Vaccine xxx (2018) xxx–xxx

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Early use of the HPV 2-dose vaccination schedule: Leveraging evidence to support policy for accelerated impact

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ARTICLE INFO

Article history:
Available online xxxx

Keywords:
Human papillomavirus (HPV)
HPV vaccine
Alternative vaccination schedule
Single dose
Cervical cancer

ABSTRACT

Although human papillomavirus (HPV) vaccines were initially licensed based on efficacy after three-dose regimens in women aged 15–26 years, it was recognized early in clinical development that comparable immunogenicity could be obtained after just two doses when administered to younger girls. In both Canada and Mexico, public health authorities made the decision to administer two doses 6 months apart with a planned additional dose at 60 months, while simultaneously doing further study to determine if the third dose would confer meaningful additional benefit. This delayed third dose approach permitted a more cost-effective program with opportunities for improved compliance while minimizing injections and leaving open the opportunity to provide a full three-dose vaccination series. It required close cooperation across many governmental and civil society leadership bodies and real-time access to emerging data on HPV vaccine effectiveness.

Although still limited, there is increasing evidence that even one-dose vaccination is sufficient to provide prolonged protection against HPV infection and associated diseases. Ongoing clinical trials and ecological studies are expected to consolidate existing data regarding one dose schedule use. However, to accelerate the preventive effect of HPV vaccination some jurisdictions, in particular those with limited resources may already consider the initiation of a one dose vaccination with the possibility of giving the second dose later in life if judged necessary. Such an approach would facilitate vaccination implementation and might permit larger catch-up vaccination programs in older girls (or as appropriate, girls and boys), thereby accelerating the impact on cervical cancer and other HPV-associated diseases.

1. Introduction

Two main factors dictate the success of a vaccination program: vaccine effectiveness and vaccine uptake. A decade of experience with HPV vaccines has shown they are safe and effective, with the potential to prevent the majority of HPV-related diseases [1–5]. Despite these important characteristics, vaccine uptake remains suboptimal with less than half of countries (82 of 195) implementing HPV vaccination programs [6,7]. This situation is due to several factors including high vaccine prices, operational difficulties of multi-dose vaccination schedules, targeted age groups outside of infant and early childhood routine schedules, anti-vaccination concerns specific to HPV vaccines including its association to sexual activity, and ignorance about the relevance of precancerous clinical endpoints assessed in clinical trials. In many countries the main barriers are related to operational and financial difficulties, including the multi-dose vaccination schedule [8,9].

2. Vaccination schedules

Pre-licensure clinical trials of HPV vaccines assessed their immunogenicity and efficacy in three-dose vaccination schedules

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https://doi.org/10.1016/j.vaccine.2018.02.004
0264-410X/

- the standard schedules for infant inactivated vaccines. These are based on the principle that two primary doses one or two months apart prime the immune system and rapidly provide short-term protection, boosted by the third dose to provide long-term protection [10–12]. However, immune responses to vaccines are generally more vigorous in preadolescents and adolescents than in infants [13], and recent experience has shown that the newer inactivated/recombinant vaccines are generally more effective than their predecessors [14]. Indeed, vaccines developed during the last 20–30 years have been found to be effective with fewer doses than those foreseen at the time of licensure. One example is hepatitis B vaccines, initially licensed in three- and four-dose schedules, but now recommended and used in two-dose schedules in some age groups [15,16]. A similar switch from three to two doses of hepatitis A vaccines has occurred [17], with successful one-dose programs in place in some countries for more than a decade [18,19]. Such changes are jurisdiction-specific and made at different time points in different socioeconomic and epidemiological contexts, affected by health care system peculiarities and often unlinked to the contemporaneous regulatory sanctioned indication. Therefore, the increasing evidence that HPV vaccines also fall into this category needs to be considered in different environments, and for this paper we consider the different circumstances in Canada and Mexico which led to the use of an extended vaccination schedule. Similar approaches might be re-applied when moving to a one dose HPV vaccination schedule.

3. The Canadian context

In Canada, healthcare is a provincial/territorial jurisdiction and each province and territory can make healthcare decisions including vaccination programs [20,21]. This results in variation of schedules for public immunization programs across Canada where implementation of HPV vaccination programs for school-aged girls varied from 2007 to 2010 [22], using quadrivalent vaccine in main vaccination programs and quadrivalent or bivalent vaccine in catch-up campaigns. At the time of writing nine of ten Canadian provinces use a two-dose schedule and one province continues with three doses [22]. Age cohorts eligible for HPV vaccination also vary across provinces from 9 to 14 years, some provinces/territories vaccinating only girls, and some both girls and boys.

3.1. The Quebec approach

Since 1990 the province of Quebec (population 8 M) has had a provincial immunization committee (QIC – *Comité sur l'immunisation du Québec*) whose active members with voting rights are public health experts, pediatricians and infectious disease specialists. This advisory committee makes recommendations to the Ministry of Health regarding the use of new vaccines and the optimization of existing programs. As prevention of HPV-related diseases exceeds the field of traditional infectious diseases the usual 16 QIC membership was extended to 36 with experts in gynecology, sexual transmitted diseases, cancer prevention, virology, anthropology and psychology. In 2005, with the imminent approval of HPV vaccines by Health Canada, an HPV working group created at the initiative of the Quebec Public Health Institute prepared an advisory report for future recommendations.

Quebec developed a vaccine decision-making framework including disease burden, vaccines characteristics, potential strategies for vaccination programs, program cost-effectiveness, acceptability, feasibility, capacity to evaluate, equity, ethics, and conformity [23]. By 2007 the quadrivalent HPV vaccine was available in Canada and the bivalent HPV vaccine was with the Health Canada regulatory board for approval so the use of one or both vaccines was not ruled out before the final decision. Thus, the characteristics of both vaccines were reviewed and compared [24].

At that time no efficacy data after one or two vaccine doses was available, so special attention was paid to immunogenicity data. As immunogenicity in adolescents and preadolescents was used by vaccine manufacturers as "bridging criteria" from efficacy data in women for HPV vaccines licensing for preadolescents and adolescents, it was thought that it could also serve for two- versus three-dose comparisons. Existing data indicated that one month post-second dose of quadrivalent vaccine (given 2 months post first dose) in 10–15 year-old girls the seroconversion rates (>97.5%) were similar to those reported one month post-third dose administered to 16–23 year-old women [25]. In the same study antibody titers as measured by GMTs post-second dose in 10–15 year-olds were higher than post-third dose in 16–23 year-olds in which high efficacy against the infections, pre-cancerous lesions (CIN2/3) and anogenital warts was reported. Presented in scientific conferences but not published at that time, data from clinical trials with two doses of the bivalent HPV vaccine in 10–14 year-old girls were also promising. Fivefold higher antibody titers were reported 18 months post-vaccination of 10–14 years-old girls when compared with those observed in 15–25 year-old women [26]. These data were discussed by experts from across Canada at the Canadian Human Papillomavirus Vaccine Research Priorities Workshop and different HPV research questions were ranked by importance. The immunogenicity and efficacy/effectiveness of two-dose schedules was voted as the most important question in the category "Intervention Research" [27], and participants questioned the need of the second dose in the 0, 2, 6 months schedule when vaccinating preadolescents and adolescents. Generally, with recombinant vaccines, an excellent priming is obtained after a single dose. The second dose induces higher antibody titers when administered 6–12 months after first dose when compared to 1–2 months interval.

While all other Canadian provinces/territories adopted the schedule recommended by the vaccine manufacturer (0, 2 and 6 months), in its 2007 report on HPV vaccination the QIC recommended an extended three-dose schedule (0, 6 and 60 months) noting that "the third dose will be given if judged necessary" [24,28]. The six months interval between the first two doses was based both on immunological expectations which were later confirmed and on operational reason (allowed co-administration with the combined hepatitis A and B vaccine). After approval by the extended QIC the report was sent for consultation to associations of provincial pediatricians, gynecologists, infectious disease and sexual transmitted disease specialists, and nurses to obtain their support for program implementation. This approach also familiarized these health professionals with immunological and operational reasons which justify the use of an extended schedule.

Consequently, in 2008 Quebec implemented a school-based HPV immunization program (0, 6 and 60 months) targeting Grade 4 girls (9–10 years-old) in the routine immunization program. This specific age group was chosen because preadolescents generally respond better to vaccination than older age groups, are more compliant with vaccination schedules, are not yet sexually active, and because a successful school-based hepatitis B immunization program in this age group had been in place since 1996 [29].

4. The global transition to two-doses HPV schedules in girls

At a WHO meeting in 2013 interim immunogenicity data from ongoing 2-dose schedule clinical trials in Canada, India, and Mexico, as well as first data on effectiveness of fewer than three-doses were presented [30]. The interim data from clinical trials with two doses given 6-month apart to 9–10 year-old girls showed non-inferior GMTs when compared to those observed in young

Please cite this article in press as: Gilca V et al. Early use of the HPV 2-dose vaccination schedule: Leveraging evidence to support policy for accelerated impact. Vaccine (2018), https://doi.org/10.1016/j.vaccine.2018.02.004