BMJ Global Health

Assessing the value of human papillomavirus vaccination in Gavi-eligible low-income and middle-income countries

Jessica Ochalek ,[1] Kaja Abbas ,[2] Karl Claxton ,[1] Mark Jit ,[2,3,4] James Lomas [1]

To cite: Ochalek J, Abbas K, Claxton K, *et al*. Assessing the value of human papillomavirus vaccination in Gavi-eligible low-income and middle-income countries. *BMJ Global Health* 2020;**5**:e003006. doi:10.1136/bmjgh-2020-003006

Handling editor Lei Si

► Additional material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/bmjgh-2020-003006).

Received 28 May 2020
Revised 17 August 2020
Accepted 19 August 2020

[1]Centre for Health Economics, University of York, York, United Kingdom
[2]Department of Infectious Disease Epidemiology, Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, United Kingdom
[3]Modelling and Economics Unit, Public Health England, London, United Kingdom
[4]School of Public Health, University of Hong Kong, Hong Kong Special Administrative Region, China

Correspondence to
Jessica Ochalek;
jessica.ochalek@york.ac.uk

ABSTRACT

Introduction Estimating the value of providing effective healthcare interventions in a country requires an assessment of whether the improvement in health outcomes they offer exceeds the improvement in health that would have been possible if the resources required had, instead, been made available for other healthcare activities in that country. This potential alternative use of the same resources represents the health opportunity cost of providing the intervention. Without such assessments, there is a danger that blanket recommendations made by international organisations will lead to the adoption of healthcare interventions that are not cost effective in some countries, even given existing donor mechanisms intended to support their affordability.

Methods We assessed the net health impact to 46 Gavi-eligible countries of achieving one of the WHO's proposed 90-70-90 targets for cervical cancer elimination, which includes 90% coverage of human papillomavirus (HPV) vaccination among girls by 15 years of age, using published estimates of the expected additional benefits and costs in each country and estimates of the marginal productivity of each healthcare system. We calculated the maximum price each country could afford to pay for HPV vaccination to be cost effective by assessing the net health impact that would be expected to be generated at different potential prices.

Results At Gavi negotiated prices, HPV vaccination offers net health benefits across most Gavi-eligible countries included in this study. However, if Gavi-eligible countries faced the average price faced by non-Gavi eligible countries, providing HPV vaccination would result in reduced overall population health in most countries.

Conclusion Estimates of the net health impact of providing a healthcare intervention can be used to assess the benefit (or lack of) to countries of adhering to global guidance, inform negotiations with donors, as well as pricing negotiations and the value of developing new healthcare interventions.

Key questions

What is already known?

- Human papillomavirus (HPV) vaccination is considered cost effective in almost every country when compared against a threshold of 1× gross domestic product (GDP) per capita.
- GDP per capita-based thresholds are no longer recommended for judging the value for money of healthcare interventions.
- Country-specific health opportunity costs enable the estimation of the impact of an intervention in terms of the population net health benefits.

What are the new findings?

- Health opportunity costs in Gavi-eligible low-income and middle-income countries can be used to estimate the scale of the expected net impact on population health of HPV vaccination.
- At Gavi negotiated prices, HPV vaccination offers positive net health benefits in most of the Gavi-eligible countries included in this study.
- If Gavi-eligible countries faced the same price as non-Gavi eligible countries, providing HPV vaccination would improve overall population health in 13 countries and reduce overall population health in 33 countries imposing a net burden of 38 million disability-adjusted life years.

What do the new findings imply?

- Gavi's negotiations on behalf of countries eligible for its support have succeeded in making adhering to the WHO guidance around HPV vaccination a beneficial aim for most countries.
- Determining prices using these methods, which account for country-specific health opportunity costs, offers an opportunity to ensure that all countries can benefit from adopting HPV vaccination or other recommendations made by global bodies.
- Assessing the likely scale and distribution of the impact of potential new interventions on net population health, at a particular price, are valuable for informing priorities in developing new healthcare interventions.

INTRODUCTION

In 2019, donors funded 27% of healthcare provided in low-income countries and 3% in lower middle income countries.[1] How donors make decisions around which interventions to fund is unclear.[2] Funding may be tied to a donor's strategic mission or aligned to international guidance or recommendations. Estimating the value of providing effective

interventions in a country—including vaccines, drugs, and diagnostics, as well as prioritising the development of new ones—requires an assessment of whether the improvement in health outcomes they offer exceeds the improvement in health that would have been possible if the resources required had, instead, been made available for other healthcare activities in that country. This potential alternative use of the same resources represents the health opportunity cost of providing the intervention. Without such assessments, there is a danger that blanket recommendations made by international organisations will lead to the adoption of healthcare interventions that are not cost effective in some countries, even given existing donor mechanisms intended to support their affordability.

To assess the health opportunity cost of providing an intervention in a given country, an assessment of the health effects if the additional resources required had, instead, been made available to other healthcare activities is needed. This requires country-specific estimates of the health effects of changes in healthcare expenditure. Such estimates are now available for a limited number of high-income countries based on within-country data and a wider range of high-income as well as low-/middle-income countries (LMICs) based on country-level data. These are typically reported as a cost per quality-adjusted life year (QALY) gained or disability-adjusted life years (DALY) averted.[3–13]

Comparing the additional cost per QALY gained or DALY averted by an intervention with an estimate of cost per QALY gained or DALY averted that reflects health opportunity costs enables a binary assessment of whether the intervention produces health at a better (worse) rate than interventions already funded by the healthcare system (HCS)—that is, is below (above) the estimate of cost per QALY gained or DALY averted that reflects health opportunity costs. However, binary assessments such as these obscure valuable information about the scale of the net benefits (or losses) associated with providing or developing an intervention, and other local context-specific important criteria of affordability, budget impact, fairness and feasibility.[14] This is particularly important when assessments of value are made across countries; an intervention may be expected to generate a net benefit in some, but a net loss in others.

Explicit consideration of the trade-offs between, for example, providing an intervention in all versus some countries requires quantifying the scale of the benefits (or losses) across countries. The scale of potential net benefits (or losses) associated with providing an intervention in a country can be measured by the net health impact of the intervention: that is the health that is generated by it minus its health opportunity cost. The health opportunity costs associated with additional healthcare expenditure in each HCS differs depending on for example, the budget for healthcare, efficiency of current spending, demographic structure and epidemiology. As such, the health opportunity cost of providing the same intervention at the same price, even to the same sized population, will be different in different HCS.

To illustrate this, we assess the net health impact to countries of achieving one of the WHO's proposed 90-70-90 targets for cervical cancer elimination, which includes 90% coverage of human papillomavirus (HPV) vaccination among girls by 15 years of age.[15] This paper shows how estimates of the expected additional benefits and costs of HPV vaccination and health opportunity costs can be used to assess the expected net health impact for each country and across countries associated with adhering to the WHO guidance. We also show how these metrics can inform pricing negotiations (eg, between Gavi, the Vaccine Alliance (hereafter Gavi) and manufacturers), and discuss how they may be used to inform the development of new healthcare interventions.

METHODS

Assessing the expected net health impact for each country and across countries requires data on the additional costs and benefits of HPV vaccination for each country and an estimate of the health opportunity costs faced by each countries' HCS. We consider countries that were Gavi eligible in 2019 (the most recent year for which a list of eligible countries is publicly available).[16] Estimates of the additional health benefits of HPV vaccination over the period 2020–2029 come from the Papillomavirus Rapid Interface for Modelling and Economics (PRIME) model developed by Jit *et al* (2014) and recently updated by Abbas *et al* (2020).[17 18] PRIME assumes lifelong vaccine protection, no indirect (herd) effects and no changes to screening programmes.

The additional (ie, net) cost of vaccination (ΔC_i) is made up of the cost of procurement (ΔC_i^P), which is a function of the per dose procurement price and number of doses, the cost of delivering the vaccine in a country (ΔC_i^D), and the cost savings that result from cervical cancers averted (ΔC_i^C)

$$\Delta C_i = \Delta C_i^p + \Delta C_i^D - \Delta C_i^C \quad (1)$$

The market price for HPV vaccine doses in countries not eligible for Gavi support is on average US$25 per dose.[19] Below private market rate procurement prices were negotiated by Gavi with HPV vaccine manufacturers, enabling Gavi eligible countries to purchase vaccines through United Nations organisations at US$4.50 per dose.[20 21] Countries purchase a share of the vaccines provided while Gavi purchases the remainder. The share funded by Gavi is based on the Gavi cofinancing mechanism depending on the funding phase the country is in.[22] We assume two doses per vaccinated girl in line with the WHO recommended schedule for HPV vaccination, and that the per dose price remains constant in real terms over the period 2020–2029.[23] Delivery costs are assumed to be US$1.76 per dose (2019 US$) for low-income countries and US$3.87 per dose (2019 US$) for middle-income countries[24] (originally in 2013 US$, scaled up

using gross domestic product (GDP) deflator 2011 Q1 to 2019 Q3 for USA from the US Federal Reserve https://fred.stlouisfed.org/series/GDPDEF). In combination with published estimates of the health opportunity costs faced by different HCS from Ochalek *et al* (2018), the scale of the net health impact of HPV vaccination by HCS, measured in DALYs averted (net DALYs averted, NDA_i, where the i subscript denotes each HCS) can be estimated for each HCS. No estimates of the health opportunity costs associated with additional healthcare expenditure are available for 12 countries, limiting our analysis to 46 Gavi-eligible countries.

$$NDA_i = \Delta DALYs_i - \frac{\Delta C_i}{k_i} \quad (2)$$

Net DALYs averted (NDA) for a given HCS is the difference between DALYs averted by an intervention ($DALYs_i$) and DALYs that could have been averted with the additional HCS resources required to implement it ($\frac{\Delta C_i}{k_i}$) (net of any additional cost savings), where k_i is the country-specific estimate of health opportunity cost to avert a single DALY. Note that if the net effect of the intervention saves HCS costs, that is, $\Delta C_i < 0$, then the net DALYs averted is the DALYs averted by the intervention plus the additional DALYs that can also be averted with the cost savings offered.

The scale of the value of the impact can also be reported in terms of the amount of additional healthcare resources which would be required to deliver similar net health impacts (net dollar value, $N\$V_i$).

$$N\$V_i = k_i * \Delta DALYs_i - \Delta C_i \quad (3)$$

The aggregate net effects of providing the HPV vaccine in a group of countries (eg, all countries in a given income category) can be calculated by summing the estimated net health impact or net dollar value by HCS. For example, where HPV is provided in a group, g, of N HCS, these can be calculated as follows:

$$NDA_g = \sum_{i=1}^{N} \Delta DALYs_i - \frac{\Delta C_i}{k_i} \quad (4)$$

$$N\$V_g = \sum_{i=1}^{N} k_i * \Delta DALYs_i - \Delta C_i \quad (5)$$

An estimate of the health opportunity costs faced by the HCS also enables the calculation of the maximum per dose procurement price, which is calculated by dividing the maximum procurement cost (C_i^{P*}) by the number of required doses (two doses are required for each person in the cohort), that each HCS could afford to pay for HPV vaccine to ensure that the health lost from the money required to fund it is not greater than the benefit it offers (ie, the cost at which the net dollar value to the HCS would be zero).

$$\Delta C_i^{P*} = \Delta DALYs_i * k_i - \Delta C_i^D + \Delta C_i^C \quad (6)$$

This can be used to inform pricing negotiations between Gavi and manufacturers in a way that ensures that global access could be provided with no net losses for any HCS.

We illustrate how these assessments can be used to inform global guidance or recommendations and pricing negotiations by assessing four potential policy options:

1. Achieving the WHO recommendation of 90% coverage of HPV vaccination in Gavi-eligible countries at the average market per dose procurement prices (US$25 per dose).
2. Informing country-specific per dose procurement prices that would ensure that HPV vaccination generates a net health benefit in each Gavi-eligible country.
3. Informing per dose procurement prices for country groups (ie, low-income and lower middle income) that would ensure that HPV vaccination generates a net health benefit in each Gavi-eligible country.
4. Achieving the WHO recommendation of 90% coverage of HPV vaccination in all Gavi-eligible countries at current Gavi-negotiated per dose procurement prices (US$4.50 per dose) first assuming current levels of support for procurement (option 4a) and second, assuming no procurement support (option 4b).

Policy option 1 reflects the implementation of blanket recommendations for providing an intervention for an entire set of countries (see, eg, World Health Organization, 2020).[25] Policy option 4 reflects the practice of negotiating prices to support countries in complying with recommendations. Policy options 2 and 3 reflect potential methods for determining prices.

While all Gavi funded countries face the same per dose price (US$4.50) for HPV vaccines, most Gavi-funded countries pay for only a portion of the vaccines they purchase while the remainder are funded by Gavi. The share funded by Gavi is based on a cofinancing mechanism, and differs for each country depending on the funding phase the country is in and its per capita income.[22] In the first instance, we assume current Gavi-negotiated per dose procurement prices and with current levels of support (policy option 4a). Since data on the proportion of vaccines purchased by Gavi are not publicly available, we have calculated them based on the number of years a country has been a Gavi funding recipient and the countries' gross national income (GNI) per capita in each of those years (see online supplemental appendix 1). Second, we assess this scenario assuming that countries pay 100% of the vaccine procurement costs (ie, US$4.50 per dose; which we term policy option 4b). Delivery costs are the same for each option and are current delivery costs.

We also undertake sensitivity analyses around discount rates and the estimates of the marginal productivity of HCSs used. Global guidance recommends that where country guidance is lacking either 0% for health benefits and 3% for costs or 3% for both are used as discount rates.[26–28] Following common practice, our base case for each policy option applies a discount rate of 3% to both costs and benefits,[29 30] and we assess the results where 0% is applied to health benefits in sensitivity analysis. Our base case uses the central estimate of health opportunity cost for each country from Ochalek *et al*.[31] We

also assess each policy option using the minimum and maximum estimates of cost per DALY for each country from Ochalek *et al* (2018) as a sensitivity analysis.[31]

The total net health impact across all countries for the first policy option, where HPV vaccination is implemented in all countries at current market prices, is calculating by aggregating the NDA for each country from equation 2.

The second policy option entails calculating the maximum price each HCS could afford to pay for HPV vaccination to be a cost-effective use of resources in that HCS if it is not already cost effective at average market price (US$25 per dose). This is calculated by determining the maximum total vaccination procurement cost a country can afford to pay, which is the monetary value of the expected health gains of HPV vaccination net of the difference between the delivery costs and cancer treatment costs averted (as set forth in equation 6).

The third policy option, to set a price by HCS group (eg, income group) rather than by country, is also informed by equation 6, but the lowest maximum price affordable from among a group of countries is applied to all countries in the group.

The fourth policy option reflects the total net health impact of implementing HPV vaccination in all countries at Gavi negotiated prices and with current levels of Gavi support (policy option 4a) or at Gavi negotiated prices without procurement support (policy option 4b) and is calculated by aggregating the NDA for each country from equation 2.

RESULTS

Figure 1A plots the health gains from the vaccine against the health opportunity cost for each country of achieving the WHO recommendation of 90% coverage of HPV vaccination in all Gavi-eligible countries at average market per dose procurement prices (US$25 per dose) and given current delivery costs (policy option 1). The diagonal line indicates zero net health impact, and (black) points that fall above it refer to countries which have a positive net health impact while (grey) points that fall below it refer to countries which have a negative net health impact.

What is evident is that at this price HPV vaccine results in net health losses in most countries. More countries are below the zero net impact line than above it. The distance between a point above (below) the line and the line is the net health gain (loss) that would result from providing the intervention. There are net health gains in some countries (totalling 2 million DALYs averted); however, these are offset by the net health losses in others (totalling −40 million DALYs averted (see table 1 column 1).

If HPV vaccination were provided only in those countries where it does not reduce overall net health at current average market price, it would be implemented in only 2 of 22 low-income countries and 11 of 24 lower middle income countries where it would generate a net health benefit. While there is a clear benefit to this policy option (ie, it would ensure that overall health across the countries increases as a result of the recommendation, and health is not reduced anywhere), it unlikely to be politically feasible or appealing to restrict access in this way. It may also not be seen as equitable to provide vaccination only to countries that can afford to pay a uniform price for it.

Pricing arrangements that ensure that HPV vaccine generates a net health benefit for each country requires calculating the per dose price at which HPV vaccination would be cost effective in each HCS for which it is not at US$25 per dose (policy option 2). This is visualised in figure 1B, where all of the countries that previously had negative net health impact (as denoted by grey points in figure 1A) are now on the zero net impact line.

Table 2 reports the per dose price at which HPV vaccination would be cost effective in each HCS for which it

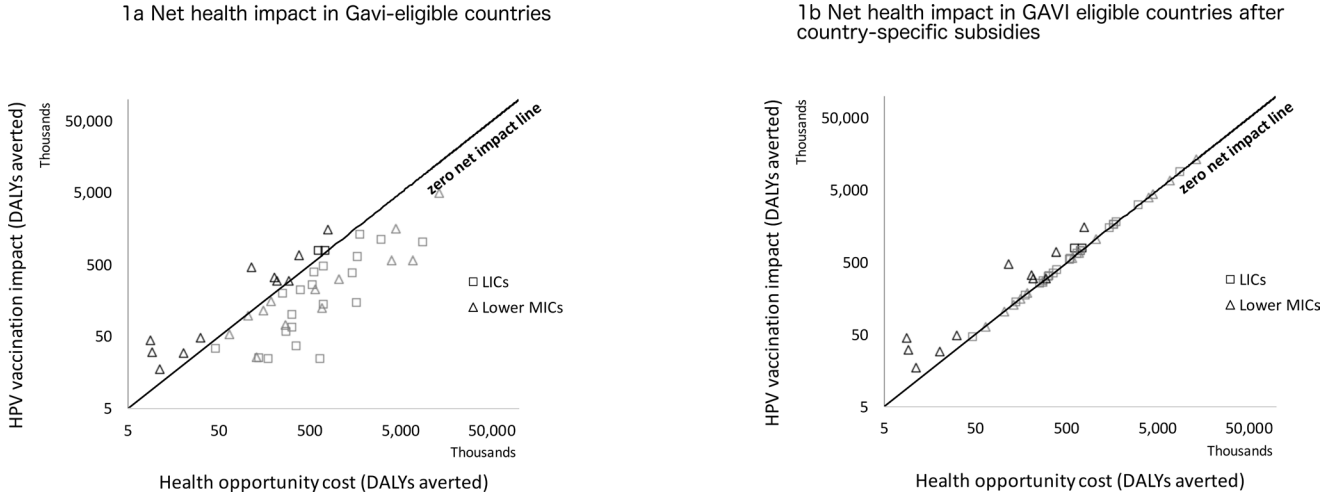

Figure 1 (A) Net health impact in Gavi-eligible countries. (B) Net health impact in Gavi-eligible countries after country-specific subsidies. DALYs, disability-adjusted life years; HPV, human papillomavirus; MICs, middle-income countries.

Table 1 Net health impact and net monetary impact at three prices

		US$25 per dose (options 1 and 2)		Gavi procurement support (per dose price differs by country, all ≤US$4.50, option 4a)		US$4.50 per dose (option 4b)	
		Net health impact (1000s)	Net monetary impact (1000s 2019 US$)	Net health impact (1000s)	Net monetary impact (1000s 2019 US$)	Net health impact (1000s)	Net monetary impact (1000s 2019 US$)
Country	Income category	(1)	(2)	(3)	(4)	(5)	(6)
Benin	Low income	−222	−47212	98	20749	42	8965
Burkina Faso	Low income	−232	−37900	526	85735	394	64298
Burundi	Low income	−164	−19599	453	54223	346	41423
Chad	Low income	−576	−85115	120	17705	−1	−123
Democratic Republic of the Congo	Low income	−7746	−495691	975	62387	−537	−34377
Eritrea	Low income	−114	−15648	21	2854	−3	−354
Ethiopia	Low income	−1944	−397625	1049	214497	530	108363
Gambia	Low income	−12	−3732	35	10652	27	8158
Guinea	Low income	−276	−36630	294	39031	195	25912
Guinea Bissau	Low income	−151	−9399	27	1701	−4	−223
Haiti	Low income	−216	−38111	53	9297	6	1077
Madagascar	Low income	−1012	−82141	822	66750	504	40934
Malawi	Low income	163	24257	896	133320	769	114410
Mali	Low income	−1085	−89221	458	37691	191	15686
Mozambique	Low income	38	9024	836	196248	698	163786
Nepal	Low income	−172	−46634	217	58934	150	40630
Niger	Low income	−1,505	−157478	69	7267	−204	−21 298
Rwanda	Low income	−55	−14362	207	54440	162	42511
Sierra Leone	Low income	−320	−39693	23	2802	−37	−4566
Togo	Low income	−250	−35745	64	9176	10	1387
Uganda	Low income	−454	−64882	1523	217831	1180	168813
Yemen	Low income	−627	−157748	−37	−9,388	−125	−31 390
Bangladesh	Lower middle income	−3,406	−504494	301	44653	−309	−45 704
Cambodia	Lower middle income	−197	−50702	63	16229	20	5079
Cameroon	Lower middle income	−736	−94408	373	47898	228	29285
Comoros	Lower middle income	6	1861	21	6122	19	5565
Côte d'Ivoire	Lower middle income	−346	−85109	239	58651	152	37331
Ghana	Lower middle income	3	1344	276	127469	276	127469
India	Lower middle income	−8,392	−2814745	2888	968749	2368	794116
Kenya	Lower middle income	307	188020	744	455613	673	412218
Kyrgyzstan	Lower middle income	17	14836	50	43895	44	38919

Continued

Table 1 Continued

		US$25 per dose (options 1 and 2)		Gavi procurement support (per dose price differs by country, all ≤US$4.50, option 4a)		US$4.50 per dose (option 4b)	
		Net health impact (1000s)	Net monetary impact (1000s 2019 US$)	Net health impact (1000s)	Net monetary impact (1000s 2019 US$)	Net health impact (1000s)	Net monetary impact (1000s 2019 US$)
Country	Income category	(1)	(2)	(3)	(4)	(5)	(6)
Lesotho	Lower middle income	22	15 009	34	23 484	32	22 375
Mauritania	Lower middle income	-11	-3,685	61	20,443	50	16,865
Nicaragua	Lower middle income	36	97 972	44	118 524	44	118 524
Nigeria	Lower middle income	–2783	–724 904	979	255 030	979	255 030
Pakistan	Lower middle income	–6147	–999 875	–174	–28 328	–1085	–176 560
Republic of Congo	Lower middle income	9	13 848	26	39 162	26	39 162
Republic of Sudan	Lower middle income	–555	–206 489	–42	–15 482	–42	–15 482
Senegal	Lower middle income	79	28 645	335	121 002	300	108 298
South Sudan	Lower middle income	-39	-14 613	122	45,478	96	35,591
Tajikistan	Lower middle income	–104	–43 036	12	4919	–7	–2727
Tanzania	Lower middle income	751	212 282	1989	562 400	1775	502 045
Uzbekistan	Lower middle income	–7	–8595	74	96 739	74	96 739
Vietnam	Lower middle income	–32	–52 974	109	181 915	109	181 915
Zambia	Lower middle income	356	190 274	527	281 374	525	280 238
Zimbabwe	Lower middle income	129	33 316	446	115 670	395	102 315
Low-income countries							
Total net benefits		201	33 281	8766	1 303 289	5203	846 353
Total net losses		–17 134	–1 874 568	–37	–9388	–909	–92 332
Total net impact		–16 932	–1 841 287	8728	1 293 901	4294	754 021
Lower middle income countries							
Total net benefits		1715	797406	9714	3635420	8185	3209078
Total net losses		-22755	-5603628	–216	–43 809	-1442	-240472
Total net impact		–21 041	–4 806222	9498	3 591610	6743	2968606
All countries							
Total net benefits		1916	830687	18 479	4 938709	13 388	4055431
Total net losses		–39889	–7 478196	–253	–53 198	–2 351	–3 32803
Total net impact		–3 7973	–6 647509	18 226	4 885511	11036	3722627

Table 2 Country-specific and income group-specific price reductions required

Country	Income group	Per dose price reduction required (2019 US$)	Cohort size (1000s)	Total reduction using country-specific price (1000s, 2019 US$, option 2)	Total reduction using country income group price (1000s, US$–1 for low-income countries, US$0 for lower middle income countries, 2019 US, option 3)
Benin	Low	18	1567	57749	80661
Burkina Faso	Low	10	2851	57074	146744
Burundi	Low	9	1703	31075	87647
Chad	Low	21	2372	101129	122104
Democratic Republic of the Congo	Low	23	12881	582915	663039
Eritrea	Low	22	425	18430	21877
Ethiopia	Low	17	14104	491992	725995
Gambia	Low	9	332	5981	17090
Guinea	Low	14	1744	48351	89790
Guinea Bissau	Low	22	256	11104	13159
Haiti	Low	21	1088	45173	55990
Madagascar	Low	15	3434	105294	176781
Malawi	Low	0	2510	0	129186
Mali	Low	19	2927	108948	150676
Mozambique	Low	2	4319	20123	222326
Nepal	Low	13	2418	62126	124454
Niger	Low	24	3811	183674	196160
Rwanda	Low	8	1587	25035	81666
Sierra Leone	Low	24	978	46162	50321
Togo	Low	21	1034	42623	53232
Uganda	Low	8	6512	108355	335200
Yemen	Low	26	3515	180923	180923
Bangladesh	Lower middle	23	12719	592799	645928
Cambodia	Lower middle	20	1549	61602	78677
Cameroon	Lower middle	17	3447	119244	175050
Comoros	Lower middle	0	103	0	5236
Côte d'Ivoire	Lower middle	16	3418	110006	173553
Ghana	Lower middle	3	3511	23785	178321
India	Lower middle	18	100082	3511214	5082526
Kenya	Lower middle	0	6225	0	316137
Kyrgyzstan	Lower middle	0	669	0	33951
Lesotho	Lower middle	0	205	0	10408
Mauritania	Lower middle	7	573	7837	29105
Nicaragua	Lower middle	0	570	0	28958
Nigeria	Lower middle	17	27327	922743	1387758
Pakistan	Lower middle	25	22940	1164963	1164963
Republic of Congo	Lower middle	0	705	0	35787
Republic of Sudan	Lower middle	23	5322	244785	270266
Senegal	Lower middle	0	2219	0	112695
South Sudan	Lower middle	9	1399	24665	71023
Tajikistan	Lower middle	23	1125	51199	57107
Tanzania	Lower middle	0	8087	0	410661
Uzbekistan	Lower middle	5	2929	29386	148753
Vietnam	Lower middle	8	6530	99216	331607

Continued

Table 2 Continued

Country	Income group	Per dose price reduction required (2019 US$)	Cohort size (1000s)	Total reduction using country-specific price (1000s, 2019 US$, option 2)	Total reduction using country income group price (1000s, US$−1 for low-income countries, US$0 for lower middle income countries, 2019 US, option 3)
Zambia	Lower middle	0	2506	0	127 288
Zimbabwe	Lower middle	0	1911	0	97 035
Low-income countries				2 334 238	3 725 020
Lower middle income countries				6 963 445	10 972 795
All countries				9 297 682	14 697 815

is not at US$25 per dose. That is the maximum that the country could afford to pay per dose for HPV vaccination to generate zero net benefit (ie, no net loss in overall population health, but also no net benefit). Among countries where a price reduction is required, the price reduction ranges from US$2 to US$26 (2019 US). If the vaccine manufacturer and/or a global donor were to fund the difference for both doses for all eligible girls for each country, it would cost US$9.3 billion (2019 US). The same money could avert 49 million DALYs if spent on existing interventions in these countries instead.

Alternatively, prices might be negotiated by country groups, such as income category if it is not possible to have country-specific pricing arrangements (policy option 3). In order to ensure providing HPV vaccination in all countries within an income group (or any group for that matter) generates a net benefit, or at minimum no net loss in overall population health, requires applying the lowest price required for HPV vaccination to be cost effective in any of the countries in the group to all countries in the group. This would be US$−1 per dose (2019 US) in low-income countries and US$0 per dose (2019 US) in lower middle-income countries. If the manufacturer and/or a global donor were to fund the difference for each country, it would cost US$14.7 billion (2019 US). More net health benefits would be generated across countries than from option 2; however, the same money could avert 70 million DALYs if spent on existing interventions in these countries instead.

The net health impact and net monetary impact of achieving the WHO recommendation of 90% coverage of HPV vaccination in all Gavi-eligible countries at current Gavi-negotiated prices (US$4.50 per dose, 2019 US), with current delivery costs and existing levels of Gavi procurement support, where many countries pay below US$4.50 per dose, are presented in table 1 (columns 3 and 4). This represents existing policy (policy option 4a) and offers positive net health impact for all but three countries, implying that at current prices and levels of Gavi support HPV vaccination generates a health benefit over and above any loss incurred as a result of the money required to fund it not being available to fund other healthcare interventions for most countries. Without the Gavi procurement support (ie, at a per dose price of US$4.50 (2019 US) for all countries, option 4b), HPV vaccination generates a net health loss in eight more countries than it would with the Gavi procurement support (see table 1 columns 5 and 6).

Sensitivity analyses

Our analysis used a discount rate of 3% for costs and benefits following common practice. While this is in line with the WHO guidance, the guidance also recommends a sensitivity analysis where health is undiscounted but costs are discounted at 3%.[26] The resulting net health impact estimates for this sensitivity analysis are reported against the base case in online supplemental appendix table 1 and the price reductions required are reported against the base case in online supplemental appendix table 2. The health benefits of HPV vaccination often occur in future years (eg, cancer cases are averted up to decades after the vaccine has been administered). Since greater weight is attached to future health outcomes when they are undiscounted, discounting the health benefits from HPV vaccination has the effect of reducing their net present value. Therefore, HPV vaccination appears better value when no discounting is applied to health benefits. The per dose price reduction required in order for HPV vaccination to generate zero net benefit (ie, no net loss in overall population health, but also no net benefit) in countries where it generates a net loss at average market price are also lower (and more often zero or not required at all) than when a 3% discount rate is used for health benefits. If country-specific pricing were possible, the total price reduction required (ie, for all doses for all eligible girls across all countries where a price required is required) would be less than a third of that required when a 3% discount rate is applied to health benefits. Where country income-group pricing is applied, the difference in funding required is lower at US$11.6 billion (compared with US$14.7 billion when a 3% discount rate is applied to health benefits). The price for low-income countries would be US$2 per dose and for lower middle income countries it would be US$6 per dose (2019 US$).

Our analysis uses the central estimate of the marginal productivity of each HCS from the range estimated by Ochalek *et al*.[31] As a sensitivity analysis, we use the minimum and maximum from the ranges for each country. Using the minimum (maximum) estimate for each country will tell us the maximum (minimum) health opportunity cost expected from adopting HPV vaccination and therefore lowest (highest) estimate of net health benefit from it for each country. The results of this sensitivity analysis are reported in online supplementary appendix tables 3 and 4. Using the minimum or maximum makes little overall difference to the number of countries for which HPV vaccination would be expected to generate a net health benefit. Among low-income countries, at market price (US$25 per dose) one fewer low-income country would be estimated to have a net health benefit from adopting HPV vaccination when the minimum estimate of the marginal productivity of each HCS is used. Results do not change when current per dose procurement prices are used (as in option 4a), but when the price is US$4.50 per dose (option 4b) three additional low-income countries would expect a net health benefit when the maximum estimate of the marginal productivity of each HCS is used while one fewer would expect a net health benefit when the minimum is used (compared with the central estimate). Among lower middle income countries adopting HPV vaccination would be estimated to generate a net health benefit in one fewer (more) country when the minimum (maximum) estimate of the marginal productivity of each HCS is used at market price (US$25 per dose), but results do not change when current per dose procurement prices (as in policy option 4a) or US$4.50 per dose (policy option 4b) are used. Even when introducing HPV vaccination would result in net health benefit for the same number of countries regardless of whether the minimum, central or maximum estimate is used, the magnitude of the net health benefit differs. The estimated net health benefits (losses) are greatest (lowest) when using the maximum estimate of health opportunity cost from the range. The price reduction required for HPV vaccination to generate a net health benefit in all countries is higher (lower) when using the minimum (maximum) estimate of health opportunity costs. When the minimum estimate is used the per dose price reduction required in both low-income and lower middle income countries is US$26 (2019 US; ie, the maximum that the country that can least afford to adopt HPV vaccination can afford to pay is US$−1 per dose). When the maximum estimates of health opportunity cost are used, the price reductions required for low-income and lower middle-income countries are US$26 and US$25 (2019 US), respectively, which is the same as the base case (ie, when the central estimate is used). When country-specific pricing is used (as in policy option 2), this amounts to a total of US$8.6 billion to US$9.9 billion in funding required when the maximum and minimum estimates are used, respectively. When country income group pricing is used (as in policy option 3), this amounts to a total of US$14.5 billion to US$14.8 billion in funding required when the maximum and minimum estimates are used, respectively.

DISCUSSION

The analysis undertaken enables an assessment of blanket recommendations (in order to, eg, inform whether, at current prices, they would be expected to improve health in all countries); an assessment of the price reduction (if any) required for a healthcare intervention to generate at minimum no net health loss; and the value of developing new healthcare interventions.

Previous analyses have used a GDP per capita threshold to judge the cost effectiveness of adopting HPV vaccination and eliminating cervical cancer.[17 18 32] The GDP per capita threshold originates from human capital arguments made by the WHO Commission on Macroeconomics and Health around the value of a year of life.[33] However, WHO no longer recommends it for country evaluations on the basis that it may not reflect country priorities and decision-making processes.[14] Estimates of the marginal productivity of HCSs reflect health opportunity cost and tend to be lower than GDP per capita, and so using a GDP per capita threshold to make decisions can lead to net health losses.[8 31] Indeed, in practice, low-income countries' actual decisions to introduce HPV vaccination, or not, reveal an implicit cost-effectiveness threshold of 30%–35% of GDP per capita.[34] Reassuringly, our results show that HPV vaccination remains cost effective for most countries at current Gavi negotiated prices when a threshold that reflects the health opportunity cost faced by the country is used (rather than human capital arguments about the value of health spending). Although there is uncertainty around existing estimates of the marginal productivity of HCSs, using the minimum or maximum from the range of estimates from Ochalek *et al* (2018) has little impact on the results.

A blanket recommendation to introduce HPV vaccination in LMICs would result in net health losses in most countries in the absence of Gavi support. This was analysed under the assumption that these countries would face the average market price faced by countries not eligible for Gavi support. Manufacturers might be able to price discriminate (ie, using tiered pricing policy), reducing prices for these countries. However, there is no guarantee that in the absence of pooled procurement and market shaping efforts by organisations like Gavi lower-income countries would pay lower prices.[35] The extent to which prices would be lower than the average market price among high-income countries in the absence of Gavi support is unclear but would result in better net health impacts, while higher prices would result in worse net health impacts. It is worth noting that our estimate for policy option 1 being conservative or optimistic has no implications for comparisons between policy options 2, 3, 4a and 4b.

The current reality of vaccine procurement prices paid by countries likely falls somewhere between policy options 2 and 4. Policy option 4 assumed all countries pay S$4.50 per dose or less (as countries purchase a share of the vaccines provided while Gavi purchases the remainder). The share funded by Gavi is based on the Gavi cofinancing mechanism depending on the funding phase the country is in (based on country income level and years of funding) rather than reflecting health opportunity costs as in policy option 2.[22] However, in practice, countries may not meet their cofinancing requirements. Gavi funding a greater proportion of vaccines would have the effect of reducing the per dose price below the prices used in 4a, and all else the same the vaccine would generate a more positive net impact in those countries. Determining prices using a more systematic method of accounting for opportunity costs, as illustrated in policy option 2, offers an opportunity to ensure that countries that do not benefit from adopting HPV vaccination at current prices would be able to introduce it without facing a reduction in population health. Future research could seek to establish the best way for donors to support the affordability of interventions, which would require information on the opportunity cost of donor financial support and the loss of revenue for the manufacturers of vaccine, in addition to the transaction costs associated with implementing donor support mechanisms.

This type of analysis can also help to inform the value of developing a new healthcare intervention that does not yet exist. For example, the Bill and Melinda Gates Foundation funds the development of new healthcare interventions targeted towards the leading causes of death and disability in LMICs. While a more uncertain prospect at this earlier stage, estimating the price at which a healthcare intervention would have a positive net health impact in each HCS (as in policy option 2) can help to inform whether it should be considered for development by the foundation, through comparison with the cost of the intervention to the provider. Using the expected net health impact of different potential healthcare interventions (and how this is distributed across countries) to rank potential investments would ensure that new healthcare interventions which are likely to generate the greatest health gains offered at affordable prices are prioritised over others. Value of information analysis provides a means to prioritise future research to resolve uncertainties with the new healthcare interventions under consideration for development. However, the development of a new healthcare intervention may be seen to address multiple objectives in addition to improving overall population health. This framework could be extended to incorporate other objectives, such as equity, following, for example, extended or distributional cost-effectiveness analysis methods. In fact, prioritisation decisions for both vaccine research and development (eg, the Vaccine Innovation Prioritisation Strategy) and financing for adoption (eg, the Gavi Investment Strategy) use a kind of multicriteria decision analysis that considers cost effectiveness alongside multiple other criteria.[36 37]

Equity concerns may also be relevant for interventions for which a net health benefit is generated in some, but not all, countries in which it is recommended. The benefit associated with providing HPV vaccination in some countries may outweigh the losses in other countries if, for example, to reflect equity being another objective in decision-making more weight is given to gains in low-income countries and this is where the bulk of the gains are. Assessing the net health impact of providing a healthcare intervention for each country enables decision-makers to be explicit about the trade-offs being made if, for example, net health losses were incurred in some low-income countries but no lower middle income countries. If more weight was put on outcomes in low-income countries, a blanket recommendation of providing the healthcare intervention would appear to be less favourable as policy choice if the price was the same in all countries as this is where a disproportionately larger amount of the overall losses in net health would be incurred.

The results are sensitive to the discount rate used. The WHO recommends initially using the discount rate used in the country, and where national guidelines do not exist recommends two scenarios: our base case (ie, 3% discounting for both health and consumption) and sensitivity analysis (ie, 3% and 0% discounting for consumption and health, respectively).[26] However, application of the same discount rates for all countries is unlikely to be appropriate. Where the objective is improving population health, for example, the appropriate discount rate for health for each country should depend on the rate at which the principal can borrow and save and the expected growth in the marginal productivity of the HCS[38 39]—both of which would be expected to vary by country. To date, there are no data on the expected growth in the marginal productivity of the HCS, and this should be a priority for future research.

CONCLUSION

This paper illustrates how estimates of the net health impact or, equivalently, net monetary value of providing a healthcare intervention can be used to estimate the expected effect to overall population health in a country of adhering to global guidance and inform negotiations with donors, as well as informing pricing negotiations and the value of developing new healthcare interventions. At Gavi negotiated prices, HPV vaccination generates net health benefits across nearly all Gavi-eligible countries included in this study. However, if Gavi-eligible countries faced the same price as non-Gavi eligible countries, providing HPV vaccination would reduce overall population health in all but two low-income and nearly half of lower middle income countries and impose a net DALY burden of 38 million DALYs globally. This suggests that Gavi's negotiations on behalf of countries eligible for its support have succeeded in making adhering to the

WHO guidance around HPV vaccination a worthy aim for most countries. Assessing the likely scale and distribution of the impact of potential new interventions on net population health, at a particular price, can also inform priorities in developing new technologies. The maximum price each country could afford to pay for HPV vaccination to be cost effective can be calculated as can the net health benefit that would be expected to be generated at different potential prices. Determining prices using these methods, which account for country-specific opportunity costs, offers an opportunity to ensure that all countries can benefit from adopting HPV vaccination or other recommendations made by global bodies. Finally, the methods used here can be applied to assess the value of developing a new technology. It will also depend on not only the expected costs and benefits of the new technology for each country in which it may be implemented, but as well the likely health opportunity costs in those countries.

Contributors JO undertook the analysis and wrote the initial draft. KA, KC, MJ and JL contributed equally to developing the analysis plan, the review and interpretation of results and the final drafting of the manuscript.

Funding This study is funded by Vaccine Impact Modelling Consortium (OPP1157270), Bill and Melinda Gates Foundation (OPP1165566).

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. Data on the costs and benefits of HPV vaccination across countries are output from the PRIME Tool, which can be accessed at https://github.com/lshtm-vimc/prime. Country-specific estimates of the health effects of changes in health care expenditure can be accessed at https://www.york.ac.uk/che/research/teehta/health-opportunity-costs/estimating-health-opportunity-costs-for-lmics/#tab-4.

ORCID iDs
Jessica Ochalek http://orcid.org/0000-0003-0744-1178
Kaja Abbas http://orcid.org/0000-0003-0563-1576
Karl Claxton http://orcid.org/0000-0003-2002-4694
Mark Jit http://orcid.org/0000-0001-6658-8255
James Lomas http://orcid.org/0000-0002-2478-7018

REFERENCES

1 World Health Organization. *Global spending on health: a world in transition*. Geneva, 2019. http://apps.who.int/bookorders
2 Bump JB. Global health aid allocation in the 21st century. *Health Policy Plan* 2018;33:i1–3.
3 Vallejo-Torres L, García-Lorenzo B, Serrano-Aguilar P. *Estimating a cost-effectiveness threshold for the Spanish*. Madrid: NHS, 2016. http://documentos.fedea.net/pubs/eee/eee2016-22.pdf
4 Claxton K, Martin S, Soares M, *et al*. Methods for the estimation of the National Institute for health and care excellence cost-effectiveness threshold. *Health Technol Assess* 2015;19:1–504.
5 Edney LC, Haji Ali Afzali H, Cheng TC, *et al*. Estimating the reference incremental cost-effectiveness ratio for the Australian health system. *Pharmacoeconomics* 2018;36:239–52.
6 Stadhouders N, Koolman X, van Dijk C, Dijk C, *et al*. The marginal benefits of healthcare spending in the Netherlands: estimating cost-effectiveness thresholds using a translog production function. *Health Econ* 2019;28:1331–44.
7 Ochalek J, Revill P, Manthalu G, *et al*. Supporting the development of a health benefits package in Malawi. *BMJ Glob Health* 2018;3:e000607.
8 Woods B, Revill P, Sculpher M, *et al*. Country-Level cost-effectiveness thresholds: initial estimates and the need for further research. *Value Health* 2016;19:929–35.
9 Ochalek J, Lomas J. Reflecting the health opportunity costs of funding decisions within value frameworks: initial estimates and the need for further research. *Clin Ther* 2020;42:44–59.
10 van Baal P, Perry-Duxbury M, Bakx P, *et al*. A cost-effectiveness threshold based on the marginal returns of cardiovascular Hospital spending. *Health Econ* 2019;28:87–100.
11 Siverskog J, Henriksson M. Estimating the marginal cost of a life year in Sweden's public healthcare sector. *Eur J Health Econ* 2019;20:751–62.
12 Edoka IP, Stacey NK. Estimating a cost-effectiveness threshold for health care decision-making in South Africa. *Health Policy Plan* 2020;35:546–55.
13 Ochalek J, Wang H, Gu Y, *et al*. Informing a cost-effectiveness threshold for health technology assessment in China: a marginal productivity approach. *Pharmacoeconomics* 2020. doi:10.1007/s40273-020-00954-y. [Epub ahead of print: 28 Aug 2020].
14 Bertram MY, Lauer JA, De Joncheere K, *et al*. Cost-Effectiveness thresholds: pros and cons. *Bull World Health Organ* 2016;94:925–30.
15 WHO. *Draft: global strategy towards the elimination of cervical cancer as a public health problem*. Geneva, 2019. https://www.who.int/docs/default-source/documents/cervical-cancer-elimination-draft-strategy.pdf
16 Gavi. Eligibility, 2020. Available: https://www.gavi.org/types-support/sustainability/eligibility [Accessed 14 Feb 2020].
17 Jit M, Brisson M, Portnoy A, *et al*. Cost-Effectiveness of female human papillomavirus vaccination in 179 countries: a prime modelling study. *Lancet Glob Health* 2014;2:e406–14.
18 Abbas KM, van Zandvoort K, Brisson M, *et al*. Effects of updated demography, disability weights, and cervical cancer burden on estimates of human papillomavirus vaccination impact at the global, regional, and national levels: a prime modelling study. *Lancet Glob Health* 2020;8:e536–44.
19 WHO. MI4A: vaccine purchase data. WHO, 2019. Available: https://www.who.int/immunization/programmes_systems/procurement/mi4a/platform/module1/en/ [Accessed 25 Feb 2020].
20 Nguyen A. Working towards affordable pricing for HPV vaccines for developing countries: the role of GAVI, 2011. Available: http://www.technet21.org/index.php/documents/view-document/1098-financing-for-hpv-vaccines-americas- [Accessed 19 Feb 2020].
21 Gavi The Vaccine Alliance. *HPV supply and procurement roadmap the market shaping goal shape vaccine markets to ensure adequate supply of appropriate, quality vaccines at low and sustainable prices for developing countries. human papilloma virus vaccine*, 2017.
22 Gavi The Vaccine Alliance. *Application guidelines: gavi's support to countries*, 2019.
23 World Health Organization. Table 1: Summary of WHO Position Papers - Recommendations for Routine Immunization, 2019. Available: https://www.who.int/immunization/policy/Immunization_routine_table1.pdf?ua [Accessed 13 Mar 2020].
24 Campos NG, Sharma M, Clark A, *et al*. The health and economic impact of scaling cervical cancer prevention in 50 low- and lower-middle-income countries. *Int J Gynaecol Obstet* 2017;138 Suppl 1:47–56.
25 World Health Organization. WHO guidelines listed by year of publication, 2020. Available: http://www.who.int/publications/guidelines/year/en/ [Accessed 28 Jul 2020].
26 Initiative for Vaccine Research of the Department of Immunization Vaccines and Biologicals. *WHO guide for standardization of economic evaluations of immunization programmes*. Geneva, 2019. https://apps.who.int/iris/
27 Robinson LA, Hammitt JK, Jamison DT, *et al*. Conducting Benefit-Cost analysis in low- and middle-income countries: introduction to the special issue. *J Benefit Cost Anal* 2019;10:1–14.
28 Wilkinson T, Sculpher MJ, Claxton K, *et al*. The International decision support initiative reference case for economic evaluation: an aid to thought. *Value Health* 2016;19:921–8.
29 Neumann PJ, Thorat T, Zhong Y, *et al*. A systematic review of cost-effectiveness studies reporting cost-per-DALY averted. *PLoS One* 2016;11:e0168512.
30 Haacker M, Hallett TB, Atun R. On discount rates for economic evaluations in global health. *Health Policy Plan* 2020;35:107–14.

31 Ochalek J, Lomas J, Claxton K. Estimating health opportunity costs in low-income and middle-income countries: a novel approach and evidence from cross-country data. *BMJ Glob Health* 2018;3:e000964.
32 Canfell K, Kim JJ, Brisson M, *et al*. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. *Lancet* 2020;395:591–603.
33 Newall AT, Jit M, Hutubessy R. Are current cost-effectiveness thresholds for low- and middle-income countries useful? examples from the world of vaccines. *Pharmacoeconomics* 2014;32:525–31.
34 Jit M. Informing global cost-effectiveness thresholds using country investment decisions: human papillomavirus vaccine introductions in 2006-2018. *Value Heal* Forthcoming.
35 Médecins Sans Frontières Access Campaign. *The right shot: bringing down barriers to affordable and adapted vaccines*. 2nd ed, 2015. https://msfaccess.org/right-shot-bringing-down-barriers-affordable-and-adapted-vaccines-2nd-ed-2015
36 Gavi The Vaccine Alliance. The vaccine innovation prioritisation strategy, 2020. Available: https://www.gavi.org/our-alliance/market-shaping/vaccine-innovation-prioritisation-strategy [Accessed 14 Aug 2020].
37 Gavi The Vaccine Alliance. Vaccine investment strategy, 2020. Available: https://www.gavi.org/our-alliance/strategy/vaccine-investment-strategy [Accessed 14 Aug 2020].
38 Claxton K, Asaria M, Chansa C, *et al*. Accounting for timing when assessing health-related policies. *J Benefit-Cost Anal* 2019:1–33.
39 Paulden M, Claxton K. Budget allocation and the revealed social rate of time preference for health. *Health Econ* 2012;21:612–8.

Supplementary Appendix 1. Calculated per dose price

Estimates of the additional cost of HPV vaccination reflect the three phases of the Gavi co-financing mechanism: 1) initial self-financing, 2) preparatory transition, and 3) accelerated transition. Countries in the first phase co-finance a portion of the HPV vaccines equivalent to $0.20 per dose (or 4.4% of the cost of a dose). Countries remain in the first phase until their gross national income (GNI) per capita exceeds $1,005.

Countries with a GNI per capita above $1,005 and up to $1,580 per capita are in the second phase (i.e., the preparatory transition phase), and pay 15% more for each dose each year. If HPV vaccination is introduced when countries are already in this phase, we calculate the price per dose as:

$$HPV\ vaccine\ price\ per\ dose\ (phase\ 2) = \$4.50 - \frac{\$0.20}{\$4.50} * 1.15^{t}$$

where t is the number of years the country has been in the preparatory transition phase.

Countries move from the second transition phase into the third phase once their GNI per capita is above $1,580, and can remain in this phase for five years, at which point they graduate from Gavi funding to become fully self-financing. For countries in the first year of this phase in 2020, price per dose increases 15% and is calculated as:

$$HPV\ vaccine\ price\ per\ dose\ (phase\ 3\ year\ 1\ of\ 5) = \$4.50 - \frac{\$0.20}{\$4.50} * 1.15^{t+1}$$

In the following four years, the co-financed share increases linearly to reach $4.50.

Supplementary Appendix Table 1. Sensitivity analysis around discount rates: Net health impact (NHI) and net monetary impact (NMI)
A: Base case (discount rate of 3% for health and 3% for costs)
B: Discount rate of 0% for health and 3% for costs

	$25 per dose		**Gavi procurement support (per dose price differs by country, all <=$4.50)**		**$4.50 per dose**	
	A	**B**	**A**	**B**	**A**	**B**
Low-income						
Net health benefits						
# of countries	2	13	21	22	15	21
Total +ive NHI (1,000s)	201	16,104	8,766	35,646	5,203	31,262
Total +ive NMI (1,000s 2019 US$)	33,281	2,671,456	1,327,194	5,490,501	837,388	4,884,613
Net health losses						
# of countries	20	9	1	0	7	1
Total -ive NHI (1,000s)	-17,134	-6,118	-37	0	-909	-50
Total -ive NMI (1,000s 2019 US$)	-2,331,849	-797,328	-9,388	0	-138,035	-12,565
Net health impact						
# of countries	22	22	22	22	22	22
Total NHI (1,000s)	-16,932	9,986	8,728	35,646	4,294	31,212
Total NMI (1,000s 2019 US$)	-2,298,568	1,874,127	1,317,805	5,490,501	699,353	4,872,048
Lower middle-income						
Net health benefits						
# of countries	12	20	22	24	19	24
Total +ive NHI (1,000s)	1,781	28,844	9,646	53,350	8,112	50,594
Total +ive NMI (1,000s 2019 US$)	819,677	12,087,170	3,609,966	19,502,849	3,181,013	18,879,844
Net health losses						
# of countries	12	4	2	0	5	0
Total -ive NHI (1,000s)	-23,277	-6,033	-216	0	-1,501	0
Total -ive NMI (1,000s 2019 US$)	-5,798,249	-982,153	-43,809	0	-262,383	0
Net health impact						
# of countries	24	24	24	24	24	24

Total NHI (1,000s)	-21,496	22,811	9,431	53,350	6,610	50,594
Total NMI (1,000s 2019 US$)	-4,978,573	11,105,017	3,566,157	19,502,849	2,918,630	18,879,844
All countries						
Net health benefits						
# of countries	14	33	43	46	34	45
Total +ive NHI (1,000s)	1,983	44,948	18,412	88,996	13,315	81,856
Total +ive NMI (1,000s 2019 US$)	852,957	14,804,203	4,913,255	24,791,372	4,027,366	23,641,054
Net health losses						
# of countries	32	13	3	0	12	1
Total -ive NHI (1,000s)	-40,411	-12,151	-253	0	-2,410	-50
Total -ive NMI (1,000s 2019 US$)	-7,672,817	-1,545,850	-53,198	0	-354,714	-12,565
Net health impact						
# of countries	46	46	46	46	46	46
Total NHI (1,000s)	-38,428	32,797	18,159	88,996	10,904	81,806
Total NMI (1,000s 2019 US$)	-6,819,860	13,258,353	4,860,057	24,791,372	3,672,652	23,628,489

Supplementary Appendix Table 2. Sensitivity analysis around discount rates: Pricing arrangements

A: Base case (discount rate of 3% for health and 3% for costs)

B: Discount rate of 0% for health and 3% for costs

Country	Income group	Per dose price reduction required (2019 US$)		Total reduction using country specific price (1,000s 2019 US$, option 2)		Total reduction using country income group price (1,000s, $2 for low-income countries, $6 for lower middle-income countries, 2019 US$, option 3)	
		A	B	A	B	A	B
Benin	Low	18	0	57,749	0	80,661	72,268
Burkina Faso	Low	10	0	57,074	0	146,744	131,475
Burundi	Low	9	0	31,075	0	87,647	78,527
Chad	Low	21	8	101,129	37,013	122,104	109,399
Democratic Republic of the Congo	Low	23	14	582,915	348,943	663,039	594,048
Eritrea	Low	22	8	18,430	6,879	21,877	19,600
Ethiopia	Low	17	0	491,992	0	725,995	650,454
Gambia	Low	9	0	5,981	0	17,090	15,312
Guinea	Low	14	0	48,351	0	89,790	80,448
Guinea Bissau	Low	22	11	11,104	5,759	13,159	11,790
Haiti	Low	21	3	45,173	7,576	55,990	50,164
Madagascar	Low	15	0	105,294	0	176,781	158,386
Malawi	Low	0	0	0	0	129,186	115,744
Mali	Low	19	1	108,948	6,179	150,676	134,998
Mozambique	Low	2	0	20,123	0	222,326	199,193
Nepal	Low	13	0	62,126	0	124,454	111,505
Niger	Low	24	18	183,674	134,466	196,160	175,749
Rwanda	Low	8	0	25,035	0	81,666	73,168

Sierra Leone	Low	24	16	46,162	30,374	50,321	45,085
Togo	Low	21	4	42,623	8,095	53,232	47,693
Uganda	Low	8	0	108,355	0	335,200	300,322
Yemen	Low	26	23	180,923	162,097	180,923	162,097
Bangladesh	Lower middle	23	13	592,799	321,937	645,928	483,731
Cambodia	Lower middle	20	0	61,602	0	78,677	58,921
Cameroon	Lower middle	17	0	119,244	0	175,050	131,094
Comoros	Lower middle	0	0	0	0	5,236	3,921
Côte d'Ivoire	Lower middle	16	0	110,006	0	173,553	129,972
Ghana	Lower middle	3	0	23,785	0	178,321	133,543
India	Lower middle	18	0	3,511,214	0	5,082,526	3,806,270
Kenya	Lower middle	0	0	0	0	316,137	236,753
Kyrgyzstan	Lower middle	0	0	0	0	33,951	25,426
Lesotho	Lower middle	0	0	0	0	10,408	7,795
Mauritania	Lower middle	7	0	7,837	0	29,105	21,796
Nicaragua	Lower middle	0	0	0	0	28,958	21,686
Nigeria	Lower middle	17	0	922,743	0	1,387,758	1,039,283
Pakistan	Lower middle	25	19	1,164,963	872,433	1,164,963	872,433
Republic of Congo	Lower middle	0	0	0	0	35,787	26,801
Republic of Sudan	Lower middle	23	6	244,785	66,516	270.266	202,400
Senegal	Lower middle	0	0	0	0	112,695	84,396
South Sudan	Lower middle	9	0	24,665	0	71,023	53,189
Tajikistan	Lower middle	23	9	51,199	21,121	57,107	42,767
Tanzania	Lower middle	0	0	0	0	410,661	307,542
Uzbekistan	Lower middle	5	0	29,386	0	148,753	111,400
Vietnam	Lower middle	8	0	99,216	0	331,607	248,338
Zambia	Lower middle	0	0	0	0	127,288	95,325

Zimbabwe	Lower middle	0	0	0	0	97,035	72,669
Low				2,334,238	747,380	3,725,020	3,337,425
Lower middle				6,963,445	1,282,007	10,972,795	8,217,453
All				9,297,682	2,029,387	14,697,815	11,554,878

Supplementary Appendix Table 3. Sensitivity analysis around estimate of health opportunity cost: Net health impact (NHI) and net monetary impact (NMI)

	$25 per dose (option 1)			Gavi procurement support (per dose price differs by country, all <=$4.50, option 4a)			$4.50 per dose (option 4b)		
	Minimum	Central estimate of health opportunity cost	Maximum	Minimum	Central estimate of health opportunity cost	Maximum	Minimum	Central estimate of health opportunity cost	Maximum
Low-income									
Net health benefits									
# of countries	1	2	2	21	21	21	14	15	18
Total +ive NHI (1,000s)	94	201	375	8,835	8,766	8,692	4,982	5,203	5,459
Total +ive NMI (1,000s 2019 US$)	12,603	33,281	76,156	1,168,107	1,327,194	1,539,249	704,538	837,388	1,017,070
Net health losses									
# of countries	21	20	20	1	1	1	8	7	4
Total -ive NHI (1,000s)	-20,107	-17,134	-13,679	-47	-37	-30	-1,171	-909	-592
Total -ive NMI (1,000s 2019 US$)	-2,471,097	-2,331,849	-2,161,792	-10,228	-9,388	-8,511	-165,112	-138,035	-104,785
Net health impact									
# of countries	22	22	22	22	22	22	22	22	22
Total NHI (1,000s)	-20,013	-16,932	-13,304	8,787	8,728	8,662	3,811	4,294	4,866
Total NMI (1,000s 2019 US$)	-2,458,495	-2,298,568	-2,085,635	1,157,879	1,317,805	1,530,738	539,426	699,353	912,286
Lower middle-income									
Net health benefits									
# of countries	10	11	12	22	22	22	20	20	20
Total +ive NHI (1,000s)	1,427	1,715	1,988	9,306	9,714	10,060	7,641	8,185	8,653
Total +ive NMI (1,000s 2019 US$)	564,543	797,406	1,093,574	2,967,884	3,635,420	4,388,940	2,557,94	3,209,078	3,943,923
Net health losses									
# of countries	14	13	12	2	2	2	4	4	4
Total -ive NHI (1,000s)	-28,007	-22,755	-18,118	-345	-	-93	-1,889	-1,442	-1,046

Total -ive NMI (1,000s 2019 US$)	-6,055,675	-5,603,628	-5,124,730	-61,184	-43,809	-22,264	-274,246	-240,472	-200,251
Net health impact									
# of countries	24	24	24	24	24	24	24	24	24
Total NHI (1,000s)	-26,580	-21,041	-16,130	8,961	9,498	9,967	5,752	6,743	7,607
Total NMI (1,000s 2019 US$)	-5,491,133	-4,806,222	-4,031,156	2,906,700	3,591,610	4,366,676	2,283,69	2,968,606	3,743,672
All countries									
Net health benefits									
# of countries	11	13	14	43	43	43	34	35	38
Total +ive NHI (1,000s)	1,521	1,916	2,363	18,140	18,479	18,752	12,623	13,388	14,111
Total +ive NMI (1,000s 2019 US$)	577,145	830,687	1,169,730	4,123,966	4,938,709	5,890,201	3,268,65	4,055,431	4,972,751
Net health losses									
# of countries	35	33	32	3	3	3	12	11	8
Total -ive NHI (1,000s)	-48,114	-39,889	-31,797	-392	-	-	-3,060	-2,351	-1,638
Total -ive NMI (1,000s 2019 US$)	-8,057,611	-7,478,196	-6,843,323	-71,412	-53,198	-30,775	-378,979	-332,803	-276,208
Net health impact									
# of countries	46	46	46	46	46	46	46	46	46
Total NHI (1,000s)	-46,593	-37,973	-29,434	17,748	18,226	18,629	9,563	11,036	12,473
Total NMI (1,000s 2019 US$)	-7,480,465	-6,647,509	-5,673,593	4,052,554	4,885,511	5,859,426	2,889,67	3,722,627	4,696,543

Supplementary Appendix Table 4. Sensitivity analysis around estimate of health opportunity cost: Pricing arrangements

Country	Income group	Per dose price reduction required (2019 US$)			Total reduction using country specific price (1,000s 2019 US$, option 3)			Total reduction using country income group price (1,000s 2019 US, option 4)		
Estimate of health opportunity cost		Min.	Central	Max.	Minimum	Central	Maximum	Minimum ($-1 for low-income countries, $-1 for lower-middle income countries)	Central ($-1 for low-income countries, $0 for lower-middle income countries)	Maximum ($-1 for low-income countries, $0 for lower-middle income countries)
Benin	Low	19	18	18	60,544	57,749	54,956	81,035	80,661	80,269
Burkina Faso	Low	11	10	7	63,934	57,074	41,470	147,426	146,744	146,033
Burundi	Low	11	9	7	36,106	31,075	22,783	88,054	87,647	87,222
Chad	Low	22	21	20	103,060	101,129	96,947	122,671	122,104	121,512
Democratic Republic of the Congo	Low	23	23	22	589,252	582,915	572,297	666,116	663,039	659,822
Eritrea	Low	22	22	21	18,858	18,430	17,886	21,978	21,877	21,770
Ethiopia	Low	18	17	16	519,696	491,992	455,269	729,365	725,995	722,473
Gambia	Low	11	9	7	7,359	5,981	4,424	17,170	17,090	17,008
Guinea	Low	15	14	12	51,670	48,351	42,168	90,207	89,790	89,355
Guinea Bissau	Low	22	22	21	11,246	11,104	10,826	13,220	13,159	13,096
Haiti	Low	22	21	20	47,084	45,173	43,511	56,250	55,990	55,718
Madagascar	Low	16	15	14	111,744	105,294	97,157	177,601	176,781	175,923
Malawi	Low	1	0	0	4,039	0	0	129,786	129,186	128,559
Mali	Low	19	19	17	111,987	108,948	102,302	151,376	150,676	149,946
Mozambique	Low	5	2	0	44,948	20,123	0	223,358	222,326	221,247
Nepal	Low	15	13	11	73,030	62,126	52,890	125,032	124,454	123,851

Niger	Low	24	24	24	185,145	183,674	180,348	197,070	196,160	195,208
Rwanda	Low	10	8	6	32,167	25,035	17,935	82,045	81,666	81,269
Sierra Leone	Low	24	24	23	46,581	46,162	45,308	50,554	50,321	50,076
Togo	Low	21	21	20	43,783	42,623	41,179	53,479	53,232	52,974
Uganda	Low	10	8	6	130,674	108,355	78,439	336,756	335,200	333,574
Yemen	Low	26	26	26	181,762	180,923	180,045	181,762	180,923	180,045
Bangladesh	Lower middle	24	23	23	607,475	592,799	575,924	652,287	645,928	637,843
Cambodia	Lower middle	21	20	19	65,569	61,602	58,604	79,452	78,677	77,693
Cameroon	Lower middle	18	17	16	123,380	119,244	112,024	176,774	175,050	172,859
Comoros	Lower middle	0	0	0	0	0	0	5,288	5,236	5,170
Côte d'Ivoire	Lower middle	17	16	15	115,698	110,006	100,313	175,261	173,553	171,380
Ghana	Lower middle	6	3	1	42,040	23,785	3,723	180,076	178,321	176,089
India	Lower middle	19	18	16	3,761,298	3,511,214	3,239,681	5,132,563	5,082,526	5,018,906
Kenya	Lower middle	0	0	0	0	0	0	319,250	316,137	312,180
Kyrgyzstan	Lower middle	0	0	0	0	0	0	34,285	33,951	33,526
Lesotho	Lower middle	0	0	0	0	0	0	10,511	10,408	10,278
Mauritania	Lower middle	9	7	4	10,097	7,837	5,041	29,391	29,105	28,741
Nicaragua	Lower middle	0	0	0	0	0	0	29,243	28,958	28,595
Nigeria	Lower middle	18	17	15	970,840	922,743	838,130	1,401,421	1,387,758	1,370,387
Pakistan	Lower middle	26	25	25	1,176,432	1,164,963	1,150,381	1,176,432	1,164,963	1,150,381
Republic of Congo	Lower middle	0	0	0	0	0	0	36,140	35,787	35,339
Republic of Sudan	Lower middle	24	23	22	250,691	244,785	237,822	272,927	270,266	266,883
Senegal	Lower middle	1	0	0	3,988	0	0	113,804	112,695	111,284
South Sudan	Lower middle	11	9	7	30,157	24,665	18,190	71,723	71,023	70,134
Tajikistan	Lower middle	24	23	22	52,923	51,199	49,400	57,670	57,107	56,392
Tanzania	Lower middle	0	0	0	0	0	0	414,704	410,661	405,521

Uzbekistan	Lower middle	9	5	1	53,265	29,386	7,204	150,218	148,753	146,891
Vietnam	Lower middle	12	8	4	156,971	99,216	54,461	334,872	331,607	327,456
Zambia	Lower middle	0	0	0	0	0	0	128,541	127,288	125,695
Zimbabwe	Lower middle	0	0	0	0	0	0	97,990	97,035	95,820
Low					2,474,668	2,334,238	2,158,140	3,742,310	3,725,020	3,706,950
Lower-middle					7,420,824	6,963,445	6,450,897	11,080,821	10,972,795	10,835,444
All					9,895,492	9,297,682	8,609,037	14,823,131	14,697,815	14,542,394