



UNIVERSITÀ
DEGLI STUDI
FIRENZE

FLORE

Repository istituzionale dell'Università degli Studi di Firenze

Safety and perception: What are the greatest enemies of HPV vaccination programmes?

Questa è la Versione finale referata (Post print/Accepted manuscript) della seguente pubblicazione:

Original Citation:

Safety and perception: What are the greatest enemies of HPV vaccination programmes? / Bonanni, Paolo; Zanella, Beatrice; Santomauro, Francesca; Lorini, Chiara; Bechini, Angela; Boccalini, Sara. - In: VACCINE. - ISSN 1873-2518. - ELETTRONICO. - (2018), pp. 0-0. [10.1016/j.vaccine.2017.05.071]

Availability:

The webpage <https://hdl.handle.net/2158/1091003> of the repository was last updated on 2021-04-12T10:23:58Z

Published version:

DOI: 10.1016/j.vaccine.2017.05.071

Terms of use:

Open Access

La pubblicazione è resa disponibile sotto le norme e i termini della licenza di deposito, secondo quanto stabilito dalla Policy per l'accesso aperto dell'Università degli Studi di Firenze (<https://www.sba.unifi.it/upload/policy-oa-2016-1.pdf>)

Publisher copyright claim:

La data sopra indicata si riferisce all'ultimo aggiornamento della scheda del Repository FloRe - The above-mentioned date refers to the last update of the record in the Institutional Repository FloRe

(Article begins on next page)

Title page

Title: Safety and perception: what are the greatest enemies of HPV vaccination programmes?

Authors: Paolo Bonanni¹, Beatrice Zanella¹, Francesca Santomauro¹, Chiara Lorini¹, Angela Bechini¹, Sara Boccalini¹

Affiliation: ¹Department of Health Sciences, University of Florence, Viale Morgagni 48, 50134 Florence, Italy

Email addresses:

Paolo Bonanni: paolo.bonanni@unifi.it

Beatrice Zanella: beatrice.zanella@unifi.it

Francesca Santomauro: francesca.santomauro@unifi.it

Chiara Lorini: chiara.lorini@unifi.it

Angela Bechini: angela.bechini@unifi.it

Sara Boccalini: sara.boccalini@unifi.it

Corresponding author: Sara Boccalini, Department of Health Sciences, University of Florence, Viale Morgagni 48, 50134 Florence, Italy. Email address: sara.boccalini@unifi.it

Safety and perception: what are the greatest enemies of HPV vaccination programmes?

Abstract

Vaccines stimulate a person's immune system to produce an adequate reaction against a specific infectious agent; i.e. the person is protected from that disease without having to get it first. As vaccines are administered to healthy subjects, they are held to the highest standards of safety. Regarding human papillomavirus (HPV) vaccines, at present three prophylactic vaccines are licensed (bivalent HPV 16/18, quadrivalent HPV 6/11/16/18 and the nonavalent HPV 6/11/16/18/31/33/45/52/58 vaccine). Pre- and post-licensure studies (i.e. not yet for nonavalent HPV vaccine) confirm that HPV vaccines are generally safe and well-tolerated, site injections symptoms are the most common adverse events (AEs) reported, and pain is the most frequently referred local symptom. Serious AEs are rare and not associated with severe sequelae, at least no vaccine-related deaths have occurred. Despite these scientific evidences, it is still difficult to explain to the population the importance of a good vaccination programme. There are many determinants for HPV vaccines hesitancy which represent a barrier that must be overcome in order to increase vaccine coverage, including psychological reactions, religious or cultural aspects, and fear of possible AEs (demyelinating diseases, Complex Regional Pain Syndrome - CRPS, or Postural Orthostatic Tachycardia Syndrome - POTS). A weak communication strategy which frequently suffers due to spread of unverified news by media and websites may lead to the failure of a vaccination programme. Such a situation happened in Japan (2013), due to which a great number of women remain vulnerable to HPV-related cancers. In order to resolve the issues around HPV vaccines acceptance, it is necessary to use good communication strategies. Multicomponent and dialogue-based interventions seem to be the most effective, especially if an adequate language is used, customized according to the vaccination programme target.

Introduction

Vaccines stimulate a person's immune system to produce an adequate reaction against a specific infectious agent, protecting the person from the disease without having to get it first [1]. Unlike most medicinal products that treat or cure diseases, vaccines prevent them [2]. Vaccines act at both individual and population levels (herd immunity) and can modify the immune status and the epidemiology of an infectious disease (ID) also reducing the circulation of an infectious agent.

As the aim of vaccines is preventive and not therapeutic, they are administered to a large number of healthy subjects (usually children or adolescents); thus, even the smallest adverse event (AE) is perceived as not tolerable. For this reason, vaccines are held to the highest standards of safety. The potential for any risk is considered less acceptable in the case of vaccines than in that of disease treatment. It will be an increasing challenge to spread the benefits of vaccination in the apparent absence of the disease but with the possible presence - even if mild - of adverse events following immunization (AEFIs) [3].

Safety - a major issue for any vaccine - is assessed at every step of vaccine development (preclinical and clinical studies) and after licensure; as a matter of fact, health authorities require an on-going commitment for post-licensure analysis of safety [4]. The Global Advisory Committee on Vaccine Safety (GACVS) - an independent scientific advisory board - provides the World Health Organization (WHO) with strict advice on vaccine safety issues of global importance [5].

Broad community confidence in the vaccines' safety is critical for generating maximum public health benefit. One reason for this is herd immunity effect, which is achieved when the vaccine coverage in the population is sufficient to prevent the circulation of the infectious agent among those who remain susceptible. This is only possible if the public has confidence in the safety of a vaccine. The study of AEs of vaccine is not only an effort to provide individuals with a basis for deciding whether to vaccinate, but also an effort to improve the safety and effectiveness of vaccines and to increase confidence in societal decisions, which weigh the costs and benefits to the society [6].

The aim of this paper is giving an overview about the main determinants, which influence in a negative way, an immunisation programme, focusing especially on HPV vaccination, trying also to provide some advices in communication strategies for overcoming this issue.

Vaccine Surveillance

Vaccine safety is continuously monitored to identify and evaluate potentially occurring rare and/or serious AEs that are temporally linked to vaccination (sudden deaths, immune-mediated disorders, narcolepsy). The Vaccine Adverse Event Surveillance and Communication (VAESCO) is an European research network, funded by European Centre for Disease Prevention and Control (ECDC), which collects data on AEFI in Europe and compare them in order to provide high quality vaccine information [7]. The Vaccine Adverse Reporting System (VAERS) – sponsored by Centers for Disease Control and Prevention (CDC) and the Food and Drug Administration (FDA) - and New Vaccine Surveillance Network Extended System (NVSN-ES) cooperate with the aim of gathering information about AEs, that may occur after the administration of vaccine licensed for use (VAERS,) and to better evaluate the impact of new vaccines or new vaccine's policies (NVSN-ES) in the US area [8]. When needed, studies are planned to assess safety signals and distinguish between possible causes and likely coincidence [9, 10, 11].

The passive vaccine surveillance is carried out with the voluntary reporting of AEs from healthcare providers, vaccine-takers, and others (parents, relatives, friends, etc.) [12] and can be designed to recognize new or rare AEs and changes in rates of previously reported AEs [12, 13]. Nevertheless, the variability of reporting, reporter bias, and potential underreporting are limitations that hinder the defining of a causality relationship [12, 14]. Instead, active vaccine surveillance is a systematic procedure for identifying clinically significant events that occur within a defined period and/or population; this can assess whether a specific AE is significantly associated with the immunization [15, 16].

Vaccines are also associated with the theoretical risk of adverse immunological responses that may lead to immune-mediated disorders: this could be due to homology between vaccine antigen and a human protein, or non-specific immune enhancement properties of the vaccine adjuvant [4, 17, 18]. Surveillance is an essential tool to generate signals and hypotheses but cannot be used to prove them. A well-designed and controlled study allows researchers to test hypotheses and to assess whether there is evidence and what is the size of the effect. The main methods used in this evaluation - case-control studies, cohort studies, and case-only methods - require the implementation of statistical calculation to support quantitative signal detection through Proportional Reporting Ratio (PRR [*]), 95% PRR Confidential Interval, and χ^2 test.

$$PRR = \frac{\text{incidence of an AE after receiving a given drug}}{\text{incidence of the same AE in the whole surveillance database}} \quad [*]$$

The PRR measures a reporting relationship between a medicinal product (e.g. vaccines) and an AE, based on the relative increase in proportion of individual cases related to an AE [19]. In essence, PRR is the proportion of all cases related to an AE reported after the administration of a vaccine, on the total number of cases of the same AE reported for all vaccines. If the expected value is one, AE is reported after the vaccine at the same probability as after all vaccines. If the value is greater than one, the AE is reported with more likelihood after that vaccine compared to what is reported after the totality of the vaccines [20].

Vaccine Hesitancy: main determinant categories

According to WHO and the Strategic Advisory Working Group (SAGE WG), *Vaccine Hesitancy* is “the delay in acceptance or refusal of vaccines despite availability of vaccination services” [21]. It is a complex issue that is context-specific, varies across times, places, and vaccines, and includes complacency, convenience, and confidence as the main determinant factors [21]. Among the global

population, during the last few years, it is raised a significant sense of criticism and alarmism to vaccines: immunization programmes have successfully reduced the incidence of vaccine-preventable diseases, leading to an increasing proportion of healthcare providers and parents with little or no personal experience about vaccine-preventable diseases. For their risk-benefit analysis, they have to rely on the historical descriptions of such vaccine-preventable diseases. The public is no longer used to seeing these diseases and may think that vaccines are no longer needed. Moreover, the AEs of vaccines become more evident due to the absence of the disease the vaccine is supposed to prevent [17]. Therefore, on one side there is the perception that an ID may not be harmful. On the other side, there is the perception that a vaccine could be dangerous for any possible AE. People are also aware that vaccines are usually accompanied by some degree of personal distress and pain, and the apprehension is generally associated with each immunization. In addition, parents searching for information about vaccines on the Internet are likely to encounter websites that encourage vaccine refusal or emphasize the risks of vaccines. Likewise, the media may sensationalize vaccine safety issues or - in an effort to present “both sides” of this topic - fail to provide perspective. The combination of these factors may have an influence on parental beliefs about immunization [17]. A national telephone survey in United States found that, although the majority of parents support immunizations, 20–25% have misconceptions that may gradually erode their confidence in vaccines [23].

HPV vaccines

Currently, three prophylactic HPV vaccines are licensed: the bivalent HPV16/18 virus-like particle (VLP) vaccine, the quadrivalent HPV 6/11/16/18 VLP vaccine, and the latest nonavalent HPV 6/11/16/18/31/33/45/52/58 VLP vaccine, which offers a broader coverage than the bivalent and quadrivalent vaccines [24]. The nonavalent HPV vaccine should provide protection against HPV types representing ~90% of cervical cancer cases and ~90% of genital wart cases, using the average of HPV-type prevalence [25]. They are highly immunogenic and protect mostly against the HPV

types included in the vaccines, with little cross-protection against non-vaccine HPV types [26, 27, 28, 29, 30]. All the vaccines are administrated in males and females from the age of nine years; boys and girls aged 9–14 (bivalent and nonavalent vaccines) or 9–13 (quadrivalent vaccine) should follow a two-dose schedule, while for people aged more than 14 years, the vaccine is generally given according to a three-dose regimen [31, 32, 33].

Though the new nonavalent HPV vaccine has five additional antigen types and a double quantitative of adjuvant (500 µg of amorphous aluminum hydroxyphosphate sulfate) compared to the quadrivalent vaccine [34], a combined analysis of seven phase-III clinical trials on nonavalent HPV vaccine confirms a similarity between the safety profile of nonavalent HPV vaccine and that of quadrivalent HPV vaccine [35]. Pre- and post- licensure studies (not yet for nonavalent HPV vaccine) confirm that all the HPV vaccines are generally safe and well-tolerated, site injections symptoms are the most common AEs reported, and pain is the most frequently referred local symptom. Serious AEs are rare and not associated with severe sequelae, at least no vaccine-related deaths have occurred [31, 32, 33, 36]. Despite these reassuring findings on vaccine safety, anxiety among parents and girls regarding serious AE and unknown side-effects is still a barrier to the acceptance of vaccination, which may lead to the failure of a vaccine programme [37].

Main “enemies” of HPV vaccination programmes

Despite scientific evidence, it is still difficult to explain to the population the importance of a strong vaccination programme: many determinants for HPV vaccines hesitancy represent a barrier that must be overcome in order to increase vaccine coverage. Public concerns and rumors about AEs, low confidence in safety findings by health authorities, cultural, religious, or social aspects, and wrong information collected from websites are some of the main factors that may cause an insufficient involvement in an HPV vaccination programme. These factors can be considered part of the three macro categories described in the model of determinants of vaccine hesitancy proposed by

SAGE WG: contextual influences, vaccine or vaccination specific issues and individual or group influences [38, 39].

Evidence suggests that some events are often psychological reactions that can spread quickly, especially among the young community, such as schools, where girls are vaccinated in groups and may observe the reactions of one another. Further, there are short video clips on *YouTube* in which - people describe their sense of anxiety towards the vaccination [40].

HPV vaccine programmes may also clash with some religious or cultural aspects of the society. In fact, as the aim of the vaccines is to prevent sexual transmission of HPV, this could evoke moral judgment in regard to sexual behavior [40], especially for those ethnic groups in which sexuality is still considered a taboo and girls and young women do not receive adequate sexual education. In light of this, some healthcare providers prefer to focus on promoting HPV vaccine as a means to prevent cancer rather than a sexual transmitted infection (STI), making it more acceptable [41, 42]. Further, parents are worried about the possibility that their young daughters may become sexually active too early or display promiscuous behavior [43, 44, 45, 46, 47, 48]; however, as many studies highlight, this hypothetical effect is not realized. A cohort study conducted between July 2006 and December 2007, with nearly 1,400 girls age 11–12 years, has demonstrated that HPV vaccination in the recommended ages for young girls is not associated with clinical markers of increased sexual activity or related outcomes such as sexually transmitted diseases or pregnancy [49].

Fear of possible AEs among the people has raised, for example, the idea that vaccination can lead to increase in multiple sclerosis, optic neuritis, transverse myelitis, acute disseminated encephalomyelitis, and neuromyelitis optica [50, 51, 52]. A cohort study (2015) of Danish and Swedish girls and women aged 10–44 years evaluated almost 4 million women and found no risk for the development of multiple sclerosis or other central nervous system-demyelinating diseases. Hence, these results do not support the alarmism about a causal relationship between quadrivalent HPV vaccination and demyelinating diseases [53].

The apprehension about the possibility of developing Complex Regional Pain Syndrome (CRPS) or Postural Orthostatic Tachycardia Syndrome (POTS) following HPV vaccination has increased among the population, mostly due to media reports alleging AEs and negative information, available internationally on the Internet. Both are disorders of unclear and heterogeneous etiology and their epidemiology is not well characterized. CRPS is a chronic pain syndrome affecting limbs, while POTS involves an abnormal increase in the heart rate while a person is standing up [54], together with symptoms such as dizziness, fainting, and weakness, or headache, body aches, nausea, and fatigue. In January 2016, the European Medicine Agency (EMA) published a review confirming that HPV vaccines do not cause CRPS or POTS. Despite the difficulties in diagnosing or fully characterizing CRPS and POTS, the scientific findings of the EMA's review suggest that there is no causal link between the three licensed vaccines (bivalent, quadrivalent, and nonavalent HPV vaccines) and the development of CRPS or POTS [55].

The importance of a good communication strategy to overcome HPV-vaccination hesitancy

As previously discussed, many factors have influenced people's opinions and their choice in regard to taking or not taking a vaccination. The dissemination of the importance of an HPV vaccine programme needs good communication strategies that may vary according to political or cultural structures. The role of the media should also be taken into account, especially for the information about AEs, because vague information could seriously affect a good vaccination programme. The incident in Japan in 2013 is an example of a weak communication approach, which also suffered of the rapid spread of unverified news by media. These information found breeding ground mostly in that part of Japanese population that had previously lost the confidence in the medical profession and the pharmaceutical industry, especially due to two past vaccine controversies [56].

In Japan, the HPV vaccine (Cervarix ®) was licensed in October 2009. In April 2013, it was added to the Japanese government's list of recommended vaccinations. Between March 2010 and March 2013, before the addition of the HPV vaccine to the National Immunization Programme, local

media channels reported some events occurring after HPV vaccination: more than 50 cases of girls complaining of CRPS, nine cases of chronic pain, about 100 cases of absenteeism from school, and videos of girls suffering from walking problems and seizure were shown during a press conference by a “victim group” [57]. Due to these highly publicized cases of alleged AEs following immunization, even though there was no proved causal relationship between the reported facts and the vaccination, the Japanese Ministry of Health, Labor and Welfare (MHLW) suspended the proactive recommendation of HPV vaccination in June 2013, continuing to provide it for free to girls aged 12–16 years. This decision of the MHLW stoked the public doubts about the vaccine’s safety [57]. Another fact that contributed to the increase in the sense of uncertainty and distrust in the population was the claim for a compensation from the leader of the Nationwide Cervical Cancer Victim Liaison Committee, whose daughter developed CRPS and lost the ability to walk after vaccination with Cervarix ® [58]. The national government and the local government of Suginami (where the girl’s family lived) refused to pay, because the HPV vaccine was not yet in the National Immunization Programme when the girl received it. But in April 2013, under strong pressure by the media, the Suginami government provided the compensation [59].

The decision of MHLW to withdraw its recommendation of HPV vaccine, along with the Japanese media’s often negative view of the vaccine, reinforced the confusion and uncertainty about the vaccination. Despite the efforts by the MHLW to add a *Question and Answer* (Q&A) page on its website about the HPV vaccine, including a section on the safety [60] and the release of a guidance for healthcare professionals [61], the sense of distrust for the vaccination increased among the people. The ambiguity in the decision to suspend the “active recommendation” of HPV vaccine but not the “administration” further allowed for misinterpretation, which spread quickly and globally on international mainstream media and on social networks (such as *Facebook* or *Twitter*). The suspension of the recommendation of HPV vaccine has obviously been widely applauded by the anti-vaccination groups, but not by the global scientific community [57]. Though the reassuring results from review of clinical data have led to the conclusion that symptoms were not vaccine-

related, it has been very difficult to reach a new consensus in order to resume HPV vaccination. Therefore, it has been evaluated that young Japanese women are being left vulnerable to HPV-related cancers that could be prevented [54].

Vaccine hesitancy is a complex issue and a single strategy cannot resolve it; therefore, multicomponent and dialogue-based interventions are the most effective plans and these should be directed at unvaccinated or under-vaccinated populations or at specific target groups (as local community or health care workers) [62]. Selecting a population has been shown to be useful, pointing out the importance of combining the intervention to the reason of the low acceptance [63]. Multiple studies show that in European countries, healthcare providers are identified as the most important and reliable source of information on protection from vaccine-preventable diseases [64, 65, 66], playing an important role mostly for parents who often have many questions or doubts about vaccines. During the last few years, some health organizations like European Centre Disease Prevention and Control (ECDC) and WHO have published guidelines in order to provide useful advice, based on scientific evidences, to all healthcare personnel. Some documents refer to immunization in wider terms, like “*Let’s talk about protection enhancing childhood vaccination uptake communication guide for healthcare providers*” [67], while others are more specific about HPV vaccine, like “*HPV Vaccine Communication - Special Consideration for a unique vaccine, 2016 update*” [68]. Health authorities should invest more in training health care workers or should prevent vaccine hesitant behaviors within health personnel in order to address the vaccine hesitancy concern among patients or parents [39].

More and more frequently, people are searching for news about health by themselves; therefore, it is necessary to provide scientific information, written in an efficacious and adequate language, to all the citizens. The main channel where people look for information is the Internet, but a communication strategy based only on online data would not be very productive for people who are not so familiar with *web-surfing* or the use of social media. Further, some evidences suggest that social media can also be exploited if not managed well [62]. In fact, regarding the Japanese case,

the ambiguous and possibly threatening setting arisen from AEs following HPV vaccination - whether deemed causal or not - accelerated an information-seeking process, which in turn reinforced the pre-existing beliefs and concerns [57].

WHO, Center for Disease Control and Prevention (CDC), and national health institutions periodically publish informative material about HPV vaccination: dedicated web pages available to the users [69, 70] or booklets describe the HPV infection, its set of problems, and how the efficacy (strongly confirmed by the clinical trials) of the HPV vaccines could prevent both the infection and the related cancers. As the *target* of the used communication strategies is variable (parents, girls, boys, or young adults), the language has to be the most suitable for the specific audience. Parents should receive reassuring words from their pediatrician, teenagers should understand the value of the vaccination through simple examples that may use also a graphic approach. Regarding young adults (as men that may think the HPV infection/vaccine is only a female problem), the language used in the information collected from papers, or websites or reported by physicians should take into account the schooling level. This would guarantee the spread of important information about the person's health, overcoming possible cultural, social, or religious obstacles and avoiding communication inequalities or disparities in vaccination service access. *Video-spot*, written testimonies, or short *video-clips* [71] of female survivors of cervical cancer who have decided to share the own experience, have a positive impact on the public and promote the importance of vaccination. As the findings released by SAGE WG suggest [39], a multicomponent dialogue-based strategy to overcome the HPV vaccine hesitancy should include the engagement of religious or influential leaders in community and the communication training for health care workers as example of possible dialogue-based parts with the target population. Further, the improvement of the access to the vaccination service, the low costs of the immunization (e.g. for women or men not included in national plan of immunization), social and mass media interventions could increase the knowledge and the awareness about the HPV infection and the HPV vaccination among the target population.

Conclusion

Since it was first licensed in 2006, more than 200 million doses of HPV vaccines have been distributed worldwide [54]. WHO recommends that the introduction of HPV vaccines into national immunization programmes be made into a public health priority, to ensure prevention of cervical cancer and/or other related diseases. Vaccine implementation is programmatically feasible and financially sustainable. Further, the cost-effectiveness of vaccination strategies in the country or region should be considered [72]. The GACVS has analytically investigated safety concerns about HPV vaccines and has released several reports on this topic [73]: to date, GACVS has not found any safety concern that would modify its recommendations for the use of the three licensed vaccines [46].

Distrust in vaccination programmes is an old issue. It was born in the mid-1980s, and in these last few years the dynamic and challenging period of indecision with regard to accepting a vaccination (vaccine hesitancy) has increased. Many factors (e. g. cultural, social, or religious aspects, spreading of unverified information by media or social media) may influence people's opinion about vaccines [38,39]. Concerning the HPV vaccination, for example many people are worried about suffering a possible AE after the immunization [50, 51, 52, 55]; or are trouble about moral judgements on their sexual activity and behavior due to the aim of the vaccine (to prevent sexual transmitted infections) [40]. . In order to resolve all the issues around HPV vaccine acceptance, it is necessary to include good communication strategies: multicomponent and dialogue-based interventions seem to be the most effective [38,39,62,63] .

The benefits of HPV vaccines continue to outweigh the known side-effects. However, the safety of these vaccines will continue to be monitored, taking into account any newly discovered evidence of any AE [55]. The constant pharmacovigilance activity ensure that concerns related to the HPV vaccines administration can be addressed with the best possible evidence. Enhanced spontaneous

reporting of AEFI should be ensured to guarantee that those who could benefit the most from the intervention are vaccinated with a medicinal product of high and adequate safety standard [54].

Regarding the importance of the new nonvalent HPV vaccine, it will be important to carry out effective communication strategies using not only traditional tools, like guidelines or booklets, but also digital interface like social media or mobile applications (“apps”). Following the concept of “Pneumo Rischio” [74, 75], it could be interesting to develop a user-friendly app, which could increase people’s knowledge and awareness about HPV infections and vaccines. The use of the adequate language - customized according to the vaccination programme *target* - should ensure the spread of the efficacy, safety, and the added value of the nonvalent HPV vaccine.

References

1. Centers for Disease Control and Prevention (CDC). Immunization: the basics. Available at: <http://www.cdc.gov/vaccines/vac-gen/imz-basics.htm> .
2. Centers for Disease Control and Prevention (CDC). Vaccine: the basics. Available at: <https://www.cdc.gov/vaccines/vpd/vpd-vac-basics.html> .
3. Bonhoeffer J, Heininger U. Adverse events following immunization: perception and evidence. *Curr Opin Infect Dis*. 2007 Jun;20(3):237-46.
4. Leroux-Roels G, Bonanni P, Tantawichien T, Zepp F. Chapter 5 in: Garçon N, Leroux-Roels G, Cheng W-F. *Understanding modern vaccines, Perspectives in vaccinology*, Vol 1, Amsterdam. Elsevier 2011;p115–50.
5. World Health Organization (WHO). *Weekly Epidemiological Record*. No. 41, 1999, pp 337-338.
6. Freeman P. *The Biology of Vaccines and Community Decisions to Vaccinate*. *Public Health Reports*. 1997;112(1):21.
7. Vaccine Adverse Event Surveillance Communication (VAESCO). <http://vaesco.net/vaesco.html>

8. Vaccine Adverse Event Reporting System (VAERS). <https://vaers.hhs.gov/index>
9. Wharton M. Vaccine safety: current systems and recent findings. *Curr Opin Pediatr*. 2010 Feb;22(1):88-93.
10. Vaccine Adverse Event Surveillance & Communication (VAESCO). <http://vaesco.net/vaesco/results.html> .
11. Centers for Disease Control and Prevention (CDC). Sudden Infant Death Syndrome (SIDS) and vaccines. Available at: <http://www.cdc.gov/vaccinesafety/concerns/sids.html> .
12. Centers for Disease Control and Prevention (CDC). Vaccine Adverse Event Reporting System. Available at: <http://www.cdc.gov/vaccinesafety/Activities/vaers.html> .
13. Lankinen KS, Pastila S, Kilpi T, Nohynek H, Mäkelä PH, Olin P. Vaccinovigilance in Europe--need for timeliness, standardization and resources. *Bull World Health Organ*. 2004 Nov;82(11):828-35.
14. Varricchio F, Iskander J, Destefano F, Ball R, Pless R, Braun MM, Chen RT. Understanding vaccine safety information from the Vaccine Adverse Event Reporting System. *Pediatr Infect Dis J*. 2004 Apr;23(4):287-94.
15. Chen RT, DeStefano F, Davis RL, Jackson LA, Thompson RS, Mullooly JP, Black SB, Shinefield HR, Vadheim CM, Ward JI, Marcy SM. The Vaccine Safety Datalink: immunization research in health maintenance organizations in the USA. *Bull World Health Organ*. 2000;78(2):186-94.
16. Baggs J, Gee J, Lewis E, Fowler G, Benson P, Lieu T, Naleway A, Klein NP, Baxter R, Belongia E, Glanz J, Hambidge SJ, Jacobsen SJ, Jackson L, Nordin J, Weintraub E. The Vaccine Safety Datalink: a model for monitoring immunization safety. *Pediatrics*. 2011 May;127 Suppl 1:S45-53.
17. Offit P, DeStefano F. Chapter 76 in: Plotkin S, Orenstein W, Offit P. *Vaccines*, 6th edition, Philadelphia, Saunders, 2012, pp. 1464–80.

18. Salemi S, D'Amelio R. Could autoimmunity be induced by vaccination? *Int Rev Immunol*. 2010 Jun;29(3):247-69.
19. European Medicine Agency (EMA). Evaluation of Medicines for Human Use. Eudravigilance Expert Working Group (EV-EWG). Guideline on the use of statistical signal detection methods in the Eudravigilance data analysis system.
20. Evans S J W, Waller P C, Davis S. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports. *Pharmacoepidemiology and Drug Safety*. 2001; 10 483-486.
21. World Health Organization (WHO). Immunization, Vaccines and Biologicals. Addressing Vaccine Hesitancy. Available at: http://www.who.int/immunization/programmes_systems/vaccine_hesitancy/en/ .
22. SAGE working group dealing with vaccine hesitancy [established March 2012]. http://www.who.int/immunization/sage/sage_wg_vaccine_hesitancy_apr12/en
23. Gellin BG, Maibach EW, Marcuse EK. Do parents understand immunizations? A national telephone survey. *Pediatrics*. 2000 Nov;106(5):1097-102.
24. Iversen OE, Miranda MJ, Ulied A, Soerdal T, Lazarus E, Chokephaibulkit K, Block SL, Skrivaneck A, Nur Azurah AG, Fong SM, Dvorak V, Kim KH, Cestero RM, Berkovitch M, Ceyhan M, Ellison MC, Ritter MA, Yuan SS, DiNubile MJ, Saah AJ, Luxembourg A. Immunogenicity of the 9-Valent HPV Vaccine Using 2-Dose Regimens in Girls and Boys vs a 3-Dose Regimen in Women. *JAMA*. 2016 Dec 13;316(22):2411-2421.
25. Merck FDA, 2015. Approves Merck's HPV Vaccine, GARDASIL®9, to Prevent Cancers and Other Diseases Caused by Nine HPV Types [cited 2015 August, 28]. Available at: <http://www.mercknewsroom.com/news-release/prescriptionmedicine-news/fda-approves-mercks-hpv-vaccine-gardasil9-prevent-cancersan> .
26. Brown DR, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, Perez G, Koutsky LA, Tay EH, Garcia P, Ault KA, Garland SM, Leodolter S, Olsson SE, Tang

- GW, Ferris DG, Paavonen J, Steben M, Bosch FX, Dillner J, Joura EA, Kurman RJ, Majewski S, Muñoz N, Myers ER, Villa LL, Taddeo FJ, Roberts C, Tadesse A, Bryan J, Lupinacci LC, Giacoletti KE, Sings HL, James M, Hesley TM, Barr E. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naïve women aged 16-26 years. *J Infect Dis.* 2009 Apr 1;199(7):926-35.
27. Smith JF, Brownlow M, Brown M, Kowalski R, Esser MT, Ruiz W, Barr E, Brown DR, Bryan JT. Antibodies from women immunized with Gardasil cross-neutralize HPV 45 pseudovirions. *Hum Vaccin.* 2007 Jul-Aug;3(4):109-15.
 28. Wheeler CM, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Perez G, Brown DR, Koutsky LA, Tay EH, García P, Ault KA, Garland SM, Leodolter S, Olsson SE, Tang GW, Ferris DG, Paavonen J, Steben M, Bosch FX, Dillner J, Joura EA, Kurman RJ, Majewski S, Muñoz N, Myers ER, Villa LL, Taddeo FJ, Roberts C, Tadesse A, Bryan J, Lupinacci LC, Giacoletti KE, James M, Vuocolo S, Hesley TM, Barr E. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16-26 years. *J Infect Dis.* 2009 Apr 1;199(7):936-44.
 29. Joura EA, Giuliano AR, Iversen OE, Bouchard C, Mao C, Mehlsen J, Moreira ED Jr, Ngan Y, Petersen LK, Lazcano-Ponce E, Pitisuttithum P, Restrepo JA, Stuart G, Woelber L, Yang YC, Cuzick J, Garland SM, Huh W, Kjaer SK, Bautista OM, Chan IS, Chen J, Gesser R, Moeller E, Ritter M, Vuocolo S, Luxembourg A; Broad Spectrum HPV Vaccine Study. A 9-valent HPV vaccine against infection and intraepithelial neoplasia in women. *N Engl J Med.* 2015 Feb 19;372(8):711-23.
 30. Toft L, Tolstrup M, Müller M, Sehr P, Bonde J, Storgaard M, Østergaard L, Søgaaard OS. Comparison of the immunogenicity of Cervarix® and Gardasil® human papillomavirus

vaccines for oncogenic non-vaccine serotypes HPV-31, HPV-33, and HPV-45 in HIV-infected adults. *Hum Vaccin Immunother*. 2014;10(5):1147-54.

31. European Medicine Agency (EMA). Cervarix human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, adsorbed). EMA/462426/2016 EMEA/H/C/000721. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000703/human_med_000805.jsp .
32. European Medicine Agency (EMA). Gardasil human papillomavirus vaccine [types 6, 11, 16, 18] (recombinant, adsorbed). EMA/429427/2010 EMEA/H/C/000703. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000721/human_med_000694.jsp&mid=WC0b01ac058001d124 .
33. European Medicine Agency (EMA). Gardasil 9 human papillomavirus 9-valent vaccine (recombinant, adsorbed). EMA/192711/2016 EMEA/H/C/003852. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/003852/human_med_001863.jsp&mid=WC0b01ac058001d124 .
34. Luxembourg A, Brown D, Bouchard C, Giuliano AR, Iversen O-E, Joura EA, Penny ME, Restrepo JA, Romaguera J, Maansson R, Moeller E, Ritter M, Chen J. Phase II studies to select the formulation of a multivalent HPV L1 virus-like particle (VLP) vaccine, Human Vaccines & Immunotherapeutics. 2015 11:6, 1313-1322.
35. Moreira ED Jr, Block SL, Ferris D, Giuliano AR, Iversen OE, Joura EA, Kosalaraksa P, Schilling A, Van Damme P, Bornstein J, Bosch FX, Pils S, Cuzick J, Garland SM, Huh W, Kjaer SK, Qi H, Hyatt D, Martin J, Moeller E, Ritter M, Baudin M, Luxembourg A. Safety Profile of the 9-Valent HPV Vaccine: A Combined Analysis of 7 Phase III Clinical Trials. *Pediatrics*. 2016 Aug;138(2).
36. Stillo M, Carrillo Santistevé P, Lopalco PL. Safety of human papillomavirus vaccines: a review. *Expert Opin Drug Saf*. 2015 May;14(5):697-712.

37. Brotherton JM. Human papillomavirus vaccination: where are we now? J Paediatr Child Health. 2014 Dec;50(12):959-65.
38. SAGE Working Group dealing with vaccine hesitancy. Strategies for addressing vaccine hesitancy- a systematic review. October 2014. Available at: http://www.who.int/immunization/sage/meetings/2014/october/3_SAGE_WG_Strategies_addressing_vaccine_hesitancy_2014.pdf?ua=1
39. SAGE Working Group dealing with vaccine hesitancy. Summary WHO SAGE conclusion and recommendation on vaccine hesitancy. January 2015. Available at: http://www.who.int/immunization/programmes_systems/summary_of_sage_vaccinehesitancy_2pager.pdf?ua=1
40. Larson H. The world must accept that the HPV vaccine is safe. Nature. 2015 Dec 3;528(7580):9.
41. Fisher H, Trotter CL, Audrey S, MacDonald-Wallis K, Hickman M. Inequalities in the uptake of human papillomavirus vaccination: a systematic review and meta-analysis. Int J Epidemiol. 2013 Jun;42(3):896-908.
42. Krupp K, Marlow LAV, Kielmann K, Doddaiiah N, Mysore S, Reingold AL, Madhivanan P. Factors associated with intention-to-recommend human papillomavirus vaccination among physicians in Mysore, India. J Adolesc Health 2010;46:379-84.
43. United Press International. Promiscuity fears hinders HPV vaccine use. December 2008. Available at: http://www.upi.com/Health_News/2008/12/19/Promiscuity-fears-hinders-HPV-vaccine-use/UPI-54571229744264/
44. Rubin R. Injected into a controversy. USA Today. October 2005. Available at: https://usatoday30.usatoday.com/news/health/2005-10-19-cervical-cancer-injection_x.htm
45. Schuler CL, Reiter PL, Smith JS, Brewer NT. Human papillomavirus vaccine and behavioural disinhibition. Sex Transm Infect. 2011 Jun;87(4):349-53.

46. Forster A, Wardle J, Stephenson J, Waller J. Passport to promiscuity or lifesaver: press coverage of HPV vaccination and risky sexual behavior. *J Health Commun.* 2010 Mar;15(2):205-17.
47. Marlow LA, Forster AS, Wardle J, Waller J. Mothers' and adolescents' beliefs about risk compensation following HPV vaccination. *J Adolesc Health.* 2009 May;44(5):446-51.
48. Waller J, Marlow LA, Wardle J. Mothers' attitudes towards preventing cervical cancer through human papillomavirus vaccination: a qualitative study. *Cancer Epidemiol Biomarkers Prev.* 2006 Jul;15(7):1257-61.
49. Bednarczyk RA, Davis R, Ault K, Orenstein W, Omer SB. Sexual activity-related outcomes after human papillomavirus vaccination of 11- to 12-year-olds. *Pediatrics.* 2012 Nov;130(5):798-805.
50. Sutton I, Lahoria R, Tan I, Clouston P, Barnett M. CNS demyelination and quadrivalent HPV vaccination. *Mult Scler.* 2009;15:116-119.
51. Chang J, Campagnolo D, Vollmer TL, Bompreszi R. Demyelinating disease and polyvalent human papilloma virus vaccination. *J Neurol Neurosurg Psychiatry.* 2011; 82:1296-1298.
52. Wildemann B, Jarius S, Hartmann M, Regula JU, Hametner C. Acute disseminated encephalomyelitis following vaccination against human papilloma virus. *Neurology.* 2009; 72: 2132-2133.
53. Scheller NM, Svanstrom H, Pasternak B, et al. Quadrivalent HPV vaccination and risk of multiple sclerosis and other demyelinating diseases of the central nervous system. *JAMA.* 2015;313:54-61.
54. World Health Organization (WHO). Weekly epidemiological record, N. 3, 22 January 2016. Available at: <http://www.who.int/wer> .
55. European Medicine Agency (EMA). HPV vaccines: EMA confirms evidence does not support that they cause CRPS or POTS Reports after HPV vaccination consistent with what would be expected in this age group, 12 January 2016, EMA/788882/2015.

56. Center for Strategic & International Studies (CSIS). Wilson R, Paterson P, Larson H J. The HPV Vaccination in Japan. Issues and Option. May 2014.
57. Larson HJ, Wilson R, Hanley S, Parys A, Paterson P. Tracking the global spread of vaccine sentiments: the global response to Japan's suspension of its HPV vaccine recommendation. Hum Vaccin Immunother. 2014;10(9):2543-50.
58. HPV Vaccine Raises Questions [Internet]. Kyodo: Japan Times; 2013 Jun 14 [cited 2014 Feb 5]. Available at: <http://www.japantimes.co.jp/opinion/2013/06/14/editorials/hpv-vaccine-raises-questions/#.U8zs-OPldV8E> .
59. Side reaction junior high heavy cervical cancer vaccine, long-term non-school [Internet]. Apital Asahi; 2013 Mar 8 [cited 2014 Feb 9]. Available at: <http://apital.asahi.com/article/news/2013030-800002.html> .
60. The Q&A on withholding vaccination aggressive encouragement of cervical cancer prevention [Internet]. Japanese Ministry of Health, Labor and Welfare (MHLW); 2013 [cited 2013 Jan 10]. Available at: http://www.mhlw.go.jp/bunya/kenkou/kekakukansenshou25/qa_hpv.html
61. To everyone to receive the vaccination for cervical cancer prevention vaccine (leaflet) [Internet]. Japanese Ministry of Health, Labor, and Welfare (MHLW); 2013 Jun [cited 2013 Jan 10]. Available at: <http://www.mhlw.go.jp/bunya/kenkou/kekakukansenshou28/> .
62. Jarret C, Wilson R, O'Leary M, Eckersberger E, Larson H, the SAGE Working Group on Vaccine Hesitancy. Strategies for addressing vaccine hesitancy – A systematic review. Vaccine. 2015, 33:4180-4190.
63. SAGE working group dealing with vaccine hesitancy. Report of the SAGE Working Group on Vaccine Hesitancy. November 2014. Available at http://www.who.int/immunization/sage/meetings/2014/october/SAGE_working_group_revised_report_vaccine_hesitancy.pdf

64. Stefanoff P, Mamelundb S, Robinsonc M, Netterlidd E, Tuellse J, Riise Bergsakerb M, et al. Tracking parental attitudes on vaccination across European countries: The Vaccine Safety, Attitudes, Training and Communication Project (VACSATC). The VACSATC working group on standardization of attitudinal studies in Europe. *Vaccine*. 2010, 28:5731–5737.
65. Heininger U. An internet-based survey on parental attitudes towards immunization. *Vaccine*. 2006, 24:6351–6355.
66. chmitt HJ, Booy R, Aston R, Van Damme P, Schumacher RF, Campins M, Rodrigo C, Heikkinen T, Weil-Olivier C, Finn A, Olcén P, Fedson D, Peltola H. How to optimise the coverage rate of infant and adult immunisations in Europe. *BMC Med*. 2007 May 29;5:11.
67. European Centre for Disease Prevention and Control (ECDC). Let's talk about protection. Stockholm: ECDC; 2016. First published 2012. Revised edition, Stockholm, April 2016.
68. World Health Organization (WHO). HPV Vaccine Communication – Special Consideration for a unique vaccine, 2016 update. WHO/IVB/16.02 .
69. World Health Organization (WHO). Immunization Vaccine and Biological. HPV Vaccine Introduction Clearing House. Available at: <http://www.who.int/immunization/hpv/en/> .
70. Centers for Disease Control and Prevention (CDC). Genital HPV infection – Fact Sheet. Available at: <https://tools.cdc.gov/medialibrary/index.aspx#/media/id/124248> .
71. Centers for Disease Control and Prevention (CDC) channel on Youtube. Available at: <https://www.youtube.com/user/CDCStreamingHealth> .
72. World Health Organization (WHO). Weekly Epidemiological Record. No. 43, 2014, pp 465-492.
73. World Health Organization (WHO). Global Vaccine Safety. Safety of human papillomavirus vaccines. Available at: http://www.who.int/vaccine_safety/committee/topics/hpv/en/ .
74. Panatto D, Domnich A, Gasparini R, Bonanni P, Icardi G, Amicizia D, Arata L, Bragazzi NL, Signori A, Landa P, Bechini A, Boccalini S. Development and preliminary data on the use of a mobile app specifically designed to increase community awareness of invasive

Safety and perception: what are the greatest enemies of HPV vaccination programmes?

Abstract

Vaccines stimulate a person's immune system to produce an adequate reaction against a specific infectious agent; i.e. the person is protected from that disease without having to get it first. As vaccines are administered to healthy subjects, they are held to the highest standards of safety. Regarding human papillomavirus (HPV) vaccines, at present three prophylactic vaccines are licensed (bivalent HPV 16/18, quadrivalent HPV 6/11/16/18 and the nonavalent HPV 6/11/16/18/31/33/45/52/58 vaccine). Pre- and post-licensure studies (i.e. not yet for nonavalent HPV vaccine) confirm that HPV vaccines are generally safe and well-tolerated, site injections symptoms are the most common adverse events (AEs) reported, and pain is the most frequently referred local symptom. Serious AEs are rare and not associated with severe sequelae, at least no vaccine-related deaths have occurred. Despite these scientific evidences, it is still difficult to explain to the population the importance of a good vaccination programme. There are many determinants for HPV vaccines hesitancy which represent a barrier that must be overcome in order to increase vaccine coverage, including psychological reactions, religious or cultural aspects, and fear of possible AEs (demyelinating diseases, Complex Regional Pain Syndrome - CRPS, or Postural Orthostatic Tachycardia Syndrome - POTS). A weak communication strategy which frequently suffers due to spread of unverified news by media and websites may lead to the failure of a vaccination programme. Such a situation happened in Japan (2013), due to which a great number of women remain vulnerable to HPV-related cancers. In order to resolve the issues around HPV vaccines acceptance, it is necessary to use good communication strategies. Multicomponent and dialogue-based interventions seem to be the most effective, especially if an adequate language is used, customized according to the vaccination programme target.