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Review Article

Assessing the effectiveness of vaccination strategies against respiratory pathogens

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ABSTRACT

Vaccination has been an effective method in preventing many childhood-related infections and reducing the risk of infections in adults. Between the mid-1960s and 2015, vaccination has been successful in saving more than 10 million lives. Respiratory pathogens have been a main target for vaccination over decades. Many vaccines were developed against respiratory pathogens such as influenza. virus, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis*. Vaccination against respiratory pathogens faces new challenges every year due to different reasons. The following databases were used in systematic research: Medline (PubMed), Web of Science, and Scopus. Summaries of the found studies were exported by EndNote X8, and duplicate studies were removed. Inclusion criteria were any study. Despite the proven effectiveness of various vaccines against respiratory pathogens, several challenges persist in this field. These include the waning of vaccine-induced immunity, prompting the need of developing vaccines that provide long-lasting protection; vaccination harmful side effects; and the emergence of new subtypes are examples of these challenges. In the aftermath of the COVID-19 pandemic, clinical trials are underway to develop more effective vaccines against a range of pathogens. However, greater large-scale efforts are needed, particularly in low-income countries, to enhance global public health outcomes.

Keywords: Vaccination, Effectiveness, Efficacy, Respiratory pathogens, Respiratory tract infection, Immunization

INTRODUCTION

Vaccination has been an effective method in preventing many childhood-related infections. Between the mid-1960s and 2015, vaccination has been successful in saving more than 10 million lives.[1] However, nearly 1.5 million children under the age of five continue to die each year from vaccine-preventable diseases, primarily due to limited access to essential childhood immunizations.[2] Achieving a world free of infectious diseases is complex and faces many challenges, emphasizing the importance of maintaining adequate vaccination coverage to prevent resurgence.

Despite extensive research and numerous clinical trials, effective vaccines against various infections remain elusive. Among these infections, respiratory pathogens are considered a huge challenge. Many vaccines were developed against respiratory pathogens such as the influenza virus, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis*.

However, these pathogens present a significant challenge to vaccination efforts due to the frequent emergence of new subtypes and waning of these vaccines. Since the COVID-19 pandemic, more attention has been implemented on vaccination against respiratory pathogens with a probable change in vaccination strategies in the next few years as new vaccine formulas are being developed.

Interestingly, recent studies have suggested that vaccines targeting certain types of pathogens may influence the virulence of other pathogens.[3,4] However, further research and clinical trials are needed to validate these findings. In this review, we are going to discuss the effectiveness of current vaccination strategies against respiratory pathogens, the development of new vaccines, and future strategies of vaccination.

METHODS

The following databases were used in systematic research: Medline (PubMed), Web of Science, and Scopus till the 19th of December 2024. MeSH database was used to retrieve the synonyms of search strategy. Search terms were then combined by ("AND" and "OR") Boolean operators according to the Cochrane Handbook for Systematic Reviews of Interventions as follows: "vaccinations" "vaccination" "immunization, active" "active immunization" "active immunizations" "immunizations, active" and "infection, respiratory tract" "respiratory tract infection" "respiratory system infections" "infection, respiratory system" "respiratory system infection".[5] Summaries of the found studies were exported by EndNote X8, and duplicate studies were removed.

VACCINATION AGAINST RESPIRATORY PATHOGENS

Streptococcus pneumoniae

Streptococcus pneumoniae (pneumococcus) is responsible for various diseases such as bacterial pneumonia and meningitis, which contribute to significant morbidity and mortality. Young children and older adults bear the highest disease burden. As of 2020, over 100 serotypes of pneumococcus have been identified. The distribution of these serotypes varies widely across countries.[6] Pneumococcal vaccines are designed to protect against infections caused by Streptococcus pneumoniae. Two formulations are available: polysaccharide vaccines (PPVs) and conjugate vaccines (PCVs).[7] The introduction of these vaccines played a crucial role in the prevention and management of a widespread and potentially fatal disease.[8,9] Since the 1970s, several PPVs have been developed.

To enhance vaccine effectiveness in children, multiple PCVs have been licensed. First, the 7-valent pneumococcal conjugate vaccine (PCV7, marketed as Prevnar by Pfizer) was introduced in the United States in 2000 and in the European Union in 2001. The PCV7 vaccine led to a rapid reduction in invasive pneumococcal disease (IPD) among young children and a significant decline in adult infections.[10] In the U.S., the incidence of IPD in 2004 decreased by 77% in infants under one year old, by 83% in one-year-olds, and by 73% in two-year-olds.[11] Additionally, non-invasive pneumococcal infections, such as acute otitis media, showed a 20% decline.[12]

However, serotypes not included in PCV7, such as serotype 19A, emerged as problematic, prompting the development of broader-spectrum vaccines like PCV10 (Synflorix by GSK) and PCV13 (Prevnar 13 by Pfizer), available since 2009.[13-15] PCV10 and PCV13 have reduced nasal colonization of vaccine-included serotypes, leading to herd immunity.[16] These vaccines contributed to a significant decline in drug-resistant pneumococcal infections.[17] Studies show an 84% reduction in multidrug-resistant IPD in children under two years and a 49% decrease in penicillin-resistant IPD in adults over 65.[18] In South Africa, the use of PCVs reduced penicillin-resistant pneumococcal disease by 82% in children and penicillin-susceptible disease by 47%.[19]

Broader-spectrum vaccines were developed to cover more serotypes such as PCV15 (Merck) and PCV20 (Pfizer). The Food and Drug Administration (FDA) has recently approved PCV15 and PCV20, which contain 15 and 20 serotypes, respectively.[20,21] These vaccines have demonstrated efficacy in reducing non-invasive illnesses, including acute otitis media, non-bacteremic pneumonia, and sinusitis.[22] In 2021, the FDA approved PCV20 and PCV15 for adults aged 18 years and older. In 2022, the FDA broadened the approved uses of PCV15 to include individuals between six weeks and 17 years of age. The Advisory Committee on Immunization Practices (ACIP) recommends either PCV20 alone or PCV15 in series with PPSV23 for adults aged 65 and older and for individuals aged 19 to 64 with risk factors or underlying medical conditions.[23]

PPSV23, a 23-valent polysaccharide vaccine, is licensed in many countries for individuals aged 65 and older and for those aged 2 to 64 with comorbidities like cardiovascular disease or diabetes. Its effectiveness against IPD in immunocompetent adults' ranges from 56% to 81%, but it is less effective in immunocompromised individuals. While PPSV23 can reduce the severity of community-acquired pneumonia, it is ineffective against non-invasive pneumonia. In addition, PPSV23 is not effective in children under two years old.[24]

Influenza

Influenza is responsible for an estimated 290,000–650,000 deaths each year, globally.[25] Children are particularly vulnerable to influenza-related complications, prompting annual vaccination recommendations for those older than six months.[26] However, in many countries, vaccination coverage remains underreported and falls below the World Health Organization's (WHO) target of 75%.[27-30] Trivalent inactivated intramuscular influenza vaccines (IV), which target two influenza A and one influenza B subtypes, have been licensed for children aged six months and older since 2001.[31] A history of severe allergic or anaphylactic reactions is the only contraindication to this vaccine.[32] Live attenuated influenza vaccines (LAIV) became available later for children aged two years and older. However, their use is contraindicated in certain populations, such as those with immunosuppression or on aspirin therapy.[32]

Quadrivalent vaccines containing an additional B subtype then were developed. These were approved by the FDA in 2012 and by the European Medicines Agency (EMA) in 2013.[33] However, starting from the 2024–2025 influenza season, the FDA, EMA, and WHO have recommended returning back to the use of trivalent vaccines.[34-36] A recent meta-analysis of test-negative studies found similar vaccine effectiveness across different vaccine types. The analysis noted lower vaccine effectiveness in Asia compared to North America but was unable to differentiate results by age group.[37]

Another meta-analysis showed that all trivalent vaccines were more effective than a placebo. Trivalent LAIV demonstrated the highest efficacy.[38] Conversely, no significant difference in effectiveness was observed when comparing quadrivalent vaccines to a placebo.[38] A systematic review and meta-analysis conducted a head-to-head comparison of influenza vaccines and found that live-attenuated intranasal vaccines are at least as effective and safe as inactivated intramuscular vaccines for those without contraindications. Additionally, live-attenuated vaccines are considered more cost-effective.[39]

As a result, the study recommends developing pediatric national flu vaccination programs based on live-attenuated nasal influenza vaccines, given their potential to achieve the World Health Organization (WHO)'s influenza strategy goals.[40] On the other hand, multiple studies demonstrate that the influenza vaccine may be associated with an increased incidence of respiratory illnesses, possibly caused by other respiratory pathogens (i.e., viruses and bacteria), that are filling the gap left by reduced influenza infection.[41]

Respiratory syncytial virus (RSV)

RSV was first identified in 1956 as causing illness in humans. Efforts to develop a vaccine for RSV have remained highly active despite the initial challenges encountered in the 1960s with the formalin-inactivated RSV vaccine.[42] Currently, many RSV vaccine candidates are in clinical development, employing six distinct approaches: recombinant vector, subunit, particle-based, live attenuated, chimeric, and nucleic acid vaccines.[43]

In May 2023, Arexvy (RSVPreF3) became the first RSV vaccine to receive approval from the U.S. Food and Drug Administration (FDA). It is specifically indicated for preventing lower respiratory tract disease (LRTD) caused by RSV in individuals aged 60 years and older.[44] Later, in August 2023, the FDA approved Abrysvo (RSVpreF), marking the first RSV vaccine authorized for use in pregnant women to protect infants from RSV-related LRTD and severe LRTD from birth through six months of age.[45] However, not all RSV vaccine candidates have demonstrated efficacy in clinical trials. Two vaccines targeting adults aged 60 years or older—one based on the RSV postfusion F protein and another using an RSV-F nanoparticle-based vaccine—failed to provide protection against RSV-related illness in clinical studies.[46]

In a systematic review and meta-analysis by Zeng et al, the findings highlight two approved vaccines, RSVpreF and RSVPreF3 OA, alongside a promising candidate, mRNA-1345.[47] Additionally, a discontinued vaccine, Ad26.RSV.preF, utilized a recombinant vector strategy. Two other vaccines, the RSV F vaccine and MEDI7510, were unsuccessful, with the former being an RSV F nanoparticle vaccine and the latter a postfusion F protein-based vaccine.

Among the six vaccines included in the review, only one—RSVpreF—is designed for use in pregnant women to prevent RSV infections in infants, while three vaccines are targeted for use in older adults. The findings showed promising outcomes for RSVpreF in infants, with a reduction of 92 RSV-related LRTD cases, 78 severe LRTD cases, and 60 hospitalizations per 10,000 participants within 90 days of birth. For older adults, the RSV vaccines also showed favorable results. Per 10,000 participants, the vaccines reduced 22 RSV-related LRTD cases, 35 acute respiratory infections (ARIs), and 9 severe LRTD cases during the first RSV season following vaccination. Importantly, no significant differences in serious adverse events (SAEs) were observed between the vaccinated and placebo groups.

Coronavirus disease 2019 (COVID-19)

COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), has affected a significant portion of the global population. In March 2020, the WHO specified it as a pandemic, leading to widespread morbidity and mortality worldwide. Until December 2022, COVID-19 has been responsible for approximately 6.6 million deaths and more than 651 million confirmed infections globally.[48]

COVID-19 vaccine platforms are divided into two types: one based on viral components and the other on the whole virus. The viral component-based type includes protein subunit, virus-like particle, DNA-based, RNA-based, non-replicating viral vector, and replicating viral vector vaccines. While the whole virus-based type comprises inactivated and live-attenuated vaccines.

Leading vaccines include Pfizer-BioNTech's BNT162, Oxford-AstraZeneca's AZD1222, Sinovac's CoronaVac, Moderna's mRNA-1273, Johnson & Johnson's Ad26.COV2.S, Sputnik-V (Gamaleya National Research Centre for Epidemiology and Microbiology), and Novavax's adjuvanted recombinant protein nanoparticles. These vaccines have achieved significant progress in combating the COVID-19 pandemic.[49,50]

DNA based vaccines

In India, Zydus Cadila company, in collaboration with the Department of Biotechnology, developed a vaccine called ZyCoV-D. It is a 3-dose intradermal vaccine designed for individuals aged 12 years and older. This was the first clinical use of a DNA-based vaccine in humans.

A multicenter, double-blind, randomized, placebo-controlled phase III clinical trial study was conducted on ZyCoV-D at 49 sites across India.[51] The study involved participants aged 12 and above, predominantly males. The vaccine was administered using a needle-free device to deliver three intradermal doses, with a 28-day interval between each dose.

Results showed that ZyCoV-D effectively induced neutralizing antibodies and cellular immune responses, achieving an efficacy rate of approximately 66.6%. Mild adverse events were reported in some cases. The safety profile of ZyCoV-D was comparable to other DNA-based vaccines in development. Overall, the findings from phase III clinical trials highlight the vaccine's immunogenicity, efficacy, and safety.

mRNA based vaccines

Several RNA-based vaccine contenders are currently at different stages of development and are being evaluated for their effectiveness against COVID-19. The Food and Drug Administration (FDA) has authorized three mRNA-based vaccines for COVID-19: Pfizer-BioNTech's BNT162b2, Moderna's mRNA-1273, and Johnson & Johnson's Janssen Ad26.COV2.S. These vaccines showed high efficacy rates, ranging from approximately 72% to 95% in trials against moderate-to-severe COVID-19 in adults.[52] The WHO Strategic Advisory Group of Experts on Immunization has recommended the use of Pfizer-BioNTech’s BNT162b2 vaccine.

Polack et al investigated BNT162b2 vaccine safety and effectiveness, finding that the vaccine commonly caused mild-to-moderate side effects such as brief pain at the injection site, fatigue, and headache, with minimal reports of severe reactions.[53] These side effects were comparable between vaccinated and placebo groups. The two-dose regimen of BNT162b2 resulted in about 95% protection against COVID-19 in individuals aged 16 and older.

A phase III trial [NCT04470427] was conducted for Moderna's mRNA-1273 vaccine, the vaccine showed 94.1% efficacy against COVID-19 and effectively prevented severe disease. Minimal secondary complications further support its safety.[54] The WHO has standardized the dosing schedule for the BNT162b2 vaccine, recommending that doses be administered 3 to 4 weeks apart. However, research found that distantly administered doses can enhance immune responses, particularly in vaccine-naive individuals, offering flexibility in vaccination schedules.[55]

Overall, mRNA vaccination programs have been highly effective in reducing the prevalence of circulating COVID-19 variants. However, further research is needed to enhance their specificity and efficacy. In addition, studies have shown that individuals previously infected with COVID-19 have stronger immune responses to all spike protein antigens compared to naive individuals.[55]

Vector-based vaccines

Ramasamy et al reported on the immunogenicity of ChAdOx1 nCoV-19 (AZD1222), a chimpanzee adenovirus-vectored vaccine.[56] The safety and efficacy of this vaccine were evaluated in a diverse population, including young adults and individuals aged 70 years or older. The study found that ChAdOx1 nCoV-19 was well-tolerated in older adults, with comparable immune responses observed between older and younger subgroups following a booster dose. However, further research is required to assess its safety and effectiveness across all age groups and among individuals with comorbidities.

Subunit vaccines

Recently, a phase III clinical trial to evaluate the immunogenicity and safety of three different formulations of the Novavax vaccine with Matrix-M™ adjuvant (NVX-CoV2373) was conducted.[57] The NVX-CoV2373 vaccine provided approximately 89.7% protection against SARS-CoV-2 infection in adult participants who received two doses. It also demonstrated significant efficacy against the B.1.1.7 variant.

More recently, studies have shown that three doses of the NVX-CoV2373 vaccine effectively neutralize Omicron subvariants, including BA.1, BA.4, and BA.5.[58] A recent systematic review and meta-analysis, encompassing 11 studies with a total of 247,186 participants, evaluated the effectiveness and safety of various vaccine platforms against COVID-19.

While all approved vaccines appeared safe and effective, mRNA-based vaccines showed superior efficacy against SARS-CoV-2 compared to other platforms. Injection site discomfort and fatigue were the most frequently reported side effects across non-replicating viral vector, mRNA, protein subunit-based, and inactivated vaccines.[59]

CONCLUSION

Despite the proven effectiveness of various vaccines against respiratory pathogens, several challenges persist in this field. These include the waning of vaccine-induced immunity, prompting the need of developing vaccines that provide long-lasting protection; vaccination harmful side effects; and the emergence of new subtypes are examples of these challenges. In the aftermath of the COVID-19 pandemic, clinical trials are underway to develop more effective vaccines against a range of pathogens. However, greater large-scale efforts are needed, particularly in low-income countries, to enhance global public health outcomes.

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