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THE VACCINE
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Building trust, managing risks: vaccine confidence and human papillomavirus vaccination

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Meeting Report*

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1. Introduction

In a combined effort, the HPV Prevention and Control Board and the London School of Hygiene & Tropical Medicine convened a symposium on vaccine confidence in London, England, to examine challenges in HPV vaccine introduction, including the degree of preparedness of all concerned parties to introduce a vaccine into pre-adolescent and adolescent populations; to review country experiences of HPV vaccine introduction and perspectives on overcoming challenges; to explore the impact of the age of the target population, i.e. adolescence, on HPV vaccination; to assess the experiences with monitoring public confidence in immunization programmes; to discuss the role of the media and the potential for monitoring of the media; and to consider ways of engaging and communicating with different audiences to manage misperceptions and misinformation about the vaccine and overcoming vaccine hesitancy.

2. The state of HPV vaccination in the world

As of May 2016, HPV immunization programs have been introduced in 74 countries, areas or territories [1] using different approaches, including school-based programs, healthcare professional (HCP)-based programs (mainly pediatricians, general practitioners and gynecologists), and community-based programs. HPV vaccination in high-income countries (HIC) have generally experienced mid-level to high-level coverage and low dropout rates regardless of the type of program. Vaccination programs have been extended to boys in seven countries.

Different dosage schedules are being implemented, from 3 doses over 6 to 12 months to 2 doses over 6 to 12 months. Based on increasing evidence that a one dose regimen might be effective [2], studies have been initiated (NCT03180034, NCT02799732; Costa Rica, and NCT02834637; Tanzania) to explore the possibility of a 1-dose schedule, as this may be especially valuable and feasible in low- and middle-income countries (LMIC).

Due to financial constraints, LMIC started HPV vaccination programs later than HIC which has exacerbated global health disparities and resulted in a devastating inequity that the countries with the highest burden of cervical cancer due to insufficient access to preventive and therapeutic options, get the vaccine last. Even though an increasing number of countries have HPV vaccine on the national schedule, very few of these countries are in places with the highest incidence rates and mortality of cervical cancer.

Many LMIC are supported by the GAVI Alliance to introduce the HPV vaccine. The uptake of HPV vaccines is clearly lagging compared to uptake of e.g. pneumococcal conjugate virus vaccine in LMIC. However, given the recent start of HPV vaccination, as of 2013, it seems more comparable to the uptake of a vaccine predominantly used in LMIC, such as the rotavirus vaccine, suggesting an increased uptake after a certain lag time.

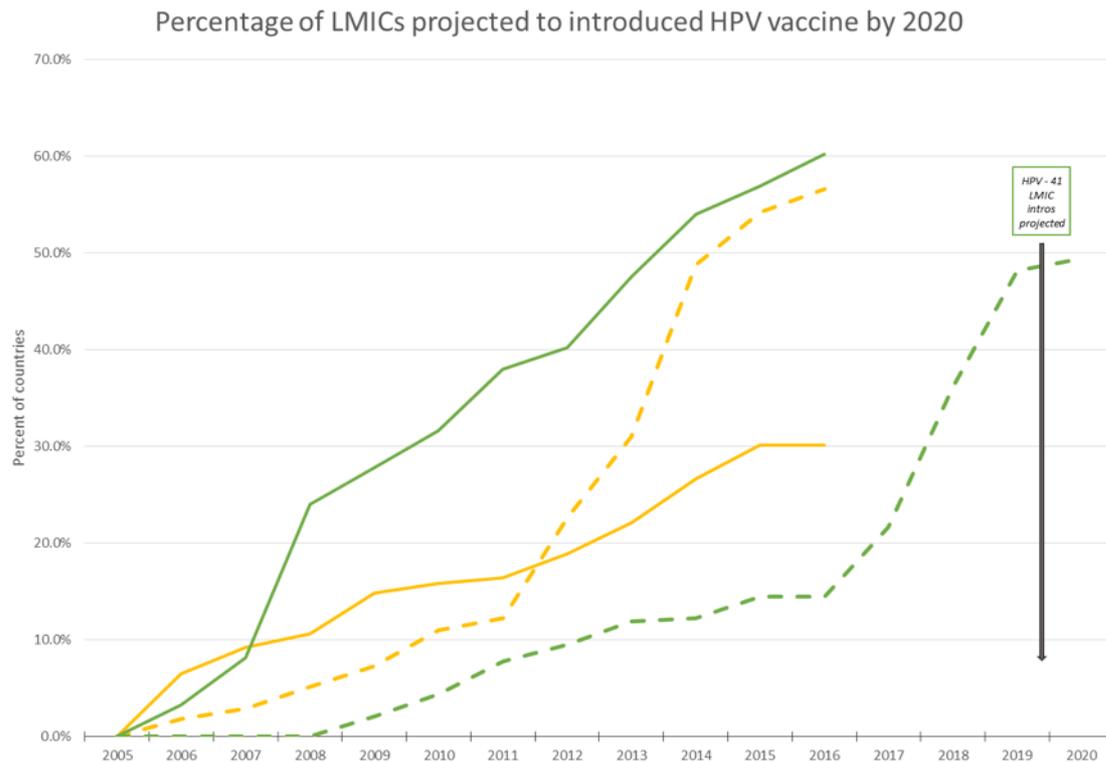


Figure 1. Uptake in HIC and LMIC of rotavirus vaccine and human papillomavirus vaccine

Solid yellow line – rotavirus vaccination in high income countries; dotted yellow line – rotavirus vaccination in low income countries; solid green line – HPV vaccination in high income countries; dotted green line – HPV vaccination in low income countries. Source: https://www.uantwerpen.be/images/uantwerpen/container39248/files/2017%2006%20London/01_%20Scott%20Lamontagne.pdf

Faster uptake in LMIC may be achieved by avoiding potential pitfalls before and during introduction by actions such as: establishing political commitment; coordinating at the national level; allowing for adequate planning time; engaging early with local community leaders, school leaders and parents; and training of school staff on how to deal with vaccination-associated rumors [3].

Over the last decade, the impact and effectiveness of HPV vaccination has become increasingly evident using observational data, especially among girls vaccinated before HPV exposure in countries with high vaccine uptake. Maximal reductions of approximately 90% for vaccine-type HPV infection, 90% for genital warts (after vaccination with the vaccine containing HPV types 6 and 11), 45% for low-grade cytological cervical abnormalities, and 85% for high-grade histologically proven cervical abnormalities have been reported [4].

A post-vaccination surveillance study (N = 409, 59% vaccinated) showed a decrease in vaccine-type HPV compared to a pre-vaccination study (N = 368, 0% vaccinated), not only among vaccinated, but also among unvaccinated study participants, indicating that vaccination programs are generating herd protection [5]. In a systematic review and meta-analysis of 20 eligible studies, representing more than 140 million person-years of follow-up, significant reductions in anogenital warts were reported among unvaccinated men younger than 20

years of age and women 20-39 years of age, which suggests HPV vaccination has resulted in protective herd effects. In countries with female vaccination coverage lower than 50%, there was no indication of such indirect protection.

Despite the evidence for impact of the vaccine, concerns about HPV vaccine safety have been a dominant feature and have persisted in some countries, leading to suspension of the recommendation of the HPV vaccination program (e.g. Japan) or dramatic drops in coverage (e.g. in Colombia, Denmark and Japan).

To limit the impact of potential concerns about the safety of the vaccine among adolescents and parents, they need to be supported in their decision-making, whether or not to be vaccinated/vaccinate their child. To this end, communication should focus on the following topics: what is the vaccine?; what is it for?; is it safe?; and is it recommended?

Discussion

While safety concerns are important both in HIC and LMIC, the large difference with HIC is that there is a heightened awareness of late stage cervical cancer morbidity and mortality in LMIC, which may result in greater acceptance of the vaccine. However, vaccine cost is generally a bigger issue than vaccine trust in many LMIC.

Furthermore, it is important to recognize that in LMIC, girls dropping out of school in year 5/6 (due to financial constraints or cultural attitude towards education of girls) are most likely to end up with the disease, therefore, it may be better to vaccinate earlier, before dropout starts.

3. Challenges with HPV vaccine introduction

This session aimed to discuss, based on previous experience, what can be done before introduction of HPV vaccination, as well as during the program, to avoid issues arising at a later stage. Finally, an case is presented of how introduction of HPV vaccination should not be done.

3.1 HPV vaccination coverage drop – common denominators?

In general, the evolution of an immunization program from pre-vaccination to disease eradication, inevitably passes through periods of increased pressure on vaccine confidence. In the initial stages (i.e. before introduction, and during the phase of increasing vaccine coverage) the number of disease cases vastly exceeds that of adverse event following immunization (AEFI) [6]. As sustained high vaccine coverage with an effective vaccine nearly eliminates the target disease, however, the number of severe AEFI may gain in prominence relative to the disease. The development and adoption of safer vaccines or a resurgence of disease may result in resumption of confidence in the vaccine, restoring high vaccine coverage and control of the disease. Since few diseases are truly eradicable, most vaccines will be applied in a situation of a limited number of disease cases (due to vaccination), and hence, a comparatively high number of AEFI [6]. Furthermore, HPV vaccination stands out from other vaccination programs (with the potential exception of hepatitis B vaccination, discussed below), because of the target age group (discussed in the section on adolescent health, below)

and the long period between vaccination and occurrence of the disease to be prevented (i.e. HPV-related cancer), and hence, no disease outbreaks due to reductions in vaccine coverage. Based on the experiences with HPV vaccine confidence crises in Colombia, Denmark and Japan, a number of events and/or stakeholders were defined as having impact on vaccination coverage:

- Events being associated with vaccination
These events, observed in vaccinated individuals, but not shown to be causally related, scare the public and can lead to long and severe impact on coverage
- Organized 'anti-vaccine' activities/groups.
These groups get a lot of attention, and seem to have large impact on social media. They tend to refer to a limited number of scientific papers of questionable quality, even if solid scientific evidence has been provided that the paper was fraudulent (i.e. comparable to Wakefield and autism).
- Public confidence (adolescents/parents)
In general, the public is very positive towards the importance, safety and effectiveness of vaccines, resulting in good coverage for other vaccines; the public generally follows recommendation by vaccinators.
- Vaccine providers / HCP
First source of information/recommendation to vaccinees/parents; in need of appropriate training, should be aware of difference between temporal association and causality.
- Media and social media
Events are covered extensively, not always taking scientific arguments into account.
- Government – Ministry of Health (MOH) – NITAG
The response is often too slow, no crisis plan is available, wrong message is sent (cessation of recommendation, funding of biased investigation).
- Academic researchers
Those who defend the vaccine are accused of being bought by industry, those who defy the vaccine produce science of questionable quality, trying to demonstrate causality between vaccine and adverse events. When accused of producing questionable results, they become martyrs for the anti-vaccination lobby.
- Vaccine manufacturers
the pharmaceutical industry has the clinical trial data, the experience and the early alert systems, however the manufacturers may be perceived negatively, due, amongst others, to assertive marketing.
- Vaccine injury court cases / reimbursements
Court cases against vaccine-producing pharmaceutical industry are supported/stimulated by anti-vaccine groups and specialized lawyers, as they provide a platform to disseminate their views. In court cases, the opinions of the involved/invited experts are not necessarily supported by the scientific community.

Reimbursement, when occurring in these court cases, is perceived as confirmation of a direct causal link, deteriorating public confidence in the vaccine.

The interpretation of causality is difficult, and it is essential to have a full picture before any conclusions can be drawn. For HCP or the general public, it is nearly impossible to obtain the full picture, especially when the majority of the target group is vaccinated. Hence, the results of the interpretation of causality by specialized groups, should be widely and timely disseminated.

3.2 Determinants of HPV vaccine hesitancy in Europe

Vaccine confidence is relatively low in the European region, with 17% of the population distrusting vaccines, compared to a global average of 13%. Particularly in France, 41% of respondents report that they disagree that vaccines are safe. Countries with high levels of schooling and good access to health services are associated with lower rates of positive sentiment, pointing to an emerging inverse relationship between vaccine sentiments and socio-economic status [7]. The most important concerns are side effects, and insufficient and inadequate information, with uncertainty being at the heart of HPV vaccine hesitancy. This vaccine has some issues that are different to other vaccines; : the role of the vaccinee in the decision making, morality issues, rumors spread in schools/in the vaccinees' social network. As there is a need for a fast response in times of vaccine crises, and the scientific literature does not capture concerns in real-time, fast data tools, such as media monitoring may provide a solution, as will be discussed later, along with the pro-active documentation of background incidence of potential AEFI.

3.3 Vaccine safety issues – lessons from hepatitis B immunization programs

The hepatitis B (HepB) vaccine is an excellent example of the damage that unsubstantiated rumors can do to vaccination programs. The initial HepB vaccine was derived from plasma at a time AIDS was first being reported. At that time the causative agent for AIDS was still unknown and it was suggested that AIDS could be transmitted through the vaccine. Once HIV was discovered it was proven that it was not present in the vaccine, but vaccination programs did not recover until the development and introduction of DNA recombinant vaccines in 1986. Like HPV, HepB can be sexually transmitted, therefore, the initial recommendation was to focus vaccination on high-risk groups: sex workers, men having sex with men, and patients with sexually transmitted infections. Similarly, due to their potential contact with blood from infected patients, healthcare professionals are also a risk group. While this strategy protected individuals, it failed to decrease rates of disease. Nowadays, more than 90% of countries use HepB vaccine routinely in infants or children, with global coverage rate of 84% (2015, [8]). Safety concerns around HepB vaccine still occur; in 1996, it was reported in France that multiple sclerosis (MS) occurred more frequently in patients who had received HepB vaccine (described in [9]). This was picked up by anti-vaccine groups and political pressure led to a suspension in France of the adolescent vaccination program and severe damage to the infant program. The WHO and the Viral Hepatitis Prevention Board quickly convened an “expert meeting” to examine the evidence and issue their findings [9, 10]. The Global Advisory

Committee on Vaccine Safety continues to closely follow the safety of HepB vaccines and rejects association between Hepatitis B vaccination and MS.

Similarly, in 2013, in Vietnam, three deaths occurred following vaccination. The media rapidly picked up the rumor that the deaths were due to the vaccine, which led to a drop in coverage rate from 76 to 56%, with an estimated impact of 90,000 chronic infections and 17,000 deaths. Investigation showed that the deaths were not related to the Hep B vaccine, but this was reported months after the events so the damage was done.

Then again communication of rational arguments does not seem to impact, while emotional arguments are much more effective. This must be kept in mind when training those who are involved in vaccination on how to respond to vaccine safety concerns to the public and the media. The AEFI data need to be carefully explained to media and public, with a focus on background rates of the adverse event in the non-vaccinated target population, and evidence for causality (or lack thereof), so that the decision whether to vaccinate or not can be based on evidence and not on rumors. The response to alleged side effects should be rapid, with a bold defense of immunization programs by the government.

3.4 HPV vaccine pilot introduction in Mongolia: HPV in a modernizing post-communist state

Mongolia has a strong public health program, with a vaccination program since the mid 90's, with high vaccine coverage, and no history of anti-vaccination history. However, Mongolia has high rates of sexually transmitted infections, especially in adolescents. Similarly, there is high burden of disease of HPV-related cancers.

In 2012, a pilot introduction, funded by the US, planned to vaccinate 14,000 girls. There was pressure to start quickly, leaving no time for public preparation, and the objectives were unclear. This led to opposition to the program, with a snowballing effect of negative views and negative press. There were no defenders of the program, not within the MOH, nor among scientists, so eventually the program was stopped, after 8,800 girls had been vaccinated. To recover some of the work done, an evaluation of effectiveness is being performed, with Australian funding. For the time being, no HPV vaccine is available in Mongolia, and there is no plan to re-introduce the vaccine. A United Nations review of cervical cancer prevention is ongoing, which will provide a more comprehensive overview, including a screening program, improved treatment, and palliative care, as well as HPV vaccination.

This failure shows that adequate and timely community information is essential, which takes time, with a clear need to enroll both communication and medical leaders for support. As there is a clear role for HPV vaccination in Mongolia, a pilot introduction was unnecessary, as no further scientific information was needed, this created uncertainty/suspicion: 'are our daughters used as guinea pigs?' Finally, at the time, roll out of HPV vaccination was impossible due to financial reasons.

3.5 Discussion

While there is general agreement on the value of a strategy to tackle vaccine issues, as countries which developed such a strategy from the very start seem to be having fewer issues,

it was suggested to use the term safety plan instead of crisis plan, as it implies a pro-active attitude, rather than a reactive one.

4. Country perspectives on avoiding and/or overcoming challenges

This session aimed to discuss countries' experiences how to avoid issues in the HPV vaccination program, or how to deal with them once they arise.

4.1 Australia

Since the introduction of the HPV vaccination program in 2007, there have been few and minor issues, which may be due to the fact that Australia has a very positive environment for the HPV vaccination program, with political commitment, a rigorous framework for policy-making, programme design and implementation, a solid research basis and sustained impact studies, proactive responses to safety concerns and communication, considerable amounts of advocacy (at parental and community levels) and strongly supportive media messaging, and finally, a dedicated group of motivated and influential people backing the vaccine.

4.2 Belgium (Flanders)

A school-based program for girls began free-of-charge in 2010, however, general practitioners (GPs) and pediatricians can also vaccinate. At nearly 90%, coverage is high in Flanders. A strength of the system is that vaccination data are collected electronically. While there is no active follow-up of circulating rumors on Internet / social media, when signs occur, there is a coordinated action between the Agency for Care and Health, academics, and other stakeholders, leading to uniform, one-voice communication.

4.3 Chile

The HPV vaccine program was introduced in 2014 targeting 9-year-old girls, with catch-up for 10-12-year-old girls, consisting of two doses of quadrivalent vaccine 12 months apart. Passive surveillance for adverse effects exists, but very few have been seen. Anti-vaccine groups are active but damage to the vaccination programme has not been as great as in Colombia, where rushed preparation and extensive media coverage of medical conditions allegedly related to vaccination has led to calls for the cessation of the HPV vaccination program. However, unlike in Japan, there is strong support from the government.

4.4 Denmark

Since the introduction of HPV vaccination in Denmark, a very high coverage was reached, between 80 -90%, which was suddenly halved in 2015. What has come to be known as "the Danish signal" consisted mainly of medically unexplained physical symptoms in girls, observed soon after HPV vaccination. These girls were referred for possible side effects of HPV vaccination to a 'One Entrance' clinic in Denmark. The main symptoms reported in these girls were: orthostatic intolerance, headache, fatigue, nausea, abdominal pain, dysaesthesia, and involuntary muscular contractions. However, there has not been any studies demonstrating

an increased risk of postural orthostatic tachycardial syndrome (POTS)-like symptoms among vaccinated girls compared to unvaccinated girls [11, 12].

A case-control study was performed by the Statens Serum Institute, comparing 361 women who reported serious adverse events following HPV vaccination to the Danish medical authority with 164,000 female controls matched on municipality, age and year of first HPV vaccine dose [13]. Care-seeking data were retrieved from the national health insurance service register for primary care data and the national patient registry for hospital contacts. In the two-year period before the first HPV vaccination, the cases more frequently consulted the GP by phone or e-mail (odds ratio [OR] 1.9; 95% CI 1.2–3.2), had more physiotherapy contacts (OR 2.1; 95% CI 1.6–2.8), and more frequent psychologist and/or psychiatrist appointments (OR 1.9; 95% CI 1.3–2.7). In contrast, contacts with the dentist were similar between cases and controls [13]. Similarly, before vaccination, cases had more frequent hospitalizations for a range of conditions including those related to the digestive (OR 1.6; 95% CI 1.0–2.4) and musculoskeletal systems (OR 1.6; 95% CI 1.1–2.2) and injuries (OR 1.5; 95% CI 1.2–1.9) [13], suggesting that the effect did not occur after the intervention, making it less likely that the symptoms are true adverse events.

A large part of the target population, i.e. the mothers of 12-year-old girls, are hesitant regarding HPV vaccination. They are affected by media coverage of adverse events. Many get all their information from social media, where health authorities are not active. Therefore, an information campaign using short educational movies has now been launched on social media venues such as Facebook and YouTube with additional informational material prepared for use by GPs.

4.5 The Netherlands

In the Netherlands, there is a low perceived risk of HPV infection and cervical cancer. Free HPV vaccination of 12-year-old girls was introduced in 2010 with a 2-dose bivalent vaccine. As with other vaccines, there has been a low uptake in the Bible Belt, a region with a high number of Calvinist Protestants. Several critical TV programs and media comments in 2016 increased ambivalent parental attitudes. This prompted the development of an online HPV information tool, resulting in a more informed choice, and higher vaccination coverage in the experimental group as found in a randomized controlled trial (RCT) conducted by the Institute of Public Health and Environment (RIVM).

4.6 Discussion

The cost-effectiveness of vaccination in boys was discussed to determine the optimal programmatic strategy. A key question of interest was whether vaccination of boys is still useful if 90% vaccination coverage has been reached in girls? Two scenarios were discussed 1) gender-neutral vaccination is introduced from the start, and 2) male vaccination is introduced sequentially only after successful introduction among females. An approach taken in Australia, has been to determine a vaccine price at which point immunization of boys was cost-effective.

Furthermore, cost-effectiveness is not always the sole consideration: gender-neutral vaccination simplifies the program, with fewer issues and potentially decreased hesitancy, and is more resistant to a sudden fall in coverage rates. Hence, gender-neutral vaccination is an insurance policy, that also impacts the price of the vaccine. Moreover, gender-neutral vaccination leads to equity, especially in men who have sex with men (MSM), as these individuals have not directly benefitted from female-only vaccination in Australia. Finally, repeat benefit-risk and cost-effectiveness analyses were advocated, for instance every 3-5 years, as success today does not guarantee success tomorrow.

Can immunization withstand safety concerns in the age of the internet? HCP play a key role in combatting negative perceptions circulating in the community as they are able to positively influence vaccination decisions, hence it is important to keep HCP well-informed about HPV vaccines including their safety profile.

While generally very effective, a downside of school-based programs is that there is no contact between parent and vaccinator, which would provide the possibility to ask questions.

Finally, it was suggested that in case of crisis the guidance to speak with one voice should be amended, as this may backfire. It is essential that there is consistency, so rather one message, than one voice. And this message should be expressed using the right language, for all to understand.

5. Adolescence and health: what else is going on?

This session aimed to discuss the specific challenges of the target age group for this vaccine: (pre-)adolescents. Three topics were addressed: the increased global focus on adolescent health, embedding vaccination as way to prevent deaths; the tension in the relation between HCP and vaccinee/parent on the sensitive topic of HPV vaccination; the country-specific feeble position of adolescents in healthcare in Japan.

5.1 Global adolescence health coming of age

There is increasing focus globally on adolescent health. The Lancet issued a commission on Adolescent Wellbeing and Health, which was reported in 2016 and has now been turned into a standing commission, expected to run for at least 5 years. Furthermore, the Sustainable Development Goals included a topic on adolescents' health covering the time period from 2016-2030.

Benefit-cost ratio (BCR) modeling showed that investment into the physical, mental and sexual health of adolescents has a BCR of 10, where 2 is already considered good. This is comparable to BCR results (BCR of 12) for investments in secondary education for adolescents which have higher returns on investment in low-income countries compared to medium-income countries [14].

The Global Accelerated Action for the Health of Adolescents (AA-HA!) provides guidance to support country implementation of adolescent health, giving advice on what to do and how to do it, using a systematic approach. Documents are available online¹. More than 3,000

¹ http://who.int/maternal_child_adolescent/topics/adolescence/framework-accelerated-action/en/

adolescents die every day, totaling 1.2 million deaths a year, from largely preventable causes [15]. In 2015, more than two-thirds of these deaths occurred in LMIC in Africa and South-East Asia. Road traffic injuries, interpersonal violence, and collective violence (war, mostly in the Middle East; Syria, Iraq) are the most prominent causes of death in 15-19-year-old boys. However, adolescent health is much more than death and illness, it is about risk and protective behaviors, as well as vulnerability and resilience. Evidence-based interventions exist to promote health, such as adolescent-friendly health services, teaching health promotion at schools, and providing comprehensive sexuality education, and vaccines, such as HPV, tetanus, Rubella, Hepatitis B, typhoid, cholera, meningococcal meningitis, and others, where appropriate.

5.2 Is HPV vaccination really about adolescent health?

HPV vaccination has largely been discussed in the context of adolescent health and prevention of infections that may initially occur in teenage and young adults when the related disease process typically occurs in adulthood. In the USA, 11-12-year-olds are currently targeted for HPV vaccination, although there are increasing calls to lower the age at 1st dose to 9-10-year-olds, in order to steer the discussion away from sexual debut among the adolescent population. A further issue is that while there is consensus that the vaccine should be characterized as cancer prevention, the long interval between vaccination and the age when most HPV-related cancers occur means that vaccination at such a young age may seem less urgent to the target population. However, the vaccine prevents infections that occur in adolescence and young adulthood, and can therefore be considered part of broader reproductive health. The focus should not be on how the infection is transmitted, but on how prevalent the infection is, how serious the consequences can be, and how easily these can be prevented – by vaccination. Yet, many HCP are uncomfortable talking about the HPV vaccination and sexuality [16]. And when they do talk about the vaccine, they may tend to delay the immunization from 11-12 years until older ages [17]. In some settings, including the USA, it might be good to give the first dose of HPV vaccine at 9, with the second dose at the age of 12, as part of a broader set of vaccinations consisting of Tdap booster, HPV vaccine and MenACWY, plus influenza vaccine, where appropriate.

5.3 Adolescent health and the HPV vaccine in Japan

After extensive media coverage of girls with alleged AEFI linked to the HPV vaccine, the Japanese government suspended the proactive recommendation to vaccinate, despite the findings of a review committee instituted by the government, concluding that there was no proof for linkage to vaccination.

A retrospective study, involving the victims support group showed that the frequency of many AEFI symptoms were higher among unvaccinated compared to vaccinated girls. Moreover, the symptoms reported were those seen frequently in teenager girls and could be related to hormonal changes occurring during the menstrual cycle.

Data from the Japanese national livelihood study showed that fewer symptoms occurred in younger age (10-14 compared to 15-19-year-olds), but the number of symptoms were not

higher in vaccinated compared to unvaccinated in the same age group, both in age groups 10-14 and 15-19. However, although this data supported HPV vaccine safety, it did not noticeably improve public confidence in the vaccine, suggesting that in Japan scientific evidence has limited impact on this issue, it is an emotional issue, even among politicians.

For Japanese adolescents, access to health care is not easy. Indeed, adolescents can no longer visit the pediatrician, there are few outpatient clinics specialized in adolescent health, and there is no GP system. There is an additional hurdle to adolescent healthcare in that there is a stigma associated with attending a gynecologist, especially for young, unmarried women. A further complicating factor is that cervical cancer screening uptake is around 30% in Japan, suggesting that unvaccinated women have a higher risk of having cervical cancer detected at a very late stage, when symptoms start occurring, which impacts the success of therapy. Although new cervical cancer educational material was recently developed for school children, this only mentions biennial screening, and does not mention HPV or HPV vaccination,

5.4 Discussion

HPV vaccination programs may be improved by vaccinating populations younger than age 9 years (assuming licensure can be achieved for younger children) and shaping communication to emphasize the prevention of HPV-related cancers that may occur later in life.

In the UK, a country with an established cervical cancer screening program, the peak incidence of premalignant cervical lesions occurs in the 25-30-year-old age group. Focus, and communication with HCP could, therefore, be on prevention of both morbidity and mortality of women in their reproductive years. Although full blown cervical cancer develops at a later age, conizations, performed to treat premalignant lesions, can lead to premature delivery among pregnant women, which could negatively impact future pregnancies.

In Japan, attitudinal research related to HPV vaccination among parents may be beneficial. This could provide a better understanding of the change in parental attitudes since the beginning of the vaccination program. Anti-HPV vaccine messaging from Japanese mainstream media tends to be pervasive and highly emotional rather than evidence-based. The use of the term HPV vaccination-associated neuroimmunopathic syndrome (HANS) is limited to a fraction of the medical community in Japan. This umbrella diagnosis is extremely broad and inclusive of psychosomatic conditions. Nevertheless, some members of the medical community utilize this diagnosis and, by doing so, provide credibility to a link with HPV vaccination even in the absence of data-driven evidence.

Immunization coverage rates in Japan in the non-pediatric population are less than optimal and would benefit from heightened political support. Further, increased focus on women's health issues in Japan may help improve HPV vaccination efforts in this country.

6. Round table discussions

This session aimed to discuss several themes in smaller groups, to increase interaction. Each group reported on the outcomes of the discussion, which is summarized below.

6.1 Ways to better support/prepare HCP when new vaccines are introduced

To provide knowledge on vaccines and vaccination, training of HCP would ideally start in the curriculum of medical and nursing schools, and include training in interpersonal communication skills, to facilitate discussion with vaccinees and/or parents.

For established practitioners, at the time when a new vaccine such as HPV is introduced, HCP should understand that consistent messaging is essential; messages provided by vaccinators must be in line with other health personnel, to avoid creating confusion. This is of particular importance in the case of clinic-based vaccination. There is a need for high quality, accessible training materials for HCP. The preparation of a FAQ (frequently asked questions) list, especially for new vaccines, in clear and simple language, would be helpful for clinicians and in more general content for the public. Educational material would be best received if tailored to country and culture.

6.2 Ways to better support/prepare HCP at the moment of a vaccine crisis

At time of a vaccine safety crisis, a position paper, prepared by the MOH, would be helpful to guide responses by HCP, as it will help to provide a common and factual framework. The vaccine program team should review the data, level of crisis and potential impact and decide the appropriate response. Clear and consistent responses should be honest and acknowledge/address knowledge gaps and identify how such gaps will be addressed and communicated.

Fact-based communication should be delivered in a confident manner and where possible, should engage other credible sources to help and supplement efforts, as well as mobilize formal and informal networks. Community health workers should be involved as they are often the first line of contact with the vaccinees and parents.

6.3 How should national/international institutions address vaccine safety issues and AEFIs

In HIC as well as in LMIC, picking up AEFIs must be counterbalanced by proper interpretation of these events, to frame risks. Data can easily be misinterpreted, which is a concrete challenge. This asks for integrating monitoring with communication.

Training is important for all involved in vaccination. Some of the HCP can be part of the problem, if they side with the anti-vaccine lobby.

Facilitate experts to talk to one another, within countries as well as between countries, this can be done by the World Health Organization (WHO), or by NITAGs at the national level.

More transparency is needed on the data that are being used for investigations, use of appropriate background rates to investigate causality.

Journalists can be very powerful, especially in narrative, therefore good journalists should be involved in communication.

It is essential to provide support to victims/individuals who experienced adverse events. Negative experiences of patients visiting HCPs are very hard to counteract, so should be prevented.

6.4 What can we learn from countries with sudden decrease of coverage of HPV vaccine following a crisis in confidence

Prevention and preparation are the most important approaches for handling potential crises in vaccine confidence.

The problem is multifactorial and interactive. It is important to provide information and interact with the community, HCP and politicians through public discourse. Identify concerns early, by keeping a finger on the pulse of (social) media. Early and timely response is critical for providing individuals with credible sources of information and to avoid individuals seeking information and support elsewhere. It is important to identify the main source of information, but to also work in a network, involve all stakeholders, including early advocacy experts, and to look across borders for support when needed. The messages should show the importance of vaccination, framing the message positively (“x cases were prevented by vaccination”) rather than negatively (“y women will die of cancer, if not vaccinated”).

As HCP remain the primary source of information, they should be well informed/prepared, this cannot wait until a crisis occurs, but should be part of the medical training curriculum.

When trying to inform the public, it may be important to keep in mind that information will be received and interpreted by both interested community members/those who may be making genuine choices regarding vaccination and/or vaccination programs and those who are vehemently opposed to vaccines and may use the information provided in ways that further support their own cause/opinions.

6.5 What is the role of Industry once their vaccine is registered

Industry’s most important post-licensure role relates to informing about the technical aspect of their vaccine, in terms of safety and immunogenicity. Vaccine manufacturers are required to gather safety-related data, and communicate findings to (inter)national authorities, as such they also play a role in pharmaco-vigilance. However, public confidence in industry-generated data is weak. The way to deal with this is through a highly-regulated framework and complete transparency, which leaves no room for fraud.

When a governmental oversight agency identifies a potential safety signal, it can request additional data from the manufacturer which often has access to international post-licensure data and experience with safety monitoring. Furthermore, pharmaceutical companies can share internal data that may be useful for investigating potential safety signals such as providing public access to clinical trial data.

Pharmaceutical companies can support sustainability by providing funds for vaccine-related training and education, but typically not through direct support due to potential conflict of interest.

7. Risk communication

This session aimed to further discuss communication between HCP and vaccinee/parent on the topic of HPV vaccination, with a special focus on how to approach recommendation of the vaccine..

Fixing a crisis in cancer prevention

The current hypothesis is that risk is scary and that knowledge of a given risk will change behavior. In reality, this is not true. The US Food and Drug Administration released a book on communicating risks and benefits: an evidence based user guide². Risk beliefs are hard to change, and when trying to change behavior, risk communication is not the way; what people think is not what people do.

Patient-provider communication is key to a successful HPV vaccination program and optimal coverage rates as the HCP is a trusted source of information. Improvements can be made to the manner in which, and perceived importance of, HCP speak to girls and boys, and their parents, about HPV vaccination. HCP often think that a conversation about the HPV vaccine will be uncomfortable, that the parents don't want the vaccine for their child, and that the discussion will take a long time. Hence, HPV vaccination is discussed last in the consultation, or not at all. But low-quality communication is harming vaccination.

In addition to HCP communication, a key factor in HPV vaccine uptake is the strength of the recommendation: without a recommendation only 23% will be vaccinated, with a low-quality recommendation coverage increases to 53%, and with a high-quality recommendation by the HCP a coverage of 73% can be reached [18].

From a questionnaire study, it became apparent that the style of recommendation is very important: while an announcement is very effective (>80% uptake) it is hardly ever used (1.5% of visits) [19]. This led to the development of a RCT comparing announcement training with conversation training among HCP. In the announcement approach, the announcement is made that three vaccines will be provided at the end of the consultation, putting the HPV vaccine in the middle. If necessary, the main concerns about the vaccine are eased, followed by a strong recommendation. If the vaccinee and/or parents are undecided, they are asked to come back in two months. In the conversation training – the session is started with a conversation about the vaccines, the main concerns about the vaccine are eased, followed by a strong recommendation. If the vaccinee and/or parents are undecided, they are asked to come back in two months. The announcement training showed a significantly greater improvement of HPV vaccine uptake, both in girls and boys [20]. Furthermore, the HCP were very happy with the approach, as it was felt that it was both easier for parents and for HCP.

Although vaccine education and communication training material may be available for HCP limitations in implementation/utilization remain and research gaps still exist. The USA National HPV vaccination round table defined research gaps in three areas: social media (increase confidence in vaccination; address parental concerns; address rumors); provider (increase provider engagement; intervene with entire medical team; increase vaccination at acute visits); and the health system (best practices for health plans; impact of quality standards; effective system level changes; impact of IIS/EHR [vaccination registry/electronic healthcare record] connectivity).

² <https://www.fda.gov/downloads/AboutFDA/ReportsManualForms/Reports/UCM268069.pdf>

8. Public health surveillance, monitoring of the media and social media listening

This session aimed to discuss how to track decreases in vaccine confidence at the earliest opportunity possible. Traditional public health surveillance (such as conducted by the European Center for Disease Control (ECDC)) can be supplemented with early indicators of vaccine crises in confidence such as monitoring of the media and social media listening. Finally, web analytics, combining multiple data sources, may be impact vaccine coverage.

8.1 Outbreak monitoring experience at ECDC to monitor potential vaccine safety crisis

One of the core functions of ECDC is epidemic intelligence i.e. the continuous monitoring of known or emerging public health threats from communicable disease (referred to as event-based surveillance), it aims for rapid detection of events, including new events, from informal sources, web aggregators and social media. Examples from the past include Middle East Respiratory Syndrome Coronavirus, Ebola and Zikavirus, where initial media discussion allowed to identify events before they become recognised public health threats.

Among the various tools used (both confidential secured tools and public tools), Medisys as a search tool has a few strong points: it is real-time, being refreshed every 10 minutes; it covers 80 languages; it simplifies analysis by making it possible to categorize, filter, geolocate and perform statistics. This tool was used for a pilot study for HPV media/threat monitoring in a limited number of languages, using the search terms 'HPV vaccine' AND 'any term related to safety'. In April 2017, 793 hits were found. Manual assessment of 40 of them showed that most were supportive, most negative media was seen in the UK, and there was little spill-over to other countries.

Media screening is labour and time intensive. Therefore, there is a need to define the most sensitive key words and study trends over a longer period of time. Secondly, the role of traditional media versus social media as a rapid "crisis" monitoring tool for vaccination still needs further investigation. Traditional media seem to be delayed in time compared to discussions in social media, in which anybody is a "reporter" whereas in traditional media, journalists are accredited, trained people.

8.2 Real-time global media monitoring – the case of HPV vaccines

The driving hypothesis for a study by the European Medicines Agency (EMA) was: does medicinal product-specific media monitoring have the potential to enhance communication in terms of being proactive and prepared to provide information to the public by a regulatory body? In July 2015, the EMA reported on the lack of proof for an association of complex regional pain syndrome (CRPS) and POTS with HPV vaccination. Vuelio was used for online media monitoring, over a period of four months, resulting in over 4000 items, including personal stories, as well as scientific and regulatory topics [21]. Explicit and implicit questions were identified, which were formulated into 50 derived questions and categorized into 12 themes. Examples of derived questions are: what is the likely magnitude of underreporting,

Plotting the number of published articles by the number of readers helps to distinguish fringe outlets from mainstream outlets; only react if there are a lot of potential readers e.g. msn.com. Intervening directly on social media is risky, it may be better to listen rather than talk, as it is unclear whether your response will increase or decrease the number of believers in the rumor.

8.4 Social media listening

Facebook and Twitter are frequently used by companies as sources for tracking of conversations on brands or topics. The same can be done for conversations about vaccines. Using this approach, the main influencers can be mapped, which can be used at a later stage to back campaigns or fight crises in vaccine confidence. Coincidentally, this underpinned the role of mainstream media, as providers of 50% of messages.

Even a simple search on Google will provide you with some insight into current sentiments, as Google will fill in public search terms. Filling in 'vaccines are' or 'do vaccines' shows that at least 50% of suggestions provided by Google have a negative sentiment (vaccines are bad/evil/poison, do vaccines cause cancer/autism).

Some suggestions on how to approach social listening are:

- Be clear on what the research objectives are
- Outline the key research questions that should be answered
- Set parameters (time period, languages, countries/markets, keywords)
- Work with experts, depending on needs and budget (free tools for research are available)
- Move quickly to insights as the amount of data can be overwhelming

8.5 Vaccine Safety Network web analytics project

As a crucial instrument for digital marketing, web analytics is mainly used by companies. However, using pooled web analytics, combining population data, vaccine coverage data, and infectious disease incidence, the Vaccine Safety Network, a global network of websites, evaluated by the WHO, providing reliable information on vaccine safety, intends to:

- Improve global vaccine coverage
- Ensure consistency in content and communication strategy
- Tailor information to the public

To perform pooled web analytics, a multidisciplinary team has been created, including epidemiologists, data scientists, physicians, journalists and IT experts.

9. The role of the media

This session aimed to discuss the role of the media in vaccine confidence, by providing a number of journalists the opportunity to share their angle on the news regarding HPV vaccination.

9.1 Experience with the HPV vaccine at Le Monde

Since 2002, 33 news items have been published on the HPV vaccine in the French newspaper, Le Monde. This started with the hope for a therapeutic vaccine against cervical cancer. Articles focused on the promise of a preventive vaccine; highlighted the choice to vaccinate or not, and/or to participate in screening or not; described the demands for compensation for damages; outlined the controversies around the vaccine; discussed the reassuring data on impact and effectiveness; joined the debate on vaccines in general; featured an interview with an expert; described the reassuring message from the EMA on the lack of association of the vaccines with CRPS and POTS; featured the complaint of Danish physicians against the EMA, concerning bias in their report; and finally, described the call for use of the vaccine for young MSM.

This media coverage should be seen in the light of the current background: the French population has the lowest confidence level in vaccines in Europe. Moreover, 10% of GPs don't trust vaccines, due to recent history, including the hepatitis B vaccine story, and the more recent pandemic flu campaign in 2009. The role of the media is to do their own research, and sometimes to dig up dirt. In doing this, the media are not limited to science, they need to keep in mind the public perception, emotion, and beliefs, and the fact that public wants to be listened to. As such, the media are not the PR machine, or communication tool, of the MOH or of public health in general, as they are expected by the users to provide independent and unbiased information and opinions.

9.2 Media's public health value: exploring where news meets public health

Both media and public health serve the public good. Both are accountable to their constituents. When setting up a health communication campaign three questions need to be asked: will it raise awareness; will it change opinion; will it change the way people behave. The answer to the last question may well be 'no'. For a message to reach the audience, context is critical, as it influences policy directions, and language is critical, as it influences reasoning.

9.3 What role can media play: HPV introduction in Pakistan

Pakistan faces major coverage and equity challenges, with geographic, wealth, gender, education, literacy and other disparities. Vaccination coverage in Pakistan is around 50%, with gender variations. The media in Pakistan are relatively independent, enjoy substantial freedom of expression, however, this does not seem to go hand in hand with a sense of responsibility.

The teenage girls and their parents will have to be convinced of three things by public health authorities: the vaccine is needed to prevent a serious (and frequent) disease; the vaccine

works; and the vaccine is safe. Towards this end, it may be helpful to give a human face to cervical cancer patients, with help of the media.

9.4 Managing misinformation and covering crisis in real-time

The goal of the media is to get out the facts, to raise awareness, to highlight gaps in knowledge, to tell a good story, and to humanize the problem(s), with the ultimate goal to have as large of an audience as possible. At the time of an outbreak, such as those of Ebola and Zika, people will start looking for information. In order to prevent them from getting misinformation, this information should ideally come from the health department, researchers, physicians, or an advocacy group. However, people will also get information elsewhere, so acknowledge what you don't know, rather than getting caught saying nonsense. To limit the spread of misinformation, be vigilant on social media to see what happens out there. If anything arises, contact media or hold press conferences to provide accurate information, to be shared on multiple platforms, trying to reach vulnerable audiences with misinformation. For optimal interaction with the media, provide journalists with fresh angles, such researcher - or patient profiles, cutting-edge research, new data on disease incidence or vaccine impact.

9.5 Discussion

In France, during the pandemic flu vaccination campaign, there were discussions among scientists, which confused the public. The main message should come from people close to the public: most notably HCP. Similarly, a story in the WHO bulletin, on an event in India, turned out to be wrong (i.e. non-event), but created confusion, also in the media. Journalists and scientists need to build trust with each other, trust will grow with more frequent interaction. Furthermore, it is essential to minimize the information gap, the media need to have full picture, so they need to be brought on board from the very beginning. It helps for vaccine program professionals to build a network of journalists knowledgeable about the issues and science, and to provide them with updates and context for vaccine stories so that they will, in return, call you in a time of crisis.

After years of struggle to get the HPV vaccine coverage up to 80-90%, the program can be destroyed "overnight", by the power of a video image, which is much more powerful than the written word, either from journalists or scientists. How can the media be made to understand the damage a single video can do? It is not the media who upload the video, anyone can upload nowadays, however, the media will react to newsworthy items online. Everyone has the right to express his/her views and perceptions. Once that occurs, all scientists can do is provide evidence-based information and expertise, being clear and factual, acknowledging knowledge gaps.

Similarly, there seems to be a preference for bad news and not for good news. A recent study on the efficiency and impact of HPV vaccination after 10 years of use, did not get any media attention. However, it is necessary for public health professionals to highlight vaccination

success stories to the media and the public. Press releases can be a positive way to get public attention to the benefits of vaccination programs and impact on disease prevention. As an example of how it should be done: when in the UK a girl died soon after vaccination, the media picked it up. At least ten experts came out and spoke about the safety of the vaccine. Shortly afterwards it was shown the girl had died of cancer.

Finally, the changing economic model of media may impact the way the media cover stories. On the other hand, as an example of a newspaper, Le Monde has a very successful website, including a team called decoders, to debunk false information: what is hoax, what is fact?

10. Engaging and communicating with different audiences

This session aimed to discuss the different attitudes that exist towards vaccination, both between and within countries. Different attitudes ask for different approaches to communicate with, and involve these groups.

10.1 Engaging and communicating with different audiences, the view from UNICEF

Within a population, not everyone will react in the same way. Five categories can be discerned, they can be reached in different ways:

- *Innovators* and *Early Adopters*, these groups need minimal communication
- *Early Majority* and *Late Majority*, these groups need more information to be convinced to participate
- *Late Acceptors*, this group can only be reached by completely different interventions

Pockets of unvaccinated people will be found in any country, especially in marginalized populations. To reach these populations you need to know the specific dynamics of this group, design context-driven approaches and avail trusted channels of communication. As interpersonal communication is the most effective communication channel, there are several important parties in a community: the village elder, the faith leader, the health worker and the teacher. When communicating, keep in mind that a good message provides information in a simple, clear way; presents information as a call to action; sticks to facts; promotes hope; and provides contact points for further information. Communication activities often start much too late and mainly rely on printed or traditional media. The role of social media is getting stronger: 71% of internet users use internet for health purposes, and 52% of users believe most information on health websites is credible; therefore, those that endorse the use of vaccines should be online too, to balance the anti-vaccine messages. Finally, communication needs sustained investments.

10.2 Engaging and communicating with different audiences, the view from WHO/Europe

The World Health Organization European region encompasses 53 countries³, and hence, is a very diverse region. Target group research explored knowledge, barriers and enablers in three groups: parents, vaccinees, and HCP. This study showed that parents are more fearful about all vaccines than expected, and distrust the motives of HCP, vaccinees are aware of the rumors around HPV vaccination, mainly through Facebook and friends, and HCP are influenced by the same rumors, and are hesitant to recommend the vaccine, especially if they are asked to guarantee that there will be no side effects.

Countries that intend to introduce the HPV vaccine can learn from current users. To this end, a field guide for introduction has been developed⁴. Furthermore, for crisis management, a best practice guidance⁵ has been developed on how to respond to vocal vaccine deniers in public.

10.3 Discussion

Communication to increase vaccine confidence is a long-term strategy, it may therefore be useful to start early and target 10-12-year-olds at school to teach them about vaccines and immunology. This may involve a very basic level game approach, focusing on how the immune system works.

The HPV vaccine has a long-term impact on cancer, but many countries with the highest burden of HPV associated cancers need help with treatment now. Nevertheless, using the vaccine will reduce the risk of future cancer, therefore, treatment and vaccination should go hand in hand.

Every community is unique, but general principles in how people interact apply. In one country different groups will exist, when communicating on (HPV) vaccination prioritize between groups and target segments in different ways.

³ <http://www.euro.who.int/en/countries>

⁴ http://www.who.int/immunization/documents/ISBN_9789241549769/en/

⁵ http://www.euro.who.int/_data/assets/pdf_file/0005/315761/Best-practice-guidance-respond-vocal-vaccine-deniers-public.pdf

11. Concluding guidelines

Based on the discussion during this meeting, and reflecting on previous meetings, several guidelines are provided, grouped in several themes, useful at different steps of the process from vaccine introduction to handling a vaccine confidence crisis, and beyond.

11.1 Before HPV vaccine introduction

- Engage the political groups and local/national government to seek advice and guidance about vaccination programs
- Devise ways to support medico-scientific staff advising politicians in LMICs on vaccine decisions
- Tailor actions to local and national circumstances
- Learn from other countries' experiences (both HICs and LMICs)
- Bring in communication specialists as early as possible
- Vaccine teams should include a journalist and role of media officers should be more broadly recognized; with journalists: links need to be established and nurtured, trust needs to be earned (takes time). Journalists should not rely on one single source of information, and should not be seen simply as PR agents for public health. Experts need to understand journalists' requirements (e.g. a new angle)
- Develop a check-list for countries' safety plan
- Policy formulation by countries considering introduction of HPV should examine vaccination of pre-adolescents
- Policy formulation by countries considering introduction of HPV should examine gender-neutral vaccination

11.2 During the vaccination program

- Review vaccination and catch-up campaigns to identify program fatigue and need for renewal of impetus
- Provide good evidence on vaccine and safety and creation of strategies and action plans, including emphasis on benefits on HPV and indeed vaccination in general, proactive advocacy and approaches to countering vaccine deniers' messages

11.3 To avoid a crisis in confidence

- Interpret and communicate data on AEFI well
- Monitor and identify the content and nature of rumors and signals, and the concerns of those involved, decide on how and who to respond, select appropriate channels of communication, and act rapidly; establish formal and informal networks
- Tailor actions to local and national circumstances
- Improve collaboration between WHO, ECDC and other national and international agencies on policies, standards, tools and guidance
- Continue work on monitoring, analysis and formulating responses about vaccine hesitancy, confidence and removing uncertainties by EMA, ECDC and the Vaccine Safety Network (VSN)

- Further develop the VSN, expanding its coverage, promoting it as a source of reliable information, ensuring consistency and tailoring output.

11.4 During a crisis in confidence

- Deliver a prompt and strong statement backing the vaccine, preferably by the MOH
- Establish a central contact point, an expert group that takes the lead and communicates at country level

11.5 General

- Move from a discussion of tactics to consideration of health systems
- Expand work on implementation science, including development and application of costing tools
- Ensure that education system prepares young people for decisions about vaccination and the value of vaccination
- Expand work on devising new ways of proactively conveying information about vaccine safety as well as health economic data comparing prevention of HPV infection with death from cervical cancer
- Devise actions and strategies to address the power of videos and visual images (including television) that convey wrong or distorted information

11.6 Take home messages

- Communication can't fix a problem you don't understand
- Combine interventions; there is no one thing that fixes problems
- Never assume what is in the mind of the public, never assume that it is not going to change
- It is important to distinguish health events in the adolescent population, that may or may not be related to vaccination. This age group in general has a relatively high number of events.
- Education of HCP should happen early, as they communicate the message later
- Cervical cancer is not an 'old woman disease'
- Learn to listen, to social media, to what people want to know
- Take each opportunity to interact and interview with the media to highlight key facts on vaccine safety and benefits

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