Original Article

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Setting priorities for introducing new vaccines into the national immunization program; a systematic review

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Abstract

This study aimed to review criteria to support decision-making on national immunization programs. A systematic review was conducted for publication during 2000-February 2016 from three major databases including PubMed, the Cochrane Library, and Scopus. Manual search from cited references and websites were also used. Inclusion criteria were theoretical concepts of new vaccine introduction and decision making tool of vaccine introduction. Exclusion criteria were clinical guideline of specific vaccines or diseases, research on vaccine development or laboratory test, proceedings, and articles not in English. Five articles were found. The criteria for a decision-making for new vaccine introduction included technical criteria, programmatic and operational criteria, and qualitative criteria. Technical criteria included epidemiology, vaccine effectiveness and safety, and economic evaluations. Programmatic and operational criteria included vaccine availability, feasibility to incorporate into the existing program, and logistics. Public health criteria e.g. public acceptance, equity, politic, policy was also considered. Although the criteria of a vaccine introduction seem similar among articles but the frameworks were different in details and weighted factors due to specific context. These analytical frameworks were useful in decision-making process but did not allow prioritization of new vaccines at the same time. However the basic criteria and evaluation methods could be applied to fit local setting in individual country.

Keyword: priority, vaccine, Immunization

1. INTRODUCTION

Vaccination has been one of the most effective interventions to decrease mortality and morbidity due to infectious diseases, e.g. diphtheria, tetanus, polio, influenza. Mass immunization program have reported in eradication of smallpox, elimination of diphtheria and polio[1]. Early vaccination programs have shown the effectiveness and cost-saving in children[2]. This success of vaccine is threatened by several factors, e.g. research and development in vaccinology, investment and potential market of vaccine. The common obstacles to new vaccine introduction include affordability, manufacturing capacity, accessibility and quality assurance[3].

The introduction of new vaccine depends on various aspects, including policy, regulation, clinical guidelines, expert recommendations, clinical efficacy, and economic evaluation. Heterogeneity of concerns for setting priorities still remain, e.g. burden of disease, effectiveness, safety, acceptability, equitability, implementation[4]. Analysis of these data can facilitate the comparisons of vaccines by informing their costs and benefits. Thus setting priorities for vaccine is essential to facilitate analysis for public health benefit, especially in resource-limited countries[4]. Several guidelines for setting priorities of health research are available but few of them are applicable for vaccines[5, 6]. Vaccines differ in the strength of evidence supporting, the extent of improving health, and economic value to various stakeholders. Vaccines also have special considerations when assessing their cost-effectiveness, including herd immunity, quality of life lost in young children, parental care and productivity lost, nonfinancial

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economic burden, uncertainty, eradication rate, macroeconomics, and tiered pricing[7].

This study aimed to review criteria to support decision-making on national immunization programs.

2. MATERIALS AND METHODS

Systematic review was used to summarize evidence and information for vaccine introduction from all relevant publications. It was needed when there was a substantive question, several primary studies and substantial uncertainty. It differs from a traditional review in a rigorous systematic approach. It also seeks to identify all relevant data, select studies for inclusion, and synthesis the findings[8]. In this study, the articles were systematically reviewed through three major medical databases including PubMed, the Cochrane Library and Scopus. PubMed includes the MEDLINE database; the Cochrane Library contains high-quality, and independent evidence to inform healthcare decision-making; and Scopus includes database of peer reviewed literature and quality web sources. These databases are well-known and reliable sources that cover a wide range of healthcare information.

Numerous combinations keywords were used as follow; vaccine, immunization, and prioritization. Search terms included vaccin*, immun* and priorit*. For an unbiased assessment, selected journals were hand-searched when necessary and some relevant references of full-text articles were searched. Websites of relevant organizations were also searched. A systematic review was followed PRISMA Statement[9]. The PRISMA Statement focuses on ways in which authors can ensure the transparent and complete reporting of systematic reviews. Inclusion criteria included theoretical concepts of vaccine introduction, decision making on vaccine introduction, evidence-based of vaccine introduction, and development of national immunization policy published during 2000-February 2016. Clinical guideline or recommendations of specific vaccines or diseases, research on vaccine development or laboratory test, proceedings, and articles not in English were excluded.

The articles were identified through the database search, each of the titles and abstracts of articles. The articles were assessed for eligibility against inclusion criteria. Any article that was considered to be relevant was included for full-text review. For each included articles, information was extracted regarding criteria for vaccine introduction, country, strength, and weakness. We reviewed and compiled all relevant criteria to be taken into consideration for vaccine introduction. The quality of each article was determined by providing the following criteria; 1) clearly reported objectives, 2) adequately described the context and methods in which the research was carried out, 3) the reliability of data collection and analysis, and 4) providing general recommendations for vaccine introduction and supporting evidence-based decision-making on national immunization program.

3. RESULTS

Six hundred and forty-two articles were found from the searching through selected keywords. Search results are shown in Figure 1. Five articles met criteria and were included in this review. Table 1 shows the details, strength and weakness of five articles. Then we synthesized and categorized the criteria for a decision-making for vaccine introduction into 3 major criteria including technical criteria, programmatic and operational criteria, and public health criteria (Table 2). Technical criteria included epidemiology, vaccine effectiveness and safety, and economic evaluations. Programmatic and operational criteria included vaccine availability, feasibility to incorporate into the existing program, and logistics. Public health criteria e.g. public acceptance, equity, politic, policy was also considered. A more detailed description of the five articles is given below:

In Canada, Erickson, *et al* (2005)[10] developed an analytical framework to assist the analysis and comparison of potential immunization programs. The framework included 58 criteria classified into 13 categories, including burden of disease, vaccine characteristics and immunization strategy, cost-effectiveness, acceptability, feasibility, and evaluability of

Table 1. Details of frameworks

Authors	Country	Detail	Strength	Weakness
Erickson, *et al* (2005)[7]	Canada	A framework included burden of disease, vaccine characteristics and immunization strategy, cost-effectiveness, acceptability, feasibility, and evaluation of program, research questions, equity, ethical, legal, and political considerations.	The burden of disease, safety, and efficacy were an important factor.	The demand from population for a new program was a powerful drive for decision-makers.
Kimman, *et al*(2006)[5]	Canada	A framework included 72 questions on vaccine safety and effectiveness, pathogen, disease, and cost-effectiveness of the vaccine were determined.	The Basic Priority Rating Score was calculated.	- This score assigned more weight on vaccine safety. - The rating of score depended on many factors, e.g. perceived risk of disease, knowledge about vaccine, controversies on acceptance
Gilca, *et al* (2008)[8]	The Netherlands	A set of 46 questions was categorized into five statements relating to 1) immunization usefulness, 2) vaccine effectiveness, 3) vaccine safety, and 4) vaccine acceptance by vaccinators and by the public.	- A cost-effectiveness analysis had an important role. - The principle of 'first do not harm' was seriously taken into consideration, both scientifically and ethically.	- Qualitative parameters may play decisive role in the final judgment, e.g. public anxiety - Public perception and trust is a top priority.
Houweling, *et al* (2010)[9]	The Netherlands	A framework included 15 criteria included seriousness and extent of the disease burden, vaccine effectiveness and safety, acceptability of the vaccination, efficiency of the vaccination, and priority of the vaccination.	- The best possible protection should be afforded to a whole population. - Benefit should be fairly distributed across population groups	- Priority should be given to the vaccination that serves the most urgent public health need or has a greater disease burden. - Application of the criteria requires considerable skill.
Piso, *et al* (2011)[10]	Not specify	A stepwise framework included 1) research questions, public health problem, 2) disease, vaccine, and cost-effectiveness analysis, 3) acceptability, feasibility, equity, ethical, legal, political, and potential side effects, 4) decision, implementation, surveillance, and revision.	- Complete and logical information. - All relevant factors are considered and addressed. - Systematic and evidenced-based approach.	- A tool could be weaker than political and economic rationalities. - Different stakeholders may weigh the factors differently. - No pre-defined or cut-off limits of criteria.

Table 2. Criteria for vaccine introduction

Technical criteria	Programmatic and operational criteria	Public health criteria
Disease burden	Vaccine characteristics	Policy issues
Effectiveness	Demand-supply	Social concerns
Vaccine safety	Acceptability	Political concerns
Economic evaluation	Logistics and infrastructure Financing	Ethical concerns

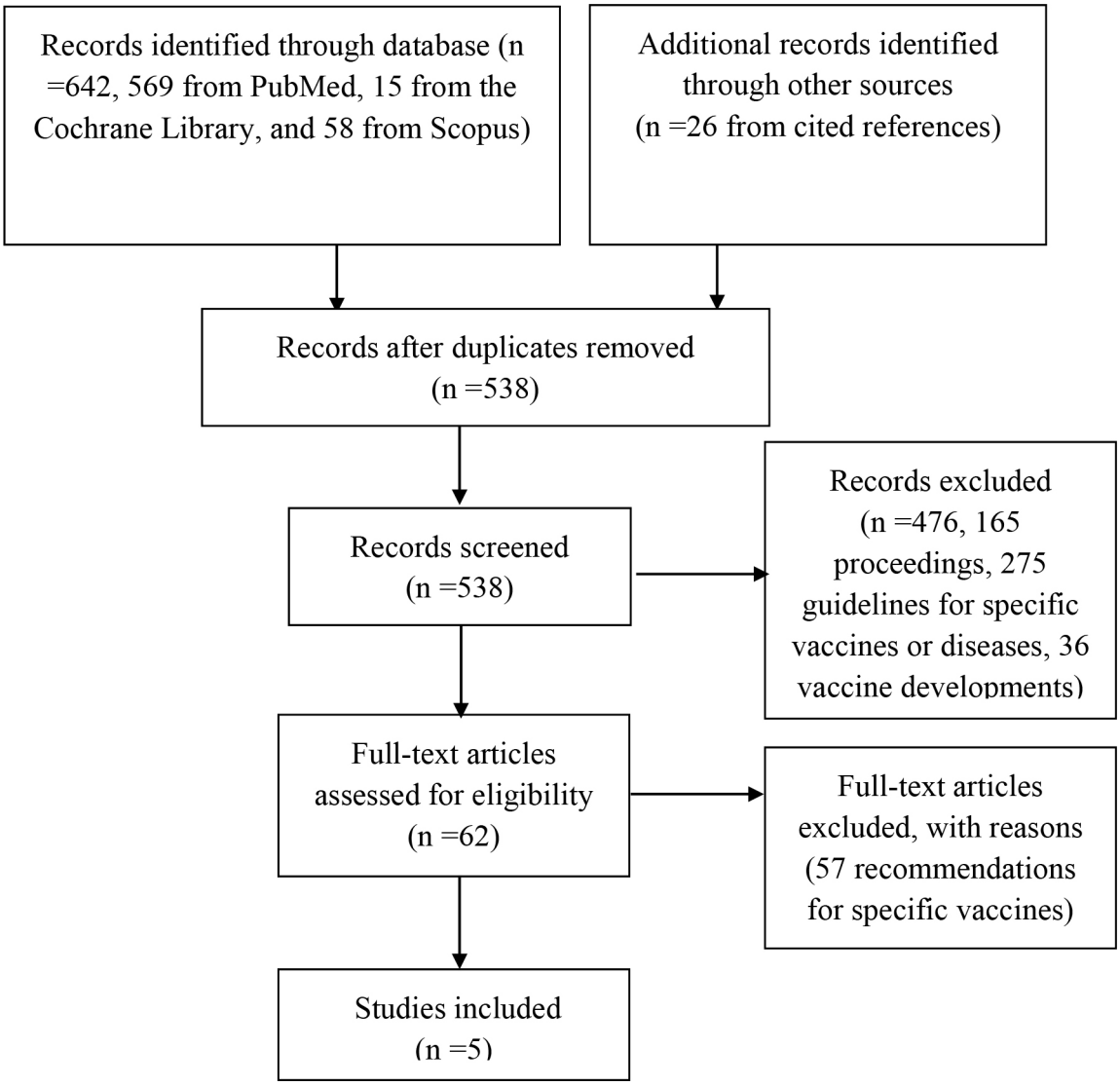

Figure 1. Search result

program, research questions, equity, ethical, legal, and political considerations. The burden of disease was an important factor to set priorities. Efficacy and safety were the main criteria in the initial evaluation of new vaccine and must be evaluated consequently. It was easier to adopt a new vaccine that can combine with an existing vaccine or administer in the same time as another vaccine. The demand from population for a new program was also a powerful drive for decision-makers. In 2008, Gilca, *et al*[6] assessed the opinions of public health professionals about routinely recommended vaccine and new vaccine. The Basic Priority Rating System (BPRS) was calculated by a set of criteria including immunization usefulness, safety and effectiveness of vaccine, and vaccine acceptance by vaccinators and by the public using a four-point Likert scale. The formula of BPR was A((B+2C)/3)D; where A was score of immunization program usefulness; B was score of vaccine effectiveness; C was score of vaccine safety; D was score of vaccine acceptance by public multiplied by accpetance of vaccinators. This formula assigned more weight on vaccine safety as the reseracher percieve its impact on the final decision about vaccine implementation comapared to vaccine effectiveness. The rating of vaccination program depended on many factors, e.g. percieved risk of disease, knowledege about vaccine, contoversies that may affect vaccine acceptance. High scores for the combined vaccine were detected because of convenience to administer while vaccination in elderly, e.g. influenza vaccine, had low score because of safety issues.

In the Netherlands, Kimman, *et al* (2006)[3] assembled a checklist from a multidisciplinary team. Seventy-two questions pointed to the information on vaccine safety and effectiveness, pathogen, disease, and cost-effectiveness of the vaccine. A cost-effectiveness analysis had an important role for quantitative information. Specific or qualitative parameters that could not be incorporated into cost-effectiveness analysis model may play a role in the final judgment, e.g. public anxiety, and public confidence. Public perception and trust in national immunization program was top priority because they yielded the high coverage rates that could reduce incidence rate of infection. As national immunization program may tailor to age, life style or other risk factor, a surveillance program should monitor coverage, shift in spreading of pathogen, long-term safety, and effectiveness. In 2010, Houweling, *et al*[11] described the experience in developing a systematic framework for assessing a vaccine into immunization program. Five criteria were seriousness and extent of the disease burden, effectiveness and safety of the vaccination, acceptability of the vaccination, efficiency of the vaccination, and priority of the vaccination. The standards of effectiveness and safety of vaccine must be higher than therapeutic drugs. The acceptability of a vaccination was determined by the discomfort for children and their parents. The fairness of the distribution across population groups and shifts in pattern of diseases after vaccination was introduced should be considered. Data on costs, benefits, and positive and negative health outcomes was necessary to examine cost-effectiveness analysis, cost-utility analysis. Priority should be given to the vaccination that had a greater disease burden or serves the most urgent public health need, measured as the greatest health benefits at reasonable individual and societal costs. The decision was based on subjective parameters and consensus.

Based on opinion of international experts, Piso, *et al* (2011)[12] established a stepwise framework which supports decisions concerning rational vaccine introduction in industrialized countries and assessed cut-off limits for those criteria. Criteria to be assessed had 7 steps. Steps 1 were research questions, alternative strategies, public health problem, conformity of programs, and scientific uncertainties. Steps 2 and 3 were disease, vaccine, and cost-effectiveness analysis. Steps 4 were considerations on acceptability, feasibility, equity, ethical, legal, political, and potential side effects. Steps 5 to 7 were decision, implementation, surveillance, and revision. Burden of disease, vaccine, side effects and ethical considerations were considered to be most important.

4. DISCUSSION

Five articles were developed in developed countries (Canada and the Netherlands) which may influence transferability due to specific considerations. Although the criteria of vaccine introduction seem similar, the frameworks are incomparable because of different in details and weighted factors. The grouping of relevant criteria also varies in detailed analysis. This may be explained by different development backgrounds, methods and work objectives. These analytical frameworks are useful in decision-making process but do not allow prioritization or comparisons of vaccines at the same time. Even though the same framework is used but differences in demographic, geographic, cultural, and policy may result in different immunization policy. Moreover the national immunization programs are also influenced by political and public opinion that may not reflect health care priorities. Many decisions have to be made when not all important information is available.

The frameworks combine both qualitative and quantitative criteria but there are no pre-defined or cut-off limits of criteria. Thus the quantitative data for priority setting is lacking. The application of the framework requires considerable skill and subjectivity approach to reach a consensus. Thus the decision to adopt a vaccine is likely to vary case by case and country by country. Moreover different stakeholders may weigh the factors differently. At the time, no international standard for assessment of vaccine is available. However the basic criteria and evaluation methods could be applied to fit local setting in individual country.

In the same country, there are different frameworks because there are many working groups for evaluating the vaccine criteria. For example, in Canada, there are the National Advisory Committee on Immunization and the Canadian Task Force on the Periodic Health Examination for evaluating new vaccines in different regions[10]. In the Netherlands, there are the National Immunisation Programme Review Committee of the Health Council and the National Institute of Public Health and the Environment for inclusion of vaccination[11, 12]. The working groups developed the criteria by themselves. They take into consideration a different set of criteria. The frameworks are incomparable but the major criteria are almost the same criteria including disease burden, vaccine characteristic, vaccine safety and effectiveness, and acceptability. Thus these criteria are categorized into 3 major criteria as shown in Table 1.

Economic analysis alone is insufficient to provide a recommendation to policy makers where equity concerns are present[13]. The influence of economic evaluations on healthcare decision-making seems to exist in a limited extent[14]. Political, policy, legal, and regulatory arguments may has a major influence in some countries. Barriers to use economic analysis include methodology, applicability, and credibility. Therefore, there is a need to carefully consider social, ethical and moral dimensions of vaccine beyond its immediate economic benefits.

Budget impact is also an essential part of estimating the financial consequences of adoption new vaccines. Budget impact can be useful in budget planning, forecasting and for estimating the impact of new vaccine adoption on health system. Whereas cost-effectiveness analysis assess the economic efficiency of vaccine over a specified a time horizon, and budget impact assess for affordability[15].

Equity or fairness in health attempts to reduce or minimize health disparities that are avoidable and unfair between social groups[16, 17]. Equity issues are the most problematic consideration in health prioritization because of multi-factorial issues and complexity to handle satisfaction of all stakeholders[16]. Sometimes public perceptions or urgent health problems are the most important factor for adopting new vaccines. Thus other public health criteria, e.g. policy, politics, equitability, social concern, should also be taken into consideration.

The basic criteria from this review can be applied to other country. In Thailand, the introductions of new vaccines are authorized by the Ministry of Public Health with recommendation established by the Thai Advisory Committee in Immunization Practice (ACIP). Factors and

evidence considered by the ACIP in developing immunization policy include policy issues (e.g. public health priority, disease burden, economic issues, vaccine safety and efficacy) and programmatic issues (e.g. strength of existing expanded program on immunization, vaccine availability)[18]. There is no specific method for developing recommendations by the ACIP. In some cases where data are inadequate, the opinion of ACIP members or other experts are used to make recommendations[18]. The ACIP members will consider the information until a consensus is reached. Thus a framework that helps judging all relevant data is necessary for making a decision of vaccine introduction.

5. CONCLUSION

The analytical frameworks were developed by different groups of researchers or public health professionals. The major criteria are almost the same criteria including technical criteria, programmatic and operational criteria, and public health criteria. They are useful in decision-making process but did not allow prioritization of new vaccines at the same time. However the basic criteria and evaluation methods could be applied to fit local setting in individual country.

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REFERENCES

1. Muzamdar JM, Cline RR. Vaccine supply, demand, and policy: a primer. J Am Pharm Assoc. 2009;49:e87-e99.
2. Ortega-Sanchez IR, Lee GM, Jacobs RJ, *et al.* Projected cost-effectiveness of new vaccines for adolescents vin the United States. Pediatrics. 2008;121(Supplement 1):s63-s78.
3. Kimman TG, Boot HJ, Berbers G, *et al.* Developing a vaccination model to support evidence-based decision making on national immunization programs. Vaccine. 2006;24: 4769-4778.
4. Houweling H, Wittevrongel C, Verweij M, *et al.* Public vaccination programmes against hepatitis B in The Netherlands: Assessing whether a targeted or a universal approach is appropriate. Vaccine. 2010;28:7723-7730.
5. Viergever RF, Olifson S, Ghaffar A, *et al.* A Checklist for health research priority setting: nine common themes of good practice. Health Res Policy Syst 2010;8: 36-44.
6. Gilca V, Sauvageau C, McNeil S, *et al.* Setting priorities for new vaccination programs by using public health officers and immunization managers opinions. Vaccine. 2008;26:4204-4209.
7. Beutels P, Scuffham PA, MacIntyre CR. Funding of drugs: Do vaccines warrant a different approach? Lancet Infect Dis. 2008; 8:727-733.
8. Hemingway P, Bereton N. What is a systematic review? 2009 [cited 2016, January 9]; second edition: [Available from: http://www.medicine.ox.ac.uk/bandolier/painres/download/whatis/syst-review.pdf.
9. Moher D, Liberati A, Tetzlaff J, *et al.* Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. Ann Intern Med. 2009;151: 264-269.
10. Erickson LJ, De Wals P, Farand L. An analytical framework for immunization programs in Canada. Vaccine. 2005;23: 2470–2476.
11. Houweling H, Verweij M, Ruitenberg EJ. Criteria for inclusion of vaccinations in public programmes. Vaccine. 2010;28: 2924-2931.

12. Piso B, Zechmeister I, Geiger-Gritsch S. Criteria for vaccine introduction: results of a DELPHI discussion among international immunisation experts on a stepwise decision-making procedure. J Public Health. 2011; 19:73-80.
13. Leelahavarong P, Chaikledkaew U, Hongeng S*, et al.* A cost-utility and budget impact analysis of allogeneic hematopoietic stem cell transplantation for severe thalassemic patients in Thailand. BMC Health Serv Res. 2010;10:209-220.
14. van Velden M, Severens J, Novak A. Economic evaluations of healthcare programmes and decision making: The influence of economic evaluations on different healthcare decision-making levels. Pharmacoeconomics 2005;23(11):1075-1082.
15. Mauskopf J, Sullivan S, Annemans L*, et al.* Principles of good practice for budget impact analysis: Report of the ISPOR Task Force on good research practices-budget impact analysis. Value Health. 2007;10(5):336-347.
16. Olusanya B. Global health priorities for developing countries: some equity and ethical considerations. J Natl Med Assoc. 2008;100(10):1212-1217.
17. Jehu-Appiah C, Baltussen R, Acquah C*, et al.* Balancing equity and efficiency in health priorities in Ghana: the use of multicriteria decision analysis. Value Health 2008;11(7):1081-1087.
18. Muangchana C, Thamapornoilas P, Karnkawinpong O. Immunization policy development in Thailand: The role of the Advisory Committee on Immunization Practice. Vaccine. 2010;28S:A104-109.