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The 100th anniversary of the 1918 influenza pandemic has arrived without a human proof-of-concept universal influenza vaccine to prevent the next pandemic. World Pneumonia Day, on Nov 12, is a good time to reflect on our improved understanding of the role of bacterial coinfections in deaths from seasonal and pandemic influenza virus, and the potential of bacterial vaccines, particularly pneumococcal conjugate vaccine (PCV) and possibly future vaccines against *Staphylococcus aureus*, to mitigate pandemic influenza mortality.

During the 1918 pandemic, abundant evidence from cultures of blood, lungs, and pleural fluid from both living individuals and from post-mortem specimens showed a substantial contribution of bacterial coinfections to mortality from the pandemic influenza virus.[1,2] Although inactivated bacterial vaccines were claimed at the time to prevent influenza, a claim inconsistent with the viral cause of the pandemic, some data suggest that such bacterial vaccines might have prevented some of the 1918 influenza-associated mortality.[3] The contribution of bacterial infection to influenza mortality during the 2009 influenza A H1N1 pandemic included evidence of bacterial infection among 43% of pandemic influenza deaths in children across the USA;[4] 55% of influenza victims in New York, NY, USA;[5] 38% of pandemic influenza deaths in Brazil;[6] 56% of hospital admissions for severe disease or deaths in Argentina;[7] and 46% of severely ill patients in intensive care units infected with proven pandemic influenza A H1N1 illness in France.[8]

The impact of PCV on influenza-associated hospital admissions was first described in a randomised trial of an investigational nine-valent PCV, in which recipients of the vaccine had a 45% (95% CI 14–64; p=0·01) reduction in hospital admissions associated with seasonal influenza virus in Soweto, South Africa, from 1998 to 2001.[9] The roll-out of a seven-valent PCV in the USA was associated with similar statistically significant annual reductions of between 39% and 50% in influenza-associated hospital admissions of infants younger than 2 years, from 2000 to 2004.[10] A subsequent case–control study in South Africa, including the 2009 pandemic A H1N1 season and extending through the 2012 influenza season, found that completion of the PCV schedule in children younger than 5 years was associated with a 26% reduction in hospital admissions due to influenza-associated acute respiratory illness (case population ratio 0·74, 95% CI 0·71–0·77).[11] Furthermore, a case control study in Spain during the pandemic season from 2009 to 2010 showed a 48% (95% CI 1–76) reduction in influenza-associated hospital admissions, but not in the subsequent season (2010 to 2011) during which PCV vaccine coverage was high in both influenza-infected and control individuals.[12]

Data from a model of the 1918 influenza pandemic in a contemporary setting with access to PCV and antibiotics suggest a substantial effect of widespread PCV coverage in infants on reducing pandemic influenza mortality in all ages.[13] In addition to PCV immunisation helping to protect infants from influenza-associated hospital admission during a future influenza pandemic, adult lives could be saved through herd protection. The only randomised trial (to our knowledge) of PCV use in adults also addressed the question of prevention of influenza-associated hospital admissions in a secondary analysis, and found an estimate of efficacy in prevention of hospital admissions due to community-acquired pneumonia associated with influenza, in line with that observed in the paediatric PCV trial.[14] 23 first episodes of community-acquired pneumonia associated with influenza were observed in the 13-valent PCV group and 35 in the placebo group for a vaccine efficacy of 34·4%; however, as this outcome was a secondary analysis for which the trial was not powered, the efficacy was not statistically significant (95% CI –11·1 to 61·2, p=0·117).

With support from government, industry, and several foundations in this 1918 centennial anniversary year, the possibility of developing a universal influenza vaccine and substantially decreasing the burden of pneumonia mortality is very exciting. In the meantime, the increased and welcome roll-out of PCV in all countries, now including low-income and middle-income countries, is likely to provide some protection against the inevitable mortality associated with the next influenza pandemic.[15]

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