Authors:
Mdm. Maharita Ab RAhman
Dr. Izzuna Mudla Mohamed Ghazali

External Reviewer:
Dr. Jamiatul Aida binti Md. Sani
Public Health Physician, Disease Control Division, MOH

For further information, please contact:

Malaysian Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia
Level 4, Block E1, Precinct 1
Government Office Complex
62590 Putrajaya.

htamalaysia@moh.gov.my
Tel: 603 8883 1229

Available at the following website:
http://www.moh.gov.my

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Background

The HPV genotypes 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, and 59 are considered as high-risk HPV genotypes. On top of that, the HPV16 and HPV18 are the most common genotypes in women worldwide and are associated with most cases of invasive cervical cancer. As prevention, three prophylactic HPV vaccines are available; bivalent HPV vaccine (2vHPV vaccine), quadrivalent HPV vaccine (4vHPV vaccine) and nonavalent HPV vaccine (9vHPV vaccine).

Previously in 2007, the World Health Organisation (WHO) recommended three-dose schedule of HPV vaccination for young girls. Later on, in new guideline update and based on available evidence at that time, WHO approved two-dose schedule for young girls age nine to 13 years old. On top of that, there were studies reported that the structural characteristics of the virus-like particles of the vaccine allowed an efficient production of the long-lived plasma cells, which continuously produced the antigen-specific antibodies, resulted in strong long-lasting immune responses with reduced dose schedules. Even different intervals between first and second doses also may affect immunogenicity response.

According to this, Director of Family Health Development Division, MOH requested an update on the HPV vaccine in order to look at the effectiveness, safety and cost-effectiveness in three scenarios; first was one-dose schedule compared to two-dose schedule of HPV vaccination among young girls at age of nine to 13 years-old, second was a long interval (>15 months) between first dose and second dose of HPV vaccine and third was two-dose schedule compared to three-dose schedule among women at age of more than five-years old.

Objective

To assess the efficacy/effectiveness, safety and cost-effectiveness of HPV vaccination in three scenarios:

i. The HPV vaccine schedule for young girls (nine to 15-years old) is reduced to one-dose.
ii. The gap between first dose and second dose is extended up to more than 15 months.
iii. The vaccine schedule for women aged of ≥15 years old is reduce to two-dose schedule

Methods

Literature search was conducted by the author with help from Information Specialist who searched for full text articles pertaining to HPV vaccination. The following electronic databases were searched through the Ovid interface: Ovid MEDLINE® In-Process & Other Non-Indexed Citations and Ovid MEDLINE® 1946 to 5th February 2021, EBM Reviews - Health Technology Assessment, EBM Reviews - Cochrane Database of Systematic Review (2005 to 5th February 2021), EBM Reviews - Cochrane Central Register of Controlled Trials (February 2021), EBM Reviews – Database of Abstracts of Review of Effects (1st Quarter 2016), and EBM Reviews - NHS Economic Evaluation Database. Parallel searches were run in PubMed, US FDA and INAHTA database. No limits were applied to the search. Additional articles were identified from reviewing the references of retrieved articles. The last search was performed on 5th February 2021.

Results and conclusion:

Vaccine Efficacy/Effectiveness

Single dose vaccination of 2vHPV showed no difference in efficacy towards HPV16 and HPV18 where the cumulative incidence for both HPV types at seven years was ranged from 1.5% (95%CI 0.2–5.3%) in the 1-dose arm to 4.3% (95%CI 3.5–5.3%) in the 3-dose arm. Similar efficacy was also observed with single dose of 4vHPV vaccine when compared before vaccination; the hazard ratio (HR) of HPV infection was significantly lower for all doses (1-, 2- and 3-dose) and remained equivalent for one-dose; (HR 0.47 [95% CI 0.38, 0.58]), 2-dose (HR 0.44 [95% CI 0.38, 0.51]) and 3-dose (HR 0.43 [95% CI 0.41, 0.45]). Although the GMTs level for single dose was lower compared to two- and three-doses, the seropositivity in single dose was as high as two- and three-dose which was 98.3% for HPV16 and 87.08% for HPV 18.

Then, while compared the efficacy of HPV vaccination at different dosing intervals either long or short interval; the included studies reported that in all HPV vaccine types, the GMTs level in longer interval was 2.5 to 5 times higher than short interval. Anogenital warts incidence rates also showed no significant difference among different intervals. The long interval was ranged at seven- to 12-months and the short interval was ranged at three- to six-months.

Only one RCT reported that 2-doses schedule in women aged 15 to 25-years old resulted in lower GMCs level than 3-doses schedule but the seropositivity was high in both groups.

Safety

Most of included studies reported that all HPV vaccine doses at any interval had comparable adverse events. The most common ADRs were pain (after HPV vaccine injection two-dose versus three doses; RR 0.96, 95% CI 0.91, 1.03), swelling (reduced in two-dose than three-dos; RR 0.76, 95% CI 0.65, 0.89) and redness (reduced in two-dose than three-dose; RR 0.85, 95% CI 0.75, 0.96) at injection site and nausea. No serious ADRs reported.

Organisational issues

Shortage in HPV vaccine supply worldwide may affect low-income countries (LIC) and low-middle income countries (LMIC) to fulfil the HPV vaccination programme. Thus, those countries required certain strategies including reducing the number of doses yet still had desired protection. In addition to that, other factors that may affect the completion of HPV vaccination especially in three-dose schedule were caregiver's educational level, and accessibility of immunization appointments.

Economic implication

One economic evaluation conducted in lower income country; Uganda was retrieved. The study simulated two scenarios; Scenario A that compared routine one dose HPV vaccination of nine-year-old girls starting in 2017 to no vaccination and Scenario B that compared routine one-dose HPV vaccination to two doses HPV vaccination of nine-year-old-girls. Overall, the cost-effectiveness of any doses will depend on the vaccination coverage observed within certain period. Although the one dose vaccination with higher coverage remained cost-saving regardless of waning assumption, two doses vaccination

was considered 'very cost-effective' when one dose protection declines at 10 to 15 years.