

# Vaccination: Epidemiological Review

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**How to cite this paper:** Younger, D.S. (2017) Vaccination: Epidemiological Review. *World Journal of Neuroscience*, 7, 55-65.  
<http://dx.doi.org/10.4236/wjns.2017.71006>

**Received:** January 3, 2017

**Accepted:** January 22, 2017

**Published:** January 25, 2017

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## Abstract

The induction of host protective immunity is an important factor in the immunization against potentially fatal disease and emerging illnesses in the U.S. and global populations especially among immunologically susceptible naïve hosts. Vaccination programs need to be evaluated as regards their health and economic population benefit among indigenous at risk populations taking into account emerging pathologies defined by the sudden appearance of a pathogen in nature or in a region of the world. Global collaboration is a necessary aspect of vaccine-preventable diseases since even a small number of wild-type cases of eradicated diseases in one region of the world present opportunities for their re-emergence in geographically remote areas. This study is a step in the direction of understanding the epidemiologic aspects of vaccination.

## Keywords

Vaccination, Childhood, Epidemiology, Public Health

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## 1. Introduction

We are in an era of intense change in the exploration and understanding of the complexity of the human microbiome and the ecosystems that surround us [1]. While we are host to a myriad of microorganisms that have assembled into complex communities outnumbering the human body by a factor of 10-fold providing many of the building blocks for shared immunity, there still exist certain pathogenic microorganisms that cause human and economic devastation, which if prevented by effective vaccination campaigns, could easily be converted into their eradication [1]. This chapter examines selected aspects of domestic and global vaccination.

## 2. Historical Aspects

In the past century, the health and life expectancy of persons residing in the

United States (U.S.) increased by >30 years, with 25 years of the gain attributable to advances in public health [2]. Vaccination of the public in the U.S. is among the 10 major public health achievements of the twentieth century [2]. At the beginning of this century, infectious diseases were widely prevalent in the U.S. and took an enormous toll on the population. With few effective antimicrobial treatments and preventative measures available, the first vaccine against smallpox was not widely enough employed to eradicate the disease, causing 894 fatalities of 12,064 reported cases [1]. Vaccination against rabies, typhoid, cholera and plague, was not widely achieved until the turn of the century. Vaccines have since been developed or licensed for 21 other diseases in the U.S., 13 of which were recommended by the Centers for Disease Control and Prevention (CDC) for use in all U.S. children [1] (Table 1).

National efforts to promote vaccines among eligible children began with the appropriation of federal funds for polio vaccination after introduction of the vaccine in 1955. Federal, state, and local governments and public and private healthcare providers have collaborated to develop and maintain the vaccine-delivery system in the U.S. [2] [3]. At the end of the 20th century, vaccination coverage exceeded 90% for three or more doses of diphtheria and tetanus

**Table 1.** CDC schedule of infant and childhood vaccinations<sup>1</sup>.

VACCINE NAME	AGE AT 1 <sup>st</sup> DOSE	AGE AT 2 <sup>nd</sup> DOSE	AGE AT 3 <sup>rd</sup> DOSE	AGE AT 4 <sup>th</sup> DOSE
Hepatitis B (HepB)	B	1 - 2 m	6 - 18 m	
Rotavirus (RV) RV1 (2 dose series); RV5 (3 dose series)	2 months	4 months	6 months	
Diphtheria, tetanus, & acellular pertussis (DTaP: <7 years)	2 months	4 months	6 months	15 - 18 months
Tetanus, diphtheria, & acellular pertussis (Tdap: >7 years)	Tdap 11 - 12 years			
Haemophilus influenzae type b5 (Hib)	2 months	4 months	6 months	12-15 months
Pneumococcal conjugate (PCV13)	2 months	4 months	6 months	12 - 15 months
Inactivated poliovirus (IPV: <18 years)	2 months	4 months	6 - 18 months	4 - 6 years
Influenza (ILV; LAIV) 2 doses for some	6 - 18 months annual vaccination (IIV only) 1 or 2 doses	2 - 8 years annual vaccination (LAIV or IIV) 1 or 2 doses	8 - 18 years annual vaccination (LAIV or IIV) 1 dose only	
Measles, Mumps, Rubella (MMR)	12 - 15 months	4 - 6 years		
Varicella (VAR)	12 - 15 months	4 - 6 years		
Hepatitis A (HepA)	12 - 18 months (2 dose series)			
Human papillomavirus (HPV2: females only; HPV4: males and females)	11 - 12 years (3 dose series)			
Meningococcal (Hib-MenCY > 6 weeks, MenACWY-D > 9 months; MenACWY-CRM > 2 month)	11 - 12 years			

<sup>1</sup>Source: Adapted from <https://www.cdc.gov/>.

toxoids and pertussis vaccine (DPT), poliovirus vaccine, *Haemophilus influenzae* type b (Hib) vaccine; and 1 or more doses against measles virus [2].

The past decade witnessed substantial declines in cases, hospitalizations, mortality and health-care costs due to vaccine-preventable illness [4], with new ones introduced covering rotavirus, quadrivalent meningococcal conjugate, herpes zoster, pneumococcal conjugate, and human papillomavirus infection, as well as tetanus, diphtheria, and acellular pertussis vaccine for adults and adolescents, bringing to 17 the number of diseases targeted by U.S. immunization policy. One economic analysis [5] showed that vaccination of each U.S. birth cohort with the current childhood immunization schedule feasibly prevented approximately 42,000 deaths and 20 million disease cases, with a net saving of \$14 billion in direct costs and \$69 billion in societal costs [1]. The pneumococcal conjugate and rotavirus vaccines, introduced in the past decade, prevented an estimated 13,000 deaths and up to 60,000 hospitalizations respectively each year. Advances achieved in the older hepatitis A and B, and varicella vaccines brought reported cases up to record low levels, reducing age-adjusted mortality in deaths per million population from hepatitis A from 0.38 by the end of the previous century to 0.26 by the end of the recent decade [6].

Expanded vaccination coverage has also been the most cost-effective means of advancing global welfare and one of the 10 major public health achievements worldwide in the past decade [7], with an estimated prevention of 2.5 million deaths each year among children <5 years through use of measles, polio, and DPT vaccines [1]. Polio eradication efforts through mandatory vaccination decreased the number of countries from 20 to four, with fewer than 1500 cases reported in 2010. With the number of countries employing hepatitis B vaccine increasing from 107 in 2000 to 178 in 2009, and global vaccination coverage of 70%, at least 700,000 deaths were averted in annual birth cohorts in 178 countries [1]. From 2000 to 2009, the number of countries using the Hib vaccine worldwide increased from 62 to 161, with a resulting global coverage of 38%, averting 130,000 pneumonia and meningitis-related deaths annually among children <5 years of age [1].

The combined achievements in vaccine-preventable diseases have mirrored modifications in the public health system [1]. These included the greater quantitative capacity of epidemiology in both study designs and period health surveys, methods of data collection that evolved from simple measures of disease prevalence to complex studies of precise analysis available in cohort, case-control, and randomized clinical trials to establish the efficacy of vaccination and demonstrate its low risk [1] [2]. The CDC, which assumes responsibility for collecting and publishing notifiable diseases, tracks more than 52 infectious illnesses. Public health efforts enjoining federal, state, county, local governmental health departments, and nongovernmental organization interact effectively to track infectious illness in the U.S. and rates of childhood vaccination.

### 3. Categories of Vaccines

Vaccines can be divided by the way they are prepared and therefore how they

confer immunity, including live-attenuated, inactivated, subunit, conjugate and toxoids [1] [8].

**Live-attenuated:** Most frequently used for viruses rather than bacterial illnesses, the method for preparing live-attenuated vaccines involves passing the viral agent through a succession of cell cultures to weaken it producing a form that is no longer able to replicate in human cells [1]. Still recognized by the body's immune system, it protects against future infection. Examples include MMR, varicella, and Hib vaccines. Although uncommon, it is plausible that the introduced virus can cause illness if it has transformed into a more virulent form through mutation.

**Inactivated:** heat, irradiation, or certain chemicals to no longer cause illness upon vaccination inactivate the microbe without altering its immune activation properties in examples of poliovirus and hepatitis A vaccine. However, a disadvantage is the need for multiple boosters to augment efficacy.

**Subunit:** When only a portion of the microbe as antigen for immune surveillance is needed by the body to confer immunity, subunit vaccination is an appropriate methodology as for example in influenza and hepatitis B subunit vaccines [1].

**Conjugate:** These types of vaccines are prepared from parts of the bacterium combined with a carrier protein which when chemically linked together to bacteria coat derivatives, generate a more potent host immune response, as for example in the pneumococcal vaccine [1].

#### **4. Domestic and Global Vaccination Programs**

Vaccination programs in the U.S. have generally been tied to school entry. The first national push to ensure that every state in the country had vaccination requirements for children entering schools occurred in the 1970s predicated on measles outbreaks during the preceding two decades [1] [9]. Some states acted on their own accord and enacted vaccination laws. Public opinion has sometimes been an effective catalyst especially among outbreaks that remind us of the devastating potential of certain diseases that have disappeared from public view because of their infrequent occurrence. Indeed, a major advance in global public health was the launch of the World Health Organization's (WHO) Expanded Program on Immunization that promoted a schedule of basic vaccines for the immunization against polio, measles, tuberculosis, diphtheria, pertussis, and tetanus (DPT), according to the standard schedule similar to childhood programs in the U.S. [1] (**Table 2**).

Vaccination as a method of disease prevention is widely accepted globally. Goal 4 of the United Nations Millennium Development Goals (MDG) to reduce childhood mortality focuses on the delivery of effective vaccinations for children under the age of five [10]. Measles vaccination prevented nearly 15.6 million deaths worldwide between 2000 and 2013. The number of globally reported measles cases declined by 67% during the same period, with 84% of children worldwide receiving at least one dose of measles containing vaccine in 2013 up

**Table 2.** WHO schedules of infant and childhood vaccinations<sup>1</sup>.

VACCINE NAME	AGE AT 1 <sup>st</sup> DOSE	AGE AT 2 <sup>nd</sup> DOSE	AGE AT 3 <sup>rd</sup> DOSE	AGE AT 4 <sup>th</sup> DOSE
BCG	B			
Hepatitis B (Option 1)	B	4 weeks	8 weeks	
Hepatitis B (Option 2)	B	4 weeks	8 weeks	12 weeks
Polio (OPV + IPV)	6 weeks	10 weeks	14 weeks	
Polio (IPV/OPV Sequential)	8 weeks	12 - 16 weeks	4 - 8 weeks after 2 <sup>nd</sup> dose	4 - 8 weeks after 3 <sup>rd</sup> dose
Polio (IPV)	8 weeks	12 - 16 weeks	4 - 8 weeks after 2 <sup>nd</sup> dose	
DTP	6 weeks	10 - 18 weeks	4 - 8 weeks after 2 <sup>nd</sup> dose	
Haemophilus influenzae type b (Option 1)	6 weeks - 59 months	4 weeks after 1 <sup>st</sup> dose	4 weeks after 2 <sup>nd</sup> dose	
Haemophilus influenza type b (Option 2)	6 weeks - 59 months	8 weeks after 1 <sup>st</sup> dose if 2 doses, 4 weeks after 1 <sup>st</sup> dose if 3 doses	4 weeks after 2 <sup>nd</sup> dose	
Pneumococcal (conjugate) (Option 1)	6 weeks	10 weeks	14 weeks	
Pneumococcal (conjugate) (Option 2)	6 weeks	14 weeks		
Rotavirus (Rotarix)	6 weeks	10 weeks		
Rotavirus (Rota Teq)	6 weeks	10-16 weeks	4 weeks after 2 <sup>nd</sup> dose	
Measles	9 or 12 months	4 weeks after 1 <sup>st</sup> dose		
Rubella	9 or 12 months			
HPV	As soon as possible from 9 years old	6 months after 1 <sup>st</sup> dose		

<sup>1</sup>Source: Adapted from <http://www.who.int/en/>.

73% from 2000 [10]. Chasing a disease down to the last few cases in underdeveloped countries to levels of the developed world remains a challenge. The goal of malaria eradication faltered in the 1960s due to the resistance of *Plasmodium falciparum* to antimicrobial therapy and the development of mosquito vector resistance to insecticides leading to an increase in cases worldwide. All vaccines against *Plasmodium falciparum* (RTS, S/AAS01) were designed using genetic sequences derived from a single well-characterized reference strain of West African origin (3D7) [11]. A multivalent version of RTS, with carefully chosen sporozoite protein variants combined with additional antigens offers broader protection [12].

While most of the record decline of childhood infectious disease is attributable to increase in the use of vaccines, a small but significant minority of parents in the U.S. oppose the use of vaccines on children [1]. The less than perfect effectiveness of certain U.S. vaccination programs such as childhood pertussis and measles that depend upon widespread acceptance, resulted in a record number of cases in the U.S. 2015 [13].

Valuable lessons have been learned from worldwide campaigns to eradicate polio [1]. In 1988, the World Health Assembly endorsed the goal of eradication of polio at a time when the number of new cases of paralysis approximated 350,000 and the disease was endemic in 125 countries [1] [14]. The March of Dimes was created in the U.S. to end the polio epidemic that plagued the nation. To ensure efficacy against wild poliovirus infection, investigators achieved strain-specific protective immunity based upon the inherent genetic diversity of the poliovirus [15]. With the last naturally occurring case detected in 1999, wild-type poliovirus type 2 has since been eradicated in the U.S. with the last naturally occurring case detected in 1999, while type 3 is close to eradication with virtually no new detected cases. Type 1 poliovirus emerged during a 2011 outbreak in China suggesting that eradication was incomplete. More recently, cases of polio have been diagnosed in Syria, Nigeria, and Bangladesh due to the disruption of populations by war and anti-vaccine sentiment expressed by some ultra-religious Muslims [1]. As long as the poliovirus circulates anywhere in the world, there is the potential for poliomyelitis to be exported to countries that are disease-free causing serious outbreaks [1].

## 5. Legal Challenges to Vaccination

The hesitation to vaccinate children continues in the U.S. with exceptions granted from school-entry immunization mandates based upon personal beliefs and non-medical reasons [1]. Buttenheim and colleagues [16] noted that while still below levels to maintain herd immunity against measles, there was a 2- to 10-fold underestimate of the true rate of vaccine refusal based upon personal beliefs on school-entry. This suggests inadequate understanding by parents as to the public necessity of measles immunization and fear of the vaccine that it may be pathogenic in one form or another.

With outbreak of measles cases reported by the CDC in December 2014 at Disneyland in Orange County, California [17] it was subsequently noted that 7% of children received two or more MMR vaccinations, 45% were unvaccinated, and 43% had an unknown vaccination status [18]. These findings led two California State Senators with personal ties to health policy, one a pediatrician and the other the son of a polio survivor, to cosponsor Bill SB 277 eliminating all non-medical vaccine exemptions.

However, there was no greater challenge for public health educators than in trying to amend the misunderstanding of the risk of autism following MMR vaccination among concerned lay parent groups at the turn of the 20th century in the United Kingdom (UK). The basis for this misconception in causality was grounded in later retracted publications of a UK investigator who drew attention to cohorts of autistic children presumed to be a result of immune conditioning by early live-attenuated measles vaccination [19] [20] [21]. More than a decade later, a retracted U.S. publication cited heightened risk for autism among only African-American boys [22] citing a reanalysis of CDC data reported earlier showing no relation of autism in a population of school-matched subjects [23].

A recent meta-analysis [24] of case-control and cohort studies found no strong evidence for a causal effect of autism due to MMR vaccination. Other examples of the legal challenge to vaccination were seen in Mississippi [25], a state that consistently led to U.S. with vaccination rates >99% for MMR in entering schoolchildren. There are legal precedents for the right of states to mandate vaccination for school entry to protect the public at large, both as a social obligation to provide herd immunity, and to protect those who cannot be vaccinated. It is thus safer to be unvaccinated living in a highly vaccinated community than to be vaccinated but living in an unvaccinated one [26].

Lawmakers and the lay public will continue to voice their opinions guided by the scientific community in support of necessary vaccinations, leaving aside ones with intolerable side effects such as the Lymerix vaccine that was voluntarily withdrawn after demonstrating adverse neurological sequela. Whether the lay public can accept the anticipated impact of a 1 in a million anticipated severe neurological side effect from influenza vaccination resulting in a serious neurologic development such as peripheral neuropathy remains a persistent challenge. Such occurrences foster the scientific community to continue to strive to develop more effective and safer approaches to vaccination.

## 6. Assessing the Impact of Vaccines for Endemic Infection

The assessment of the impact of vaccination on an individual or population requires an analysis of both the direct and indirect effects of immunization [27]. The theoretical concept of vaccine efficacy describes the individual level benefit or how much less likely an individual is to acquire infection following a given exposure [1] [27]. Most clinical trials however assess vaccine effectiveness at the population level [1] [27] however the indirect effect of vaccination accounting for the reduction in transmission to unvaccinated subjects in the wider population may go unnoted [1] [27]. It is the combination of direct and indirect effects that should interest public health experts in fully evaluating vaccination impact since there may be little known about the apparent or real vaccine impacts, as well as the risk of reinfection and mechanism of protection [1] [27]. Halloran and colleagues [28] used the terms leaky, all-or-nothing, or waning vaccine to describe their apparent success and biology. Farrington and colleagues [29] cited the vaccine for pertussis as a leaky vaccine, while those for measles and rubella were all-or-nothing, and the cholera was a waning type. Magpantay and colleagues [30] added mathematical modelling to extrapolate the epidemiological efficacy and ramifications of such imperfect vaccines considering that an imperfect vaccine might exhibit failures in degree or leakiness and take or all-or-nothingness. Edlefsen [31] noted that such a simple dichotomy could have serious implications for analysis of methodologies since leaky vaccines in effect protected highly exposed recipients at a lower rate, and could induce a violation of the proportional hazards condition. The latter was often assumed in survival analysis due to a changing fraction of at-risk subjects over time in both vaccinated and unvaccinated individuals.

## 7. Microeconomic Impact of Vaccination

Jit and coworkers [32] analyzed the economic impact of vaccination. The authors noted that investment in immunization programs dramatically increased in developed and developing countries over the past two decades because of the development of new vaccines against major diseases [33], and the emergence of new financing mechanisms. Organizations such as Gavi, the Vaccine Alliance that subsidize the cost of vaccines for some lesser-developed countries and the Pan American Health Organization contributed to their economic feasibility and success of vaccination programs [34]. Spending growth heightened the importance of investing in immunization [35].

Microeconomic evaluations can be employed to facilitate decision-making by national and multinational stakeholders through comparisons of the economic cost of implementing vaccine program infrastructure, purchase, and delivery, against the health and economic benefits of vaccination. Economists have argued that improvements in health can lead to economic growth by decreasing fertility, strengthening macroeconomic stability, and improving educational outcomes [32] [36] [37]. Other beneficial aspects included the accrued benefits of health gains, health-care cost savings, reductions in the time costs of caring for the sick, improved economic productivity due to prevention of mental and physical disabilities and child survival, as well as, the development of herd immunity, and prevention of antibiotic resistance [1]. Bishai and coworkers [38] noted a significant reduction in the poverty-related gradient in under-five mortality by measles vaccination improving health equity directly. Using a cost-benefit analysis approach to assess the impact of *Haemophilus influenzae* type b vaccination, Bärnighausen and colleagues [39] demonstrated that past economic evaluations had mostly adopted narrow evaluation perspectives, focusing primarily on health gains, health-care cost savings, and reductions in the time costs of caring, while usually ignoring other important benefits. The latter include outcome-related productivity gains [improved economic productivity due to prevention of mental and physical disabilities], behavior-related productivity gains [economic growth due to fertility reductions as vaccination improves child survival], and community externalities [herd immunity and prevention of antibiotic resistance] [1].

While vaccination is most cost-effective in low-income groups, their benefits may be the most difficult to ascertain leading to exacerbation or narrowing of the indicators of equity. Rheingans and colleagues [40] estimated distributional effects of rotavirus vaccination in 25 Gavi countries noting that the greatest potential benefit of rotavirus vaccination in Gavi countries were in the poorest quintiles while existing trends were skewed towards the richest quintiles. Maximizing health benefits for the poorest children while assuring the best value-for-money may require increased attention to these distributional effects.

Verguet and colleagues [41] hypothesized that public financing of rotavirus vaccination in India and Ethiopia with an estimated 4% of global child deaths or approximately 300,000 deaths, attributed to rotavirus in 2010, could substantially

decrease child mortality and rotavirus-related hospitalizations, prevent health-related impoverishment and bring significant cost savings to households. Using extended cost-effectiveness analysis to evaluate a hypothetical publicly financed program for rotavirus vaccination, their analyses showed direct benefits of rotavirus vaccination in substantially decreasing rotavirus deaths mainly among the poorer, with reduced household expenditures across all income groups, and effective provision of financial risk protection concentrated among the poorest. Notwithstanding, the potential indirect benefits of vaccination of herd immunity would lead to increased program benefits among all income groups.

## 8. Conclusion

Mass-vaccination campaigns have lowered the incidence of measles, mumps, and rubella in lesser developed countries to low levels but that may not be good enough since these diseases like others, can recur. Two big improvements underscore the argument for wider eradication and prevention campaigns, in a list of communicable diseases including better techniques for locating and monitoring cases of global diseases, and improved medical technology to produce superior vaccines. The scientific community will guide political and lay public attitudes to effectively deal with the most serious threats to our public health through vaccination.

## Disclose

The Author has nothing to disclose.

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