

Strategic Advisory Group of Experts on Immunization

Working Group on Human Papillomavirus (HPV) immunization

Report to SAGE

Meeting held on 27-28 September 2018

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Introduction

The SAGE Working Group on HPV immunization held its first face to face meeting on 27-28 September 2018 in Menthon-Saint-Bernard, France.

The Terms of Reference for the Working Group, list of participants with Working Group membership, and agenda are provided in Appendix.

The objectives of the meeting were:

- To examine the evidence and assess the potential contribution of HPV vaccination to the achievement of the proposed cervical cancer elimination goals under various scenarios.
- To discuss preliminary outcomes of systematic reviews and meta-analyses on burden of HPV-related cancers and anogenital warts, immunogenicity and efficacy of HPV vaccines in clinical trials, and effectiveness of HPV immunization programmes.
- To review preliminary modelling estimates on incremental effectiveness and cost-effectiveness of different combinations of vaccination and cervical cancer screening strategies.

This report provides a summary of the discussions and conclusions of the Working Group. A document summarizing the evidence and copies of the reports from each of the reviews will be posted in the SAGE website.

Background

Cervical cancer is the fourth most common cancer among women globally, with 570,000 new cases and 311,000 deaths in 2018¹. The majority of these deaths were in low- and middle-income countries. Within countries, women from the poorest income quintile, those with lesser education levels, those in rural areas and those facing adverse gender norms, amongst other intersecting social factors, benefit less and often not at all from programmes aimed at early detection of cervical cancer and more likely to die from cervical cancer, than those from more advantaged backgrounds².

The WHO Director General made a global call for action towards the elimination of cervical cancer at the World Health Assembly in May 2018. The elimination of cervical cancer is also a priority under the Thirteenth WHO General Programme of Work. Working towards elimination will also contribute to the realization of universal health coverage (SDG 3.8). It will also contribute to fulfilment of SDG 5 on achieving gender equality and empowering women and girls.

¹ Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018 Sep 12.

² Ginsburg O, Bray F, Coleman MP, et al. The global burden of women's cancers: a grand challenge in global health. *Lancet* 2016. Available at: [http://dx.doi.org/10.1016/S0140-6736\(16\)31392-7](http://dx.doi.org/10.1016/S0140-6736(16)31392-7)

QUESTIONS CONSIDERED BY THE WORKING GROUP

QUESTION 1. What are the potential effects and cost-effectiveness of various vaccination strategies towards the achievement of cervical cancer elimination?

1.1 VACCINATION OF GIRLS ONLY WITH HPV VACCINE

There are three HPV vaccines – bivalent, quadrivalent and 9-valent – licensed and two bivalent HPV vaccines (Phase II and III) and one quadrivalent HPV vaccine (Phase II) currently in clinical development. Current evidence suggests that, from the public health perspective, the three current licensed vaccines offer comparable immunogenicity, efficacy and effectiveness for the prevention of cervical cancer. HPV16 and 18 are associated with more than two thirds of all cervical cancer cases worldwide^{3,4}. Therefore, choice of a higher valency product should be very carefully considered in light of cost considerations and limited additional impact. The Working Group members noted the important supply constraints at least until 2024.

Mathematical models produced consistent conclusions on the herd immunity effects, vaccine effectiveness and cost-effectiveness of all the currently licensed vaccines. The 9-valent vaccine is likely to be cost-effective in high and low- and middle-income countries compared to bivalent and quadrivalent vaccines but its cost-effectiveness would be highly influenced by its price per dose and the degree of cross-type protection against HPV types provided by each vaccine.

Evidence from a systematic review ³, based on 26 observational studies, suggests that a two-dose schedule with at least 6-month interval between doses induces comparable levels of protection from HPV 16/18 infection as a three-dose schedule of any HPV vaccine at least in girls aged 9-14 years.

In addition, the Working Group members reviewed the available evidence on one-dose schedules. There are currently no published randomized controlled trials (RCTs) that directly assess one-dose schedules. There are at least two ongoing RCTs evaluating the efficacy of one dose of HPV vaccine, with results expected over the next few years (Trial registries: NCT02834637, NCT03180034). There are data from 18 observational studies with various designs reporting on clinical and immunological outcomes, of which two were post-hoc analyses of non randomised data from RCTs, and two case-control studies that contained data on clinical or immunogenicity

³ 'Currently licensed HPV vaccines in females and males aged 9-26 years: Systematic review and meta-analysis of immunogenicity and efficacy data from published and unpublished studies prepared and presented by Cochrane Response on the SAGE Working Group on HPV immunization meeting on 27-28 September 2018.

⁴ Arbyn M, Xu L, Simoens C. Prophylactic vaccination against human papillomaviruses to prevent cervical cancer and its precursors (Review). Cochrane Database of Systematic Reviews 2018;Issue 5. Art. No.: CD009069.

outcomes from females in this report. No studies were identified which assessed the effectiveness of one dose of HPV vaccine in males. For most outcomes there is insufficient evidence to determine whether there is a difference between one dose of HPV vaccine and two or three doses, and the evidence available is at high risk of bias. The RCTs will help clarify non-inferiority of one dose of HPV vaccine compared to two doses, in terms of immunogenicity and HPV infection. The estimates from RCTs will provide a higher level of certainty than the currently available observational studies.

Regarding a one-dose schedule, the evidence for most outcomes is insufficient to determine whether there is a difference between one dose of HPV vaccine and two or three doses, and the evidence available is at high risk of bias. Therefore, the Working Group members concluded that there is insufficient evidence on efficacy of single HPV vaccination to change immunization policies. On-going 1-dose trials are summarized at the end of this report (see Question 5).

A systematic review, based on 53 studies, showed the additional benefit of girls-only vaccination on herd effect to older women and boys/men. Modeling results revealed that compared to no vaccination, girls-only vaccination results in reduction of HPV 16/18 prevalence, and both percentage and absolute reduction in cervical cancer incidence. Girls-only vaccination is deemed to be highly cost-effective and the main driver of prevention of cervical cancer. Its cost-effectiveness is sustained even when additional beneficial impacts from vaccination, such as herd protection, cross-protection and reduction in non-cervical diseases, are ignored in the models.

Conclusions and recommendations

The Working Group members reiterated that all three licensed HPV vaccines have excellent safety, efficacy and effectiveness profiles. The choice of HPV vaccine should be based on the assessment of locally relevant data and a number of other factors, including the scale of the prevailing HPV-associated public health problem (cervical cancer, other HPV-associated cancers, or anogenital warts) among others.

Decision-makers should also consider unique product characteristics, such as price, vaccine availability and programmatic considerations.

For the prevention of cervical cancer, the Working Group reiterated that the current WHO-recommended primary target population for HPV vaccination should continue to be girls aged 9-14 years, prior to becoming sexually active, with a 2-dose schedule. Vaccination strategies should initially prioritize high coverage in this priority population.

Achieving high vaccination coverage in girls (>80%) also reduces the risk of HPV infection for boys by herd protection.

The Working Group members emphasized the importance of continuing research on a single-dose schedule. A single-dose schedule has potential of simplifying delivery and lowering programme cost.

Further, in countries having delayed introduction of HPV vaccine because of supply, logistical or financial barriers, a single-dose schedule (followed by a delayed second dose if ongoing studies confirm that the two-dose schedule is still required), could accelerate HPV vaccine introduction into the national immunization programmes.

However, more evidence is still needed to determine if a single dose of HPV vaccine can provide a sufficient and durable level of efficacy against persistent HPV infection before a recommendation in policy change to a single-dose vaccination strategy can be made.

1.2 VACCINATION OF MULTIPLE AGE-COHORTS OF GIRLS WITH HPV VACCINE

A systematic review based on data from 53 studies reports substantial direct impact, as well as herd effect (to older women and boys/men), of HPV vaccination in girls only. These effects could be reached faster if a larger proportion of females were vaccinated through multiple age-cohort vaccination.

Modeling estimates confirmed the conclusion that multiple age-cohort vaccination provides more rapid herd effects than single age-cohort vaccination. However, catch-up vaccination of females older than 15 years of age is less cost-effective than vaccination of females 9-14 years.

Economic analysis suggested that multiple age-cohort vaccination of girls aged 9-14 years is highly cost-effective (if gross national income [GNI] or gross domestic product [GDP] per capita are used as a threshold).

The incremental cost-effectiveness for each additional age cohort of females aged ≥ 15 years depends on the country context, because vaccination at this age requires a 3-dose schedule and proportionally more girls and women in older cohorts would have already become sexually active.

Conclusions and recommendations

The Working Group members reiterated that vaccination of multiple age cohorts of girls aged 9-14 years should continue to be recommended. Due to broader direct protection and faster herd effects, vaccination targeting multiple age cohorts would result in faster population-level impact than vaccination of single age cohorts. It may also offer opportunities for economies of scale in delivery and could make programmes more resilient to unintended interruptions in vaccine delivery. However, HPV vaccine introduction targeting multiple age cohorts will require further operational planning and adequate finances and vaccine supply, at a time when

vaccine supply may not support the potential increase in demand that this might generate.

1.3 GENDER-NEUTRAL VACCINATION WITH HPV VACCINE

A systematic review ³ including 8 randomized and non-randomized studies (2 or 3 doses), for all vaccine types, reported that there are no significant differences in seroconversion rates between males and females from 7 months after vaccination.

A randomized controlled trial and a non-randomized comparative study in men who have sex with men (MSM) concluded that HPV vaccine was effective in reducing clinical outcomes of HPV infection in MSM and no significant difference was observed in seropositivity for HPV antibodies between MSM and females, and between MSM and heterosexual males at 7 months.

Modelling results indicate that vaccination in girls provides strong herd effects in older women and boys/males. Vaccinating boys would provide additional impacts. However, increasing coverage in girls would provide greater impacts than vaccinating boys in terms of reduction in HPV 16/18 in both males and females.

A cost-effectiveness analysis also revealed that cost-effectiveness of gender-neutral HPV vaccination is influenced by the vaccination coverage in girls. Gender-neutral vaccination is more cost-effective when the vaccination coverage in girls is low than when it is high. If vaccination coverage in girls is up to 70-80%, gender-neutral vaccination that includes adolescent boys is less cost-effective than vaccination targeting only females aged ≤18 years. However, if increasing vaccination coverage above 70-80% amongst girls becomes very costly or unfeasible, gender-neutral vaccination would be a cost-effective option to increase overall population level coverage and herd effects.

Conclusions and recommendations

The Working Group members reiterated the current recommendation on vaccinating girls aged 9-14 years is still valid and its implementation is critical to the achievement of any control or elimination goals. However, if high coverage in girls has been achieved and financial support is available or, vaccinating boys could provide some additional benefit, then gender-neutral vaccination could be considered based on other elements, such as competing health priorities, disease burden, equity, programmatic implications, cost-effectiveness, affordability.

Current evidence suggests that tangible benefits of gender-neutral vaccination include, but are not limited to, more rapid population-level impact, indirect protection of unvaccinated women, and direct protection of MSM. However, girls-only vaccination is more effective and cost-effective than gender-neutral

vaccination especially when vaccination coverage in girls is high. Achieving high vaccination coverage in girls (>80%) reduces the risk of HPV infection for boys.

Vaccination of secondary target populations, e.g. females aged ≥ 15 years or males, is recommended only if this is feasible, affordable, cost-effective, and does not divert resources or vaccine doses from vaccination of the primary target population worldwide or from effective cervical cancer screening programmes.

QUESTION 2. What is the potential contribution of HPV vaccination towards cervical cancer elimination?

In response to the global call for action to eliminate cervical cancer that was made by the Director-General of WHO in May 2018, a model comparison exercise was commissioned by the WHO Secretariat to inform decisions regarding strategies towards global cervical cancer elimination.

A comparison of various individual models used for cervical cancer elimination as well as collaborative work using many models with various combination of vaccination and cervical cancer screening strategies were presented ⁵.

The Immunization and Vaccines-related Implementation Research Advisory Committee (IVIR-AC) was requested to review the individual mathematical models and the collaborative modeling comparison exercise, in particular to address whether the Committee has any specific concerns on the model comparison process and methods of the individual models used in the cervical cancer elimination comparison study.

The Working Group members also reviewed the evidence generated by these epidemiological and economic modelling studies to inform their discussions and conclusions. Various combinations of vaccination and cervical cancer screening strategies were modeled using standardized intervention parameters and coverage and scaling up assumptions to assess and compare their potential impact on the achievement of cervical cancer elimination. Multiple models were used to illustrate the robustness of prediction and identify areas of greater uncertainty, and the main conclusion was that the models produced consistent predictions.

In the modeling exercise, cervical cancer elimination was defined *ad interim* as reduction in cervical cancer incidence to less than 4 or 10 cases per 100,000 women-years, i.e., the range typically found in populations at the lowest cervical cancer risk because of adequate screening or unusually low HPV prevalence.

⁵ The cervical cancer elimination comparison study was performed by three modeling teams from Université Laval, Canada; Harvard T.H. Chan School of Public Health, USA; and Cancer Council NSW, Australia.

These thresholds have been proposed by two Technical Experts Group meeting in March and July 2018, and by the WHO Global Stakeholder Consultation on Cervical Cancer Elimination in September 2018, based on the mean and median of cervical cancer incidence in countries (using data from GLOBOCAN 2012 ⁶ and 2018 ⁷) as well as preliminary results of the modeling exercise.

Moreover, several assumptions were made in the modeling exercise for the analyses in low and lower middle income countries i.e. HPV testing which is the current gold-standard screening test for cervical cancer although not widely introduced into LMICs; 100% treatment efficacy and 10% loss to follow-up; lifelong protection provided by HPV vaccines against HPV 16/18/31/33/45/52/58 infection with 100% efficacy; and vaccination could be initiated and 90% coverage in girls aged 9-14 years in all countries in 2019 (the best vaccination scenario). Cervical cancer screening strategy, when included in the model, was set at once or twice in a life time screening with HPV testing.

It is important to note that the time framework for the achievement of the *interim* elimination goals is quite long (e.g. five to six decades).

Overall, achieving cervical cancer elimination is most sensitive to the definition of elimination threshold (e.g. 4 or 10 cases per 100,000 women-years), starting level of cervical cancer incidence in a country, assumptions regarding girls-only vaccination, and at least one lifetime cervical cancer screening test.

Model estimates suggest that elimination (defined as 4 or 10 cases per 100,000 women-years) could be accelerated by about 10 years using the strategy of girls-only or multiple age-cohort vaccination with at least once in a lifetime cervical cancer screening test. If the girls-only vaccination coverage is high (e.g. 80-90%), vaccination of boys with the addition of three lifetime cervical cancer screening test would provide limited additional impact towards reaching elimination.

For countries with starting cervical cancer incidence <30/100,000 women-years, girls-only vaccination coverage of more than 80% and 1 life screening could lead to elimination (defined as 4 or 10 cases per 100,000 women-years).

However, for countries with higher baseline cervical cancer incidence (i.e. >30/100,000 women-years) cervical cancer incidence to achieve interim elimination goals is highly dependent on the threshold used to define cervical cancer elimination. High coverage with cervical cancer screening and vaccination would be required.

⁶ Ferlay J, Soerjomataram I, Ervik M, Dikshit R, Eser S, Mathers C, et al. GLOBOCAN 2012 cancer incidence and mortality worldwide: IARC cancerbase No. 11. Lyon, France: International Agency for Research on Cancer 2013.

⁷ Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018 Sep 12.

For countries with starting cervical cancer incidence >70/100,000 women-years, *interim* elimination goals may not be reached even under the most optimistic scenarios within the next century, which is likely to be a disincentive for country engagement in this process.

In addition to the challenges of achieving elimination for countries with higher baseline rates of cervical cancer at baseline, the difference in distribution of serotypes in various regions may pose additional challenges.

As part of the ongoing modeling exercises, projections of cases and deaths averted at interim goals (e.g. 2030, 2045 and 2060) towards the elimination targets and country-specific economic analysis should be conducted to examine affordability and value for money of different strategies.

Conclusions and recommendations

The Working Group members agreed that the modeling exercise performed for the cervical cancer elimination was robust, helpful and informative. However, the model assumptions were considered as too optimistic, especially with respect to pace of introduction of HPV vaccines and the potential of reaching 90% coverage by 2019.

The Working Group members suggested an interim goal of achieving 80% vaccination coverage among girls aged 9-14 years by 2030.

The Working Group members also debated whether the use of a fixed elimination threshold (4 or 10 cases per 100,000 women-years in the current modeling exercise) was desirable given that these goals will be achieved in several decades and innovations in vaccines, vaccination and screening and treatment tools are anticipated.

Alternative measures of success were discussed. For example, the concept of *ad interim* elimination thresholds based on a percentage reduction in cervical cancer incidence (especially in very high incidence populations), instead of an absolute incidence level.

This could help address the fact that there is a broad range of current (baseline) cervical cancer incidence in various Member States.

However, independent of the thresholds selected to define cervical cancer elimination, the Working Group members highlighted the importance of exploring different – more realistic - scenarios including achieving 80% vaccination coverage and, if when screening was included in the model, 70% screening coverage with 90% of women screened positive treated by 2030.

This was beyond the scope of the Working Group terms of reference, but some members noted that a discussion about when different countries may decide to stop screening because of the potential high number of false positives relative to the true positives may be pertinent.

Although it may have limited impact on the current global estimates, the Working Group members noted that the current modeling exercise did not consider potential contributions of new non VLP-based prophylactic vaccines, new and innovative screening/diagnostic technologies and treatments such as new antiviral treatments improved POC treatments or other prevention measures that may become available in the future. Likewise, the modeling exercise did not assess the potential influence on vaccine short-term or long-term efficacy that may be caused by high population prevalence of impaired immunity such as HIV-infection.

Any major advances in these areas have the potential to shorten or prolong the time required to achieve a cervical cancer elimination goal. The model exercise needs to be adapted accordingly as new interventions may become available in the future.

In conclusion, it may be possible to achieve cervical cancer elimination within a timeframe of 60 years depending on the combination of current vaccination and cervical cancer screening strategies and the definition of the elimination targets.

To do so, introduction into all national programmes of HPV vaccines as well as the introduction of HPV testing, appropriate referral and improved treatment technologies for cervical precancer and cancers should be strongly recommended and facilitated.

At the national level, the priority should be to introduce HPV vaccine and, if logistically possible, high-quality HPV tests and related triage and cervical precancer treatment, country-wide as soon as possible.

Routine vaccination of 9-year-old girls with two doses of vaccine and multi-age cohort vaccination of girls aged 10-14 years at the time of vaccine introduction is highly recommended.

QUESTION 3. What are the interim goals that can be achieved through immunization as part of the efforts towards cancer elimination?

With respect to immunization, the following interim goals were proposed:

- 80% of countries in the world have introduced at least single age-cohort HPV vaccination into the national immunization programmes and,
- 80% coverage (final dose) among targeted girls (ideally those aged 9-14 years) by 2030.

QUESTION 4. What indicators can be proposed to monitor the accomplishment of these interim goals?

The following indicators are proposed:

- monitoring national HPV vaccine introduction and coverage in countries;
- assessment of reduction in genotype prevalence of high-risk type HPV 16/18 in young women (i.e. age 19-24 years);
- monitoring cervical cancer screening coverage and treatment rate of women screened positive;
- assessment of reduction in rate of CIN2+ (Cervical Intra-epithelial Neoplasia grade 2 or higher), if a cervical cancer screening programme is introduced; and
- assessment of reduction in cervical cancer incidence, if national or smaller regional cancer registration can be introduced.
- assessment in reduction in cervical cancer mortality.

If it is economically and logistically feasible, cervical cancer incidence and the above intermediate outcomes should be measured prior to and after the implementation of interventions towards cervical cancer elimination so as to assess the accomplishment of the interim goals.

However, a comprehensive program for monitoring HPV infection/disease is not required for the initiation of a vaccination program.

Indeed, the development of surveillance systems may foster progress in the elimination goal. While it may be not possible in all countries, indicators for measuring the impact of HPV vaccine on cervical cancer burden should be developed and bridged to countries in the same broad region that are not able to develop their own surveillance programs.

The surveillance systems discussed included those monitoring genotype prevalence of high-risk type HPV 16/18, rate of CIN2 and CIN3 and HPV vaccine effectiveness (of 1/2/3 doses and of delayed second dose) in representative population samples.

QUESTION 5. What is the additional research related to vaccines and immunization needed to attain these goals? And outline potential innovations that may help enhance the achievement of these goals.

There is a need for additional research related to efficacy and effectiveness of a one-dose HPV schedule and two-dose schedules with longer interval between doses, effectiveness and cost-effectiveness of 9-valent HPV vaccine (as compared to bivalent and quadrivalent), burden of anogenital warts, and burden and vaccine effectiveness studies in cervical cancer high-risk groups, e.g. women infected with HIV.

There are at least two ongoing RCTs and others planned to evaluate the efficacy of one dose of HPV vaccine. These RCTs will help clarify non-inferiority of one dose of HPV vaccine compared to two or three doses, in terms of immunogenicity and persistent HPV infection.

The estimates from RCTs will provide a higher level of certainty than the currently available data from observational studies. With the potential advantages of a single-dose schedule to simplify delivery and lower programme costs, additional research on the efficacy of single-dose schedule would help to inform policy decision-making.

The potential negative consequences of the anticipated shortfall in vaccine supply in the coming years might be partially mitigated by ensuring available doses globally are used to vaccinate priority populations.

Furthermore, additional evidence and explorations of potential benefits and feasibility of delaying the delivery of the second dose should be conducted. Studies to evaluate the antibody response to a second dose administered 3-7 years after the prime would contribute to inform decisions to adopt this type of schedule.

As the price for 9-valent vaccine remains unknown for low- and middle-income countries, the cost-effectiveness of vaccination with 9-valent HPV vaccine is still uncertain and further economic evaluations are required to determine more accurately the value for money of 9-valent HPV vaccination.

There is a paucity of evidence relating to the incidence and prevalence of anogenital warts in the general population, with most good quality studies coming from high-income countries. There is a need for high quality studies from all regions of the world. Existing studies on anogenital warts burden report estimates for females more than for males. Additional research on anogenital warts burden in males is desirable.

Direct evidence of benefit of HPV vaccination for anal and oral clinical outcomes and, in general, in HIV-infected persons is still limited. More research focusing on HIV-infected individuals and MSM would help fill this research gap. This should include

research on the impact of HIV seroconversion on vaccine effectiveness in adolescents or women who have already been immunised.

The Working Group members noted with concern that delay in HPV vaccine introduction may occur in some countries due to the current limited vaccine availability, affordability, incremental cost, affordability, capacity, access issues and hesitancy. Concerns about the impact of social media on vaccine hesitancy associated with HPV vaccination in both HIC and LMICs was also discussed.

Therefore, innovative approaches should be explored to reduce these barriers.

Actions to further understand the vaccine supply issues include monitoring production capacity/supply and negotiation with current manufacturers to increase production, exploring new suppliers and technology transfer to assure access to vaccines at an affordable price, and thereby enabling sustainable and high HPV vaccination coverage in all countries.

The importance of involvement of all stakeholders before the launching of any national intervention toward cervical cancer elimination and preparedness to deal with controversies about vaccine safety cannot be overemphasised.

Appendix

Terms of Reference for the Working Group

List of participants (including Working Group membership)

Meeting agenda

List of reviews and evidence considered

Terms of Reference for the Working Group

Call for nomination for experts to serve on a Strategic Advisory Group of Experts (SAGE) Working Group on potential contribution of HPV vaccines and immunization towards cervical cancer elimination

Background:

Despite the availability of effective prevention tools, cervical cancer continues to be a significant public health concern globally. Cervical cancer is the fourth most common cancer among women with 528,000 new cases and 266,000 deaths in 2012. Nearly 90% of these deaths were in low- and middle-income countries.

The WHO Director General plans to announce a global effort towards the elimination of cervical cancer at the World Health Assembly in May 2018. In preparation for this announcement, a WHO working group with the support of other UN agencies⁸ and key partners is developing a full draft of the strategy document, including the definition of elimination and the main indicators and targets to reach the elimination goal. Following the WHA 2018 announcement, the strategy document, including the proposed definition and targets for elimination, will undergo stakeholder review and revision, with a global consultation anticipated in September 2018. A resolution on cervical cancer elimination will be considered at the Executive Board meeting in January 2019, and then put forward for endorsement and launch at the World Health Assembly meeting in May 2019. Moreover, HPV vaccine coverage was included in the WHO's Global Program of Work for 2018-2023, with the target of increasing vaccination coverage from 10% at baseline to 50% by 2023. This target is linked to the Sustainable Development Goals (3.7). There is also a Global STI Strategy target of 70% of countries having introduced HPV by 2020.

As of January 2018, 79 countries (41%) have introduced the HPV vaccine. At the current pace of introductions, the world is not on track to reach the 70% target by 2020. Most of the countries that have introduced the vaccine are high-income. So far, 94% of GAVI-eligible countries have not yet introduced the vaccine. It is anticipated that additional countries in Africa will introduce the HPV vaccine in the coming few years with GAVI support. Lower middle-income countries may continue to struggle to identify financing to support vaccine introduction. HPV vaccines are safe and highly effective but there are remaining issues related to affordability and challenges delivery. Recent changes in WHO recommendations have enabled countries to accelerate introductions, including opportunities for multi-cohort catch-ups. A recent vaccine supply shortage has limited the ability to meet country requests. Observational data suggest that a single-dose regimen could contribute to

⁸ UN Joint Global Programme on Cervical Cancer Prevention and Control includes WHO, IAEA, IARC, UNAIDS, UNFPA, UNICEF, UN Women and UNODC. Preliminary partners include GAVI, GFATM, UNITAID, UICC, CHAI and others are invited to join.

change this landscape of challenges by offering more flexible implementation programs and reduced supply requirements. However, clinical trials assessing one-dose schedule are ongoing.

Terms of reference:

- To critically appraise the evidence and potential effect and cost effectiveness of various vaccination strategies towards the achievement of cervical cancer elimination.
- To review the potential contribution of HPV vaccination towards cervical cancer elimination.
- To develop and propose interim goals that can be achieved through immunization as part of the efforts towards cancer elimination.
- To develop and propose indicators to monitor the accomplishment of these interim goals.
- To discuss and propose additional research related to vaccines and immunization needed to attain these goals and outline potential innovations that may help enhance the achievement of these goals.

Timeline:

The SAGE Working Group on cervical cancer elimination is expected to be set up and start functioning as soon as possible and is expected to accomplish its task and tentatively present its conclusions and recommendations to the SAGE in October 2018. Given its link to a long-term goal, it is anticipated that the WG will be active for a period of 2 years.

Expertise needed in:

1. Immunization
 - a. Immunization programmes and vaccine delivery
 - b. HPV Epidemiology
 - c. HPV vaccines
 - d. HPV vaccines implementation and monitoring
2. Cervical cancer screening and treatment
3. Mathematical modelling - Modelling of infectious diseases with expertise in HPV vaccines, cervical cancer screening and treatment

Proposals for nominations should be sent by email to sageexecsec@who.int with a Curriculum Vitae, indication of relevant expertise, and a completed declaration of interest form. Only complete nominations received by Sunday 6 May 2018, will be considered. Information on the purpose, structure and functioning of SAGE Working Groups is available at

http://www.who.int/immunization/sage/SAGE_Working_Groups_general_information.pdf?ua=1

List of participants (including Working Group membership)



Initiative for Vaccine Research
Immunization, Vaccines & Biologicals

SAGE Working Group on human papilloma virus

27-28 September 2018

Hotel Palace de Menthon, Menthon-Saint-Bernard, France

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Meeting agenda



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World Health Organization*

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SAGE WORKING GROUP ON HUMAN PAPILLOMAVIRUS IMMUNIZATION

27 – 28 SEPTEMBER 2018

Palace de Menthon, Menthon-Saint-Bernard, France

Agenda

Objectives

- To examine the evidence and assess the potential contribution of HPV vaccination to the achievement of the proposed cervical cancer elimination goals under various scenarios.
- To discuss preliminary outcomes of systematic reviews and meta-analyses on burden of HPV-related cancers and anogenital warts, immunogenicity and efficacy of HPV vaccines in clinical trials, and effectiveness of HPV immunization programmes.
- To review preliminary modelling estimates on incremental effectiveness and cost-effectiveness of different HPV immunization strategies.

Expected output

- Background paper drafted, including preliminary conclusions and potential recommendations on potential immunization strategies, anticipated impact of the various strategies, and evidence-to-decision tables outlined.
- Propose mid-term goals and indicators to monitor the progress of the potential cervical cancer elimination.

Proposed questions to SAGE

1. To eliminate cervical cancer what are the most effective and cost effective vaccination strategies?
2. Given the long-term outlook of attaining cervical cancer elimination, what interim goals can/should be achieved through HPV vaccination?
3. What are the most robust indicators to monitor the attainment of these goals?
4. What innovations in the vaccination field may expedite achievement of these goals?

Day 1: Thursday 27 September 2018

Chair: Rakesh Aggarwal

From 08:15	Registration	
08:30–09:00	Opening remarks Consultation objectives and tasks Introduction of participants Declaration of interests	WHO R. Aggarwal
09:00–10:30	Session 1: HPV vaccine uptake and coverage <i>Question: What is the current HPV vaccine uptake and coverage and which are the main barriers?</i>	
09:00–10:00	Evidence related to question (15' each): <ul style="list-style-type: none"> • Update on HPV vaccine uptake and coverage • Operational costs of HPV vaccine delivery in Gavi and -non-Gavi countries • HPV acceptance study in South Africa – preliminary updates • HPV Vaccine Global Supply Analysis 	P. Bloem R. Hutubessy F. Scorgie T. Cernushi
10:00–10:30	Questions for clarification	
10:30–10:45	Coffee	
10:45–13:00	Session 2: Potential for cervical cancer elimination <i>Questions: What are the effects and cost effectiveness of various vaccination strategies towards achievement of cervical cancer elimination?</i> <i>What is the potential contribution of HPV vaccination towards cervical cancer elimination?</i>	
10:45–12:00	Cervical cancer elimination model comparison	M. Brisson
12:00–13:00	Questions for clarification	Plenary
13:00–14:00	Lunch	
14:00–15:45	Session 3: Girls-only HPV immunization to prevent cervical cancer <i>Question: What is the incremental effectiveness and cost-effectiveness for cervical cancer prevention of different HPV vaccines based on girls-only immunization?</i>	
14:00–15:00	Evidence related to question (20' each, including 5' on methodology): <ul style="list-style-type: none"> • Burden of cervical cancer by HPV type and country • Efficacy and immunogenicity of licensed HPV vaccines • Modelling estimates of incremental effectiveness 	IARC N. Henschke M. Brisson
15:00–15:45	Questions for clarification	Plenary
15:45–16:00	Coffee	

16:00–18:00 Session 4: Gender-neutral HPV immunization

Question: What is the incremental effectiveness and cost-effectiveness for prevention of HPV-related diseases of adolescent gender-neutral HPV immunization compared to girls-only HPV immunization?

16:00–17:00 Evidence related to question (15' each):

- Burden of HPV-related cancers by site, sex and country
- Burden of anogenital warts
- Efficacy and immunogenicity of licensed HPV vaccines
- Modelling estimates of incremental effectiveness

IARC
N. Henschke
N. Henschke
M. Brisson

17:00–18:00 Questions for clarification

18:00–18:30 Summary of Day 1 conclusions

Plenary

18:30 Closure of the Day 1 – Cocktail reception**Day 2: Friday 28 September 2018**

Chair: Rakesh Aggarwal

08:30 Continuation

08:30–10:15 Session 5: Routine and catch-up HPV immunization

Question: What is the incremental effectiveness and cost-effectiveness for cervical cancer prevention of catch-up immunization of females (multiple cohorts within a defined age range) compared to routine immunization of girls only aged 9–14 years or of both girls and boys aged 9–13 years?

08:30–9:15 Evidence related to question (15' each):

- Emerging evidence from countries using catch-up immunization
- Observed population-level impact and herd effects
- Modelling estimates on incremental effectiveness

I. Ogbuanu
M. Brisson
M. Brisson

09:15–10:15 Questions for clarification

10:15–10:30 Coffee**10:30–12:00 Session 6: Monitoring progress towards cervical cancer elimination**

*Question: What proposed goals can be achieved through immunization as part of the efforts towards cancer elimination
What proposed indicators are appropriate to monitor progress of these goals?*

Plenary

12:00–13:00 Lunch

13:00– 14:00	Session 7: Research related to vaccines and immunization	
	<i>Question: What additional research related to vaccines and immunization is recommended to reach the goals towards cervical cancer elimination?</i>	Plenary
	Outline potential innovations	
14:00–14:30	Session 8: Evidence on HPV immunization to provide informed decisions	
14:00–14:15	HPV country profiles dashboard	W. Van Panhuis
14:15–14:30	Questions for clarification	Plenary
<i>End of open sessions</i>		
CLOSED SESSION		
14:30–17:30	Final session: Proposed recommendations and SAGE background document	
		SAGE WG Members
14:30–15:30	Proposed conclusions and recommendations	
15:30–15:45	<i>Coffee</i>	
15:45–17:30	Content of SAGE background document and evidence-to-decision tables to support proposed conclusions and recommendations	SAGE WG Members
	Next steps	
17:30	Closure of consultation	

List of reviews and evidence considered

- [Systematic review and meta-analysis of HPV vaccine clinical trials](#): 1 final report and 12 individual studies, 351 pages in total
- [Systematic review of burden of anogenital warts](#), 83 pages
- [Summary of scenarios for cervical cancer elimination](#), 1 page
- [Articles of HPV introduction and costing](#), three articles with 17, 13 and 8 pages
- [Systematic review and meta-analysis of HPV vaccination impacts](#), 10 pages
- Single-dose HPV vaccination: [general summary](#), [technical synthesis](#), [white paper](#) and [systematic review](#), 159 pages in total
- [Article of potency of HPV prophylactic vaccines](#), 6 pages
- [HPV Vaccine – Global Market Study](#), 30 pages
- [Systematic review of cost-effectiveness of HPV vaccination](#), 16 pages