

Title: 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.

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

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.

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 only recommended for routine use in the target age group. 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.

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 health concern have been exploited by mimicking the natural immune response. As science has advanced, more technical methods have allowed development of vaccines against diseases for harder-to-control organisms. Currently innovation is driven largely but not exclusively by highly engineered techniques which are expensive and are primarily limited to academic and pharmaceutical laboratories with advanced technologies [Figure 1].[10,11] Historically, the major factors steering vaccine development have been disease epidemiology, burden and severity, and vaccine efficacy and safety. Vaccine development costs have increased significantly in recent years, primarily due to evolving regulatory requirements.[12,13] Several factors – increasing cost, the fact that big-ticket low-hanging fruit have already been picked , and the impact of policy recommendations about vaccine use – have created an environment that jeopardizes vaccine innovation, even while the scientific opportunities for such innovation have increased. Moreover, many newer vaccines (e.g. *Clostridium difficile*) may be more

likely to be targeted to specific high-risk groups. In the future, costs for vaccine research and development, especially for outbreak pathogens (e.g. Ebola and Zika virus) may need to be subsidized by government or public-private partnerships, to make development more feasible.

Post-licensure vaccine recommendations in the developed world

In economically-developed countries, the process for taking a new vaccine from licensure to recommendation – where the licensed vaccine is recommended for large subpopulations – is similar across multiple settings, with perhaps a major difference being consideration of cost-effectiveness. Moreover, vaccines are typically administered to non-sick individuals in the hope of preventing the targeted disease. Regulatory labeling typically restricts use of a product only to those patients for whom definitive benefit has been demonstrated (though off-label use is permitted), for vaccines, use is subsequently further restricted relative to what is on the label by the vaccine use recommendations. For comparative purposes, we examine the recommendation processes in Australia, Canada, the United Kingdom (UK), and the United States (US) as case studies.

Australia

In Australia, vaccines against 16 diseases are provided at no cost to the individual through the publicly funded National Immunisation Program (NIP). The Australian Technical Advisory Group on Immunisation (ATAGI) was established in 1997, provides technical advice to the Minister for Health on the medical administration of vaccines available in Australia, including those in the NIP. Since 2005, following a review of immunization policy structure and price setting mechanisms, there has been a separation of powers with respect to the process for a vaccine to be added to the NIP in Australia such that cost-effectiveness of vaccines is now considered by the Pharmaceutical Benefits Advisory Committee (PBAC) in the same way as the rest of health care. The Australian government is not bound to include a vaccine on the NIP if it can be procured at the cost-effective price, but is bound by a negative recommendation

(i.e., it cannot add a vaccine to the NIP if there is a negative PBAC recommendation). The converse is true in United Kingdom as noted later. In a “grandfather clause”, vaccines that were already on the NIP prior to 2005 were deemed to meet PBAC cost-effectiveness criteria at that time point. This enables new vaccines against the same antigens to be assessed as being equivalent or superior to current NIP funded vaccines.

ATAGI membership includes a broad array of technical expertise [See Table 2 for a complete list].

ATAGI’s Terms of References include providing “*advice to research funding bodies regarding the status of current immunisation research and areas where additional research is required.*” [14]

ATAGI conducts an annual meeting with the vaccine industry to identify potential new vaccines in the pipeline for PBAC submission and, where appropriate, will establish a working party under specific terms of reference as part of the preparatory phase. If the sponsor is seeking approval to be funded under the NIP, ATAGI provides pre-submission advice to the sponsor and the PBAC. Once the submission is lodged with the PBAC, ATAGI then provides post-submission advice to the sponsor and the PBAC.

Canada

In Canada, the National Advisory Committee on Immunization (NACI) makes expert and evidence-based recommendations regarding use of vaccines authorized for use in Canada, advises on the need for national vaccination strategies, and makes recommendations for vaccine development research.[Table 2] While NACI is the recognized scientific advisory group, implementation of programs, schedules, vaccine purchase and services delivery occurs at the provincial-level via other scientific advisory groups. At present, NACI does not review cost-effectiveness data or make program implementation recommendations.[15–17] Recommendations including programmatic and cost-effectiveness considerations are made by provincial advisory committees or by the Canadian Immunization Committee consisting of representatives from federal/provincial/territorial health ministries.

159 *United Kingdom*

160 The first body of its kind, the Joint Committee on Vaccination and Immunisation (JCVI) was established
161 in 1963 to provide scientific advice for the UK immunization program and is independent from the
162 Government. [18] [Table 2] JCVI does consider evidence on cost-effectiveness. [19] Economic
163 considerations currently follow the process used by the National Institute for Health and Care Excellence
164 (NICE). NICE provides guidance to the National Health Service (NHS) on clinical and cost-effectiveness of
165 technologies used in the system (e.g. medicinal products, diagnostic techniques, surgical procedures,
166 etc.). NICE uses an incremental cost-effectiveness ratio (ICER) threshold with a range between £20,000
167 and £30,000 (~30,000 – 40,000 USD) per quality adjusted life year (QALY) gained not specific to vaccines
168 but is used for consideration of other recommendations as well. [20,21] Assuming a vaccine is
169 considered safe, effective and desirable for the UK population, the cost-effectiveness analysis becomes
170 the final arbiter that drives a recommendation for use. If a vaccine is cost-effective and recommended
171 by JCVI, the Government is bound to introduce it under the NHS constitution if it can be procured at the
172 cost-effective price. In the absence of favorable cost-effectiveness, vaccines are not usually
173 recommended by JCVI. In some situations programs can still be advised by the committee (e.g. outbreak
174 response advice) even when not cost-effective, but in this situation the Government is not
175 constitutionally bound to accept the advice.

176 *United States*

177 The Advisory Committee on Immunization Practices (ACIP) makes recommendations for immunizations
178 to be used for public health in the United States. Formed in 1964 ACIP makes recommendations to the
179 Director of the CDC which become official policy when accepted by the Director and published in
180 MMWR. The ACIP advises on immunization schedules, dosages and routes of administration, and
181 indications and contraindications for use of agents for communicable disease control

(immunizations).[22] ACIP makes vaccine recommendations for two schedules: the childhood and adolescent immunization schedule and the adult immunization schedule. Since ACIP was established, the US childhood and adolescent vaccination schedule has grown from universal recommendations for vaccines targeting 6 diseases to 16 diseases. The adult immunization schedule contains recommendations for vaccines targeting 11 diseases. The process by which the committee considers evidence is based on a variety of factors (see Table 2) but no formal guidance is provided for deciding which factors to prioritize for any given vaccine. Key elements for developing recommendations include Grading of Recommendations, Assessment, Development and Evaluation (GRADE) for vaccine safety, vaccine efficacy and effectiveness, and burden of disease.[23] While evidence regarding economic analysis and implementation issues is not subject to GRADE, these may be considered during policy development. [24,25]

The Vaccines for Children (VFC) program, is an entitlement program which assures government financing for eligible children (~ 50% of children aged <19 years of age are eligible to receive vaccines through VFC; eligibility criteria primarily focus on the un-insured and those covered by government insurance for low income families).[26,27] While ACIP has the authority to add vaccines to the VFC formulary for eligible children without US Government approval, CDC must still negotiate a federal contract with the manufacturer(s) and theoretically could fail to do so.[28].

Major factors that influence recommendations in developed countries

Historically the most influential factors appear to have been disease epidemiology, disease burden and severity, vaccine efficacy and safety, immunization strategies and feasibility of their implementation, and public perception and demand. To some extent, cost-effectiveness has played a role in some countries, though the measure itself is inextricably linked to the aforementioned named variables. Cost-effectiveness is an especially problematic consideration once a disease has been controlled, due to the

205 very high cost of evaluating improved vaccines in the absence of high disease burden, particularly in the
206 absence of correlates of protections (e.g. pertussis) and also the likelihood of the improved vaccine
207 being priced substantially higher compared to the existing vaccine.

208 An example of cost-considerations in the US being set aside concerns the measles containing vaccine
209 (MMR). After a substantial decline in cases of measles, recurrent measles outbreaks among vaccinated
210 school-aged children prompted both the ACIP and AAP in 1989 to recommend that all children receive
211 two doses of measles-containing vaccine. Measles antibodies develop among approximately 95% of
212 children vaccinated at 12 through 15 months of age as recommended; greater than 99% of persons who
213 receive two doses of measles vaccine develop serologic evidence of measles immunity.[31] Though a
214 second dose only increased effectiveness by ~4%, the public health mandate to eliminate measles – a
215 major public health goal – was the overriding factor in the 1989 decision to add a 2nd dose.

216 As of 2009, most childhood vaccines in the US routine childhood schedule were determined to be cost-
217 saving. Some new vaccines were determined to be not cost-saving but cost-effective and were
218 implemented into the routine childhood schedule in the US, including hepatitis A vaccine and rotavirus
219 vaccines.[32] Cost-effectiveness analysis has become a standard method to use in estimating how much
220 benefit a vaccine offers relative to its costs, and it has become an influential element in decision making.
221 However, the transferability and comparability among economic analyses from different developed
222 countries remains problematic. Local data and guidelines and different methodologies have been used
223 in the analyses for each country. These differences included discount rates for costs and health
224 outcomes, perspectives (societal or payor), measurement of health-related quality of life and modeling
225 approaches. For example, different discount values were recommended for each country: 5% for
226 Australia, 5% for Canada, 3.5% for UK, and 3% for USA.[33–36]

227 In the US, the Department of Health and Human Services provides a mechanism for advancing the
228 development and purchase process of vaccines for use in public health medical emergencies through
229 the Biomedical Advanced Research and Development Authority (BARDA). BARDA has the authority,
230 funding, mechanisms and partners to transition medical countermeasures across the “valley-of-death”,
231 i.e. — according to Plotkin: “the critical steps after good preclinical data have been obtained, comprising
232 manufacture to Food and Drug Administration standards, a phase 1 clinical trial, and proof of concept in
233 terms of protective immune responses”.[12,37,38] BARDA was explicitly created to help product
234 manufacturers transition medical countermeasures across the so-called “valley-of-death” represented
235 by the late stages of product development, when the conduct of clinical trials, scale-up of
236 manufacturing, and investment in process development pose significant technical challenges and
237 significantly escalate costs. Because of these challenges, the “valley-of-death” is frequently identified as
238 a particularly vulnerable stage in the development of products that address unmet public health needs.
239 BARDA has mechanisms to expedite these trials by cost-sharing development with manufacturers as one
240 mechanism to facilitate safe and effective product development for public health emergencies. Other
241 mitigating approaches BARDA uses include public-private partnerships, joint oversight committees, and
242 core service networks to help developers with clinical, non-clinical, manufacturing and fill/finish
243 activities. BARDA also supports innovation by investing in research, tools and technologies.[39,40]
244 BARDA’s funding and role in helping vaccines across the “valley-of-death” is critical since many of these
245 vaccines for potential emergencies have no market unless the emergency actually occurs and
246 manufacturers would have very limited incentives to make the necessary investments to bring these
247 products forward. Beginning vaccine development during a public health emergency would clearly not
248 provide for the timely delivery of needed vaccines. BARDA also provides vaccine manufacturers with
249 access to subject matter experts in critical disciplines such as regulatory and quality affairs, clinical trial
250 design and implementation, and bio-manufacturing as well as access to laboratory, clinical trial network,

and manufacturing infrastructure. BARDA further supports innovation by investing in relevant research, tools and technologies.

The future of vaccine innovation in the developed world

In addition to disease epidemiology, vaccine safety and efficacy, and cost-effectiveness, other attributes may need to be emphasized in the development of future vaccines. For example, the long term duration of immunity is often unknown at the time of vaccine licensure and initial recommendations for vaccine use. If immunity to a newly licensed and implemented vaccine turns out to be short lived, there may be an incentive to develop a vaccine with longer lasting immunity. For instance, while the initial effectiveness of acellular pertussis vaccines was high and led to recommendations for its use, it has now been shown that immunity wanes with time. The US and many other countries have experienced a major resurgence of pertussis after switching to a schedule using only acellular pertussis vaccines. The current DTaP and Tdap vaccines induce good immunity immediately following completion of the vaccination series, but this immunity begins to wane as early as the 2nd year post-administration in adolescents and in general within 4-12 years of administration.[41,42] Recent resurgences of pertussis have put pressure on the market to respond. However, it is unclear whether this will be sufficient pressure to result in a new, more efficacious vaccine since there is no serologic correlate of protection and doing clinical trials of duration of efficacy will be difficult and expensive. Programmatic feasibility also may be an important consideration in spurring vaccine innovation as seen with the push to create a universal influenza vaccine (i.e., a vaccine which will protect against all strains of influenza both at the present time and in the future). A universal influenza vaccine with long term immunity could eliminate both the need for yearly vaccinations and the problem of strain mismatches in any given year. Efforts are underway to achieve a universal influenza vaccine, but the science and technology are complex. Another factor that impacts programmatic feasibility of a new vaccine is timing of the dose(s), especially

274 for vaccines given outside of the routine childhood schedule. When recommendations are made for new
275 vaccines, particularly with young children, an attempt is made to fit it in to the existing schedule to
276 reduce the burden on the patient and parents. At least one adolescent visit has been added to
277 immunization schedules in most countries to accommodate booster doses of Tdap and meningococcal
278 vaccines, paving the way for HPV series initiation. Subsequent dose(s) of HPV (total doses vary by
279 country) can be difficult to administer in countries with limited school-based vaccine delivery programs
280 due to subsequent doses falling during a time when no standard healthcare visit is normally scheduled.

281 Two other considerations for incentivizing development of new vaccines are allaying public fear and
282 easing societal burden. Though the developed world may not be in great danger of Ebola outbreaks, the
283 severity of the disease has caused fear and panic even in developed countries resulting in public outcry
284 for an Ebola vaccine in many places where the risk of an Ebola outbreak is very low. During the most
285 recent outbreak of Ebola, this public fear and demand spurred governments to help push forward
286 existing Ebola vaccine candidates whose development had stagnated during Ebola-free periods.

287 However, as the fear wanes, it is uncertain whether funding and impetus will remain sustainable enough
288 to elicit a viable vaccine for future outbreaks. Alternately, development of vaccines for the prevention of
289 HIV as well as for viruses and bacteria that have acquired antimicrobial resistance (AMR) such as
290 *Clostridium difficile* (*C. difficile*) or methicillin-resistant *Staphylococcus aureus* (MRSA), though targeting
291 a potentially narrow segment of the population, may be important in reducing the major societal
292 burdens being incurred by the long-term treatment of HIV and/or persistent or recurring infections with
293 antimicrobial resistant organisms. There are currently multi-partner, multi-disciplinary international
294 efforts designed to facilitate development of HIV vaccines that are funded by private and public sources
295 and, to some extent, unified in purpose and direction.[43] The WHO and the US government have issued
296 calls to accelerate research and development for, among other things, vaccines to combat AMR
297 organisms by preventing infections with these organisms rather than treating AMR infections.[44–46]

298 What impact these calls will have on research and development efforts, in the absence of tangible
299 financial incentives, is unclear.

300 Previous attempts in the US to identify specific vaccine development priorities include IOM reports in
301 1985 and 1999 that focused on vaccines for use in the US. Of the 14 vaccines that were prioritized in
302 1985, 7 have been developed, licensed, and recommended for widespread use, and 7 are still in various
303 stages of research and development. In the later IOM report completed in 1999, 26 vaccine candidates
304 were prioritized from most to less favorable and these 26 included all 9 unrealized vaccines from the
305 previous (1985) list.[50,51] Overall, of the 26 identified candidates, only one (*Histoplasma capsulatum*)
306 has languished with no apparent or substantial progress, 19 have ongoing attempts in progress, 4 have
307 been licensed and recommended for widespread use, 3 have been licensed and recommended for
308 limited use¹. [See Table 3 for breakdown by IOM Prioritization].[52] However, of the 26 candidates
309 identified as development priorities in the US, less than 15% of them (4 vaccines) have been licensed and
310 recommended over the past few decades. Development of some vaccines stall due to insufficient funding
311 when pharmaceutical companies indicate a weak market for specific vaccines despite being
312 recommended for development.[53] Barriers to vaccine development that were identified in the IOM
313 report in 1999 included manufacturer potential liability for both development of vaccines that target
314 special subpopulations such as pregnant women and populations that fall outside coverage of the
315 Vaccine Injury Compensation Program (VICP)² which only covers vaccines recommended for routine use

¹ A vaccine against *Borrelia burgdorferi*, or the cause of “Lyme Disease”, was licensed in 1998 and withdrawn in 2002 due to unsubstantiated concerns over vaccine safety and insufficient consumer demand.

² The program is funded by a \$.75 excise tax on vaccines recommended by the Centers for Disease Control and Prevention for routine administration to children, the excise tax is imposed on each dose (i.e., disease that is prevented) of a vaccine. Trivalent influenza vaccine for example, is taxed \$.75 because it prevents one disease; measles-mumps-rubella vaccine, which prevents three diseases, is taxed \$2.25. The Department of Treasury collects the excise taxes and manages the Fund’s investments and produces Vaccine Injury Compensation Trust Fund Monthly Reports. Funded by an excise tax on vaccines routinely recommended for children, VICP in the United States provides compensation to eligible people found to be injured by certain vaccines because for most vaccines a decision to accept the vaccine not only provides individual benefit but also induces community

in children, although adults, including pregnant women, injured by these vaccines are eligible for compensation.[54] Some of the immunization development gaps identified in the IOM report have been addressed and there are efforts underway to address others, such as issues regarding vaccines targeting pregnant women. Reducing manufacturer liability will help ensure adequate vaccine supply and stabilize vaccine costs.[55] Other considerations recommended by the IOM at that time continue to resonate: the need for development of combination vaccines to promote more rational vaccine schedules and development of alternatives to injected vaccines (e.g. oral drops, sprays, and more recently microneedles).

In developed countries vaccine development and innovation is funded largely by governments (e.g., NIH, NIAID, UK Medical Research Council) and industry (e.g., pharmaceutical manufacturers, biotechnology companies). Private organizations (e.g., Bill & Melinda Gates Foundation, PATH, Wellcome Trust) play a larger role in funding vaccine research and development for use in developing countries. Coordination among government, vaccine manufacturers including biotech firms, and private organizations to better focus and align efforts at a high level may be needed to navigate the complex future of vaccine development. Furthermore, new and improved publicly-funded risk-mitigation strategies may be necessary to retain industry interest and focus on disease prevention rather than disease treatment. Examples of such risk-mitigation strategies that have been used in the private sector for developing countries and may have implications for use by government recommending bodies are the use of target product profiles and advance market commitments. Target product profiles are technical strategies whereby stakeholders identify priorities that a vaccine candidate must achieve to maximize utilization once developed. Advance market commitments establish a guaranteed market for vaccines that meet

protection. Even in cases in which such a finding of vaccine injury is not made, individuals may receive compensation through a settlement. Thus, in the rare instances that a person is injured by a vaccine due to a recognized adverse event, the injured can be compensated and do not need to go to the tort system.

pre-determined public health objectives (e.g. immunogenicity, safety, price).[58] The development of specific target product profiles and implementation of risk-mitigating measures like advance market commitments can focus vaccine development efforts on the areas of highest need. Moreover, strategies such as those used by BARDA to support vaccine development against defined public health threats could, in theory, be turned to address deficits in innovation for non-emergency use vaccines through the establishment of a global vaccine development fund as recently has been called for. [12] BARDA's efforts to promote the development of vaccines and other products to address public health emergency preparedness requirements have resulted in the licensure, approval, or clearance of 23 medical products in the last 9 years. The core elements of BARDA's success have been having a mandate from Congress and the President to operate, a clear statement of requirements, and ample funding. These elements would likely be required for any similar effort to promote vaccine innovation in areas characterized by market failure or apathy.

Conclusion

Development and production of future vaccines face enormous economic hurdles as available approaches and technologies become more complex and target populations for vaccine use may be narrow and not universal. As such, cost-mitigating strategies and incentives, public, private or a combination of the two, will likely be needed to continue to spur major advances in vaccine technologies and development, especially for diseases affecting smaller risk groups or limited geographic locations, or for rare outbreak pathogens, where there is less commercial incentive. Moreover, groups or organizations involved in the development, licensure and implementation of specific vaccines are faced with many competing demands for attention and will need a focused and aligned approach in future efforts. Governments will need to ensure that public funds – a major source of funding for biological and vaccine related research – are directed towards modern technologies with

360 the most promise to yield impactful results via established pathways such as through recommending
361 bodies setting priorities.

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References

- [1] Plotkin SA, Orenstein WA, Offit PA. A short history of vaccination. *Vaccines*. 6th ed., 2013, p. Table 1–1, page 6.
- [2] The Royal College of Pathologists of Australasia. *Immunisation and Vaccine Preventable Diseases*. 2012.
- [3] Public Health Agency of Canada. The Chief Public Health Officer’s Report on the State of Public Health in Canada, 2013 *Infectious Disease—The Never-ending Threat*. 2013.
- [4] Centers for Disease Control and Prevention. Notifiable Diseases and Mortality Tables. *Morb Mortal Wkly Rep (MMWR)* 2012;60:1762–75.
- [5] Roush SW, Murphy T V. Historical comparisons of morbidity and mortality for vaccine-preventable diseases in the United States. *JAMA* 2007;298:2155–63.
- [6] Menzies R, Turnour C, Chiu C, McIntyre P. Vaccine preventable diseases and vaccination coverage in Aboriginal and Torres Strait Islander people, Australia 2003 to 2006. *Commun Dis Intell* 2008;32 Suppl:S2–67.
- [7] Centers for Disease Control & Prevention (CDC). *Active Bacterial Core Surveillance Provisional Report: Streptococcus pneumoniae, 2010*. 2010.
- [8] Cortese MM, Parashar UD, Centers for Disease Control & Prevention (CDC). Prevention of rotavirus gastroenteritis among infants and children: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2009;58:1–25.
- [9] Hinman AR, McKinlay MA. Immunization Equity. *Am J Prev Med* 2015;49:S399–405.
- [10] McCullers JA, Dunn JD. Advances in vaccine technology and their impact on managed care. *P T* 2008;33:35–41.
- [11] Dertzbaugh MT. Genetically engineered vaccines: an overview. *Plasmid* 1998;39:100–13.
- [12] Plotkin SA, Mahmoud AA, Farrar JJ. Establishing a Global Vaccine-Development Fund. *New Engl J Med* 2015;373:297–300.
- [13] Coleman MS, Sangrue N, Zhou F, Chu S. Factors Affecting U.S. Manufacturers’ Decisions to Produce Vaccines. *Health Aff* 2005;24:635–42.
- [14] Australia Government Department of Health. Australian Technical Advisory Group on Immunisation. *Immunise Aust Progr* 2015.
- [15] De Wals P. Optimizing the acceptability, effectiveness and costs of immunization programs: the Quebec experience. *Expert Rev Vaccines* 2011;10:55–62.

394 [16] Ismail SJ, Langley JM, Harris TM, Warshawsky BF, Desai S, FarhangMehr M. Canada's National
395 Advisory Committee on Immunization (NACI): Evidence-based decision-making on vaccines and
396 immunization. *Vaccine* 2010;28.

397 [17] Public Health Agency of Canada. Immunization in Canada. *Can Immun Guid* 2013.

398 [18] The Joint Committee on Vaccination and Immunisation. The Green Book: Immunisation against
399 infectious disease. 3rd ed. United Kingdom Department of Health; 2013.

400 [19] Public Health England. Joint Committee on Vaccination and Immunisation Code of Practice. 2013.

401 [20] Devlin N, Parkin D. Does NICE have a cost-effectiveness threshold and what other factors
402 influence its decisions? A binary choice analysis. *Health Econ* 2004;13:437–52.

403 [21] McCabe C, Claxton K, Culyer AJ. The NICE cost-effectiveness threshold: What it is and what that
404 means. *Pharmacoeconomics* 2008;26:733–44.

405 [22] Smith JC, Hinman AR, Pickering LK. History and Evolution of the Advisory Committee on
406 Immunization Practices — United States, 1964–2014. *Morb Mortal Wkly Rep* 2014;63:955–8.

407 [23] Ahmed F, Temte JL, Campos-Outcalt D, Schunemann HJ, Group AEBRW. Methods for developing
408 evidence-based recommendations by the Advisory Committee on Immunization Practices (ACIP)
409 of the U.S. Centers for Disease Control and Prevention (CDC). *Vaccine* 2011;29:9171–6.

410 [24] Walton LR, Orenstein WA, Pickering LK. The history of the United States Advisory Committee on
411 Immunization Practices (ACIP). *Vaccine* 2015;33:405–14.

412 [25] Smith JC, Snider DE, Pickering LK. Immunization policy development in the United States: The role
413 of the advisory committee on immunization practices. *Ann Intern Med* 2009;150:45–9.

414 [26] Whitney CG, Zhou F, Singleton J, Schuchat A. Benefits from immunization during the vaccines for
415 children program era - United States, 1994-2013. *MMWR Morb Mortal Wkly Rep* 2014;63:352–5.

416 [27] Centers for Disease Control and Prevention. Vaccines for Children Program. Quick Overv Parents
417 2014.

418 [28] U.S.C. Omnibus Budget Reconciliation Act, (Medicaid - Immunizations), 13.B4-1 Part IV
419 Immunizations, Section 1928(e) - Use of Pediatric Vaccines List. 1993.

420 [29] Miller M a, Sutter RW, Strebel PM, Hadler SC. Cost-effectiveness of incorporating inactivated
421 poliovirus vaccine into the routine childhood immunization schedule. *JAMA* 1996;276:967–71.

422 [30] Prevots DR, Burr RK, Sutter RW, Murphy T V. Poliomyelitis prevention in the United States.
423 Updated recommendations of the Advisory Committee on Immunization Practices (ACIP).
424 *MMWR Recomm Rep* 2000;49:1–22; quiz CE1–7.

425 [31] Centers for Disease Control and Prevention. Measles, Mumps, and Rubella -- Vaccine Use and
426 Strategies for Elimination of Measles, Rubella, and Congenital Rubella Syndrome and Control of
427 Mumps: Recommendations of the Advisory Committee on Immunization Practices (ACIP). Morb
428 Mortal Wkly Rep (MMWR)C 1998;47:1–57.

429 [32] Zhou F, Shefer A, Wenger J, Messonnier M, Wang LY, Lopez A, et al. Economic evaluation of the
430 routine childhood immunization program in the United States, 2009. Pediatrics 2014;133:577–85.

431 [33] Australia Government Department of Health. Guidelines for preparing submissions to the
432 Pharmaceutical Benefits Advisory Committee. Version 4. 2015.

433 [34] Canadian Agency for Drugs and Technologies in Health. Guidelines for the economic evaluation
434 of health technologies: Canada. 3rd Editio. 2006.

435 [35] National Institute for Health and Care Excellence. Guide to the methods of technology appraisal
436 2013. 04 April 2. 2013.

437 [36] Haddix AC, Teutsch SM, Corso PS, editors. Prevention Effectiveness: A Guide to Decision Analysis
438 and Economic Evaluation. 2nd Editio. New York, NY: 2002.

439 [37] Schnirring L. Experts propose \$2 billion global vaccine fund. Cent Infect Dis Res Policy 2015.

440 [38] Robinson R. BARDA Vaccines. Natl. Vaccine Advis. Comm. Meet. Febr. 11, 2014, Washington,
441 D.C.: 2014, p. 1–18.

442 [39] Larsen J. BARDA’s Broad Spectrum Antimicrobial (BSA) Program. Natl. Vaccine Advis. Comm.
443 Briefing, Febr. 2015, Washington, D.C.: 2015, p. 1–19.

444 [40] Department of Health and Human Services. BARDA unveils path forward in the BARDA Strategic
445 Plan 2011-2016. Public Heal Emerg 2015.

446 [41] Klein NP, Bartlett J, Fireman B, Baxter R. Waning Tdap Effectiveness in Adolescents. Pediatrics
447 2016;137:1–9.

448 [42] Wendelboe AM, Van Rie A, Salmaso S, Englund J a. Duration of immunity against pertussis after
449 natural infection or vaccination. Pediatr Infect Dis J 2005;24:S58–61.

450 [43] Fred Hutchinson Cancer Research Center. HIV Vaccine Trials Network. About HVTN n.d.

451 [44] The White House. National Strategy for Combating Antibiotic Resistant Bacteria. 2014.

452 [45] World Health Organization. Antimicrobial Resistance Global Report on Surveillance. 2014.

453 [46] World Health Organization. WHO Global Strategy for Containment of Antimicrobial Resistance.
454 2001.

455 [47] Dekker CL, Gordon L, Klein J, NVAC Subcommittee on Vaccine Development and Supply. Dose
456 Optimization Strategies for Vaccines: The Role of Adjuvants and New Technologies. 2008.

457 [48] Vogel FR. Improving vaccine performance with adjuvants. Clin Infect Dis 2000;30 Suppl 3:S266–
458 70.

459 [49] Scheerlinck JPY. Genetic adjuvants for DNA vaccines. Vaccine 2001;19:2647–56.

460 [50] Committee to Study Priorities for Vaccine Development Division of Health Promotion and Disease
461 Prevention Institute of Medicine. Vaccines for the 21st Century: A Tool for Decision Making.
462 National Academies Press; 1999.

463 [51] AIDS Info. IOM Report Offers New Look at U.S. Vaccine Priorities. HIV/AIDS News 1999.

464 [52] The College of Physicians of Philadelphia. The History of the Lyme Disease Vaccine. Hist Vaccines
465 2015.

466 [53] Sando L. Towards the first Helicobacter pylori vaccine? Technol Online 2014.

467 [54] Health Resources and Services Administration. National Vaccine Injury Compensation Program
468 n.d.

469 [55] Health Resources and Services Administration. National Vaccine Injury Compensation Program.
470 HRSAGOV 2015.

471 [56] Department of Health and Human Services. National Vaccine Plan Implementation: Protecting
472 the Nation’s Health Through Immunization. 2010.

473 [57] Department of Health and Human Services. The Annual Report of the State of the National
474 Vaccine Plan. 2014.

475 [58] National Vaccine Advisory Committee. Enhancing the Work of the Department of Health and
476 Human Services National Vaccine Program in Global Immunization: Recommendations of the
477 National Vaccine Advisory Committee. Public Health Rep 2014;129:12–73.

478 [59] Plotkin SA, Orenstein WA, Offit PA, editors. Section 3: Vaccines in development and new vaccine
479 strategies. Vaccines. 6th ed., Elsevier Saunders; 2013, p. 1008–181.

480 [60] The Royal College of Pathologists of Australasia. Fact File: Immunisation and Vaccine Preventable
481 Diseases 2012:1–14.

482 [61] National Centre for Immunisation Research and Surveillance of Vaccine Preventable Diseases.
483 Summary of National Surveillance Data on Vaccine Preventable Diseases in Australia, 2008–2011.
484 Commun Dis Intell 2016;40:S1–70.

485 [62] Menser M, Hudson J, Murphy A, Upfold L. Epidemiology of congenital rubella and results of
486 rubella vaccination in Australia. Rev Infect Dis 1985;Mar-Apr:S37–41.

487 [63] Khandaker G, Zurynski Y, Jones C. Surveillance for congenital rubella in Australia since 1993:
488 Cases reported between 2004 and 2013. *Vaccine* 2014;32:6746–51.

489 [64] Sullivan EM, Burgess MA, Forrest JM. The epidemiology of rubella and congenital rubella in
490 Australia, 1992 to 1997. *Commun Dis Intell* 1999;23:209–14.

491 [65] Cheffins T, Chan A, Keane RJ, Haan EA, Hall R. The impact of rubella immunisation on the
492 incidence of rubella, congenital rubella syndrome and rubella-related terminations of pregnancy
493 in South Australia. *Br J Obs Gynaecol* 1998;105:998–1004.

494 [66] Condon R, Bower C. Rubella vaccination and congenital rubella syndrome in Western Australia.
495 *Med J Aust* 1993;158:379–82.

496 [67] Chan J, Dey A, Wang H, Martin N, Beard F. Australian vaccine preventable disease
497 epidemiological review series: rubella 2008–2012. *Commun Dis Intell* 2015;39:E19–26.

498 [68] Public Health Agency of Canada. Immunization and Vaccine-Preventable Diseases—Staying
499 Protected. Chief Public Heal Off Rep State Public Heal Canada, 2013 Infect Dis Never-Ending
500 Threat 2013.

501 [69] United Kingdom National Department of Health. Immunisation against infectious disease. Green
502 B 2008.

503 [70] Notifications of Infectious Diseases. Mumps Notifications in England and Wales (England only), by
504 Age Group, 1989 - 2012. *Natl Arch* 2013.

505 [71] Registrar General’s Annual Report. Notifications by Age Group and Sex, England and Wales: 1969
506 - 2014. *Off Natl Stat Commun Dis Stat Ser MB2 Cent Infect Notif Infect Dis* 2014.

507 [72] Centers for Disease Control and Prevention. Notifiable Diseases and Mortality Tables. *Morb*
508 *Mortal Wkly Rep* 2015;63:ND – 733 – ND – 746.

509 [73] Schuchat A. Controlling Vaccine Preventable Diseases in the US and Global Immunization Efforts.
510 2012.

511 [74] Hagan JE, Wassilak SG, Craig AS, Tangerman RH, Diop OM, Burns CC, et al. Progress toward polio
512 eradication - worldwide, 2014-2015. *2Morbidity Mortal Wkly Rep* 2015;64:527–31.

513 [75] World Health Organization. The Smallpox Eradication Programme - SEP (1966-1980) 2010.

514 [76] Nolan TM. The Australian model of immunization advice and vaccine funding. *Vaccine* 2010;28.

515 [77] Parliament of Australia. National Health Amendment (Immunisation Program) Bill 2005. 2005.

516 [78] Australian Government Department of Health. Australian Technical Advisory Group on
517 Immunisation (ATAGI) Bulletin 55th Meeting: 16–17 October 2014, Canberra: 2014.

518 [79] Australian Government Department of Health. Australian Technical Advisory Group on
519 Immunisation. Immunise Aust Progr 2016.

520 [80] Public Health Agency of Canada. National Advisory Committee on Immunization (NACI). About
521 NACI 2015.

522 [81] Public Health Agency of Canada: National Advisory Committee on Immunization. Evidence-based
523 recommendations for immunization - Methods of the National Advisory Committee on
524 Immunization. Canada Commun Dis Rep 2009:1–10.

525 [82] United Kingdom National Health Service. JOINT COMMITTEE ON VACCINATION AND
526 IMMUNISATION. Code Pract 2013:1–45.

527 [83] United Kingdom National Health Service. Joint Committee on Vaccination and Immunisation
528 2013.

529 [84] Centers for Disease Control and Prevention. Advisory Committee on Immunization Practices.
530 ACIP Chart 2014.

531 [85] Institute of Medicine. Vaccines for the 21st Century: A Tool for Decisionmaking. 1999.

532 [86] National Institute of Allergy and Infectious Diseases. IOM Report Offers New Look at U.S. Vaccine
533 Priorities. HIV/AIDS News 1999.

534 [87] National Research Council. Vaccine Supply and Innovation. 1985.

535

536 **Conflict of Interest**

537 KS: No conflicts

538 AP: No conflicts

539 PdW: Received research grants, and reimbursements of travel expenses from vaccine manufacturers
540 including Glaxo-Smith-Kline, Novartis, Sanofi Pasteur, and Pfizer, as well as from governmental agencies
541 including the Quebec Ministry of Health and Social Services, Health Canada, and the Public Health
542 Agency of Canada.

543 RA: No conflicts

544 FZ: No conflicts

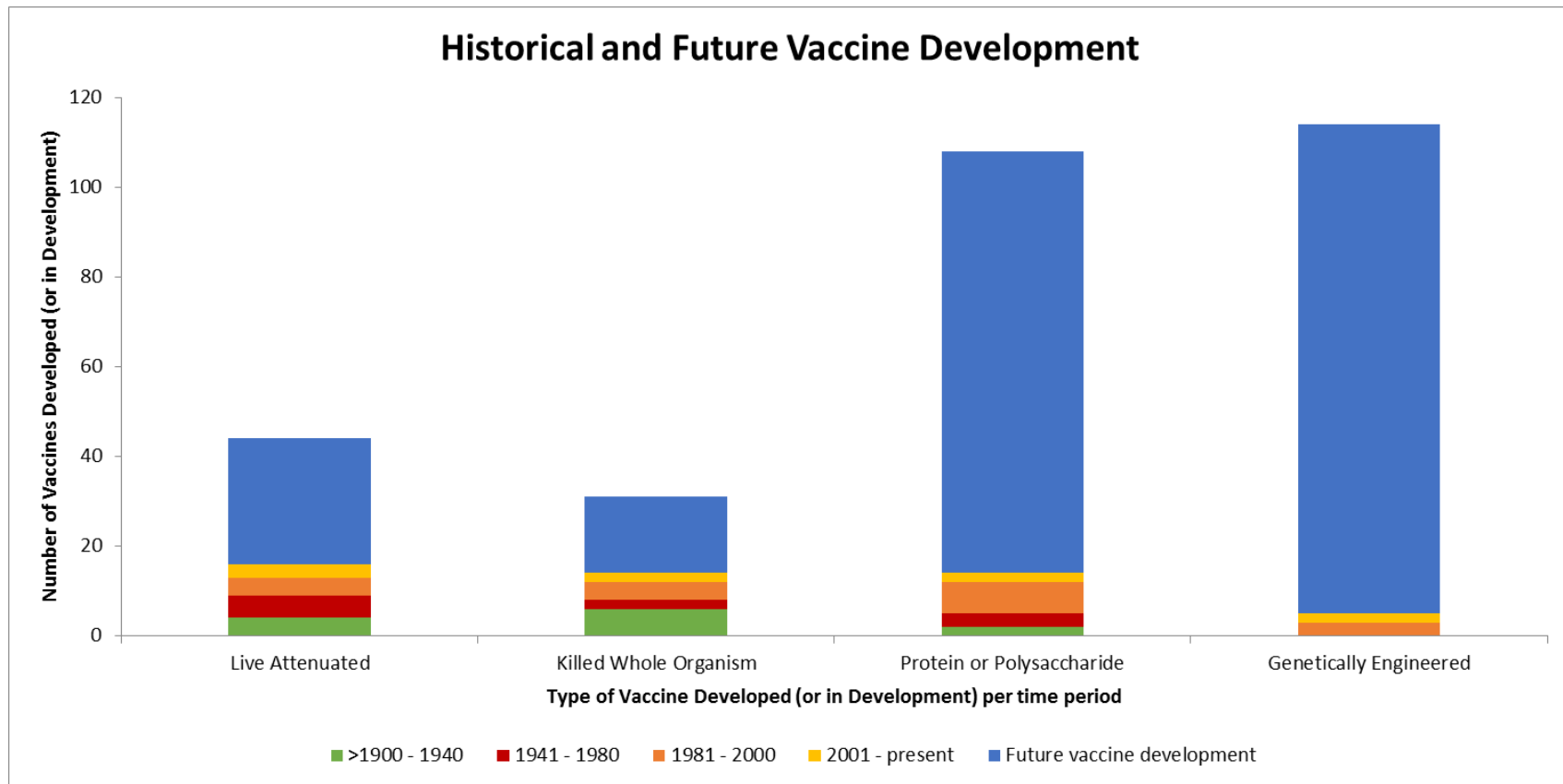
545 RH: No conflicts

546 LP: No conflicts

547 WO: Travel support to meeting on vaccine innovation provided by GSK

548 **Figures and Tables (submit in separate files)**

549 **Figure 1. Historical Vaccine Development and Future Vaccine Candidates**



550

551 Numbers for historical vaccine development (1900-2010) are from Table 1-1 Outline of the Development of Human Vaccines from Chapter 1: A
552 Short History of Vaccines in Vaccines 6th ed. [1]

553 Supplemental table 1-1 provides a more detailed breakdown of how we estimated future vaccines for this figure which came from Section 3:
554 Vaccines in Development and new vaccine strategies in Vaccines 6th ed. [59]

555

556 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%
<i>Haemophilus influenzae</i> 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%

557 (a) Deaths in 1993 compared with deaths in 2007 for Hib; Deaths from disease in 1926-1935 period (prior to introduction of these vaccines)
558 compared to deaths in 1996-2000 for Diphtheria, Measles, Pertussis, Tetanus [60] Percentages for CRS, Mumps and Rubella in Australia are
559 1985 data compared to 2011 data[61–67], but recent resurgences of mumps among young adults threaten progress.

560 (b) Comparing 5 years prior to vaccine introduction to 2007-2011 peak annual number of cases, pre-vaccine introduction ranges: CRS=1979-
561 1983, Diphtheria=1925-1929, Hib=1986-1990, Measles=1950-1954, Mumps=1950-1954, Pertussis=1938-1942, Rubella=1950-1954,
562 Tetanus=1957-1961 [68]

563 (c) Comparing reduction from year prior to introduction and most recent data available, pre-vaccine year and most recent data year are: CRS:
564 1971 & 2003; Diphtheria: 1914 & 2002; Hib: 1990 & 2004; Measles: 1968 & 2004; Mumps: Prior to recent outbreak; decrease was estimated at
565 90%; Pertussis: 1940 & 2003; Rubella: 1982 & 2005; Tetanus: 1989 & 2004 for under age 65 years old[69–71]

566 (d) Comparing 20th century morbidity to reported cases in 2014 [72,73]

567 (e) Polio declared eliminated in 2000 in Australia, 1991 in Canada & US, 2002 in UK [74]

568 (f) Smallpox worldwide eradication declared 1980 [75]

569

570 Table 2. Comparison of Committees Which Advise Governments on Vaccination Policy Regarding Recommendations and Usage in Select
571 Developed Countries

Recommending body	Australia: Australian Technical Advisory Group on Immunisation (ATAGI) (a)	Canada: National Advisory Committee on Immunization (NACI) (b)	United Kingdom: Joint Committee on Vaccination and Immunisation (JCVI) (c)	United States: Advisory Committee on Immunization Practices (ACIP) (d)
Established	1992	1964	1963	1964
Universal Childhood antigens	13	16	16	16
Voting Members	12	12	15	15
Ex Officio and Liaison Members	5	17	N/A	38
Expertise	epidemiology pediatric infectious diseases public health indigenous health immunobiology clinical trial laboratory vaccine research consumer general practice microbiology	pediatrics infectious diseases Immunology medical microbiology internal medicine public health	infectious diseases epidemiology virology bacteriology immunology vaccinology neurology public health	mathematical modelling health economics general practice nursing paediatrics program-management Infectious diseases Immunology Virology Bacteriology Pediatrics including adolescent medicine Internal medicine Family medicine Nursing State/local health department Public health, preventive medicine Vaccine research and policy Consumer concerns
Key considerations	burden of disease vaccine safety and effectiveness cost effectiveness and evidence based advice	burden of disease vaccine safety and effectiveness product monograph and other relevant scientific and technical information	burden of disease vaccine safety and efficacy impact cost-effectiveness	burden of disease vaccine effectiveness and efficacy vaccine safety feasibility equity
Cost effectiveness influence	recommendations from Pharmaceutical Benefits Advisory Committee (PBAC)(e)	not considered	heavily considered(f)	guidance is subjective
Guidance given for development of new vaccines?	yes, see TOR below	does not appear to	does not appear to	does not appear to
Terms of Reference for recommending new vaccines	-provide technical advice on the medical administration of vaccines available in Australia, including those on the National Immunisation Program - provide advice to research funding bodies regarding the status of current Immunisation	available on request from the Secretariat (functions provided by the Centre for Immunisation & Respiratory Infectious Disease) - requested, pending receipt	-provide advice on matters relating to the provision of vaccination and immunisation services, being facilities for the prevention of illness -advise on matters relating to vaccination and immunisation -make recommendations relating to new provision for vaccination (other than	-provide advice for the control of diseases for which a vaccine is licensed in the U.S. -address use of vaccines and may include recommendations for administration of immune globulin preparations and/or antimicrobial therapy -For each vaccine, the committee advises on population groups and/or circumstances in

research and areas where additional research is required
 -advise on matters relating to the ongoing strength of evidence pertaining to existing, new and emerging vaccines in relation to their effectiveness and use in Australian populations
 -consult on matters relating to the implementation of Immunisation policies, procedures and vaccine safety.

vaccination relating to travel or occupational health) under a national vaccination programme or to changes to existing provision under such a programme, that are based on an assessment which demonstrates cost-effectiveness.

which a vaccine or related agent is recommended, route/dose/frequency of administration, and contraindications/precautions for use

572

573 (a) Sources for Australia's ATAGI [76–79]

574 (b) Sources for Canada's NACI [80,81]

575 (c) Sources for UK JCVI [82,83]

576 (d) Sources for US ACIP [84]

577 (e) The PBAC does not apply a fixed cost-effectiveness threshold for positive funding recommendations. The PBAC has a Managed Entry Scheme to recommend the listing of a new medicine at a price justified by the existing evidence at launch. The price of the product will be adjusted (upward or downward) on the basis of cost-effectiveness estimates arising from the generation of postlaunch randomized clinical trial or "fit-for-purpose" evidence. (Ref: Wonder M1, Backhouse ME, Sullivan SD. Australian managed entry scheme: a new manageable process for the reimbursement of new medicines? Value Health. 2012 May;15(3):586-90.)

581

582 (f) The Appraisal Committee, an independent advisory body, makes recommendations to the NICE regarding the clinical and cost effectiveness of treatments for use within the National Health Service (NHS). It is also the role of the Appraisal Committee not to recommend treatments if the benefits to patients are unproven, or if the treatments are not cost effective. The NICE is responsible for the dissemination of the final guidance to the NHS. The Appraisal Committee does not use a precise maximum acceptable cost-effectiveness ratio (CER) above which treatment would automatically be defined as not cost effective or below which it would. Below a most plausible CER of £20,000 per QALY gained, the decision to recommend the use of the treatment is normally based on the cost-effectiveness estimate and the acceptability of the treatment as an effective use of NHS resources. Above a most plausible CER of £20,000 per QALY gained, judgements about the acceptability of the treatment as an effective use of NHS resources will take account of several other factors. Above a most plausible CER of £30,000 per QALY gained, the Committee will need to identify an increasingly stronger case for supporting the treatment as an effective use of NHS resources, (Ref 35)

590

591 Table 3. Progress on Vaccines Prioritized for Development in the US by IOM in 1985 and 1999

Vaccine*	Target Population	IOM Category	Current Status (as of 2015)
<i>Cytomegalovirus</i> **	12-year-olds	Most Favorable	In progress
Influenza virus**	general population	Most Favorable	Licensed and Recommended
Insulin-dependent diabetes mellitus therapeutic	targeted	Most Favorable	In progress
Multiple sclerosis therapeutic	targeted	Most Favorable	In progress
Rheumatoid arthritis therapeutic	targeted	Most Favorable	In progress
Group B <i>streptococcus</i>	pregnant women high-risk adults	Most Favorable	In progress
<i>Streptococcus pneumoniae</i>	infants high-risk adults	Most Favorable	Licensed and Recommended
Chlamydia	12-year-olds	More Favorable	In progress
<i>Helicobacter pylori</i>	infants	More Favorable	In progress
Hepatitis C	infants	More Favorable	In progress
Herpes simplex virus**	12-year-olds	More Favorable	In progress
Human Papillomavirus	12-year-olds	More Favorable	Licensed and Recommended
Melanoma therapeutic	targeted	More Favorable	Licensed, limited use
<i>Mycobacterium tuberculosis</i>	high risk	More Favorable	In progress
<i>Neisseria gonorrhoeae</i> **	12-year-olds	More Favorable	In progress
Respiratory syncytial virus**	infants 12-year-olds	More Favorable	In progress
Parainfluenza virus**	infants primigravida	Favorable	In progress
Rotavirus**	infants	Favorable	Licensed and Recommended
Group A <i>streptococcus</i>	infants high-risk adults	Favorable	In progress
Group B <i>streptococcus</i> **	12-year-old girls primigravida resident infants	Favorable	In progress
<i>Borrelia burgdorferi</i> (Lyme Disease)	migrants all ages high-risk geographic areas resident infants	Less Favorable	Licensed, withdrawn
<i>Coccidioides immitis</i> **	migrants all ages high-risk geographic areas	Less Favorable	In progress
Enterotoxigenic <i>Escherichia coli</i>	infants travelers	Less Favorable	In progress
Epstein-Barr	12-year-olds resident infants	Less Favorable	In progress
<i>Histoplasma capsulatum</i>	migrants all ages high-risk geographic areas	Less Favorable	No known candidate in progress
<i>Neisseria meningitidis</i> group b	infants	Less Favorable	Licensed, limited use
<i>Shigella</i>	infants & travelers travelers only	Less Favorable	In progress

592 *denotes vaccines recommended for development in 1999 IOM report [85,86]

593 **denotes vaccines recommended for development in previous 1985 IOM Report[87]

594