Title: Impact of New Vaccine Introduction on the Immunization and Health Systems: a Review of the Published Literature

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Abstract

Introduction

The Expanded Program on Immunization (EPI) was established by the World Health Organization (WHO) in 1974 to provide protection against six vaccine-preventable diseases (tuberculosis, poliomyelitis, diphtheria, tetanus, pertussis, and measles) through routine infant immunization. Since then, many new vaccines have become available, and global public funding for immunization, including the GAVI Alliance, has increased accessibility to these vaccines [REF]. Most of the new vaccines, including hepatitis B (HepB), *Haemophilus influenzae* type B (Hib) vaccine, pneumococcal conjugate vaccine (PCV), and rotavirus (RV) vaccines are intended to be included in the routine infant program. Other new vaccines, such as human papilloma virus (HPV), meningococcal meningitis, yellow fever, and typhoid vaccines are intended for older or at-risk populations.

The introduction of a new vaccine can have both positive and negative impacts on the immunization system and the broader health system. It may add stress to an already weak infrastructure or, alternatively, it may provide opportunities and resources to strengthen an existing system. Evidence of impact of new vaccine introduction on health and immunization systems has not been systematically reviewed and summarized. Based on a request in 2010 from the Strategic Advisory Group of Experts (SAGE) on Immunization that guides the World Health Organization (WHO) on global immunization policies, we conducted a systematic review of the published literature to examine these impacts.

Methods

Search strategy

We developed search terms to identify articles that included information describing the impact of new vaccine introduction on immunization systems and health systems [1] (Table 1). The terms were selected to be inclusive and were developed with input from immunization experts. The search terms were divided into two broad categories: 1) vaccines, and 2) immunization and health systems (Table 1).
We searched six publication databases (Medline, Embase, Nursing Update, West African Journal of Nursing, CINAHL, Web of Science and Global Health) that are known to be relevant to vaccines and immunization programs, and were likely to contain reports from developing countries. We attempted to use identical terms to search each database; however, as each database had certain specifications, it was sometimes necessary to modify some terms. We limited the search to reports involving human subjects, published in any language. The final search date was September 29, 2010 and was not limited to a beginning year.

**Inclusion criteria**

For an article to be included in the review process it had to be captured by at least one search term in each of the two search categories (vaccines and immunization health systems), and had to consider information and data from the first five years after vaccine introduction, unless the assessed outcome manifested more than five years after vaccine introduction (e.g., HepB vaccine and hepatocellular carcinoma or cirrhosis, HPV vaccine and cervical cancer). We reviewed the title and abstract of each article meeting this criterion to determine whether the article was potentially relevant, i.e., it contained quantitative or qualitative information on the impact of new vaccine introduction on immunization or health system, or both. Articles that discussed disease incidence, disease burden, vaccination coverage, serotype replacement, immunization campaigns, or adverse events following immunization were included if they contained data or discussion of vaccine impact on the health or immunization system. Cost effectiveness studies were considered if they included real time data and real situations and savings. Expert opinion pieces were included if they reported data. We excluded clinical trials, because they did not show impact on the immunization and health systems following vaccine introduction. Potentially relevant articles were recommended for a full abstraction.

**Abstraction process**

We used EndNote X3.0.1S (Thompson Reuters) to organize and track the articles, adding databases sequentially beginning with Medline, and performing automated and manual de-duplication following the inclusion of each subsequent database. Each article was reviewed to determine if it addressed the impact of the vaccine introduction on the immunization and health system. Sixteen expert reviewers from WHO, CDC, UNICEF, LSHTM and PATH participated
in the abstraction process. Information from relevant articles was abstracted using a standardized MS Access 2007 data collection form. Non-English articles were abstracted by native speakers, whenever possible. A random sample of 10% of the articles were abstracted and reviewed by a second reviewer. If discordance was found, the article was reviewed by a principal reviewer to resolve discrepancies. Published articles were reviewed and organized according to the WHO Framework for Action (Figure 1); this framework was created by WHO in 2007 to promote a common understanding of health systems by providing a systematic means for considering the essential functions of a health care system [1]. The Framework comprises six building blocks: service delivery; health workforce; information; medical products, vaccines and technologies; financing; and leadership and governance.

Results

**Search and abstraction**

The search yielded 24,768 articles from 1911 through September 29, 2010, among which 8,925 (36%) were found to be duplicates (Figure 2). Reviewers applied the inclusion criteria to the remaining 15,795 titles and abstracts. Among these, 654 (4%) articles met the inclusion criteria and were referred for full abstraction; 49 (7%) of these were in languages other than English. One hundred twenty-nine (20%) were found to be relevant for the analysis. In addition, one key article known to the authors that were not identified by the systematic search of the published literature were included, resulting in a total of 130.

**General overview**

Among the 130 studies included in this review (Table 2), the majority were from highly industrialized countries: 97 (75%) were from high income countries (by World Bank Definition); 21 (16%) were from middle income countries; and only 4 (3%) were from GAVI countries. Vaccines targeting 10 diseases (hepatitis A (3, [2%]), hepatitis B (24, [19%]), *Haemophilus influenzae* type b disease (28, [22%]), human papilloma virus infection (13, [10%]), influenza (1, [1%]), Japanese encephalitis (1, [1%]), meningococcal meningitis (17, [13%]), *Streptococcus pneumoniae* disease (28, [22%]), Rotavirus diarrhea (14, [11%]) and typhoid (2, [2%])) with multiple formulations and different combinations were represented in the studies. Over half of the studies (64; [56%]) considered vaccine introductions that took place between 2000 and 2008.
Service delivery

New vaccine introduction may affect the delivery of other immunization and health services. In many high and upper middle income countries including China, Germany, Singapore, Thailand and the US, coverage with vaccines administered through routine childhood or school-based programs increased or remained the same when new vaccines were introduced [2-10]. PCV introduction in two US counties was not associated with delays in other childhood vaccinations or additional primary care visits [2]. In Canada, offering HepB vaccine and PCV at no cost removed existing inequities in PCV distribution [11], increased uptake and improved on-time vaccination [11, 12].

New vaccines have been introduced using a number of delivery modalities, including routine immunization programs, one-time catch up schemes, mass campaigns, school-based programs, or a combination of these, depending on the vaccine and age recommendation for vaccination [13-20]. For instance, Australia’s government-funded HPV vaccination program included school-based routine vaccination of 12 year-old girls with a 2-year adolescent catch-up program and general practice-based vaccination of women aged 18-26 [15]. The vaccination visit for 18-26 year old women was also intended to provide an opportunity for general practitioners to broaden sexual health education and discuss cervical cancer prevention [15]. Ensuring completion of the series for those who missed school-based vaccination required additional effort, including coordination with general practitioners, additional mop-up campaigns at the end of the year, or establishing an individual recall system. To facilitate school-based vaccination in Canada, a new consent procedure – sending the consent form home for parental signature before the school vaccination clinic – was implemented in some settings [12].

Delivery of new vaccines was often coupled with communication and education activities. Social mobilization to publicize the vaccination activity – including through mothers’ clubs and professional organizations – was part of successful efforts to ensure wide acceptance of HepB vaccine in Singapore [5], China [21], Taiwan [22] and Peru [9], and of Hib in Uruguay, Chile, Qatar, and Kuwait [23]. Introduction of HPV vaccine in the UK involved engagement of multiple stakeholders and was facilitated through the establishment of an HPV implementation
group [24]. Knowledge and education about the disease and the vaccine, including safety issues, aided the successful introduction of Hib [25] and HepB vaccine [26] in Canada and the UK [27], and in Zimbabwe the program included training of health care workers, development of HepB communication materials and community mobilization activities [28]. In the US and Canada, in contrast to other routinely recommended childhood immunizations, HPV vaccine was actively marketed through direct consumer advertising and public awareness campaigns that targeted legislators and policy makers in addition to consumers [29]. In the UK, funding for media communication about meningococcal conjugate C vaccine was included in the budget for vaccine introduction [30]. In Israel, immunization planners chose a Hib vaccine with a 2-dose primary series rather than one with a 3-dose series, in part, to avoid three injections at the 6 month visit [31]. In settings where there was insufficient information or provider concern about safety or number of injections, implementation was less successful. Reluctance by vaccine providers to administer three injections at one time was observed with PCV introduction in Australia [32].

Health workforce

There was variability in the impact of new vaccine introduction on health workforce. In settings where vaccination was introduced into regularly-scheduled clinics, there was little impact on staffing and appointment times, as was the case with Hib vaccine introduction in Sweden [33], HPV vaccine introduction in Australia [34], and PCV7 introduction in the United States [2]. Vaccine introduction into adolescent and adult immunization programs sometimes required additional staff or adjustment of appointment times: in Scotland, adding pneumococcal vaccine to appointments for influenza vaccination among older adults increased consultation times by about 2 minutes [35]. Additional staff were also needed for HPV vaccine introduction in the UK [36], where public health nurses, pediatric nurses, health visitors, and managers were recruited into teams, and additional funding was made available to address a shortage of school nurse vaccinators; as well as in remote areas of Australia [15], and in juvenile justice facilities in the United States [37]. Additional training of health staff at national, regional and local levels was required for successful HepB vaccine introduction in China [38] and Zimbabwe [28], hepatitis A and
Japanese encephalitis (JE) vaccine in China [39], Hib vaccine in the Americas [40, 41], and meningococcal polysaccharide vaccine in Egypt [13]. When the new vaccine was introduced as a combination product that included a vaccine already used in the program [23], training was relatively straightforward. In Indonesia, training, and periodic re-training in the local language were needed to successfully implement the school-based typhoid program [20]. Continuing education was also conducted in Italy to promote the birth dose of HepB vaccine [42].

To ensure funding for training, the vaccine introduction budget for HepB and Hib vaccines in Ethiopia included a training and education component [43]. In Australia’s HPV vaccination program, a time-limited incentive payment of $6 per notification of vaccination was offered to general practitioners to improve completeness of the vaccine register [44].

Information

In China [4, 45], Malawi [46], South Africa [47], Nicaragua [48], Canada [49] and Egypt [13], existing disease surveillance systems were used for impact evaluation, policy formulation, and program advocacy related to immunization against HepB [4], JE [45], invasive Hib disease [46, 47], rotavirus [48], pneumococcal pneumonia [49] and meningococcal meningitis [13]. In other countries, vaccine introduction stimulated the development of new surveillance or vaccine registry systems, including comprehensive surveillance for meningococcal meningitis in the UK [14], pediatric invasive pneumococcal disease in Canada [50], hepatitis B virus-associated nephropathy in South Africa [51], and an HPV immunization registry in Australia [10, 44]. In Chile and Uruguay, Hib case definitions and reporting forms were standardized, and a technology transfer program was developed following Hib vaccine introduction [40]. A national immunization register, implemented at the same time as a meningococcal conjugate B vaccination campaign in New Zealand, was used to monitor coverage, safety and effectiveness assessments [52].

Medical products, vaccines and technologies

The availability of new technologies, including combination vaccines and auto-disable syringes, had an impact on the immunization system. In Chile [53], the USA [6] and Zimbabwe [28], use
of combination vaccines resulted in fewer injections, and the need for fewer needles and syringes; lower administrative costs; and reduced storage capacity, compared with introducing it as a separate vaccine [6, 28, 53]. Introduction of DTP-Hib vaccine in The Gambia, however, resulted in initial interruption of routine DTP immunization due to irregular supply of the combination vaccine at that time [54].

In other instances, introduction of new vaccines created additional requirements for cold chain and logistics systems. In Ethiopia, the replacement of 10-dose vials of whole cell diphtheria-tetanus-pertussis vaccine (DTwP) with single-dose vials of pentavalent DTwP–Hep B–Hib increased transport and cold chain requirements [43]. The need for additional cold chain capacity was also reported for rotavirus in several Latin American countries [55], hepatitis A and B vaccine introduction in China [21, 39], HPV vaccine introduction in the US [37], and 23-valent pneumococcal polysaccharide vaccine (PPV23) for older adults in Scotland [35]. In contrast, introduction of Hib vaccine in Chile and Uruguay did not require additional cold chain capacity [40].

As part of new vaccine introduction, auto-disable (AD) syringes were introduced into GAVI-eligible countries. AD syringes were bundled with new vaccines, and, through a time-limited program, GAVI provided support for AD syringes for all vaccines for infants and women in the country’s immunization program. Most countries were able to continue the use of AD syringes after GAVI funding ended. Some countries reported that GAVI support for AD syringes for immunization influenced their decision to expand AD syringes into non-immunization services, and to develop injection safety policies for the health sector. [56, 57].

**Financing and sustainability**

Cost was a consideration in planning new vaccine introduction, including introduction in developed countries [58]. Utilizing existing infrastructure or combination vaccines reduced the costs for introduction, as was documented with introduction of DTP-Hib in the US [6], combination HepA/HepB vaccines in Spain [59], and Hib vaccine in Sweden [33]. In a number of settings, cost concerns about new vaccine introduction [23] and loss of donor support [28] resulted in vaccine shortages and program interruptions.
A decrease in ambulatory consultations and hospitalizations, disease-related complications, and long-term sequelae associated with new vaccine introduction was reported from developing and industrialized countries; these led to reductions in health care utilization, and in some cases resulted in changes in treatment recommendations, [33, 51, 54, 60-90] (Table 3). Mortality in sickle cell patients in the US decreased; however, guidelines for penicillin prophylaxis remained unchanged, because not all pneumococcal serotypes are covered by currently available vaccines [91]. In Brazil, all-cause diarrhea costs declined following introduction of RV vaccine, but they were not sufficient to offset the costs of program implementation [83]. Racial and ethnic disparities in rates of Hib disease incidence in Israel [92] and Australia [93, 94] and of pneumococcal disease in the US [95] were decreased or eliminated following vaccine introduction. Populations not targeted by the vaccine experienced reductions in morbidity and mortality associated with Hib disease [25, 40, 92, 96-101], *Streptococcus pneumoniae* [50, 84, 102-108], meningococcal disease [13, 19, 109-115], hepatitis A [59], hepatitis B [116], typhoid fever [16], rotavirus [117-124], human papilloma virus [125, 126], and Japanese encephalitis [45]; these reductions were attributed to a herd protective effect.

An analysis of 50 country financial sustainability plans [127] developed between 2000 and 2006 in the poorest countries, found that program costs increased from $6.0 per infant before new vaccine introduction to an average of $17.5 per infant after new vaccine introduction. Expenditures per infant doubled in countries that introduced tetravalent HepB vaccine, and increased by a factor of three to four after pentavalent vaccine was introduced. While national government funding accounts for 42% of overall funding, the study showed funding gaps of $4.3 per infant per year, with some 25% of the expenditure needs remain largely unmet.

Funding sources for immunization are diversifying, including development of innovative mechanisms such as bridge funding from the Vaccine Fund [46]; World Bank, UNICEF, USAID and WHO [43]; and the GAVI alliance [127]. An evaluation of four African countries that applied for early GAVI funding suggested that there was little planning at the country level to ensure financial sustainability after GAVI funding ended [128]. The government of Malawi committed to paying 20% of Hib vaccine introduction, but could not sustain a higher financial share without external support [46].
Leadership and governance

New vaccine introduction requires a framework for vaccine licensing, purchasing, legislative issues, development of introduction plans and national recommendations, public awareness campaigns, impact evaluation, and safety monitoring. In many countries, including Australia, Belgium, Canada, Chile, Greece, Taiwan, UK, US, and Uruguay [14, 22, 29, 40, 129, 130], existing national regulatory institutions and advisory committees were used to license and develop recommendations for new vaccines. Frequently, subcommittees were formed to develop the recommendations for the specific vaccine, often in collaboration with academic pediatric and infectious disease organizations [40] and disease-specific societies [22, 130].

Planning of vaccination campaigns has gone beyond the immunization program to include the departments of education, health, and defense; academic institutions and local government [20, 22]. In some countries, legislation was enacted to promote vaccine implementation or evaluation. For example, Italy had a law requiring routine infant HepB vaccination and catch-up vaccination of unvaccinated adolescents [131], and failure to comply had the potential to result in the temporary suspension of paternal authority to ensure immunization of the minor [132]. In Australia, legislation enabled the establishment of the National HPV Vaccination Program Register, a national registry to collect data to assess HPV vaccination coverage [44].

DISCUSSION

In this comprehensive review of the published literature, we found that new vaccine introduction had a mixed effect on – and often provided opportunities to strengthen – existing components of the immunization system. Findings related to impact on the larger health system, however, were limited. Few reviewed papers were designed to evaluate impacts on immunization systems or health systems. The information relevant to our review was frequently an incidental finding noted in the discussion section of the papers. In addition, most of the reviewed papers were from high- or middle-income countries, whose experiences may not represent those from lower-income countries, where the impact related to new vaccine introduction – both positive and negative – is likely to be greater. Our conclusions, therefore, need to be interpreted in the context of these caveats.
The impact on costs and efficiency of introduction differed according to the delivery platform and vaccine formulation. When vaccine introduction made use of existing delivery strategies, such as the routine infant immunization program, costs and impact on staffing needs were substantially less than when vaccines were introduced through newly-created platforms. School-based programs were documented to be effective platforms for introducing new vaccines to school-aged children and adolescents, although additional staff was required, even for existing programs. Venues outside the school were sometimes needed to complete the vaccination series in a timely fashion. Combination vaccines that added the new antigen or antigens to an existing vaccine were less costly and more efficiently introduced than those that required an additional injection.

New vaccine introduction also had an impact on vaccine program logistics and technology. Disruptions in routine vaccination services were reported, related to insufficient on-hand stock of vaccine when programs commenced, and in lower-income countries, to funding shortfalls. Disruptions have also been reported related to global vaccine shortages. A commonly-reported impact of new vaccine introduction was the need for increased cold chain capacity, such as was common with the introduction of the early formulations of rotavirus vaccine. A comprehensive assessment of cold chain capacity should be included in all pre-vaccine introduction assessments. New vaccine introductions have highlighted existing shortfalls in the cold chain and logistics systems. These shortfalls are being resolved through partner and donor contributions and infrastructure strengthening. As a result of early introduction experiences with inadequate infrastructure, effective vaccine management (EVM) assessments and regular cold chain inventories are now a precondition for new GAVI support in order to assure system readiness for the new vaccine.

Reduced disease incidence following new vaccine introduction led to reported declines in the use of vaccine preventable disease-related curative health services. Decreased use of antibiotics resulted in reduced antimicrobial resistance, and herd immunity extended these benefits to populations not targeted by the vaccines. There was some evidence in high-income countries that new vaccine introduction was associated with lower use of ambulatory and hospital services and reduced costs. An important benefit to the health system that has been facilitated by new vaccine introduction has been the widespread use of AD syringes and awareness of injection safety.
Existing infrastructures were utilized and often strengthened to provide information for vaccine introduction. For example, in many countries, established health information and disease surveillance systems were enhanced to collect data for policy development, program advocacy, and impact assessment. In other countries, new systems were developed, especially to monitor vaccination coverage, safety and effectiveness. These new or enhanced systems can be expanded and adapted to facilitate introduction of other vaccines, and to improve disease surveillance.

The importance of social mobilization for the public and training and education for health care workers was frequently noted. The introduction of new vaccines led to the establishment of legislation intended to improve vaccine delivery or program assessment, including mandatory newborn vaccination or school entry laws and national vaccine registries.

This review was subject to a number of limitations. Only published papers were included in the review, although much of the information about the impact of new vaccine introduction is, in fact, contained in the grey literature [133]. In addition, because the information related to the impact of new vaccine introduction was rarely the main focus of the reviewed studies, we were unable to compare studies or evaluate the quality of the data. Because most papers were from high-income countries, it is difficult to generalize those experiences to low-income countries, which often have weaker infrastructure, and require donor support to fund their immunization programs. Although the majority of papers we reviewed were published during the past decade, we also included reports of introductions from more than 20 years ago; these reports may be less relevant to current introductions of new vaccines. While it is likely that the impact of vaccine introduction on a country’s existing immunization and health system reflected the underlying system strength, evaluating this was beyond the scope of this review.

Health programs in developing countries rarely have predictable, long-term funding from donors. However, many new mechanisms have been developed to improve financing such as the Vaccine Independence Initiative [136], the Advanced Market Commitments (AMC) [137] to bring new vaccines such as pneumococcal vaccine to market sooner with committed donor support and the International Finance Facility for Immunisation (IFFIms) [138] which uses long-term donor support to sell ‘vaccine bonds’ have created an unprecedented inflow of funding to global immunization through GAVI replenishments, improved focus on accountability as part of the GAVI Alliance, and the Decade of Vaccines Global Action Plan. Another review of country
strategies for sustaining immunization and new vaccines [139] found that countries sought to mobilize additional resources, improve the reliability of existing resources and funding sources, and increase the efficiency of service delivery. However, even if countries were to fully implement these strategies, funding gaps would remain and financial sustainability would be far from assured in most cases. In addition to new funding initiatives, priorities for new vaccine introduction have expanded include focus on interdepartmental (MoH, MoE) approaches to vaccine delivery for HPV vaccine, a new UNICEF communications framework, further emphasis on cold chain readiness before introducing a new vaccine, new and improved adapted vaccine, presentations with substantially reduced cold chain volume, additional work on out-of-cold-chain use of vaccines for outreach sessions, new delivery technologies (e.g. jet injectors, films), and enhanced training of health care workers.

This review of the published literature summarizes the impact of new vaccine introduction on the immunization system and the larger health system through 2010. While new vaccine introduction often includes an assessment of disease burden and impact on morbidity and mortality, a component of future evaluations should include the systematic and objective assessment of how the vaccine introduction affects the country’s immunization system and broader health system, especially in lower-income countries.
Figure 1: Health Systems Framework

THE WHO HEALTH SYSTEM FRAMEWORK

SYSTEM BUILDING BLOCKS

- SERVICE DELIVERY
- HEALTH WORKFORCE
- INFORMATION
- MEDICAL PRODUCTS, VACCINES & TECHNOLOGIES
- FINANCING
- LEADERSHIP / GOVERNANCE

OVERALL GOALS / OUTCOMES

- ACCESS
- COVERAGE
- QUALITY
- SAFETY

- IMPROVED HEALTH (LEVEL AND EQUITY)
- RESPONSIVENESS
- SOCIAL AND FINANCIAL RISK PROTECTION
- IMPROVED EFFICIENCY

THE SIX BUILDING BLOCKS OF A HEALTH SYSTEM: AIMS AND DESIRABLE ATTRIBUTES

- Good health services are those which deliver effective, safe, quality personal and non-personal health interventions to those who need them, when and where needed, with minimum waste of resources.
- A well-performing health workforce is one which works in ways that are responsive, fair and efficient to achieve the best health outcomes possible, given available resources and circumstances. i.e. There are sufficient numbers and mix of staff, fairly distributed; they are competent, responsive and productive.
- A well-functioning health information system is one that ensures the production, analysis, dissemination and use of reliable and timely information on health determinants, health systems performance and health status.
- A well-functioning health system ensures equitable access to essential medical products, vaccines and technologies of assured quality, safety, efficacy and cost-effectiveness, and their scientifically sound and cost-effective use.
- A good health financing system raises adequate funds for health, in ways that ensure people can use needed services, and are protected from financial catastrophe or impoverishment associated with having to pay for them.
- Leadership and governance involves ensuring strategic policy frameworks exist and are combined with effective oversight, coalition-building, the provision of appropriate regulations and incentives, attention to system-design, and accountability.

http://www.who.int/healthsystems стратегия/everybodys_business.pdf
| Vaccine search term category | 1 | exp *Hepatitis B Vaccines/ |
| | 2 | exp *Haemophilus Vaccines/ |
| | 3 | exp *Pneumococcal Vaccines/ |
| | 4 | exp *Rotavirus Vaccines/ |
| | 5 | exp *Meningococcal Vaccines/ |
| | 6 | exp *Yellow Fever Vaccine/ |
| | 7 | exp *Japanese Encephalitis Vaccines/ |
| | 8 | exp *Papillomavirus Vaccines/ |
| | 9 | exp *Typhoid-Paratyphoid Vaccines/ |
| | 10 | exp *Cholera Vaccines/ |
| | 11 | (HPV vaccine or HPV vaccines).ab,ti. |
| | 12 | (HBV vaccine or HBV vaccines).ab,ti. |
| | 13 | (hib vaccine or Hib vaccines).ab,ti. |
| | 14 | new vaccine.ab,ti. |
| | 15 | new vaccines.ab,ti. |
| | 16 | ((under utilised or under-utilised or under utilized or under-utilized or underutilised or underutilized) and (vaccine or vaccines)).ab,ti. |

| Immunization and health system search term category | 17 | exp Immunization Programs/ |
| | 18 | health planning/ or health care rationing/ or health plan implementation/ or health planning guidelines/ or health planning technical assistance/ or health priorities/ or health resources/ or national health programs/ or exp regional health planning/ |
| | 19 | Capacity Building/ |
| | 20 | exp Inservice Training/ |
| | 21 | capacity building.ab,ti. |
| | 22 | building capacity.ab,ti. |
| | 23 | skill development.ab,ti. |
| | 24 | "delivery of health care"/ or health services accessibility/ or healthcare disparities/ |
| | 25 | equity.ab,ti |
| | 26 | "quality of health care"/ or clinical competence/ or guideline adherence/ or exp "outcome and process assessment (health care)"/ or program evaluation/ or quality assurance, health care/ or benchmarking/ or clinical audit/ or medical audit/ or nursing audit/ or total quality management/ |
| | 27 | health system.ab,ti. |
| | 28 | health systems.ab,ti. |
| | 29 | (health service or health services).ab,ti. |
| | 30 | Health Manpower/ |
| | 31 | exp "Patient Acceptance of Health Care"/ |
| | 32 | (community mobilisation or community mobilization).ab,ti. |
| | 33 | community advocacy.ab,ti. |
information systems/ or integrated advanced information management systems/ or management
information systems/ or ambulatory care information systems/ or clinical pharmacy information
systems/ or database management systems/ or healthcare common procedure coding system/ or
"personnel staffing and scheduling information systems"/
safety.ab,ti.
systems integration/
employee incentive plans/ or personnel loyalty/ or "personnel staffing and scheduling"/ or personnel
turnover/ or physician incentive plans/ or "salaries and fringe benefits"/ or workload/
Curriculum/
Forecasting/
Group Purchasing/
procurement.ab,ti.
logistics.ab,ti.
cold chain.ab,ti.
financial management/ or exp budgets/ or fund raising/ or risk management/ or financial support/
Health Services/
Health Personnel/
Social Change/
"Organization and Administration"/
Product Surveillance, Postmarketing/
medical waste/ or medical waste disposal/
Decision Making, Organizational/
policy making/ or advisory committees/
Government Regulation/
stock.ab,ti.
Immunologic Surveillance/
population surveillance/ or sentinel surveillance/
(strain surveillance or serotype surveillance or virological surveillance or epidemiological
surveillance).ab,ti.
access to services.ab,ti.
(affordability or affordable).ab,ti.
((timeliness or timely) adj3 vaccination).ab,ti.
delivery strateg*.ab,ti.
integrated disease control.ab,ti.
social mobilization.ab,ti.
(incentiv* adj3 health care worker*).ab,ti.
pre-training.ab,ti.
(in-service training or inservice training).ab,ti.
(career path or career paths).ab,ti.
wages.ab,ti.
supportive supervision.ab,ti.
data quality.ab,ti.
data collection.ab,ti.
data management.ab,ti.
health management information system.ab,ti.
impact monitoring.ab,ti.
adverse events following immunization.ab,ti.
AEFI.ab,ti.
(post marketing adj3 evaluation).ab,ti.
(demand and supply forecasting).ab,ti.
(demand adj3 forecasting).ab,ti.
(supply adj3 forecasting).ab,ti.
(stock* adj3 manag*).ab,ti.
pooled procurement*.ab,ti.
(effective adj3 vaccine management).ab,ti.
financing.ab,ti.
(vaccine* adj3 price*).ab,ti.
healthy market*.ab,ti.
fiscal space.ab,ti.
budget support.ab,ti.
(donor* adj3 pool*).ab,ti.
SWAp.ab,ti.
opportunity cost*.ab,ti.
(national regulatory agenc* or national immunization technical advisory group* or national immunisation technical advisory group* or legislation or governance or accountability or inter-agency coordinating committee* or interagency coordinating committee*).ti,ab.
(treatment adj3 cost*) or (hospitalization adj3 cost*) or (hospitalisation adj3 cost*) or (norms adj3 standards)).ti,ab.
(storage adj3 capacity).ab,ti.
(storage adj3 volume).ab,ti.
(vaccine* adj3 stor*).ab,ti.
(vaccine* adj3 handl*).ab,ti.
(vaccine* adj5 distribut*).ab,ti.
(vaccine* adj5 transport*).ab,ti.
((supply or supplies) adj5 (frequen* or interval*)).ab,ti.
logistic*.ab,ti.
((immunization adj3 expenditure*) or (immunisation adj3 expenditure*)).ab,ti.
exp "health care economics and organizations"/
(economics or legislation jurisprudence).fs.
Figure 2: Search method algorithm used for systematic literature review of the impact of new vaccine introduction on the immunization and health system

- **24,768**
- **Databases searched:**
  - Global Health: 7,295
  - Embase: 5,439
  - Medline: 5,363
  - Web of Science: 5,121
  - CINAHL: 1,442
  - Nursing Update: 60
  - W.African J of Nursing: 48

- **15,795**
- **De-duplicate**
- Apply inclusion/exclusion criteria to titles, abstracts

- **655**
- **Apply inclusion/exclusion criteria to articles**
- Initial data analysis

- **130**
- Relevant articles: comprehensive data analysis
Table 2. Literature cited according to World Bank income level, country, and vaccine(s) discussed for vaccines introduced 1980-2008*

<table>
<thead>
<tr>
<th>World Bank income level‡</th>
<th>Country</th>
<th>No. references</th>
<th>Vaccine(s) [reference]</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Australia</td>
<td>10</td>
<td>Hib [93, 94]; HPV [10, 15, 34, 44, 125]; PCV [32, 107]; Rota [124]</td>
</tr>
<tr>
<td></td>
<td>Austria</td>
<td>1</td>
<td>Rota [118]</td>
</tr>
<tr>
<td></td>
<td>Belgium</td>
<td>1</td>
<td>HPV [129]</td>
</tr>
<tr>
<td></td>
<td>Canada</td>
<td>15</td>
<td>HBV [12, 26]; Hib [25, 96]; Influenza [71]; MenPS/Conj [19, 111-113]; PCV [11, 50, 78, 140]; PPV23 [49]</td>
</tr>
<tr>
<td></td>
<td>Finland</td>
<td>1</td>
<td>Hib [67]</td>
</tr>
<tr>
<td></td>
<td>Germany</td>
<td>2</td>
<td>HAV [3]; PCV [103]</td>
</tr>
<tr>
<td></td>
<td>Great Britain</td>
<td>13</td>
<td>Hib [27, 64, 97]; HPV [24, 36]; MenPS/Conj [14, 17, 30, 110, 114, 115]; PCV [73]; PPV23 [35]</td>
</tr>
<tr>
<td></td>
<td>Greece</td>
<td>1</td>
<td>HBV [130]</td>
</tr>
<tr>
<td></td>
<td>Israel</td>
<td>2</td>
<td>Hib [31, 92]</td>
</tr>
<tr>
<td></td>
<td>Italy</td>
<td>9</td>
<td>HBV [42, 57, 79, 80, 131, 132]; PCV [89]; PPV23 [88], Rota [76]</td>
</tr>
<tr>
<td></td>
<td>New Zealand</td>
<td>1</td>
<td>MenB [52]</td>
</tr>
<tr>
<td></td>
<td>Singapore</td>
<td>1</td>
<td>HBV [5]</td>
</tr>
<tr>
<td></td>
<td>Spain</td>
<td>3</td>
<td>HAV/HBV [59]; Hib [98]; Mening [109]</td>
</tr>
<tr>
<td></td>
<td>Sweden</td>
<td>1</td>
<td>Hib [33]</td>
</tr>
<tr>
<td></td>
<td>Taiwan</td>
<td>4</td>
<td>HBV [22, 81, 82, 116]</td>
</tr>
<tr>
<td></td>
<td>USA</td>
<td>27</td>
<td>Combo (DTP/Hib/HB/IPV) [6]; Hib [86]; HPV [37]; PCV [2, 60, 61, 63, 65, 66, 68, 72, 75, 84, 87, 90, 91, 95, 102, 104, 105, 108]; PPV23 [77]; Rota [85, 120-123]</td>
</tr>
<tr>
<td></td>
<td>Multi†</td>
<td>1</td>
<td>Hib [70]</td>
</tr>
<tr>
<td></td>
<td>Multi‡,‡,‡,‡</td>
<td>3</td>
<td>HPV [18, 29, 126]</td>
</tr>
</tbody>
</table>

Total refs, (% of total) high income countries 97 (75)

<p>| Middle                   | Brazil                       | 1              | Rota [83]                                                                            |
|                          | Chile                        | 1              | Hib [53]                                                                              |
|                          | Cuba                         | 1              | Hib [99]                                                                              |
|                          | Egypt                        | 1              | Mening PS [13]                                                                       |
|                          | El Salvador                  | 1              | Rota [119]                                                                            |
|                          | Indonesia                    | 1              | Typhoid [20]                                                                          |
|                          | Mexico                       | 1              | Rota [117]                                                                            |
|                          | Nicaragua                    | 1              | Rota [48]                                                                             |
|                          | Peru                         | 1              | HBV [9]                                                                               |
|                          | People’s Republic of China   | 5              | HBV [4, 21, 38]; JE [45]; HAV/JE [39]                                                 |
|                          | Senegal                      | 1              | Combo (DTP/Hib/HB/IPV) [100]                                                         |
|                          | South Africa                 | 2              | HBV [51]; Hib [47]                                                                    |</p>
<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccine Type</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thailand</td>
<td>HBV [7]</td>
<td>1</td>
</tr>
<tr>
<td>Multi&lt;sup&gt;5,6&lt;/sup&gt;</td>
<td>Hib [40]</td>
<td>1</td>
</tr>
<tr>
<td>Multi&lt;sup&gt;7&lt;/sup&gt;</td>
<td>Typhoid [16]</td>
<td>1</td>
</tr>
<tr>
<td>Multi&lt;sup&gt;8&lt;/sup&gt;</td>
<td>Rota [55]</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total refs, (% of total) lower and upper middle income countries**

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccine Type</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethiopia</td>
<td>Combo (DTP/Hib/HB/IPV) [43]</td>
<td>1</td>
</tr>
<tr>
<td>Gambia</td>
<td>Hib [54]</td>
<td>1</td>
</tr>
<tr>
<td>Malawi</td>
<td>Hib [46]</td>
<td>1</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>HBV [28]</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total refs, (% of total) low income countries**

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccine Type</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethiopia</td>
<td>Hib [54]</td>
<td>1</td>
</tr>
<tr>
<td>Malawi</td>
<td>Hib [46]</td>
<td>1</td>
</tr>
<tr>
<td>Zimbabwe</td>
<td>HBV [28]</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total refs, (% of total) not classified**

<table>
<thead>
<tr>
<th>Country</th>
<th>Vaccine Type</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>18 European countries</td>
<td>HPV [58]</td>
<td>1</td>
</tr>
<tr>
<td>50 GAVI-eligible countries</td>
<td>HBV &amp; Hib [127]</td>
<td>1</td>
</tr>
<tr>
<td>Americas</td>
<td>Hib [41]</td>
<td>1</td>
</tr>
<tr>
<td>Multi&lt;sup&gt;9,10&lt;/sup&gt;</td>
<td>Hib [23, 128]</td>
<td>2</td>
</tr>
<tr>
<td>Global</td>
<td>HBV [8]</td>
<td>1</td>
</tr>
<tr>
<td>Global&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Hib [101]</td>
<td>1</td>
</tr>
</tbody>
</table>

**Total refs, (% of total) not classified**

- **Year of vaccine introduction (Number [%] of references):** 1980-1989 - 14 (12%); 1990-1999 - 37 (32%); 2000-2007 - 64 (56%); 115/129 (89%) specified studies the year of introduction

- **Based on Gross National Income (GNI) per capita. Low:≤USD1005; Middle: USD1006-12,275 (includes lower middle [USD1006-3975] and upper middle [USD3976-12275]); High:≥USD12,276

- **Studies done in multiple countries with different World Bank income levels

1 reference which came were identified by the authors and not by the literature search for inclusion are not included in the table

1Finland, Iceland, Germany, Switzerland
2USA & Canada
3USA, Puerto Rico, Canada
4Italy & Belgium
5Chile & Uruguay
6South Africa & Argentina
7Thailand, China, Vietnam, India, Indonesia, Pakistan
8Brazil, Ecuador, El Salvador, Panama, Mexico, Nicaragua, Venezuela
9Ghana, Mozambique, Tanzania, Lesotho
10Qatar, Uruguay, Chile, Kuwait
11US Army beneficiaries
12US, UK, Norway, Netherlands, Germany, Canada, Switzerland, Spain, Australia
Table 3. Impact on health care utilization and economic impact (where documented) following new vaccine introduction in selected countries.

<table>
<thead>
<tr>
<th>Vaccine(s)</th>
<th>Outcome(s)</th>
<th>Country(ies)</th>
<th>Reference(s)</th>
<th>Reported economic impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBV</td>
<td>Decrease in acute hepatitis B; hepatocellular carcinoma, HBV-associated glomerulonephritis</td>
<td>Italy, South Africa, Taiwan</td>
<td>[51, 79-82]</td>
<td>Estimated US$224M saving; care costs [79, 80] per year</td>
</tr>
<tr>
<td>Hib</td>
<td>Decrease in ambulatory consultations and hospitalizations for meningitis, epiglottitis, orbital and periorbital cellulitis and septic arthritis; change in empiric antibiotic recommendations</td>
<td>Gambia, Sweden, Finland, Wales, US, Iceland, Germany, Switzerland, Canada, UK, Netherlands, Australia, New Zealand</td>
<td>[33, 54, 64, 67, 70, 86]</td>
<td>Modeled cost savings to society [33]</td>
</tr>
<tr>
<td>Influenza</td>
<td>Decrease in hospitalizations</td>
<td>Canada</td>
<td>[71]</td>
<td></td>
</tr>
<tr>
<td>PCV7,10,13</td>
<td>Fewer antibiotic-resistant infections; decrease in hospitalizations for pneumonia, outpatient and emergency department visits for otitis media, pneumonia, and other respiratory infections, fever; invasive pneumococcal disease in HIV-infected persons; decrease in antibiotic prescriptions, insurance claims for otitis media, tympanostomy tube placement; change in recommendations for fever evaluation among vaccinated children</td>
<td>US, Canada, Italy, England, multi-country literature review</td>
<td>[60, 63, 65, 66, 68, 69, 72-75, 78, 84, 87, 89, 90, 140]</td>
<td>Vaccine cost-effective, and cost-saving [84]</td>
</tr>
<tr>
<td>PPV23</td>
<td>Decrease in otitis media and pneumonia</td>
<td>Italy, US</td>
<td>[77, 88]</td>
<td>Vaccination cost-saving [88]</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>Decrease in hospitalizations, outpatient and emergency department visit for all-cause and rotavirus gastroenteritis</td>
<td>Brazil, Italy, US</td>
<td>[61, 76, 83, 85]</td>
<td>Decreased curative health [76, 83]; increase [83] or no health system costs.</td>
</tr>
</tbody>
</table>
References


