



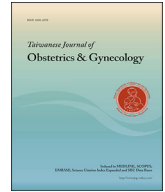
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Review Article

A review of vaccine effects on women in light of the COVID-19 pandemic

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ABSTRACT

The pandemic situation triggered by the spread of COVID-19 has caused great harm worldwide. More than six million people have been infected, and more than 360,000 of them have died. This is the worst catastrophe suffered by mankind in recent history. In the face of this severe disaster, people all over the world are frightened of the prospect of facing an outbreak or an annual recurrence. However, the development of a vaccine will help control the impact of COVID-19.

Women in particular have been more seriously affected by the pandemic. Since the pressure and physical load they suffer are often greater than what men endure, women are more threatened by COVID-19. Though women have a poorer quality of life and work and face worse economic conditions, they also tend to have better physiological immunity than men, which can ease the effect of COVID-19. The early development of a vaccine against COVID-19 is an important issue that must take into consideration women's better immune response to the virus along with the technique of hormone regulation. Relevant research has been conducted on female-specific vaccines in the past, and women's issues were considered during those clinical trials to ensure that complications and antibody responses were positive and effective in women. National policies should also propose good strategies for women to be vaccinated. This could improve consciousness, give women a better vaccination experience, enhance their willingness to vaccinate, and protect them from COVID-19 infection.

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Preface and background

It has been more than three months since the outbreak of COVID-19 (also known as novel coronavirus pneumonia), which has spread to more than 150 countries and regions around the world [1]. In response to the pandemic, countries have begun vaccine development and taken other prevention measures in an attempt to prevent or slow down the impact of the pandemic [2,3].

In response to this pandemic, more and more medical and public health experts, scholars, and philanthropists have invested in vaccine research [4]. For example, Bill Gates has made great contributions to World Health Organization (WHO) developing a vaccine, hoping that the vaccine will provide a glimmer of light in this dark situation [5].

Unfortunately, gender, social, and economic status inequality make some populations particularly vulnerable to COVID-19, which must be considered during vaccine development. Such populations will suffer from high mortality rates because of poverty, lack of medical care, gender inequality, and poor living environments [6,7]. For example, in countries without public health care, poverty will limit an individual's access to medical assistance. Existing gender inequalities will result in different treatment for men versus women affected by the pandemic, and the spread of the virus could worsen gender inequality as well [8,9].

Problems and impacts

Looking back at several major crises in human history, such as the 2003 severe acute respiratory syndrome (SARS) outbreak in Asia or the 2014–2016 Ebola virus epidemic in West Africa, shows

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that gender plays an important role. However, after such crises, lack of gender-oriented investigation is often ignored [10]. Since the rapid spread of COVID-19, the gender factor has also been ignored, especially in research on antibodies produced by vaccination [11,12]. Due to traditional cultural and socioeconomic situation, women are in a special predicament in the face of the pandemic, thus causing a higher risk of infection [13,14]. Therefore, in the face of the global impact of the pandemic, it will be very important for vaccine researchers and clinical workers to investigate the implications of gender during their analyses and vaccine development. Since COVID-19 is particularly dangerous, the early development of a vaccine will be the most important thing to help women deal with the pandemic [15,16].

Research purpose and motivation

The spread of COVID-19 depends on vaccine development. In recent years, many studies have pointed out that there are differences in the immune response of both sexes and its effect on vaccines. This paper reviews the literature to explore the possible impact of vaccines on women and the mechanisms of possible immune responses in order to provide a reference for the development of new coronavirus vaccines and to explore possible issues.

Vaccine application in pandemic considerations

In the current investigation on pandemic control, vaccine research and development are expected to be the most effective way to combat the novel coronavirus. Several studies have shown that influenza vaccination is the most effective way to prevent influenza infections in the elderly, reduce the incidence of serious complications, and reduce hospitalization or death [17]. It has been pointed out that vaccination can reduce the hospitalization rate for influenza by 35%, and all death by 50% [18–20].

The use of vaccines in general can decrease medical expenses, and influenza vaccines can effectively reduce the hospitalization expenses. Research shows that patients who receive the influenza vaccine can reduce their hospitalization expenses. In terms of the effect of the influenza vaccination in Taiwan, when the vaccination completion rate is 80% (and after deducting the cost of vaccination, examination, administration, and subsidy), medical expenditure can be reduced by 1.935 billion yuan [20].

The majority of COVID-19 deaths occur in the elderly population, female especially, and the risk of death is higher in patients with hypertension, heart disease, and diabetes, which is similar to the influenza virus. At present, most influenza vaccines in the world are recommended for those who are over 65 years old [21–23], and in 1998, Taiwan began to give priority for the influenza vaccine to those over 65. With many countries unable to control the pandemic situation, a vaccine will be the weapon of choice for the elderly. In the global vaccine competition, the key to success or failure depends on the rapid production of vaccines and of antibodies in humans without side effects [24,25].

Risks of vaccine development

There are many potential risks of vaccines, including no antibody production after vaccination or serious allergic reactions resulting in greater harm, which need to be considered with great care in clinical trials [26–28]. After the 2009 H1N1 influenza pandemic, countries in the Americas continue to strengthen influenza surveillance on high-risk groups (especially pregnant women), obtain more perfect information system through the immunization platform, strive to improve the adverse effects of high-risk groups on seasonal influenza vaccine, and greatly

improve the spread of the pandemic. The vaccination of influenza vaccine needs to select the right vaccine strain and the most appropriate time for injection in order to achieve the best risk control. Countries should closely monitor the risk of influenza vaccine, prepare for the vaccination plan, strengthen the quality of the vaccine, and possibly produce adverse antibody immune response [29–31].

Differences and mechanisms of gender impact vaccines

There are interesting differences between men and women when the body is attacked by pathogens. Women usually have stronger humoral immunity than men [32]. Immunity relies on the production of antibodies by B cells, especially to produce more antibodies to achieve self-protection. When considering infectious diseases that require antibodies for resistance, women tend to show lower incidences and weaker courses of disease when compared to men, and the effect of vaccination to produce protective antibodies to prevent infectious diseases is often better in women. However, compared to men, women are more likely to suffer from autoimmune diseases [33,34].

Biological mechanisms of antibody activation after vaccination in women

The biological mechanisms of an individual are different based on gender, which results in different antibody immune responses. A previous study found that human CC chemokine ligand 21 (CCL21) has a new G-protein-coupled receptor (GPR174) that can regulate B cell localization and inhibit the germinal center of developed male mice. However, female mice not have the same G-protein-coupled receptor, or was a vaccine used in relation to this receptor that did not work on female mice, displaying gender differences in humoral immunity and forming an internal gender dimorphism mechanism. This provided new ideas and potential new therapeutic targets for enhancing the effect of vaccines and for the treatment of autoimmune diseases caused by antibodies [34].

The antibodies produced by vaccine are produced after the B cells are stimulated by the antigen (attenuated vaccine) to differentiate into plasma cells. In order to differentiate into plasma cells more efficiently and produce more antibodies, B lymphocytes will migrate from follicles to germinal centers after being stimulated by antigens to combine with guidance receptors and become antigen-activated B cells. These receptors include chemokine receptors CXCR5 [35,36] and CCR7 [37,38] sphingosine-1-phosphate receptor 2 (S1PR2) [39], and G-protein-coupled receptor 183 (GPR183) [40,41].

These receptor molecules have no gender differences under normal conditions, but under the conditions activated by GPR183 and GPR174, genes for naïve B cells and germinal center B cells located on the X chromosome can also be activated by vaccination. GPR174 can move B cells further away from the germinal center and toward the T cell area. It is currently known that ligands that bind to G-protein-coupled receptors (GPCRs) include odors, pheromones, hormones, neurotransmitters, chemokines, etc., and these receptor components can be small molecules of sugars, lipids, or peptides, or they can be biological macromolecules such as proteins. G proteins are located next to receptors and cooperate with each other. Once the receptor and hormone are combined, a G protein will be activated to carry out related physiological reactions. A receptor activates different G proteins according to different bound hormones, and different G proteins can also regulate various physiological responses when properly activated by various vaccines. In mice of different genders, GPR174 has different effects on germinal centers. GPR174 can inhibit the ability of male mice B cells to form germinal

centers and produce plasma cells, which does not occur in female mice [42–44]. If female mice are injected with male hormones, female B cells will become like male B cells and begin to bind more $G\alpha$ protein, which will move toward CCL21 more effectively. These results indicate that the GPR174- $G\alpha$ complex induced by CCL21 has a gender difference that results in gender dimorphism in humoral immunity. It is worth noting that the gender difference in the mechanism of CCL21-GPR174- $G\alpha$ can explain the susceptibility difference between male and female autoimmune diseases. Male individuals rely on hormones to regulate the efficiency of specific GPCRs binding to $G\alpha$ proteins at specific stages of immune responses in cells, thereby fine-tuning antibody immune responses to achieve a different balance from females [44].

Different immune responses between men and women cause differences in vaccine effectiveness

The research team of the American Society for Microbiology (ASM 2016) presented observations on the differences in the effectiveness of vaccines between men and women [45]. Katie Flanagan of the University of Tasmania, Australia, published another example of a gender vaccine difference [46]. The study found that a tuberculosis vaccine inhibits the anti-inflammatory protein in girls, thus enhancing the effectiveness of the immune response to the vaccine [47].

The effect of hormones on the immune response has long been noticed in the field of biomedicine [48]. For example, estrogen can activate cells involved in antiviral reactions, and testosterone can inhibit inflammation [49,50]. Recently, Derezt et al. conducted experiments on nasal epithelial cells and found that estrogen can inhibit the replication of influenza A virus in female cells [51]. Additionally, many studies found the TLR7 gene located on the X chromosome, and one of the functions of the protein made by this gene is to detect viruses and initiate immune responses and is found to cause stronger immune responses in women than men. The exact reason for this is not yet known by biologists [52,53].

Since the immune responses of both genders are different, should gender be considered in vaccine development? Many biologists believe that it most certainly should be. In 2014, the NIH required researchers to indicate and examine gender differences when reporting the results of animal experiments [54]. In addition, the Audit Department of the US government recommended that the study of human body implemented on gender information should be open and transparent, and gender differences should be analyzed [55,56].

Gender difference related to the measles vaccine

The measles infection is the main cause of death among children. Although the measles virus has been controlled and eliminated in the modern day, there may be significant changes in measles epidemiology in the coming decades. With the gradual reduction of antibodies in the mother's body, the probability of infants suffering from measles will be higher and higher. Girls lose their antibodies from their mothers faster than boys, so they could get measles earlier than boys. Measles mortality depends on the intensity of exposure to the virus [57–59].

Development of women-based vaccines

Receiving the measles vaccine early can reduce mortality by 30% (41% for girls). This is the most effective vaccine to increase children's disease survival rate at present, especially for girls. Although it is not known why girls react more strongly to the measles

vaccine, the future development of a COVID-19 vaccine should also take gender into account [60,61].

After confirming that the human papillomavirus (HPV) infection is an important factor leading to cervical cancer in women, scientists have been committed to the research and development of effective and safe HPV vaccines [62,63]. Using biotechnology to make the protein of the HPV virus shell, we can make virus-like particles (VLPs) that, together with a special adjuvant, can cause a strong immune response and produce a high antibody concentration in order to achieve the desired preventive effect [64–66].

The HPV vaccine is used for prevention rather than treatment, and three doses of it produce the best protection. According to the scientific literature, the HPV vaccine can prevent persistent infections of HPV by 90%–100% [67,68]. The antibody concentration and response caused by HPV infections after vaccination are much higher than natural infections [69]. The Advisory Committee on vaccination practices (ACIP) recommends that the best age for vaccination is 11 or 12 years old, while women aged 13–26 years who are not vaccinated should be vaccinated [70–72]. It is also recommended that the HPV vaccine be set as a routine vaccination for boys aged 11 or 12 years old, and they should be vaccinated with the 4-valent human papillomavirus (4vHPV) vaccine [73,74]. The countries in the world began to provide a public vaccination program for women aged 12–26 years [75–77]. British public health points out that the coverage rate of the HPV vaccine in British women aged 12–13 years is close to 87% [78–80].

Angiotensin-converting enzyme 2 (ACE2) and female-based vaccine relations

The ACE2 receptor is the key for SARS coronavirus to enter human cells [81,82]. After the outbreak of COVID-19, research on its nature confirmed that it also entered into human cells using the ACE2 receptor. A virus channel was established in mice to develop “ACE2 gene-cloned mice,” which can be used for new vaccines and drug tests along with screenings to prove whether a vaccine is effective. Evidence from a large-scale study indicates that the concentration of ACE2 in the blood of men is higher than in women, which makes men more susceptible to COVID-19 than women [83–85]. The official US report found that the death rate is 55% for men and 45% for women. From a biological and immunological point of view, women usually have a stronger and faster immune response than men. While some researchers discovered that estrogen and testosterone may affect the novel coronavirus response [86,87], it has been found in animal experiments that male hormones have a higher affinity for ACE2. It means that COVID-19 is more likely to attack male cells, which is important to consider to the future for development of vaccines by the way avoiding the coronavirus from entering the cell through the ACE2 receptor [88–90].

Gender-related issues for the continuity of vaccines

Studies in West African countries also point out that girls' antibody loss rate is faster, which causes them to be infected with measles earlier than boys, and those girls need to strengthen vaccine injections in the future, otherwise may get infection recurrently [91,92]. Children who are not vaccinated against measles or who do not respond well to the vaccine, if not vaccinated continuously, will become the targets of infection in the future. Above problem has already appeared in West Africa. There were many pregnant young women found infected with measles, H7N9 avian influenza A virus pneumonia and ARDS can cause the death of the fetus or mother, with the hope of further vaccine development to prevent [93,94].

The relative effect of females on vaccines

Garenne (1994) pointed out that the proportion of females who died of the measles vaccine was higher than that of males [95]. Garenne believed that this was the result of hormone differences. In addition to exposure intensity and transmission mode, a child's own health conditions may also affect the death rate of the measles vaccine. People with chronic diseases such as Kwashiorkor and tuberculosis (TB) have a high risk of death in relation to the measles vaccine. Vaccination with other unrelated vaccines may also affect the severity of the measles infection in children [96,97]. In the Guinea Bissau study, it was found that if girls had recently received a live vaccine, the proportion of them who needed to be hospitalized after a measles infection was lower than that of boys, but if they had recently received an inactive vaccine, the opposite result occurred [98]. The severity of the symptoms of girls and boys is affected by age and social environment. In European society, young boys are more likely to be exposed to the virus, so the mortality rate is higher. Regular measles vaccination and prevention education are the control measures. The main mode of measles infection. Some studies have pointed out that, in addition to measles prevention, measles vaccination also has the effect of promoting immunity, which has a significant impact on women [99,100].

Discussion

Problems of the COVID-19 vaccine: too little time, too few clinical trials, too little gender experience

Vaccine development will be a particularly useful weapon against COVID-19. For more than two centuries, human beings have successfully used this medical technology to fight against viruses such as measles and influenza, proving that vaccines can stop disease outbreaks before they spread [101,102]. COVID-19, according to the WHO, currently has at least 62 candidate vaccines under development. The evidence shows that patients infected by the novel coronavirus can produce antibodies in the blood that can attack and neutralize the COVID-19 virus, so experts are optimistic that a vaccine will be successfully developed [103].

Considering the history of vaccine development, it will take a year or more before the world sees a COVID-19 vaccine [104]. The mumps vaccine is regarded as the fastest approved vaccine, but it was four years between the initial collection of virus samples and obtaining a drug license in 1967 [105]. There are three phases of clinical trials, and vaccine experts believe that COVID-19 candidate vaccine trials are completed. In the first phase, the results will not be seen until at least this autumn or the spring of 2021 [106–108].

There is a good reason to spend time testing vaccine safety. For example, in model experiments, some preliminary vaccines for SARS (a related coronavirus) actually enhance the disease. Peter Hotez thinks that completing the vaccine in a year to 18 months is unprecedented. Approaching the situation too anxiously could affect the health of the injected person, and researchers must be careful to evaluate the development of a vaccine. Traditional techniques rely on the immune system to respond to pathogen-specific proteins, which usually coat the surface of the virus, causing the body to react and produce many antibodies [109,110]. Vaccine developers have found that they do not need a complete virus and can use a single protein as a substitute to produce a strong immune response in the human body. Maria Elena Bottazzi believes that vaccines based on these proteins are easier and cheaper to make, and this has become the most commonly used method by medical professionals [111,112]. However, it is necessary to continue to study whether hormones affect the antibody production of vaccines and their impact on women [113,114].

One of the main problems in developing a COVID-19 vaccine is that there is no medically proven vaccine precedent for existing human coronaviruses. SARS in 2002 and Middle East Respiratory Syndrome (MERS) in 2012 were caused by close relatives of the novel coronavirus. Although the SARS mortality rate was approximately 15% over the course of three months [115]. According to the Texas Children's Hospital Center for Vaccine Development, coronaviruses are fatal, and SARS disappeared before the vaccine passed the clinical trials. In addition, there were too few cases of MERS in 2012 to allow researchers to gain more coronavirus vaccine-related experience [116,117].

Reasons for women refusing to vaccinate

According to the National Institute of Disease Control (NIS), the top five reasons for adolescents not receiving the HPV vaccine are parental lack of knowledge or need, safety concerns about side effects, or lack of advice [118,119]. Of these, the main reason for female adolescents to not receive the vaccine is lack of knowledge, and the main reason for male adolescents is lack of advice [120]. Another US survey of women aged 19–26 years pointed out reasons for not receiving the HPV vaccine, which included marital status, lack of information, concern over side effects, and medical insurance costs [121]. In a study in the UK that included a survey of women aged 16–19 years, three-quarters of the participants expressed concern over the side effects of the vaccine [122]. Another newer study analyzed the reasons why women aged 15–16 years in London, UK, did not vaccinate or did not complete three doses of the HPV vaccine. The most common reasons for women refusing to vaccinate include lack of awareness of their need for vaccination and safety concerns. Among the women who did not complete the three doses, the reasons they proposed included the need for more information and fear of medical procedures such as injections [123]. In the rural areas of Southeast Asia, women often refuse to get the HPV vaccine because they doubt the safety and effectiveness of it, are unaware of the risk of HPV infection, and are embarrassed by the vaccination's relation to sexually transmitted diseases [124]. According to many studies, the main reasons for not vaccinating against HPV are that the vaccine has safety and side effect concerns, there is a lack of vaccine information, or there are cognitive and cost issues [125–127].

Vaccination is effective for pregnant women against pandemic infections

The influenza vaccine is a kind of inactive vaccine. Antibodies will be produced in the body about 2–4 weeks after vaccination. It is important to note that the immune system of a fetus or newborn is not complete and must receive antibodies from the mother in order to prevent infections [128,129]. Two of the most important processes to achieve this occur when the mother transfers antibodies produced by her body to the fetus through the placenta during pregnancy and through the milk during breastfeeding [130]. The stronger the ability of the mother to produce antibodies, the more likely she is to transmit them to her child to prevent disease. In terms of biological evolution, this explains why mothers need strong immune systems. Antibodies passing through the placenta to the fetus can last for six months following childbirth. If the fetus is infected during pregnancy, transferred antibodies can at least slow down the infection symptoms, help prevent the spread of the disease and reduce the probability of complications [131,132]. The most effective way to prevent influenza is to vaccinate on time, and pregnant women can be vaccinated during any period of pregnancy. In addition, family members are advised to vaccinate together [133,134].

Complications of vaccination in pregnant women

During 2000–2003, two million doses of influenza vaccine were used on pregnant women in the United States, and 20 adverse events were reported, three of which were abortions [135,136]. Epidemiological studies showed that the rate of caesarean sections, premature deliveries, and congenital malformation of newborns, as well as negative neurological development and cancer incidence in pregnant women who received the influenza vaccine, were similar to pregnant women who did not receive the vaccine [137,138].

The physiological changes in pregnant women during pregnancy include decreased resistance to influenza and an increase in complications after contracting influenza [139–141]. The probabilities of premature delivery and stillbirth are also increased. Although the influenza virus rarely directly infects the fetus through the placenta, influenza in pregnant women may still have adverse effects on the fetus, including fetal neural tube defects, cleft lip, hydrocephaly, congenital heart disease, spontaneous abortion, premature delivery, low birth weight, and other issues [142–144].

Factors influencing women's intention to vaccinate

The factors that influence vaccination can be divided into background variables, health beliefs, and knowledge of vaccination [145]. A study by Wen Lifan et al. (2008) explored the intention of adolescent girls in Central China to vaccinate themselves against cervical cancer and the related influencing factors [146]. The study found that the significant differences between female high school students' intention to vaccinate at their own expense depended on family economy, smoking situation, and occurrence of cervical cancer within the family [147]. Additionally, female high school professional and technical students exhibited differences in intention based on number of sexual partners. In conclusion, family economy of low income is an important predictor of the intention to vaccinate at one's own expense [148,149].

Another study explored the vaccination rate of HPV among female college students in Greece and the factors for predicting vaccination. It was found that the factors for positive prediction of vaccination included higher education level of self and parents and easy access to health care services [150]. An previous study of women who received a free HPV vaccine found that at least one dose was significantly related to women's marital status, higher socioeconomic status, as well as whether they lived in a remote area [151]. Kessels et al. conducted a systematic study on the HPV vaccination among adolescent girls and its underlying factors [152]. The results showed that higher vaccination behavior was related to older age, access to a medical service provider as an information source, and a positive attitude toward vaccination [153–155].

A national survey was conducted to investigate the influencing factors on a parent's willingness to allow adolescent girls to receive the HPV vaccine. The results showed that the safety and efficacy of the vaccine were related factors affecting acceptability [156]. Marlow et al. (2009) studied young girls in the UK aged 16–19 years and pointed out that higher self-awareness of disease is related to vaccine acceptance [157]. The study showed that the higher the "general or special interest of self-awareness" score, the more likely the subject was to be vaccinated, and the higher the "special obstacle of self-awareness" score, the more unlikely the subject was to be vaccinated. The score obtained was a significant predictor of receiving the HPV vaccine [158]. A study of women between the ages of 19–26 in the United States found that "getting a doctor's advice and discussing the HPV vaccine with doctors" had an overwhelming predictive power, while student identity and personal perception of vaccine importance also had a good predictive power for vaccination [121,159]. Krawczyk et al. provided the health belief

model as the framework to investigate female college students and found that the negative impact of vaccination on health, doctor's advice, and positive attitude toward vaccination were significant related factors of HPV vaccination [113,160,161].

According to a study in Taiwan, to a certain extent, women's knowledge about vaccination action clues mainly comes from schools, media, and health units. Women's awareness of disease, action clues, vaccination health beliefs, and vaccination action intentions are significantly higher than men's [162]. According to the vaccination analysis by the staff of Taiwan's statistics and medical institutions, the main concerns about influenza vaccination are fear of side effects after vaccination (24.2%), doubt about vaccine safety (15.5%), and belief that influenza will still be acquired after vaccination (12.2%) [163]. Of the subjects who participated in this analysis, 70.1% believed that influenza vaccination should be carried out every year. However, 41.2% believed pregnant women did not need to be vaccinated against the influenza virus, and 36.7% believed that lactating mothers did not need to be vaccinated either.

Women's experience with vaccination is also an important consideration for their unwillingness to continue [164]. It was found that discomfort is a key factor affecting the willingness of women to vaccinate against influenza [165]. The main reasons are discomfort in response to vaccination, feelings toward previous vaccinations, and other factors belonging to personal and physical feelings. Xiao Huixin et al. pointed out that the willingness to vaccinate is consistent with the adverse reactions caused by 56.0% of influenza vaccinations [166]. Guo Xiue et al. pointed out that the rate of continuous vaccination cross two years accounts for 76.9%, but those who had been vaccinated for two consecutive years were no longer willing to do so, primarily due to feelings associated with vaccination during the previous year [167]. In addition, Su Bingguang and other scholars investigated 494 nurses, and 50.8% of the unwillingness to vaccinate was related to bad experiences with side effects after the injection [168]. In terms of women vaccination, willingness is related to the way vaccination is delivered. Research shows that the women's willingness to change the vaccine delivery method will increase by 70.4%, of whom 4.1% hope to provide a vaccine with four valence and multiple combinations, and 28.5% hope to provide an oral or nasal spray to replace the injection, however, 54.1% chose a brand of being trusted, of which usually made by foreign factories [169].

The government policy of gender vaccination

The current vaccination policies are formulated by the state. For example, the measles vaccination policy is to wait until the antibodies from the mother disappear in the baby, so the vaccination time in advanced countries is 12–15 weeks of age. In low-income countries, it is nine months [170].

The European Institute for Gender Equality (EIGE) specifically mentioned that the research and development process of new COVID-19 vaccines should pay attention to gender differences. Clinical trials must include men and women to eliminate gender blindness in medical research. This will help researchers understand the effectiveness and impact of possible vaccines on different genders, and it will also encourage them to pay attention to women's health rights and interests. Some research results show that in order to improve the vaccination rate, we need to change the way vaccines are delivered. For example, we might use tetravalent vaccines or oral administration. Nasal sprays and needle-free skin injections to reduce the occurrence of uncomfortable symptoms are other methods to improve availability and willingness. To improve the attitude and awareness toward vaccines, medical institutions can implement educational courses and advocacy activities to help

people understand the safety of domestic or foreign vaccines [171,172]. In addition, it is necessary to establish a convenient vaccination process to avoid unwillingness due to inconvenience or time-consuming vaccinations. Meanwhile, it is also necessary to actively contact people and assist in helping them understand the repercussions for not being vaccinated, which can improve the vaccination rate [173].

Conclusion

During the spread of COVID-19, women have suffered more pressure and a higher physiological load than men, and they have also suffered more from the threat of infection. Although women face relatively poor conditions in life and work and face worse economic impacts than men, women tend to have a better immune response to vaccines, which can help women reduce the effects of COVID-19 on them later. Using knowledge about better immune response and hormone regulation in women could help researchers develop a vaccine against COVID-19 sooner, which is an important anti-pandemic task. In the future, the research and development of vaccines should also consider women's issues during clinical trials to ensure that complications and antibody responses for women are positive and effective. National policies should also put forward good strategies for the vaccination of women in addition to having good consciousness. This will provide women with a better vaccination experience, which could enhance their willingness to receive vaccinations in the future.

Limitations and expectations

Considering women's issues during the development of vaccines is still relatively rare. Therefore, there is not much literature on women's issues in relation to novel coronaviruses. One must review the literature on SARS and MERS, influenza, HPV, and measles to review and discuss the effect of vaccines on women. In today's era of equal rights between men and women, there are still many differences. In the future, all research units should be encouraged to conduct relevant research on female-specific vaccines in order to more accurately understand their impact on women after vaccination.

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Declaration of Competing Interest

The authors have no conflicts of interest relevant to this article.

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