Report to the GAVI Alliance Board

16-17 November 2011

Subject:	**Next steps on new vaccine windows: HPV, JE, Rubella and Typhoid**
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Agenda item:	06
Category:	For Decision
Strategic goal:	SG1 - Underused and new vaccines

Section A: Overview

1. Purpose of the report

1.1 The GAVI Alliance Board is requested to approve next steps for GAVI's vaccine portfolio and specific implementation strategies for human papilloma virus (HPV) and rubella vaccines.

2. Recommendations

2.1 The GAVI Alliance Programme and Policy Committee (PPC) recommended the GAVI Board to:

a) **Open** a funding window for HPV and rubella vaccines such that the GAVI Secretariat can invite country proposals for support in 2012;[1]

b) **Request** the Secretariat to work with technical partners to develop an HPV pilot programme following the Board meeting in November 2011;

c) **Note** that JE is a critically important vaccine, particularly for South East Asia. GAVI should consider opening a window once an appropriate vaccine is prequalified. Continued efforts are needed on surveillance;

d) **Not** to revisit its previous decision on typhoid noting that the Alliance looks forward to the development of an appropriate conjugate vaccine.

[1] September application round

3. Executive Summary

3.1 In September 2011, the PPC considered implementation plans to support the introduction of HPV, JE, rubella and typhoid vaccines. These vaccines had been previously endorsed by the Board as priority vaccines.[2] The PPC recommended moving forward with HPV and Rubella as proposed above.

3.2 In addition to asking the Secretariat to work on an HPV pilot programme, the PPC requested GAVI provide detailed programme implementation costs for HPV and appropriate levels for GAVI support, and clearly define criteria in order for countries to be approved for HPV vaccines. Working with technical partners, GAVI has developed estimates for HPV start-up and recurring costs as well as preliminary recommendations for HPV applications (below and in annexes III and IV).

3.3 HPV and rubella vaccine programmes offer significant opportunities for GAVI. Successful HPV implementation could improve adolescent health consistent with GAVI's mission and increase synergies among broad coalitions in the public health community (for example, HIV prevention, family planning, nutrition, safe motherhood, maternal/child health). Further, through an immunisation programme that supports the replacement of measles antigens with a combined measles/rubella vaccine, GAVI can contribute to the dual goals of measles and rubella eradication.

3.4 Projected total costs for the proposed strategy are US$ 310M from 2012-2015 and $1.318B from 2012-2023.[3] Implementing the vaccine programmes through 2023 would avert 1.56 million future deaths and 8.29 million cases.

Table 1 Summary of Metrics (Cost and Impact) - 12 year timeframe (2012 to 2023)

2012-2023	Deaths averted (x1000)	Cases averted (x1000)	Total vaccine cost (in US$M)	GAVI vaccine cost (in US$M)	Country vaccine cost (in US$M)	GAVI cost*/death averted	GAVI cost*/cases averted	Total GAVI cost* (in US$M)
HPV- routine 10 yo	960	1,200	$703	$642	$61	$673	$538	$646
JE - catchup campaign 9mth-15 yo	110	507	$74	$50	$24	$711	$155	$78
Rubella- catchup campaign 9mo-15yo	443	1,478	$586	$364	$222	$1,251	$375	$554
Typhoid- catchup campaign 1-15yo	51	5,103	$56	$39	$17	$783	$8	$40
Strategy Total	**1,564**	**8,288**	**$1,420**	**$1,095**	**$325**	**$843**	**$159**	**$1,318**

* GAVI cost per death/case and total GAVI cost account for GAVI vaccine cost, operational support costs for both campaigns and introductory grants for routine, where applicable.

Note that for Rubella case is defined as a case of Congenital Rubella Syndrome. An age-structured model of the transmission dynamics of rubella was used to estimate the average and 95% range in the number of CRS cases prevented for 51 countries. The model is an extension of the model used to calculate the global burden of CRS for 2000-2008. Case fatality rate is assumed to be 30% (expert opinion based on published studies). JE and Typhoid impact are estimated using Long Range Cost and Impact model.

The estimates of HPV-related deaths and cases averted from 2012-23 were produced by Sue Goldie and team, based on an updated analysis that incorporates the most recently available data, and that builds upon the model published in Vaccine in 2008 (Goldie SJ, O'Shea M, Campos NG, Diaz M, Sweet S, Kim SY. Health and economic outcomes of HPV 16,18 vaccination in 72 GAVI-eligible countries. Vaccine. 2008 Jul 29;26(32):4080-93)

[2] GAVI Alliance Board Meeting, 29-30 October 2008

[3] Includes estimates of a JE vaccine programme (2015-2023) once an appropriate vaccine is prequalified and typhoid conjugate vaccine implementation in routine programmes (2018-2023)

4. Context

4.1 In June 2008, the GAVI Board approved a vaccine investment strategy (VIS) objective to "reduce the overall disease burden". They also requested that GAVI monitor the development of vaccines for malaria and dengue. Later that year, the Board endorsed HPV, JE, rubella and typhoid as key vaccines that could contribute to this public health goal.

4.2 The GAVI Board selected these diseases from a list of 18 provided by the WHO in 2007. Their decision was based on the potential health impact as well as the costs and challenges of introducing each vaccine in developing countries.[4]

4.3 The GAVI Board also "encouraged the Secretariat to develop the vaccine portfolio taking into full account technical advice and developments related to discussions of the WHO Strategic Advisory Group of Experts (SAGE)". However, given the financial climate in 2008, the Board did not make a financial commitment related to the vaccine investment strategy at that time.

4.4 In anticipation of a successful pledging conference, in May 2011 the PPC endorsed a process of developing implementation strategies and guidelines for the four vaccines such that new windows of funding could be opened in the next round of applications (2012).

4.5 In collaboration with technical partners representing eight organizations, GAVI's Accelerated Vaccine Introduction (AVI) initiative coordinated a four-month process to refine 2008 implementation strategies for each vaccine. Sub teams were formed for each vaccine to review WHO guidelines and SAGE recommendations, availability of vaccines and revised strategic demand forecasts.[5] Recommendations were aligned with the most recent WHO and Strategic Advisory Group of Experts' guidance on the vaccines.

4.6 In parallel, the GAVI Secretariat commissioned a market analysis to update the assumptions on the supplier landscape, development timelines, supply capacity and pricing strategies for each vaccine. The Secretariat is currently developing a "road map" for its supply and procurement of the recommended vaccines. Following Board approval and prior to opening a window, the GAVI Alliance would secure price commitments from industry.

4.7 After careful review, the PPC supported opening windows for HPV and rubella vaccine funding this year as well as developing a pilot programme in support of HPV introduction. The PPC also requested the Secretariat continue work with technical partners on requirements for HPV support (e.g.

[4] 2008 Working Group reviewed 1) vaccine readiness (extent to which there is consensus within the disease expert community on whether introduction in GAVI-eligible countries is appropriate given the current state of knowledge around safety, effectiveness, and feasibility of the available vaccine products and their recommended or associated implementation strategies; 2) deaths averted; 3) deaths averted < 5; 4) cases averted; 5) total vaccine cost (including the country co-payment for vaccines); 6) GAVI cost per death averted; country-level implementation costs and 7) public health impact.

[5] Version 4.0

defining criteria for GAVI countries to be approved for national HPV vaccine introduction). If the window is approved, these will be further developed to inform the application process and IRC review.

4.8 With regard to JE, the PPC noted the crucial importance the vaccine could play in catalyzing vaccine uptake throughout the region but felt that it would be inappropriate to open a window until a cost-effective and suitable vaccine received WHO prequalification.[6]

4.9 With regard to typhoid, because of the existence of alternative treatment options and continued uncertainty about polysaccharide vaccines' duration of protection and timing of the development of a conjugate vaccine, the PPC did not recommend reconsidering the previous Board decision.

4.10 The PPC also discussed the issue of vaccine introduction grants, particularly with regard to HPV, and requested the Secretariat continue to work with WHO and other partners to detail programme implementation costs for HPV and appropriate levels for GAVI support. Estimates per girl to be vaccinated are provided in annex III.[7] If GAVI supported all of these costs in full, i.e. without a portion covered by countries, the result would be an increase in costs of US$ 22M for the 2012-2015 timeframe and US$ 296M for the period up to 2023.

4.11 However, because the current policy is to provide US$.30 per infant in the initial year of GAVI support, these amounts have not been included in the current financial projections. The HPV costing analysis, however, will inform a review of the vaccine introduction grants currently underway which will be submitted to the PPC and Board for consideration in spring 2012.

4.12 Of note, and as requested by the Board in 2008, GAVI continues to follow the progress of other vaccines that could have significant impact on public health in poor countries and plans to review its vaccine investment strategy in 2013. Vaccines for both malaria and dengue are currently in late stage development and could be available for large-scale implementation in endemic regions as early as 2015 and 2016/17, respectively. GAVI also is working with the Global Polio Eradication Initiative (GPEI) and the Bill & Melinda Gates Foundation to understand options for inactivated polio vaccines (IPV) and appropriate programmatic interventions post-eradication.

5. Next steps

5.1 Following approval from the Board, GAVI would secure price commitments from industry for HPV and rubella vaccines. New windows could thus open as early as 2012.

[6] Chengdu's vaccine developed in China and supported through PATH has been used for many years in Asia and is expected to be prequalified by 2013. This vaccine is significantly more cost-effective than other vaccines expected to be WHO prequalified in the coming years.
[7] Includes two categories of costs, start-up estimates for first year of introduction ($3.00) and recurring annual costs ($3.00) per eligible girl.

5.2 The GAVI Alliance would also move forward with technical partners to develop a pilot programme for HPV and review the requirements for support of HPV introduction.

5.3 GAVI will continue to monitor developments in the area of malaria, dengue and polio.

5.4 GAVI will review its vaccine investment strategy for presentation to the Board in 2013.

6. Conclusions

6.1 At the projected total GAVI cost of US$ 1.318B[8], implementing the vaccine programmes from 2012- 2023 would result in 1.56 million future deaths and 8.29 million cases averted.

Section B: Implications

7. Impact on countries

7.1 Development of the vaccine investment strategy included extensive consultation with GAVI countries. The 2008 Board decision set expectations that once funding was available, countries would have the opportunity to apply for these vaccines. Following the successful pledging conference in June, GAVI now has the opportunity to support countries with their introduction plans.

7.2 Rubella vaccines are inexpensive and in-line with the price of traditional vaccines, i.e. their estimated cost is in the same magnitude as the minimum co-financing commitment of 20 cents per dose for low income countries. To increase country ownership and sustainability, GAVI recommends funding catch-up campaigns with countries paying for routine introduction.[9]

7.3 Although vaccine prices are decreasing, GAVI must continue to monitor the programmatic and financial impact of multiple vaccine introductions on GAVI eligible countries. Over the long-term, immunisation will dramatically decrease healthcare costs in developing countries. However, some of the more fragile countries could find escalation of vaccine programmes cost-prohibitive over the short-term.

8. Impact on GAVI stakeholders

8.1 Working with countries on the introduction of HPV vaccines will require a new way of coordinating with multiple stakeholders and new partnerships at country and global levels. Specifically, it will require the active engagement of reproductive health and cancer control programmes. The vaccine is

[8] Includes estimates of a JE vaccine programme assuming an appropriate vaccine is available in 2015 and conjugate vaccine implementation in routine programmes beginning in 2018.
[9] As noted above, countries would be eligible for an introduction grant for their routine programme.

targeted at adolescents and prevents a sexually transmitted infection and cervical cancer. Thus, groups from the field of reproductive health, adolescent health, women's health and cancer who have not traditionally played a role in childhood immunisation should be engaged to promote screening and to coordinate efforts on vaccine implementation. At the country level a school based programme will require active engagement of leadership and staff within the Ministry of Education.

8.2 Since the rubella vaccine comes in a vial combined with the measles vaccine ("MR" vaccine) a successful rubella programme also will require increased engagement with the measles and rubella community, most specifically the Measles Initiative, a long-time GAVI partner. In addition to raising GAVI's profile as a main driver in global efforts to reinvigorate measles elimination goals, increased synergies with disease groups can help leverage surveillance and monitoring of coverage critical to a successful rubella vaccination strategy.

9. Impact on the Business Plan / Budget / Programme Financing

9.1 The 2012 portfolio is estimated to cost $1.318B over 12 years. The total includes estimates for support of a JE vaccine programme implemented from 2015-2023, following expected WHO prequalification of an appropriate vaccine in 2013. It also includes estimates for the introduction of a typhoid conjugate vaccine beginning in 2018. In addition, the Rubella demand forecast was adjusted following further consultation with WHO resulting in a reduction in total portfolio costs for the period 2012-2015 ($559M to $310M) and a slight increase from 2012-2023 (1.292B to $1.31B) from the budget estimates provided to the PPC in September.

9.2 Estimates of total vaccine costs over a 12 year period have decreased significantly compared to the 2008 portfolio (US$ 3.065B to US$ 1.095B). The main drivers for the differences are a reduction in projected prices for HPV and JE vaccines combined with decreases in volumes for JE and typhoid vaccines.

9.3 The projected costs of the portfolio include vaccine costs, introduction grants and campaign support (as per the current policies). This is consistent with the figures included in the accompanying financial projections also presented to the Board (see agenda item13). Board members should note, however, that a revision of the policy on campaign support and vaccine introduction grants may result in an increase in the total cost of supporting these vaccines, as well as GAVI's other vaccine programmes.

9.4 With regard to the business plan, the Secretariat, WHO, UNICEF and AVI/TAC have all submitted budgets as part of the 2012 planning process which reflect the PPC recommendations to the Board.

10. Risk implications and mitigations

10.1 Increasing the number of vaccines supported by GAVI could represent a potential “overload” for country systems as well as increased work for Alliance implementing partners. This risk is in part mitigated through increased funding through the business plan to support both decision making at country levels and technical assistance for introduction.

10.2 In addition to the overall risk, there are also specific vaccine challenges and opportunities outlined below for both HPV and rubella vaccines.

(a) With regard to HPV, the vaccine needs to be administered to 10-13 old girls, a population that has not previously been routinely served by infant immunisation services. A GAVI-sponsored HPV programme may thus require the establishment of new systems for reaching adolescents with three vaccine doses. To ensure countries are prepared for national programmes, GAVI will include programme criteria/filters which differ from other vaccine support windows (e.g. requiring a description of educational systems for girls for school-based outreach and acceptability of HPV vaccines by community and health providers (see annex IV for preliminary recommendations).

(b) Countries without experience delivering HPV vaccines may also not be ready to apply for support of a national roll out. In order to help them make an informed decision and gather appropriate information to support a national plan, countries would have an option of applying for support for a pilot programme. GAVI would work with its technical partners to design the criteria and application requirements for the pilot after the Board meeting in November.

(c) The current prices of HPV vaccines may pose a barrier to introduction and need to be carefully negotiated to ensure long-term sustainability.

(d) With regard to rubella and congenital rubella syndrome, surveillance and monitoring of coverage are critical. When routine childhood coverage is low, the virus continues to circulate and children remain susceptible until they reach adulthood. In these settings, there may be a potential risk for an increase in CRS cases. To mitigate this risk, GAVI would support large-scale catch-up campaigns which have been demonstrated to drastically reduced rubella and CRS in many developed and developing countries. Also, in order to help ensure commitment to routine introduction following campaigns, GAVI will require countries to verify that they have begun to procure MR vaccines for routine programmes in their application for campaign support and introduction grants.

10.4 Finally, with regard to health impact, if GAVI does not open these windows, the organization could jeopardize its ability to achieve the impact put forward in the 2011-2015 strategic plan and deliver on its mission to save lives and protect health.

11. Legal or governance implications

11.1 Once windows are open for these vaccines, grant arrangements will be made with countries for approved proposals in line with existing GAVI arrangements.

12. Consultation

12.1 GAVI's Vaccine Investment Strategy included an extensive consultation process with immunisation programme and disease experts, including, most recently, sub-teams updating 2008 recommendations, country partners and industry. The implementation plans have been developed by AVI with WHO, UNICEF, PATH/TAC, CDC and the Sabin Vaccine Institute. n addition, the HPV recommendations have been shared with additional stakeholders, and the Immunisation Financing and Sustainability Task Team has reviewed implications of the paper's recommendations for GAVI's co-financing strategies.[10]

13. Gender implications/issues

13.1 In introducing HPV and rubella vaccines, GAVI would place a focus on women's reproductive health for the first time in its history.

(a) The GAVI Alliance can play a crucial role in encouraging support for comprehensive cervical cancer strategies including appropriate screening and treatment. Introduction of HPV vaccines will set a new public health precedent in establishing primary preventive care for girls and could be used to improve access to other health services for this population. Where HPV is introduced through a school based delivery system, GAVI has the opportunity to have a wider impact on other health issues among young girls.[11]

(b) Through a targeted wide-age rubella campaign targeting both males and females, GAVI can contribute to slashing cases of congenital birth defects over the long-term. The organization also hopes to work with others in the public health community to encourage efforts to reach women of child bearing age (WCBA) who remain susceptible to the rubella virus.

14. Implications for the Secretariat

14.1 Resources related to the introduction of HPV and rubella have been included in the Business Plan submitted for Board approval.

[10] For HPV included UNFPA, Union for International Cancer Control, and the NGO CHESTRAD.

[11] For example, could include 12-year old check-ins; girl-friendly reproductive services/referrals; counselling on early marriage alternatives. *Start with a Girl: New Agenda for Global Health, Center for Global Development; 2009*

Annex I

1. Implementation Strategies and New Windows — HPV

1.1 Worldwide, cervical cancer is the 2nd most common cancer in women with an estimated 529,000 new cases of cervical cancer and 275,000 deaths in 2008. More than 85% of the global disease burden occurs in developing countries.[12] With population growth and aging, the number of cervical cancer cases is expected to increase 1.5 fold by 2030. Primary prevention of cervical cancer is now possible through vaccination of girls. As well, improvements to cervical cancer screening of women which make screening more effective and feasible than in the past strengthen the options for secondary prevention.

1.2 In the five years since the first HPV vaccine was licensed in 2006, 36 countries have introduced HPV vaccines.[13] However, effective implementation poses challenges. The public health community is still exploring optimal strategies to routinely reach girls with three doses of vaccine in ways that are acceptable, affordable and sustainable, and that achieve high coverage.

1.3 Socio-cultural barriers to HPV vaccines may arise in a wide range of countries and groups due to concerns about a vaccine against a sexually transmitted infection. As well, vaccination of girls only and not boys requires careful communication so that misunderstandings about selective vaccination do not rouse suspicions.

1.4 Pilot programmes in Tanzania, Rwanda, Peru, Uganda and India have focused on multiple delivery strategies, including school-based vaccination. A school-based programme requires engagement and training of school staff, high school enrollment and high attendance.

1.5 Furthermore, in order to reach girls who are likely to have less access to cervical cancer screening later in life, it will be necessary to vaccinate girls who are not enrolled or attending school. GAVI expects to work closely with applying countries to design appropriate outreach activities in-line with WHO recommendations.

[12] World Health Organization; WHO position paper, Human Papillomavirus, 2009
[13] As of October, 2011

Disease Burden – HPV

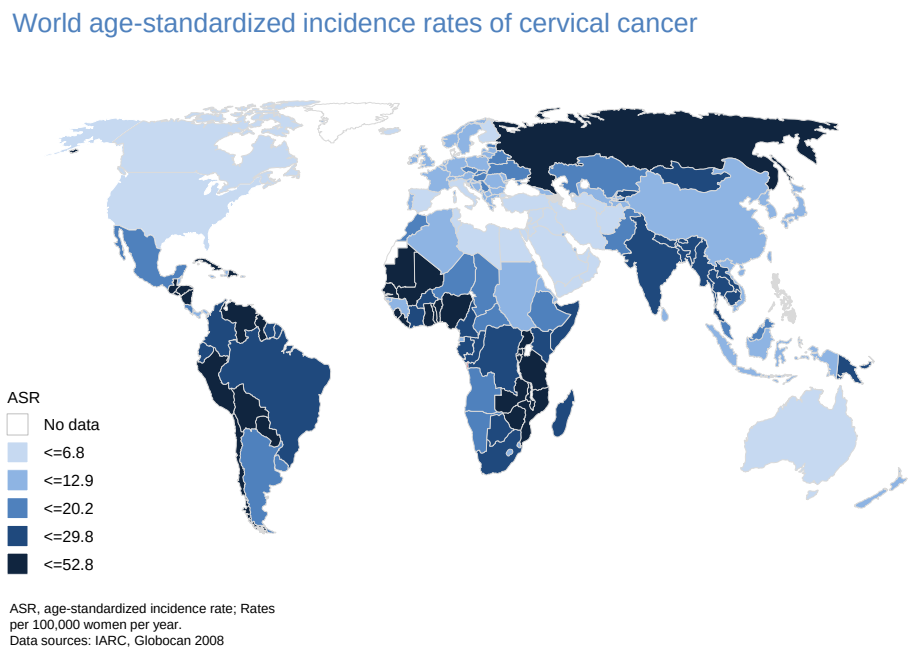


Figure 1

2. WHO position paper and SAGE recommendations

2.1 The WHO position paper (2009) recommends that routine HPV vaccination be included in national immunisation programmes provided that: prevention of cervical cancer or other HPV-related diseases, or both, constitutes a public health priority; vaccine introduction is programmatically feasible; sustainable financing can be secured; and the cost-effectiveness of vaccination strategies in the country or region is considered. HPV vaccines should be introduced as part of a coordinated strategy to prevent cervical cancer and other HPV-related deaths. Also, HPV vaccine introduction should not undermine or divert funding from effective screening programmes for cervical cancer.

2.2 With regard to delivery strategies, WHO recommends that countries should use approaches that are compatible with their health delivery infrastructure and cold-chain capacity; that are affordable, cost-effective and sustainable; and that achieve the highest possible coverage. Priority should be given to strategies that include populations who are likely to have less access to screening for cervical cancer later in life.

WHO Global recommendations for HPV
1) Routine HPV vaccination should be included in national immunisation programmes 2) Approaches should be compatible with country health delivery infrastructure. 3) Priority should be given to strategies that include populations who are likely to have less access to screening for cervical cancer later in life.

3. GAVI Support for HPV Introduction

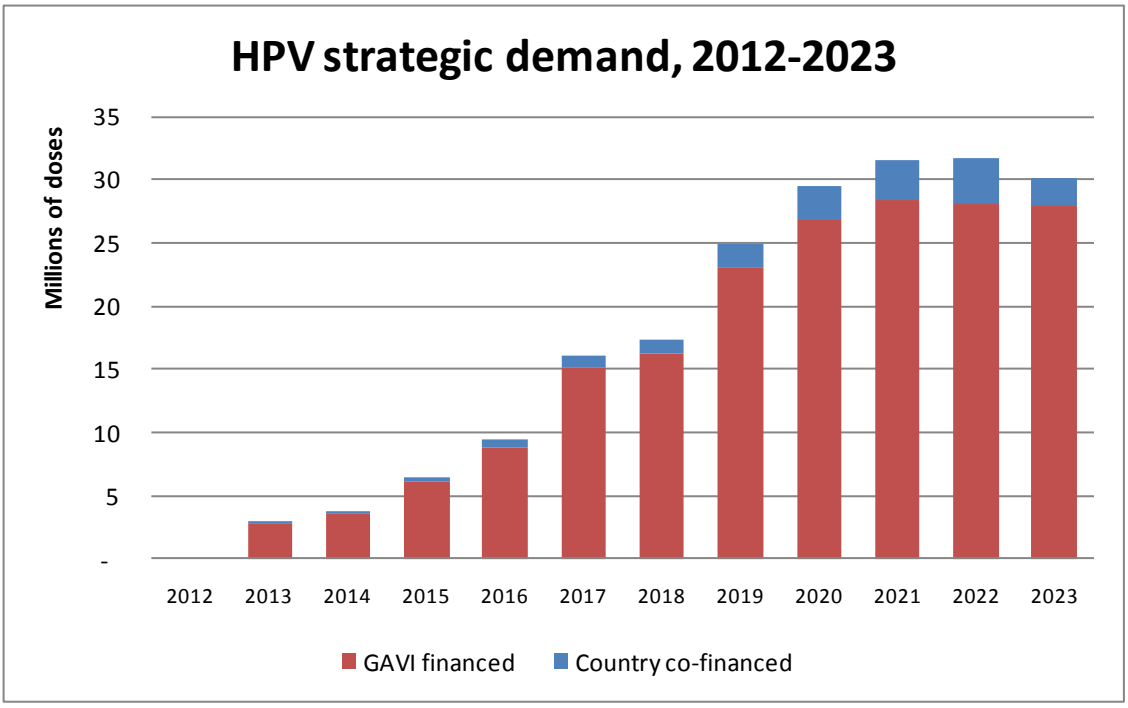
3.1 All countries may apply for national introduction of HPV vaccines and would need to address requirements specific to HPV vaccine in their application (see Appendix II). For the introduction year and each subsequent GAVI-supported year, countries would select and vaccinate the same single-year cohort selected from the WHO-recommended target population of girls aged 10-13 years old.

3.2 GAVI will work with technical partners to develop a pilot programme to assess strategies for national rollout.

4. Target countries — all GAVI countries are eligible to apply

5. Target populations — girls aged 10-13

6. Demand — HPV



No. of introductions by year	2012	2013	2014	2015	2016	2017	2018	2019	2020	Total
HPV	**0**	**2**	**3**	**4**	**7**	**6**	**7**	**4**	**7**	**40**

7. Market Access — HPV

7.1 Supply landscape: The HPV vaccine market is currently a duopoly between GSK and Merck, with both manufacturers having WHO pre-qualified vaccines in 1- and 2-dose vials (GSK) or 1-dose vials (Merck). Both vaccines protect against HPV 16 and 18, which cause approximately 70% of cervical cancer, while Merck's vaccine is also protective against HPV 6 and 11, which cause genital warts. Merck is currently undertaking Phase III clinical trials for a second generation 9-valent vaccine. Many emerging manufacturers are also currently developing HPV vaccines. A major challenge in estimating the time to market for these products lies in determining the clinical and immunological endpoints required. Under the most optimistic scenario, the earliest new entrant gaining WHO pre-qualification would reach the market in 2016. A more realistic scenario would be 2020, with a potential upside for 2017-18 if a shortened regulatory route was possible combining Phase II and III trials and submitting dossiers for licensure and WHO pre-qualification in parallel.

7.2 Impact on the supply landscape of the recommended GAVI support: It is estimated that adequate supply capacity would be available through 2020 as current manufacturers are likely to have significant excess capacity. Therefore,

GAVI demand could be met with appropriate signaling to manufacturers. It is assumed that steep increases in global demand that would be driven by China or India would be met by each country developing new products through its local manufacturers. Initially launched in 2006 at US$ 120 a dose for a three-dose course, prices for HPV vaccines have rapidly decreased. The current price to PAHO is approximately US$ 14-15 per dose. In June 2011, Merck announced an offer to provide its vaccine at US$ 5 per dose[14] to GAVI. Further assessment is on-going to assess production cost drivers and potential price levers.

7.3 **Implications for GAVI supply and procurement**: In the medium-term, few new entrants are expected, resulting in no increase in the competitive supply base for HPV vaccines. The GAVI country projected demand may not be sufficiently high to substantially impact manufacturer utilization and therefore costs. GAVI has a number of options to reach a price below US$ 5 per dose and to mitigate the risks associated with a duopoly market in the medium-term through its procurement strategy.

8. Surveillance and Post-Introduction Monitoring

8.1 Monitoring HPV disease is not a prerequisite to initiating an HPV vaccination programme. There is a potential need for limited special studies to assess distribution of HPV types or to provide support for vaccine impact monitoring in GAVI-eligible countries. Monitoring the impact of HPV vaccine will be complex and should be done with good technical support and a clear understanding of the caveats to avoid drawing erroneous conclusions. Because HPV testing technology and algorithms for screening for cervical cancer are evolving, approaches to monitoring the impact of the vaccine are also likely to evolve.

[14] Prices quoted are ex-manufacturer or “unloaded” costs, excluding freight, syringes, safety boxes, and further downstream costs.

Annex II

1. Implementation Strategies and New Vaccine Windows – Rubella

1.1 Rubella is usually a mild viral disease mainly affecting children and young adolescents. However, when a pregnant woman becomes infected, particularly in the first trimester, serious consequence can occur. Congenital Rubella Syndrome (CRS) causes birth defects ranging from cataracts and hearing impairment to heart defects. It remains a major public health problem with an estimated 112,000 cases occurring globally, of which 90,000 are in GAVI eligible countries.[15]

1.2 Currently, 68% of WHO countries use Rubella-containing vaccines (RCV) in their childhood immunisation programmes, and three regions (Americas, Europe, Western Pacific Regions) have rubella elimination/control programmes. In 2003, the Region of the Americas established their 2010 rubella and CRS elimination goal, achieved it on time and is now in the process of documenting elimination. African and South-east Asian regions have not established goals for rubella control or elimination and they have the highest estimated number of CRS cases.

Disease Burden

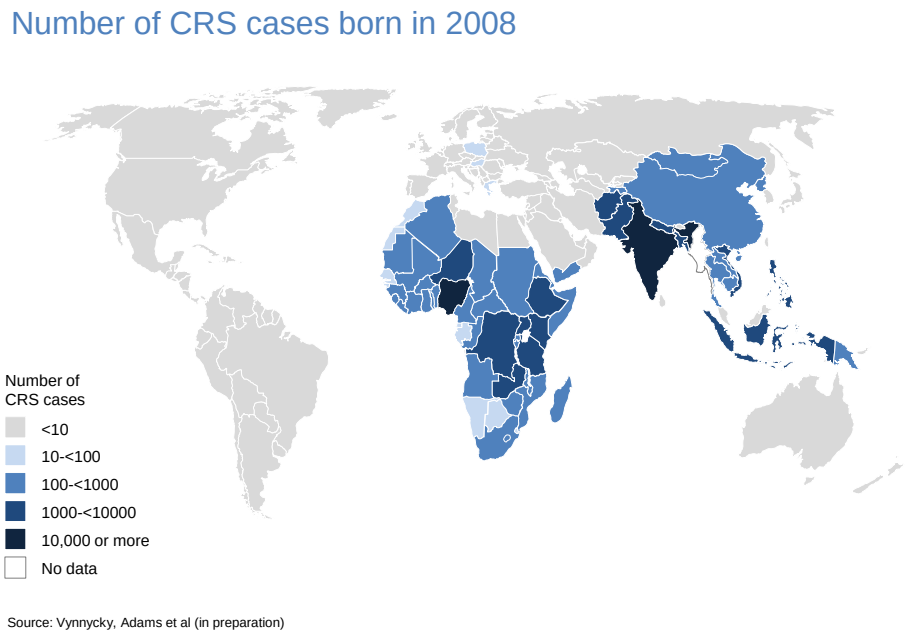


Figure 2

[15] World Health Organization; WHO position paper, Rubella, 2011

2. WHO Position Paper and SAGE Recommendations

2.1 In 2011, WHO updated the rubella vaccine position paper, recommending countries take advantage of the measles platform of two doses of measles vaccine to introduce MR or MMR[16]vaccine using the strategy recommended.

2.2 The WHO new guidelines also supported a paradigm shift in vaccination strategy for introduction of rubella-containing vaccines. The 2000 guidelines placed an emphasis on direct protection of women of child bearing age (WCBA). However, in many settings women were difficult to access resulting in limited vaccine coverage and the rubella virus continued to circulate. Thus, susceptible pregnant women were at risk of exposure and subsequent rubella infection. In addition, since 2000, all countries have added delivery of a second dose of measles vaccine for all children either in campaigns or through the addition of a routine immunisation visit. The second measles dose provides an opportunity to use combined MR vaccines that can reach 80% of all children thereby effectively blocking rubella transmission and its associated risk of CRS.

2.3 Based on country and regional experiences, the 2011 updated WHO Rubella position paper focuses on the interruption of rubella transmission targeting children and adolescents.[17] The WHO recommends a catch-up campaign, followed immediately with introduction of the MR vaccine in the routine programme. WCBA vaccination is now considered an additional strategy.

WHO Global recommendations for Rubella

1) Catch-up campaign
2) Routine childhood vaccination – incorporating RCV with MCV1
3) Regular follow-up campaigns with MR containing vaccines, in countries with coverage of MCV1 < 90-95%
4) Efforts to reach women of childbearing age (WCBA)
5) Surveillance for rubella and CRS

[16] Measles-Rubella (MR), Measles-Mumps –Rubella (MMR)
[17] The position paper cites two approaches to prevent congenital rubella infection: 1) one approach focuses exclusively on reducing CRS by immunising adolescent girls or women of child bearing age, or both groups. The other approach is “more comprehensive,” focusing on interrupting transmission of rubella virus, thereby eliminating rubella as well as CRS. This calls for introducing rubella vaccines into the routine childhood immunization schedule, combined with the vaccination of older age groups.

3. GAVI Support for Rubella Vaccine Introduction

3.1 Following the WHO guidelines to build on the success of accelerated measles control and elimination activities, GAVI recommendations will focus on combined measles-rubella vaccine approaches.

3.2 Combining measles and rubella is feasible due to ease of delivery of vaccines using MR, MMR and integrated rubella-measles surveillance.

3.3 To apply for funding, countries should demonstrate that they can achieve and maintain immunisation coverage of 80% or greater with rubella containing vaccines (RCV) delivered through routine immunisation and/or regular supplementary immunisation strategies (SIAs).

3.4 To ensure that the countries implement the comprehensive strategy for RCV introduction, funding both the measles and rubella components of the MR vaccine will be critical. Thus, GAVI will finance the cost of the vaccine (bundled vaccine)[18] and the operational costs for the WHO-recommended children and adolescent campaign.

3.5 The price of MR is cost-effective at $30-50 cents per dose, slightly higher than low-income co-pay requirements under current policy. GAVI suggests fully funding the catch-up campaign, but asking countries to cover MR for routine programmes. Countries would be eligible for introduction grants covering routine immunisation start-up costs. However, in order to secure GAVI support, countries would be required to verify that they have begun the process of procuring MR vaccines for routine programmes.

3.6 The GAVI Alliance will continue to fund applications for measles 2nd dose for countries in conjunction with the rubella MR routine rollout. If GAVI countries applying for measles 2nd dose opt to provide a 2nd dose of MR in their routine schedules[19] they will be required to finance the rubella antigen. No co-financing is required by the countries for measles 2nd dose and GAVI support is restricted to five years duration.

3.7 The sub-team noted the importance of continuing efforts to reach Women of Child Bearing Age (WCBA) in the immunisation programe. The current WHO position paper confirms that the “highest risk of CRS is found in countries with high rates of susceptibility to rubella among WCBA.”[20] However, the new WHO strategy seeks to interrupt transmission of the rubella virus, eliminating rubella as well as CRS over the long-term.[21] Given the challenges of reaching adolescents and women in GAVI countries, and the significant range of birth cohorts to cover (15-39), GAVI recommends working directly with countries to

[18] Required AD syringe, reconstitution syringe and safety box

[19] The high response rate to a single dose of rubella vaccine (>95%) and long-term persistence of protection do not support a routine requirement for a second dose of rubella

[20] Before the introduction of rubella vaccines, the incidence of CRS varied from 0.1-0.2/1000 live births during rubella epidemics, and from .8-4/1000 live births during rubella epidemics

[21] Delayed impact strategy for Rubella approved by the Board in 2008

define specific vaccination programmes for this population. These programmes would need to be self-financed by the countries.

4. **Target Countries** — Six GAVI countries have already introduced rubella, thus out of GAVI's 57 eligible countries, fifty-one are eligible to apply.

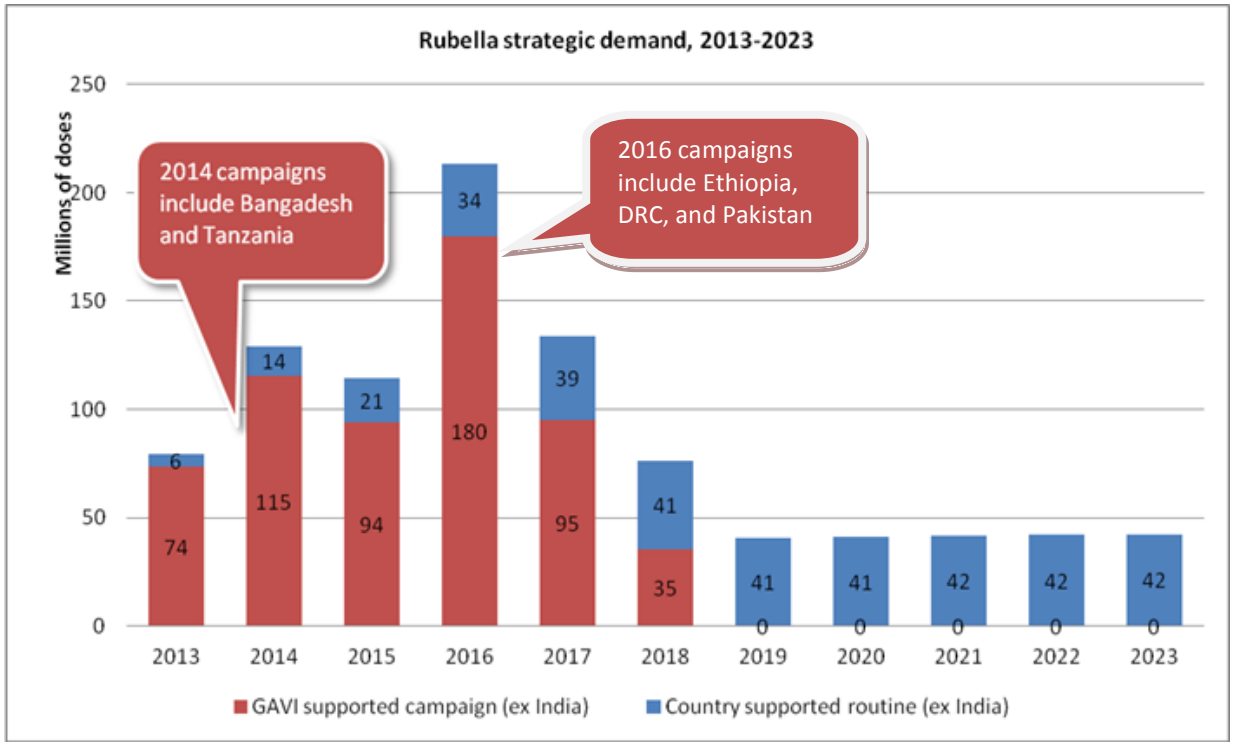
5. Target Population

a) **Proposed targeted age range of catch-up campaign**: males and females aged 9 or 12 months to 14 years.[22]

b) **Proposed targeted population for routine program**: same as MCV1 (1 birth cohort).

c) **Proposed additional targeted population (women of childbearing age**) up to the countries' discretion and country-financed.

6. Demand



No. of introductions by year	2013	2014	2015	2016	2017	2018	2019	2020	Total
Rubella	**9**	**9**	**12**	**9**	**4**	**8**	**0**	**0**	**51**

[22] Exact target range will depend on rubella epidemiology in the country

7. Market Analysis — Rubella Vaccines

7.1. Supply landscape: Rubella containing vaccines were first available starting in the late 1960s, either as a standalone antigen or in combinations with other antigens to form combination vaccines of measles-rubella (MR), measles-mumps-rubella (MMR) and measles-mumps-rubella-varicella (MMRV) vaccines. There are many Rubella Containing Vaccine (RCV) manufacturers, with MMR being the most commonly demanded product globally, driven by middle- and high-income country preference. Prices charged to PAHO and UNICEF for the MMR products vary between US$ 0.85 and US$ 2.70 per dose, while the MR vaccine is currently sold at approximately US$ 0.55 (and the measles vaccine for approximately US$ 0.25). In light of the 2- to 5- fold difference in price between the MR and MMR vaccines and the WHO position paper[23] supporting the use of the MR vaccine, the market analysis focuses on this vaccine. Out of the seven suppliers with capacity for the relevant RA27/3 rubella strain, only three produce the MR vaccine. Two of these producers, Serum Institute of India and Crucell, have WHO pre-qualified vaccines, although soon there will be only one remaining in the market following Crucell's decision to cease production. However, one new MR vaccine producer may enter the market and would potentially gain WHO pre-qualification around 2016 with the potential for a similar cost range as the remaining manufacturer.

7.2 Impact on the supply landscape of the recommended GAVI support: The profile of country demand for MR vaccines would be comfortably met through the estimated supply capacity of the dominant manufacturer Serum Institute of India. Currently, MR vaccines can be purchased for approximately US$ 0.55[24]per dose. The production of MR vaccines is highly scale and location dependent. Therefore, a potential future price range for the product could be between US$ 0.30-0.60 per dose with sufficient volume levels and the reduced uncertainty given GAVI support for MR vaccines. The MR vaccine price would thus potentially be no more than 25% above the price of a single antigen rubella vaccine.

7.3 Implications for GAVI supply and procurement: Within the current supply landscape, it is unlikely that there will be an increase in the competitive supply base with new entrants bringing significant volumes until about 2016 when one additional supplier may enter. Hence, although Serum Institute of India has more than adequate capacity to meet demand, the most critical issue will be to mitigate risks associated with supply security, for example, in the event of quality issues arising. The MR vaccine can be expected to remain within the same price range with potential for further decreases thanks to the higher, more stable demand profile for MR vaccines achieved with GAVI support for the vaccine. However, GAVI would also take steps to hedge against the risk of price increases in the absence of competition. Based on these factors and the interdependencies in production between the different RCVs, GAVI will need

[23] WHO. Rubella vaccines: WHO position paper. No. 29, 2011, 86, 301-316
[24] Prices are quoted as ex-manufacturer or "unloaded" costs, excluding freight, syringes, safety boxes, and further downstream costs, source UNICEF SD website,

to signal its preference for the MR vaccine to ensure adequate supply capacity is available to meet GAVI country demand.

8. Surveillance

8.1 The WHO position paper recommends that in "all stages of rubella control, including countries that have not introduced RCVs, rubella surveillance should be integrated with measles surveillance systems."

8.2 Countries with measles surveillance systems should integrate rubella surveillance into the existing platform, and strengthen or establish CRS surveillance.

a) Components should include integrated measles-rubella surveillance, CRS surveillance, vaccine coverage monitoring and adverse events monitoring.

b) All countries should already have three of the four monitoring systems in place: measles surveillance, vaccine coverage and AEFI systems.

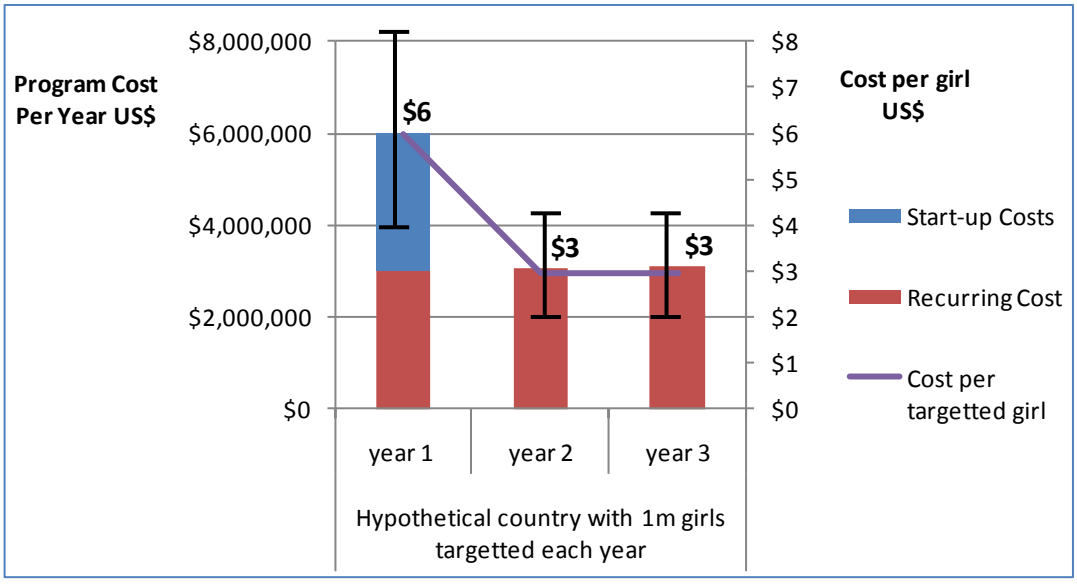
Annex III

Estimating HPV vaccine delivery costs in GAVI countries based on pilot projects and national introductions: analysing start-up and recurring costs.

The establishment of appropriate delivery systems for HPV vaccine introduction represents a significant new challenge and opportunity for the public health community. If schools are used as venues for vaccination, it will require the set up of a new routine vaccine delivery system in schools[25], effectively creating an extension of the Expanded Program for Immunisation (EPI) for adolescent children. A school based programme will require active engagement of leadership and staff within the Ministry of Education. No matter what HPV vaccine delivery strategy is selected (school, health centre, campaign, or combination), there is also the need to develop and implement a clear and sensitive social mobilization campaign to ensure high uptake and coverage levels for a new target group.

To inform the GAVI Board, the WHO, PATH, and the London School of Hygiene and Tropical Medicine analysed initial financial costs obtained through several HPV pilot projects in Uganda, Peru, India, Vietnam, and Tanzania as well as from expenditure data from Bhutan's national introduction with catch-up campaigns, and from cost projections of national introductions in Tanzania (from the new WHO costing tool[26]) and in Uganda (from PATH).

Figure 1



Two categories of costs are estimated in this initial analysis: start-up costs during the first year of introduction and recurrent costs of operating the programme for each subsequent year.[27] Initial estimates assume the start-up cost is approximately US$ 3

[25] In some countries it will be a combination of delivery strategies - schools, health centres, clinics and campaigns.
[26] The WHO Comprehensive Cervical Cancer Prevention and Control Costing Tool (C4P tool)
[27] Costs do not include resources already paid for by the Ministry of Health such as salaries of health personnel or vaccines paid for by partners. Costs will vary from country to country.

per girl to be vaccinated, and the recurrent cost to deliver 3 doses of vaccine per eligible girl is assumed to range from US$ 2 – 4, with midpoint of US$ 3 (refer to fig 1). Main drivers of start up costs are development and implementation of social mobilization, planning, training, and, in some countries, the cost of vehicle and cold chain equipment. Recurrent costs are mainly transport (healthcare staff to schools), per diems, monitoring and supervision.

Using the above, the estimates for start-up and recurring cost for all subsequent years are outlined in Table 1.

Table 1: HPV vaccine cost estimates for GAVI-eligible countries

HPV delivery cost (US$ millions)	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	Total
Delivery cost - startup*	$0	$0	$4	$4	$4	$6	$3	$9	$5	$2	$0	$0	$38
Delivery cost- recurring*	$0	$0	$4	$8	$13	$19	$22	$32	$38	$40	$41	$41	$258
Total delivery cost	$0	$1	$8	$13	$17	$25	$25	$41	$43	$42	$41	$41	$296

Number of countries introducing†	0	2	3	4	7	6	7	4	7	2	0	0	**42**
Number of immunized girls (millions)††	0.00	0.03	0.34	1.04	2.20	3.85	5.39	6.86	8.63	10.01	11.31	12.33	**62.00**

*The estimated delivery cost for national rollout, with the assumptions -startup at 3US$, recurring cost at 2-4 (midpoint 3US$)/child per targeted population annually. This has not been split between GAVI and country.

† based on SDF 4.0,

† †based on SDF 4.0 (on the number of countries forecasted to introduce the vaccine and coverage assumptions) and the targeted population.

The cost for the GAVI introduction grant included in actual financials is calculated using the $0.30 per eligible girl in the year of introduction as per current GAVI policy and results in a total cost of US$ 3.75M from 2012-23.

Using the assumptions above, in advance of the GAVI policy review on introduction grants, gives us the guidance of costs in table 1 above. The total delivery cost (to country and GAVI, split not determined) is US$ 296M for 2012-23. The operational cost for three doses per eligible girl is approximately $4.17.

Annex IV Preliminary Recommendations on Requirements for National Applications for HPV Vaccines

An HPV vaccine application will require the same DTP3 coverage requirement as required by applications for other GAVI vaccines. There is currently no EPI indicator analogous to DTP3 coverage which can serve as a proxy measure for whether an immunisation programme can successfully deliver vaccine to populations other than infants. Thus, in addition to DTP3 coverage, application requirements specific to HPV vaccine would need to include:

1. Demonstrated ability to successfully deliver vaccine to this particular new target population *(Note: for countries currently vaccinating this target population with other antigens, e.g., Td or rubella, may want coverage data for those other antigens for this population).*
2. Identification of the single-year cohort of girls to be vaccinated.
3. Identification of size of target population, source of data that was used for this estimation, and where to best access the population.
4. Description of delivery strategy or strategies to be implemented.
5. Assessment of acceptability of HPV vaccine by community and health providers.
6. Report on costing analysis of delivery strategy or strategies and evidence of non-GAVI resources to support delivery in conjunction with GAVI operational funds.
7. A country assessment of the cervical cancer burden and status of cervical cancer prevention and control activities, together with a national roadmap or strategy for establishing or strengthening a national comprehensive approach to cervical cancer prevention and control.[28]
8. Brief description of any adolescent health programme.

For countries choosing to deliver HPV vaccine via schools, additional information that would be needed for the application includes:

1. Description of educational system for girls (number of schools, private versus public schools, etc.).
2. School year calendar (start/finish, holidays, exam period)
3. Data on proportion of girls of the target age who are:
    a. enrolled in school
    b. attending school (absenteeism rate)
4. Identification of whether girls will be vaccinated by selection of a specific grade or by a specific age.
5. If girls are to be vaccinated by a specific grade, data on distribution of the ages of girls in the selected grade.
6. Description of any existing school-based health programming

[28] Timelines and prioritization for using or enhancing different interventions may vary by country.

7. Documentation that Ministry of Education (MoE) is a member of the Inter-agency Coordination Committee (ICC).
8. Documentation that MoE signature is provided with the HPV vaccine application.
9. Description of the strategy that will be used to deliver HPV vaccine to girls who are not attending or not enrolled in schools.

Naturally, the technical elements which are common to any new vaccine introduction and which need to be addressed as a standard component of a GAVI application would also be necessary for an HPV vaccine application: cold chain equipment and logistics, waste management, vehicles and transportation, surveillance and monitoring, programme management, human resources and training, social mobilization, IEC, and advocacy, and new vaccine introduction plan.