# Direct and Indirect Benefits of a Comprehensive Approach to Vaccinating Adults with Influenza and Pneumococcal Vaccines, Especially in Patients with Chronic Diseases

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Litjen Tan and Christian Theilacker

It is clear that there is a global ageing phenomenon. According to population estimates by the United Nations, 10% of the world's population was over 60 in 2000. This demographic segment will account for 15% of the overall population by 2025 and 21.8% by 2050, reaching a gross total of over two billion. There is no precedent for a society with this demographic structure, and there is an urgency to encourage health promotion and disease prevention. In this regard, immunization to reduce mortality and morbidity and improve quality of life is very important as we move forward to face the ageing challenge.

Globally, adult immunization faces many challenges. Paediatric vaccinations save an estimated two to three million lives each year [1], and many developed countries have well-established, robust childhood vaccination programmes. Initiatives, such as the Expanded Programme on Immunisation and the Global Alliance for Vaccines and Immunisation, are helping developing countries to build childhood immunization infrastructures and introduce new vaccines. However, worldwide, as in the United States, less attention has been paid to adult immunization, even in developed countries with strong public health infrastructures.

The global burden of adult vaccine-preventable disease (VPD) is considerable, and influenza (flu) and pneumococcal disease are major contributors to morbidity and mortality in older populations, with substantial burdens of death and disability around the world as assessed by disability-adjusted life years (DALYs), a metric that combines years lived with disability plus years of life lost. Globally, there is a

L. Tan (✉)
Immunization Action Coalition, Saint Paul, MN, USA

National Adult and Influenza Immunization Summit, Saint Paul, MN, USA
e-mail: lj.tan@immunize.org

C. Theilacker
Medical Development and Scientific Affairs International Developed Markets, Pfizer, Paris, France


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substantial burden of disease, with the sole caveat that there are not many reliable sources of data, especially for Africa and South East Asia.

A 2013 report commissioned by the SAATI (Supporting Active Ageing Through Immunisation) Partnership provides an overview of the state of adult immunization in 27 countries of the European Union (EU) and the value of implementing better immunization policies for the European adult population from a public health and macroeconomic perspective [2]. This report showed that during the 2010–2011 flu season in Europe, adults aged <65 years of age had the most severe disease, and most had underlying medical conditions (Fig. 12.1). Conversely, in the previous interpandemic period, adults older than 65 years with underlying conditions had the most severe disease, with considerable pressure on hospital and intensive care services in all countries. Regarding invasive pneumococcal disease (IPD), data from the report show that the groups at highest risk of contracting IPD include children, immunocompromised subjects and older people (>65 years of age). Indeed, the rates of reported confirmed IPD cases are highest among children <5 years and adults over 65. An improvement in the EU surveillance systems since 2010 has shown an increasing number of cases, and although mortality from IPD is low, pneumonia represents a major cause of death. Countries such as the United Kingdom have seen dramatic decreases in the number of cases thanks to the implementation of effective childhood immunization programmes, consequently benefitting adults through herd protection.

Focusing on the United States, the burden of adult VPD is similarly high. With a total of 29,500 cases and 3350 total deaths in the United States in 2015, 91% of IPD cases and nearly all IPD deaths occur in adults over 65 years of age [3]. Estimates of annual flu-associated deaths range from 3000 to 49,000, also affecting primarily older adults (65 years and over) [4]. There were a total of 20,762 reported cases of pertussis in the United States in 2015, of which 4650 were among adults aged 20 years and over [5]. Finally, there were an estimated 18,100 new hepatitis B infections in 2014 [6], and about one million cases of zoster occur per year in the United States [7].

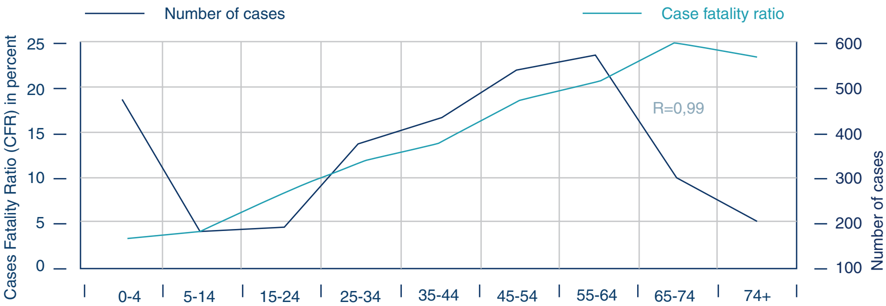


**Fig. 12.1** Distribution of influenza-related severe acute respiratory infection cases and case-fatality ratio by age, EU/EEA countries, 2010–2011 season. From [2]

The estimated cost burden (both direct and indirect) from VPDs is also enormous, exceeding 15 billion USD annually for flu, pneumococcal disease, zoster and pertussis in those aged 65 years and over, plus another 11 billion USD annually if the 50–64-year age group is also considered [8].

Indirect effects of vaccination include aspects that are not often covered in clinical trials, namely, the prevention of the consequences of infection. For example, patients who suffer a VPD may be subsequently frailer and more prone to adverse health outcomes, resulting in a decline in functional status. For many seniors, the loss of quality of life is sometimes more important than concerns about mortality. When measuring vaccine effectiveness, there are challenges with measuring benefits from vaccination of the elderly. Some authors have reported that the benefits of vaccination may be overestimated in cohort studies due to frailty selection bias and the use of non-specific endpoints such as all-cause mortality [9]. Furthermore, people's personal health-seeking behaviours as well as opportunities for access to care also play a role, and the uptake of vaccination by preferentially healthy seniors can introduce a bias that is sufficient to account for the observed benefit [9–11], underlining the posit that better vaccines are needed to protect elderly patients who are particularly vulnerable to complications of influenza [12].

Regardless, ample evidence supports the need for vaccination strategy for adults. However, in order to justify, sustain and improve adult immunization programmes, we need to have systems that can monitor and measure the impact of these programmes—for example, on coverage rates. Surveillance systems from the European Union indicate that flu vaccine coverage rates in older age groups are well below target levels. Globally, it is hard to establish accurate coverage rates, because no systematic global data are available to assess vaccine provision or the effect of immunization policies. In this context, surrogate measures such as dose distribution have been used to estimate flu vaccine provision [13]. Results indicate that globally, vaccination rates are poor and stagnant, and not meeting WHO goals, except in certain regions where there is active management of the influenza programme. The situation is similar for pneumococcal vaccination. The WHO estimates global coverage at 37% [1], and while 21 EU countries have recommendations for vaccination of high-risk patients, of which 17 include elderly patients, only 3 countries provide coverage estimates. Yet without consistent and adequate surveillance of coverage rates, it is difficult to generate the data needed to justify moving policy forward into implementation. And without good surveillance data on the impact of disease, it can be hard to motivate countries to begin adult immunization programmes.

## 12.1 What Is the Impact of Vaccination?

### 12.1.1 Persons with Chronic Illness

A study by Kyaw et al. using 1999 and 2000 data from the Active Bacterial Core surveillance (ABCs) and the National Health Interview Survey (NHIS) showed that, as compared to healthy adults, the risk of IPD was increased three- to sevenfold in patients with chronic conditions such as diabetes; chronic lung, heart, kidney or liver disease; and alcohol abuse [14]. They also observed a more than 20-fold increase in risk among patients with HIV/AIDS and in those with solid or haematological cancers, underlining the need for better prevention strategies in immunocompromised patients [14].

Flu-like illness has been found to be significantly associated with an increased risk of acute myocardial infarction, and flu vaccination effectiveness was estimated at 29% (95% CI, 9–44%), which is on a par with standard secondary prevention measures after acute myocardial infarction [15]. Similarly, in a meta-analysis of published randomized clinical trials, Udell et al. reported that the use of flu vaccine was associated with a significantly lower risk of major adverse cardiovascular events (risk ratio 0.64, 95% CI, 0.48–0.86, $p = 0.003$) [16]. Indeed, the American College of Cardiology/American Heart Association 2014 guidelines for the management of patients with non-ST-elevation acute coronary syndromes recommend annual flu vaccination for all patients with cardiovascular disease [17].

### 12.1.2 Pregnant Women

Among the groups at increased risk of adverse outcomes from influenza and flu-related illnesses, pregnant women have a fourfold higher risk of hospitalization, especially in the third trimester and in those with comorbid conditions [18]. The risk of influenza-associated complications, including death, is increased by up to eight-fold in pregnant women, especially those with comorbid conditions such as diabetes mellitus, pulmonary disease (including asthma), heart disease, renal disease or anaemia. There is also an increased risk for the newborn infant of mothers with influenza during pregnancy, for adverse outcomes such as preterm birth or low birthweight, and infants <6 months old who develop flu infection have the highest rates of hospitalization and death among all children [18].

### 12.1.3 Those Over 65 Years of Age

Among elderly populations, chronic underlying diseases are more frequent, yet vaccine efficacy usually declines with increasing age. However, VPD incidence is such that there is a net benefit to vaccination overall [19].

Taken together, these data demonstrate that immunization across the lifespan is clearly beneficial to society. In this context, just as society committed to systematic childhood immunization in the twentieth century, due to its recognized benefit in the healthy growth of society, so we must now commit to adult immunization and embed it in healthy ageing initiatives for the coming century.

There are varying data regarding the effectiveness of various vaccines in adults. For example, data on the VE of the pneumococcal polysaccharide vaccine against non-bacteraemic pneumococcal pneumonia reports rates ranging from not effective at all to 28% for all-cause pneumonia and 50 to 80% for the prevention of IPD among immunocompetent older adults or adults with various underlying illnesses [20–22]. Bonten et al. reported that VE of PCV13 was 45% against vaccine-type pneumococcal pneumonia and 75% against vaccine-type IPD in adults aged 65 years and older [23]. Between 1999 and 2016, at least ten different meta-analyses on PPV23 effectiveness were published, with widely inconsistent results [22, 24–31]. Regarding influenza, in an individual participant data meta-analysis on a total of 4975 patients, influenza vaccination was found to be significantly effective during epidemic seasons irrespective of vaccine match status, with a protective effect observed among elderly people with cardiovascular or lung disease [32]. Overall, data regarding the effectiveness of influenza vaccine are highly variable and depend on antigenic match, the age and health of the person being vaccinated.

Since vaccine effectiveness in adults is dependent on the outcome that is being measured, the success of an adult vaccination programme should not be measured solely by the outcome of incidence of disease prevented. Another way to look at vaccine effectiveness is to look at negative outcomes averted, and the benefit of flu vaccination in terms of vaccine-preventable disability is a weighty argument that appeals to people more easily than effectiveness statistics and may be a game changer for many older adults. Indeed, there is a high burden of VPDs in the elderly, particularly in terms of disability-adjusted life years (DALYs), which include years of life lost as well as years lived with disability. In a study from the Netherlands, Kristensen et al. showed that among older adults, the disease burden in the period 2010–2013 in terms of DALYs was highest for pneumococcal disease, mostly because of high mortality, followed by influenza [33].

Herd protection is an important indirect effect of vaccination, with a particularly major role for children and youngsters. A cluster randomized trial involving 947 Canadian children and adolescents aged 36 months to 15 years who received influenza vaccine and 2326 unvaccinated community members reported a protective effectiveness of 61% (95% CI, 8–83%; $P = 0.03$), showing that immunization of children and adolescents significantly protected unimmunized residents of rural communities against influenza [34]. Similarly, data from observational studies have shown a significant reduction in influenza illness in contacts of vaccinated patients (OR 0.57; 95% CI, 0.43–0.77) [35], although no significant association was observed in randomized studies in the same meta-analysis. It is likely that variability by season, vaccine coverage and circulating strains, as well as difficulties in monitoring outpatient illness among adult contacts, render accurate evaluations of herd effect challenging in the community.

Nonetheless, once the evidence in favour of vaccination is convincing, it is necessary to implement strong policies that commit to vaccination. The US adult immunization schedule recommends flu vaccination for all persons aged 6 months and older, once a year, and recommends pneumococcal vaccine for all those aged 65 years and older (PCV13 and PPSV23, one dose of each). There is a scientific rationale for encouraging concomitant vaccination with flu and pneumococcal vaccines, as pneumococcal infections increase with spikes in influenza disease [36]. Furthermore, pneumococcal infection secondary to influenza disease predicts more severe outcomes and increased deaths in the elderly, with almost 90% of annual deaths with underlying pneumonia and flu causes occurring in persons older than 65 years and accounting for excess mortality during flu epidemics [37]. Similarly, secondary bacterial pneumonia (mostly *S. pneumoniae*) is estimated to account for up to 50% of deaths during seasonal flu in the United States, due to the damaged caused to the airway epithelium by influenza, and enhanced bacterial colonization due to reduced clearance [38]. Co-administration of influenza and pneumococcal vaccines has been found to have greater cost-effectiveness. In a review of the literature, Gilchrist et al. showed that eight of nine clinical studies found that a concomitant programme conferred clinical benefits, while the two studies that compared the cost-effectiveness of different strategies found concomitant immunization to be more cost-effective than either vaccine given alone [39]. Co-administration has also been shown to be safe, in terms of adverse reactions [40].

The broad potential impact of influenza and pneumococcal vaccination in adults is therefore clear, and vaccines are available that are shown to be effective. In this context, any impact of vaccines is dependent on improving coverage rates and public awareness, as well as improving clinicians' willingness to give the vaccine, the public's ability to get access to vaccines (payment/cost policies) and improving surveillance of disease and availability of data on the impact of vaccines and vaccination.

## References

1. Immunization coverage factsheet. 2017. http://www.who.int/mediacentre/factsheets/fs378/en/. Accessed 04 Oct 2017.
2. SAATI Partnership. Adult vaccination: a key component of healthy ageing. The benefits of life-course immunisation in Europe. 2013. http://www.ilcuk.org.uk/images/uploads/publication-pdfs/Adult_vaccination_-_a_key_component_of_health_ageing.pdf. Accessed 04 Oct 2017.
3. Centers for Disease Control and Prevention. Bacterial Core Surveillance Report, Emerging Infections Program Network, Streptococcus pneumoniae. http://www.cdc.gov/abcs/reports-findings/survreports/spneu15.pdf. Accessed 04 Oct 2017.
4. Centers for Disease C, Prevention. Estimates of deaths associated with seasonal influenza—United States, 1976–2007. MMWR Morb Mortal Wkly Rep. 2010;59(33):1057–62.
5. Centers for Disease Control and Prevention. 2015 Final Pertussis Surveillance Report. https://www.cdc.gov/pertussis/downloads/pertuss-surv-report-2015.pdf. Accessed 04 Oct 2017.
6. Centers for Disease Control and Prevention. Surveillance for Viral Hepatitis—United States. 2014. https://www.cdc.gov/hepatitis/statistics/2014surveillance/pdfs/2014HepSurveillanceRpt_Rev2016-09-26.pdf. Accessed 04 Oct 2017.
7. Harpaz R, Ortega-Sanchez IR, Seward JF, Advisory Committee on Immunization Practices Centers for Disease C, Prevention. Prevention of herpes zoster: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Recomm Rep 2008;57(RR-5):1–30; quiz CE2-4.
8. McLaughlin JM, McGinnis JJ, Tan L, Mercatante A, Fortuna J. Estimated human and economic burden of four major adult vaccine-preventable diseases in the United States, 2013. J Prim Prev. 2015;36(4):259–73.
9. Simonsen L, Taylor RJ, Viboud C, Miller MA, Jackson LA. Mortality benefits of influenza vaccination in elderly people: an ongoing controversy. Lancet Infect Dis. 2007;7(10):658–66.

10. Jackson LA, Jackson ML, Nelson JC, Neuzil KM, Weiss NS. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. Int J Epidemiol. 2006;35(2):337–44.
11. Jackson LA, Nelson JC, Benson P, Neuzil KM, Reid RJ, Psaty BM, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. Int J Epidemiol. 2006;35(2):345–52.
12. Glezen WP, Simonsen L. Commentary: benefits of influenza vaccine in US elderly–new studies raise questions. Int J Epidemiol. 2006;35(2):352–3.
13. Palache A. Seasonal influenza vaccine provision in 157 countries (2004–2009) and the potential influence of national public health policies. Vaccine. 2011;29(51):9459–66.
14. Kyaw MH, Rose CE Jr, Fry AM, Singleton JA, Moore Z, Zell ER, et al. The influence of chronic illnesses on the incidence of invasive pneumococcal disease in adults. J Infect Dis. 2005;192(3):377–86.
15. Barnes M, Heywood AE, Mahimbo A, Rahman B, Newall AT, Macintyre CR. Acute myocardial infarction and influenza: a meta-analysis of case-control studies. Heart. 2015;101(21):1738–47.
16. Udell JA, Zawi R, Bhatt DL, Keshtkar-Jahromi M, Gaughran F, Phrommintikul A, et al. Association between influenza vaccination and cardiovascular outcomes in high-risk patients: a meta-analysis. JAMA. 2013;310(16):1711–20.
17. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 AHA/ACC guideline for the management of patients with non-ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;64(24):e139–228.
18. Rasmussen SA, Jamieson DJ, Uyeki TM. Effects of influenza on pregnant women and infants. Am J Obstet Gynecol. 2012;207(Suppl. 3):S3–8.
19. Gessner BD, Feikin DR. Vaccine preventable disease incidence as a complement to vaccine efficacy for setting vaccine policy. Vaccine. 2014;32(26):3133–8.
20. Leventer-Roberts M, Feldman BS, Brufman I, Cohen-Stavi CJ, Hoshen M, Balicer RD. Effectiveness of 23-valent pneumococcal polysaccharide vaccine against invasive disease and hospital-treated pneumonia among people aged >/=65 years: a retrospective case-control study. Clin Infect Dis. 2015;60(10):1472–80.
21. Dominguez A, Soldevila N, Toledo D, Torner N, Force L, Perez MJ, et al. Effectiveness of 23-valent pneumococcal polysaccharide vaccination in preventing community-acquired pneumonia hospitalization and severe outcomes in the elderly in Spain. PLoS One. 2017;12(2):e0171943.
22. Moberley S, Holden J, Tatham DP, Andrews RM. Vaccines for preventing pneumococcal infection in adults. Cochrane Database Syst Rev. 2013;1:CD000422.
23. Bonten MJ, Huijts SM, Bolkenbaas M, Webber C, Patterson S, Gault S, et al. Polysaccharide conjugate vaccine against pneumococcal pneumonia in adults. N Engl J Med. 2015;372(12):1114–25.
24. Cornu C, Yzebe D, Leophonte P, Gaillat J, Boissel JP, Cucherat M. Efficacy of pneumococcal polysaccharide vaccine in immunocompetent adults: a meta-analysis of randomized trials. Vaccine. 2001;19(32):4780–90.
25. Hutchison BG, Oxman AD, Shannon HS, Lloyd S, Altmayer CA, Thomas K. Clinical effectiveness of pneumococcal vaccine. Meta-analysis. Canadian family physician Medecin de famille canadien, vol. 45; 1999. p. 2381–93.
26. Melegaro A, Edmunds WJ. The 23-valent pneumococcal polysaccharide vaccine. Part I. Efficacy of PPV in the elderly: a comparison of meta-analyses. Eur J Epidemiol. 2004;19(4):353–63.
27. Schiffner-Rohe J, Witt A, Hemmerling J, von Eiff C, Leverkus FW. Efficacy of PPV23 in preventing pneumococcal pneumonia in adults at increased risk—a systematic review and meta-analysis. PLoS One. 2016;11(1):e0146338.
28. Kraicer-Melamed H, O'Donnell S, Quach C. The effectiveness of pneumococcal polysaccharide vaccine 23 (PPV23) in the general population of 50 years of age and older: a systematic review and meta-analysis. Vaccine. 2016;34(13):1540–50.

29. Conaty S, Watson L, Dinnes J, Waugh N. The effectiveness of pneumococcal polysaccharide vaccines in adults: a systematic review of observational studies and comparison with results from randomised controlled trials. Vaccine. 2004;22(23–24):3214–24.
30. Huss A, Scott P, Stuck AE, Trotter C, Egger M. Efficacy of pneumococcal vaccination in adults: a meta-analysis. CMAJ. 2009;180(1):48–58.
31. Diao WQ, Shen N, Yu PX, Liu BB, He B. Efficacy of 23-valent pneumococcal polysaccharide vaccine in preventing community-acquired pneumonia among immunocompetent adults: a systematic review and meta-analysis of randomized trials. Vaccine. 2016;34(13):1496–503.
32. Darvishian M, van den Heuvel ER, Bissielo A, Castilla J, Cohen C, Englund H, et al. Effectiveness of seasonal influenza vaccination in community-dwelling elderly people: an individual participant data meta-analysis of test-negative design case-control studies. Lancet Respir Med. 2017;5(3):200–11.
33. Kristensen M, van Lier A, Eilers R, McDonald SA, Opstelten W, van der Maas N, et al. Burden of four vaccine preventable diseases in older adults. Vaccine. 2016;34(7):942–9.
34. Loeb M, Russell ML, Moss L, Fonseca K, Fox J, Earn DJ, et al. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. JAMA. 2010;303(10):943–50.
35. Mertz D, Fadel SA, Lam PP, Tran D, Srigley JA, Asner SA, et al. Herd effect from influenza vaccination in non-healthcare settings: a systematic review of randomised controlled trials and observational studies. Euro Surveill. 2016;21(42).
36. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis. 2008;198(7):962–70.
37. Centers for Disease Control and Prevention (CDC). Estimates of deaths associated with seasonal influenza—United States, 1976–2007. MMWR Morb Mortal Wkly Rep. 2010;59(33):1057–62.
38. McCullers JA. Insights into the interaction between influenza virus and pneumococcus. Clin Microbiol Rev. 2006;19(3):571–82.
39. Gilchrist SA, Nanni A, Levine O. Benefits and effectiveness of administering pneumococcal polysaccharide vaccine with seasonal influenza vaccine: an approach for policymakers. Am J Public Health. 2012;102(4):596–605.
40. Honkanen PO, Keistinen T, Kivela SL. Reactions following administration of influenza vaccine alone or with pneumococcal vaccine to the elderly. Arch Intern Med. 1996;156(2):205–8.