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Influenza vaccination for patients with chronic obstructive pulmonary disease: understanding immunogenicity, efficacy and effectiveness

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***Abstract*:** Influenza infection is an important cause of global mortality and morbidity with the greatest impact on older people and those with chronic disease. Patients with chronic obstructive pulmonary disease (COPD) are particularly vulnerable to influenza, with evidence for increased incidence and severity of infection. In this patient group influenza is associated with exacerbations and pneumonia which result in a significant healthcare burden and premature mortality. Influenza vaccination and in particular the use of the seasonal trivalent influenza vaccine (TIV) is recommended for patients with COPD. The evidence base for its effects in this population is, however, limited. Available data suggest that immunogenicity is variable in COPD but the underlying mechanisms are not completely understood. The contribution of age, disease severity, comorbidity and treatments to vaccine responses has only been investigated in a limited manner. Existing data suggest that key immune mechanisms governing T- and B-cell responses are adversely affected by these factors. The efficacy of TIV has been studied in a number of small clinical trials which form the basis of a Cochrane review. Here evidence for effect is conflicting depending on individual trial design and inclusions. Overall, TIV offers protection against influenza infection in the trial setting but further studies are required to stratify patients and enable prediction of inadequate responses. Larger-scale clinical studies have largely been observational and have often been conducted in consort with pneumonia vaccination. Overall the mortality benefit of TIV in COPD is suggested by a number studies but the impact on exacerbation prevention is less clear. Influenza vaccination currently plays an important role in disease prevention in COPD. However, we postulate that a more in-depth understanding of mechanisms of response in the context of a highly heterogeneous disease will lead to a more informed approach to vaccination and greater benefit for the individual patient.

Keywords: chronic obstructive pulmonary disease, influenza, vaccine

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Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by chronic inflammation that results in irreversible airflow obstruction and a progressive decline in lung function [Britton, 2003; Stämpfli and Anderson, 2009; NICE, 2010]. As the fourth leading cause of mortality and morbidity in the world, associated with 2.75 million deaths per annum, it is unsurprising that COPD places a massive burden on the global healthcare system [Raherison and Girodet, 2009]. COPD is estimated to cost healthcare services £1639.08 per patient per annum in the UK, a major cost component of which is driven by acute exacerbations, with 25% of patients with COPD hospitalized as a direct result of their disease [Britton, 2003]. Despite continuous public health efforts to discourage smoking, both the prevalence and mortality rate of COPD has increased over time, arguably due to the cumulative effect

of past smoking habits and an ageing population [Britton, 2003; Doherty and Briggs, 2004; Landis *et al.* 2014]. By 2020, COPD will be the third leading cause of mortality in the world, just below cardiovascular disease [Lundbäck *et al.* 2003; Raherison and Girodet, 2009; Burel *et al.* 2012]. Much of the clinical burden of disease is driven by respiratory viral infection. The impact of current vaccination policy is considered in this review and a rationale for the development of new influenza vaccines is explored.

The burden of influenza in COPD

Much of the morbidity caused by COPD is as a result of acute exacerbations. These are defined as an acute worsening of the patient's respiratory symptoms beyond normal variation requiring a change in medication [GOLD, 2016]. Exacerbations are associated with an accelerated rate of decline in lung function, reduced quality of life and a 1 year mortality of up to 23% [Wedzicha and Donaldson, 2003; Papi *et al.* 2006; Sapey and Stockley, 2006; Anzueto, 2010; Makris *et al.* 2007]. In addition to being the most frequent cause of hospital admission for acute respiratory pathology, exacerbations are responsible for an average hospitalization time of 10 days per exacerbation per patient [Donaldson and Wedzicha, 2006]. The most common causes of exacerbations are respiratory infections, with the resulting incidence of exacerbations showing seasonal variation, increasing in the winter months when there is greater circulation of respiratory viruses [Seemungal *et al.* 1998; Wedzicha and Donaldson, 2003; Doherty and Briggs, 2004; Papi *et al.* 2006; Sapey and Stockley, 2006]. In the healthy lung, innate defences protect the lower respiratory tract from infection [Sethi, 2010]. However, in COPD, pathological changes in the airways provide the ideal condition for bacterial colonization. Hypersecretion of mucus through goblet cell hyperplasia and submucosal gland hyperplasia coupled with impaired function of the mucocillary escalator make patients with COPD more susceptible to bacterial infection [Wilson, 2001; Sethi, 2010]. A cycle of infection and inflammation may persist in disease even after smoking cessation; this can be further impacted by acute viral infection. Previously, only a small proportion of exacerbations were attributed to viral infection, but through polymerase chain reaction techniques, it is now acknowledged that viral infection could account for up to 50% of exacerbations, with the influenza virus being detected in up to 28% of exacerbating COPD patients [Papi *et al.* 2006; Sapey and Stockley, 2006]. Whilst rhinovirus is the most common cause of exacerbations, influenza is also a common causative organism in exacerbations of COPD severe enough to require hospital admission, and thus is a major driver of mortality and morbidity in COPD [Lall *et al.* 2016; Papi *et al.* 2006].

The World Health Organization (WHO) estimates that influenza is responsible for 1 billion infections worldwide every year, which equates to 20% of the world's population annually, with an annual mortality rate of 300,000–500,000 [WHO, 2015; Wesseling, 2007]. Of the 12,500 deaths that occur in the UK annually as a result of influenza infection, 90% of these occur in older people with chronic health conditions, such as COPD [Weinberger *et al.* 2008]. Mechanistic studies suggest that individuals with COPD are more susceptible to influenza infection [Hsu *et al.* 2015]. In addition, the presence of comorbidities, such as COPD, influences the severity of infection and risk of developing influenza-related complications, such as pneumonia and secondary bacterial infections [NICE, 2015]. It is important to note that, in patients with COPD, baseline disease severity is a major influence on outcome following infection, with increased disease severity, hypoxaemia and hypercapnia being factors that are associated with a poor prognosis [Wilson, 2001; Ramsey and Hobbs, 2006].

Acute viral infections may also alter the natural history of disease beyond the acute exacerbation. The presence of CD8+ and CD4+ T lymphocytes in increased numbers in COPD airways is suggestive of chronic or recurrent immune stimulation. Chronic inflammation may occur in response to microbial dysbiosis triggered by acute viral infections, which in turn contributes to dysfunction of innate immune defences and destruction of the lung parenchyma or airway remodelling [Sethi, 2010]. Chronic stimulation from infection could be attributed to a number of factors, including failure of innate immunity in COPD lungs, dysfunction of antiviral functions of CD8+ T lymphocytes and a deficiency in immunoglobulin A in the airways [Schleimer, 2005; Polosukhin *et al.* 2011; McKendry *et al.* 2015], all mechanisms which may impact on the need for and immunogenicity of influenza vaccination.

Vaccination against influenza is associated with a reduction in the incidence of influenza by up to 60% and is responsible for decreasing rates of hospitalization by up to 40% [Burge and Wedzicha, 2003]. As well as acting as prophylaxis against influenza infection, the trivalent influenza vaccine (TIV) acts to reduce the incidence of complications of influenza, such as pneumonia, by up to 80% [McElhaney *et al.* 2006]. TIV is also associated with a reduction in the incidence of other significant causes of mortality, such as stroke and diabetes mellitus [Wang *et al.* 2007]. As a consequence, influenza vaccination has been established as a key intervention in management of COPD.

Current practice: influenza vaccination

In the UK, vaccination against influenza is recommended to all individuals above the age of 65 and those with chronic health conditions such as COPD. Annual vaccination is indicated due to the emergence of variant strains *via* antigenic drift [Carrat and Flahault, 2007]. There are two commonly used formulations of the influenza vaccine – the TIV and the live attenuated influenza vaccine (LAIV) [He *et al.* 2006]. TIV is an inactive vaccine that comprises three viral strains and carries a typical total haemagglutinin (HA) protein content of 45 μg. This currently includes 15 μg of H1N1, 15 μg of H3N2 and 15 μg of an influenza B strain [Stephenson and Nicholson, 2001; He *et al.* 2006; Lambert and Fauci, 2010; Wong and Webby, 2013]. TIV is commonly administered as a single intramuscular injection. The process of TIV formulation is complex, involving surveillance for influenza in 142 national influenza centres in 113 countries [Carrat and Flahault, 2007; CDC, 2015b]. This information is analysed in an annual review by WHO and is reliant on predictions made about the viral strains in the upcoming influenza season, resulting in the selection of three strains for inclusion in the vaccine. The effectiveness of TIV is dependent on the eventual circulating viral strain matching with the strains contained in the TIV. Unfortunately, this is not always the case and discrepancies between the predicted and circulating strain may occur due to antigenic drift that can occur in the 9 months between influenza vaccine recommendations and influenza season [Carrat and Flahault, 2007]. For example, in the 2014/15 influenza season, there was a mismatch between the predicted and circulating viral strains in the northern hemisphere, resulting in an estimated vaccine effectiveness of just 23%. This was associated with an increase in the incidence of influenza infection in the 2014/15 influenza season [Xie *et al.* 2015]. The influenza A(H3N2) strain that was selected for inclusion in this vaccine was circulating strain in the 2013/14 influenza season. However, new viral strains became predominant after WHO recommendations had already been made [WHO, 2015; Xie *et al.* 2015]. Although this contrasts with the 50–60% effectiveness that is seen in years where the predicted and circulating strains match, WHO still recommends vaccination against influenza in cases of mismatching viral strains due to the inclusion of multiple strains, which could still result in a significant reduction in the incidence of influenza.

Unlike TIV, LAIV contains a live attenuated virus and is commonly administered intranasally [Hovden *et al.* 2007; WHO, 2015]. The cold-adapted LAIV contains three strains of live attenuated viruses which are directly administered to the respiratory tract *via* an intranasal spray [He *et al.* 2013]. Production of LAIV relies on reassortment of the viral genome to include genes encoding for HA and neuraminidase (NA) [Cox *et al.* 2004]. Immunity to influenza is achieved by mimicking natural infection, resulting in a local inflammatory response. As the strains are temperature sensitive, the virus is limited in its capacity to replicate at temperatures present in the lower respiratory tract [Cox *et al.* 2004; He *et al.* 2013]. Despite the fact that individuals produce a longer-lasting immune response to LAIV, TIV remains the most commonly used formulation of influenza vaccine in the UK [He *et al.* 2006]. This is due to the fact that LAIV is only suitable for individuals between the ages of 5 and 49 years. Randomized, controlled trials (RCTs) comparing the efficacy of LAIV with that of TIV seem to conclusively indicate that LAIV is more efficacious in children (aged between 6 months and 17 years) but showed similar levels of efficacy to (or was less efficacious than) TIV in individuals above the age of 17 [Ambrose *et al.* 2011]. Due to the upper age limit for administration of LAIV, TIV is the formulation given to patients with COPD. In addition, as a vaccine dependent on viral replication, LAIV has the potential to induce airway inflammation which may lead to increased side effects in established COPD.

It is also worth mentioning the emerging presence of quadrivalent influenza vaccine (QIV), which contains two influenza A viral strains and two

influenza B viral strains. Given that there are two distinct lineages of influenza B stains in circulation during influenza season, QIV was developed with the intention of offering better protection than TIV [Belshe, 2010; Lee *et al.* 2012; CDC, 2015a]. Like influenza vaccines containing three viral strains, QIV comes in the form of an intramuscular infection and a nasal spray [CDC, 2015a].

Measuring vaccine success: immunogenicity and beyond

The influenza virus has two major external structural antigens, HA and NA, which are commonly targeted in vaccination. HA is a glycoprotein that allows the influenza virus to bind to the key target in man: respiratory epithelial cells; whilst NA is an enzyme which enables release from infected host cells [Mallia and Johnston, 2007]. In response to the influenza vaccine, antigen presenting cells, such as macrophages and dendritic cells, present influenza antigenic peptides to B cells and CD4 T lymphocytes [Weinberger *et al.* 2008]. This activates both cell types which respond by either differentiation from naive into memory cells into the context of a first exposure to novel antigens or expansion of active memory cells and antibody secreting B lymphocytes in the case of a recall response [He *et al.* 2006; Weinberger *et al.* 2008; Lambert and Fauci, 2010; Burel *et al.* 2012; Lambert *et al.* 2012]. The key effector response of the TIV is the production of antibodies against the influenza HA and NA. Production of immunoglobulins by B lymphocytes in response to HA and NA is reliant on the development of plasmablasts and confers immunological protection against the influenza virus by neutralizing viral particles, preventing the attachment of the virus to the epithelium and preventing infection and ultimately the release of new virions [Potter and Oxford, 1979; Cox *et al.* 2004; McElhaney, 2005, 2011; Hovden *et al.* 2007; Weinberger *et al.* 2008; Burel *et al.* 2012].

There are different ways of measuring successful immunization. The first method is to measure immune reactions in response to the influenza vaccine. It is well established that production of a sufficient concentration of antibodies to HA and NA confers immunological protection from influenza [He *et al.* 2006; Stephenson and Nicholson, 2001; Lambert and Fauci, 2010; Wong and Webby, 2013]. Therefore, HA inhibition (HAI) assays measuring anti-HAI antibody titres are used to assess whether protection against influenza has been achieved and are an established correlate of protection [Burel *et al.* 2012; Stephenson and Nicholson, 2001]. Following vaccination, 90% of healthy young individuals achieve seroconversion, which is defined as a fourfold increase in antibody titres post vaccination [Mallia and Johnston, 2007; Stephenson and Nicholson, 2001; Wong and Webby, 2013; Lambert *et al.* 2012]. This is deemed a successful immune response to the vaccine and is one way of measuring potential vaccine efficacy [Lambert *et al.* 2012]. However, HAI assays record a surrogate measure of true clinical efficacy. Studies which measure clinical impact of TIV assess reductions in the incidence of influenza in the vaccinated patients compared ideally with unvaccinated controls [Darvishian *et al.* 2014]. Despite being the gold standard measurement of vaccine efficacy against influenza, there are limitations to correlating this response to a clinical reduction in the incidence of influenza [McElhaney, 2011]. This is particularly seen in an older population, who often experience influenza-like illness despite achieving seroconversion, demonstrating that antibody levels do not always translate as clinical protection. An inability to distinguish between antibody subtypes could result in a mismatch between laboratory and clinical assessment of successful vaccination, which can be attributed, in part, to failure of the antibody to bind to the viral particle [McElhaney, 2005]. This is demonstrated in an RCT conducted by Govaert and colleagues which found no significant correlation between antibody responses to TIV and protection against laboratory-confirmed influenza illness in a cohort of vaccinated healthy individuals [Govaert *et al.* 1994; McElhaney, 2011]. In addition, this is supported by another study which demonstrated no significant difference in serum antibody titres in older individuals who developed influenza post vaccination compared with those who did not [McElhaney, 2011]. Therefore, it must be acknowledged that immune response to vaccination is multifaceted, requiring competency in various components of immune function to achieve a successful response. Alternative measurements of vaccine could include virus neutralization assays [McElhaney, 2005, 2011].

For ethical reasons, there are very few double-blind RCTs that record the incidence of laboratory-confirmed influenza illness in vaccinated and unvaccinated individuals [McElhaney, 2011; Darvishian *et al.* 2014]. One previous RCT concluded that the influenza vaccine was 50% effective in reducing the incidence of influenza

[McElhaney, 2011]. Most studies that aim to measure the true clinical effectiveness of the influenza vaccine often involve retrospective analysis of surrogate endpoints, such as the presence of influenza-like respiratory illness, hospitalization rates and all-cause mortality rates [McElhaney, 2011; Darvishian *et al.* 2014]. Definitive clinical diagnosis without laboratory confirmation can be inaccurate due to the large number of respiratory agents that could result in influenza-like illness, but other outcomes such as all-cause mortality may not be specific enough to evaluate TIV effectiveness [Darvishian *et al.* 2014]. In addition, the validity of such studies has been questioned, with concerns raised about the impact of selection bias and the 'healthy-user effect' which would result in overestimation of the clinical effectiveness of TIV [Jackson *et al.* 2006; Darvishian *et al.* 2014]. Baxter and colleagues reported reduced incidence of vaccination in older populations and thus concluded that the association of vaccination with reduced total mortality inaccurately reflects the clinical effectiveness of TIV, due to selection bias in individuals that choose to get vaccinated being younger and generally of greater health [Baxter *et al.* 2010]. Jackson and colleagues aimed to address this selection bias by using health status between vaccinated and unvaccinated subjects as a confounding factor to determine the true effect of the vaccine. This study report argued that the protective effects of the influenza vaccination should be limited to periods of time in which there is influenza viral circulation, and therefore analysis of noninfluenza periods, as well as influenza season, should account for this bias. The results of this study showed that the biggest reduction in pneumonia-related hospitalization and mortality rate occurred prior to influenza season, suggesting that the vaccine is not responsible for this observed effect [Jackson *et al.* 2006]. To diminish the impact of confounding factors and bias on conclusions of vaccine effectiveness, Darvishian and colleagues explored the use of test-negative designed case-control studies, whereby vaccine status is compared in patients with laboratory confirmed influenza and patients with influenza-like symptoms who tested negative for laboratory confirmed influenza. Arguably, this diminishes the bias associated with differing health statuses amongst vaccinated and unvaccinated individuals as both groups of participants are recruited in the same way and thus are assumed to have similar health-seeking behaviours [Darvishian *et al.* 2014].

Immune responses to TIV are variable with a significant proportion of individuals exhibiting an inadequate immune response to the influenza vaccine. Responses in at-risk groups have been studied with most data captured in older individuals, with reduced responses attributed to loss of immune function with age or immune senescence [Monto *et al.* 2001; Aspinall *et al.* 2007; Weinberger *et al.* 2008; McElhaney, 2011; Sasaki *et al.* 2011]. Trials data suggests that the influenza vaccine is protective in 70–90% of young adults in comparison to only 17–51% individuals aged 65 and above [Aspinall *et al.* 2007, Sasaki *et al.* 2011]. An effect which is more marked with extreme age, seroconversion, occurs in only 29–46% of individuals aged 75 years and above compared with 41–58% in individuals aged 64–74 years old [Weinberger *et al.* 2008; Goodwin *et al.* 2006].

Surprisingly little research documents the immune response to TIV among patients with COPD. One observational study conducted in Australia found that patients with COPD produce a lower-fold increase in antibody concentrations in response to TIV, concluding that individuals with COPD mount a reduced humoral immune response to the influenza vaccine [Burel *et al.* 2012; Nath *et al.* 2014]. This study found that 90% of healthy subjects showed seroconversion in response to TIV compared with only 43% of patients with COPD. Further immunological analysis was conducted to identify the mechanisms underlying this reduced immune response, including *in vitro* analysis of peripheral blood mononuclear cells to assess innate and adaptive immunity and analysis of cytokine interleukin (IL)-21 to evaluate its role in driving responses in T and B lymphocytes. Upon analysis of 28 day postvaccination serum samples, concentrations of IL-21 were found to be significantly lower in patients with COPD than in the healthy controls. It was concluded that this diminished immune response to TIV was linked to adaptive rather than innate immunity, specifically involving B-lymphocyte functionality [Burel *et al.* 2012; Nath *et al.* 2014]. However, there are a few limitations to this study. Firstly, prevaccination blood samples were only taken from some of the cohort and not all participants had previously been vaccinated against influenza prior to the study. Consequently, there was limited scope to compare immune responses at baseline between healthy controls and patients with COPD. Another criticism of this study is that there was

inadequate age-matching between COPD participants and healthy controls, potential affecting the validity of these conclusions.

Vaccine efficacy in clinical trials in COPD

A 2006 Cochrane review evaluated the results of 11 trials to determine the efficacy of the influenza vaccine in patients with COPD. A summary of these randomised controlled trials assessing influenza vaccine efficacy is shown in table 1. It was found that patients with COPD who were administered the inactivated influenza vaccine experienced significantly fewer exacerbations per year than patients with COPD who were administered a placebo. It thus concluded that the influenza vaccine reduced the incidence of influenza-related respiratory infections [Poole *et al.* 2006] (Table 1). Interestingly, one of the studies analysed in this Cochrane review differentiated between early and late exacerbations, depending on the length of time after TIV administration that the exacerbation occurred. Here Howells and colleagues concluded that that the influenza vaccine showed no statistically significant protective effect in comparison to a placebo as prophylaxis for early exacerbation, but did result in significant reduction in late exacerbation rates [Howells and Tyler, 1961]. The period of time after the vaccination in which study participants are monitored for exacerbations could explain why the literature on this topic is inconclusive. In one study, Ting and colleagues compared the incidence of acute exacerbations in vaccinated and unvaccinated patients with COPD. It was concluded that there was no significant difference in exacerbation rates between the two groups, but participants were only monitored in the immediate postvaccination period [Ting *et al.* 2011].

Clinical effectiveness of TIV in COPD

In 2004, the UK advisory body NICE (National Institute for Health and Care Excellence) published guidelines stating that TIV should be offered every year to all patients in the UK with COPD as a prophylactic treatment against influenza [NICE, 2010]. Evidence suggesting that TIV is clinically effective prophylaxis, outside small RCTs in patients with COPD, mainly comes from observational studies conducted in older patients. For example, a retrospective cohort study by Nichol and colleagues concluded that the influenza vaccine reduced the incidence of hospitalization from pneumonia and influenza by 52% and resulted in a 70% reduction in all-cause mortality in a study following a cohort of 1898 older individuals with chronic lung disease [Nichol *et al.* 1999]. However, the results of this study have been put into question as it has been argued that that individuals who choose to get the influenza vaccination also tend to engage in more health-enhancing activities than their nonvaccinated counterparts. Thus, the results of this study are potentially affected by selection bias because they do not account for different health status between vaccinated and unvaccinated individuals [Jackson *et al.* 2006; Burel *et al.* 2012; Nath *et al.* 2014].

Other studies also evaluated the utility of TIV in combination with other vaccinations. Gorse and colleagues assessed the additive effect of coadministration of the LAIV and TIV vaccine in patients with COPD. Whilst this study reported no statistically significant advantage of giving this combination compared with TIV combined with a placebo, it does bring to question whether some formulations of the influenza vaccine can be more efficacious in patients with COPD [Gorse *et al.* 2003]. Several studies evaluate the effectiveness of TIV in combination with another vaccine, most commonly the pneumococcal vaccine. Furumoto and colleagues concluded that, in combination, the influenza and pneumococcal vaccine were effective in preventing infectious acute exacerbations in patients with COPD but not pneumonia or noninfectious acute exacerbations [Furumoto *et al.* 2008]. Another study compared the protective effects of the influenza vaccine with the pneumococcal vaccine in patients with COPD, concluding that TIV is efficacious in reducing all-cause mortality but pneumococcal vaccine is not [Schembri *et al.* 2009]. Similarly, an evidence-based review conducted in Canada quantified the prophylactic effect of TIV in reducing the incidence of influenza-related respiratory illness as 76% [Sehatzadeh, 2012]. These studies seem to show that the influenza vaccine is an effective intervention in patients with COPD on a population level, but response in individuals varies. Interestingly, the latter study concluded that the efficacy of TIV as prophylactic treatment in patients with COPD is dependent on the level of airflow obstruction and disease severity. Further study is needed, stratifying patients with COPD into groups of varying disease severity, to quantify this relationship and to identify risk of vaccine failure.

Another factor that is important to consider when evaluating how efficacious TIV is in patients with COPD is the concentration of HA in a dose. The normal adult human dose of TIV contains 15 μg of

Table 1. Summary of the details of randomized controlled trials evaluated in the Cochrane review, measuring vaccine efficacy of the trivalent influenza vaccine amongst older patients and individuals with chronic lung disease [Poole *et al.* 2006].

Study	Author	Study design	Setting	Details of patient recruitment	Primary outcome measurement	Results and conclusion
Clinical trials of bivalent influenza/A/ New Jersey/76-A/ Victoria/75vaccines in the elderly,	Cate *et al.*	Double-blind RCT	Texas Medical Centre, 1976	A cohort of 413 older subjects were recruited, 5% of whom had chronic lung disease	Adverse reactions to vaccination were measured in the 1- and 2-day postvaccination period	A mild and moderate adverse systemic reaction to vaccination was seen in 7.8% and 4.9% of this cohort respectively. In contrast, control subjects who received a saline placebo did not experience any moderate or severe adverse reactions. 18.5% of patients experienced erythema at the injection site compared with none in the control group
Longer term effects of live influenza vaccine in patients with chronic pulmonary disease	Fell *et al.*	Double-blind RCT	Oxfordshire, 1975	This cohort comprised 44 subjects with chronic bronchitis, 21 of whom were vaccinated and 23 were placebo treated	Self-assessment of the presence and severity of symptoms such as cough, dyspnoea, tightness, wheeze and sputum production following vaccination. A symptom score was assigned to every individual in the first 2 weeks after vaccination or placebo treatment to establish a baseline	At baseline, symptoms were more commonly reported in the vaccinated cohort compared with the placebo-treated group. This was not statistically significant, except for the occurrence of wheeze, which was significantly higher in vaccinated individuals than their placebo-treated counterparts Breathlessness was significantly lower in incidence amongst the vaccinated subjects who had a serological response to vaccination compared with the placebo group During the 18-week postvaccination surveillance period, symptoms of dyspnoea, chest tightness, wheeze and cough were significantly more common in vaccinated subjects compared with their placebo-treated counterparts, correlating with more common antibiotic usage in this group
Increased anti-influenza A viruscytotoxic T-cell activity following vaccination of older patients with chronic disease with live attenuated or inactivated influenza virus vaccine	Gorse *et al.*	Single-blinded RCT	1993–1994, St Louis VA Medical Centre and at St Louis Altenheim nursing home	A cohort of 50 older nursing home residents were given TIV, which was coadministered with either the bivalent live attenuated influenza A vaccine or a saline placebo	Virus memory cytotoxic T cell response was measured in each subject.	The authors concluded that it could be advantageous to co-administer LAIV with TIV because a rise in anti-influenza A cytotoxic T lymphocyte activity was more commonly seen in subjects who were co-administered both formulations of the influenza vaccine compared to those administered TIV with a placebo.

(Continued)

Table 1. (Continued)

Study	Author	Study design	Setting	Details of patient recruitment	Primary outcome measurement	Results and conclusion
Influenza virus vaccination of patients with chronic lung disease.	Gorse *et al.*	Single-blinded RCT	Outpatient clinics of St Louis Department of Veterans Affairs Medical Centre, 1994–1995	29 volunteers, aged between 42 and 88 years old, with pre-existing COPD were recruited. Each volunteer received an intramuscular injection of TIV, in addition to either the bivalent LAIV or a saline solution placebo intranasally	Clinical status was assessed alongside pulmonary function, measured *via* spirometry. Levels of anti-HA immunoglobulin A antibodies were measured in nasal washings	Vaccination status did not affect clinical status or pulmonary function. There was no significant difference in the incidence of exacerbations or in reports of respiratory tract symptoms between the two groups in the cohort Levels of anti-HA immunoglobulin A antibodies in nasal washings and levels of IL-2 and IL-4 increased significantly post vaccination in subjects with combined LAIV and TIV compared with pre vaccination, but did not significantly increase post vaccination in subjects administered TIV with a placebo. The authors concluded that there could be some benefit of administering TIV with LAIV
Adverse reactions to influenza vaccine in older people: randomized double-blind placebo controlled trial	Govaert *et al.*	Double-blind RCT	15 general practises in the southern Netherlands, 1991–1992.	1806 participants aged 60 or older were recruited on to the study. The cohort was divided into a group which received the influenza vaccine and a group that received a placebo	Adverse reactions reported on postal questionnaire completed 4 weeks after vaccination	Local side effects were significantly more common in the vaccinated group compared with the placebo group but there was no difference in systemic adverse reactions. All side effects were mild
The efficacy of influenza vaccination in older individuals. A randomized double-blind placebo-controlled trial	Govaert *et al.*	Double-blind RCT	15 general practises in the southern Netherlands, 1991–1992	1836 participants aged 60 years or older were recruited on to the study. Individuals in the cohort were randomly assigned either the purified split-virion vaccine or an intramuscular saline placebo	Patients presenting with influenza-like illness up to 5 months after vaccination; self-reported influenza in postal questionnaires 10 weeks and 5 months after vaccination. The presence of serological influenza was also measured *via* antibody titres	The incidence of serological influenza and clinical influenza was lower in the vaccinated group than the placebo group. The authors concluded that vaccination against influenza was responsible for a 50% reduction in the incidence of serological and clinical influenza

Table 1. (Continued)

Study	Author	Study design	Setting	Details of patient recruitment	Primary outcome measurement	Results and conclusion
Prophylactic use of influenza vaccine in patients with chronic bronchitis. A pilot trial	Howells *et al.* (1961)	Double-blind RCT	Winter 1960, NW Wolverhampton	55 participants with chronic bronchitis were recruited on to the study, 26 of whom were randomly selected to be in the vaccinated group and 29 in the placebo group	The incidence of exacerbations was recorded by clinical examination and peak expiratory flow, with bacteriological and complement fixation to find the causative microorganism. Hospitalization rates and mortality were also recorded	This study demonstrated no significant difference in the incidence of early exacerbations between the vaccinated and placebo group. There was a significant reduction in the number of patients with late exacerbations in the vaccinated group compared with the placebo group. It was therefore concluded that vaccination significantly reduced the number of exacerbations during the follow-up period, per patient
Recognizing influenza in older patients with COPD who have received influenza vaccine	Neuzil *et al.*	Double-blind RCT	Various veterans affairs sites throughout the US and Puerto Rico during the 1998–1999 Influenza season	2215 veterans with COPD were recruited on to this study. Each individual then received TIV, which was coadministered with either LAIV or an intranasal placebo	The presence of symptomatic, laboratory-documented influenza was recorded in this cohort	The authors state that it was difficult to clinically distinguish the symptoms associated with influenza-related illness from noninfluenza illness. Myalgia was reported in 80.9% of patients with laboratory-confirmed influenza but the presence of laboratory-confirmed influenza was low in the vaccinated population The authors concluded that receipt of LAIV as well as TIV, in comparison to TIV and a placebo, was associated with improvement in chronic lung disease severity index, which was used to assess functional status and wellbeing
A study of live influenza virus vaccine in patients with chronic bronchitis. Report to Medical Research Council's Committee on Influenza and Other Respiratory Virus Vaccines. Advisory Group on pulmonary function tests in relation to live influenza virus vaccines	Medical Research Council	Double-blind RCT	No details	86 participants with chronic bronchitis were initially recruited. Of these, 16 subjects had no baseline data and 15 had incomplete records. Thus only 55 were included in the final analysis. Each subject was randomly assigned to be administered the live attenuated RIT 4050 (H2N3) vaccine virus whilst others received a placebo preparation	7-day post vaccination, subjects were assessed for respiratory and systemic symptoms. Spirometry was also conducted On day 21 in the postvaccination period, all of these measures were repeated and a HAI antibody test was also conducted	The authors concluded that the influenza vaccine did not cause a clinical or physiological deterioration, but that there was a small and insignificant decrease in lung function tests 1 and 3 weeks following vaccination in the vaccinated group compared with the placebo group

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Table 1. (Continued)

Study	Author	Study design	Setting	Details of patient recruitment	Primary outcome measurement	Results and conclusion
Protective efficacy of combined live intranasal and inactivated influenza A virus vaccines in older people	Treanor *et al.*	Double-blind RCT	Three large nursing homes	A total of 523 nursing home residents were recruited on to the study. Subject were coadministered TIV with either the live attenuated influenza A vaccine or a placebo	Laboratory-documented influenza A was diagnosed in patients with respiratory illness in addition to isolation of influenza A in nasal secretions or serological response	It was concluded that intranasal immunization with LAIV provided additional protection as prophylaxis against influenza infection when coadministered with TIV, resulting in significantly reduced rates of laboratory-confirmed influenza A and outbreak-associated respiratory illness
Evaluation of cold-adapted, reassortant influenza B virus vaccines in older and chronically ill adults	Treanor *et al.*	Double-blind RCT	Outpatient clinics of Strong Memorial Hospital; Rochester, NY and a private practice	81 older subjects were recruited from outpatient clinics, 34 of whom were given LAIV, 30 of whom were given parenteral TIV and 11 controls who were given a placebo	In the 3–4 day postvaccination period, pulse oximetry, spirometry, virus cultures and HAI tests were measured. It was also assessed whether the patient had any respiratory or systemic symptoms At 4 weeks post vaccination, serology was repeated. It was also recorded whether any subjects were hospitalized	Symptoms of malaise and myalgia were reported in 12% of subjects vaccinated with LAIV, 10% of subjects vaccinated with TIV and in no placebo-treated subjects. Lower and upper respiratory tract symptoms were reported in 26% and 29% of subjects vaccinated with LAIV respectively, 13% and 37% of those vaccinated with TIV respectively, and 9% and 18% of the placebo group respectively. Febrile illness was experienced by 6% of those who received LAIV, 2.5% of those were vaccinated with TIV and by no one in the placebo group There was no significant difference in lung function between groups 8% of the treatment groups developed respiratory illness compared with 20% of the control group after a documented outbreak of influenza A occurred. Additionally, only 4% of the treatment group experienced influenza-like illness compared with 11% if the control group
Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination: a randomized controlled study	Wongsurakiat *et al.* (2004)	Stratified randomized double-blind placebo-controlled trial	1997–1998 at a single university hospital	125 patients with COPD were recruited and then stratified based on disease severity. Individuals within each stratified group were randomized into a vaccinated group and a placebo group	Number and severity of episodes of acute respiratory illness, including influenza-like respiratory illness. Number and severity of episodes of acute respiratory illness (ARI) including influenza-like respiratory illness. This was measured *via* outpatient treatment, the incidence of hospitalization and requirement of mechanical ventilation	It was concluded that regardless of severity, vaccination against influenza is effective in prevention of influenza-related acute respiratory illness in patients with COPD. However, there was no significant difference in the incidence or severity of total acute respiratory illness between the vaccinated and placebo group, suggesting that TIV does not prevent other ARIs unrelated to influenza

COPD, chronic obstructive pulmonary disease; HA, haemagglutinin; HAI, haemagglutinin inhibition; IL, interleukin; LAIV, live attenuated influenza vaccine; RCT, randomized controlled trial; TIV, trivalent influenza vaccine.

HA per strain, and therefore a total of 45 μg of HA [Hovden *et al.* 2007]. However, some of the literature suggests that increasing this dose could increase the preventative effect of TIV in more vulnerable patient groups. A double-blind RCT conducted in Thailand concluded that TIV is 76% effective in protecting against influenza-related acute respiratory illness in patients with COPD, but it used vaccine concentrations that are twofold higher than typical TIV [Wongsurakiat *et al.* 2004]. The concept of improved response upon increasing TIV dosage, as shown in the Thai study, is supported by a retrospective cohort analysis published in *The Lancet* by Izurieta and colleagues. This study compared the efficacy of high-dose *versus* standard-dose TIV in older individuals. The high-dose TIV in this study contained 60 μg HA antigen, which is approximately four times as much as the standard dose. The study concluded that the high-dose TIV was 22% more effective than the standard dose for prevention of probable influenza infections and prevention of influenza hospital admissions for all age groups [Izurieta *et al.* 2015]. This brings into question whether a higher-dose TIV vaccine in patients with COPD would be more effective prophylactic treatment against acute exacerbations caused by influenza.

Potential mechanisms underlying suboptimal immune vaccine responses in COPD

If vaccine responses are found to be inadequate or heterogeneous in patients with COPD, it is important to consider the potential mechanisms behind failed responses. This will enable both the development of more immunogenic vaccines and the approach for the stratification of patients to target them most effectively.

The immunology of vaccine response in the context of chronic disease is a complex and incompletely studied field. While many of the mechanisms of failed response are related to frailty driven by age and chronic inflammation, one more established but still controversial explanation is the concept of original antigenic sin. This is the concept that previous exposure to an antigen results in substandard immune response when exposure to a novel but closely related antigen occurs [Kim *et al.* 2009]. Utilization of immunological memory based on previous infection prevents the immune system from being able to mount a potentially more effective response during subsequent infections due to the dominance of a nonantigen aligned recall response [Kim *et al.* 2009; Nath *et al.* 2014]. However, this may not be a key mechanism peculiar to COPD: the study conducted by Burel and colleagues only used the H1N1 strain of influenza when vaccinating study participants. Despite it being likely that both patients with COPD and healthy participants had previously encountered this strain, study subjects with COPD still mounted a reduced adaptive immune response to TIV in comparison to healthy individuals [Burel *et al.* 2012; Nath *et al.* 2014].

COPD and the immune system

One factor that could contribute to suboptimal immune responses to pathogens and hence influenza vaccine in patients with COPD in comparison to healthy individuals is T-cell exhaustion, a phenomenon which is frequently seen in states of chronic infection such as HIV and cancer [Yi *et al.* 2010; Wherry, 2011; Kahan *et al.* 2015]. In cases of antigen persistence, chronic activation of T cells results in dysfunction of CD4 and CD8 cells [Yi *et al.* 2010; Kahan *et al.* 2015]. Loss of function occurs in a hierarchical manner, with production of IL-2 and tumour necrosis factor α being some of the first functions to be inactivated. There is increased expression of inhibitory receptors and increased expression of immunosuppressive cytokines, which results in altered function of T cells and subsequent deletion of CD8+ and CD4+ cells [Yi *et al.* 2010; Wherry, 2011, Kahan *et al.* 2015]. The exact teleological advantage behind this response is unknown, but it has since been hypothesized that this is done to limit immunopathology [Kahan *et al.* 2015]. This is supported by recent research conducted by McKendry and colleagues, which found a greater proportion of T lymphocytes express the exhaustion marker programmed death 1 (PD-1) in COPD lungs compared with healthy controls. As an important regulator of T-lymphocyte function which is associated with a loss of cytotoxic function, the upregulation of PD-1 in T lymphocytes reduces CD8+ T-cell function in response to influenza. Specifically, this was associated with diminished T-cell cytotoxic degranulation in response to viral infection, supporting the concept of diminished T-lymphocyte response to viral infection in patients with COPD [McKendry *et al.* 2015].

Alternative immune mechanisms are suggested in a study by Kalathil and colleagues, which found a higher prevalence of immunosuppressive T-regulatory cells and myeloid-derived suppressor

cells, as well as functionally exhausted effector T cells in patients with COPD compared with healthy participants [Kalathil *et al.* 2014]. Increased numbers of these cells can be protective in some ways as T-regulatory cells may modulate inflammatory damage, but also contribute to the susceptibility to infection in patients with COPD and suboptimal immune response to TIV.

A detailed study by Polosukhin found that bronchial epithelial dysplasia that occurs in COPD leads to a deficiency of mucosal secretory immunoglobulin A (IgA). Diseased epithelium was unable to transport adequate amounts of secretory immunoglobulin A (SIgA), particularly in advanced disease associated with stratified squamous epithelial metaplasia. This study also found that proportion of patients with COPD harbouring latent viral agents was significantly higher than in control subjects and that 90% of virally infected airways were surface IgA deficient in COPD airways [Polosukhin *et al.* 2011]. This highlights the possible role of mucosal pathology in contributing to the defective immunity to viruses, even in the context of an adequate systemic antibody response.

Smoking and vaccine responses in COPD

Despite continuous public health efforts to discourage smoking, there are over 1.1 billion smokers worldwide, an estimated 50% of whom are at risk of developing COPD [Lundbäck *et al.* 2003; Stämpfli and Anderson, 2009]. Given the strong involvement of smoking in the pathogenesis of COPD, smoking is responsible for up to 85–90% of COPD cases in developed economic countries and it increases the risk of dying from COPD by 13 fold [Doherty and Briggs, 2004; Shahab *et al.* 2006]. Therefore, it can be argued that smoking is one of the most significant determinants of prognosis, symptom severity and disease progression [Lange *et al.* 1989].

It is well established that smoking is associated with increased prevalence and severity of respiratory infections, including increased susceptibility to epidemic influenza [Finklea *et al.* 1971; Cruijff *et al.* 1999; Sopori, 2002]. As well as increasing the risk of infection, smoking also reduces the capability of the innate and adaptive immune systems to combat these infections by modifying the functionality of various immune cells and altering signalling pathways [Sopori, 2002; Stämpfli and Anderson, 2009]. Cigarette smoke diminishes the ability of alveolar macrophages to phagocytose bacteria and cellular debris, the accumulation of which causes secondary inflammation [Sopori, 2002; Birrell *et al.* 2008; Stämpfli and Anderson, 2009]. Equally, smoking impacts the functionality of other innate immune cells, such as causing dysfunction of natural killer cells and dendritic cells [Sopori, 2002; Stämpfli and Anderson, 2009]. In terms of the adaptive immune system, smoking results in reduced antibody responses to various antigens, decreases serum levels of many immunoglobulin classes and is associated with decreased T-cell function and increased autoantibody production [Kalra *et al.* 2000; Sopori, 2002; Stämpfli and Anderson, 2009]. It is well established that smoking negatively impacts the immune system and that smoking cessation in patients with COPD is associated with improved respiratory symptoms, improved prognosis and decelerated disease progression [Kanner *et al.* 1999; Pride, 2001]. However, there is less research conducted on how smoking affects the efficacy of TIV. One randomized, controlled study conducted in the Netherlands demonstrated no statistically significant difference in the efficacy of the influenza vaccine between smokers and nonsmokers in an older population [Cruijff *et al.* 1999]. Additionally, another observational study concluded that there was no association observed between influenza vaccine response and whether the study participant was a current smoker [Nath *et al.* 2014]. More research is needed before concluding there is an effect of smoking on the vaccine immunogenicity of TIV, but the evidence would suggest that TIV plays a key role in smokers and exsmokers with COPD.

Corticosteroids

Amongst other pharmacological treatments, patients with COPD are often prescribed inhaled or oral corticosteroids [NICE, 2010]. It is well established that systemic corticosteroids suppress the immune system, including suppression of antibody production [Inoue *et al.* 2013]. There is limited literature on the effect of corticosteroid administration on influenza vaccine immunogenicity or efficacy, but there is some evidence that suggests corticosteroids do not alter the effectiveness of TIV. Direct comparison of responses found no significant difference in MF59-adjuvanted influenza vaccine immune response between older patients with chronic pulmonary disease who take corticosteroids and those who did not [De Roux *et al.* 2006]. Another study on serum antibody response to influenza vaccine in patients with pulmonary disease receiving corticosteroids established that patients who are on long-term corticosteroid

therapy are able to generate sufficient antibodies in response to TIV [Kubiet *et al.* 1996]. A prospective study by Inoue and colleagues also demonstrated no statistically significant reduction in serological response to the influenza vaccine in a population of older patients with chronic pulmonary disease who were receiving oral or inhaled corticosteroids, compared with those who were not [Inoue *et al.* 2013]. There are limited data on the effects of inhaled corticosteroids in COPD, but one large RCT concluded that the chronic use of inhaled corticosteroids in patients with asthma did not adversely affect the efficacy of the influenza vaccine in this cohort [Hanania *et al.* 2004]. Thus, whilst it is evident that corticosteroids are anti-inflammatory and immunemodulatory drugs used in COPD, their use does not appear to explain the heterogeneity of vaccine responses. Overall, the literature thus far would suggest that there is no significant difference in vaccine immunogenicity in patients with chronic lung disease who took corticosteroids compared with those who did not.

Nutritional status

Malnutrition and weight loss are common presentations among patients with COPD, affecting up to 45% of patients [Hsieh *et al.* 2016]. Among individuals with COPD, low body mass index is associated with a poor prognosis, higher mortality rate, increased incidence of respiratory failure with a more severe degree of airflow obstruction, and increased incidence of exacerbations [Hallin *et al.* 2007; Gupta *et al.* 2010; Hsieh *et al.* 2016]. Metabolic complications of malnutrition in patients with COPD could also result in sarcopenia and cachexia [Hsieh *et al.* 2016].

The mechanisms linking COPD to malnutrition are complicated and multifactorial but involve changes to metabolism as a result of a multitude of factors such as inflammation, hypoxaemia, oxidative stress and steroid therapy [Ezzell and Jensen, 2000; Hallin *et al.* 2007; Aniwidyaningsih *et al.* 2008]. Additionally, the effect of frequent exacerbations is likely to result in increased basal metabolic activity and reduced appetite, with prolonged periods of hospitalization commonly being associated with reduced dietary intake [Ezzell and Jensen, 2000]. Subsequently, patients with COPD are reported to have elevated basal metabolic rates and a resting energy expenditure 15–20% above predicted values [Ezzell and Jensen, 2000; Hallin *et al.* 2007].

It is evident that malnutrition is a negative prognostic factor in patients with COPD. It is therefore important to establish the consequences that this may have on vaccine responses. While it is known that malnutrition can impact the immune system by decreasing cellular immunity and resulting in poor resolution of inflammation, its effect on vaccine responses is not as well established [Gupta *et al.* 2010]. Protein malnutrition and impaired glucose metabolism have been associated with low antibody responses to the influenza vaccination in older people, whilst micronutrient deficiency of vitamin E is also associated with poor vaccine response [Hara *et al.* 2005; Trtica-Majnaric *et al.* 2012]. One study reported no significant difference in improvement during hospitalization for an acute exacerbation in patients with COPD who had nutritional supplementation compared with those who did not [Vermeeren *et al.* 2004]. Conversely, interventional nutritional supplementation of protein has been shown to increase rates of seroconversion in response to TIV in an older cohort, further supporting the role of protein malnutrition in suboptimal vaccine responses [Chavance *et al.* 1985]. Thus it is possible that poor nutrition in patients with COPD could contribute suboptimal immune response to TIV. This requires further study and may provide a potential route for intervention to improve vaccine-related outcomes.

Ageing and immunosenescence

The incidence of COPD increases with age, with the highest prevalence of the disease being in individuals over the age of 65 [Faner *et al.* 2012]. It is evident that there are parallels between detrimental changes to the immune system associated with ageing and those that come with chronic conditions such as COPD. The mechanisms that lead to reduced immune response in older people are similar to those that are involved in the pathogenesis of COPD, and similarly, the structural and functional changes seen in ageing lungs are comparable to those seen in COPD lungs. For example, oxidative stress is one of the physiological process that results in suboptimal immune function in older people [Faner *et al.* 2012]. It is well established that oxidative stress plays an important part in the pathogenesis of COPD and that patients with COPD show signs of oxidative stress in their lungs. Equally, a reduction in telomeres length is seen in smoking, COPD and ageing, indicating that cellular aging rather than chronological age may be the key axis to map immune senescence against. It is evident that the progressive decline in immune function that occurs with age is closely related to suboptimal

immune response in patients with COPD. The exact nature of this relationship remains unclear. It could be argued that reduced immune function in older patients makes this patient group more vulnerable to chronic conditions such as COPD. Equally, the increased incidence of chronic conditions in older people could cause deterioration in immune function. Ito and colleagues hypothesize that COPD could be described as a 'disease of accelerated lung ageing', arguing that the similarities between the structural and functional defects between COPD and ageing lungs suggests that ageing is part of the pathogenesis of COPD [Ito and Barnes, 2009].

Ageing is associated with a number of detrimental changes to the immune system and thus inadequate vaccine responses. This includes thymic involution, a shift from naïve T lymphocytes to memory T lymphocytes, restricting the ability to respond to new infections, and failure to expand the effector memory helper T-cell response to influenza [McElhaney, 2011]. Additionally, ageing is associated with reduced cytolytic activity of cytotoxic T lymphocytes, which contributes to suboptimal vaccine response in this patient group due to the vital role that these cells play clearing influenza infection [McElhaney, 2005, 2011; McElhaney *et al.* 2006]. A shift from a T-helper cell 1 predominant response to a T-helper cell 2 (TH2) response results in decreased activation of cytotoxic T lymphocytes, and thus reduced ability to destroy infected host cells and clear the virus from infected tissue [McElhaney, 2005, 2011; McElhaney *et al.* 2006]. A study by McElhaney found significantly lower levels of granzyme B post vaccination in older patients who developed laboratory-confirmed influenza. As an early marker of cytotoxic lymphocyte activity, this was associated with a reduction in cytotoxic T-cell immunity and thus diminished protection against influenza viruses [McElhaney, 2005, 2011]. Subsequently, this shift towards a TH2 response in older patients demonstrates the role of cytotoxic T cells in response to influenza infection and presents a potential mechanism for suboptimal vaccine responses to TIV in older people [McElhaney, 2005; McElhaney *et al.* 2006]. McElhaney suggests that novel vaccines be developed in vulnerable patient groups, such as older people, that more effectively stimulate cytotoxic T lymphocytes [McElhaney, 2005, 2011]. Research needs to be conducted to evaluate whether similar detrimental changes result in suboptimal vaccine responses in patients with COPD.

Conclusion

Influenza viral infection remains a threat to global health and a driver to seasonal morbidity and mortality. Patients with COPD present as one of the most vulnerable groups to the effects of influenza infection and current vaccine strategies reliant on TIV play an important role in limiting its impact. The limited literature available would suggest that TIV is variably immunogenic in patients with COPD and that there is an increased risk of inadequate immune response in this patient group. Overall, it seems evident that TIV is clinically effective among patients with COPD on a population level but little research has been done to assess the individual benefit of administrating TIV as prophylactic treatment in patients with COPD. The conflicting evidence is complicated by effects of follow-up time after vaccine administration, coadministration of other vaccines and disease severity or comorbidity affecting outcomes.

Through the uncertainty of the current evidence base it would appear safe to conclude that further research is needed to understand defects in immune response both systemically and at the level of the respiratory mucosa. Once risks of vaccine failure can be quantified and understood, stratification of patients to pragmatic changes in vaccine administration could be rapidly considered. Use of higher doses of TIV antigens may be a straightforward initial step [Wongsurakiat *et al.* 2004; Nath *et al.* 2014]. A higher antigen dose has shown superiority over the standard dose for prevention of probable influenza infections and prevention of influenza hospital admissions for all age groups in a recent study in older people [Izurieta *et al.* 2015]. Comprehensive systems biology based approaches are identifying key pathways at play in optimal and aberrant vaccine responses [Sobolev *et al.* 2016]. Adopting this approach to support rationale vaccine design for at-risk groups will enable the influenza vaccine to enter the era of precision medicine and patients with COPD to benefit as a consequence.

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