Estimating Total Number of Influenza Cases From Reported Hospitalizations: A Multi-Country Comparison of the Multiplier Method

Yoonyoung Park,[1]* Christina Chandra,[2] Mike Goodman,[2] Raffael Nachbagauer,[1] Deborah Rudin[1]

[1]Moderna Inc, Cambridge, MA, USA; [2]Rollins School of Public Health at Emory University, Atlanta, GA, USA
*Presenting author.

BACKGROUND

- Seasonal influenza is a common respiratory disease with substantial health and economic impacts each year; accurate estimation of influenza disease burden is critical to inform public health policy and resource allocation[1,2]
- Sentinel data on influenza hospitalizations represent a fraction of total disease burden because not every individual with influenza will seek medical care, undergo testing, have a positive test, and therefore be included in influenza surveillance[1]
  - In addition, the sensitivity of routinely available diagnostics tests varies[1]
- Efforts have previously been undertaken to estimate the burden of influenza across multiple countries using a single modeling approach, including the counterfactual method by the Global Burden of Disease Study[3] and imputation by the IcEBErg group[4]
- The US Centers for Disease Control and Prevention (CDC) uses a numeric multiplier methodology to account for factors leading to under-detection of influenza-associated hospitalizations and to estimate the number of all symptomatic cases of influenza[1,5]
  - The multiplier method is a relatively quick and simple way of estimating the health impact of the influenza epidemic[5]
- The applicability of this methodology in other countries is unclear

OBJECTIVE

- To assess the practical implications of estimating total influenza burden using the multiplier method in select countries with robust influenza surveillance systems

METHODS

US CDC Multiplier Method to Estimate Total Influenza Disease Burden

- The CDC defines "total influenza" as all symptomatic illnesses in a season
  - Parameters are estimated using surveillance data, which are then supplemented with other data sources to create multipliers that adjust for under-detection or under-reporting (Figure 1)

Figure 1. General Framework for Estimating Influenza Disease Burden in the United States Using FluSurv-NET Surveillance Data[1]
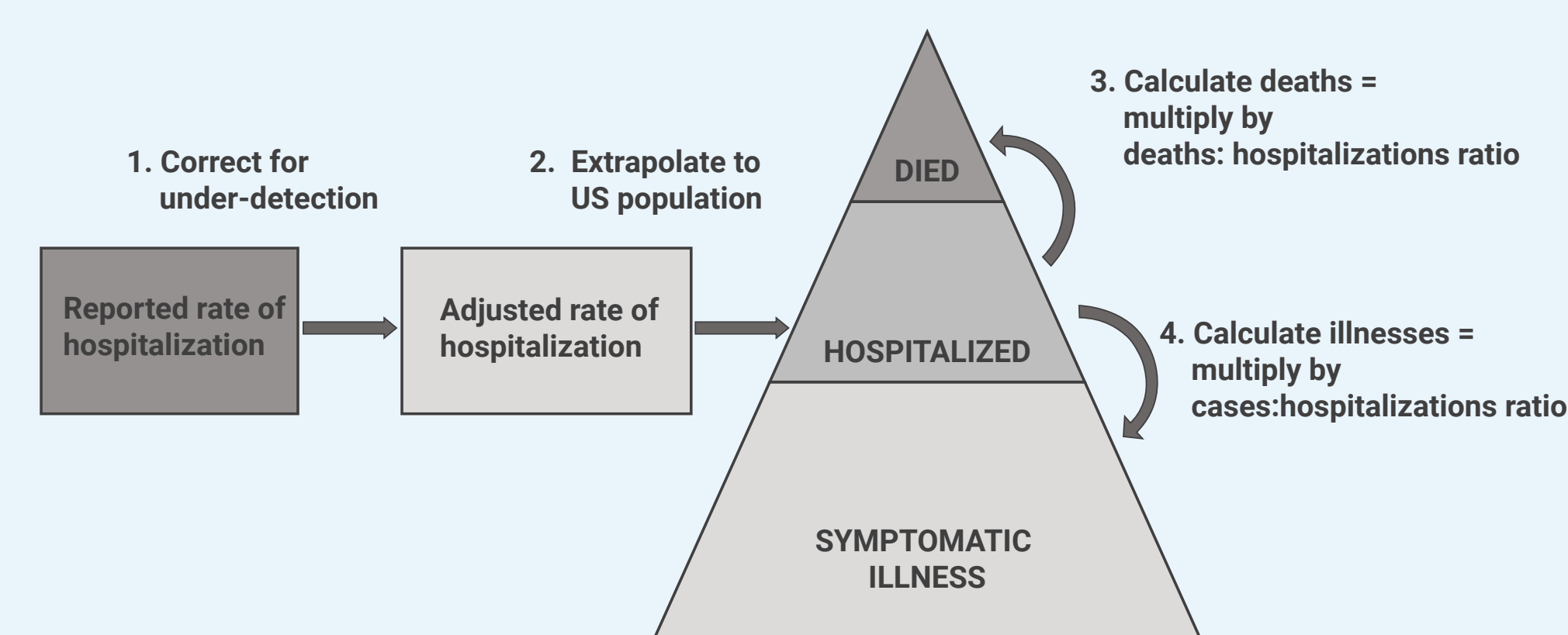
Adapted from Reed et al 2015[1] under the terms of Creative Commons CC0 public domain dedication.

Influenza-Associated Hospitalizations

- Data on laboratory-confirmed influenza hospitalizations are obtained through FluSurv-NET, a surveillance network of acute care hospitals serving more than 90 counties in 14 states; it covers approximately 9% of the US population[1,6,7]
- As the likelihood of a confirmed influenza hospitalization depends in part on the healthcare provider's decision to perform the testing and on the sensitivity of the test, CDC corrects for this by applying a multiplier based on[1]:
  - The probability that a person hospitalized with a respiratory infection underwent influenza testing, and
  - The probability that an individual with influenza would test positive on influenza tests (sensitivity of influenza testing)
- Finally, adjusted rates of influenza-associated hospitalization are applied to the annual US Census population estimates by age group to calculate the total number of influenza-associated hospitalizations for each season (Figure 1)[1,5]

Total Symptomatic Influenza Cases

- To obtain the total number of influenza cases in the general population, the US CDC applies a separate multiplier to the number of influenza-associated hospitalizations
- Data on laboratory-confirmed influenza illness cases are adjusted for the following 4 factors: medical care seeking, specimen collection, submission of specimens, and confirmation of influenza[5,8]
- A case-to-hospitalization ratio multiplier is calculated based on total estimated influenza cases and influenza-associated hospitalizations[5]
- Lastly, total national number of influenza cases is estimated by multiplying the case-to-hospitalization ratio with the adjusted and extrapolated number of influenza-associated hospitalizations (Figure 1)[5,9]

Applying US CDC Multiplier Method to Estimate Total Influenza Burden in Other Countries

- The number of influenza-associated hospitalizations for the 2018-2019 season was obtained from the US CDC, Public Health Agency of Canada, and Public Health England
- A targeted literature search was conducted to identify multipliers used by the US CDC and the analogous multipliers from Canada and England
- Country-specific multipliers were compared, and cross-applicability was examined

RESULTS

- Difference in surveillance system and data availability made obtaining multipliers for all 3 countries challenging (**Figure 2** and **Table 1**)
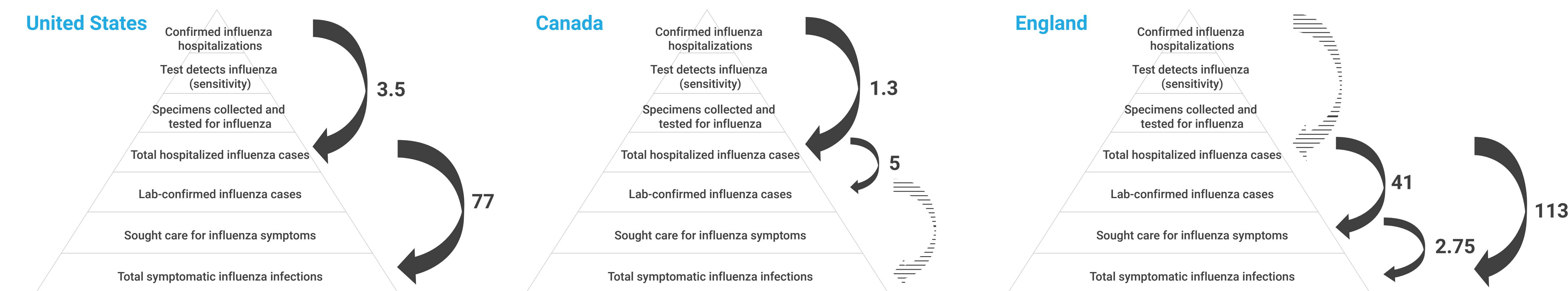
Estimating Total Influenza-Associated Hospitalizations

- The multiplier for under-reporting of influenza-associated hospitalizations was lower for Canada than the US (1.3 vs 3.5; **Figure 2**), partly because literature from Canada did not account for test sensitivity
  - No analogous multiplier was found for England

Estimating Total Symptomatic Influenza Cases

- The composite symptomatic case-to-hospitalization ratio for the United States (77; **Figure 2**) in the 2018-2019 season was based on both age-specific multipliers (range: 11-365) and age distribution among cases (**Table 1**), which can vary in seasons with different case-age distribution
  - The estimated total symptomatic influenza incidence (not age-adjusted) for the 2018-2019 season was 881 per 10,000 persons
- In Canada, only the number of all laboratory-confirmed rather than symptomatic cases were obtainable, using a single multiplier for all ages (~5) (**Table 1** and **Figure 2**)
- In England, the symptomatic case-to-hospitalization ratio (~113) was obtained by a product of 2 multipliers, influenza visit-to-hospitalization ratio (~41) and symptomatic case-to-visit ratio (~2.75) (**Table 1** and **Figure 1**)
  - The estimated total symptomatic influenza incidence (not age-adjusted) for the 2018-2019 season was 678 per 10,000 persons

Figure 2. Pyramid of Multipliers Used to Obtain Estimates of Total Influenza Cases From Confirmed Influenza Hospitalizations

Dashed arrows indicate that the multiplier could not be identified from the literature. Specific multipliers are applied to 2018-2019 data.

Table 1. Application of Multipliers to Estimate Total Influenza Burden From Influenza-Associated Hospitalizations, 2018-2019 Season

Country	Confirmed influenza hospitalizations	Test detects influenza (sensitivity)	Specimens collected and tested for influenza	Total hospitalized influenza cases	Lab-confirmed influenza cases	Influenza cases who sought care for symptoms	Total symptomatic influenza infections	Crude[a] "total influenza" incidence estimate
United States	18,470[10,b] Estimated total confirmed influenza hospitalizations in the US: 107,179 (375,126/3.5)	3.5[1,c]	Incorporated in the prior multiplier	375,126[11] Age-stratified influenza hospitalizations: 0-4 years: 21,046 5-17 years: 18,159 18-49 years: 54,978 50-64 years: 76,617 65+ years: 204,326	Not identified in literature	Not used in calculations	28,908,721[11] Age-specific case-to-hospitalization ratios (rounded): 0-4 years: 143.4 5-17 years: 364.7 18-49 years: 178.2 50-64 years: 94.3 65+ years: 11.0 Weighted average of age-specific ratios: 77	28,908,721/328,239,523[12] × 10,000 = 881 per 10,000 persons
Canada	3657[b] Estimated total hospitalizations after applying to Canada population data: 17,787[13,14]	Not identified in literature	Multiplier: 1.3[15]	23,123[d]	115,615 Lab-confirmed influenza case-to-hospitalization ratio: 5[16,e]	Not identified in literature	Unable to calculate, since multiplier for symptomatic case-to-hospitalization ratio is not reported in the literature	Not available
England	5667[b] Estimated total hospitalizations after applying to England population data: 33,823[17,18]	Not identified in literature	Not identified in literature	33,823[17,18] Multipliers to correct for test sensitivity and testing in hospitals were unable to be identified; values reflect a starting point of our calculations and may be an underestimate	Not identified in literature	1,386,743 Visit-to-hospitalization ratio: 41[19,f]	3,813,543 Cases seeking care-to-symptomatic cases ratio: 2.2-3.3[20] (or average of 2.75)[g] Multiplier from total hospitalized influenza cases to symptomatic influenza infections: 41 × 2.75 = 113	3,813,543/56,286,961[17] × 10,000 = 678 per 10,000 persons

[a]Not age-adjusted.
[b]Limited to surveillance sites.
[c]Average of age-specific multipliers.
[d]Derived from confirmed influenza hospitalizations and multiplier for specimens collected and tested for influenza.
[e]Derived from previously calculated hospitalized influenza cases and case-to-hospitalization ratio.
[f]Derived from influenza hospitalizations and visit-to-hospitalization ratio.
[g]Derived from previously calculated influenza cases who sought care for symptoms and cases seeking care-to-symptomatic cases ratio.

CONCLUSIONS

- The US CDC multiplier approach could theoretically estimate overall influenza burden, but it remains subject to substantial variability and uncertainty when applied to other countries with robust surveillance systems
- Implementing this approach to estimate total influenza disease burden in different countries requires targeted data collection and understanding of country-specific surveillance systems, population structures, and care-seeking behaviors

ADDITIONAL INFORMATION

References

1. Reed C, et al. PLoS One. 2015;10(3):e0118369.
2. World Health Organization. A manual for estimating disease burden associated with seasonal influenza. https://apps.who.int/iris/handle/10665/178801
3. GBD Influenza Collaborators. Lancet Respir Med. 2019;7(1):69-89.
4. Iuliano D. Global Estimates of Influenza-associated Hospitalization from the Influenza Burden, Global Project (IcEBErG). Presented at: Options X for the Control of Influenza; Singapore; 2019.
5. Reed C, et al. Emerg Infect Dis. 2009;15(12):2004-2007.
6. Centers for Disease Control and Prevention. Frequently Asked Questions about Estimated Flu Burden. https://www.cdc.gov/flu/about/burden/faq.htm
7. Centers for Disease Control and Prevention. Influenza Hospitalization Surveillance Network (FluSurv-NET). https://www.cdc.gov/flu/weekly/influenza-hospitalization-surveillance.htm
8. Biggerstaff M, et al. Am J Public Health. 2012;102(10):e21-e26.
9. Shrestha SS, et al. Clin Infect Dis. 2011;52(Suppl 1):S75-S82.
10. Centers for Disease Control and Prevention. Laboratory-Confirmed Influenza Hospitalizations. https://gis.cdc.gov/grasp/fluview/FluHospChars.html#virusTypeDiv
11. Centers for Disease Control and Prevention. Estimated Flu-Related Illnesses, Medical Visits, Hospitalizations, and Deaths in the United States — 2018–2019 Flu Season. https://archive.cdc.gov/#/details?url=https://www.cdc.gov/flu/about/burden/2018-2019.html
12. US Census Bureau. 2019 U.S. Population Estimates Continue to Show the Nation's Growth Is Slowing. https://www.census.gov/newsroom/press-releases/2019/popest-nation.html
13. Public Health Agency of Canada. FluWatch Annual Report: 2018-19 Influenza Season. https://www.canada.ca/en/public-health/services/publications/diseases-conditions/fluwatch/2018-2019/annual-report.html
14. Government of Canada Statistics Canada. Canada's Population, July 1 2019. https://www150.statcan.gc.ca/n1/pub/11-627-m/11-627-m2019061-eng.htm
15. Schanzer DL, et al. Influenza Other Respir Viruses. 2018;12(1):113-121.
16. Kumar A. JAMA. 2009;302(17):1872.
17. Office for National Statistics. Population Estimates for the UK, England and Wales, Scotland and Northern Ireland: mid-2019. https://www.ons.gov.uk/peoplepopulationandcommunity/populationandmigration/populationestimates/bulletins/annualmidyearpopulationestimates/mid2019estimates
18. Public Health England. Weekly National Flu Reports: 2018 to 2019 Season. https://www.gov.uk/government/statistics/weekly-national-flu-reports-2018-to-2019-season
19. Pitman RJ, et al. J Infect. 2007;54(6):530-538.
20. Tillston NL, et al. BMC Public Health. 2010;10(1):650.

Acknowledgments

Disclosures