**Appendix to “Current Global Pricing For Human Papillomavirus Vaccines Bring The Greatest Economic Benefits To Rich Countries”**

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# 1. Calculation of global economic surplus

*Overview*

*Methodological assumptions*

Calculations of the global economic surplus were done from the perspective of the consumer (national health care providers in each country) and producer (vaccine manufacturers). Hence societal (productivity) costs were excluded. Costs and DALYs were discounted at a rate of 3% per annum as recommended by the World Health Organization (1). The time horizon was the lifetime of the cohort of 12-year old girls vaccinated.

For the return on investment analysis, calculations were done from the perspective of vaccine manufacturers, with a time horizon of 2006 – 2014.

All costs were converted to USD and inflated to 2013 prices using the US consumer price index for urban customers (CPI-U).

*Consumer surplus*

Benefit of vaccination to consumers = Cervical cancer treatment cost savings due to vaccination + (DALYs due to cervical cancer prevented due to vaccination x Willingness to pay to prevent a DALY)

Cost of vaccination to consumers = (Vaccine purchase cost + Vaccine delivery cost) x Number of 12-year old girls x Vaccine coverage (100%) x Number of doses given per vaccinated girl

Consumer surplus = Benefit of vaccination to consumers – Cost of vaccination to consumers

*Producer surplus*

Benefit of vaccination to producers = Revenue per vaccine dose sold x Number of 12-year old girls x Vaccine coverage (100%) x Number of doses given per vaccinated girl (summed over all countries in the world)

Cost of vaccination to producers = Vaccine discovery cost + Vaccine R&D costs + Vaccine manufacturing costs + Vaccine marketing costs

Producer surplus = Benefit of vaccination to producers – Cost of vaccination to producers

*Total economic surplus*

Total economic surplus = Consumer surplus + Producer surplus

# 2. Data sources for costs

*Summary*

|  |  |  |
| --- | --- | --- |
| **Parameter** | **Value** | **Source** |
| Cervical cancer treatment cost savings due to vaccination | Varies by country | Output of PRIME model (2) |
| DALYs due to cervical cancer prevented due to vaccination | Varies by country | Output of PRIME model (2) |
| Willingness to pay to prevent a DALY | GDP per capita of the country | World Health Organization’s Choosing Interventions that are Cost-Effective (WHO-CHOICE) (1) |
| Vaccine purchase costs | Gavi countries: $4.55 | Gavi press release (3) |
|  | Countries in the PAHO Revolving Fund: $8.50 | PAHO Revolving Fund prices (4) |
|  | Other countries: $9.50 - $114.50 | Literature review and extrapolation to countries without data (see below). |
| Vaccine delivery costs | $5 (low income countries) $15 (middle income countries)$25 (high income countries) | Previous PRIME analysis (2) |
| Number of 12-year old girls | 2010 United Nations Population estimates | World Population Prospects: The 2010 Revision (5) |
| Vaccine discovery costs | $3.6 million (value of grants awarded)$0.8 billion (30% of clinical trial costs) | Research Portfolio Online Reporting Tools (RePORTER); Tufts University study (6) |
| Vaccine clinical trial costs | $1.8 billion | Extrapolation of influenza vaccine trial costs (7) |
| Vaccine marginal manufacturing costs | $4.50 a dose | Statement by Merck in 2013 (8). |
| Vaccine marketing costs | 9% of sales revenue | Cost of drug promotional activities to consumers and providers in the United States in 2010 (9) |
| Revenue from vaccine sales (2006 - 2014) | $14.1 billion | Security and Exchange Commision Form 20-F filed by Merck and GSK in 2006 – 2014, inflated to 2014 USD |

*Literature review*

A review of published literature (via PubMed) and grey literature (via Google and key database searches) was conducted to identify relevant information on HPV vaccine prices (retail and tender), delivery costs and vaccine development costs. The search strategy that was used is as follows:

|  |  |
| --- | --- |
| Databases used | * National Library of Medicine’s PubMed
* Google search engine
* US National Cancer Institute research grants data base (for vaccine discovery costs)
* US Clinical Trials data base (for vaccine trial costs)
* National drug and vaccine price databases, V3P WHO Vaccine price database (for vaccine prices)
 |
| Search terms | (HPV OR Human Papillomavirus) AND Vaccin\* AND Female AND one of the following: * Delivery AND Cost
* Equity
* Distribut\* AND Income
* Pric\* AND Strategy
* Develop\* AND Country
* Product\* AND Manufact\* AND Cost
* Value
 |
| Inclusion criteria | Dates: limited to include sources dated from the year 1990 when initial scientific discoveries were made that contributed to vaccine development or later. Language: English only.Main focus of paper: Papers for inclusion had a primary focus on vaccine pricing, vaccine development costs, the costs and benefits of HPV vaccines at global or national level. The paper should also focus on female only vaccination strategies. |
| Exclusion criteria | Literature whose main focus is the biological or immunological aspects of the HPV vaccine or cervical cancer screening were excluded. |

*Revenue from vaccine sales*

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **CPI-U** | **Gardasil** | **(in 2014 USD)** | **Cervarix** | **(in 2014 USD)** |
| 2014 | 237 | 1,738 | 1,738 | 118 | 118 |
| 2013 | 233 | 1,831 | 1,861 | 172 | 175 |
| 2012 | 230 | 1,631 | 1,682 | 270 | 278 |
| 2011 | 225 | 1,209 | 1,272 | 506 | 533 |
| 2010 | 218 | 988 | 1,073 | 242 | 263 |
| 2009 | 215 | 1,118 | 1,234 | 187 | 206 |
| 2008 | 215 | 1,402 | 1,542 | 125 | 137 |
| 2007 | 207 | 1,480 | 1,690 | - | - |
| 2006 | 202 | 235 | 276 | - | - |
| Total |  | 11,632 | 12,367 | 1,620 | 1,710 |

CPI-U: US Consumer Price Index for Urban Consumers

Source: Annual 20-F forms submitted by Merck and GlaxoSmithKline to the US Securities and Exchange Commission, inflated to 2014 USD (available on www.merck.com and www.gsk.com, accessed on 30 August 2015).

*Vaccine development costs*

Pre-clinical studies were assumed to be 30% of total development costs as suggested by a recent study (6). We compared these costs to the size of public sector grants leading to patents that enabled HPV vaccine development as a validation check.

Pre-clinical work leading to patents that enabled HPV candicate vaccine development was conducted by researchers in Queensland University (Australia), Rochester University (USA), Georgetown University (USA) and the US National Cancer Institute (10). These patents were eventually acquired by vaccine manufacturers. We assumed that the acquisition price was the cost of the public sector grants leading to the patients. All public sector grants that contributed to these studies were identified. The value of grants that formed the basis of vaccine development was identified where such information was available, and average values were extrapolated to other grants without details of funding.

We reviewed publications related to HPV written by researchers in Queensland University (Australia), Rochester University (USA), Georgetown University (USA) and the US National Cancer Institute who conducted the pre-clinical work leading to patents that enabled HPV candicate vaccine development (10). The value of grants to the University of Rochester and Georgetown University was identified through the National Institute of Health research grants database, Research Portfolio Online Reporting Tools (RePORTER). The grants identified are listed below:

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Research group** | **Grant code** | **Sub grants** | **Value** | **Year** | **Awarding Body** |
| University of Rochester, New York | AI-82509 |  Not available | 209,404  |   | NIAID, USA |
| CA37667 | 5R01CA037667-07 | 180,607  | 1990 | NCI, USA |
| CA37667 | 5R01CA037667-08 | 192,547  | 1991 |  NCI, USA |
| CA37667 | 2R01CA037667-09 | 255,058 | 1992 | NCI, USA |
|  |  | Total | 837,616  |   |   |
| Georgetown University, Washington DC | R01CA 53371 | 5R01CA 5337102 | 325,567 | 1992 | NIH, USA |
| R01CA 53371 | 1R01CA 5337101 | 309,637  | 1991 | NIH, USA |
| R01CA 4624 |   | 317,602  |   |   |
|  | Total | 952,806  |  |  |

However, many of the grants were awarded in the early 1990s so financial information for these grants was not publicly recorded. For values not identified we assumed similar grant values for all research groups and so the average research grant amounts from those identified were assigned.

Final estimated research grant values in 2013 USD are presented below:

|  |  |  |
| --- | --- | --- |
| **Research Group** | **Research grants value (1992 USD)** | **Research grants values (2013 USD)** |
| Queensland University in Brisbane, Australia | 807,030 | 1,340,009 |
| National Cancer Institute | 807,030  | 1,340,009  |
| Georgetown University, Washington DC | 966,787 | 1,065,272  |
| University of Rochester, New York | 647,273  | 1,074,745  |
| Total estimated vaccine discovery costs | 3,228,121  | 4,820,035  |

*Vaccine trial costs*

We estimated clinical trial costs based on the number of trial participants and cost per participant by trial phase in a study of influenza vaccine trials (7), taking into account the cost of raising capital and the potential for vaccine candidates to fail to reach licensure. Hence our estimates capture compensation for innovation i.e. a risk-taking premium in investing in candidates that may fail to reach the market.

Details of relevant HPV vaccine clinical trials were compiled from the US clinical trils database (clinicaltrials.gov) and the literature. All trials with female participants conducted prior to the vaccines being licensed by the US Food and Drug Administration were included. The relevant date ranges were 1 January 1997 – 31 December 2006 for trials of Gardasil and its precursors (apart from a pivotal Phase 3 trial which ended July 2007) and 1 January 1997 – 31 December 2009 for trials of Cervarix and its precursors. Data was collected on NCT trial number, trial location, number of centres the number of participants, location, dates of trials, intervention, phases, intervention, number enrolled, phase and start and primary completion dates.

Fixed and per-participant costs by phase of trial were assumed to be the same as estimates for influenza vaccine trials (7). Influenza was chosen because like HPV it is a vaccine administered to children and adults outside the infant immunization schedule. However, per-participant costs were multiplied by the duration of the HPV vaccine trial (in years) to account for the fact that influenza trials are generally shorter than HPV vaccine trials. Here we conservatively estimated that influenza vaccine trials would be 12 months long. Costs were converted into US dollars using the 2011 exchange rate of 1 CAD = 1.01145 USD.

Trial costs were deflated to their year of implementation and then capitalised to 2013 levels applying a 9% per annum to represent the opportunity cost of capital in the pharmaceutical sector, as used by Chit et al. (7).

The following equations show the calculations used to obtain overall vaccine research and development costs:

Let *xi,j,k* and *yi,j,k* be the number of participants and the trial length (in years) respectively for the *i*th trial in phase *j* (*j*=1,2,3) of vaccine *k* (*k* = 1 for Gardasil, 2 for Cervarix).

Let *pj* be the variable costs per participant for an influenza trial in phase *j* (*j*=1,2,3) as reported by Chit et al. (7). Let *r* be the fixed cost of any trial as reported by Chit et al. (7).

Then the cost of all trials of vaccine *k*, *ck*, in 2011 USD is given by the following:

$$c\_{k}= \sum\_{j=1}^{3}\left(\sum\_{i}^{}r+x\_{i,j,k}y\_{i,j,k}p\_{j}\right) $$

Let *y(i,j,k)* be the year the *i*th trial in phase *j* of vaccine *k* started, Iy(*i,j,k)* be the corresponding US consumer price index for urban consumers (CPI-U) in that year, and I2011 be the CPI-U in the year 2011 (the base year for influenza trial costs in Chit et al. (7)). Then the deflated and then capitalised cost of all trials of vaccine *k*, *Ck*, in 2013 USD is given by the following:

$$C\_{k}= \sum\_{j=1}^{3}\left(\sum\_{i}^{}\left(r+x\_{i,j,k}y\_{i,j,k}p\_{j}\right)\frac{I\_{y\left(i,j,k\right)}}{I\_{2011}}(1+9\%)^{2013-y(i,j,k)}\right) $$

The table below gives the estimated cost of each trial:

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Vaccine** | **Year** | **Phase** | **Number of subjects** | **Duration** | **Estimated costs** | **Estimated capitalised cost (2013 USD)** |
| Gardasil | 1997 | I | 140 | 36 |  2,968,813  | 8,410,409  |
| Gardasil | 1998 | I | 109 | 36 |  2,327,197  | 6,142,617  |
| Gardasil | 1998 | IIA | 480 | 24 |  4,313,455  | 11,385,329  |
| Gardasil | 1999 | II | 2409 | 54 |  47,975,632  |  118,741,331  |
| Gardasil | 2000 | I | 40 | 7 |  232,170  |  544,903  |
| Gardasil | 2001 | III | 1877 | 42 |  22,942,320  | 50,805,310  |
| Gardasil | 2002 | III | 3055 | 21 |  18,683,684  | 38,558,523  |
| Gardasil | 2002 | III | 3882 | 24 |  27,100,865  | 55,929,513  |
| Gardasil | 2002 | III | 12167 | 73 |  257,751,010  |  531,934,620  |
| Gardasil | 2003 | III | 1781 | 25 |  12,988,676  | 25,152,602  |
| Gardasil | 2003 | III | 1514 | 18 |  7,977,475  | 15,448,400  |
| Gardasil | 2005 | III | 176 | 7 |  428,616  |  741,511  |
| Total Gardasil | 405,689,912 | 863,795,066 |
| Cervarix | 1999 | I | 49 | 54 |  1,592,443  | 3,941,350  |
| Cervarix | 1999 | I | 60 | 17 |  657,614  | 1,627,618  |
| Cervarix | 1999 | I/II | 61 | 36 |  879,872  | 2,177,715  |
| Cervarix | 1999 | IIA | 210 | 59 |  4,633,834  | 11,468,898  |
| Cervarix | 2000 | IIA | 60 | 48 |  1,131,757  | 2,656,232  |
| Cervarix | 2001 | IIB | 1113 | 27 |  11,137,534  | 24,663,848  |
| Cervarix | 2003 | II | 776 | 44 |  12,644,790  | 24,486,667  |
| Cervarix | 2004 | III | 18729 | 66 |  358,689,587  |  654,220,951  |
| Cervarix | 2004 | III | 2067 | 21 |  12,664,324  | 23,098,709  |
| Cervarix | 2004 | III | 770 | 10 |  2,305,096  | 4,204,310  |
| Cervarix | 2004 | III | 667 | 52 |  10,133,629  | 18,482,924  |
| Cervarix | 2005 | III | 798 | 17 |  4,006,926  | 6,932,036  |
| Cervarix | 2005 | II | 383 | 13 |  1,904,718  | 3,295,188  |
| Cervarix | 2005 | III | 1245 | 39 |  14,157,850  | 24,493,270  |
| Cervarix | 2006 | IIIB | 5752 | 58 |  96,859,056  |  158,690,703  |
| Cervarix | 2006 | II | 1046 | 34 |  13,167,708  | 21,573,542  |
| Cervarix | 2006 | II | 383 | 5 |  776,394  | 1,272,018  |
| Cervarix | 2006 | III | 300 | 15 |  1,376,720  | 2,255,573  |
| Cervarix | 2006 | III | 354 | 17 |  1,817,118  | 2,977,107  |
| Cervarix | 2006 | III | 1330 | 17 |  6,630,749  | 10,863,602  |
| Cervarix | 2006 | III | 271 | 15 |  1,250,519  | 2,048,809  |
| Cervarix | 2006 | III | 770 | 31 |  6,996,297  | 11,462,504  |
| Cervarix | 2007 | I | 540 | 17 |  5,349,003  | 8,267,351  |
| Cervarix | 2007 | I | 30 | 7 |  191,925  |  296,637  |
| Cervarix | 2007 | II | 433 | 8 |  1,346,816  | 2,081,622  |
| Cervarix | 2007 | III | 751 | 13 |  2,903,609  | 4,487,781  |
| Cervarix | 2007 | III | 100 | 9 |  332,297  |  513,594  |
| Cervarix | 2007 | III | 225 | 8 |  593,403  |  917,155  |
| Cervarix | 2007 | III | 100 | 8 |  303,285  |  468,753  |
| Cervarix | 2007 | III | 805 | 15 |  3,574,361  | 5,524,486  |
| Cervarix | 2007 | III | 814 | 12 |  2,905,059  |  4,490,023  |
| Cervarix | 2008 | II | 116 | 22 |  1,010,970  |  1,488,868  |
| Cervarix | 2008 | III | 152 | 15 |  732,659  |  1,078,996  |
| Cervarix | 2008 | III | 744 | 16 |  3,524,751  |  5,190,942  |
| Cervarix | 2009 | III | 750 | 14 |  3,117,425  |  4,197,005  |
| Total Cervarix | 591,300,100 | 1,055,896,787 |
| Grand Total | 996,990,012 | 1,919,691,853 |

*Accounting for vaccine candidates that fail to become commercially successful*

We also assumed that a number of vaccine candidates would fail to become commercially successful. The predicted number of vaccine candidates per phase of development was calculated using the number of influenza vaccine candidates who were successful, abandoned or censored from Chit and co-workers’ study. However, we adjusted the numbers in that study to account for the fact that there were two successful vaccines that reached the market, given that this was the situation in the world prior to the licensure of the nonavalent vaccine in 2015. The candidates that were censored were proportionally distributed between the successful and abandoned categories based on existing numbers in those categories. The table below shows the number of vaccine candidates in each phase of clinical trials:

|  |
| --- |
| **Influenza Vaccine Candidate Transitions** |
| Transition Phase | Phase I-II | Phase II-III | Phase III- Market |
| Successful  | 22.45 | 15.83 | 10.00 |
| Abandoned | 16.55 | 3.17 | 0 |
| **HPV Vaccine Candidate Transitions** |
| Transition Phase | Phase I-II | Phase II-III | Phase III- Market |
| Successful  | 4.49 | 3.17 | 2.00 |
| Abandoned | 3.31 | 0.634 | 0 |

Applying these costs increases the cost of vaccine development to $2.2 billion. Including 30% of clinical trial costs as the cost of pre-clinical development gives overall development costs of around $2.9 billion.

*Annualisation of vaccine development costs*

Vaccine development costs were more than fully recovered from revenues from vaccine sales by 2013. However, to be comprehensive, we conducted a scenario where we annualised development costs over the product lifetime of the vaccine. We assumed that vaccine sales will only take place between 2006 (when Gardasil was licensed by the US Food and Drug Administration) and 2020 (six months after the date of extended patent expiry for Gardasil, when the market for generics will be fully open) (source: http://www.uspto.gov/sites/default/files/web/offices/pac/dapp/opla/term/certs/5820870.pdf). This assumption is highly conservative since it is unlikely that all revenues from sale of Gardasil will cease in 2020. We divided development costs of $2.9 billion by the 15 years between 2006 and 2020 to get an annualised figure for 2013 of $191 million.

# 3. Vaccine procurement prices

Procurement costs were assumed to be $4.55 per dose for countries eligible for Gavi support and $8.50 per dose for countries part of the PAHO Revolving Fund (4). For other countries, we obtained information on vaccine prices from the literature, and extrapolated them to countries without such information. We assumed delivery costs of $25, $15 and $5 per course for high-income, middle-income and low-income countries (2). In the base case, we assumed that 3 doses of vaccine were given per vaccinated girl.

We contacted representatives of both vaccine manufacturers (Merck & Co., Inc. and GlaxoSmithKline plc.) to ask for any available information on retail and tender prices for HPV vaccines. GlaxoSmithKline were able to supply us information on retail prices that were in the public domain; neither manufacturer were able to supply us any information on tender prices. Hence we conducted a literature search to identify further information on such prices in countries not eligible for Gavi or PAHO prices.

We found five countries (three high-income and one upper middle-income) where both retail and tender prices were available:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Country** | **Source** | **Retail price** | **Tender price** | **Price reduction (%)** |
| **Cervarix** | **Gardasil** | **Cervarix** | **Gardasil** | **Cervarix** | **Gardasil** |
| Italy | (11,12)  | 172 | 173 | 45 | 45 | 74% | 74% |
| Norway | (13,14) | 203 | 186 | 53 | 58 | 74% | 69% |
| South Africa | (15) | 55 | 57 | 13 | 13 | 76% | 77% |
| Spain | (16)  | 159 | 159 | 41 | 49 | 74% | 69% |
| United States | (17) | 129 | 147 | 108 | 121 | 16% | 18% |

In four of these countries, tender prices were about 69-77% lower than retail prices. The exception is the United States. However, tender vaccine prices in the United States are dissimilar to the rest of the world because of the particular features of health care in that country, and because tender prices refer to the price that the Centers for Disease Control and Prevention pays for supplying vaccines to immunization programs receiving immunization grant funds. Hence we consider the United States situation to be dissimilar from most other countries, and applied a 75% markdown on retail prices to obtain tender prices.

We found a further a further 29 countries with only tender or retail vaccine prices available. We applied the 75% markdown to retail prices to obtain estimated tender prices (and vice versa). The countries with retail prices are shown below:

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Country** | **Data source** | **Type** | **GDP per capita (2013 USD)** | **Vaccine price per dose (USD)** |
| **Cervarix** | **Gardasil** | **Unspecified** |
| Australia | (18) | Retail | 67473 |  | 109 |  |
| Belgium | (15) | Retail | 46927 | 92 | 157 |  |
| Bosnia and Herzegovina | (19) | Retail | 4662 | 133 | 193 |  |
| Bulgaria | (19) | Retail | 7499 | 102 | 145 |  |
| Croatia | (19) | Retail | 13598 |  | 186 |  |
| Czech Republic | (19) | Retail | 19858 | 94 | 180 |  |
| Denmark | (20) | Retail | 59819 | 144 | 211 |  |
| Estonia | (19) | Retail | 18877 | 149 |  |  |
| France | (15) | Retail | 42631 | 148 | 164 |  |
| Germany |  | Retail | 46255 | 215 | 215 |  |
| Hungary | (19) | Retail | 13487 | 139 | 139 |  |
| Israel | (21) | Tender | 36051 |  |  | 33 |
| Italy | (11) | Retail | 35477 | 172 | 173 |  |
| Latvia | (19) | Retail | 15357 | 38 |  |  |
| Lebanon | (19) | Retail | 9928 | 78 | 188 |  |
| Lithuania | (19) | Retail | 15689 | 146 | 162 |  |
| Macedonia, FYR | (19) | Retail | 5110 |  | 183 |  |
| Morocco | (15) | Retail | 3095 | 49 | 94 |  |
| New Zealand | (22) | Tender | 42409 |  |  | 92 |
| Norway | (13) | Retail | 102832 | 203 | 186 |  |
| Poland | (19) | Retail | 21523 | 80 | 80 |  |
| Romania | (19) | Retail | 13829 | 75 | 139 |  |
| Serbia | (19) | Retail | 6354 | 70 | 171 |  |
| Slovak Republic | (19) | Retail | 18050 | 90 | 150 |  |
| Slovenia | (19) | Retail | 23297 | 114 | 143 |  |
| South Africa | (15) | Retail | 6886 | 55 | 57 |  |
| Spain | (16) | Retail | 29881 | 159 | 159 |  |
| United Kingdom | (23) | Retail | 41777 | 133 | 124 |  |
| United States | (17) | Retail | 53042 | 129 | 147 |  |

Lastly, we found information about tender prices in 9 unspecified high or upper-middle income countries in the price database of the Vaccine Product, Price and Procurement (V3P) Project hosted by the World Health Organization:

|  |  |  |
| --- | --- | --- |
| **Country code** | **Gross national income (GNI) per capita** | **Tender price per dose (USD)** |
| **Cervarix** | **Gardasil** |
| HIC106 | 48820 | 20.9 |  |
| HIC139 | 46290 | 38.1 |  |
| HIC175 | 15290 | 38.7 |  |
| HIC207 | 51060 | 22.8 |  |
| HIC230 | 21270 |  | 39.7 |
| HIC269 | 29940 | 41.4 |  |
| HIC279 | 23220 |  | 48.0 |
| UMIC158 | 11550 | 54.0 | 54.0 |
| UMIC190 | 4870 |  | 93.4 |

We combined all relevant information in order to relate vaccine retail and tender prices with country GDP or GNI per capita. A linear model was used to find the best linear relationship between the two variables, in order to interpolate prices for all other countries. The graphs below show the results of the linear model:



Both model fits had a non-significant coefficient and low R-squared, suggesting that there is not a very strong relationship between prices and country income.

*Retail price of vaccine ~ GDP or GNI per capita*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Coefficient | Estimate | Standard Error | t-statistic | p-value |
| (intercept) | 146 | 18.2 | 7.999 | <0.001 |
| GDP or GNI per capita | 0.0002722 | 0.0005149 | 0.529 | 0.6 |

Residual standard error: 67.44 on 36 degrees of freedom

Multiple R-squared: 0.007701, Adjusted R-squared: -0.01986

F-statistic: 0.2794 on 1 and 36 degrees of freedom, p-value: 0.6003

*Tender price of vaccine ~ GDP or GNI per capita*

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Coefficient | Estimate | Standard Error | t-statistic | p-value |
| (intercept) | 34.5 | 5.58 | 6.195 | <0.001 |
| GDP or GNI per capita | 0.0002155 | 0.0001577 | 1.367 | 0.18 |

Residual standard error: 20.66 on 36 degrees of freedom

Multiple R-squared: 0.04932, Adjusted R-squared: 0.02291

F-statistic: 1.867 on 1 and 36 degrees of freedom, p-value: 0.1802

# 4. Non-cervical cancers

The numbers of cervical cancers and cancers at other sites (penis, vulva, vagina, anus, mouth and oropharynx) that are associated with HPV infection in different regions of the world have been compiled by the International Agency for Research on Cancer (IARC) (24). Another study by IARC also estimated the proportion of HPV-related cancers in each site that were due to HPV 16 and 18, the two HPV types in all available HPV vaccines (25). We used these results to estimate the ratio of cervical to non-cervical cancers that are associated with HPV 16/18 in different regions:

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Region** | **HPV cancers** | **Cervical cancer** | **Non-cervical cancer** | **HPV 16/18 cervical cancers** | **HPV 16/18 non-cervical cancers** | **% non-cervical** | **Ratio non-cervical : cervical** |
| AFR | 78000 | 75000 |  3,000  |  54,591  |  2,543  | 4% | 0.046574 |
| AMR | 101000 | 80000 | 21,000  |  70,688  |  17,798  | 20% | 0.251779 |
| EMR | 11000 | 9200 |  1,800  | 7,699  |  1,526  | 17% | 0.198153 |
| EUR | 80000 | 55000 | 25,000  |  55,990  |  21,188  | 27% | 0.378417 |
| SEAR | 193000 | 169000 | 24,000  |  135,077  |  20,340  | 13% | 0.150583 |
| WPR | 148440 | 136500 | 11,940  |  103,890  |  10,119  | 9% | 0.097403 |

Abbreviations represent World Health Organization regions: African region (AFR), the Americas region (AMR), Eastern Mediterranean region (EMR), European region (EUR), South-East Asian region and Western Pacific region (WPR).

These ratios were then used to project the additional value of HPV vaccination in preventing non-cervical cancers due to HPV 16/18. For simplicity and due to lack of detailed data, It was assumed that non-cervical cancers caused the same treatment costs and DALYs as cervical cancer.

The table below provides a breakdown of the monetised benefits of HPV vaccination of a 12-year old cohort by country income group, with and without the inclusion of non-cervical cancers:

|  |  |  |
| --- | --- | --- |
| **Income group** | **Cervical cancers only** | **All HPV-related cancers** |
| High income | 4,128,831,298 | 5,279,809,972 |
| Upper-middle income | 5,191,323,182 | 6,221,421,738 |
| Lower-middle income | 3,848,265,637 | 4,432,794,695 |
| Low-income | 962,317,320 | 1,058,906,388 |
| Total | 14,130,737,437 | 16,992,932,793 |

# 5. Methodological justification for the monetisation of DALYs using a GDP per capita-based conversion factor

We calculate the economic surplus associated with HPV vaccination in a particular country by converting the DALYs averted by vaccination into monetary terms using a GDP per capita-based multiplier. This calculation leads to most of the economic surplus being captured by high income countries.

Broadly speaking, three approaches have been taken to valuing health in economic terms (reviewed by Shilcutt et al. (26) in the context of cost-effectiveness analyses). When making inter-country comparisons, all three methods inevitably end up converting convert DALYs (or other measures of health) into monetary measures of economic value across countries using national income (or a close proxy) as the conversion factor. One of these three methods is implicit in every international cost-effectiveness and cost-benefit calculations evaluation using a GDP per capita-based threshold, i.e. the majority of the international economic evaluation literature.

Here we outline the three methods and how they could apply to our calculation of economic surplus below:

(a) **The value of human capital.** This method values increased health in terms of the productive capacity of a healthy individual. Someone who is sick is able to produce fewer economic goods; someone who is dead will produce none at all. This is the argument taken by WHO’s Commission on Macroeconomics and Health (27) which led to a rough estimate that each DALY averted gives economic benefit equivalent to at least a year’s per capita income, and possibly as high as three times per capita income to reflect factors beyond economic production such as human suffering. In low income countries, the productive capacity of a DALY averted (i.e. an extra year of disability-free life) is lower because of poorer levels of technological, infrastructure and human capital development. Hence low income countries benefit less in absolute economic terms from each DALY averted.

(b) **The opportunity cost of health spending.** If (for example) $1000 was not spent on HPV vaccination in a low income country, the same amount of money could be spent on other interventions (eg. bednets, water sanitation, measles vaccines) that would save many lives. However, if we did not pay the same $1000 on HPV vaccines in a high income country, the options for additional spending on health are likely to be more limited (eg. adding hospital capacity, funding for new cancer drugs) and to save fewer lives. Hence the opportunity cost of spending on health is higher in low income countries.

Work by economists at the University of York suggests that the health foregone by healthcare resources being committed to a particular intervention may be consistent with a conversion factor for QALYs gained of about 0.52 x GDP per capita, and that the conversion factor in low income countries is even lower than this because these countries spend a smaller portion of their total GDP on healthcare (28).

(c) **Willingness to pay.** The Lancet Commission on Investment in Health (29) advocates a “full income” approach to valuing the economic benefits of improved health. This uses willingness-to-pay studies to capture the value that people place on living longer and healthier lives. Using this approach, the Commission estimated that the value of a 1-year increase in life expectancy is 2.3 times per-person income. A similar approach was used by Ozawa et al. (30) to measure the economic value of vaccines that may be delivered during the Decade of Vaccines (2011-2020) in low- and lower-middle income countries

# Endnotes

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