Proposed recommendations

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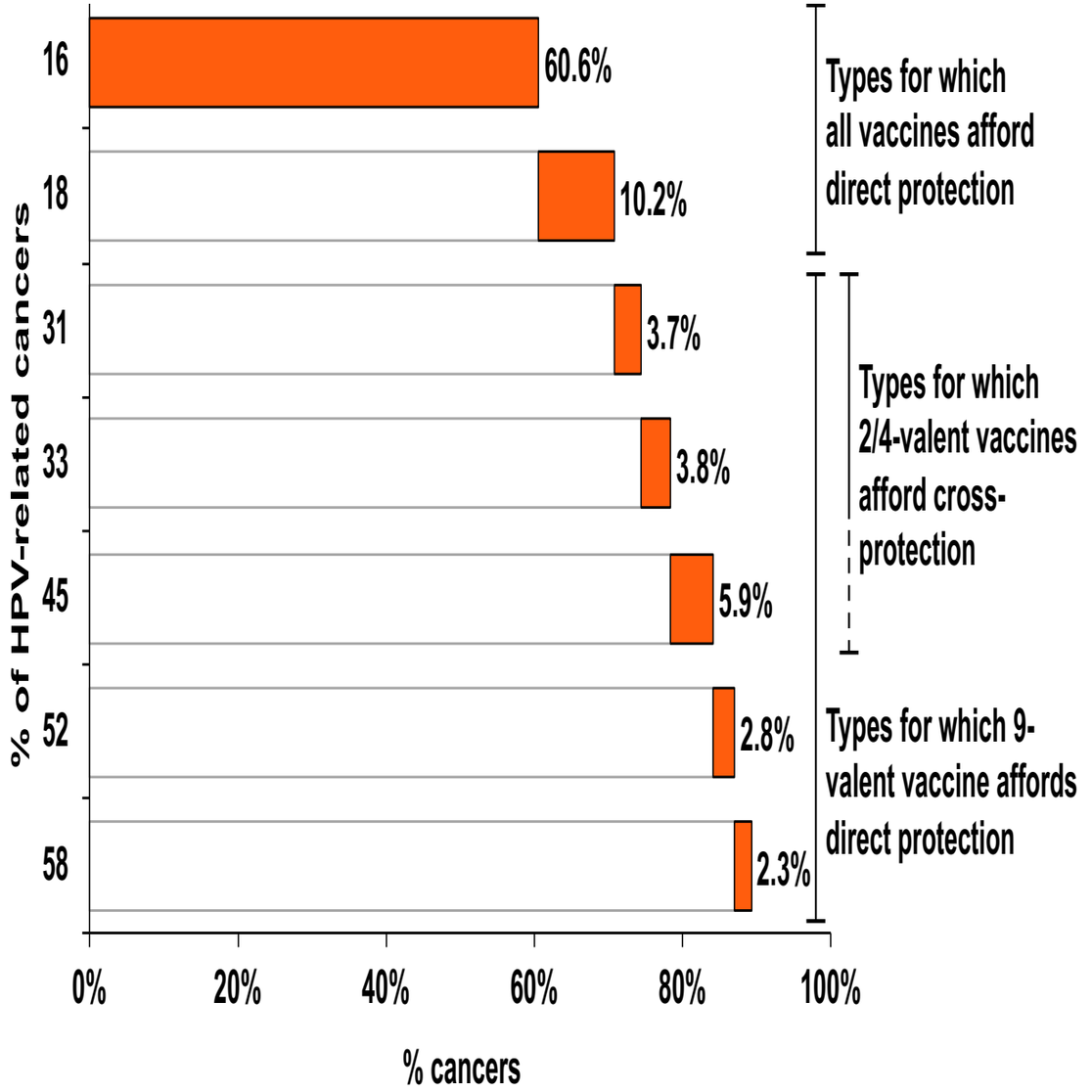
1

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

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 other issues, such as price, vaccine availability and programmatic considerations.



For the prevention of cervical cancer, 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.

Achieving high vaccination coverage in girls (>80%)

- Has the largest impact on reduction of cervical cancer
- Also reduces the risk of HPV infection for boys by herd protection.

Hence, vaccination strategies should initially prioritize high coverage in this population.

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.

HPV vaccine introduction in multiple age cohorts requires greater operational planning, and adequate finances and vaccine supply.

Vaccinating girls aged 9-14 years is still valid recommendation and its implementation is critical to the achievement of any elimination goals.

Gender-neutral vaccination results in limited additional benefits when coverage in girls is 80%.

Model estimates suggest that achieving 90% coverage in girls has similar effect that a gender neutral vaccination at 80% coverage.

For the same number of doses the effect is greater if girls are vaccinated compared to a gender neutral strategy.

Vaccinating girls aged 9-14 years is still valid recommendation and its implementation is critical to the achievement of any elimination goals.

However, once high coverage in girls has been achieved and financial support is available or, vaccinating boys can provide some additional benefit.

Introduction of gender-neutral vaccination needs consideration of other elements, such as competing health priorities, disease burden, equity, programmatic implications, cost-effectiveness and 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.

2

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

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.

Future innovations in vaccines, vaccination and screening and treatment tools have the potential to shorten or prolong the time required to achieve a cervical cancer elimination goal. The model exercise will need to be adapted as such innovations occur or new interventions become available.

The Working Group members 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.

- These goals will take several decades to achieve.
- Too low for some countries
- Too high (and not achievable) for other countries
- A threshold based on relative reduction in disease incidence may be an alterative
- Decision on threshold will need multi-sectoral inputs for decision

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 achieve cervical cancer elimination, at the national level, the priority should be to introduce HPV vaccine.

Introduction of HPV vaccines as well as introduction of HPV testing for cervical cancer screening into all national programmes should be strongly recommended and facilitated.

- Routine vaccination of 9-year-old girls with two doses of HPV vaccine and multi-age cohort vaccination of girls aged 10-14 years
- If logistically possible, high-quality HPV tests and related triage and cervical precancer treatment, country-wide as soon as possible.

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* are proposed:

By 2030,

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 y).

4

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

With respect to immunization, the following *indicators* are proposed:

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

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 interim goals.

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

The development of surveillance systems 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.

5

What is the additional research related to vaccines and immunization needed to attain 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.

A single-dose schedule has potential of simplifying delivery and lowering programme cost. Further, a schedule with a delayed 2nd dose could help accelerate HPV vaccine introduction into the national immunization programmes.

The results of at least two ongoing RCTs should help clarify non-inferiority of one dose of HPV vaccine compared to two or three doses, in terms of immunogenicity and efficacy.

Effort should be made to obtain additional evidence to explore the potential benefits and feasibility of one-dose schedule and delaying the delivery of the second dose.

Need to further evaluate the effectiveness and cost-effectiveness of 9-valent HPV vaccine (as compared to bivalent and quadrivalent).

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.

Existing studies on anogenital warts burden report estimates for females more than for males, and for some regions of the world.

Direct evidence of benefit of HPV vaccination for anal and oral clinical outcomes is still limited.

Additional research on anogenital warts burden in males and from all regions of the world is desirable.

There is need for further studies on benefit of HPV vaccination on anal and oral warts.

Direct evidence of benefit of HPV vaccination 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 immunized.

Innovative approaches should be explored to reduce barriers for HPV vaccine introduction and access.

Delays in HPV vaccine introduction may occur in some countries due to:

- ☒ Limited vaccine availability
- ☒ Affordability
- ☒ Incremental costs
- ☒ Access issues
- ☒ Hesitancy

Methods to reduce these barriers will be useful.

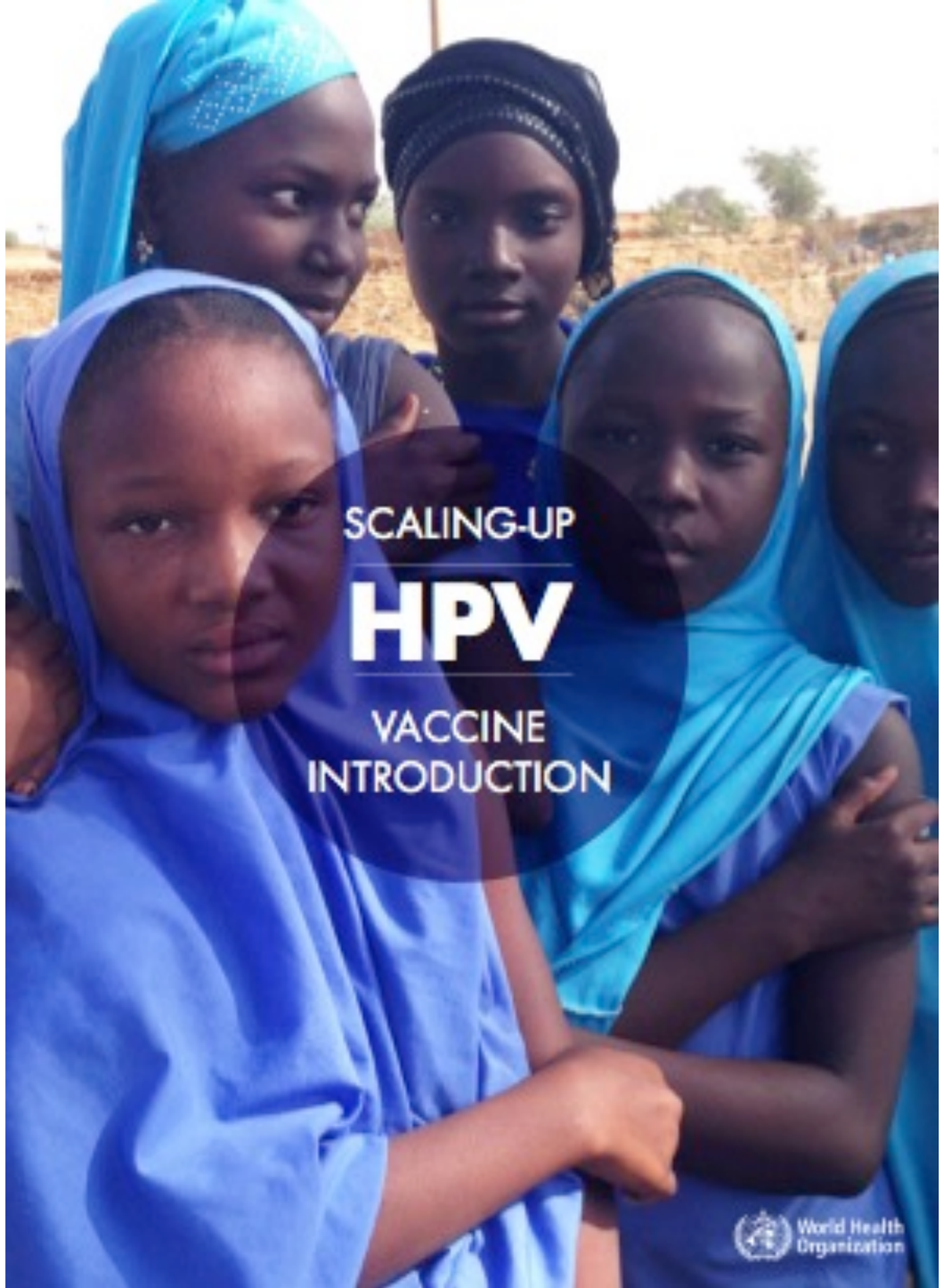
Actions needed to further understand the vaccine supply issues and thereby enabling sustainable and high HPV vaccination coverage in all countries.

The actions to assure access to vaccines at an affordable price will include:

- ☒ monitoring production capacity/supply
- ☒ negotiation with current manufacturers to increase production
- ☒ exploring new suppliers and technology transfer

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.

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 overemphasized.



THANK YOU

Working Group meeting, 27-28 Sep 2018
Evidence reviewed

- HPV disease burden in different countries
- HPV vaccine uptake, coverage and barriers (lack information, disease awareness, hesitance and vaccine supply)
- Potential contribution of HPV vaccination towards cervical cancer elimination
- Effectiveness and cost-effectiveness for cervical cancer prevention based on different vaccination strategies (systematic reviews of all evidence and modelling exercise)
  - Girls-only HPV vaccination
  - Gender-neutral HPV vaccination
  - Multiple age-cohort HPV vaccination