Review

Women and vaccinations

From smallpox to the future, a tribute to a partnership benefiting humanity for over 200 years

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Vaccines were first developed in England over 200 years ago and have made a significant positive impact on human society since. Not often realized is the intimate relationship shared between vaccines and women. Women were key to the initial development of vaccines; some were even advocating the concept of protection against infectious disease through prior asymptomatic infection (by variolation) before the publication of the report of the first successful smallpox vaccination in 1798.

Since that milestone, women have been important partners in the development of vaccines and advocates for their widespread introduction. Modern vaccine development would not be possible without the altruistic informed consent granted by many women for the participation of themselves or their children in vaccine clinical trials all over the world.

Vaccines have rewarded women handsomely in return. Individual women benefit in many ways ranging from safer pregnancies to preventing cancers to attractive, unblemished skin. Some vaccines are even specifically designed to prevent diseases primarily affecting women such as cervical cancer.

Vaccines also have offered societal benefits to women. These include better maternal health and fostering an environment more amenable to effective family planning. With these advances, women become more empowered and have access to better economic opportunities.

The challenge of meeting the millennium development goals specifically targeted for women will be facilitated by vaccines. A better realization by women of the benefits of this partnership secured over the past 200 years will enable them to reap fully the rewards of the future.

Introduction

The total value of vaccination includes aspects specific to the decrease of disease burden as well as benefits to society.1 Since vaccines are generally administered to children they are usually perceived to be the main beneficiaries of vaccination. However, even when vaccines are given exclusively to children, herd effect often renders benefit to other segments of society.2-4

Not often is it realized that women have had a close association with vaccines from their advent. They have been key players in the development and implementation of vaccines and, in return, have been major beneficiaries of their use. This article is a compilation of views from experts in vaccinology and women’s health examining this unique association.

The Role of Women in the Early History of Vaccination

Prior to its eradication by vaccination 30 years ago, smallpox was a major public health problem. In the late 18th century Edward Jenner, an English country physician, realized that while many of his patients bore the scars of smallpox, one group had unblemished skin. These were the milkmaids. Realizing that most of these women had previously suffered from cowpox he inferred that the widely held local belief that cowpox infection rendered protection against smallpox was indeed likely to be valid and extrapolated that this protection may be extended to other individuals if exposed to cowpox.5 Jenner subsequently inoculated a young boy (James Phipps) with cowpox and, to his satisfaction, found him protected against smallpox (Fig. 1), publishing his findings in 1798.6 Indeed, the word vaccine is derived from vaccinia (or cowpox), which subsequently protected the recipient from variola (or smallpox).5

While this landmark discovery is well documented and Jenner’s genius widely commended, women played two important and under-appreciated roles. Firstly the excellent cooperation of milkmaids made Jenner’s investigations possible. Secondly, one of their number (Sarah Nelms), who was suffering from cowpox at the time, volunteered a lesion on her arm as a source for the inoculum used on the boy.5

Sarah Nelms established a precedent—other women and girls have since also provided the seed for new vaccines. For example, the Jeryl-Lynn mumps vaccine strain, now established globally as the safest mumps vaccine, was derived some decades ago from a mumps infection of a young girl of the same name.7,8

Interestingly, in Western countries, a woman pioneered the concept of protection from infectious disease via asymptomatic exposure to an infectious agent even prior to the advent of vaccination. Before Jenner’s publication in 1798, the approach most widely used
for the prevention of smallpox was the somewhat unsafe practice of variolation. This method of scratching a person who is well with inoculum from a smallpox pustule was practiced in the East (probably for centuries), but was introduced to the West in 1721 by Lady Mary Montagu (the wife of a British diplomat in Turkey), who was also an advocate for its wider use.9

Women and Vaccines Today

Modern pediatric vaccine development would not be possible without clinical studies, and ethical studies require appropriate informed consent. Mothers normally accompany their children to vaccination centres (where such studies are often conducted) and they, often with limited or no scientific education, grant consent for their child's participation, primarily for altruistic reasons. Of course, these good intentions must never be abused.10

Not only do women permit their children’s participation in clinical studies but also volunteer themselves. For example, over 50,000 women have volunteered to participate in clinical studies for the development of human papillomavirus (HPV) vaccines by two manufacturers, including two recently published large-scale efficacy studies.11,12

Following vaccine development, one often finds women as key advocates for their introduction and implementation (as many primary public healthcare vaccinators are women) in society. Without widespread use and optimal implementation, vaccines would have limited public health and epidemiological impact.

Individual Benefits to Women

Vaccines making pregnancy safer. Almost all infections can cause complications during pregnancy, including a heightened risk of miscarriage. Unhygienic conditions, especially in developing countries, may predispose to maternal tetanus during delivery or backstreet abortions. An estimated 30,000 fatalities occur annually due to maternal tetanus (which is distinct from neonatal tetanus).13 Tetanus toxoid may be administered to women during pregnancy.14 Hence, the WHO program to eliminate maternal tetanus (in conjunction with neonatal tetanus elimination programs) has succeeded in reducing the number of high-risk countries for maternal tetanus from 57 in 1999 to 49 by the end of 2005, increasing the coverage of at least two doses of tetanus toxoid (TT2+) among pregnant women from -10% in 1980 to -70% in 2006 and thus reducing the number of reported cases of neonatal tetanus from over 25,000 cases in 1990 to under 8,400 in 2006.15,16

Certain infections are especially associated with more severe disease during pregnancy than at other times. For example influenza infection, especially during the second trimester of pregnancy, is associated with higher morbidity than influenza infection of similarly aged women who are not pregnant.17 Consequently, even though no clinical studies of influenza vaccine have been conducted on pregnant women, experts recommend the use of the vaccine in this population, as the benefits outweigh any potential safety concerns for either the mother or the fetus.18

Vaccines may also be used during pregnancy for post-exposure prophylaxis. Chick-embryo culture rabies vaccine is used in this manner with pregnant women exposed to bites from rabid animals. The vaccine has proven to be both safe and efficacious in this population against an otherwise fatal disease.19

Experts now recommend the use of most inactivated vaccines such as hepatitis A and B, inactivated polio vaccine (IPV), meningococcal vaccine and typhoid vaccine during pregnancy should the woman be at high risk, especially post-exposure.14 The use of live-attenuated vaccines such as rubella and measles during the puerperal period has also demonstrated public health benefits.14

Hepatitis E is a pathogen that causes more severe disease during pregnancy. The case fatality rate among pregnant women for hepatitis E can be as high as 25%, compared to 1–3% in the general population; the infection can also cause many other complications during pregnancy.20,21 A candidate hepatitis E vaccine has demonstrated over 90% clinical efficacy against hepatitis E disease and, in parts of the world where access to clean water is difficult, may be expected to protect pregnant women from this disease.22

Protecting mothers and infants during the perinatal period. Every pregnant woman wishes to have a normal, healthy child. Coupled with the benefits in maternal health by the prevention of infections during pregnancy, vaccination improves neonatal health. For example, rubella infections during pregnancy may cause congenital rubella syndrome, which can give rise to neurological deficits, blindness, cardiac disease or other defects in the newborn.23 The risk of congenital rubella syndrome has been reduced greatly (with rubella even eliminated in some cases) in countries that have implemented universal rubella vaccination (Fig. 2).24 Varicella infections during pregnancy may also cause a congenital varicella syndrome, along with an increased risk of herpes zoster, which can be expected to be prevented by vaccination.25 Vertical transmission of hepatitis B is prevented by vaccination of neonates at birth.26

An additional benefit of women being immunized is protection of the neonate via maternal antibodies.27 These antibodies can be acquired via trans-placental passage of IgG or from the colostrum.28 In this manner, vaccinating child-bearing age women with tetanus toxoid (even during pregnancy) prevents neonatal tetanus.13,14 Maternal influenza vaccination has also been demonstrated to be
highly effective in protecting neonates, even in a developing world setting.\(^{29}\)

However, care must be taken in scheduling the immunisation of infants as maternal antibodies can interfere with long-term effectiveness of vaccines if given too early in life.\(^{30}\) This is the case with measles vaccination which may be scheduled as early as six months of age in the developing world due to high local disease burden but often found to have limited effectiveness (when given so early in life) in the long term due to the interference by maternal antibodies on the child’s immune response to the live attenuated vaccine.\(^{31}\)

Reducing the incidence of infection in new mothers (and other care-givers of neonates) forms a disease-free cocoon around a newborn child. Targeted vaccination of family members and caregivers against specific diseases (e.g., pertussis) reduces the likelihood of a child coming into contact with these pathogens.\(^{32}\) This strategy can protect a child against diseases he (or she) may otherwise be too young to be vaccinated against, or may not have completed a full course.

**Cancer prevention.** Certain cancers are caused by infectious pathogens that predispose to oncogenesis. A particular example is cervical cancer, predisposed by persistent infection by certain oncogenic types of HPV. Of these, HPV types 16 and 18 (HPV 16/18) cause approximately 70% of the global cervical cancer burden.\(^{33}\) Annually cervical cancer claims the lives of over 270,000 women, many in their prime, with almost half a million new cases.\(^{34}\) An efficacious HPV-16/18 vaccine (especially with cross-protection of disease caused by other phylogenetically related oncogenic types) would be expected to prevent over 70% of this burden.\(^{11,35}\)

Benefits may also extend to other malignancies related to HPV such as carcinoma of the vulva and vagina among women, and the oropharynx and the anus in both sexes.\(^{36}\)

Certain cancers have been shown to express some specific antigens, when compared to normal cells. For example, breast cancers may express the HER-2 antigen. Immunotherapeutics using the HER-2 antigen based on vaccine technology may offer a novel, less reactogenic but nevertheless effective approach to the treatment of this disease.\(^{37}\)

**Vaccines primarily benefiting women.**

As discussed earlier, certain diseases affect women more than others and prophylactic vaccine uptake can be targeted primarily to them. For example, the current HPV vaccines have demonstrated -100% efficacy in the prevention of pre-cancerous cervical lesions caused by HPV 16/18 among women. With high coverage of women (above 70%) being pivotal, adding men to an HPV vaccine program would apparently double the cost of the program without necessarily demonstrating a proportional effect on the societal disease burden.\(^{38}\) Nevertheless, mathematical modelling suggests the herd effect of vaccinating the whole population, including men, may (depending on overall coverage) protect up to 30% of unvaccinated women from cervical cancer, who may or may not be screened concurrently.\(^{39,40}\)

For infectious agents with high basic reproductive rates, \(R_0\) (i.e., having the potential to infect a large number of individuals in a susceptible population), 100% efficacious vaccines are often not available and high community coverage needs to be reached for effective control.\(^{41}\) If the vaccine can be given economically (for example, in combination with vaccines for protection against other diseases) the disease may be better controlled by vaccinating the whole population.\(^{42,43}\)

This is the case with rubella. While a vaccine program involving only women and adolescent girls reduced the incidence of congenital rubella, rubella infection (and therefore congenital rubella) can be effectively eliminated through vaccinating the whole population. This was facilitated by the introduction of universal measles-mumps-rubella (MMR) vaccination.\(^{44,45}\)

Interestingly, a herpes simplex virus-2 (HSV-2) vaccine in development only demonstrated efficacy in females who were previously HSV-seronegative, with no significant efficacy in males.\(^{46}\) Such a vaccine may have a significant epidemiological impact if used in all women, especially as women are more likely to have HSV-2 infection than men.\(^{47-49}\) To the best of our knowledge, this is the only vaccine to have demonstrated an effect this pronounced due to the gender of the vaccinee.
The finding that male circumcision has a protective effect for female-to-male transmission of HIV/AIDS suggests that there may be alternative (albeit probably suboptimal) preventive measures available for men. However, this accentuates the urgent need for a prophylactic HIV/AIDS vaccine to protect women from this disease, as they continue to remain especially vulnerable to contract HIV infection and to suffer its societal and medical consequences, including a greater likelihood to suffer (vaccine preventable) cervical cancer.51,52

While the search for an effective prophylactic HIV vaccine continues, protection against sexually transmitted diseases (such as HSV) may also help prevent the spread of HIV infection among women.53,54

Societal Benefits for Women due to Vaccinations

Vaccines enabling better family planning. Basic vaccine programs have made possible significant improvements in infant and child mortality.55 This has been attributed to many reasons, including improvement of the basic healthcare infrastructure.56

One benefit of improved child survival is that women are freed to have fewer children through enhanced family planning.56 This would, of course, reduce the risks associated with high parity to both mother and child.

Cosmetic benefits associated with vaccination. In most parts of the world, a woman's physical appearance continues to be widely appreciated. While such views may be misguided, they do constitute a factor that can lead to increased stress for women.57,58

Since the advent of smallpox vaccine (and with the subsequent global eradication of the disease), both women and men have been given increased opportunities of having unblemished skin. Varicella vaccine also reduces the likelihood of unsightly scars and marks.

Although medical reasons should be paramount for the administration of any vaccine, women everywhere value the additional cosmetic benefits.

Vaccines enabling economic growth and improving maternal health. Investment in healthcare and especially vaccination programs has been established as an important mechanism to generate economic growth—indeed, return on investment for vaccination programs has been estimated at 12–18% and their overall and long-term benefit to society and especially the economy, is generally underestimated.59-61

For example, varicella vaccination of infants and children enhances the productivity of their parents (especially mothers) by enabling them to take fewer days off from work to look after their children if they happen to fall sick—an indirect health economic gain not always evident when considering the direct cost of varicella disease.62

Additionally, vaccines reduce inequities in society, another important mechanism to generate economic growth.1

The importance of economic growth for the health of women has been documented. For example, economic growth in the past has been accompanied by increasing mean birth weights, thus indicating an improvement in maternal health.63

Vaccines improving women's empowerment. An important consequence of the improvements in maternal and neonatal health and improved family planning is that it enables women to make the choice of bearing fewer children, allowing them to spend more time in education or the work-force than they would otherwise have. Coupled with the economic growth assisted by vaccinations (discussed above), this means that women have increased opportunities in today's society.

Women are found to be higher performers in school, provide better investment returns and a driving force for a growing economy.64 This leads to positive feedback to improve the environment for greater economic participation by women.

Additionally, vaccines make the workplace healthier. For example, healthcare workers (the majority of which are women, especially nursing staff) may be protected from many diseases that they would otherwise have been susceptible to following contact with their patients.65

All of these factors lead to enhanced female empowerment.

Conclusion

Women have been closely connected with vaccinations since their advent in the late 18th century and continue to be key to their development and introduction. In return, they have received a multitude of rewards, from safer pregnancies to cosmetic benefits to enhanced economic opportunities and empowerment. This symbiotic relationship is likely to continue, with more vaccines designed specially to control conditions afflicting mainly (or even exclusively) women.

Considering the Millenium Development Goals, our review suggests that vaccines will play an important part to achieve the two goals especially concerned with women, i.e., goal 3, to promote gender equality and empower women, and goal 5, to improve maternal health, as well as having a positive impact on many of the other goals.66,67 We consider it paramount that women realize this relationship so that they can consciously maximize their benefits from vaccination.

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