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REVIEW

Multidimensional social and cultural norms influencing HPV vaccine hesitancy in Asia

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ABSTRACT

HPV vaccine hesitancy in Asia is unique compared to Western countries due to multidimensional social-cultural norms that influence beliefs regarding vaccination. Reviews on HPV vaccine hesitancy in Asia lack of in-depth discussion regarding the traditional and social-cultural norms dimensions. This paper puts forward opinions in which culture, normative beliefs, and religion influence HPV vaccine hesitancy in Asian countries. Issues surrounding HPV hesitancy among parents, young adult women, adult women, men and the sexual and gender minority people in Asian countries were highlighted. The shortage of HPV vaccine supply would soon be reduced as some Asian countries are on the way to producing the HPV vaccine which production is currently dominated by Western European countries. The culture of favoring imported Western products among many in Asia and in addition to long-existing fake vaccine crisis pose a challenge for the newly emerging HPV vaccine produced in Asia. Some recommendations, research gaps, and future research needs were discussed.

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1. Introduction

Cervical cancer is the fourth most frequent cancer in women, with estimated 570,000 new cases in 2018, representing 6.6% of all female cancers.[1] It is well known that cervical cancer epidemiology varies widely around the world, with striking disparities in incidence and mortality between low- and middle-income countries (LMICs) and high-income countries (HICs).[2] Approximately 90% of deaths from cervical cancer occur in LMICs.[1] The Asia-Oceania region accounts for more than 50% of all cases and deaths from cervical cancer worldwide, with South Central and Southeast Asia having the highest incidence and mortality rates.[3] The largest disease burden in less developed regions, such as in Asia, is largely due to a lack of appropriate cervical screening.[3] Human papillomavirus (HPV) is one of the most common causes of sexually transmitted infections worldwide, and it has been recognized as the leading cause of cervical and several other cancers. Vaccines against HPV offer a promising breakthrough to curb the global burden of cervical cancer. Since licensure in 2006, HPV vaccines have been introduced for girls and women in many countries around the world and for boys and men in some countries. As of June 2017, 91 countries had initiated national HPV vaccination programs and an additional 38 countries had implemented pilot programs.[4] In low-resource setting, in particular, HPV vaccines are a major step forward in tackling cervical cancer, as the implementation of appropriate and effective cervical screening programs has not been feasible.

The HPV vaccination rate in the Asian region is generally low, especially in less affluent countries such as Thailand and Cambodia, where the HPV vaccination coverage is estimated to be near 10%.[5] Even in affluent areas, such as Hong Kong, South Korea, and Singapore, very low rates of HPV vaccine administration have been recorded. Hong Kong, for instance, has not yet implemented a universal HPV vaccination program, and the uptake rate was reported to be only 7–9% of school-aged girls[6,7] and 9.7% of university-aged women.[8] In South Korea, the HPV vaccine coverage was 12% among adult women[9] and around 1–10% among high school girls.[10] In Singapore, the HPV vaccination rate is slightly higher, with nearly 14% of women aged 18–26 y having been vaccinated against HPV.[11]

School-based HPV vaccine programs have been shown to drastically increase HPV vaccination coverage in many countries of Asia. Of note, emerging market and developing countries in Asia that have implemented national school-based

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HPV vaccination programs have seen relatively higher HPV vaccination rate compared to developed countries without proper national or governmental HPV vaccination programs. For instance, Malaysia is the first country in the Southeast Asia region to implement a national HPV immunization program, which is a free vaccination program for 13-y-old girls in government and private schools. Since 2010, the program has achieved vaccination coverage of 83–91% of 13-y-old girls.[12] Likewise, in Thailand, the HPV vaccination coverage was 91.0% and 87.4% for the first and second dose, respectively, when it was integrated into the immunization program.[13] In a recent study where a school HPV vaccination program involved several schools in Hong Kong, uptake rates as high as 81.4% for the first dose and 80.8% for the second dose were shown.[7] In Japan, the HPV vaccination rate reached about 70% for 12 to 13-y-old girls, where a subsidized HPV vaccine was introduced into the national immunization program. However, after false attributions of harm due to vaccination were spread by Japanese media, the Japan Ministry of Health, Labor and Welfare suspended their recommendation for HPV vaccination and the acceptance rate fell rapidly to <1%, where it has remained for several years.[14,15]

Vaccine hesitancy is an increasingly important issue and was identified in 2019 by the World Health Organization as one of the top 10 threats to global health.[16] It is anticipated that countries without HPV vaccination in their national immunization program, vaccine hesitancy may potentially play an important role in poor HPV vaccine administration rates. For instance, sexual promiscuity may serve as an obstacle to seeking HPV vaccine proactively; however, once the HPV vaccine is integrated into a country's national immunization program, receiving the HPV vaccine may no longer an issue of stigmatization. Evidence also indicates that vaccine hesitancy poses a serious threat to countries that have a HPV vaccination program, for instance, the spread of unwarranted concerns about severe adverse reactions following Japan's suspension of their recommendation for HPV vaccination.[17,18] The public health rationale behind vaccination is to achieve herd immunity by ensuring vaccination of a significant proportion of the population, which may result in the elimination and eventual eradication of the disease. In many countries, even among those having HPV vaccination programs, coverage is insufficient to reach herd immunity. Thus, understanding the sources of HPV vaccine hesitancy and addressing them is important to achieving herd immunity through vaccination.

There have been study and systematic reviews reporting factors influencing HPV vaccine hesitancy in Asia.[19–21] Nevertheless, studies or review focusing primarily on the social and culture norms influencing HPV vaccine hesitancy are scarce. Vaccine hesitancy in Asia is unique compared to Western countries. In Asia, social, cultural, traditional, and religious elements strongly influence health-seeking behaviors and, particularly, vaccination.[22,23,] For decades, traditional conservatism and social norms have been values that are highly emphasized in Asian cultures compared to other parts of the world. To date, despite Asia's rapid development, both economically and in terms of social modernization, adherence to traditional values, cultural nuances, and conservatism remain values that play a significant role in prevention practices and the seeking of treatment. This paper puts forward opinions in which culture, normative beliefs, and religion influence HPV vaccination decisions in Asian countries, providing recommendations regarding HPV vaccination hesitancy and pointing out potential future research.

2. Cultural and religious sensitivity to sexually transmitted HPV

In many countries around the world, including Western countries and Asia, a positive diagnosis of HPV carries negative moral connotations.[24–26] Likewise, with vaccination against HPV infections, embarrassment surrounding receiving the vaccine has been an issue since the introduction of the first HPV vaccine up to the present day. Compared to Western countries, people in Asian countries are more sexually conservative. In Asian culture, sex-related issues are taboo topics and even considered obscene. For instance in Malaysia, a Muslim majority country, sensitivities regarding sex-related issues create various types of barriers to sexual and reproductive health information, support, and practices.[27] Such deeply rooted cultural taboos inhibit parents from discussing sex with their children, and open discussion about sexual health is limited in the family and society.

In the U.S.,[28] likewise many countries in the Asian region, HPV vaccination is routinely recommended for adolescents aged 11 to 12 y, though it can be initiated with children as young as 9 y of age. Routine catch-up HPV vaccination is recommended for individuals aged 13 through 26 y, and, recently, the HPV vaccine was approved for adults 27 through 45 y of age. As such, cultural sensitivity regarding HPV vaccination has been profound for the following three groups of women: young adolescent girls of 9–12 y of age, young women aged 13–26 y, and adult women aged 27–45 y.

2.1 HPV vaccine hesitancy among parents of adolescent girls

The fear that vaccinating adolescent girls against HPV infection will encourage sex due to the protection against sexually transmitted HPV is common across many Asian countries. Parents from affluent Asian regions, such as Hong Kong and South Korea, as well as developing Muslim countries in Asia, were hesitant and expressed concern over vaccinating their young adolescent children against HPV because of the fear that it might condone early sexual initiation.[29–31] Religion has an important influence on the administration of HPV vaccines to adolescent girls in Asian countries. Parents with stronger religious beliefs are more likely to oppose the HPV vaccine compared to parents with less strong religious beliefs.[32,33] In Malaysia, in Muslim countries, Islamic values and ethical guidelines often shape healthcare-seeking behaviors. Muslim parents are concerned that the vaccine would promote risky sexual behaviors among teenagers.[34] Apart from the concern that daughters will see administration of the HPV vaccine as condoning sex and promoting risky sexual behavior, some parents view sexual activity among

adolescents or intercourse before marriage as uncommon in their society due to strict religious practices and teachings. In addressing parental HPV vaccine hesitancy, it has been suggested that healthcare providers' communication with HPV vaccine-hesitant parents is found useful in that it both imparts knowledge and addresses erroneous beliefs.[35] Healthcare providers should inform parents that the HPV vaccine is best given before the onset of sexual activity. Informing parents that evidence shows no increase in the sexual activity of girls who have received the HPV vaccine compared to unvaccinated girls would be useful.[36]

In Asia, religion has an important influence on beliefs and the acceptance of the HPV vaccination. It is also well established that parents with strong religious or cultural views are less likely to accept HPV vaccination.[37] A better understanding of the role of religion in influencing HPV vaccination is vital. It is important to involve religious leaders to address vaccine concerns among parents with strong religious beliefs.

2.2 HPV vaccine hesitancy among adult young women

Although adult young women can make their own decisions about their own vaccination, many may face social stigma associated with seeking vaccinations that protect against sexually transmitted infections. In many Asian culture, premarital sexual intercourse is viewed as a deviant behavior by society due to culture and religion constraints.[38–40] Many societies uphold the norms of sexual abstinence before marriage and social values that emphasize virginity until marriage for girls. As a result, young adult women fear being labeled as already sexually active or about to engage in premarital sex if they seek HPV vaccination.[41] In India, just seeking HPV vaccination may stigmatized by the community and viewed as tarnishing a family's prestige.[42] Furthermore, a study among Asian young women living in a Western country revealed that young women's beliefs about the role of religion/spirituality on sexual decision-making were associated with the administration of the HPV vaccine.[43] Those having higher mean scores on the religious/spiritual belief items were less likely to have received the HPV vaccine compared to those with lower religious/spiritual belief scores.[43] This finding highlights the need for partnerships with religious authorities or spiritual organizations in order to improve HPV vaccine acceptability among young adult women.

Young adult Asian women, particularly unmarried and staying with parents, tend to adopt a passive role in their own HPV vaccination decision-making because they abide by household rules and gender roles in decision-making. For fear of offending or disrespecting parents or the elders in the family, young adult women often seek permission from elderly family members despite being of an age at which they can make full decisions regarding HPV vaccination.[44] This highlights the need to better educate parents and the elderly in the community regarding HPV vaccination. Acceptance of HPV vaccination requires community engagement as a key to success[44] particularly in communities bound by strong religious and cultural beliefs.

2.3 Sensitivity surrounding HPV vaccination of adult women

Given the continued risk that adult women face and research showing that HPV vaccination is efficacious, safe, and immunogenic in women up to the age of 45 y,[45] in 2018, the U.S. Food and Drug Administration approved a supplemental application for Gardasil 9 [Human Papillomavirus (HPV) 9-valent Vaccine, Recombinant], expanding the approved use of the vaccine to include women and men aged 27 through 45 y.[46] Sensitivity surrounding HPV vaccination for adult women, especially women who are married, is the most challenging. Even participation in HPV testing has the potential to communicate messages of distrust, infidelity, and promiscuity to women's partners, family, and community.[24] To date, little has been reported on married adult women's perspectives or experiences when seeking HPV vaccination. A recently published study on adult Chinese women's intention to receive HPV vaccination revealed an important influence of spouse/partner decisions in HPV vaccine uptake.[47] In some societies in Asia and around the world, women's healthcare decision-making is subjected to religion and social–cultural norms.[48,49] It is anticipated that married women will feel heightened stigma if they seek HPV vaccination within the context of marriage.

3. Beliefs in traditional local remedies

For centuries, indigenous cultures around the world have used traditional local remedies to treat cancer; although, only a few have been clinically tested for their bioactivity.[50–52] Traditional local remedies remain popular health resources for many Asian countries, and, often, low-income countries (LICs) record a higher prevalence of use.[53] In many cases, despite the absence of robust evidence for their effectiveness, custom and folk religion shape people's traditional medical care practices.[54] In Southeast Asia, cancer patients (including female reproductive cancers such as breast and cervical cancers) spend a considerable amount of money on traditional local medicine.[55] A study from an African country reported the use of traditional medicine for the prevention and treatment of cervical cancer.[56] In the study, there were numerous factors that influenced the use of traditional local remedies, ranging from cultural norms and traditional beliefs to other triggers, which included fear and embarrassment of being known to have the illness, stigmas associated with cervical cancer, and the health system-related barriers influence women to resort to traditional medicine.[56] Alarmingly, women viewing traditional remedies as being used to prevent and cure cervical cancer may possibly result in neglect in preventative care, such as preventive screening or vaccination against HPV. In Malaysia, a Southeast Asian country, healthcare providers reported that despite free vaccinations provided by the national immunization program, which included the HPV vaccination, there were parents who oppose vaccination and refused to vaccinate their children. The reliance on traditional medicine for health needs is very popular in Asian countries due to historical and cultural reasons. Instead, parents who oppose vaccination believed in

traditional herbal remedies, homeopathy vaccines, and the use of high doses of vitamins as alternatives to vaccinations.[23]

There is the need for a targeted, culturally sensitive awareness campaign to enlighten people about the unscientifically proven safety and efficacy of traditional remedies and their potential dangers, and, at the same time, to promote effectiveness of modern medicine in the treatment and prevention of cervical cancer through vaccination. Since other external factors, namely stigma and health system-related barriers, may also cause women to seek unconventional treatments, it is important to understand local community needs and to establish a friendly and culturally competent patient-centered healthcare to facilitate the seeking of conventional treatments. Recommendations by family members or friends, sanctioning by families, and the creditability of traditional healers were also among the reasons that people in Asia prefer traditional remedies for cancer and vaccination.[17,57] The public should be warned against anecdotal evidence cautioned about the use of traditional medicines in the treatment and prevention of cervical cancer. The recent resurgence of public interest in herbal remedies, attributed to both traditional and social media, has enabled the spread of false information, and unverified testimonies of traditional healings have fostered growth in the use of traditional remedies to an extent that many forgo conventional prevention practices and treatments.[23,58,59] The spread of false online information in social media is a threat to curing vaccine-preventable diseases, and it should be tackled by local authorities.

4. Dilemma of the halal HPV vaccine

Muslims refusing immunizations on the grounds that vaccines are non-halal (i.e., not permissible under Islam) has been a major issue that has resulted in global concerns, especially in Asia, which is currently home to the largest Muslim population. The major concerns are the presence of ritually unclean materials (*najs*) in vaccines, especially porcine or porcine-derived components.[60,61] When the HPV vaccine was approved for use, like with other vaccines, Muslim parents raised concerns about whether the HPV vaccines were in compliance with the strict permissible standards outlined in Islam. Unlike other vaccines, the fact that the HPV vaccine is a vaccine that prevents sexually transmitted HPV further heightened resistance to vaccination. There is mounting evidence showing that young Muslim women and parents refuse HPV vaccination because they are uncertain if vaccination against HPV infection is permissible in Islam, considering the long-existing debate about the halal uncertainty of vaccines in general.[34,41,62,63] The acceptance of HPV vaccines is challenged by halal uncertainty over the component ingredients and the manufacturing process of the vaccines, as well as the morality of seeking protection against an STI infection where one of the risk factor of the infection is having multiple sexual partners.[64]

The concept of halal in Islam is complex. A non-halal material is permissible under certain circumstances. In Muslim country like Malaysia, for instance, this is reflected in a guideline for the usage of non-halal product in medicine produced by the Ministry of Health and the local Islamic authorities.[65] Based on the guidelines, a non-halal containing medicine is permissible to be used in Islam provided that (1) there are no other alternatives, (2) the content, indication including risk and benefit is informed to the patient, (3) the usage of the medication is with informed consent, (4) usage of the medicine would prevent harm or necessary for the treatment based on healthcare professional evaluation. The main concept that is further pressed is *darurah* (an impure substance is permissible to save lives in the event of no other alternatives).

In addition, not all vaccine contains non-halal product. The content that is usually debatable is the culture media that is used for propagation of live vaccine such as human fetal cell for Rubella vaccine and monkey kidney cell (Vero cell) in the production of poliomyelitis vaccine. The animal or fetal cell is considered *najs* (impure) in Islam. However, the medium is not inserted directly into the vaccine and the traces of the non-halal medium have undergone characteristic changes from impure substances into pure substances. This concept is called *istihalah* in Islam. Although this concept is not accepted by some of the Muslim sect, coupled with the rulings of *darurah*, vaccines are permissible to be used in Islam.

There has also been a concern that HPV vaccine is a recombinant viral-like particle (VLP) that is produced using insect cells (Sf9) from *Spodoptera frugiperda* or fall armyworm. In Islam, the consumption of worm is debatable among scholars.[66] Some of the scholars agree that it is permissible if it is not harmful. Additionally, there are neither fetal cell nor porcine-based substances used in the production of HPV vaccines. Despite that, some of the Muslim hesitant communities were ill-informed of these facts. They resort to assumption that HPV vaccine contains non-halal substances therefore it is not permissible.[34]They resort to generalization that all vaccine contains non-halal substances therefore it is not permissible. To date, of the three globally licensed HPV vaccines, Gardisil®4 and Gardisil®9 are produced using yeast cells, while the antigens in Cervarix are produced using the Sf9 cell (as host cells). The recently approved bivalent Innovax's HPV vaccine (Cecolin®) by the China National Medical Products Administration (NMPA) is developed using Escherichia coli. These information should be provided to the Muslim communities to assist them in clearing their doubts regarding the halal status of HPV vaccine.

Currently, there are no vaccines that have been fully certified as halal.[60] In the circumstances where no halal-certified vaccine is available, Muslim communities need to be supported by their respective countries' Fatwa council. In Muslim society, vaccination is permissible if the countries or the communities adopt a stand articulated by the edicts or fatwas implying that the vaccine is permissible for administration to Muslims. However, in some countries, Islamic authority varies by states. Malaysia, for example, has different Fatwa council and Mufti (chief Islamic leader) for every state. Nevertheless, none of the state Fatwa council deemed that usage of vaccine is not permissible nor non-halal. In fact, a few of the state Fatwa mandate that vaccination in regard to National Immunization Schedule is mandatory (wajib) in Islam.[67] However, due to the non-unified stance of the Fatwa

council, uncertainty still lingers among Muslim communities thus further worsen vaccine confidence.

It is imperative that the Ulama (religious leaders) and the Fatwa Council members take a unified stance and inform the public about the Islamic view on the permissibility of vaccination including HPV vaccine so that they could help to alleviate public fear. Furthermore, religious leaders should emphasize the fact that not all vaccine contains non-halal materials and if there is any, the amount of the material is insignificant, or almost negligible. In addition, the WHO for the Eastern Mediterranean confirmed that the porcine sources used in some vaccine have undergone characteristic changes from impure substances into pure substances (*istihalah*) that are permissible for use.[60]

In Muslim majority countries, where the main concern of vaccine acceptance is concerning the impure substances in the vaccine, a reliance on religious ruling such as fatwa would help to improve vaccine confidence.[12,68]

Addressing the second issue, which is the morality of administrating a vaccine that prevents a sexually transmitted infection, in a Muslim context remains a great challenge. Above all, Muslim religious leaders play an important role in resolving ethical controversies surrounding vaccination against sexually transmitted infections. Muslim religious leaders should come together with a unified stance regarding the benefit and importance of vaccination.

5. Anti-vaccine conspiracy theories

Believing in anti-vaccine conspiracy theories considerably impacts vaccine hesitancy. The anti-vaccination movement has used conspiracy theories as an attempt to influence people into believing the dangers of vaccines, causing them to subsequently refuse vaccination. A common conspiracy theory about vaccines is the myth that vaccination is a profiteering motive of all parties along the immunization supply chain, including pharmaceutical companies, authorities, and physicians, although it does not specifically pertain to HPV vaccines. Apart from the claims that pharmaceutical companies are making tremendous profits from vaccines, there are anecdotal beliefs that researchers cover up evidence of the harmful side effects of vaccines and inflate statistics on vaccine efficacy.[69] In Western countries, the profit-making conspiracy theory has greatly reduced intention to vaccination.[69] No studies have been conducted on the impact of the profit-gaining conspiracy on vaccine uptake in Asia. Nevertheless, healthcare providers in an Asia country noted that there are widely spreading profit-gaining conspiracy theories over social media in Asia and that physicians experience patients rejecting vaccination due to this reason.[23] Although no report has specifically described the profit-gaining conspiracy in regard to the HPV vaccine, with the HPV vaccine being one of the most expensive vaccines in routine vaccinations, it is likely to be perceived as an attempt simply to make profits. It would be useful to counter this perception by explaining to public the high price of HPV vaccines, such as the complexity of manufacturing the HPV vaccines, especially multivalent HPV vaccines, as well as the cost associated with supply chain logistics.

The second common conspiracy theory is the unfounded theory of vaccine as an anti-Muslim plot by Western countries to sterilize the Muslim population. The anti-Muslim plot targeted many countries in Asia and Africa with a majority Muslim population. Concerns about vaccines being part of a Western plot against Muslims have fueled a polio outbreak in Afghanistan and has caused the resurgence of polio in northern Nigeria.[70–72] Likewise, the HPV vaccination is particularly susceptible to this conspiracy theory due to the fact that the vaccine targets young girls. There is strong evidence showing that misconceptions that HPV vaccination is a method for sterilizing girls have resulted in the rejection of HPV vaccines in several LMICs.[73]

It is important for government authorities and religious leaders to work together to stop the circulation of the conspiracy and to combat people's faith in false conspiracy theories. In many Muslim countries in Asia, religion is important; thus, addressing vaccine hesitancy within an Islamic context requires strong partnerships between religious leaders and civil authorities to re-affirm the truths and benefits of vaccination.

6. Gender roles in decision-making

In many places in Asia, men traditionally have had more power and the final say in household decisions. In regard to healthcare, a woman may make her own decisions, but for many women, the decision still may not be an individual affair, but may involve joint decision-making with a partner or the decision of elder members in the family. Often, women are not involved at all in the decision-making of their own healthcare, particularly with regard to sexual reproductive health matters. For instance, in terms of family planning and contraceptive use in many Asian countries, various studies have revealed that the role of husbands is important in approving contraceptive practices and family size[72,73] Although no study has reported social norms condoning male dominance in HPV vaccine uptake of women, there was a study in India reported that women would seek permission from their partners or spouse before getting vaccinated against HPV.[74] Particularly in Muslim countries, fathers or husbands were identified as primary decision makers for the administration of the HPV vaccine.[75–77] In some cultures, women also need approval from their husband to vaccinate their child against HPV.[75,76,78]

In the event that the 9-valent HPV vaccine comes to be recommended for women who have initiated sexual behavior, it is important to gain male opinion about their partner being vaccinated against the sexually transmitted HPV infection and to determine whether or not men would support their partner seeking HPV vaccination. Married women in most Asian sociocultural contexts will seek their husband's permission regarding their own healthcare before making a decision.[79] Some women associate asking permission with being respectful toward their husbands.[79] In many cases, women may not able to override their husband's decision. Married women may find it difficult to seek permission from their husbands to get vaccinated against sexually transmitted HPV infections. Furthermore, acquiring an HPV vaccine in a married context

may imply distrust of the husband, stimulate a husband's fear that his wife is engaging in extramarital sex, or the condoning of extramarital sexual conduct in a marital context. It is unknown how married men would respond to their spouse seeking an HPV vaccination. To date, men's perspectives on their wives seeking HPV vaccination have never been reported. Future studies are warranted since the perspective of men would provide information for intervention messages to improve male partner support for the vaccination of women. Perspectives from married men and women in Asia are needed to debunk the myth that seeking HPV vaccination is inevitably viewed as deconstructing the institutions of marriage, family, and morality in an Asian context.

Additionally, women's autonomy in household decision-making is found to be positively associated with younger age, greater educational attainment, and having paid employment.[80] Often, women in Asia are disadvantaged by a lack of awareness of their legal rights. Enhancing health-related decisional authority and social status of women can act as a fundamental measure to improve maternal and child health status, including vaccination.[81] To increase the vaccination rate among women in Asia, health-related empowerment of women is needed so that more women can make their own decisions, including vaccinations for their children.[82]

7. Negative events of HPV vaccines

Negative events due to vaccines can be catastrophic and cause a considerable sudden reduction in vaccine uptake. In Asia, one of the most prominent catastrophic negative events of HPV vaccination that shattered public confidence was the HPV vaccine crisis in Japan. A subsidized HPV vaccination program commenced in Japan in 2010, and the HPV vaccine was introduced for routine use in the national immunization program for girls aged 12–16 y in 2013. In 2012, the HPV vaccination rate for Japanese girls aged 12–16 y was as high as about 70%.[15] Shortly after the introduction of the HPV vaccine in the national immunization program in 2013, a series of news reports on severe adverse effects following administration of the HPV vaccine (unsubstantiated) resulted in the recommendation for vaccination being suspended in consideration of heightened public concerns.[83] As a result, the HPV vaccination rate fell sharply to less than 10% by 2014.[14,84-86] Public confidence in HPV vaccination can be easily shattered by anecdotal news in social networks, therefore warranting serious attention. The strong negative publicity over the news surrounding the HPV vaccine in Japan, despite no empirical evidence of adverse side effects, has unnecessarily resulted in a drastic and sustained reduction in confidence in HPV vaccination.[83,87]

Other well-known negative events in Asia are the vaccine safety-related events where people, including children, were given counterfeit, faulty, or expired vaccines. Though these events have not involved HPV vaccines, nonetheless they have created distrust in obtaining HPV vaccines in mainland China and Hong Kong.[88] Negative events of vaccine are common in China. Between 2003 and 2018, a total of 39 reports of vaccine safety-related events were found. Of which, 16 had an identified adverse event following immunization (AEFI), including death.[89] One of the results of these kinds of safety failures is that Chinese women continued to travel to Hong Kong for HPV vaccine even after the HPV vaccines became available in their country (supply shortages in China also played a role). Of direct relevance to HPV vaccine is that in April 2019, a fake HPV vaccine was found in the Chinese market.[90] This incident further exacerbated concerns among the general public in China over the safety of HPV vaccine administration. Disturbingly, a few months after the fake vaccine incident in China, women in China who sought HPV vaccination in Hong Kong were confronted with the news that some HPV vaccines in Hong Kong were reportedly fake, and possibly contaminated.[91] Although no serious AEFI was reported, Chinese women were left with a dilemma in terms of the decision to vaccinate against HPV over the negative vaccination events.

It is of utmost importance that women who seek HPV vaccination receive efficacious and safe vaccines that protect them from getting infected with HPV. Therefore, a more restrictive supervision system for vaccine production and more emergency preparedness, including health and risk communication strategies, for vaccine safety should be implemented to put an end to these events.[89] Additionally, stringent rules and severe penalties can provide a powerful deterrent to the production of disqualified and counterfeit vaccines.[92] Much effort is needed to restore and maintain women's confidence in HPV vaccine in affected countries.

8. Acceptance and confidence in local Asian vaccines

The global demand for HPV vaccines has soared in recent years, and current HPV vaccine manufacturers have been unable to keep up with demand. The existing HPV manufacturers are urged to increase their manufacturing capacity. Nevertheless, the process of making vaccines is complex, and the WHO predicts supply will not meet demand before 2024.[93] It is of deepest concern that the current HPV vaccine shortage could result in failure to introduce or sustain programs in some countries, particularly those with a high burden of cervical cancer.[94] As a result, the WHO is calling on countries that are vaccinating boys against HPV to suspend these programs until supplies for girls who need the vaccine are sufficiently met.[93] It is projected that the China and India HPV vaccine market may account for one-third of the global market by the year 2030.[95]

Being the highest global demand for HPV vaccine, it is fortunate that HPV vaccine manufacturing companies based in China and India, namely Innovax (licensed in Dec 2019) and Walvax (HPV-16 and HPV-18), China National Biotech Group (HPV-16, HPV-18, HPV-52 and HPV-58), and Serum Institute of India (HPV-6, HPV-11, HPV-16 and HPV-18), are among the companies that are developing new HPV vaccine.[96] In particular, the products and Xiamen Innovax Biotech from Shanghai Zerun Biotechnology, a subsidiary of Walvax Biotechnology, are currently in advanced clinical development. And most recently, the bivalent Innovax's HPV vaccine (Cecolin®) was approved by the China NMPA on December 31, 2019.[97] The HPV vaccine supply is currently

monopolized by Western pharmaceutical companies. The HPV vaccine developed by LMICs not only helps meet the high demand in Asian countries but they also help solve the current global HPV vaccine shortage and overcome low immunization rates in many LMICs. Additionally, the price of the new bivalent Innovax's HPV vaccine is 1000 Yuan (approximately 145 USD) per 3 doses compared to the price of the imported bivalent HPV recombinant vaccine (Cervarix), which is 1800 Yuan per 3 doses. The lower cost of the Asian vaccine certainly created an opportunity for LMICs to vaccinate a greater number of girls against cervical cancer.

Of note, one of the potential challenges faced by new HPV vaccine manufacturing companies in LMICs are gaining the acceptance and confidence of consumers. The acceptance of domestically manufactured HPV vaccines is particularly challenging in China since the country's food and drug safety has constantly been a public concern. A repeated series of safety incidents (described above) and genuine concerns related to domestically produced vaccines, as well as the faulty domestic cold chain management of vaccines over the decade, have shattered Chinese consumer's confidence in almost all domestic vaccines, shaping their choice in favoring imported vaccines. Therefore, improving vaccine safety issues is important to restoring local acceptance, as well as gaining international consumer confidence in the HPV vaccines manufactured by LMICs.

Apart from trustworthiness issues, another possible concern is the acceptance of the young Asian generation over locally manufactured products. The young generation, especially the millennial generation, is becoming more westernized in lifestyles choices. Prestige, social norms, and values in modern society influence young people's favoring of imported products.[98,99] Since catch-up HPV vaccination is recommended through 26 y of age for those who missed routine recommendations for HPV vaccination during adolescence, young millennials in Asian countries represent a large market for HPV vaccines. It is thus crucial to understand their confidence in Asian healthcare products and to intervene in terms of their healthcare consumption behaviors in order to not only accelerate HPV vaccine administration but to also benefit the economies of LMICs.

9. HPV vaccine uptake in males

HPV infection does not exclusively impact women. As in women, HPV is associated with anogenital cancers in men, specifically of the anus and penis. The prevalence of external genital HPV infection in men is higher than cervical HPV infection in women.[100] Global comparison suggests that HPV-associated anal cancers in males are higher in Asia (India and China) than in the US.[101] The burden of anogenital HPV infections in Asia men, as measured by HPV DNA prevalence, ranges widely, from estimates of 1.3% (among university students in Japan) to 89.4% (men who have sex with men [MSM] in Thailand).[100] Similar to the trend worldwide, the prevalence of HPV infection among HIV positive Asian men is higher, it ranges from 30% (Thailand HIV-MSM) to 99% (China HIV-MSM).[100]

Currently, only the quadrivalent vaccine (Gardasil®, protecting against HPV 6/11/16/18) and the nonvalent vaccine (Gardisil®9, protecting against HPV 6/11/16/18/31/33/45/52/58) are recommended for men.[102] Of important note, most of the national HPV vaccination programs are targeted for young female adolescents. HPV vaccination in men remains unsubsidized and it is excluded from many national immunization programs worldwide,[103,104] with only 11 countries in the world included boys in their HPV immunization schemes.[105] Despite the WHO call for suspension of male vaccination, HPV vaccination in men is essential due to numerous reasons, namely, it is more difficult to achieve herd protection with female-only vaccination, gender equity issues, and a lack of protection for MSM.[104] A recent Australian study demonstrated that having a male HPV vaccination program with 84% coverage will result in a 90% reduction in HPV in MSM.[106]

Studies on the Asian male perspective of HPV vaccination are scarce. It is estimated that Asian males face similar barriers to HPV vaccine uptake as those reported in studies conducted among males in Western countries, such as a lack of awareness, recommendations from healthcare providers, and the belief that the HPV vaccine does not directly benefit them.[107,108] One additional potential barrier to HPV vaccination among males is the traditional masculine gender norms that may deter help-seeking and preventative behaviors among men. Traditionally, men are averse to seeking help since seeking help could be perceived as a sign of weakness.[109] Worldwide, traditional masculine traits influence men's reluctance to use health services and to seek help for health problems. Similarly, in Asian men, masculinity plays an important role in shaping men's help-seeking behavior.[110] Likewise, in seeking HPV vaccination, masculinity could have an effect on men seeking prevention of HPV infections. To date, no studies have been conducted on the role of masculinity traits in Asian men and their impact on seeking HPV vaccination to prevent themselves and/or their partners from HPV infection. Further investigations are warranted since understanding this can provide insight into strategies to increase HPV vaccination among Asian men.

In many countries in Asia, stigmas and discrimination related to same-sex activities are heightened due to social and religious beliefs deeming same-sex sexual acts as unacceptable. Many sexual and gender minority (SGM) people experience stigmatization by society, family, and the healthcare system,[111] This has resulted in additional barriers to them seeking health prevention, including HPV vaccination. In the U.S., HPV vaccination among SGM populations is only 5–21%.[112,113] As it is well established that MSM faces various challenges when seeking health services,[111,114] hence, similar challenges are faced when seeking HPV vaccination. The various forms of stigma that SGM populations experience in both their public and private lives that can undermine HPV prevention efforts remain largely unknown in Asian countries, warranting investigation.

Studies have shown high self-reported acceptance of HPV vaccination among SGM populations in some Asian countries, varying from just over 23%[115] to over 90% when they were well informed about HPV-related diseases.[116,117] Actual

HPV vaccination among SGM people in Asia is understudied. Nonetheless, it is estimated that many remain unvaccinated despite the high prevalence of HPV infections. There is a need to increase awareness regarding the risks of HPV-related diseases and the importance of HPV vaccination among adult males and SGM populations in Asia. It has been suggested that SGM-competent providers as well as healthcare settings and services that are friendly to SGM individuals may help to reduce stigmas associated with seeking STI prevention and hence increase HPV vaccination.[118]

10. Social–cultural approaches to providing information about HPV vaccination

All knowledge, including understanding cervical cancer, its burdens, HPV infections, and HPV vaccines, is important for HPV vaccine decision-making among Asian people.[119–125] Of note, most studies have shown the necessity of promoting HPV-related health literacy to increase HPV vaccination coverage across socioeconomically disadvantaged groups.[33,124,126] Culture and health literacy influence the content and outcome of health care practices.[127] Fundamentally, health literacy initiatives and interventions addressing HPV vaccination gaps should also be culturally tailored. However, little has been published about culturally tailored education towards achieving cultural appropriateness in HPV promotion activities in Asia. Perspectives from Asians living in Western countries have revealed a variety of needs related to health information, warranting a culturally sensitive approach to increasing the acceptability of the HPV vaccine.[44] For instance, some young adults indicated a preference toward educating parents about HPV vaccination.[44] Alternatively, some women fear the topic will offend the elderly or cause disrespect, and they would prefer that the information be delivered within the religious community.[44] The cultural diversity and ethnic composition among countries in Asia, as well as within an individual Asian country, warrant for individual countries in Asia to tackle such diversity with tailored, culturally sensitive health education to effectively increase health literacy and to accelerate uptake of HPV vaccines in their respective countries.

11. Conclusion

This paper highlights the impacts of different social–cultural factors on HPV vaccination decisions in Asia. Cultural and religious sensitivity to sexually transmitted HPV poses a threat to HPV vaccine uptake for women of all ages, and as well as men, for which the vaccine is recommended; thus, specific, targeted culture-specific interventions at the individual and community levels are desired. Social–cultural approaches to the provision of education to overcome HPV vaccine hesitancy are essential in Asia and should involve community and religious leaders. Notably, the bivalent Innovax HPV vaccine is now available to curb the current supply shortage and to make vaccination more affordable for the implementation of national HPV immunization programs in Asia and worldwide. However, the culture of preference for imported or western products and fear of fake HPV vaccine needs to be addressed to gain consumers' confidence in the HPV vaccines manufactured by LMICs. In summary, social culture norms related to hesitancy in receiving HPV vaccine and accepting HPV vaccines manufactured by LMICs are challenges warrant attention.

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