REVIEW ARTICLE

Vaccines for Orthopoxviruses: A Review

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ABSTRACT

Human and animal infections with Orthopoxvirus have become more prevalent in recent years. Although smallpox has been eradicated, vaccinations continue to play a role in controlling the spread of Orthopoxvirus diseases. First generation vaccines were successfully commercialized, and they were widely used previously. Besides, several second-generation vaccines that emphasize sterile cell culture techniques for vaccine production have been developed. Some of the third-generation vaccines also successfully trigger immune responses in the host, and they are being researched as safer substitutes for smallpox vaccines. Extensive work is still being done on the creation of fourth-generation smallpox vaccines, which include the creation of DNA subunit vaccines. Clinical studies must be conducted to evaluate the efficacies of these vaccines. Vaccine was effective in preventing smallpox infection. To achieve the Sustainable Development Goals of the United Nations, a new paradigm for vaccination research and product development must be established.
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INTRODUCTION

Orthopoxvirus is a genus that includes viruses such as smallpox, cowpox, horsepox, camelpox, and monkeypox (1). These viruses have the potential to produce deadly localized or widespread skin lesions. At its 33rd meeting on May 8, 1980, the World Health Assembly formally announced that the world and its whole population had won the war against smallpox (2). They also urged that the people stop receiving smallpox vaccinations (2). A significant portion of the world's population lacks immunity against smallpox and other zoonotic Orthopoxviruses (2, 3). Human and animal infections with Orthopoxvirus have become more prevalent in recent years. Although smallpox has been eradicated, vaccinations continue to play a role in controlling the spread of Orthopoxvirus diseases such as monkeypox, which have been recorded in numerous endemic nations since May 2022 (3).

Due to the eradication of smallpox and the discontinuation of mass immunization against the disease after 1980, the population's susceptibility to variola virus (VARV) and other lethal Orthopoxviruses has progressively increased (2). In addition, VARV is viewed as a potential agent of bioterrorist attacks, which would have severe consequences for the entire global population (4). The lack of effective antiviral drugs and the risk associated with current vaccinia virus (VACV)-based live immunizations demand the development of new, safe Orthopoxvirus vaccines and usage instructions (5). The threat posed by the intentional release of the viruses will need the quick detection of the condition, as action is likely to occur 10 to 14 days after the initial diagnosis (3, 5). A combination of vaccines and antiviral drugs may be an option for those who are infected. This review discusses the past, present, and future recommendations of vaccines used to prevent Orthopoxviruses infection.

Several of the Sustainable Development Goals (SDGs) of the UNESCO are dependent on the development of new vaccines. To achieve SDG 3: Good Health and Well-being (SDG 3), vaccines for Orthopoxviruses are potent tools for preventing infectious diseases and decreasing the burden of illness and death. The development of vaccines helps ensure the health and well-being of individuals and communities by protecting against diseases caused by Orthopoxviruses. Besides, the vaccines have a significant impact on SDG 1: No Poverty. When individuals are protected from vaccine-preventable diseases, they are less likely to incur expensive medical bills and endure permanent impairments.

FIRST GENERATION VACCINES

By the induction of an immune response specific to the antigen and targeting monkeypox proteins, vaccines work to stop the spread of the smallpox virus infection. Monkeypox has taken the place of smallpox as the most serious Orthopoxvirus in terms of public health since smallpox was eradicated in 1980 and smallpox vaccine was subsequently discontinued (6). In central and western Africa, where it usually occurs close to tropical rainforests, monkeypox has been on the rise (5). The need for more effective Orthopoxvirus vaccines has grown because of the potential use of monkeypox as a bioterrorist weapon.

The first-generation vaccinations that were used in the smallpox eradication campaign were very effective smallpox immunizations. Unfortunately, the vaccinations were produced in calf skin under circumstances that did not follow basic manufacturing requirements (7). Throughout the smallpox eradication campaign, the New York City Board of Health (NYCBH), Lister, and EM-63 strains of VACV were often used (7). The smallpox vaccine is generally passaged in primary cells obtained from chicken embryos, in rabbit kidney cells, or in the chorioallantoic membrane of chicken embryos. Lister is the first VACV strain utilised to make smallpox vaccine produced in cell culture (8). Commonly, these non-clonal live vaccinations were delivered via scarification with a two-pronged needle, resulting in a cutaneous response because of nearby viral multiplication (7). Historically, the scar forms after the injection, has been thought to correspond with smallpox protection (7). However, several side effects ranging from mild to severe were linked to these first-generation smallpox vaccines, including malaise, mild rash, and fever (9). As time went on, atopic dermatitis, immunosuppression, and heart disease all increased a person's vulnerability to more serious issues (9). Dryvax is also one of the current USA-licensed smallpox vaccines. In the US eradication programme, it was propagated in calf skin and replaced by ACAM2000 in 2007. Currently, vaccination against the smallpox is not advised for anyone with these illnesses or those who have interactions with them (10).

SECOND GENERATION VACCINES

Several second-generation vaccines that emphasize sterile cell culture techniques for vaccine production have been developed. For instance, the Elstree-BN vaccine from Bavarian Nordic was developed on chick embryo fibroblasts, while the cell-cultured smallpox vaccine (CCSV) from DynPort Vaccine Company was made from the NYCBH strain grown on typical diploid MRC-5 human lung cell cultures (11). Similarly, ACAM2000, a single clone created from the Dryvax vaccine and grown in Vero cells, was discovered by Acambis, a biotechnology company creating vaccines (now a branch of Sanofi Pasteur) (12). Clinical studies on nonhuman primates showed that ACAM2000 had comparable immunogenicity to Dryvax and was less neurovirulent in mice (13). It was approved in the United States in 2007 (13). Nevertheless, ACAM2000 and other second-generation smallpox vaccines have similar rates of side effects to first-generation vaccines like Dryvax in terms of overall safety (14). Elstree-BN smallpox vaccine is typically propagated in corneal endothelial cells and the vaccine has showed safety and immunogenicity in both primate and human clinical studies. Before smallpox was eradicated, this vaccine was also created in Japan using chicken embryo fibroblast cells, and its safety profile was satisfactory (15). Additionally, at a dose 50 times lower than the dose permitted for Dryvax, the cell-culture smallpox vaccine produced significant immunogenic responses in volunteers who had never received a vaccination (15). For both those who are vaccinia-naive and those who have had vaccinia in the past, the vaccine looks to be a secure and immunogenic substitute to calf-lymph-derived inoculation (16). Modified Vaccinia Ankara (MVA), which was produced by repeatedly passing the VACV strain Ankara through the fibroblasts of chick embryos over 570 times (17). Despite most mammalian cells and animals being unable to become infected after MVA vaccination, viral genes are still generated (18). Nonetheless, only a few additional mammalian cell lines and chick embryo fibroblasts can replicate MVA, and their output is minimal, and the immunogenicity is not as strong as in prior generations of smallpox vaccine (19). For instance, immune responses to a Bavarian Nordic (Imvamune) MVA-based vaccine in phase I and phase II clinical studies are concentration-dependent and may take two injections to induce immune responses comparable to those of first-generation vaccinations (20).

THIRD GENERATION VACCINES

Third-generation smallpox vaccinations, or DNA vaccines are being researched as safer substitutes for smallpox vaccines. The generation of extremely attenuated VACV strains was further aided by genetic alteration of the virus' genome (21). The Copenhagen strain of VACV is reportedly immunogenic, although compared to Dryvax or Lister first-generation vaccine strains, NYVAC elicits lower antibody responses in humans (21). It is created by deleting 18 non-essential genes from the Copenhagen strain, which significantly attenuates it and reduces its ability to replicate in human cells. In addition, it does not stimulate the production of anti-A27 antibodies, which are essential for the immune system's ability to respond to first-generation vaccines and which can destroy intracellular mature virus (IMV) (21). Intense preclinical and clinical research is being conducted on NYVAC-based recombinants as recombinant vaccines against various viral infections. Highly attenuated VACV strains like MVA and NYVAC have the two key disadvantage of not causing a scar in vaccine recipients and having an unknown level of effectiveness against smallpox (21). Imvamune is a live attenuated, non-replicating vaccine that is approved for protection against smallpox and other orthopoxvirus related infections (22). In 1968–1980, it was administered to over 120,000 persons in Germany as a safe, highly attenuated smallpox vaccination with no significant side effects. In addition, Imvamune induces antibody responses comparable to Dryvax in mouse and non-human primate challenge models (22).

Third-generation vaccine attenuated VACV LC16m8, which was developed from the Lister strain, demonstrated exceptional safety (23). In contrast to MVA, which does not cause an immune response in those who have received the vaccination, LC16m8 has a mutation in the B5R gene that allows the virus to form fewer plaques and replicate less efficiently (24). One disadvantage that needs to be considered is the fact that LC16m8 does not induce antibody responses against the B5 protein, which is the main target for extracellular enveloped virus (EEV) neutralizing antibodies (6). The Elstree/Lister vaccine's uracil-DNA-glycosylase (UDG) gene was also removed to make the dVV-L vaccine. Since the UDG enzyme is required for viral replication, viral replication is inefficient in its absence (24). The vaccine may be made using complementary cell lines and is safe to use. Third-generation vaccinations that are created from first-generation vaccinia strains through serial passage in non-human tissues or through genetic modification of such strains in modern viral genetic laboratories have the potential to be effective vaccines (25).

FOURTH GENERATION VACCINES

The development of fourth-generation smallpox vaccinations, which reduce the possibility that the VACV vector will have adverse effects or respond back to a more pathogenic phenotype, is still under extensive development (26). The development of DNA subunit vaccines is one of them; these are often built of membrane proteins from the VACV and produce antibody responses against the IMV and EEV virus types (26). Typically, DNA vaccines consisting of VACV-induced neutralizing antibodies against the intracellular mature virus (IMV) and extracellular envelope virus (EEV). It has been shown to be protective using animal models, but none are currently being examined in clinical research, which are probably required for to study its effectiveness. Nonetheless, DNA vaccinations call for booster shots. A novel approach to immunization involves using conserved and immunogenic multi-T-cell epitopes in a DNA-prime, peptide-boost schedule (26). Animal studies have shown the effectiveness of these fourth-generation vaccines against smallpox; however, none are currently completing clinical trials, and booster doses will probably be needed. Despite their demonstrated efficacy, the first generation of smallpox vaccines is no longer acceptable due to their problematic side effects and antiquated manufacturing processes (8). Since they include the same vaccinia strains as those of the first generation, second-generation vaccines with expected efficacy have been created (12). ACAM2000, has proven to be superior to first-generation vaccinations and has been included to the National Strategic Stockpile (27). Including those who are HIV-positive and have atopic dermatitis, the subjects have been examined for the safety of modified Vaccinia Ankara (MVA) (28). With MVA, the National Strategic Stockpile has been expanded (28). Because it can be lyophilized, administered using a bifurcated needle, and causes a skin reaction, the Japanese vaccine LC16m8 seems to be successful for limiting outbreaks (29).

Numerous candidates of the fourth generation have been created by contemporary immunologic and viral approaches. Protein-based vaccination, typically constituted of VACV, which induces neutralising antibodies against the IMV and EEV versions of the virus. Using animal models, it has been demonstrated to be protective and efficacious against smallpox; however, no clinical trials are currently underway (30). T-cell epitope vaccination is still under clinical study at present moment. The F8L protein of the monkeypox virus has two epitopes, ISPDGCYSL and LTFDYVVTF, which have been found to stimulate the CD8+ T cell population and the release of interferon- in rhesus macaques (31). A humanized mouse model used in the

epitope-based vaccine VennVax, which offers 100% protection against the vaccinia virus, causes a T cell response (32). VennVax has recently been found to be effective as an MPXV therapy.

They are either vaccinations made by adding numerous vaccinia epitopes or other immunogens to chemically produced molecules, or they are vaccinia components from which several genes have been deleted (16). These vaccines may not be fully developed as smallpox vaccines due to the expense and difficulty of demonstrating their effectiveness, but they may prove to be excellent vector vaccines for other infectious agents because the immunogenic components of these agents can be added to their genetic structure (22). A replication-competent smallpox vaccine (ACAM2000) and a replication-deficient modified vaccinia Ankara (MVA) vaccine, both of which are still safe to use today, can be used to prevent smallpox and other orthopoxviruses (11).

CONCLUSION

The spread of zoonotic Orthopoxviruses to humans and other animals can only be prevented by early detection and control of animal infections by vaccination. The vaccines for orthopoxviruses were generally classified into 4 categories based on their nature. The characteristics of vaccines were discussed thoroughly in this review. Vaccine was effective in preventing smallpox infection. A new unified paradigm for vaccination research and product development must be formed in order to achieve the Sustainable Development Goals of the United Nations. Developing nations should play a crucial role in selecting and disseminating the specific vaccine products they require, in addition to this convergence of efforts and improved coordination.

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