The mortality data must be interpreted with similar caution. In the whole cohort, a stated mortality of approximately 25% during 5 years of follow-up is substantially less than in any idiopathic pulmonary fibrosis population previously reported, but there are three factors that could contribute to this outcome, other than treatment efficacy. Patients presenting with severe disease and those with major comorbidities likely to reduce life expectancy are included in real-world populations, but were excluded from the INPULSIS study (and from most other trials of idiopathic pulmonary fibrosis). Perhaps more importantly, data were not collected from patients who withdrew from therapy (beyond a final visit 6 weeks after treatment cessation). In effect, vital status is not known for more than half of the patients enrolled in the study with, it seems likely, a bias towards a worse outcome in patients lost to follow-up. These caveats must be constantly kept in mind whenever mortality data are presented from the open-label trials of either nintedanib or pirfenidone.

The ethos of open-label studies is clearly different from rigorous controlled investigation, in which an intention-to-treat study design is viewed as mandatory. Perhaps it is time to challenge the assumption that less rigorous methodology is needed in extension studies. Non-controlled data are inherently non-definitive but this surely necessitates an optimal study design to maximise their clinical use. One cannot help but feel that a major opportunity was lost in this study and, equally, in the pirfenidone extension study. An intention-to-treat study design would have provided invaluable long-term efficacy data and should be prioritised in future.

Athol U Wells
Royal Brompton Hospital, London, SW3 6HP, UK
athol.wells@rbht.nhs.uk

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Reconciling estimates of the global influenza burden


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Influenza remains an important cause of morbidity and mortality, even in high-income countries. Yet quantification of its burden is contentious. Although influenza virus infections are commonly associated with respiratory symptoms, some infections can cause more severe disease, resulting in hospitalisation or death. Influenza can also trigger other health outcomes—eg, acute myocardial infarction[1] which probably arises because infection stimulates inflammation, atherosclerosis, and coronary lesions.[2] For simplicity, however, most estimates of the burden of influenza focus on respiratory disease. To that end, the Global Burden of Disease (GBD) 2017 Influenza Collaborators have attempted to quantify the burden of influenza on lower respiratory tract infections (LRTIs), which they define as pneumonia or bronchiolitis, in *The Lancet Respiratory Medicine*.[3] Their efforts might be the first attempt to estimate the influenza burden within specific demographic categories of geography, age group, sex, and outcome.

Although the study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting protocol and the team have made efforts towards increased transparency, reproduction of the results of this study would be difficult. Most of the methods are buried within references and appendices. The authors do not seem to have strictly adhered to their own search strategy for the review, by including, for example, studies that only examined pandemic influenza A(H1N1)pdm09 virus, that included less than a year's data, or that reported surveillance or administrative data. Additionally, their estimates rely on some questionable assumptions, such as the application of the prevalence of influenza detection

among children younger than 5 years with LRTIs to other age groups. Children have much higher susceptibility to influenza than adults because of their immature immune systems, and their intense social mixing patterns probably enhance transmission. How much bias has been introduced as a result of this assumption is unclear.

The mortality estimates reported in this study of 145 000 deaths (95% uncertainty interval [UI] 99 000–200 000) are substantially lower than those reported by Iuliano and colleagues[4] in early 2018 (409 111 deaths [95% credibility interval 291 243–645 832]). Some of this difference is explained by the outcome measured. The GBD 2017 Influenza Collaborators estimated the proportion of LRTI deaths that were attributable to influenza, whereas Iuliano and colleagues estimated influenza-associated respiratory mortality. However, it would be a challenge to find sufficient non-LRTI respiratory deaths to explain the discrepancy. To what extent the discrepancies are due to differences in the methods used, or the underlying data sources, merits further exploration. By contrast, the 2017 GBD estimate of influenza-associated LRTI mortality[3] is substantially higher than the 2016 estimate (58 193 deaths [95% UI 43 953–74 145]).[5] The explanation provided for this discrepancy is a change to the methods used and the inclusion of data from more countries. The extent to which GBD estimates will continue to change as new data from more countries and age groups become available is unclear.

It is probably unhelpful for policy makers to have such divergent estimates on which to base health-care decision making, especially when the subtle differences are buried in referenced material and appendices. Similarly, one could question the usefulness of hospitalisation estimates that span an order of magnitude. Countries with established health information systems can choose whether to use their own administrative data to estimate local influenza burden or to use the GBD estimates. However, this choice might not be available for many countries that do not have reliable health data available. When estimates substantially differ among published sources, confidence in all estimates is undermined, which can justify inaction. Furthermore, when used as inputs to mathematical models forecasting expected reductions in mortality due to intervention strategies, differences in estimates can lead to quite different conclusions about the modelled intervention, and therefore meaningful differences in recommended action.

Aside from inconsistencies in methods, a limitation of most influenza burden studies is the assumption that all influenza viruses are equal, when infections, hospitalisations, and deaths vary within age groups by type, subtype, and lineage. Therefore, the next challenge is to establish the relative subtype-specific and lineage-specific burden of influenza. Influenza A(H3N2) probably accounts for a disproportionate share of mortality, particularly among older people,[6] but whether it also causes most excess hospitalisations among children, for example, is less clear, and data for the comparative severity of the two influenza B lineages are scarce. The distinctions are important for modelling of influenza control strategies because influenza vaccination effectiveness varies by virus,[7] and is probably lowest for influenza A(H3N2), the subtype that could cause the greatest burden. When model inputs include subtype-specific and lineage-specific estimates of burden and vaccine effectiveness, the view of the challenges of influenza control will be more realistic.

Sheena G Sullivan, Benjamin J Cowling
WHO Collaborating Centre for Reference and Research on Influenza at the Peter Doherty Institute for Infection and Immunity, Melbourne, VIC, Australia (SGS); Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA, USA (SGS); Centre for Epidemiology and Biostatistics, School of Population and Global Health, University of Melbourne, Melbourne, VIC, Australia (SGS); and WHO Collaborating Centre for Infectious Disease Epidemiology and Control, School of Public Health, University of Hong Kong, Hong Kong Special Administrative Region, China (BJC)
sheena.sullivan@influenzacentre.org

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