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2019

Background

Cervical cancer is ranked as fourth most frequently diagnosed cancer worldwide and the fourth leading cause of cancer death in women. According to the most recent Malaysian National Cancer Registry Report, the age-standardized rate of cervical cancer is 7.8 per 100,000 females. Based on Malaysia HPV types prevalence study in 2017, overall prevalence of HPV infection in Malaysia's multi-ethnic population was 7.2% whereby 6.5% being high-risk genotypes. Recent study reported that the most common HPV infections in Malaysia were caused by HPV16 (35.7%), HPV18 (26.0%), HPV58 (9.1%), HPV33 (7.1%), HPV 31 (1.9%), HPV 45 (1.9%) and HPV 52 (1.3%). However, data for HPV 6 and HPV 11 were not available.

In developed countries, vaccination programmes are in place which enable girls to be vaccinated against HPV and women to get screened regularly. Screening allows pre-cancerous lesions to be identified at stages when the lesions can easily be treated. Early treatment prevents up to 80% of cervical cancers in these countries. Meanwhile in developing countries, there is limited access to these preventive measures and cervical cancer is often not identified until it has further advanced and symptoms developed.

Thus, the WHO recommended a comprehensive approach to cervical cancer prevention and control. The recommended set of actions includes interventions across the life course, on of it is vaccination. It should be multidisciplinary, including components from community education, social mobilization, vaccination, screening, treatment and palliative care. In 2011, one technology review (TR) was conducted by Malaysian Health Technology Assessment Section (MaHTAS) on bivalent (2vHPV) and quadrivalent (4vHPV) vaccine. Both vaccines were focused to be effective for specified HPV types (6, 11, 16 and 18), however, there was concerned on the safety profile. In February 2015, the Advisory Committee on Immunization Practices (ACIP) included the nonavalent HPV (9vHPV) vaccine in its recommendation for routine HPV vaccination of pre-adolescent aged 11 or 12 years, female aged 13 to 26 years and males aged 13 to 21 years who had not previously received bivalent HPV vaccine or quadrivalent HPV vaccine.

Since the approval of nonavalent HPV vaccine, Ministry of Health (MOH) is planning to improve the vaccination program in Malaysia. Thus, the Head of Vaccine Preventable Disease / Food & Water Borne Disease Sector, Disease Control Division, MOH requested the technology review in order to look at the effectiveness, safety and cost-effectiveness of nonavalent HPV vaccine compared to quadrivalent and bivalent HPV vaccines in prevention of cervical cancer in female-only vaccination program and whether the added benefit of nonavalent HPV vaccine worth the investment? The requestor also would like to assess whether the upgrading of vaccination program from female-only vaccination to universal vaccination program using the nonavalent HPV vaccine will it be more cost-effective compared to current practice (female-only vaccination with bivalent or quadrivalent HPV vaccines.

Objectives

To assess the safety, efficacy/effectiveness and cost-effectiveness of nonavalent HPV vaccine compared to bivalent or quadrivalent HPV vaccine.

Methods

Electronic databases were searched through Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1948 to present, EBM Reviews-Cochrane Database of Systematic review, EBM Reviews-Cochrane Methodology Register of Controlled Trials, EBM Reviews-Health Technology

Assessment, EBM Reviews-NHS Economic Evaluation Database, and Embase 1996 to 5 August 2019. Searches were also run in PubMed, FDA website and INAHTA for any published reports.

No limit in the study year. Google and Google Scholar were also used to search for additional web-based materials and information about the technology. Besides, additional articles were also search by reviewing the references of retrieval articles

Results and Conclusions
The included studies consisted of seven systematic reviews (SR), three RCT and one cost analysis study. Those studies were conducted in Brazil, Netherlands, Italy, Norway and Australia. The study populations were all over the world including European country, USA and Asia.

Efficacy / Effectiveness

i. Infections Risks

Among non-HPV infected populations (female aged 16 to 26 years old), nonavalent HPV vaccine was highly effective in reducing diseases related to HPV types that were covered by the nonavalent HPV vaccine. Compared with quadrivalent HPV vaccine, there was no cases of cervical disease, vulva disease or vaginal disease related to HPV 31, 33, 45, 52 and 58 were detected in nonavalent HPV vaccinated group. Furthermore, HPV-52 and 58 related infections were most frequent in all countries with quadrivalent HPV vaccination.

In vaccination programme which used either quadrivalent HPV vaccine or bivalent HPV vaccine, the overall prevalence of HPV types 16 and 18 in girls aged 13 to 19 years old was significantly decreased compared with in women aged 20 to 24 years old. However, for HPV types 31, 33, 45, 52 and 58 and non-high-oncogenic risk, the overall prevalence was not significantly changed. In high-female vaccination coverage, anogenital warts was significantly reduced in girls and boys15 to 19 years old, and women 20 to 35 years old women.

ii. Immunogenicity and Non-Inferiority

Within one to seven month, the nonavalent HPV vaccine successfully seroconverted with high GMTs level for all the HPV types covered. Compared with quadrivalent vaccine, the immunogenicity and non-inferiority response was similar for HPV 16, 18, 6 and 11. In terms of age, the GMTs level decreased as the age increased; the GMTs level for all HPV types covered by nonavalent HPV vaccine was higher in girls and boys aged nine to 15 years old than in women aged 16 to 26 years old. Among Asian populations, Indian females showed highest GMTs level than other races.

Concomitant administration of nonavalent HPV vaccine with MCV4 vaccine, Tdap vaccine and polio vaccine showed positive results as non-concomitant group. The nonavalent HPV vaccine was successfully seroconverted with elevated GMTs for all HPV types covered by the vaccine. Meanwhile, the immune response for other vaccine; diphtheria, tetanus, all pertussis and polio antigen were also established.

Girls and boys aged nine to 14 years old receiving the two doses of nonavalent HPV vaccine was non-inferior to a three doses nonavalent HPV vaccine in adolescent girls and young women aged 16 to 26 years old.

In vaccination programme which used either quadrivalent HPV vaccine or bivalent HPV vaccine, the seroconversion was significantly higher for both HPV types 16 and 18.

iii. Vaccination Coverage

Strong herd effects were expected from vaccinating girls-only at 40% coverage or even with coverage as low as 20%. Besides that, with high female-vaccination coverage (70% to 80%), the anogenital warts were significantly reduced by 32% in women (age of 20 to 39 years old) and boys (age of 15 to 19 years old). On the other hand, additional boys in girls-only vaccination just resulted in small increment in relative reduction prevalence ($RR_{prev)}$ in both women and men.

Overall, the prevalence of HPV types 16 and 18 were significantly reduced in girls aged 13 to 19 years old and not significantly reduced in women aged 20 to 24 years old. However, the association of dose response and vaccination coverage was significant in the women group compared to the girl's group. Although, the prevalence of HPV types 31, 33, 45, 52 and 58 was significantly reduced in girls (aged 13 to 19 years old), no significant association between dose response and vaccination coverage were observed.

Safety

Based on above review, the adverse events were more common in nonavalent HPV vaccine compared to quadrivalent HPV vaccine. The most common AEs were fever, pruritus, GI symptom and injection-site related AEs. There was also small number of serious AEs reported which more cases were occurred in nonavalent HPV vaccine than quadrivalent vaccine. However, the SAEs was not described in detail. There were no death-related to the HPV vaccine reported.

By gender, more adverse events occurred among females than male's population. The adverse events were also more common in concomitant vaccination compared to non-concomitant vaccination.

Cost/Cost-Effectiveness Analysis

The SR of cost-effectiveness included studies published (2014-2016) concluded that if the HPV vaccination coverage for female was above 75%, gender neutral vaccination was less cost-effective than when targeting only girls aged nine to 18 years. The multi cohort immunization strategy was cost-effective in the age range nine to 14 years but the upper age limit which vaccination were no longer cost-effective needs further assessment. Furthermore, there was inconclusive evidence to proof greater cost-effectiveness of nonavalent HPV vaccine compared to the quadrivalent or bivalent HPV vaccine as the price for nonavalent HPV vaccine was still uncertain.

One cost-effectiveness study conducted in Italy showed that switching from the quadrivalent HPV vaccine to the nonavalent HPV vaccine girls-only vaccination was cost-effective. Although there was a local cost-effectiveness study conducted, however, no full-text article was retrieved. Financial implication of using nonavalent HPV vaccine in national HPV-vaccination programme was conducted. The difference from the current national HPV-vaccination programme to nonavalent HPV-vaccination programme is expected approximately >90% increase in expenditure. Overall, the cost-effectiveness of nonavalent HPV vaccine in Malaysia was inconclusive with potentially high budget implication.