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Review

Policy making for vaccine use as a driver of vaccine innovation and development in the developed world

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ABSTRACT

In the past 200 years, vaccines have had unmistakable impacts on public health including declines in morbidity and mortality, most markedly in economically-developed countries. Highly engineered vaccines including vaccines for conditions other than infectious diseases are expected to dominate future vaccine development. We examine immunization vaccine policy as a driver of vaccine innovation and development. The pathways to recommendation for use of licensed vaccines in the US, UK, Canada and Australia have been similar, including: expert review of disease epidemiology, disease burden and severity; vaccine immunogenicity, efficacy and safety; programmatic feasibility; public demand; and increasingly cost-effectiveness. Other attributes particularly important in development of future vaccines are likely to include: duration of immunity for improved vaccines such as pertussis; a greater emphasis on optimizing community protection rather than direct protection only; programmatic implementation, feasibility, improvements (as in the case of development of a universal influenza vaccine); public concerns/-confidence/fears related to outbreak pathogens like Ebola and Zika virus; and major societal burden for combating hard to treat diseases like HIV and antimicrobial resistant pathogens. Driving innovation and production of future vaccines faces enormous economic hurdles as available approaches, technologies and regulatory pathways become more complex. As such, cost-mitigating strategies and focused, aligned efforts (by governments, private organizations, and private-public partnerships) will likely be needed to continue to spur major advances in vaccine technologies and development.

Contents

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1. Vaccine recommendation policy as a key driver in vaccine market innovation, development and sustainability

The impact of vaccines is arguably one of the greatest public health interventions, possibly after clean water, with greatest impact occurring in economically-developed countries with strong public health infrastructure to manufacture and deliver vaccines to populations for whom they are recommended routinely [1]. In addition to the worldwide eradication of smallpox and polio serotype 2 and the elimination of the remaining polio serotypes in most parts of the world, economically-developed countries have seen substantial reductions in diseases for which vaccines have been introduced including the near disappearance of measles, mumps, rubella and congenital rubella syndrome, tetanus, diphtheria, and *Haemophilus Influenzae* type b (Hib) [2–5] (Table 1). While substantial reductions in child mortality have been achieved in less developed countries through the implementation of childhood vaccination programs, many of these diseases still rage in countries with inadequate or no vaccine coverage. Developed countries also have experienced substantial reductions in pertussis, hepatitis A and B, rotavirus, varicella and pneumococcal disease, where vaccines against these disease have been deployed [5–8]. Developing countries with lower or no vaccine coverage for these diseases still suffer far greater morbidity and mortality from these diseases than economically-developed countries [9].

After a vaccine is developed and licensed, the vaccine may be considered by country-level immunization bodies for recommendation in either the general population or targeted populations such as populations with high risk factors (e.g., pregnant women, indigenous populations, immunocompromised groups, or the elderly) or, more often, in the routine childhood and adolescent immunization and adult schedules. This includes consideration for "off label" use of licensed vaccines for populations not included in the approved labeling. The process for deciding which populations licensed vaccines are routinely recommended for is usually vital to the success of a product since commercial entities may be most interested in developing and producing a vaccine with a large market such as a vaccine that will be recommended routinely for the general population. In this way, vaccine policy-making leading to widespread use can be a major incentive in determining which vaccines are developed. Manufacturers must consider that once a new vaccine is developed, what is the likelihood that it will be recommended for widespread use and a sustainable market? For example, vaccines against Meningitis B were recently licensed in the US but are not recommended for routine use. They can be used if the individual healthcare provider decides to recommend them. In limiting the recommended target market, this recommendation has implications for use, limiting the return on investment for the developers of the vaccines. There are many factors that influence decisions regarding which vaccine(s) should be developed; in this paper, we specifically examine how establishment of policy for use of new vaccines influences vaccine innovation, development and future use.

2. Historical impact and key drivers of vaccine innovation

Development of the earliest vaccines was driven by disease severity and the determination of impassioned individual scientists, and later expedited by major advances in laboratory science. The first known modern human vaccinations (smallpox in 1796 and rabies in 1885) were live attenuated formulations, followed by, the first killed whole organism vaccine (typhoid) in 1896. Techniques to develop subunit vaccines (protein or polysaccharide) began in 1923 with the diphtheria toxoid vaccine. The first genetically engineered vaccine, hepatitis B (surface antigen recombinant) did not appear until 1986, almost two centuries after the first vaccines [1]. Vaccines against diseases such as measles and polio which themselves produce strong, durable immunity have proved comparatively easy to develop and many such opportunities for vaccine development against diseases of significant public

Table 1
Disease morbidity and/or mortality reduction from pre-vaccine era to modern era in select developed countries.

Disease	Australia[a]	Canada[b]	United Kingdom[c]	United States[d]
Congenital Rubella Syndrome (CRS)	95%	100%	95%	>99%
Diphtheria	100%	>99%	>99%	100%
Haemophilus influenzae type b (Hib)	>99%	98%	89%	>99%
Measles	>99%	99%	>99%	>99%
Mumps	95%	97%	~90%	>99%
Pertussis	>99%	90%	86%	92%
Polio[e]	100%	100%	100%	100%
Rubella	95%	>99%	88%	>99%
Tetanus	99%	68%	>90%	98%
Smallpox[f]	100%	100%	100%	100%

[a] Deaths in 1993 compared with deaths in 2007 for Hib; Deaths from disease in 1926–1935 period (prior to introduction of these vaccines) compared to deaths in 1996–2000 for Diphtheria, Measles, Pertussis, Tetanus [60]. Percentages for CRS, Mumps and Rubella in Australia are 1985 data compared to 2011 data [61–67], but recent resurgences of mumps among young adults threaten progress.
[b] Comparing 5 years prior to vaccine introduction to 2007–2011 peak annual number of cases, pre-vaccine introduction ranges: CRS = 1979–1983, Diphtheria = 1925–1929, Hib = 1986–1990, Measles = 1950–1954, Mumps = 1950–1954, Pertussis = 1938–1942, Rubella = 1950–1954, Tetanus = 1957–1961 [68].
[c] Comparing reduction from year prior to introduction and most recent data available, pre-vaccine year and most recent data year are: CRS: 1971 & 2003; Diphtheria: 1914 & 2002; Hib: 1990 & 2004; Measles: 1968 & 2004; Mumps: Prior to recent outbreak; decrease was estimated at 90%; Pertussis: 1940 & 2003; Rubella: 1982 & 2005; Tetanus: 1989 & 2004 for under age 65 years old [69–71].
[d] Comparing 20th century morbidity to reported cases in 2014 [72,73].
[e] Polio declared eliminated in 2000 in Australia, 1991 in Canada & US, 2002 in UK [74].
[f] Smallpox worldwide eradication declared 1980 [75].