

1 **Vital progress in immunization yet an unfinished agenda**

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4 ***Preface***

5 Vaccination against infectious diseases has changed the future of the human
6 species, saving millions of lives every year, both children and adults, and
7 providing major benefits to society as a whole. However, national and sub-
8 national coverage of vaccination varies greatly and major unmet needs persist.
9 Whereas scientific progress opens exciting perspectives in terms of new
10 vaccines, the road from discovery to sustainable implementation can be long
11 and rocky, from financing, development and licensing to programme
12 implementation and public acceptance. Immunisation is one of the best
13 investments in health and should remain a priority for research, industry,
14 public health and society.

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16 On 14 May 1796, 73 years before *Nature's* first issue, and inspired by Lady
17 Montagu's "variolation" concept, Edward Jenner inoculated 8-year old James
18 Phipps with cowpox pus to prove that the less virulent cowpox would protect
19 against smallpox. This experiment was a game changer in medicine and health.
20 For the first time it was possible to medically prevent infection in a healthy
21 person. Whereas vaccines were widely introduced in high income countries
22 since the late 1950s, it took 180 years since Jenner before the Expanded
23 Programme on Immunisation was launched in 1974, promoting access to 6
24 essential vaccines in all countries worldwide. Today, vaccines against 26
25 infectious diseases are internationally available according to WHO¹, although
26 more have been licensed worldwide, changing the future of the human
27 species. Others are in experimental public health use, such as Ebola vaccines,
28 or pilot implementation such as the RTS,s malaria vaccine, and about 240
29 vaccine candidates are in development². The US Centers for Disease Control
30 and Prevention declared vaccination the number one success story for public
31 health in the 20th century³.

32 However, progress in vaccine coverage remains highly uneven, between and
33 within countries, threatening hard-won progress and raising uncertainty about
34 how to make further advances. Vaccine-preventable diseases such as measles
35 are on the rise, and episodes of vaccine reluctance and refusal are occurring

36 globally, questioning one of the most transformative interventions for survival
37 and health.

38 This review focuses on *preventive immunisation in humans* and its impact
39 (rather than on *vaccines* themselves), including in low, middle and high income
40 countries. We discuss the current status of vaccine coverage, as well as unmet
41 needs, four hurdles to overcome to ensure sustainable immunisation
42 programmes starting with discovery of a new vaccine, the growing issue of
43 vaccine confidence, and conclude with a number of opportunities and needed
44 actions in order to ensure the full potential of immunisation for human health
45 and society. Vaccine product development challenges for low and middle
46 income countries, which were recently discussed in separate articles^{4,5}, and
47 therapeutic vaccines are not discussed.

48 Vaccines are biological products that induce protective immunity against
49 infection and disease; they consist of sub-components, killed, or inactivated
50 organisms which train the immune system for a future response to a natural
51 infection. They are probably the only medical intervention recommended for
52 every single individual on the planet. Unlike therapeutics, vaccines are used in
53 healthy people, demanding a very high standard of safety, and requiring
54 continuous monitoring for potential side effects. Besides considerations of
55 safety, effectiveness, impact, and cost, this raises complex governance,
56 regulatory, and public trust issues. All countries have a national immunisation
57 plan, often with goals inspired by the Global Vaccine Action Plan (GVAP) global
58 immunization goals for 2011-2020⁶.

59 ***How immunisation has critically contributed to health and society***

60 It is hard to imagine a world without vaccines. A decade ago, WHO, UNICEF
61 and the World Bank estimated that routine childhood immunization
62 programmes were preventing over 2.5 million deaths annually⁷. With the
63 increase in vaccine coverage, the growth of populations, and the introduction
64 of new life-saving vaccines, immunization is ever more important for survival.
65 Apart from preventing deaths, vaccines prevent disease and disability,
66 including in adults and the elderly. In a high income country such as the USA,
67 for a single birth cohort, vaccines prevent nearly 20 million cases of disease,
68 and over 40,000 deaths⁸.

69 A vaccine has for the first time in history eradicated a human disease,
70 smallpox. Efforts to eradicate polio are in the final stages with only two

71 countries, Afghanistan and Pakistan still experiencing wild polio virus
72 transmission. All countries except 13, have eliminated neonatal and maternal
73 tetanus. Without vaccination, there would be far more infections requiring
74 antibiotic therapy, exacerbating the major problem of drug resistant infections.

75 Between 1990 and 2017, immunisation contributed to a 55% global decline in
76 under-5 mortality with a drop from 87 to 39 deaths per 1000 live births⁹. Over
77 14 million deaths are estimated to be prevented through measles vaccination
78 alone between 2011 and 2020⁶.

79 Vaccination benefits not only those who are vaccinated, but others in their
80 family and community. This population wide benefit, called “herd immunity”,
81 reduces the exposure of unvaccinated individuals to pathogens through a
82 reduction or interruption of the chains of transmission. A recent study in
83 Kenya not only showed that the introduction of a pneumococcal vaccine
84 resulted in a major reduction in invasive pneumococcal disease, but also a
85 nearly 100% decline in incidence among infants too young to be vaccinated,
86 and over 74% reduction among unvaccinated children¹⁰. Community- or herd
87 immunity is an important consideration when estimating the full public health
88 value of immunisation. The threshold to achieve such community protection
89 can be as high as 95% for measles, but as low as 80% for rubella, and 60% in
90 high income settings for the effect to begin for pneumococcal vaccination,
91 meaning the programme strength required to derive additional impact varies
92 substantially by vaccine¹¹⁻¹³. These differences of required critical vaccination
93 coverage rates are due to R_0 ¹⁴, the basic reproductive ratio of an infection,
94 which can vary greatly among various infectious diseases. R_0 of a specific
95 infection indicates the average number of cases one case generates in a
96 population- in the case of measles it is 12 to 18, which is among the highest¹⁵.
97 It is an indicator of how contagious an infection is, and determines the
98 minimum level of vaccination coverage needed to generate herd immunity.

99 Potential long-term effects beyond direct protection against a specific
100 pathogen or disease have been attributed to a number of vaccines, in
101 particular the BCG vaccine against tuberculosis and measles vaccine, where
102 observational studies suggested a survival advantage compared to children
103 who had remained unvaccinated. These non-specific effects (also called
104 heterologous) would add to the disease-specific, proven benefits of vaccines,
105 and have been attributed to epigenetic changes in innate immune cells as
106 opposed to the adaptive immunity induced by the antigen-specific responses

107 to the vaccine^{16,17}. However, the importance of heterologous effects remains
108 controversial and plausible immunological findings still need to be validated in
109 large-scale clinical trials.

110 The benefits of vaccines in general go beyond health, and include economic,
111 educational, health security and other benefits¹⁸. Their full economic value is
112 not sufficiently quantified in assessments of cost-benefit, nor in investment
113 terms, and is an increasing area of inquiry and empiric measurement¹⁹.

114 Vaccination is a sound investment. Thus, the return on investment from
115 childhood immunization in Low and Middle Income Countries (LMIC) is high.
116 For every \$1 invested in immunization against 10 diseases, \$16 to \$18 are
117 saved in health care costs, and the net return is as high as \$44 per dollar spent
118 when the broad economic benefits are considered, though return on the
119 investment varies by individual vaccine²⁰. This is compared with the cost per
120 DTPcv3 (having received all three doses of DTP containing vaccine) vaccinated
121 child of \$27²¹. In the USA, net economic benefits of vaccination in one birth
122 cohort amount to almost \$69 million²².

123 Modelling and observational data suggest that in LMIC vaccination contributes
124 to poverty alleviation and protection. Financial risk protection benefits of
125 vaccination are accrued by the poorest households through reduction of
126 catastrophic and impoverishing health expenditures^{23,24}. There is also evidence
127 that vaccination improves childhood physical development, educational
128 outcomes, and equity in distribution of health gains²⁵. Finally, without
129 vaccines, absenteeism from school and work would be much higher, and
130 periodic epidemics would disrupt society. The economic impact of periodic
131 influenza epidemics for example is enormous²⁶⁻²⁸, and can be reduced by
132 immunization²⁹.

133 ***Vaccination is a life time investment (Figure 1)***

134 In addition to being the backbone of maternal and child health, vaccines
135 provide important health benefits for all stages in life. Given adaptations of the
136 immune system throughout life, not all vaccines work equally well at all stages
137 of life or in all geographical regions^{30,31}.

138 Starting in infancy, the presence of maternal antibodies in the newborn can
139 impede vaccine response, as the neonatal immune system undergoes its own
140 journey of ontogeny, which allows its adaptation from the “sterile” in utero
141 environment to the confrontation with colonising and potentially pathogenic
142 microorganisms³². Particular immunologic pathways have been identified³³.

143 Despite significant progress in reducing under-5 mortality, important gaps
144 remain in addressing neonatal morbidity and mortality. Neonates are
145 particularly vulnerable to infection with gram-negative bacteria and Group B
146 streptococcus, for which no neonatal vaccines currently exist^{33,34}. The gap in
147 early protection can potentially be bridged by administering vaccines to
148 women in pregnancy, relying on passively transferred antibody to protect
149 infants in the first few months of life, until vaccinations administered in infancy
150 or later can provide protection. Based on this principle, tetanus, influenza and
151 pertussis vaccination are recommended for pregnant women to prevent
152 neonatal infections, such as neonatal tetanus³⁵. This maternal immunisation
153 strategy may be expanded with promising vaccines against Group B
154 streptococcus and Respiratory Syncytial Virus³⁶.

155 For *adolescents*, lifesaving vaccines against human papilloma virus (the cause
156 of cervical, anal, penile and head and neck cancers) are being increasingly
157 introduced and must be administered prior to the likely acquisition of HPV via
158 sexual contacts. Vaccines against meningococcal meningitis, a potentially
159 lethal infection with a second peak in adolescence, have also been introduced
160 into this age group in some countries. New platforms such as schools had to be
161 engaged to administer these vaccines .

162 Outbreaks of mumps have very occasionally been seen in teenagers, despite a
163 solid vaccination record. This highlights the need for surveillance of all age
164 groups for outbreaks and could be due to waning of protection induced by
165 vaccines otherwise regarded as highly efficacious³⁷⁻³⁹.

166 Booster vaccines against diphtheria, tetanus and polio are required to
167 guarantee long-lasting protection and are required throughout adulthood to
168 maintain protective immunity levels – though recommendations may vary by
169 country.

170

171 A life course approach to vaccination has become ever more pressing with
172 pneumonia, influenza and shingles differentially affecting *older adults*, and
173 death rates from pneumonia and influenza are 130 times higher for adults
174 over 85, as compared to younger adults⁴⁰. Vaccination of the elderly with
175 existing vaccines could prevent up to 90 000 deaths per year in the United
176 States alone⁴¹.

177 *Adult* immunization does not have a clear prioritization in low- and middle
178 income countries, and is a complex programme across high income countries.

179 It is different from pediatric immunization which has a global programme and
180 focused, substantial funding. As the demographics are shifting across the world
181 to an older distribution a focus on adult immunization will become increasingly
182 relevant, as advocated by the World Coalition on Adult Immunization⁴².
183 Despite national recommendations^{43,44}, vaccine coverage among adults in high
184 income countries is uneven⁴⁵ (vaccine coverage for herpes zoster among adults
185 aged ≥ 60 was 24% compared with 65% for influenza among those aged ≥ 65 in
186 the US), and very low or not even available in most low and middle income
187 countries⁴⁶. Yet, several studies have shown good cost-effectiveness of adult
188 vaccinations against influenza, pneumococcal infection, shingles, human
189 papilloma virus and tetanus-diphtheria-pertussis⁴⁷.

190 Important gaps also exist in our understanding of fundamental biology of adult
191 immunisation. Due to “immunosenescence,” vaccination of older adults is in
192 general not as effective as in younger people, but the reasons for poorer
193 responsiveness are not well defined, requiring a new effort in terms of
194 strategies and products for immunization of adults. However, it is likely that
195 several compartments of the immune system are affected⁴⁸.

196 There are three areas where alterations to increase vaccine efficacy in the
197 elderly could be considered: (i) increase vaccine potency; (ii) use adjuvants to
198 enhance immunity; and (iii) apply immune modulators or other interventions
199 to alter host immunity generally.

200 As populations age across the world, it will be increasingly important to
201 identify how to integrate immunisation programmes in health and care
202 services to reach all age groups.

203 In addition, travel, certain professions or health conditions require specific
204 vaccinations⁴⁹⁻⁵¹, and international travel has played a role in the resurgence of
205 measles in the USA and elsewhere⁵².

206 ***From discovery to impact : overcoming four major hurdles***

207 There are still major infectious diseases whose control and ultimate
208 elimination would require an effective vaccine, such as HIV infection and
209 tuberculosis. Therefore continuing development of new vaccines is a public
210 health imperative. Unfortunately, the majority of early vaccine candidates in
211 discovery phase never make it as a safe and effective product. Development
212 and deployment of vaccines is a long and complex process. We describe here

213 briefly four hurdles that have to be overcome from the discovery phase of a
214 new vaccine to sustainable population impact.(Table 2).

215 The *first hurdle* is a so-called “valley of death” from discovery to early clinical
216 development, when a potential antigen, adjuvant or new vaccine formulation
217 developed in the laboratory is further tested for clinical proof of concept and
218 safety in humans, in addition to optimizing production elements. Real progress
219 has been made in recent years thanks to a number of public and private
220 initiatives, which are helping partly to overcome this first major challenge ,
221 such as CEPI, the Coalition for Epidemic Preparedness Innovation⁵³ created
222 after the 2014-2015 Ebola epidemic in West Africa to accelerate development
223 of vaccines against epidemic pathogens^{2,4,54}.

224 The *second hurdle* in vaccine development, also referred to as “second valley
225 of death”, relates to the shift from early clinical development to the large and
226 very expensive efficacy trials most often needed⁴, unless a previous similar
227 vaccine is already developed and a new product can be licensed using an
228 established correlate of protection. This is also the most expensive phase of
229 vaccine development, absorbing over two thirds of the total costs of
230 development of a new vaccine, including building special manufacturing
231 facilities and conducting Phase 3 trials in several countries, ideally with
232 independent research partners. Often, this major financial effort is beyond the
233 means of smaller biotech companies, and in general only big pharmaceutical
234 companies and large foundations or public institutions have the financial
235 bandwidth to support such trials which can cost as much as hundreds of
236 millions of dollars. For vaccine candidates without a prospect of a high income
237 market, ensuring return on investment, when the potential market for the new
238 vaccine is limited to low and middle income countries, there is a quasi
239 unsurmountable valley of death unless philanthropic and public funding
240 intervene².

241 The needs and unique challenges of vaccines against epidemic pathogens
242 demand innovation in product development pathways. The Merck rVSV Ebola
243 vaccine has been deployed on a large scale during the outbreak in eastern DR
244 Congo prior to product licensure, even for indications for which no efficacy
245 data are available such as primary prevention in health care workers. Well
246 informed country leadership and transparent governance of such use are
247 critical, as is genuine community involvement. The “animal efficacy rule” when
248 human efficacy trials are not feasible or ethical⁵⁵, should also be considered for

249 vaccines against epidemic pathogens. The development of Ebola vaccines has
250 shown how this type of ‘learning by doing’ model, can offer early access in
251 humanitarian situations^{56,57}, though it should be stressed that nearly five years
252 after the first Ebola vaccine clinical trials in West Africa, no Ebola vaccine is
253 licensed despite well documented immunogenicity, safety, and human and/or
254 non-human primate efficacy data. When a crisis such as Ebola is no longer
255 head line news, the sense of urgency is lost, and regulators and normative
256 committees go back to often extraordinarily long processes.

257 Following a successful phase 3 trial, there is a complex road to licensure of any
258 new vaccine, requiring reproducibility and safety tests of multiple batches of
259 vaccines, while manufacturing facilities are finalized. Several countries still
260 request clinical trial data conducted locally, delaying country licensure and
261 implementation significantly, while further raising costs of development. In
262 Europe there is advanced harmonization in regulatory approval of vaccines
263 through the European Medicines Agency, and in sub-Saharan Africa the Africa
264 Vaccine Regulatory Forum (AVAREF) is aiming to strengthen regulatory
265 capacity for clinical trials and harmonization of regulatory practices⁵⁸.

266 Following all of these activities which can take as long as ten years or more, a
267 new vaccine is now ready for deployment, but a *third hurdle* can occur
268 between licensure of a vaccine and broad scale implementation, which is
269 dependent on both a policy recommendation and the ability to implement.
270 Many years can go by before important new vaccines reach communities in
271 need, the cost of which is measured in human lives that could have been saved
272 as well as money for their development.

273 There are many contributors to this third hurdle: first is cost, especially
274 relevant for countries that are neither wealthy enough to procure vaccines at
275 high cost, nor poor enough to receive funding assistance from Gavi the
276 Vaccine Alliance. However, when a Gavi eligible country transitions out of the
277 program on the basis of an increase of it’s GNI per capita, it must increasingly
278 mobilise domestic resources or other development assistance⁵⁹. Even when
279 the broader value proposition of a new vaccine is substantial, there remains
280 the question of affordability. Second, is the question of country capacity to
281 take on new vaccines: the past decade has been an extraordinary era for
282 vaccine introduction with 113 countries having introduced at least one new
283 vaccine – a real success story⁶⁰. Country capacity to introduce and sustain ever
284 growing programmes involves human and financial resources, and time to

285 build political support and community demand. Both pneumococcal conjugate
286 vaccine and rotavirus vaccine now have coverage in low income Gavi countries
287 that meets or exceeds the global average, however this reflects that not all
288 countries in any income strata have yet introduced these vaccines in spite of
289 their availability⁶¹. Even high income countries can experience delays. Thus, in
290 the UK, a meningococcal B vaccine was licensed in January 2013,
291 recommended for introduction in March 2014 and finally announced for
292 introduction in May 2015. It then took over 12 months to resolve procurement
293 discussions to enable implementation⁶².

294 For products that address priority diseases for low income countries the
295 uncertainty of the market may risk products collapsing unless a full end-to-end
296 product solution is articulated, with non-commercial support . Inclusion of the
297 new vaccine in WHO's Pre-qualification list is a requirement for procurement
298 through Unicef and Gavi and other funders. Some of these are vaccines
299 against parasitic diseases, which are much more complex than bacterial or viral
300 vaccines due to the the wide range of antigens with often a complex life cycle
301 exhibiting different antigens relevant for vaccine protection. Thus the RTS,s
302 vaccine, the first ever malaria vaccine deployed in a routine immunization
303 system⁶³, took nearly 30 years since it's creation by GSK in 1987⁶⁴ before EMA
304 issued a positive scientific opinion in 2015, and in 2016 WHO recommended
305 large scale pilot programmes. These took another three years to start in
306 several African countries, and illustrate the sometimes extraordinary long
307 development, licensure, and introduction times. It is also an example of a
308 vaccine whose clinical trial performance of partial protection led to a policy
309 decision to advance in a step-wise manner rather than full programmatic
310 deployment. This may become a more common pathway for future products,
311 in part because these vaccines have performance and implementation
312 characteristics that are more complex than those of current vaccines.

313 We are entering an era where the path from vaccine licensure to routine
314 implementation requires more than safety and efficacy data. Policy
315 recommendations for new vaccines may only be realized following
316 implementation research to determine how to most effectively ensure use and
317 impact. Cost effectiveness deliberations, full value of vaccine assessments, and
318 country priorities in the face of constrained resources remain drivers for delays
319 associated with the third hurdle . National immunisation technical advisory
320 groups (NITAGS) will be increasingly important to guide evidence based
321 decision making.

322 Even after the lengthy and costly trajectory to introduce a new vaccine,
323 ensuring sustainable impact faces a *fourth set of hurdles* that must be
324 overcome. These include supply and demand sustainability, and resilience and
325 acceptance of immunisation. Logistical issues such as in-country cold chain,
326 procurement management, and the organisation of vaccination clinics in
327 remote areas, vaccine hesitancy, equity of access can all present challenges. In
328 addition, the misuse of vaccination campaigns as political tools has seriously
329 damaged vaccine confidence in areas such as the Philippines, Nigeria,
330 Afghanistan, Italy and Pakistan⁶⁵. Some side effects or limitations of duration of
331 protection may only become obvious after larger scale use, such as for live oral
332 rotavirus vaccination in high-mortality settings⁶⁶, pertussis vaccine⁶⁷ and
333 others⁶⁸. A recent example is the finding from a retrospective analysis of long
334 term efficacy trials showing that although there is a clear overall population
335 benefit of the Dengvaxia vaccine against dengue, the vaccine also caused an
336 excessive risk of severe dengue in seronegative vaccinees (i.e. those not
337 exposed to dengue virus⁶⁹). In the Philippines this new risk was reported after
338 over 800,000 school children were vaccinated, prompting a dramatic reaction
339 by the public in 2018⁷⁰.

340 Stock outs and vaccine manufacturing capacity have been problematic for
341 certain vaccines, even in high income countries. Manufacturers emphasize the
342 time needed to build and commission a factory⁷¹. Whereas middle income
343 country manufacturers are now supplying most low cost vaccines globally, they
344 face low profit margins, ferocious tenders, and often unpredictable
345 procurement schemes. More efficient and modular production technologies
346 may allow decentralised production with lower capital costs.

347 Each of the four hurdles can be overcome, though the fourth one should be a
348 continuing concern for every national immunisation programme. Depending
349 on the phase, they may require different sets of actors, and sometimes are a
350 matter of policy, management and leadership, rather than money.

351 Throughout development and use of vaccines, vaccine safety is an overriding
352 concern, and requires a continuous and careful scientific and societal
353 assessment. Safety monitoring during manufacturing typically occupies a major
354 part of the process and costs of a vaccine, and is a key element of any vaccine
355 programme. In specific high income populations, such as in the elderly,
356 personalized medicine approaches have been proposed to maximize both
357 immunogenicity and safety in the presence of chronic conditions and changes

358 related to older age, but large scale applicability is questionable for the time
359 being⁷²⁻⁷⁴.

360 ***Persistent unmet needs for vaccination***

361 The extraordinary achievement of vaccines is reflected in countries having
362 vaccinated over 116 million infants in 2018 alone⁷⁵, a similar success story to
363 that of 2017 when a similar number of infants were estimated to have been
364 vaccinated ---the greatest number, ever. Figure 2 shows global and regional;
365 coverage of DPT3 vaccination between 1980 and 2018, showing overall high
366 coverage, with regional variations, but also stagnation in coverage over the last
367 10 years⁷⁶. Nonetheless, there still remained 19.4 million un- or under-
368 vaccinated children, leaving them vulnerable to diseases they could and should
369 be protected from. In some countries substantial improvements in coverage
370 have been achieved, while in others coverage is backsliding, often because of
371 social disruption, conflict, or political upheaval, pointing out the highly dynamic
372 nature of vaccine programme performance.

373 Around 60% of all children who did not receive basic immunisation in 2018 live
374 in 10 countries: , Angola, Brazil, the Democratic Republic of the Congo,
375 Ethiopia, India, Indonesia, , Nigeria, Pakistan, The Philippines, and Vietnam ⁷⁷.
376 To achieve rapid change in this situation requires the full commitment of
377 governments, supported by international organisations. Gavi provides funding
378 for vaccination programmes in low- and low-middle income countries and has
379 had substantial impact. The technical support provided by the Gavi Alliance
380 partners will be key to addressing persistent gaps. Consistently delivering
381 vaccines with high coverage, reaching at least the minimum coverage required
382 to achieve herd immunity in line with the basic reproductive ratio of an
383 infection as mentioned above, remains a struggle in many other countries
384 including in middle- and high- income settings, with poor children not being
385 reached^{78,79}. For example, in the USA in 2017 100,000 children under 2 years
386 (1.3% of the population of that age) were not immunised against DTP/MMR, a
387 fourfold increase since 2001^{79,80}.

388 Of particular concern are countries whose vaccination coverage has declined.
389 There are 19 countries who had over 80% first dose measles coverage at some
390 point between 2011-2017 and whose 2018 coverage is at least 10% lower than
391 their peak coverage. The measles vaccine coverage of those 19 backsliding
392 countries now ranges from 38% - 88%, with 10 well below 80%⁶¹. Some of the
393 backsliding on coverage may represent improvements in data rather than

394 actual slippage in coverage. The data systems to accurately monitor both the
395 number of children born and the number of children vaccinated are highly
396 variable in quality^{81,82}. In some settings management and reward systems likely
397 incentivize inaccurate reporting of coverage data to meet targets, rather than
398 incentivizing accurate reporting.

399 Measles, diphtheria, and yellow fever outbreaks are the result of what
400 happens when the world is complacent and immunisation coverage declines.
401 Diphtheria outbreaks surged in Russia in the early 1990s, and among Rohingya
402 refugees from Myanmar in 2017, outbreaks of meningitis occurred in refugee
403 camps, and transmission of polio persists in parts of Afghanistan and
404 Pakistan⁸³. Measles outbreaks are occurring in all regions of the world. The
405 recent 80-fold increase in reported measles cases in the WHO Europe Region
406 over 4 years to over 82,000 cases in 2018 with 72 deaths^{84,85} are a result of a
407 mix of vaccine refusals, cultural beliefs, and access issues including
408 interruptions in vaccine supply, such as in Ukraine⁸⁶, leading to a WHO
409 declaration of a grade 2 health emergency⁸⁷. In the Americas, thousands of
410 cases have been reported in Venezuela due to the political and economic crisis,
411 with cases also appearing in Brazil, Colombia and Ecuador, resulting in the loss
412 of regional elimination status granted in 2016.

413 These outbreaks reflect failures to achieve and maintain high vaccination
414 coverage, community by community. Low vaccination coverage and high
415 heterogeneity in coverage are most deeply seen among African countries
416 where routine immunisation rates in many countries are well below the GVAP
417 targets⁸⁸.

418 Since 2010, routine immunization levels have either stagnated or decreased in
419 54 of 85 *middle income countries*, who do not qualify for Gavi support⁷⁸.
420 Vaccine expenditures per child are often lower in middle income countries
421 than in low income Gavi countries. The issue may not be so much lack of
422 funding capability, but lack of prioritization of immunization, not participating
423 in pooled procurement mechanisms such as via Unicef, low volumes,
424 insufficient efforts to reach vulnerable populations, vaccine choices, and
425 duplicative local regulatory requirements delaying introduction of new
426 vaccines.

427 Another unmet need concerns new vaccine introduction. Rapid progress has
428 been made to scale up the introduction of vaccines through Gavi investments
429 in low income countries, but not all vaccines have progressed at the same

430 rapid pace. The adolescent HPV vaccine has been particularly slow to be
431 introduced outside of high income settings because of programmatic
432 challenges, public access issues, supply constraints and pricing.

433 Addressing these unmet needs will require both dogged implementation of
434 strategies that have been shown to be effective, like detailed microplanning of
435 local efforts to assure all children are identified and immunized, special
436 campaigns, to implementation of novel approaches like drone delivery of
437 vaccines in hard to reach areas⁸⁹. Systematic evaluation and implementation
438 research should be part of these efforts in order to develop a firm evidence
439 base for overcoming such programmatic challenges. The World Health
440 Organization has elaborated guidance on implementing high impact
441 immunization programmes (Global Routine Immunization Strategies and
442 Practices, GRISP) to address these unmet needs. Middle income countries not
443 benefiting from Gavi funding need procurement mechanisms that can secure
444 more predictable tiered pricing. No set of strategies, however, will succeed
445 without substantially enhanced domestic investment and local political
446 commitment, which continue to limit progress in many parts of the world. As
447 demand for services from communities increases, responsiveness to that
448 demand from governments, the funder of such services in most countries is
449 more likely⁹⁰.

450 In addition to the unmet needs related to existing vaccines, nearly half of all
451 deaths from infectious diseases are from *infections for which no vaccine is*
452 *available* (e.g. more than 0.5 million deaths under 5 years from enteric
453 infections for which there is no vaccine⁹¹). These should be priorities for
454 vaccine R&D, while improvements are needed for vaccines such as against
455 rotavirus, pertussis, polio, and yellow fever. Innovations in delivery devices are
456 also important (e.g. micro patches, temperature stable vaccines, improved cold
457 chain equipment).

458 ***The Equity Imperative***

459 Equity has been a primary goal of immunization programmes. Reaching those
460 in greatest need means addressing issues of vaccine availability, affordability,
461 accessibility, acceptability, and financing. An effective immunization system
462 that delivers vaccine with high equity across social and ethnic strata, maternal
463 and community education, and geographies, is a purpose built programme to
464 deliver impact, and has been shown to be the critical programmatic target.

465 Country level coverage values mask subnational inequity, risking disease
466 outbreaks and backsliding on achievements of vaccination. Immunization
467 improvement should focus at the subnational level, as well as on other
468 determinants of inequity, not all of which would be addressed through focused
469 supplemental vaccine campaigns.

470 There is a special case for vaccine development for pathogens that cause
471 epidemics. These diseases have little to no market incentive to drive product
472 development hence the need for innovative arrangements such as CEPI⁵³, US
473 BARDA (Biomedical Advanced Research and Development Authority)⁹² and the
474 European IMI (Innovative Medicines Initiative)^{93,94}.

475 *Humanitarian crises* are another increasing impediment to immunisation. The
476 number, size and duration of conflicts, migration of refugees, and natural
477 disasters, have caused major disruptions to immunisation programmes and
478 resulted in serious disease outbreaks. The persisting hurdles to polio
479 eradication reveal how political, social and conflict situations can disrupt
480 access to populations and risk violence targeting vaccinators such as in
481 Pakistan and Afghanistan⁹⁵. Nearly 100 polio vaccinators and their security
482 guards have been targeted and killed while attempting to reach children for
483 vaccination⁹⁶.

484 ***The growing challenge of vaccine confidence***

485 Despite the success and wide-acceptance of the importance of immunization,
486 there are growing groups of people delaying or refusing vaccines. In 2013
487 WHO/SAGE established a working group to investigate the scope and scale of
488 vaccine hesitancy⁹⁷, the US National Vaccine Advisory Committee (NVAC)
489 convened a Vaccine Confidence Working Group to investigate the situation in
490 the US (National Vaccine Advisory Committee, 2015), and the European Centre
491 for Disease Prevention and Control (ECDC) published a review of the state of
492 vaccine hesitancy in Europe⁹⁸. In January 2019, the World Health Organization
493 named vaccine hesitancy as one of the top ten global health threats.

494 Since 2015, the Vaccine Confidence Index™ has surveyed over 300,000
495 respondents globally to pick up early signals of waning public confidence in
496 vaccine importance, safety, and effectiveness in order to prompt early
497 intervention where needed (See *Figure 3* for world map of confidence in
498 vaccine safety in 2018). The European Commission adopted the Index as part
499 of a new effort to strengthen cooperation against vaccine-preventable
500 diseases⁹⁹, and the Wellcome Global Monitor on Trust in Science and Health as

501 part of their 144 country study¹⁰⁰. Safety was not only identified as a key issue
502 in the 2018 European study, but also in a larger 144-country global study using
503 the VCI™. In the Wellcome Global Monitor, public confidence in vaccine safety
504 was consistently lower than confidence in vaccine effectiveness and
505 importance¹⁰⁰.

506 Whereas lack of familiarity by both physicians and parents with many
507 childhood diseases because of years of successful vaccination programmes
508 may play a role in a lack of interest in vaccines, the reasons for a decline in
509 vaccine confidence are far more complex. Newer challenges to vaccine
510 confidence include social media campaigns which have disrupted measles-
511 rubella vaccination efforts in southern India, collapsed HPV vaccination efforts
512 in Japan, provoked false scares of vaccine poisoning in Pakistan, and
513 undermined vaccination programmes in Indonesia.

514 Vaccine confidence issues are highly varied by setting and vaccine. In a three-
515 year review (2015-2017) of the WHO/UNICEF Joint Reporting Form (JRF)
516 completed annually by national immunization programmes, over 90% of the
517 194 countries reported that they experienced vaccine hesitancy. The top three
518 reasons for hesitancy were “risk-benefit (scientific evidence)” i.e. safety
519 concerns, “lack of knowledge on benefits of immunization,” and “religion,
520 culture and socio-economic issues”¹⁰¹.

521 Challenges around building confidence in vaccine safety are well beyond
522 communication, although more accessible public communication around the
523 complex issues of safety and risk benefit analysis are important. What needs to
524 be addressed is not only better communication around the known, albeit
525 sometimes misinterpreted, risks and benefits of vaccination, but investing in
526 more research in the areas where the public is asking questions and the
527 science is incomplete. Findings that *Pandemrix*, an AS03-adjuvanted influenza
528 vaccine, was linked to increased cases of narcolepsy in Europe prompted
529 further research, but a systematic review concluded that more research is
530 needed¹⁰².

531 While uncertainty is the norm in science, the political and social worlds of the
532 public have become less tolerant of ambiguity and risk¹⁰³. New modes of
533 listening to the public, with rapidly evolving technologies to monitor social
534 media, can harvest emerging safety questions as well as pick up signals of
535 possible issues that need investigation. Working towards better aligned public
536 questions and accessible, evidence-based answers, should be a goal. The

537 Vaccine Safety Net initiative at WHO is an important resource and can be
538 further built on to address new questions as they emerge, as well as make new
539 research accessible¹⁰⁴.

540 Social and political contexts and the reliability of health services are important
541 levers of trust, and a low trust setting will have less tolerance for risk than one
542 with high trust. A 2015 study showed that high trust in immunization services
543 clearly correlated with lower rates of vaccine hesitancy¹⁰⁵. The public's
544 experience with health services and health workers is highly influential in
545 vaccine decision, but both are needed. The Wellcome Monitor showed that, in
546 Japan for example, despite low trust in vaccines and low trust in government,
547 confidence in health providers remained high.

548 Introducing new vaccines into populations requires adequate time to train and
549 prepare front line health workers and vaccinators to be ready to manage public
550 questions, and ongoing dialogue between scientists and the public will be
551 important to build confidence from the start, as well as anticipate and manage
552 adverse events.

553 In the Philippines reported risks of a recently introduced dengue vaccine¹⁰⁶
554 amplified into public outrage mediated through Facebook pages, made more
555 complex because the events occurred during political elections. The result was
556 a dramatic drop in public confidence in vaccines more generally from 99.5% in
557 2015 to 76.2% in 2018, while confidence in vaccine safety plummeted from
558 99.5% to 65.2%⁶⁵. (Figure 4) The overall drop in public trust affected
559 willingness to accept even the measles vaccine, prompting measles outbreaks
560 with over 25,000 measles cases and 355 deaths by March 2019¹⁰⁷ requiring
561 considerable efforts to rebuild public confidence and increase vaccine uptake.

562

563 Conflict situations also affect confidence in vaccines and vaccinators due to an
564 environment of distrust and uncertainty, such as in Pakistan and Afghanistan,
565 and in the Democratic Republic of Congo where local violence and conflict in
566 the Ebola affected areas has been an obstacle to vaccination efforts.

567 ***The future of immunisation: sustainability and new opportunities***

568 The contribution of immunisation to human health, security and prosperity,
569 has been matched by few other activities in health and development, and has

570 been crucial for progress in child survival. As immunisation coverage among
571 adults is generally low, it is another area where greater advances can be made.

572 Addressing the following issues will be crucial to ensure optimizing the impact
573 of vaccination:

574 **1. Leadership and funding:** Achieving immunisation for all those in need
575 should be a top priority for every country. This will require stronger political
576 leadership and a continuing increase in investments in immunisation, both
577 domestically and internationally⁶. The power of immunisation to achieve wider
578 health and societal benefits should be further documented. Prioritization of
579 vaccines is particularly critical for middle income countries no longer benefiting
580 from Gavi support and for countries that are transitioning out of Gavi support.

581 A successful replenishment of Gavi resources in 2020 for the proposed Gavi 5.0
582 strategy¹⁰⁸ is vital for the next decade of progress in child survival, and will be a
583 test of the international community's commitment to immunisation and global
584 health.

585 **2. Universal vaccine coverage and equity:** Overcoming the stagnation in
586 reaching all people in need with even the basic vaccines is an overriding
587 priority in all countries, especially in those with the lowest coverage and the
588 greatest number of unvaccinated children. As we look toward the next decade
589 ensuring that vulnerable people all countries are not left behind should be a
590 top concern, particularly in middle income countries since there will be more
591 poor people living there than in poorer countries⁷⁸.

592 Ensuring a sustainable and affordable supply of quality vaccines, with
593 differential pricing according to the wealth of a country, is fundamental to
594 achieving sustainability and equity of immunisation. Only a few multinational
595 companies are producing vaccines, and a growing number of middle income
596 manufacturers are major suppliers. There is a risk that continuous lowering of
597 prices may lead to new monopolies, and possibly higher prices. Healthy vaccine
598 markets with sustainable supply is an important objective for vaccine
599 programmes. Harmonisation and strengthening of regulatory capabilities of
600 LMIC are key. Initiatives such as the Africa Vaccine Regulatory Forum
601 (AVAREF)⁵⁸ deserve support. The fact that some countries require local clinical
602 trials despite WHO prequalification, can be a source of major delays in the
603 introduction of vaccines.

604 **3. People-centred programmes** Immunisation programmes can become more
605 effective with a systems-driven and "precision public health" approach, taking

606 into account local variation in immunisation levels, specific needs, cultural
607 specifics, and circumstances of vulnerable populations. Quality data at
608 administrative levels closer to communities should be collected to inform
609 “micro-planning” and adaptive programme delivery. Thoughtful integration of
610 immunisation into health services, education systems, and elderly care, among
611 other innovative efforts are needed.

612 As most vaccines have incomplete efficacy, tailored approaches to optimize
613 their impact will be needed particularly for vaccines against malaria, influenza,
614 dengue, and probably HIV when it becomes available.

615 **4. Vaccine confidence:** Vaccine confidence must be addressed up front and be
616 an integral part of immunisation programmes. Many approaches to increasing
617 vaccine uptake do not take into account the social, historical and political
618 realities of the public for whom information alone is not the antidote to
619 vaccine reluctance. Instead of older demand-creation models, a new model
620 and language of engaging with the public is needed, starting with better
621 listening and prompt responding to concerns as well as building on local
622 capacities. Inclusion of non-traditional partners, new modes of digital
623 communication, social scientists, and religious and traditional leaders have
624 been invaluable in addressing hesitancy around polio vaccination, and the
625 engagement of teenage girls in co-designing social media outreach to address
626 HPV vaccination concerns had positive impacts on vaccine uptake in Denmark.
627 With safety anxieties being reported as one of the top reasons for vaccine
628 hesitancy, aligning vaccine safety research with dominant safety concerns will
629 also be important for confidence building.

630 **5. Invest in research and innovation:** Many issues mentioned in the other
631 recommendations require further research in a wide range of disciplines.
632 Product innovation as a result of the formidable progress in immunology and
633 infection pathogenesis has been a strong driver of immunization programmes.
634 There is reluctance of industry to develop vaccines, when market incentives
635 are limited, and licensure is uncertain. While companies such as Merck and
636 Johnson & Johnson invested considerably in the development of Ebola vaccine
637 candidates, partly supported by public funds in North America and Europe, but
638 without a prospect of a return on investment, it would be unrealistic to expect
639 that industry will follow this example for each new emerging pathogen. There
640 is a major role for the public sector and philanthropy to support mechanisms
641 such as CEPI to develop vaccines for low income countries². As discussed
642 under the “2nd hurdle” on the challenge to fund and conduct late clinical

643 development to market introduction for vaccines for which there is no market
644 incentive, there is an urgent need to address this gap through possibly a
645 specific global initiative or at least a concerted action of several funders.
646 There is also a need for innovation in trial design (for faster trials with smaller
647 sample size and including collection of valuable biosamples to inform
648 correlates of protection) and in trial analysis, as well as in vaccine delivery.
649 Escalating antimicrobial resistance (AMR) is a powerful incentive to develop
650 vaccines against bacterial infections, malaria, TB and HIV infection¹⁰⁹⁻¹¹¹.
651 Innovation in delivery of vaccination programmes is as important as product
652 innovation.

653 The world cannot afford to turn the clock back on immunisation, and ever
654 more innovative vaccines will offer additional opportunities to reduce
655 mortality and improve quality of life for every person on the planet. This will
656 require the best of science, entrepreneurship, programme implementation on
657 the ground, and politics.

658

659 **Tables**

- 660 **1.** Historic timeline of introduction of vaccines.
- 661 **2.** From discovery to sustainable impact: Overcoming four major hurdles

662

663 **Figures**

- 664 **1.** Vaccines across the human life cycle.
- 665 **2.** Coverage of DTP3 (containing products) immunisation over time globally,
666 combining coverage and regional variations, 1980-2018.
- 667 **3.** Global confidence in vaccine safety by country
- 668 **4.** Changing levels of vaccine confidence in The Philippines between 2015 and
669 2019.

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1016 **Author contributions**

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1018 **Competing Interests Statement**

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1030 [Table 1. Historic timeline of introduction of vaccines \(year of licensure indicated](#)
1031 [wherever possible\)](#)

1032 Notes: Adapted from Plotkin & Plotkin (2018)¹¹². a. Capsular polysaccharide conjugated to carrier
1033 proteins. b. An investigational vaccine, rVSV-ZEBOV, was used under “expanded access” during the
1034 Ebola outbreak in west Africa in 2015 and the 2018 outbreak in DR Congo. c. Positive opinion from
1035 EMA under article 58 issued in 2015. Approved for routine use in pilot implementation settings in
1036 Ghana, Malawi, Kenya in 2018. d. Reverse vaccinology. WC: whole cell. rBS: recombinant B subunit.

Year	Disease	Year	Disease
1798	Smallpox	1999	Rotavirus (reassortant)
1885	Rabies	2000	Pneumococcal conjugate (heptavalent) ^a
1896	Cholera	2003	Influenza (intranasal, cold-adapted)
1896	Typhoid	2005	Meningococcal conjugates (quadrivalent) ^a
1897	Plague	2006	Human papillomavirus recombinant (4-valent)
1923	Diphtheria toxoid	2006	Rotavirus (attenuated and new reassortants)
1926	Pertussis (WC)	2006	Varicella Zoster
1926	Tetanus toxoid	2008	Rotavirus (monovalent)
1927	Tuberculosis (bacille Calmette-Guérin)	2009	Japanese encephalitis (Vero cell)
1935	Yellow fever	2009	Cholera (WC only)
1936	Influenza	2009	Human papillomavirus recombinant (2-valent)
1937	Tickborne encephalitis	2010	Meningococcal type A conjugate (monovalent)
1938	Typhus	2010	Pneumococcal conjugate (13-valent)
1955	Polio (inactivated)	2014	Human papillomavirus (9-valent)
1963	Measles	2014	Meningococcal type B (fH factor)
1963	Polio (oral)	2015	Ebola (unlicensed) ^b
1967	Mumps	2015	Malaria ^c
1969	Rubella	2015	Dengue
1970	Anthrax secreted proteins	2015	Meningococcal type B ^d
1974	Meningococcus polysaccharide	2016	Cholera (oral)
1977	Pneumococcus polysaccharide (14-valent)	2018	Typhoid conjugate ^a
1980	Adenovirus	2006	Human papillomavirus recombinant (4-valent)
1980	Rabies (cell culture)	2006	Rotavirus (attenuated and new reassortants)
1981	Tickborne encephalitis	2006	Varicella Zoster
1981	Hepatitis B (plasma derived)	2008	Rotavirus (monovalent)
1983	Pneumococcus polysaccharide (23-valent)	2009	Japanese encephalitis (Vero cell)
1985	<i>Haemophilus influenzae</i> type b polysaccharide	2009	Cholera (WC only)
1986	Hepatitis B surface antigen recombinant	2009	Human papillomavirus recombinant (2-valent)
1987	<i>H. influenzae</i> type b conjugate ^a	2010	Meningococcal type A conjugate (monovalent)
1989	Typhoid (<i>Salmonella</i> Ty21a)	2010	Pneumococcal conjugate (13-valent)
1991	Cholera (WC-rBS)	2014	Human papillomavirus (9-valent)
1992	Japanese encephalitis (mouse brain)	2014	Meningococcal type B (fH factor)
1993	Cholera (recombinant toxin B)	2015	Ebola (unlicensed) ^b
1994	Typhoid (Vi) polysaccharide	2015	Malaria ^c
1994	Cholera (attenuated)	2015	Dengue
1995	Varicella	2015	Meningococcal type B ^d
1996	Hepatitis A	2016	Cholera (oral)
1996	Pertussis (Acellular)	2018	Typhoid conjugate ^a
1998	Lyme OspA	2006	Human papillomavirus recombinant (4-valent)
1999	Meningococcal conjugate (group C) ^a	2006	Rotavirus (attenuated and new reassortants)

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1040 Table 2: From discovery to sustainable impact of immunization: overcoming four major hurdles

	<i>Issues</i>	<i>Selected actions needed</i>		
First hurdle: from discovery to early clinical development	<ul style="list-style-type: none"> • Few discoveries make it to actual products • High risk for companies • Safety key issue 	<ul style="list-style-type: none"> • Incentives for industry for vaccines with no high income countries market • Public-private partnerships and philanthropy 		
Second hurdle: from early clinical development to large efficacy trials	<ul style="list-style-type: none"> • Very expensive—two thirds of total costs of new vaccine development • Particularly challenging for vaccine candidates without high income market potential • Safety major issue, besides immunogenicity and efficacy • Complex road to licensure • Can take 3 to 10 years or longer 	<ul style="list-style-type: none"> • End-to-end product planning Need for major boost from private and public funding • Clinical trial capacity and rationalizing trial methodology • Regulatory harmonization and speed • Manufacturing availability for GMP-products to be used in trials 		•
Third hurdle: from vaccine licensure to broad scale implementation	<ul style="list-style-type: none"> • Dependent on policy recommendations, cost effectiveness deliberations, and political priority • Country capacity to take on new vaccines i.e. – human and financial resources and the time to build political support and community demand • Logistical issues, e.g. cold chain, procurement management, organisation of vaccination to ensure equity of access • Supply not always sufficient • Highly variable time-line by country 	<ul style="list-style-type: none"> • End-to-end product solution • National and international funding, Gavi transition management, tendering processes. • National regulatory harmonisation • Policy clarification and political leadership • Manufacturing capacity • Research on full societal value of vaccine assessment, implementation research and relevant cost-effectiveness models • Equity of access 		•
Fourth hurdle: achieving consistent, long term supply and demand sustainability	<ul style="list-style-type: none"> • Continuing concern for every national immunisation programme • Issues may arise even after years of implementation • Complex interplay of service delivery, supply and demand, societal trust, political and humanitarian conflicts • Never ending 	<ul style="list-style-type: none"> • Policy and political commitment • Sustainable funding • Management and logistics • Tender processes • Manufacturing capacity • good communication, safety surveillance and vigilance, including promptly addressing safety signals and signs of vaccine hesitancy 		

1042 **Figures**

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1044 **Figure 1. Vaccines across the human life cycle**

1045 Legend: Not only do vaccines provide important health benefits for all stages in life. They also do so
1046 for travellers, health care workers as well as those who are in special health conditions.

1047 Note: The list of vaccines by different phases of life-course are illustrative, rather than exhaustive,
1048 and do not imply these are universally recommended for each life phase in all countries. Vaccines
1049 recommended by WHO by phase of lifecourse is available at
1050 https://www.who.int/immunization/policy/immunization_tables/en/ (last accessed: 3 September
1051 2019).

1052 **Figure 2. Coverage of DTP3 (containing products) immunisation over time globally,
1053 combining coverage and regional variations, 1980-2018**

1054 Legend: The coverage of DTP3 immunisation improved rapid in the 80s with large regional
1055 variations. Stagnation over the last 10 years meant 19.4 millions children remained un- or under-
1056 vaccinated.

1057 Solid lines represent regional coverages. Vertical bars represent global coverages with percentages
1058 shown at the top of each bar.

1059 Source: WHO/UNICEF coverage estimates 2018 revision, July 2019.

1060 Note: DTP3: Diphtheria, tetanus, and pertussis; AFR, AMR, EMR, EUR, SEAR, and WPR are World
1061 Health Organization subregions of Africa, Americas, Eastern Mediterranean, Europe, South-East Asia,
1062 and Western Pacific, respectively.

1063 Reprinted from “Progress Towards Global Immunization Goals - 2018: Summary presentation of key
1064 indicators”, updated July 2019, WHO/UNICEF, “Global and Regional Immunization coverage with
1065 three doses of diphtheria, tetanus, and pertussis (DTP3) containing vaccines, 1980-2018, global
1066 coverage at 86% in 2018”, Copyright (2019).

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1068 **Figure 3 . Global Confidence in Vaccine Safety, 2018**

1069 Legend: Levels of confidence in vaccine safety varied considerably across countries and regions with
1070 a number of countries showing very low levels of confidence.

1071 The colour chart at the bottom shows increasing levels of confidence from red and dark green.

1072 Source: Vaccine Confidence Index™ data from Wellcome 2018 Global Monitor 144 country survey on
1073 Trust in Science and Health.

1074 Note: The question asked in the survey is “vaccines are safe?”.

1075 Map Credit: Alexandre De Figueiredo, The Vaccine Confidence Project

1076 **Figure 4. Changing levels of vaccine confidence in the Philippines between 2015 and
1077 2019 (in percentages)**

1078 Legend: Dramatic fall in public confidence in vaccine safety in the Philippines due partly to the impact
1079 of social media and local politics

1080 The months and years of the surveys conducted are represented by the vertical bars in different
1081 colours.

1082 Source: The Vaccine Confidence Project, Data collected by Gallup International (PSRC)

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