

Methods: The literature review was conducted to achieve the study objectives. Searching of literature used MEDLINE electronic database by PubMed interface as well as Google scholar search engine and employed a number of keywords.

Results: There are three most common types of vaccination externalities, namely: Herd immunity, serotype replacement, and antibiotic resistance. Herd immunity gives positive effects to the benefit of vaccination, the opposite of that of serotype replacement; while antibiotic resistance could give either positive or negative effects to the benefit of vaccination. Most emergence of serotype replacement occurred after pneumococcal conjugate vaccine vaccination. Most of pharmacoeconomic studies of vaccination used dynamic models to capture vaccination externalities which often included only herd immunity effects. Taking herd immunity into account in pharmacoeconomic studies tends to increase the outcomes and reduce the cost; hence, the cost per outcome or incremental cost-effectiveness ratio will decrease, resulting more favorable cost-effectiveness ratio.

Conclusions: Vaccination externalities might have effect on the results of pharmacoeconomic studies. Attentiveness should be made to interpret the results of pharmacoeconomic studies which potentially altered by the effect of vaccination externalities.

Keywords: Vaccination externality, Herd immunity, Serotype replacement, Antibiotic resistance, Pharmacoeconomic, Dynamic model.

INTRODUCTION

An externality is either cost or benefit resulted from actions that been taken by consumers or producers that affect other consumers or producers, for which producers do not pay or consumers are not compensated. Externalities occur in almost all our daily acitivities live, could be positive or negative externalities [1]. Thus, it also occur accompanying vaccination activities. Vaccination is one kind of health care program that could be categorized as public goods and affecting the public community. The policy to include such type of vaccination into national immunization program need rational considerations; one of those is an accurate and appropriate pharmacoeconomic study result [2]. With regard to the effect of vaccination externalities, addressing them in pharmacoeconomic studies of vaccination programs is important to increase the accuracy of cost-effectiveness measures since its result would affect the policy formulation of such program for the public [3-5]. This paper aimed to study the concept of vaccination externalities and explores the application in pharmacoeconomic studies of vaccination program, and finally presents in the simple summary of information regarding the concept of vaccination externalities and the application in pharmacoeconomic studies of vaccination program.

METHODS

The literature review was conducted to achieve the study objectives. Searching of the literature used MEDLINE electronic database by PubMed interface as well as Google scholar search engine and employed a number of keywords. First, we searched literature using keywords of vaccine, vaccination, and externalities. After review several articles resulted from the first searching, we expanded the searching using also other keywords including herd immunity, serotype replacement, and antibiotic resistant. We also selected the articles for review using the following criteria: The articles that relate to and contain enough information about vaccination externalities; herd immunity, serotype replacement, and antibiotic resistant related to vaccination; as well as pharmacoeconomic/economic evaluation studies capturing vaccination externalities effects. Selected articles were reviewed, summarized, and presented in this paper. The literature review was conducted in July 2012; therefore, the review involved articles published before July 2012.

RESULTS AND DISCUSSION

Vaccination externalities

Vaccination externalities can be summarized as the benefits, can be positive or negative, and resulted from vaccination activities that been taken by one party that affects other parties, for which they do not pay or are not compensated [1]; the benefits accrue because vaccination affects outcomes among unvaccinated community members [5]; therefore, the externalities were raised from the widespread immunization of communities [3].

Type of vaccination externalities

Barnighaussen *et al.* (2011) categorized the benefits of vaccination into several groups include health gain, health care cost-savings, care-related productivity gains, outcome-related productivity gains, behavior-related productivity gains, and community externalities [5]. The last category is the most often issues appeared in literature. It includes indirect effect of vaccination (herd immunity) and prevalence of antibiotic resistant. Some articles also suggest that serotype replacement occurs following vaccination and gave negative benefits to vaccination [6,7].

In this paper, we focused to study vaccination externalities in part of community or ecological externalities including herd immunity, serotype replacement, and antibiotic resistance. These three types of vaccination externalities are the most often issues appearing in literature.

Herd immunity

Definition of herd immunity

The term of herd immunity and herd effect, also called as indirect effect of vaccination, is often used interchangeably. Herd immunity is the proportion of subjects with immunity in a given population; herd effect is the reduction of infection or disease in the unimmunized segment as a result of immunizing a proportion of the population. Therefore, the term of herd immunity or herd effect can be understood as the immunity occurs among unvaccinated community as the result of vaccination in other community in a given population. It has meanings as follows: The resistance of a group to attack by a disease because of the immunity of a large proportion of the members; prevalence of immunity in the population which it becomes difficult for the organism to circulate and reach new susceptibles; and in the simple words, not everyone in a population needs to be immunized to eliminate disease [8,9].

Mechanism of herd immunity

Several articles explained the mechanisms of herd immunity as follows: Prevent acquisition of new strains, thus limiting new colonization and transmission [4]; reduce disease transmission in a population, reductions in unvaccinated persons' risk of contacting a disease due to the vaccination of others [5]; and reduce the number of susceptible individuals who can spread the disease among both vaccinated and unvaccinated persons [10].

Characteristics of herd immunity

In accordance with those mechanisms, herd effect has some characteristics that can be summarized as follows:

- Herd immunity is a function of the transmissibility of the infectious agent, the nature of the immunity induced by the vaccine, the pattern of mixing and infectious transmission in populations, and the distribution of the vaccine and immunity in the population [11]. Therefore, herd immunity of the same vaccine varies in different population [4]
- Herd immunity is not the same as biologic (immunologic) immunity; individuals protected only by indirect herd effects remain fully susceptible to infection [11]. Furthermore, the extent of protection conferred by herd immunity depends on the amount of continuing infection in the community [12]
- Susceptible individuals are afforded protection from infection if a sufficiently large fraction of the population is immune [13]; the more individuals who are immune, the lower the chance that a susceptible person will come into contact with an infectious person; and thus, herd immunity is not achieved when vaccines are rejected by a segment of the population [14].

Benefits of herd immunity

Normally, herd immunity gave the positive benefits to vaccination such as: Give the protection of vaccinated individuals whose immunity is waning [4]; acquire lower vaccination coverage and enabling targeted vaccination since the disease eradication does not necessary require vaccination of the entire population or universal vaccination [13]; protect individuals with contraindications to vaccination or those who for other reasons miss vaccination [11]. Despite that large positive effect of herd immunity, there is also negative effect of herd immunity as was shown in varicella. In which, through herd immunity, vaccination could lead to an upward shift in the average age at infection, when disease tends to be more severe, then could result in increasing the overall morbidity due to varicella [15,16]; in other case, mass vaccination of varicella could increase the incidence of zoster in unvaccinated individuals who mostly are adults [15].

Herd immunity accounted from some vaccinations

Most of studies reported the herd immunity in pneumococcal conjugate vaccine (PCV)-7 vaccination; some were as shown in Table 1. The herd immunity was accounted in the decreasing of disease incidence and proportion of pneumococcal carriage both in vaccinated and unvaccinated population.

In Table 2 also shows herd immunity in some other type of vaccinations; herd immunity was presented in decreasing of cases in vaccinated and unvaccinated population, as well as the exceeding protection rate from vaccination rate.

Serotype replacement

Serotype replacement is defined as the expansion of non-vaccine serotypes as a result of the removal from the population of vaccine types which compete with them to colonize new hosts [6]; resulting an increase in the incidence of cases/diseases caused by non-vaccine types after vaccine introduction [7].

The emergence of serotype replacement will subset the benefit of vaccination. Most of serotype replacement emergence occurred following PCV vaccination as was shown in Table 3. The findings of serotype replacement after PCV-7 vaccination have lead the development of new vaccine contains more serotypes not included in previous vaccine; PCV-7 was approved in 2000 covers 7 of 91 pneumococcal serotypes (4, 6B, 9V, 14, 18C, 19F, and 23F), PCV-10 was approved in 2009 covers 10 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 5, and 7F); and Finally, PCV-13 was developed in 2009 covers 13 serotypes (4, 6B, 9V, 14, 18C, 19F, 23F, 1, 3, 5, 6A, 7F, and 19A) [29].

Antibiotic resistance

Many bacterial infections are treated with antibiotics. The probability of antibiotic resistance increases with the number of patients treated with an antibiotic. Vaccination can avoid the development of drug resistance by reducing the use of antibiotic for treatment infectious disease [5]. Some vaccines were developed to prevent bacterial infection such as PCV, meningococcal vaccine, and haemophilus influenzae Type B vaccine [4].

Antibiotic resistance decrease due to the reducing of cases and antibiotic use for infectious diseases caused by vaccine type of microba. Antibiotic resistance increase due to the use of antibiotic for treatment infectious diseases caused by non-vaccine type of microba. Due to the changing of antibiotic resistance rate following the implementation of vaccination, it can be either positive or negative effects to the benefit of vaccination.

Table 4 shows some studies exploring antibiotic resistance in some vaccinations.

Pharmacoeconomic studies capturing vaccination externalities

Most of the pharmacoeconomic studies in vaccination use decision analytic model. The WHO also has recommended the guideline to determine the appropriate model used in pharmacoeconomic studies of vaccination [2]. The choice of model may have a significant impact on the overall assessment of the benefit of vaccination [12].

Table 5 shows pharmacoeconomic studies capturing vaccination externalities. Most of studies used dynamic model to capture vaccination externalities which mostly was herd immunity. Dynamic model is the most appropriate model to capture vaccination externalities. It has several strength compare to static model; in dynamic model, the rate of infection force (number of susceptible persons become infected) is dependent on the number of infectious individuals in the population and not a fixed parameter, and this model captures herd immunity effects hence account the direct and indirect effect of vaccination; finally, the result gives an appropriate estimation of cost-effectiveness of vaccination program. Compare to dynamic model, the result from static model tends to underestimate the cost-effectiveness of vaccination program [5,12]. However, some pharmacoeconomic studies of vaccinations used only the static model and employed several scenarios to explore the impact of vaccination externalities as part of the uncertainty analysis. Despite the strength of dynamic model, it has

Table 1: Herd immunity in PCV-7 vaccination

Study and setting	Period of observation	Effects
Hammit *et al.*, 2006 [17] Alaska	1998-2000 to 2004	The proportion of adult carriers with PCV7-type pneumococcal carriage decreased from 28% to 4.5% following pediatric vaccination with PCV-7
Hanna *et al.*, 2008 [18] Australia	1999-2001 to 2005-2007	Disease incidence in adults decreased 75% following vaccination of children
Jackson et al., 2008 [19] US	1998-1999 to 2004	Disease incidence in adults decreased 38% following vaccination of children
Ardanuy *et al.*, 2009 [20] Spain	1997 to 2007	Disease incidence in adults decreased from 19.5 to 12.3 episodes per 100,000 population following PCV-7 vaccination in children
Roca *et al.*, 2011 [21] Gambia	2003 to 2008	The proportion of carriage in all age groups decreased following vaccination in young children (from 23.7% and 26.8% to 7.1% and 8.5% in vaccinated and control group)

PCV: Pneumococcal vaccine

Table 2: Herd immunity in some vaccinations

Study	Type of vaccine and setting	Effects
Ramsay *et al.*, 2003 [22]	MCV England	Disease incidence in the unvaccinated population decreased by 67%
Emch *et al.*, 2006 [23]	Cholera Bangladesh	Vaccination gave protection to the neighborhood population about 65-75%
Stephens *et al.*, 2008 [4]	Hib UK	About one-third of disease reduction occurred from herd immunity
Clark *et al.*, 2009 [24]	Rotavirus US	The protection rate had exceeded 50% of vaccination rates as the result of herd immunity
Lewin *et al.*, 2010 [14]	Influenza Texas	With a vaccine uptake rate of only 20-25% in children, indirect protection of 8-18% of the adults occurred
Kim *et al.*, 2011 [9]	Pertussis Sweden	Disease incidence in non-vaccinated infants decreases by 56%

MCV: Meningococcal vaccine, Hib: Haemophilus influenzae Type B vaccine

Table 3: Serotype replacement in PCV-7 vaccination

Study and setting	Effects	Type of non-vaccine serotypes
Hanna *et al.*, 2008 [18] Australia	Disease incidence caused by non-PCV7 serotypes increased to be more than tripled	Serotype 1
Pai *et al.*, 2005 [25] US	Disease incidence caused by non-PCV7 serotypes increased significantly from 2.6 cases/100,000 populations to 6.5 cases/100,000 populations	Serotype 19A
Cohen *et al.*, 2011 [26] France	Non-PCV7 serotype was found in 10.4% of the overall population following vaccination of PCV-7 in more than 98% of children	Serotype 19A
Simoes *et al.*, 2011 [27] Portugal	Three non-PCV7 serotypes were found following widespread use of PCV7	Serotype 15A, 19A, 24F
Munoz-Almagro et al., 2008 [28] Spain	Disease incidence caused by non-PCV7 serotypes increased by 72%	Serotype 1, 5, 6A, 19A

PCV: Pneumococcal vaccine

Table 4: Antibiotic resistance in some vaccinations

Study	Setting	Effects
Karnezis *et al.*, 2009 [30]	US	The proportion of penicillin-non-susceptible strains increased from 27% to 49% after PCV-7 vaccination
Kyaw *et al.*, 2006 [31]	US	Among children under 2 years of age and persons 65 years of age or older, disease caused by penicillin-non-susceptible strains decreased 81% and 49%, respectively, after PCV-7 vaccination
Talbot *et al.*, 2004 [32]	Tennessee	The proportion of penicillin-non-susceptible disease isolates from the children younger than 2 years group declined from 59.8% to 30.4% after pediatric PCV-7 vaccination

PCV: Pneumococcal vaccine

limitations such as dynamic models require good understanding of the infection process and are usually more complex than static models, require a large amount of data to support model assumptions, as well as the parameterization of the dynamic model may be difficult [5,16].

Most study only explore the benefit of herd immunity effect and only few that also explore other externalities such as serotype replacement and antibiotic resistance. The effect of serotype replacement in increasing non-vaccine serotype disease, though significant, is puny in comparison to the decrease of disease due to vaccine serotype [14]; probably that the reason of pharmacoeconomic studies of vaccination did not concern much on serotype replacement effects. The effects of vaccination on antibiotic resistance require information such as data on the speed of resistance development at different levels of vaccination coverage and disease incidence; those data may not be currently available [5]. In addition, antibiotic resistance can give both positive and negative effect that might be comparable hence resulting non-significant effect to the benefit of vaccination.

Results from pharmacoeconomic studies of vaccination capturing externalities (indirect effect) mostly gave favorable cost-effectiveness ratio compare to study including only direct effect. Accounting for indirect effects of vaccination leads to decrease costs and increase outcomes, hence decrease the incremental cost-effectiveness ratio (ICER). Health administrators should pay more attention to vaccination program that the result is sensitive to both direct and indirect effects of vaccination.

CONCLUSION

There are three most common types of vaccination externalities being issues in the literature, namely: Herd immunity, serotype replacement,

Table 5: Pharmacoeconomic studies capturing vaccination externalities

Study and setting	Type of vaccine and model	Effects/results
Trotter *et al.*, 2006 [16] UK	MCV (dynamic)	Taking the herd immunity into account resulted 3 times greater benefits than the direct benefits alone
Lopez *et al.*, 2007 [33] Argentina	Hepatitis A (dynamic)	The vaccination program would be cost-savings to society and can be achieved even at 70% vaccination coverage
Pradas-Velasco *et al.*, 2008 [34] Spain	Influenza (dynamic and static)	The indirect effect of vaccination on the non-vaccinated individuals (the herd immunity effect) is greater than the direct effect on individuals vaccinated. The impact of vaccination was efficient when employing a dynamic approach and was not if using static approach
Anonychuk *et al.*, 2009 [35] Canada	HPV (dynamic)	The inclusion of herd immunity reduced the cost per QALY gained by 12-31%. The cost per QALY gained was less sensitive to changes in parameter values when herd immunity was included in the model
Jit *et al.*, 2009 [36] Five European - countries	Rotavirus (dynamic and static)	Incorporating the effect of possible indirect protection had a moderate impact on the cost-effectiveness ratio in all the countries; in some countries, it improved the cost-effectiveness ratios to be nearly favorable
Kim *et al.*, 2010 [37] Gambia	PCV (static)	Less immunity waning and serotype replacement as well as more herd immunity will decrease the ICER (improve the cost-effectiveness favorability)

MCV: Meningococcal vaccine, HPV: Human papillomavirus vaccine, PCV: Pneumococcal vaccine

and antibiotic resistance. Herd immunity gives positive effects to the benefit of vaccination, the opposite of that of serotype replacement; while antibiotic resistance could give either positive or negative effects to the benefit of vaccination. Most emergence of serotype replacement occurred after PCV vaccination. Most of pharmacoeconomic studies of vaccination used dynamic models to capture vaccination externalities which often included only herd immunity effects. Taking herd immunity into account in pharmacoeconomic studies tends to increase the outcomes and reduce the cost; hence, the cost per outcome or ICER will decrease, resulting more favorable cost-effectiveness ratio.

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