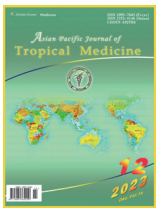

Perspective

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Developing an evaluation model to support evidence-based decision-making on provincial vaccination program of Zhejiang province

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Vaccines are considered as one of the most cost-effective interventions to improve the global public health by reducing mortality and morbidity[1]. At an ever-increasing pace, new vaccines are being developed and licensed in China, driven by initiatives from both domestic and international vaccine companies. New vaccines are evaluated by Chinese Advisory Committee on Immunization, which makes decisions regarding the use of vaccines based on the epidemiological context in China. Some of these vaccines are included in the Chinese Expanded Program on Immunization (EPI) and are provided at no cost to specific target groups, while others are considered as voluntary vaccines and are offered as "self-paid" services[2]. Additionally, expert committees at the provincial level may also make recommendations for vaccination or guidelines for vaccination staff and decide which vaccine should be purchased using public fund or provided free of charge to target populations.

In many cases, vaccination programs must adapt or evolve in response to changes such as the emerging or re-emerging infectious diseases, the decline or disappearance of certain infectious diseases, new insights into epidemiological or immunological factors, changes in population immunity, rapid development of higher quality vaccines, vaccine availability, and financial resources[3-5]. Therefore, it is essential to establish an evaluation model for evidence-based decision-making regarding the future development of vaccination programs. This will significantly enhance the health status of populations in a cost-effective way. However, up to now, there have been no standardized evaluation models at the provincial level, leading to negative consequences for the uniformity and fairness of vaccination programs in China.

Zhejiang, a relatively developed province in eastern China, has a population of 70 million. The province initiated the EPI in 1978 with four vaccines and the number of vaccines has since increased to 11, with approximately 20 million doses vaccine administration annually.

Based on previous guidelines and similar approaches, we have developed an analytical framework to assess the geographical, demographic, cultural and political factors that influence decision-making in vaccination programs.

First, we assembled a multidisciplinary team of 29 experts in Zhejiang province, including microbiologists, immunologists, epidemiologists, experts in vaccine safety, and health economists.

Second, a self-designed questionnaire was distributed to the experts, seeking their insights on the most significant factors impacting decision-making for publicly-funded vaccination programs. The questionnaire also requested information on the structures and processes for program planning.

Upon receiving the completed questionnaires, we entered the responses representing potential decision-making criteria into an Excel database. Duplicate descriptions of the same criteria or concept were removed.

Subsequently, the list of 67 distinct criteria, grouped into 11 categories, was returned to the same experts for validation. Specific criteria lacking data were identified as uncertainties in decision-making and were highlighted as areas for future research. The final version of the framework is presented in Table 1.

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Table 1. Checklist of criteria included in the analytical framework for evaluating vaccination program at provincial level.

Items	No.	Criteria
1. Pathogen	1)	Nature and characteristics of the pathogen including reservoirs, routes of transmission, and pathogenic mechanisms.
	2)	Incubation period, symptomatic infection, carriership of the pathogen.
	3)	Variation in pathogenicity and antigen.
	4)	Vaccination induced evolutionary pressure leading to the emergence of antigenic or virulence variants.
	5)	The percentage of symptomatic infection, the clinical manifestations and complications of symptomatic infection.
2.Burden of disease	6)	Epidemiology of the disease, including the incidence, secular trends, seasonal and geographic variations, clustering of cases.
	7)	Sub-populations with higher incidence or more severe forms of disease, as well as the risk factors.
	8)	Current disease treatment and preventive measures rather than vaccination.
	9)	Health impact among the population, including frequency of cases, of deaths, loss of quality of life expressed in quality-adjusted life-years or disability adjusted life years.
	10)	Social impact of the disease, including intensity of suffering, frequency of survivors with sequelae, reduction of quality of life, long-term disability, impact on families/caregivers, fear of disease, stress on society.
	11)	Economic impact of the disease, including direct and indirect costs to patients or families, productivity losses, health service utilization and costs to the health system.
3. Availability of vaccine	12)	Candidates of vaccine for the new vaccination program.
	13)	Characteristics of the products (preparation, stabilizing agents and preservatives, dosage, combination, storage, handling, *etc*).
	14)	Vaccine manufactures' capacity of production and the availability of vaccine and long-term supply.
	15)	Availability of funding for vaccine purchase.
	16)	Target population for vaccination.
4. Vaccine characteristics	17)	Nature and characteristics of agent in vaccine (live attenuated, killed, absorbed/non-absorbed, *etc*). Contraindications and precautions.
	18)	Immunization schedule, number of doses and the interval between doses.
	19)	Nature and characteristics of immune response.
	20)	Immunogenicity in different sub-groups.
	21)	Short and long-term vaccine immunogenicity, efficacy, effectiveness.
	22)	The expected duration of protection.
	23)	Effect on the transmission (reduction in carriage rate).
	24)	Interference with other vaccines or vaccine components.
	25)	Risk groups for primary vaccine failure.
	26)	Incidence of adverse reactions, severity of adverse reactions.
	27)	Risk groups or risk factors for adverse reactions.
5. Strategy	28)	Existing recommendations/guidelines for use of the vaccine in other jurisdictions or countries.
	29)	Existing goals of disease control, elimination, or eradication in other jurisdictions or countries.
	30)	Alternative vaccination strategies and programs for meeting goal.
	31)	Potential impact of the new vaccination program on resistance to antibiotics and antivirals.
	32)	Specific program objectives in terms of reduction of incidence, complications, sequelae and mortality.
	33)	Expected vaccination coverage rate that sufficient to reach herd immunity.
	34)	Specific operational objectives in terms of coverage for different target groups, and vaccine wastage.
6. Cost-effectiveness	35)	The costs of available vaccines.
	36)	In a societal perspective, the total and opportunity implementation costs of the new vaccination program, including the direct and indirect costs for families and the health system.
	37)	The short- and long-term use of health care of infected individuals.
	38)	The costs associated with short- and long-term health care of infected individuals.
	39)	The magnitude or cost of school/work absenteeism of infected individuals.
	40)	The magnitude or cost of work absenteeism of parents and caretakers of infected individuals.
	41)	Evidence on the short- and long-term effectiveness, including reduction in morbidity, complications, sequelae and mortality.
	42)	Evidence on benefits including reduction in health care costs, improvement in life expectancy, in quality of life and productivity gains
	43)	Other indirect benefits such as reduced microbial resistance or outpatient/emergency room visits.
	44)	Costs, benefits, quality-adjusted life-years or disability adjusted life years saved by the new vaccination program or other alternative preventive measures.
	45)	Net present costs and cost-benefit ratios (societal perspectives) compared with other alternative strategies or other health care interventions, evaluation of robustness of economic model using sensitivity analyses, pertinence for local settings.
7. Social acceptability	46)	Public perception of disease risk, severity fear and demands for control and prevention.
	47)	Acceptability of the new vaccination program among target groups, health professionals and political authorities.
	48)	Priority for the new vaccination program with respect to other potential or approved programs.

Table 1. Continued.

Items	No.	Criteria
8. Feasibility	49)	Possibility of integration of the new vaccination program with existing vaccination programs and schedule.
	50)	Impacts of the new vaccination program on existing vaccination services and other health care sectors.
	51)	Accessibility of target population and expected vaccination coverage.
	52)	Availability of human, technical and financial resources for implementing the new vaccination program.
	53)	Availability of system for recording/registering vaccine administration.
	54)	Availability of resources for communication to the public, information and training of vaccination staff.
9. Ability for evaluation	55)	Desirability of evaluation to families, health professionals and political authorities.
	56)	Availability of information system to monitor the vaccination coverage and vaccine utilization, quality of vaccination service.
	57)	Availability of surveillance system for evaluating the reduction of morbidity, complications, sequelae, and mortality.
	58)	Availability of surveillance system for evaluating adverse reaction following vaccination.
	59)	Availability of systems for linking health outcomes databases, vaccination registries and population registries.
10. Other considerations	60)	Equity of the new vaccination program including universality, accessibility and gratuity of services for the most vulnerable groups.
	61)	Ethical considerations including informed consent and protection of confidentiality.
	62)	Conformity of the new vaccination program with the existing programs in other jurisdictions or countries.
	63)	Potential political benefits and risks with the new vaccination program.
	64)	Legal considerations concerning the use of vaccines.
11. Research questions in future	65)	Main uncertainties concerning the effect of vaccine and impacts of the implementation of the new vaccination program.
	66)	New research projects in the fields of immunogenicity, efficacy, effectiveness and safety of the vaccine.
	67)	Research to assist evaluation, planning and decision-making regarding the new vaccination program to meet the specific needs in a timely manner.

The primary goal of a vaccination program is to reduce the burden of disease morbidity and mortality in a cost-effective manner by collecting and evaluating information from various fields. As impact factors and their degrees are sometimes unknown, the vaccination program should be updated and re-evaluated regularly.

In a proposing vaccination program, scientific data may not always be the most reliable evidence for decision-making. Factors such as political pressure, public anxiety, and lack of financial resources rather than objectively assembled scientific and economic data. Other crucial considerations include the pathogen involved, disease burden, vaccine characteristics, cost-effectiveness analysis results, social acceptability, and the feasibility and capacity of service.

Cost-effectiveness analysis plays a pivotal role in the decision-making process of public health programs. It determines the necessity of funding a program with quantitative evidences, effectively promoting heath equality[6]. Cost-utility analysis is an economic technique that expresses the utility of health care in QALYs[7]. The health output, cost, and future health gains should be considered in these analyses.

Currently, there is no standard methodology for these analyses. Small health improvement in a large group of people may bring similar QALYs gained by an intervention to reduce the death of a very small number of people. Many people think that preventing severe or life-saving disease merits highest priority, although often no consensus can be reached when specific choices have to be made. Some of these analyses neglect the herd immunity and dynamic model of infectious disease, while others take these factors into consideration. Additional determinants of the cost-effectiveness analyses include whether an additional year of life has the same value regardless of the target population's age, and whether the intangible cost and benefits should be considered[8]. However, the selection of parameters in a cost-effectiveness model may not always be the decisive factor for the final decision.

The reasons for including a vaccine in a vaccination program may vary widely. For example, the acellular pertussis vaccine was introduced in some countries due to is improved safety compared to whole cell vaccines[9]. The polio vaccine is focused on eradicating the virus, while the influenza vaccination aims to reduce the incidence of disease and severe complications[10]. Polio vaccination thus has a greater public health impact than influenza vaccination, despite the significant medical burden associated with influenza infection. It is important to note that there is usually no conflict of interest between general and individual interests in designing the vaccination program. However, exceptions may exist when a very expensive vaccine is being paid to benefit a few instead of obtaining a cheaper vaccine that could cover a larger population.

When selecting a specific vaccine, long-term and consistent supply and availability should be taken into account, especially during outbreaks or epidemics[11]. Domestic vaccines would be a better choice for vaccination program since it reduces the risk of short-

supply of vaccines but some may doubt the qualities of domestic vaccines and the potential conflict of interests should be avoided[12].

The vaccination program may require a balance between epidemiological, economic factors, and practical considerations. Different vaccines require different immunization schedules to achieve the optimal protection efficacy[13]. For practical and economic considerations, a good "average" schedule for combined administration should be chosen, though it may not be the optimal choice for each single antigen.

To achieve a higher coverage rate for establishing herd immunity, vaccination programs are often obligatory or implemented under psychological pressure. However, this "one-size-fits-all" principle may not always be feasible as the number of vaccines increases in the program. The interests of general and individuals should be fully considered. These vaccines may be offered without making them obligatory or advised with a lower priority[14-16]. For example, influenza in healthy children is usually not considered as a significant problem. However, bacterial complications, infections outside the respiratory tract, acute otitis media, and bronchiolitis following influenza can lead to a high hospitalization rate in children under 2 years of age. Therefore, infants aged 6-23 months, children with recurrent acute otitis media or respiratory tract infection, and children attending day-care centers or elementary schools have been recommended for influenza vaccination with high priority. If this trend continues, vaccination programs should be tailored to age, life style, or other individual risk factors.

Ensuring the public's confidence is crucial for the sustainable development of the vaccination program[17]. The importance of trust in the vaccination program and its vulnerability has been shown in many countries. In UK, the coverage rate of combined measles, mumps and rubella vaccine fell from $\geqslant$90% to <80% after rumors that the vaccine might cause autism[18] and the incidence of measles and mumps rose. Similarly, declined trust in the vaccination program caused a drop in coverage rate and an approximately 100-fold rise in the incidence of pertussis in the United States[19]. The number of injections given to a person at one visit should be limited to ensure the high coverage rate since increased number of injections may cause the concern on "vaccine overloaded". However, to the best of our knowledge, no evidence has shown that antigenically overloaded immune system can be induced by multiple immunizations simultaneously. Actually, simultaneous vaccination is acceptable and encouraged by WHO and other professional institutions[20-22]. However, most physicians have the strong concerns about administering 3 injections for anybody at one visit. Continued education and reassurance addressing the concerns on simultaneous vaccination should therefore be directed to physicians.

As an alternative to a comprehensive vaccination program, the Chinese government offers a national vaccination program directed to diseases with the greatest public health impact, together with a voluntary and self-funded package meeting the individual's needs[23]. However, this kind of development may potentially induce the inequalities in use of vaccines, thus setting the task for governments of assuring equal opportunities for vaccination and access to information. Additional advice on vaccination that tailored to the individuals' needs and the administration of the voluntary vaccine can be provided by vaccination clinics.

Complex situations may occur when a vaccine is expensive but cost-effective or when it has an unfavorable cost-benefit ratio. Even though the health burden of a target disease is high, the high cost of a vaccine would prohibit its universal vaccination. Affordable and well-informed individuals may decide to pay these expensive vaccines, resulting in inequalities that is undesirable but perhaps unavoidable.

The long-term effects of the vaccination program should also be considered. There is still limited knowledge on the evolutionary consequences of vaccination, such as unpredictable events, unwanted adverse reactions or insufficient efficacy. Theoretically, vaccination can completely disrupt microbial transmission and thus stop microbial evolution[24]. However, in most situations, vaccination cannot completely halt the disease transmission but accelerates the evolutionary of pathogen. This consequence may include the changes in antigenic composition affecting the vaccine efficacy, or in virulence and transmissibility of the pathogen. In spite of comprehensive pertussis vaccination, the disease is re-emerging worldwide[25]. The emergence of the escape variants has been illustrated as one of the important reasons for its resurgence. Other potential long-term consequences of vaccination program include a shift in age distribution of infection and changes in severity of disease. For example, varicella vaccination in children can reduce varicella-zoster virus circulation, causing waning immunity in the elders and making them more vulnerable for herpes zoster[26]. In fact, the occurrence, direction, and magnitude of these long-term effects are speculative, but they should be considered and estimated as accurately as possible. We recommend that we should implement surveillance for detecting the long-term consequences of vaccination.

After a decision to change the vaccination program, the safety and effectiveness of vaccines should be monitored carefully, not only to evaluate the current status, but also to prepare for future changes[27]. Clinical-epidemiological surveillance is a necessary tool to measure the effectiveness in reducing the disease burden and the temporal trends. Vaccination coverage evaluation is also needed to predicate the acceptance of the program. Regions or sub-populations that have lower vaccination coverage should be identified and timely measures to maintain the herd immunity should be taken. Immune surveillance for monitoring the markers and degree of protection for the target populations can help us detect the waning of immunity and alter

circulation of pathogens. For example, vaccine-induced reduction in measles virus circulation may decay levels of maternal antibodies, demanding a solution to protect the infants earlier[28]. Surveillance of microbial dynamics, resulting from natural or vaccine-driven evolution, can help us know the replacement of a vaccine strain by a better matching prevalent strain. Safety surveillance, such as AEFI surveillance, can allow a comparison between benefits and adverse events of the vaccination program. By comparing the benefits and risks of vaccination, many countries replaced the oral polio vaccine that led to vaccine-associated paralytic polio in rare cases, with safer inactivated polio vaccines[29].

In this analysis, a series of essential questions have been raised and factors which should be analyzed in the planning of publicly-funded immunization programs are presented. The proposed analytical framework may be utilized to implement a new program, or to structure discussions and consensus-building activities in expert committees at provincial or peripheral level. It can also serve as a tool for teaching and public education. This tool can be used in appropriate structures or processes to assistant decision-makers in various contexts and make decisions more efficiently.

Any decision of implementing a vaccination program should be made based on evidence as much as possible, but some consequences of introducing a new vaccine or changing a schedule may not be predictable. A decision on the introduction of a vaccine always brings uncertainties such as antigenic changes, altered microbial interactions, evolutionary consequences, and future economic circumstances, *etc*. However, reducing these uncertainties should be one of the core tasks of vaccination programs. The decision to introduce a vaccine into the vaccination program should be taken seriously, scientifically and ethically. Similarly, removing a vaccine from the existing vaccination program should be more prudently.

Conflict of interest statement

The authors declare that they have no competing interests.

Ethics approval and consent to participate

This study was exempted for ethics approval as it did not contain any personal information and include no human research participants.

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Authors' contributions

YH conceived and designed the experiments; FXC and LLD performed the experiments; YH and FXC analyzed the data; HL and YW contributed reagents/materials/analysis tools; YH wrote the paper.

References

[1] Oliveira CR, Avni-Singer L, Badaro G, Sullivan EL, Sheth SS, Shapiro ED, et al. Feasibility and accuracy of a computer-assisted self-interviewing instrument to ascertain prior immunization with human papillomavirus vaccine by self-report: Cross-sectional analysis. *JMIR Med Inform* 2020; **8**(1): e16487.

[2] Chen F, Pan X, Liang H, Shen L, Wang Y, Chen Y, et al. Real-world safety profile of the 9-valent human papillomavirus vaccine: A study in Zhejiang, China from 2019 to 2021. *Hum Vaccin Immunother* 2022; **18**(7): 2152256.

[3] Erickson LJ, De Wals P, Farand L. An analytical framework for immunization programs in Canada. *Vaccine* 2005; **23**: 2468-2474.

[4] MacDonald N, Embree J. Access to vaccines: A call to action. *Can J Infect Dis* 2003; **14**: 9-10.

[5] Tapia-Conyer R, Betancourt-Cravioto M, Saucedo-Martínez R, Motta-Murguía L, Gallardo-Rincón H. Strengthening vaccination policies in Latin America: An evidence-based approach. *Vaccine* 2013; **31**(37): 3826-3833.

[6] Hubble MW, Renkiewicz GK. Estimated cost effectiveness of influenza vaccination for emergency medical services professionals. *West J Emerg Med* 2021; **22**(6): 1317-1325.

[7] Anderson R, Kim S, Roberts N, Petrou S. Systematic review of economic evaluations of varicella vaccination programmes. *PLoS One* 2023; **18**(3): e0282327.

[8] Jefferson T, Rivetti A, Di Pietrantonj C, Demicheli V. Vaccines for preventing influenza in healthy children. *Cochrane Database Syst Rev* 2018; **2**(2): CD004879.

[9] Alghounaim M, Alsaffar Z, Alfraij A, Bin-Hasan S, Hussain E. Whole-

cell and acellular pertussis vaccine: Reflections on efficacy. *Med Princ Pract* 2022; **31**(4): 313-321.

[10]Shukla VV, Shah RC. Vaccinations in primary care. *Indian J Pediatr* 2018; **85**(12): 1118-1127.

[11]Cohen JUS. Vaccine supply falls seriously short. *Science* 2002; **295**: 1998-2001.

[12]Chowdhury P, Paul SK, Kaisar S, Moktadir MA. COVID-19 pandemic related supply chain studies: A systematic review. *Transp Res E Logist Transp Rev* 2021; **148**: 102271.

[13]Rockwell PG. ACIP approves 2023 child/adolescent and adult immunization schedules. *Am Fam Physician* 2023; **107**(3): 319-322.

[14]Nachbagauer R, Palese P. Is a universal influenza virus vaccine possible? *Annu Rev Med* 2020; **71**: 315-327.

[15]Tanner AR, Dorey RB, Brendish NJ, Clark TW. Influenza vaccination: Protecting the most vulnerable. *Eur Respir Rev* 2021; **30**(159): 200258.

[16]Favato G, Easton T, Vecchiato R, Noikokyris E. Ecological validity of cost-effectiveness models of universal HPV vaccination: A systematic literature review. *Vaccine* 2017; **35**(20): 2622-2632.

[17]Dubé È, Ward JK, Verger P, MacDonald NE. Vaccine hesitancy, acceptance, and anti-vaccination: Trends and future prospects for public health. *Annu Rev Public Health* 2021; **42**: 175-191.

[18]Green MS. Rational and irrational vaccine hesitancy. *Isr J Health Policy Res* 2023; **12**(1): 11.

[19]Phadke VK, Bednarczyk RA, Salmon DA, Omer SB. Association between vaccine refusal and vaccine-preventable diseases in the United States: A review of measles and pertussis. *JAMA* 2016; **315**(11): 1149-1158.

[20]Salman O, Topf K, Chandler R, Conklin L. Progress in immunization safety monitoring-worldwide, 2010-2019. *MMWR Morb Mortal Wkly Rep* 2021; **70**(15): 547-551.

[21]Bauwens J, de Lusignan S, Weldesselassie YG, Sherlock J, Künzli N, Bonhoeffer J. Safety of routine childhood vaccine coadministration *versus* separate vaccination. *BMJ Glob Health* 2022; **7**(9): e008215.

[22]Bauwens J, de Lusignan S, Sherlock J, Ferreira F, Künzli N, Bonhoeffer J. Co-administration of routine paediatric vaccines in England often deviates from the immunisation schedule. *Vaccine* 2021; **9**: 100115.

[23]Yingxiong W. A review of China's compensation program for adverse reactions following immunization. *Front Public Health* 2023; **11**: 1211976.

[24]Miller IF, Metcalf CJE. Assessing the risk of vaccine-driven virulence evolution in SARS-CoV-2. *R Soc Open Sci* 2022; **9**(1): 211021.

[25]Kuchar E, Karlikowska-Skwarnik M, Han S, Nitsch-Osuch A. Pertussis: History of the disease and current prevention failure. *Adv Exp Med Biol* 2016; **934**: 77-82.

[26]Sharomi O, Xausa I, Nachbar R, Pillsbury M, Matthews I, Petigara T, et al. Modeling the impact of exogenous boosting and universal varicella vaccination on the clinical and economic burden of varicella and herpes zoster in a dynamic population for England and Wales. *Vaccines (Basel)* 2022; **10**(9): 1416.

[27]Hardt K, Bonanni P, King S, Santos JI, El-Hodhod M, Zimet GD, et al. Vaccine strategies: Optimising outcomes. *Vaccine* 2016; **34**(52): 6691-6699.

[28]Mina MJ. Measles, immune suppression and vaccination: Direct and indirect nonspecific vaccine benefits. *J Infect* 2017; **74** (Suppl 1): S10-S17.

[29]Chumakov K, Ehrenfeld E, Agol VI, Wimmer E. Polio eradication at the crossroads. *Lancet Glob Health* 2021; **9**(8): e1172-e1175.

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