Review Article

Tackling COPD Globally: The Essential Role of Immunization – A Mini Review

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ABSTRACT

Chronic obstructive pulmonary disease (COPD) is a progressive respiratory disorder characterized by persistent airflow limitation and driven by factors such as smoking, environmental exposures and genetic predisposition. It poses a significant global health burden, being the third leading cause of death worldwide with high prevalence in low- and middle-income countries and among populations with lower socioeconomic status. COPD patients frequently experience exacerbations, hospitalizations, and comorbidities, leading to reduced quality of life and increased healthcare demands. Vaccination has emerged as a crucial non-pharmacological strategy in COPD management, with pneumococcal, influenza, COVID-19 and RSV vaccines shown to reduce respiratory infections, exacerbations, and mortality. This narrative review synthesizes current literature and guideline recommendations on six vaccines in relation to COPD. Despite strong clinical evidence supporting their benefits, vaccine uptake remains suboptimal due to hesitancy, lack of awareness, and limited COPD-specific data for some vaccines. Key research gaps include immunogenicity in high-risk subgroups, evaluation of broader outcomes and strategies to improve coverage across low- and middle-income countries. This review highlights the need for tailored vaccination strategies within comprehensive COPD care for better implications for clinical practice, health policy and future research.

Keywords: Chronic obstructive pulmonary diseases, COPD vaccination, influenza vaccine, pneumococcal vaccine, respiratory syncytial vaccine, COVID-19 vaccine.

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1.0 Introduction

Chronic obstructive pulmonary diseases (COPD) is a chronic progressive disease characterized several pathophysiologic changes in respiratory system. It is marked by irreversible airflow limitation and hyperinflation due to increased resistance in the small airways and loss of pulmonary elastic recoil from emphysematous destruction (1). It also involves inflammatory cells influx such as neutrophils, macrophages and lymphocytes, and causes significant structural changes in lung including airway narrowing, mucus hypersecretion, ciliary dysfunction and alveolar destruction (2, 3). Persistent of these conditions may result in immune dysregulation manifested by a reduction in immune response to antigens which compromise the respiratory defense system and increase susceptibility to infections (3). Patients with COPD also often have an altered airway microbiome that influenced by increased eosinophil counts. This dysbiosis might predispose patients to infections and further exacerbate inflammation (4).

Smoking is the predominant risk factors for COPD which causing chronic inflammation, remodelling and narrowing of the small airways as well as destruction of the lung parenchyma. Other risk factors include occupational exposures to toxins and irritants, air pollution, airway hyper-responsiveness, asthma and genetic factors (5). Non-smokers with COPD exhibit different characteristics such as a normal one second forced expiratory volume decline, equal sex distribution, younger age of onset, fewer comorbidities, milder airflow obstruction, preserved diffusing capacity of the lungs for carbon monoxide and distinct radiological features compared to smokers with COPD (6). Other than that, genetic factors, familial history and childhood lower respiratory tract infections also play an important role in the aetiology of COPD (5, 7).

Patients with COPD typically complain of dyspnoea, activity limitation and/or cough with or without sputum production and may experience acute respiratory events characterized by increased respiratory symptoms called exacerbations that require specific preventive and therapeutic measures. They also frequently harbour other comorbid diseases that influence their clinical condition and prognosis and require specific treatment as well. These comorbid conditions can mimic and/or aggravate an acute exacerbation (8). COPD is a common, preventable and treatable disease, but it is often under- or misdiagnosed leading to patients receiving no treatment or inappropriate treatment. The realization that environmental factors other than tobacco smoking can contribute to COPD, that it can begin in early life and affect young people, and that there are precursor conditions (pre-COPD), opens a new windows of opportunity for its prevention, early diagnosis and appropriate therapeutic intervention (9).

Apart from accelerated lung decline, frequent COPD exacerbations following respiratory infections are associated poorer quality of life and increased healthcare costs (10). Patients may have health-related quality of life (HRQOL) impairment due to COPD symptoms and experience social isolation with low physical function, risking them with depression and anxiety (11). The presence of comorbidities such as cardiovascular diseases will further aggravate the quality of life by increasing morbidity and mortality (12). Furthermore, COPD patients are imposed with a pronounced economic burden due to frequent hospitalizations, emergency visits and long-term treatments. Acute exacerbations are the primary drivers of these costs which account for significant portion of

the total healthcare expenditure. The costs are further amplified by the need for long term oxygen therapy, frequent use of antibiotics and management of comorbidities (13).

Non-pharmacological strategies such as infection prevention and vaccination are very crucial and central to COPD comprehensive care along with pharmacotherapies. Vaccination is a vital component in this disease management by offering several benefits in reducing the frequency and severity of exacerbations, hospitalizations and overall healthcare costs, which are often triggered by respiratory infection. However, the evidence that guiding vaccination in COPD remain fragmented. There are gaps in data on newer formulations, immunogenicity in high-risk subgroups and broader outcomes such as cardiovascular protection. Therefore, this mini review aims to synthesize current knowledge and highlight research priorities for optimizing immunization in COPD, particularly focusing on pneumococcal, influenza, respiratory syncytial virus (RSV), COVID-19, pertussis and herpes zoster vaccines.

2.0 Burden of COPD

2.1 Prevalence

COPD remains a major contributor to global morbidity and mortality. According to the Global Burden of Disease (GBD) 2021 study, COPD is the fourth leading cause of death with the age-standardized death rate of 45.2 per 100,000 population (14). It also was projected to approach 600 million cases worldwide by 2050 (15). A high prevalence rates are notably observed in South and Southeast Asia regions, especially in India, Bangladesh and Indonesia, where exposure to biomass fuel combustion and elevated smoking rates are the major contributing factors (16). China is reported as among the highest national burdens of COPD with estimated 8.6% prevalence among adults, driven by extensive tobacco use and increasing ambient air pollution (17). This finding also has similar trends in Latin America and Eastern Europe (18, 19). In contrast, the reported prevalence in Sub-Saharan Africa remains comparatively lower, although this may be underestimated due to underdiagnosis and poor access to spirometry (20).

Traditionally, COPD was considered more prevalent in men, primarily resulting from higher rates of smoking and occupational exposures. However, this gender gap is getting narrowed in several high-income countries as consequences of change in smoking pattern among women. Recent studies indicate that women are now equally or more affected than men in some regions (21). Furthermore, women appear to be more susceptible to the harmful pulmonary effects of tobacco smoke and biomass fuel exposure, possibly due to biological, hormonal and behavioural differences in response to available therapeutic modalities. However, the extent of differences in COPD prevalence between gender is not well-understood and may vary by geography or other factors (22).

Socioeconomic status (SES) plays a pivotal role in COPD distribution. Individuals residing in the most socioeconomically disadvantaged neighbourhoods experience poorer COPD outcomes, lower health status scores and marked impairment in physical function (23). This is largely driven by great exposure to occupational hazards and indoor air pollution, and less likely benefits from smoking cessation programs and preventive healthcare. Lower SES individuals are more likely to work in high-risk occupations, exposing them to dust, fumes and chemicals and consequently increases the risk of

chronic respiratory disease (24). For examples, workers with long term exposure to firewood smoke and farming were significantly associated with fixed airflow obstruction among rural community in Nueva Ecija, Philippines (25). Similarly, households with lower SES mostly rely on biomass fuels for cooking and often experience overcrowded living conditions. These might generate poor indoor air quality, increase the risk of respiratory infection and contribute to COPD development and progression (26).

2.2 Morbidity and Mortality

The morbidity associated with COPD is multifaceted, encompassing chronic symptoms, functional limitations, acute exacerbations and comorbidities. COPD is the most common pervasive chronic respiratory disease and the leading contributor to the global disease burden, increased in rank of disability-adjusted life years (DALYs) among all causes between 1990 and 2019 (16, 27). In 2021, COPD caused 3.72 million deaths and 79.8 million DALYs, with age-standardized DALYs rate of 940 per 100,000 (15, 28). Individuals with COPD often experience persistent cough, sputum production and dyspnoea that interfere with daily activities and diminish physical capacity. The chronic and progressive nature of disease results in substantial disability which often requiring long-term oxygen or ventilatory support (8). Acute exacerbations of COPD represent a major driver of morbidity. It leads to increase in hospitalization risk, accelerate lung function decline and associated with poor prognosis and quality of life (29). To date findings, indicate that morbidity due to COPD escalates with age, and the development of comorbidities such as cardiovascular disease, diabetes, depression, osteoporosis, and lung cancer are seen at an earlier age in patients with COPD, which will further compound the disease burden and complicate the management strategies (30-33).

It is estimated that 2.28 billion cumulative exacerbations will occur because of COPD globally by 2025, and projected to have a relative growth by 584% in 2050 (34). This is driven by disease severity, frequency of exacerbations, comorbid conditions and socioeconomic factors. Notably, the 5-years mortality rate for moderate-to-severe COPD ranges from 40% to 70%, with the risk significantly increasing among patients requiring hospital admission for exacerbations (35). Longitudinal analyses have shown that while mortality due to communicable respiratory diseases has declined, non-communicable respiratory diseases such as COPD have become prominent contributors to premature death, especially in aging populations (28). Nevertheless, COPD mortality is often underreported particularly in settings with poor diagnostic infrastructure and may be misclassified, leading to underestimation of its true burden.

2.3 Economic Burden

COPD is associated with significant disease burden. In the European Union, the total direct costs of respiratory disease are estimated to be approximately 6% of the total annual healthcare budget, with COPD accounts for 56% (38.6 billion Euros) of the cost of respiratory disease (36). Meanwhile, the cost attributable to COPD in the United States are expected to increase over the next 20 years, with projected costs of 40 billion per year. Dynamic modelling also predicted that women are expected to incur higher direct costs than men and lose more quality-adjusted life years (37). COPD exacerbations account for the greatest proportion of the total

COPD burden on the healthcare system. Not surprisingly, there is a striking direct relationship between the severity of COPD and the cost of care, where its distribution changes as the disease progresses. For example, hospitalization and ambulatory oxygen costs soar as COPD severity increases. Any estimate of direct medical expenditure for home-based care under-represents its true costs to society because it ignores the economic value of the care provided by family members to COPD patients (38).

The direct and indirect costs of COPD may be substantial in lower to middle income countries (LMICs). Recently, WHO and other organizations report that inhaled medicines for COPD are poorly available and largely unaffordable in LMICs (39). Most inhaled medications are still originally branded and only few options currently available for generic inhalers. The situation is similar for access to diagnostic spirometry. Besides, this disease also poses huge impacts to the economy through various channels primarily due to work loss and productivity. COPD patients experience major productivity loses, with mean annual sick leave ranging from 1.3-19.4 days and significantly higher rates of absenteeism than those without COPD (6.88% vs 3.74%) (40). They also exhibited higher healthcare resource utilization including frequent hospital and outpatient clinic visits (40).

3.0 Vaccinations in COPD

The initiation COPD pharmacological management depends on individualized assessment of symptom's severity, exacerbations history and blood eosinophil count. Inhaled bronchodilators remain the foundation of the therapy, with long-acting β2 agonists (LABAs) and long-acting muscarinic antagonists (LAMA) being preferred for maintenance. Combination therapy of LABA, LAMA and inhaled corticosteroids (ICS) is recommended in patients with blood eosinophils of ≥ 300 cells/μL (8, 41). Besides that, other interventions are also important to complement the existing treatment to form a comprehensive management of COPD. These include enforcement on the importance of smoke free environment, empower adherence to prescribed medication, ensure proper inhaler technique, promote physical activity and vaccinations (8). COPD exacerbations often triggered by respiratory infections, which infect the lower airway and increase inflammation (29). Vaccination in COPD is an effective intervention that helps to minimize infectious exacerbations, together with associated morbidity and mortality. The use of vaccines has become widespread recently, not only targeting specific infections but also contributing to long-lasting immunity (42). Current guideline recommends the administration of six vaccines against *Streptococcus pneumoniae*, influenza virus, SARS-CoV-2, respiratory syncytial virus, *Bordetella pertussis* and varicella-zoster virus for all COPD patients (8, 42).

3.1 Pneumococcal Vaccines

Pneumococcal conjugated vaccine (PCV20 or PCV15) and pneumococcal polysaccharide vaccine (PPSV23) are the approved vaccines in patients with comorbidities of chronic lung disease. Recently, PCV21 is approved to cover 11 unique serotypes which not included in PCV20 (43). These pneumococcal serotypes protect against pneumococcal disease including pneumonia, meningitis and bacteraemia which commonly caused by *Streptococcus pneumoniae* (44). It is recommended for COPD patients aged ≥ 65

years who never received a pneumococcal conjugate previously, or unknown history of pneumococcal vaccination and is typically renewed every 5 years (45). The Nation Against Pneumococcal Infections Expert Panel Opinion (NAP-EXPO) recommends these vaccines for all COPD patients, regardless of their severity (46).

Pneumococcal vaccination in COPD patients has been shown to reduce the risk of infective exacerbations, thereby reducing morbidity and associated healthcare costs (47, 48). Studies have demonstrated that it also can lead to a reduction in number of COPD exacerbations, hospital admissions and disability days, ultimately alleviating the clinical state of patients. This will further help in maintaining a stable health status and improving the quality of life for COPD patients (48, 49). Besides, it also has been associated with a decrease in the likelihood of developing community-acquired pneumonia (CAP) and reduction in a number needed to treat for an additional beneficial outcome (NNTB) (48). As a result, by preventing pneumonia and reducing exacerbations, pneumococcal vaccination may minimize the deaths related to respiratory complications in COPD patients (50).

While pneumococcal vaccination is recommended to COPD patients, several challenges might complicate its implementation and effectiveness. There is ongoing debate about the optimal timing for initial vaccination and the need for revaccination. The appropriate intervals for revaccinations and the selection of vaccine types (e.g. polysaccharide vs. conjugate vaccines) remain contentious (51, 52). The specific data on the efficacy of PPSV and PCV are also limited. Injectable polyvalent pneumococcal vaccination provides significant protection against CAP in COPD patients, although evidence does not indicate a reduction in the risk of confirmed pneumococcal pneumonia, which is a relatively rare event (50). The immunogenicity of pneumococcal vaccines in COPD patients can vary. While some studies show good immunogenicity with PPSV23, there are substantial differences in antibody responses by serotype which can affect the overall effectiveness of the vaccine in preventing infections (53).

3.2 Influenza Vaccine

Influenza vaccine is designed to protect against the influenza virus, which can cause severe respiratory infections. It consists of inactivated influenza vaccine (IIV) and live attenuated influenza vaccine (LAIV) which contains killed virus particles and weakened live virus respectively (54). IIV have been recommended for over 50 years and have an excellent safety record while LAIV have a broader immune response induction, including local and systemic antibody and T cell responses (54). The Centres for Disease Control and Prevention (CDC) recommend high-dose inactivated (HD-IIV3) and adjuvanted inactivated (aIIV3) influenza vaccines as acceptable options for influenza vaccination in older adults (55). This vaccine composition should be updated annually to match the circulating virus strains, as the virus frequently undergoes antigenic changes (56).

Influenza vaccination plays a crucial role in the treatment and prevention of COPD, offering several clinical benefits and impacting the disease's progression through immunological mechanisms. It helps in reducing the frequency of exacerbations and hospitalizations associated with influenza infections especially in vaccinated COPD patients compared to non-vaccinated patients, although the difference in some studies was not statistically significant (57).

Influenza vaccination also has been associated with a reduction in mortality rates among COPD patients. This is particularly important given the high vulnerability of these patients to influenza-related complications (57, 58). It also contributes to reduction in the incidence of other serious conditions such as ischemic heart disease, acute coronary syndrome, and lung cancer which are prevalent in COPD patients (59).

Despite recommendations, the coverage of influenza vaccination in COPD patients is far from satisfactory, indicating a significant barrier to uptake (60). Many of them exhibit vaccine hesitancy due to concerns about side effects, doubts about vaccine efficacy and fear of exacerbations triggered by the vaccine. A study showed that low influenza vaccination rates among COPD patients, with forgetfulness and lack knowledge about vaccine effectiveness being the main barriers (61). On top of that, insufficient training and awareness among healthcare providers about the importance of influenza vaccination for COPD patients also can result in missed opportunities for vaccination (62). Thus, multimodal interventions combining patient-focused and clinical-focused interventions, such as reminders, educational posters and electronic health record prompts can effectively increase vaccination rates (63). Provision of accurate and consistent information about the safety and benefits of influenza vaccine also may help reducing vaccine hesitancy (64).

3.3 Respiratory Syncytial Virus (RSV) Vaccine

RSV is prevalent in both stable COPD patients and those experiencing acute exacerbations (65). This infection is associated with higher incidences of dyspnoea, wheezing and co-infections particularly with Mycoplasma, which often require non-invasive mechanical ventilation and have longer hospital stays compared to those with influenza (66). In the United States, RSV infections caused an estimated 60,000 – 160,000 hospitalizations and 6,000 – 10,000 deaths among adults aged ≥ 65 years each year (67). Furthermore, RSV infection in adults may have a significant impact in other organs. Nearly 25% of hospitalized individuals over 60 years old with an RSV infection had an acute cardiac event, most often acute heart failure, reported by a cross-sectional study conducted across five RSV seasons. Of these, 1 in 12 persons (8.5%) had no known underlying cardiovascular illness (68).

The advisory Committee on Immunization Practices (ACIP) and the European Commission recommend use of RSV bivalent prefusion F protein-based vaccine and prefusion F protein vaccine for all individuals aged ≥ 75 years and for those ≥ 60 years with high risk of severe RSV illness due to chronic heart or lung disease, immunocompromised or living in a nursing home or long-term care facility (69-71). Clinical trials have demonstrated high efficacy of RSV vaccine in preventing lower respiratory tract disease in older adults, including those with COPD comorbidities. It shows 91% effectiveness in preventing RSV-related hospitalizations and emergency department visits (72). It also associated with 8.7% of outpatient-managed COPD exacerbations and found to be safe, with no significant adverse effects (72, 73).

Nevertheless, there is a significant gap in the safety and efficacy data of RSV vaccines specifically in COPD patients. Although they were included in clinical trials, the outcomes for this subgroup were not extensively reported (74). The unique immunobiology of RSV and the lack of clear protective immunological correlates also might complicate the development and assessment

of effective vaccines for high-risk patients (75). While the general safety profile of this vaccine is considerably good, the specific adverse reactions in COPD patients are not well-documented. Thus, there is a need for more detailed long-term studies to monitor the impact of RSV vaccination in COPD overall disease progression (76).

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3.4 COVID-19 Vaccine

COVID-19 vaccines are designed to protect from the severe effects of SARS-CoV-2 virus, which cause COVID-19 disease. There are different types of vaccines available including mRNA-based vaccines, adenoviral vector-based vaccines, inactivated virus vaccines and recombinant protein vaccines (77). Patients with COPD are particularly vulnerable to severe COVID-19 due to their compromised respiratory function due to over-expression of the angiotensin-converting enzyme 2 (ACE2) receptor in lungs, which facilitates easier viral entry into the cells (78, 79). COPD also is associated with endothelial cell dysfunction and increase tendency towards thrombus formation, which further complicates COVID-19 outcome (79). These explain COPD patients recovering from COVID-19 may experience long-term respiratory issues such as persistent dyspnoea, impaired lung function and fibrosis which significantly affect their quality of life and increase healthcare dependency (80).

COVID-19 vaccination plays a significant role in managing symptoms and outcomes for patients with COPD. It has a protective effect against this population by reducing the risk of severe illness and mortality. Vaccinated individuals show a lower risk of first healthcare utilization for COPD, including emergency room visits, hospitalizations and the need for mechanical ventilation. The effectiveness increases with the number of doses, highlighting the importance of booster shots. This reduction indicates a lower burden on healthcare system and better health outcomes compared to their unvaccinated counterparts (81). It is also associated with a notably lower risk of death in COPD patients with cardiovascular comorbidities which might complicate the clinical management and prognosis. Vaccinated patients exhibited a 7.95 times lowers risk of death and reduction rates of severe pulmonary involvement (82). The vaccination rate among COPD patients is relatively high (78.6%) but some remain unvaccinated due to hesitancy. Thus, it is important to address this issue and ensure that patients are well-informed about its safety and effectiveness (83).

3.5 Other Vaccines

Diphtheria, Tetanus and acellular Pertussis (DTaP) and its adult formulation, Tdap, play an important role in preventing exacerbation-triggering infections in COPD patients. Among the pathogens covered, Bordetella pertussis possesses a significant threat to COPD patients, as it can cause persistent cough, bronchial irritation and respiratory compromise, potentially leading to severe exacerbations and hospitalizations in this vulnerable population (84, 85). Despite the perception of pertussis as a paediatric disease, studies indicate that it is underdiagnosed in adults, especially in those with chronic pulmonary disease (86). Owing to that, the CDC recommends a single dose of Tdap for adults who has not previously vaccinated, particularly for those with chronic respiratory conditions, followed by a booster in every 10 years (87). Furthermore, this vaccination also has been endorsed as part of a comprehensive preventive strategy to reduce infectious triggers in COPD (8). By

maintaining immunity against pertussis, diphtheria and tetanus, Tdap vaccination perhaps can reduce exacerbations frequency, lower secondary bacterial infections risk and stabilize respiratory health in COPD patients, especially in the elderly and immunocompromised patients (86, 88).

Other than that, patients with COPD are also at increased risk of herpes zoster (HZ) due to advancing age and disease-related immunosuppression. The reactivation of latent varicella-zoster virus (VZV) in these individuals can lead not only to painful dermatomal rashes but also postherpetic neuralgia (PHN) and other complications that may exacerbate respiratory symptoms and worsen quality of life. In a survey 25.5% of COPD patients who had herpes zoster infection reported to experience increased COPD symptoms (89). A study in the United States found that COPD patients with HZ had increased use of medical services and healthcare costs compared to those without HZ (90). The recombinant zoster vaccine (RZV) has demonstrated 90% efficacy in preventing shingles and PHN in older adults and those with chronic diseases, including COPD (91). The CDC and other expert bodies recommend RZV for adults aged ≥50 years and immunocompromised individuals aged ≥19 years, including those with COPD (92). Incorporating RZV into routine COPD care may reduce the risk of zoster-related complications, prevent exacerbations, minimize hospitalization and contribute to better long-term disease outcome (92).

4.0 Conclusion

Effective COPD management requires a multifaceted approach that addresses both symptom control and prevention of acute exacerbations. While pharmacological therapies such as bronchodilators and corticosteroids remain foundational, non-pharmacological strategies particularly vaccination play a vital role in minimizing disease progression and complications. The integration of vaccines against respiratory pathogens such as influenza, pneumococcus, RSV, COVID-19, pertussis and varicella-zoster into routine COPD care prominently reduces infection related exacerbations and hospitalizations. Nevertheless, gaps have persisted in vaccine coverage especially in underserved regions and among older adults. Therefore, future research should focus on optimizing vaccine schedules, evaluating long-term outcomes in COPD subgroups and developing targeted educational interventions. Clinicians also must remain vigilant in promoting vaccine uptake, tailoring preventive strategies to individual patient risk profiles and overcoming barriers to implementation, thereby ensuring comprehensive care.

Authorship contribution statement

EEMR: Conceptualization, writing original draft, editing manuscript. **NST:** Conceptualization, draft corrections, editing manuscript, supervised.

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Conflict of Interest

The authors declare no conflict of interest in the current work.

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