



Global Efforts to Understand Influenza Disease Burden

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Why Estimate Influenza Disease Burden

- **Address a critical knowledge gap for seasonal and pandemic influenza**
 - Especially in middle- and low-income and tropical climate countries
- **Assess severity of seasonal influenza epidemics or pandemic periods**
- **Inform economic analyses, such as cost benefit studies**
- **Inform policy decisions**
 - Possible vaccine introduction or expansion of existing programs
 - Guide antiviral treatment availability or recommendations for use
- **Estimate the effect of influenza on non-respiratory causes of death**
- **Understand relative burden of influenza disease compared to other diseases at country level to inform prevention and control strategies**

Challenges for Estimating Influenza Disease Burden

- **Influenza symptoms are nonspecific**
- **Not all sick individuals seek medical care**
- **Influenza testing not routine**
- **Influenza diagnostic tests differ in detection sensitivity**
- **Quality of viral surveillance data**
 - Number specimens collected and tested weekly
 - Number of available surveillance data years

Challenges Quantifying Hospitalization and Mortality

■ Hospitalization burden:

- Lack of accurate catchment population
- Definition of hospitalization and threshold for admission varies widely
- Different case definitions used
- Sensitivity of case definition application
- Non-systematic case ascertainment

■ Mortality burden:

- Lack of worldwide population-based surveillance to monitor vital records and to detect the occurrence of diseases and infections
- Systematically coded vital records data not available in all countries
- Deaths due to influenza rarely coded on death certificates as influenza

Evolution of Efforts for Influenza Surveillance and Burden

2004

- CDC international influenza program funds first 6 countries to initiate influenza surveillance in response to avian influenza A(H5N1)

2006

- SARI case definition and generic protocol is developed by CDC and PAHO

2011

- WHO publishes “Global Standards and Tools for Influenza Surveillance”
- CDC begins to estimate proportion of respiratory hospitalizations due to influenza

2012

- CDC launches effort to estimate global seasonal influenza-associated deaths

2014

- WHO publishes revised “Global Epidemiological Surveillance Standards for Influenza”

2015

- WHO publishes “A Manual for Estimating Disease Burden Associated with Seasonal Influenza”

2016

- WHO in collaboration with CDC establishes an initiative to estimate global influenza-associated hospitalization rates

Global Burden Efforts

- Global Respiratory Hospitalizations – Influenza Proportion Positive “GRIPP”
- Global Seasonal Influenza-associated Mortality Collaboration
- Influenza Burden, Global (IceBERG) Project

Global Respiratory Hospitalizations – Influenza Proportion Positive “GRIPP”

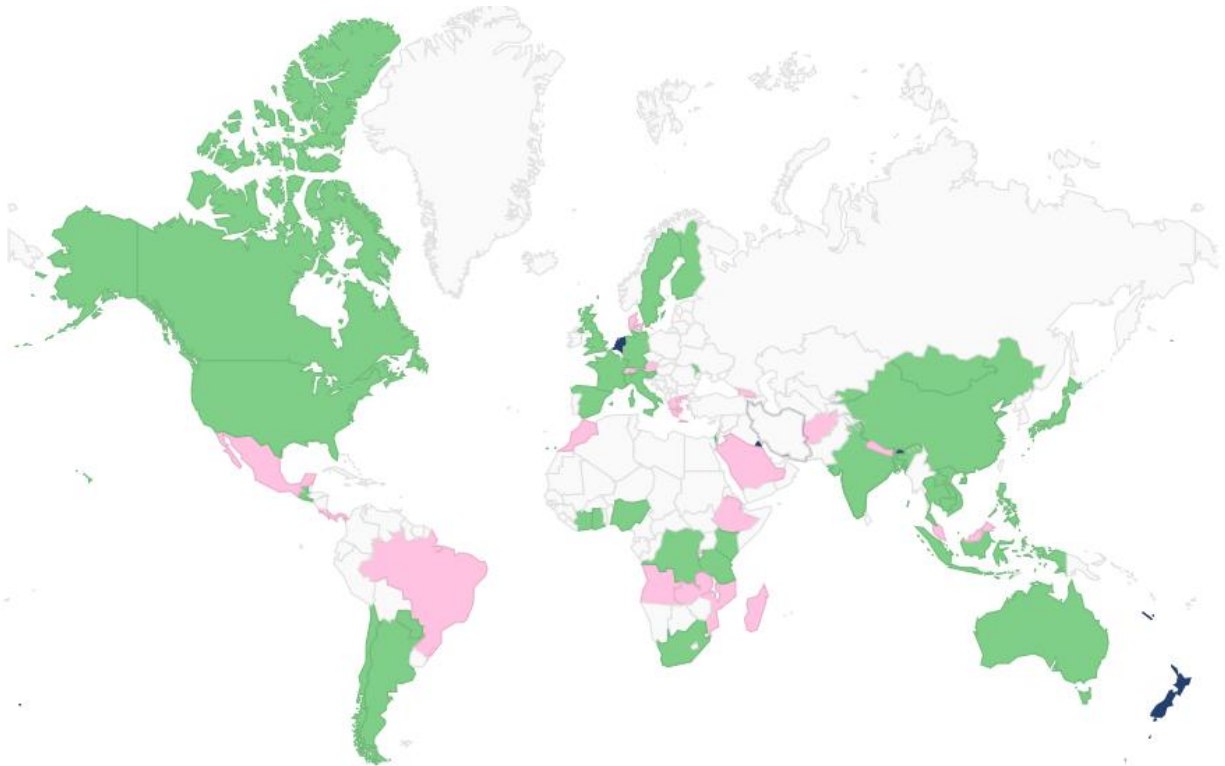
- **Objective:**

- To generate pooled estimates of proportion of respiratory hospitalizations attributable to seasonal influenza among children and adults


- **Methods:**


- Multiplier approach to estimating the burden of influenza hospitalizations by age group
- Aggregating data from published literature and collaborating partners
- Calculating pooled estimates for proportion of respiratory hospitalizations due to seasonal influenza

GRIPP Contributing Countries



 Pediatric estimates contributed (n= 22)

 Adult estimates contributed (n= 5)

 Pediatric and adult estimates contributed (n= 39)

As of March 16, 2018

GRIPP Pediatric Analysis

Parameter	# Datasets	Pooled percent positive (95% CI)	Global influenza-associated hospitalizations (in thousands)
Age Group			
<6 mo	15	4.8 (3.3–6.9)	228 (150–344)
<1 y	26	6.1 (5.1–7.4)	374 (264–539)
<5 y	48	7.4 (6.2–8.8)	870 (610–1,237)
5-17 y	27	16.4 (13.6–19.8)	—
<18 y	42	9.5 (8.1–11.0)	—
<5 Year Pooled Analysis			
Development Status			
Industrialized	7	5.9 (4.6-7.5)	33 (19-56)
Developing	41	7.7 (6.4-9.3)	862 (603-1,238)
WHO Region			
Africa	16	8.2 (6.4-10.6)	253 (127-508)

Lafond KE, et al. (2016) Global Role and Burden of Influenza in Pediatric Respiratory Hospitalizations, 1982-2012: A Systematic Analysis. PLoS Medicine.

Ongoing GRIPP Efforts

▪ Adult Analysis

- Updating to include published and unpublished surveillance data through 2016 for age groups: 18-64, ≥65 years
- Dataset eligibility: those that conduct systematic year-round influenza surveillance among adult inpatients and use polymerase chain reaction (PCR) for diagnosis
- Data requested: number of inpatient cases tested and positive for influenza by calendar year, age group, and influenza type/subtype and information about surveillance platform
- To participate, contact:
 - Katie Lafond (Klafond@cdc.gov)

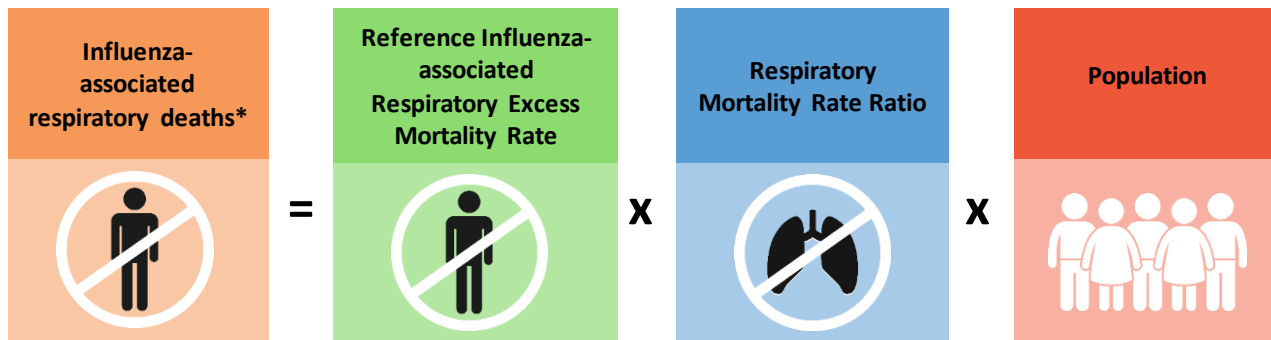
Global Seasonal Influenza Mortality Collaboration

▪ Objectives:

- To estimate country-specific, regional, global influenza-associated respiratory and circulatory deaths
 - Include influenza-associated excess mortality rates from more countries
 - Account for differences between countries for risk of influenza death, healthcare access, quality of care, population structure, and underlying health status of populations
 - To calculate summary estimates of influenza-associated death and annual estimates for available seasons/years

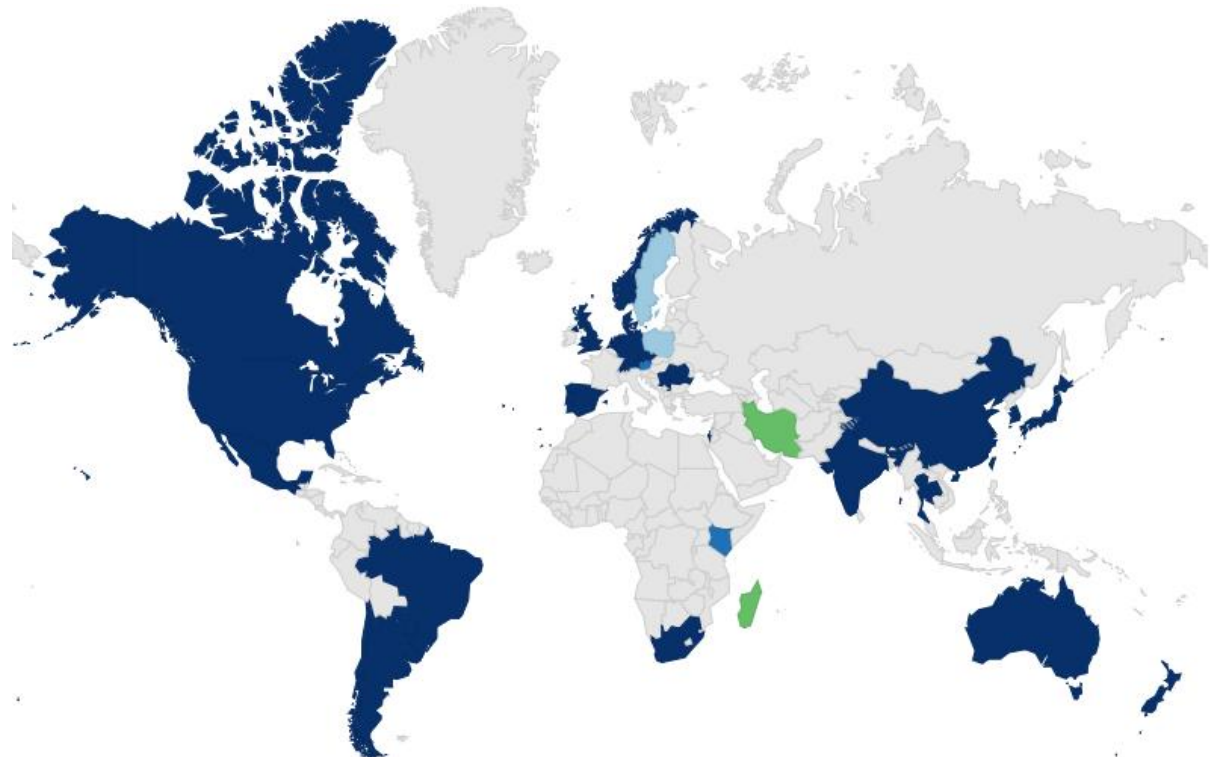
Influenza-associated Respiratory Mortality Model Approach

Formula to Calculate Influenza-Associated Respiratory Deaths



* Formula calculated within each analytic division for age groups: <65 years, 65–74 years, and ≥75 years using excess mortality rate estimates from 1999-2015

Global Seasonal Influenza Mortality Contributing Countries



- Respiratory and Circulatory Estimates Contributed (N=31)
- Respiratory Estimates Contributed (N=2)
- Circulatory Estimates Contributed (N=2)
- Analysis Ongoing (N=2)

As of March 16, 2018

Global Influenza-associated Respiratory Mortality Estimates

Age Group	Death Estimate (95% CrI)*	Mortality Rate per 100,000 (95% CrI)*	Proportion of Total Estimated Deaths
<65 Years	67,255 – 342,576	1.0 – 5.1	42%
65-74 Years	48,810 – 102,187	13.3 – 27.8	17%
≥75 Years	122,876 – 237,933	51.3 – 99.4	41%
Worldwide	291,243 – 645,832	4.0 – 8.8	--

* 95% CrI = 95% Credible Interval

Iuliano AD, Roguski KM, Chang HH, Muscatello DJ, Palekar R, Tempia S, Cohen C, Gran JM, Schanzer D, Cowling BJ, Wu P, Kyncl J, Ang LW, Park M, Redlberger-Fritz M, Yu H, Espenhain L, Krishnan A, Emukule G, van Asten L, Pereira da Silva S, Aungkulanon S, Buchholz U, Widdowson MA, Bresee JS; Global Seasonal Influenza-associated Mortality Collaborator Network. Estimates of global seasonal influenza-associated respiratory mortality: a modelling study. *Lancet*. 2017 Dec 13. doi: 10.1016/S0140-6736(17)33293-2. [Epub ahead of print]

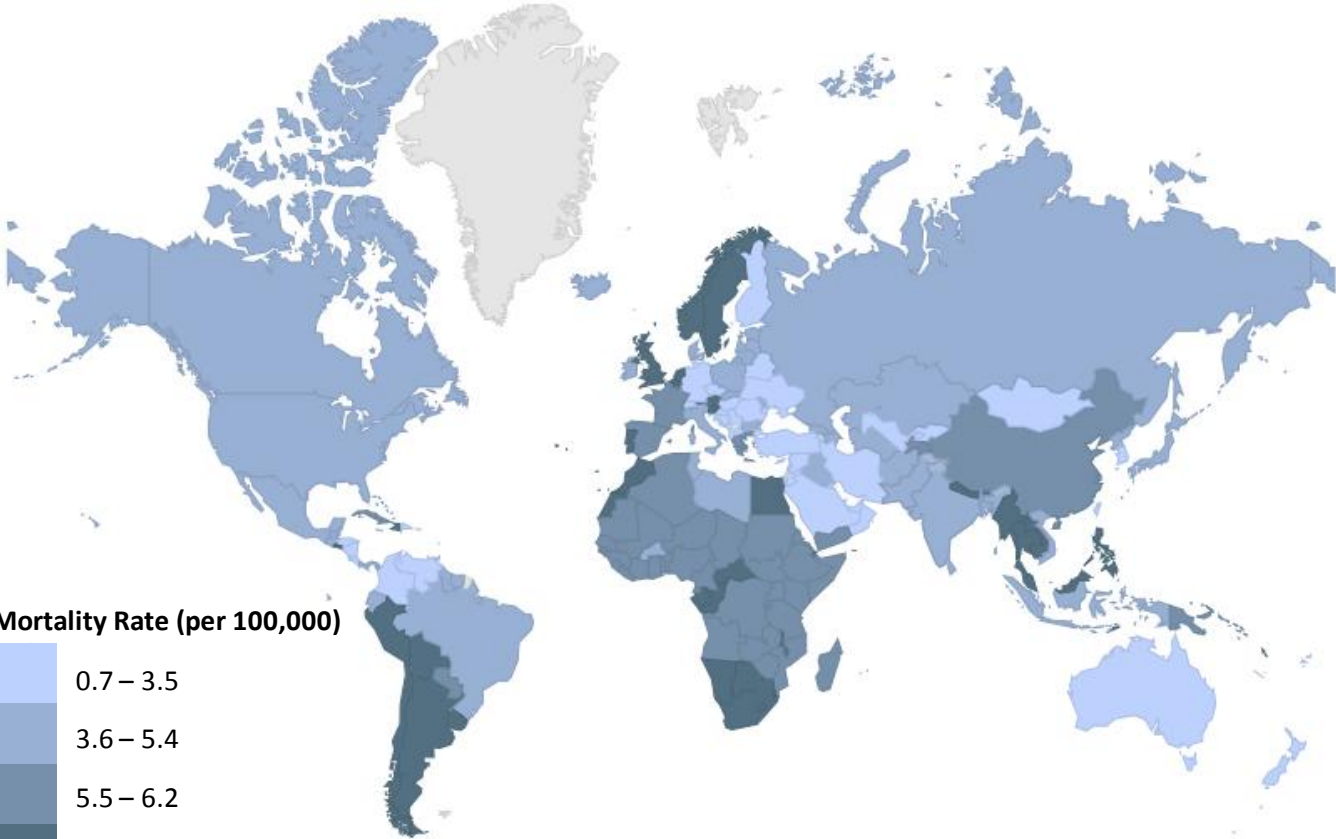
Influenza-associated Respiratory Death Estimates, WHO Region

Region	<65 Years		65-74 Years		≥75 Years	
	Deaths (95% CrI)*	Rate (per 100,000) (95% CrI)*	Deaths (95% CrI)*	Rate (per 100,000) (95% CrI)*	Deaths (95% CrI)*	Rate (per 100,000) (95% CrI)*
AFRO	9,607 – 127,569	1.0 – 13.3	2,648 – 17,744	12.0 – 80.4	3,477 – 27,502	36.3 – 286.9
AMRO	7,027 – 20,203	0.8 – 2.3	6,236 – 12,776	10.5 – 21.5	21,624 – 43,777	52.2 – 105.7
EURO	4,179 – 19,518	0.5 – 2.5	3,732 – 12,753	5.0 – 17.2	15,679 – 47,438	23.4 – 70.7
EMRO	4,468 – 71,208	0.7 – 11.6	1,349 – 9,905	7.4 – 54.1	2,035 – 12,114	21.8 – 129.9
SEARO	21,044 – 119,561	1.2 – 6.6	10,499 – 35,014	14.2 – 47.5	16,602 – 48,618	44.6 – 130.5
WPRO	7,197 – 28,946	0.4 – 1.7	8,903 – 33,078	7.4 – 27.7	33,858 – 99,617	45.3 – 133.2
Globe	67,255 – 342,576	1.0 – 5.1	48,810 – 102,187	13.3 – 27.8	122,876 – 237,933	51.3 – 99.4

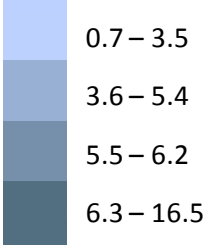
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Influenza-associated Respiratory Mortality Rate, All Ages



Mortality Rate (per 100,000)



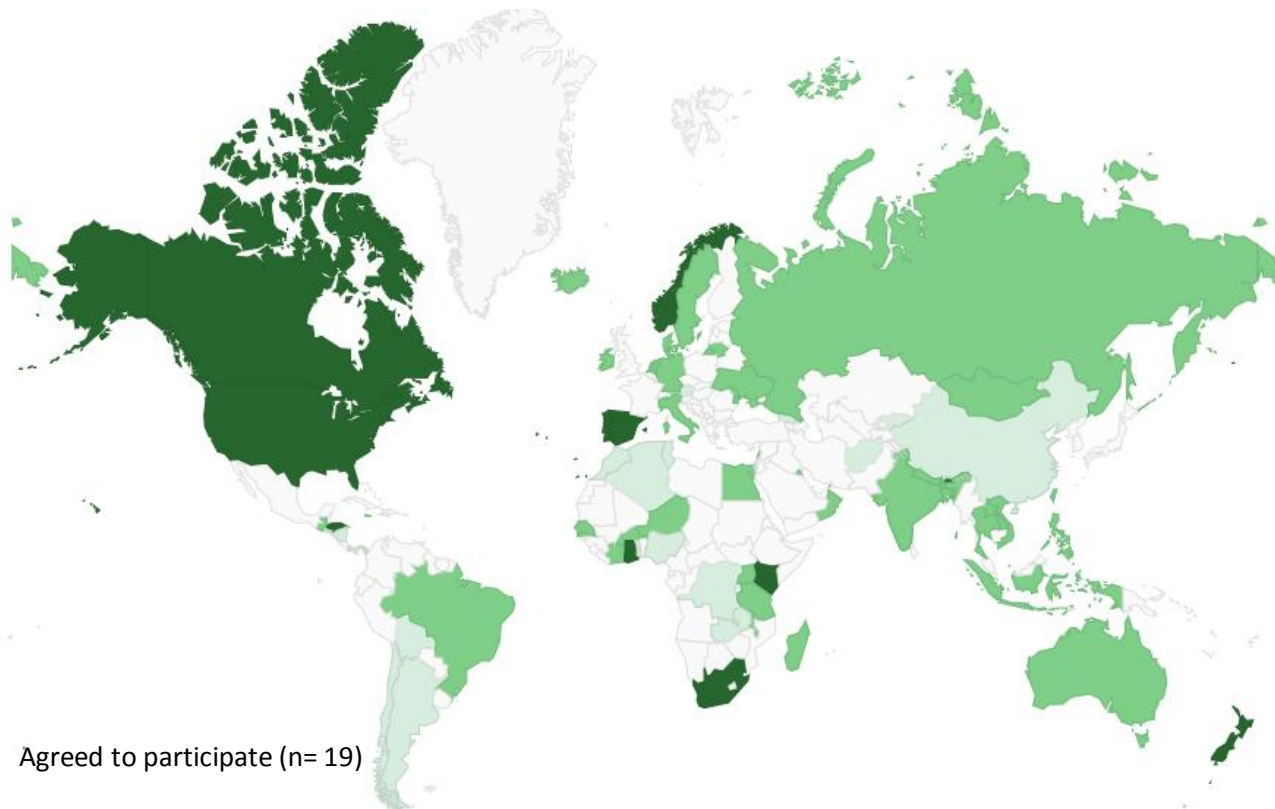
Ongoing Global Seasonal Influenza Mortality Efforts

- Projects
 - Estimate annual influenza-associated respiratory deaths for years between 2001-2015
 - Estimate summary and annual influenza-associated circulatory deaths
 - Exploring different model approach to estimate circulatory deaths
- Data Requirements:
 - Minimum of five years of vital records respiratory and circulatory death counts by age group and week
 - Age groups: <65 years, 65-74 years, ≥75 years
 - Influenza virus surveillance data for same time period
- To participate, contact:
 - Danielle Iuliano (aiuliano@cdc.gov)

InfluEnza BurdEn, Global (IcEBErG) Project

- Objective:
 - To estimate age-specific global and regional seasonal influenza-associated respiratory hospitalizations using data from 2008-2017
- Data Needs
 - Influenza-associated hospitalization rates for populations calculated
 - WHO Manual for Estimating Disease Burden methods
 - ICD-coded administrative databases
 - Time series models
 - Health administrative surveys (HAS) or health utilization surveys used (HUS) to estimate catchment population and calculate rates
- Age groups of interest:
 - 0–4 years, 5–49 years, 50–64 years, and ≥65 years

IcEBErG Collaborating Countries



- Agreed to participate (n= 19)
- Evaluating surveillance/burden methods (n= 39)
- Influenza-associated hospitalization rate estimates received (n= 15)

As of March 16, 2018

IcEBErG Project Status

- Current status:
 - Evaluating information provided by countries
 - Exploring potential methods to generate global estimates
 - Consider data sources and statistical methods to account for differences in risk of hospitalization between countries
 - Engaging additional countries to contribute
- To participate, contact:
 - Danielle Iuliano (aiuliano@cdc.gov)
 - Julia Fitzner (fitznerj@who.int)
 - Vanessa Cozza (cozzav@who.int)

National Disease Burden Estimation

Considerations for National Disease Burden Estimation

- **National influenza surveillance systems**
 - Influenza-like illness (ILI), severe acute respiratory infection (SARI), or other definitions (e.g. severe pneumonia, acute respiratory illness)
- **Evaluation of surveillance system and data collected***
 - At least three to five years of quality data
 - Geographically diverse sites
 - Representative of population age-structure
 - Sufficient number of samples collected and tested by week or month
- **Vital records death counts or hospitalization counts**
- **Age-specific population estimates: national or catchment area population**

*<https://www.cdc.gov/flu/international/program/index.htm>

Alternatives to Disease Burden Estimation

- **Burden estimation may not be possible without sufficient and high quality surveillance and outcome data**
- **Alternatives to estimating disease burden may be useful to inform policy decisions**
 - Proportion of all hospitalizations due to influenza
 - Identifying risk groups (e.g., chronic conditions or age groups) within a population that experience severe illness

Global Efforts Only Possible with Country Engagement

- **Global estimation efforts rely upon the contribution of diverse and geographically representative countries to share**
 - National estimates of influenza-associated death
 - National or regional estimates of influenza-associated hospitalization
 - Laboratory-confirmed influenza from inpatient surveillance platforms
- **Effort to engage collaborators representing**
 - Low-income, low-middle income countries
 - Tropical climate countries
 - Diverse influenza transmission zones
- **If interested:**
 - Reach out to project investigators for more information or engage with country or regional partners to evaluate data and determine needs for assistance
 - Approaches to estimation can be discussed and potential support identified

Thank you

For more information, contact CDC
1-800-CDC-INFO (232-4636)
TTY: 1-888-232-6348 www.cdc.gov

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



EXTRA SLIDES

Evolution of Efforts for Influenza Surveillance and Burden

2004

- CDC international influenza program funds first 6 countries to initiate influenza surveillance in response to avian influenza A(H5N1)

2006

- SARI case definition and generic protocol is developed by CDC and PAHO

2009

- Influenza A(H1N1) pandemic virus emerges

2010

- CDC begins effort to estimate global deaths for the first year of circulation of influenza A(H1N1) pandemic virus

2011

- WHO publishes "Global Standards and Tools for Influenza Surveillance"
- CDC begins to estimate proportion of respiratory hospitalizations due to influenza

2012

- CDC launches effort to estimate global seasonal influenza-associated deaths

2014

- WHO publishes revised "Global Epidemiological Surveillance Standards for Influenza"

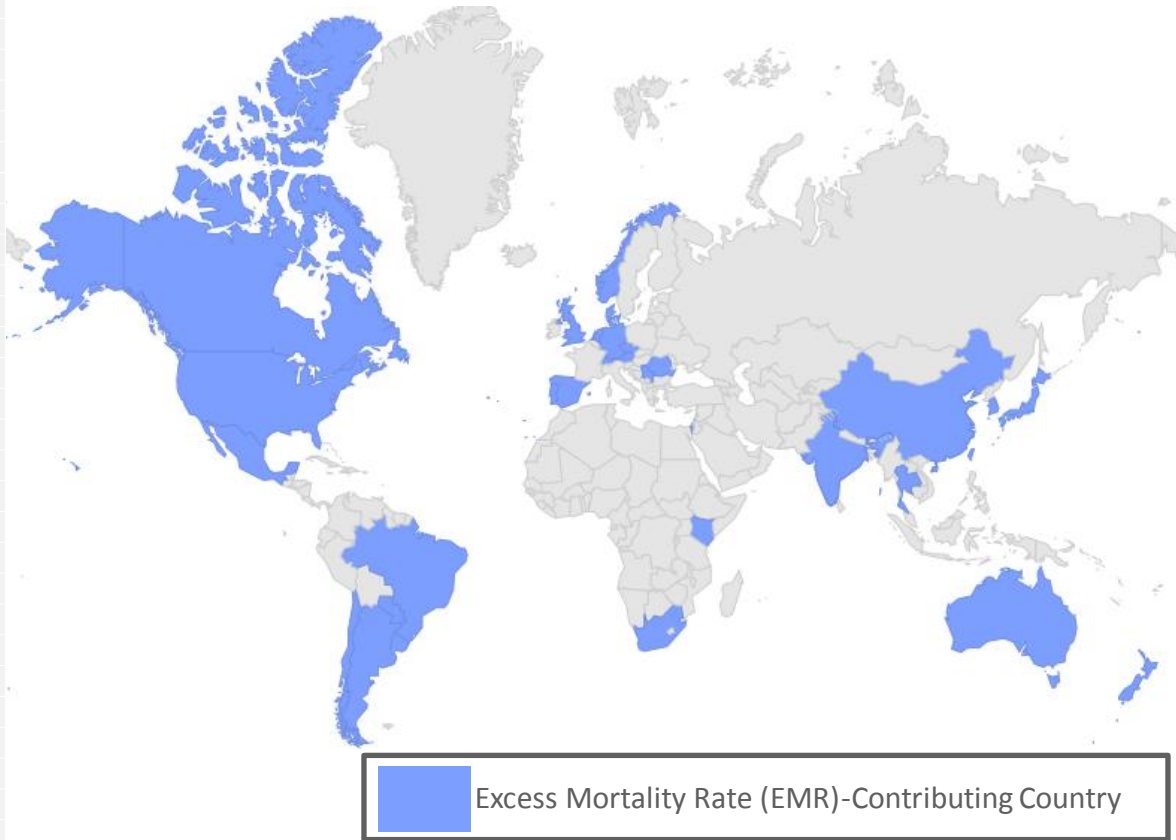
2015

- WHO publishes "A Manual for Estimating Disease Burden Associated with Seasonal Influenza"

2016

- WHO in collaboration with CDC establishes an initiative to estimate global influenza-associated hospitalization rates

Excess Mortality Rate (EMR)-Contributing Countries



Country*

- Argentina
- Australia
- Austria
- Southern Brazil
- Canada
- Chile
- China
- Czech Republic
- Denmark
- Germany
- Hong Kong
- India
- Israel
- Japan
- Kenya
- Mexico
- Netherlands
- New Zealand
- Norway
- Paraguay
- Portugal
- Romania
- Serbia
- Singapore
- South Africa
- South Korea
- Spain
- Switzerland
- Taiwan
- Thailand
- Uruguay
- United Kingdom
- USA

* Country refers to WHO Member States, Taiwan, and Hong Kong Special Administrative Region

Model Approach

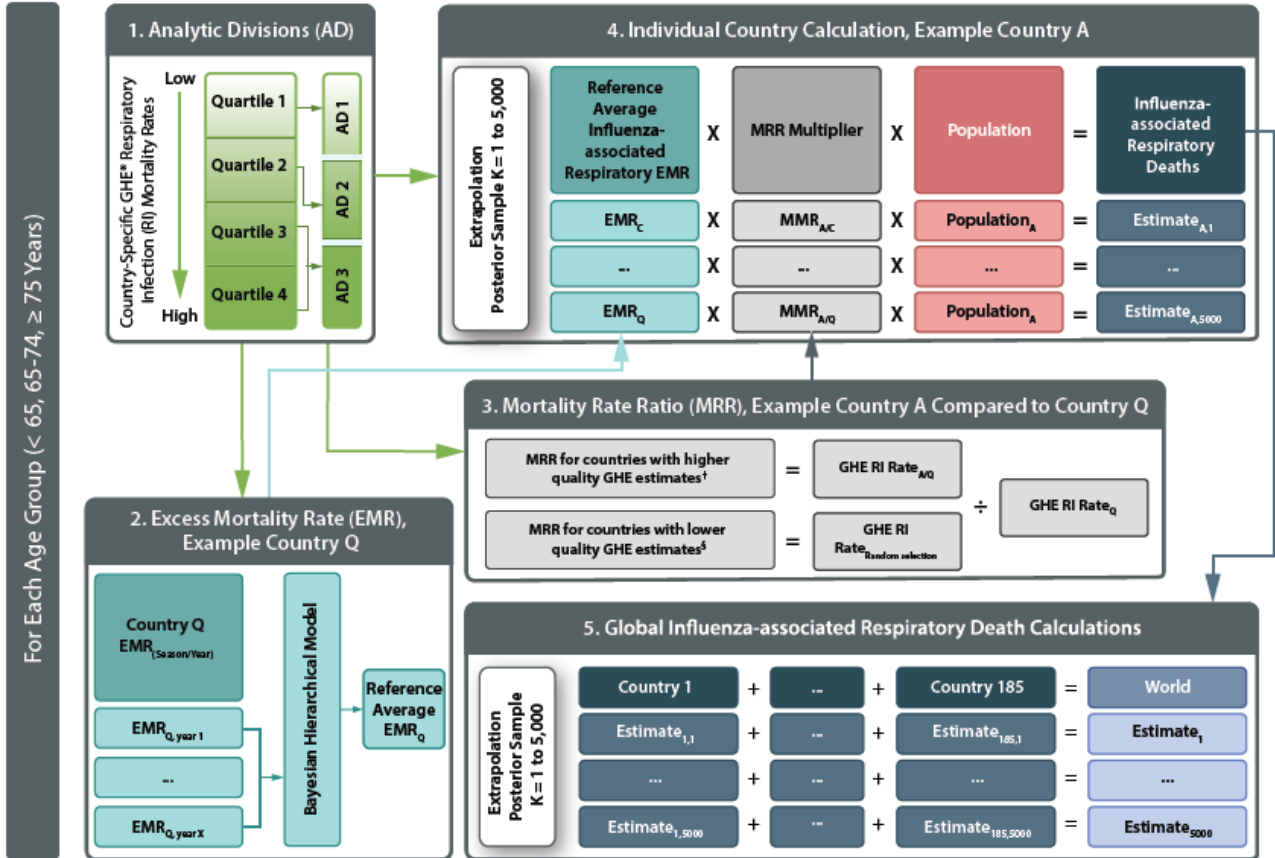
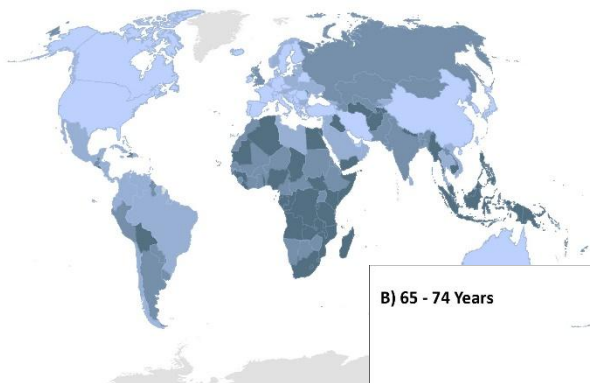
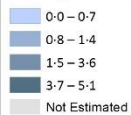


Figure 1. Extrapolation model approach for individual country^a and global estimates of influenza-associated respiratory deaths.

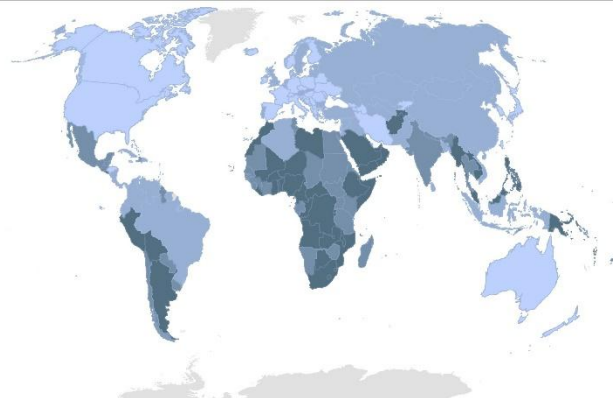
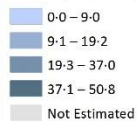
A) < 65 Years

Mortality Rate



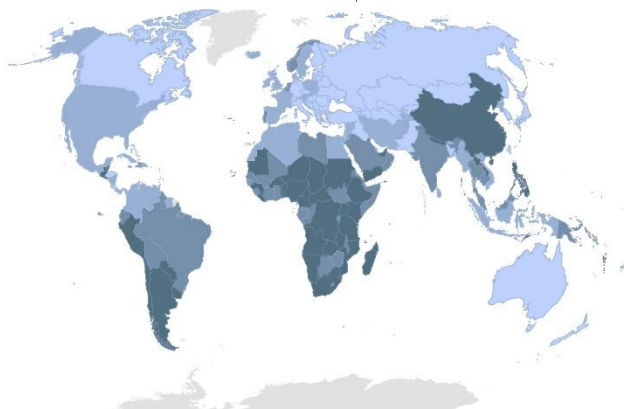
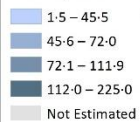
B) 65 - 74 Years

Mortality Rate



C) ≥ 75 Years

Mortality Rate



<5 YEARS

Estimates of Excess Influenza Respiratory Deaths, Sub-Analysis

Special Extrapolation for Children <5 Years of Age

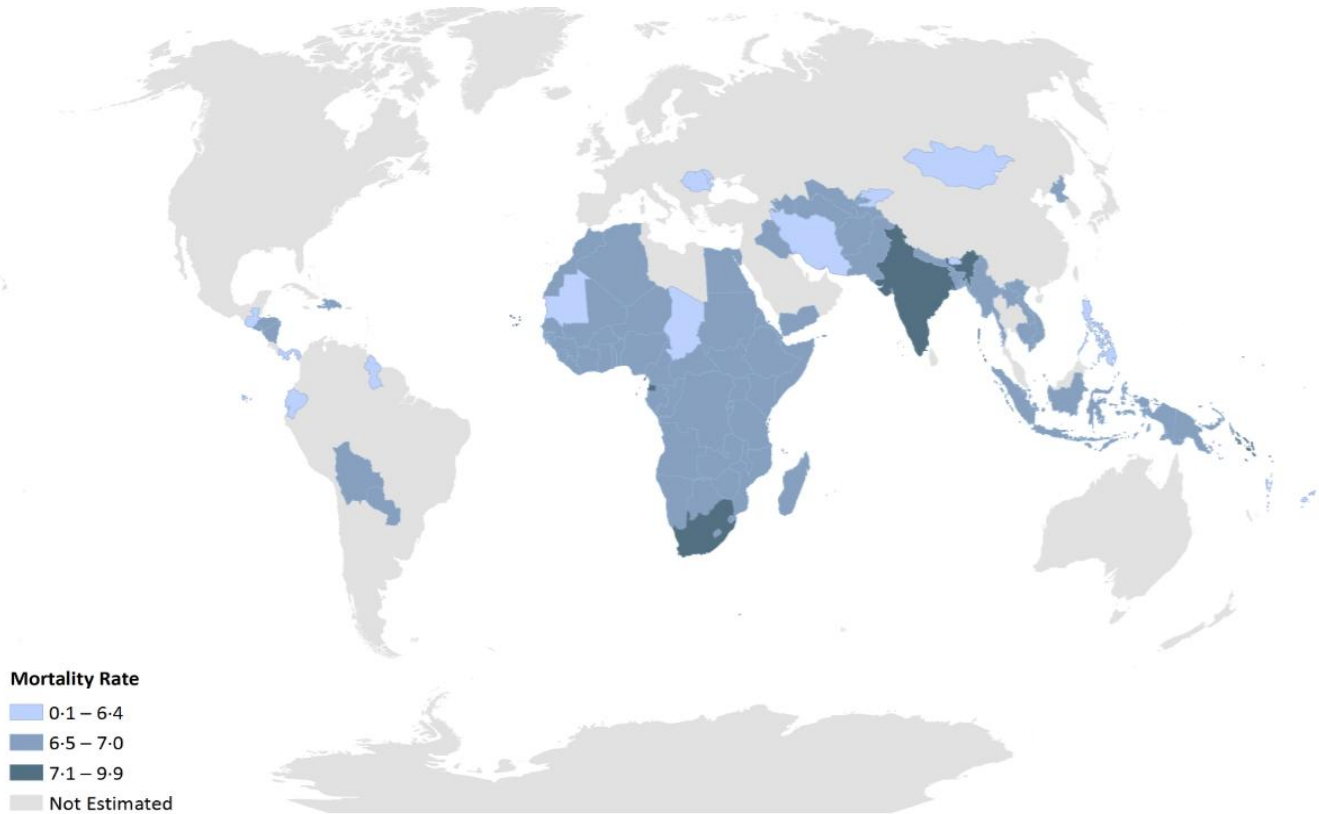
- Estimates of influenza-associated excess mortality available from
 - India, Kenya, Romania, South Africa
- Extrapolated EMR estimates to 92 countries with high child WHO GHE respiratory infection mortality
- Used same analytic and extrapolation approach as main analysis

Estimates of Influenza-associated Respiratory Mortality, <5 Years of Age

Region	Number of Countries (% of Region)	Death Estimate (95% CrI)*	Mortality Rate per 100,000 (95% CrI)
Overall	92 (50)	9,243 – 105,690	2.1 – 23.8
AFRO	45 (96)	721 – 46,336	0.5 – 29.0
SEARO	8 (73)	5,565 – 42,536	3.2 – 24.5

* 95% CrI = 95% Credible Interval

Influenza-associated Respiratory Mortality Rate Estimates (per 100,000), <5 Years



Special Extrapolation for Children <5 Years of Age

- Estimated 9,000 – 106,000 annual excess influenza-associated respiratory deaths
- Nair, et al. previously estimated 28,000-111,500 deaths
- Comparable as Nair, et al. concluded 99% of estimated deaths occur in developing countries and we focused on countries with highest burden
- Focused on these countries as excess mortality estimates from countries with lower burden of respiratory infection mortality were not available

ANNUAL ESTIMATES

Estimated Annual Influenza-associated Respiratory Deaths by Year, All Ages

Year*	Death Estimate (95% CrI) [†]	Death Rate (per 100,000) (95% CrI) [†]	Predominant Influenza Circulating Virus Subtype, global [†]
2001	187,342 - 450,990	3.0 – 7.3	H3N2 / B
2002	171,591 - 362,710	2.7 – 5.8	H3N2 / B
2003	260,760 - 527,426	4.1 – 8.3	H3N2
2004	287,638 - 698,662	4.5 – 10.9	H3N2
2005	211,543 - 462,614	3.3 – 7.1	H3N2 / B
2006	217,215 - 481,210	3.3 – 7.3	H3N2
2007	249,477 - 513,950	3.7 – 7.7	B
2008	201,095 - 400,689	3.0 – 5.9	H1N1
2009	266,160 - 775,577	3.9 – 11.3	H1N1pdm09
2010	156,892 - 390,974	2.3 – 5.7	H1N1pdm09
2011	252,739 - 592,891	3.6 – 8.5	H3N2

* Estimates calculated by calendar year were combined with seasonal estimates which began during the same calendar year (e.g., 2001 calendar estimate was combined with the 2001/2002 seasonal estimate).

† 95% CrI = 95% Credible Interval

Estimated Annual Influenza-associated Respiratory Deaths by Year and Age Group

Year*	Death Estimate (95% CrI) [†]		
	<65 Years	65–75 Years	≥75 Years
2001	44,565 - 291,760	26,376 - 67,732	79,646 - 146,033
2002	36,720 - 200,136	28,016 - 68,361	76,929 - 135,120
2003	63,140 - 308,886	44,837 - 98,153	99,778 - 188,216
2004	63,021 - 469,098	42,527 - 109,382	126,434 - 227,277
2005	49,555 - 269,275	32,535 - 76,957	89,914 - 172,106
2006	48,112 - 287,124	36,545 - 80,864	92,354 - 167,632
2007	54,079 - 284,279	39,417 - 93,151	109,415 - 212,095
2008	41,181 - 218,015	27,445 - 64,801	97,883 - 180,894
2009	117,021 - 626,328	28,038 - 72,206	69,856 - 146,607
2010	58,118 - 287,943	26,919 - 65,882	41,034 - 89,932
2011	55,952 - 371,974	23,556 - 69,939	118,355 - 256,232

* Estimates calculated by calendar year were combined with seasonal estimates which began during the same calendar year (e.g., 2001 calendar estimate was combined with the 2001/2002 seasonal estimate).

† 95% CrI = 95% Credible Interval

IcEBErG Project

IcEBErG Collaboration Process

- WHO invited potential collaborators to participate
- Requested information about surveillance platforms and methods to calculate hospitalization rates including:
 - Surveillance protocols, standard operating procedures, influenza burden publications, evaluation reports, or case report forms
- Information assessed to understand rates to be shared:
 - Surveillance system: case definitions, case enrollment practices, laboratory testing methods
 - Catchment area determination and population estimation methods
 - Influenza-associated hospitalization rate calculation methods
- After evaluation, collaborators asked to share influenza-associated hospitalization rates by age groups