

**INCIDENCE, SEVERITY AND
IMPACT OF INFLUENZA**

16-18 JANUARY 2019 STOCKHOLM

PROGRAMME

WELCOME



European Centre for Disease Prevention and Control (ECDC)
Gustav III:s Boulevard 40, 16973 Solna, Sweden
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Dear Fellow Influenza Scientists & Epidemiologists,

As the world is coming to grips with the latest Ebola outbreak in the Democratic Republic of Congo and the public health community is starting to formulate a global approach to pandemic preparedness and response, it is an opportune time to gather around the first and foremost pandemic disease, influenza.

Influenza poses a significant burden, both as a pandemic threat and during non-pandemic seasons. The latest influenza A(H3N2) seasons have once again reminded us of the potential health and economic impact of influenza in different populations and healthcare settings. This gives even more weight to Recommendation #8, issued by the IHR Review Committee following the 2009 pandemic, i.e. to “Develop and apply measures to assess severity”.

This meeting will bring together epidemiologists, modellers, public health experts, clinical researchers and regulatory experts. The focus will be on defining, assessing and monitoring incidence, severity and impact of influenza and other respiratory viruses. This ISIRV Epidemiology Group conference at the ECDC in Stockholm follows the “Incidence, Severity and Impact of Influenza” meeting in Paris, and the Epi Panel at Options IX in Chicago in 2016.

We have created an interdisciplinary agenda that will provoke thought and provide ample opportunity for fruitful discussion and the exchange of ideas. We aim to inspire new research activities and collaboration towards innovative solutions to the challenges faced by all of us in our respective areas of research.

You are warmly welcome! Thanks to your participation, we can look forward to a lively and memorable event!

**On behalf of the Scientific Committee,
the Co-chairs of the meeting
Barbara Rath, ISIRV and Pasi Penttinen, ECDC**

09:30 – 10:30 Registration / Poster mounting

11:00 – 11:30 WELCOME ADDRESS

BARBARA RATH & PASI PENTTINEN ISIRV and ECDC meeting chairs

11:30 – 13:00 KEY METHODOLOGICAL CHALLENGES

MIKE CATCHPOLE (ECDC)

The need and use of Influenza risk assessments in EU

KATELIJN VANDEMAELE (WHO)

Pandemic Influenza Severity Assessment as a tool to guide public health decision-making globally

DANIELLE IULIANO (US CDC)

Improving estimation of the global burden of influenza hospitalizations and mortality

13:00 - 14:00 LUNCH

14:00 – 15:00 DEFINING CHALLENGES / EXPECTATIONS

SMALL GROUP BREAKOUT SESSIONS – each with a focus on 1 of 6 key topics

- 1 Linking clinical research and surveillance
- 2 What happens outside the hospital?
- 3 Learning from real-world clinical and patient data
- 4 Predicting outcomes on the individual and population level
- 5 Advancing public health surveillance of severity
- 6 Surveillance of severity in low resource or crowded settings

15:00 - 16:00 ORAL SESSION 1

JOLITA MERECKIENE - Health Protection Surveillance Centre, Dublin, Ireland

Seasonal influenza vaccination recommendations, vaccination coverage and payment mechanisms in EU EEA countries, between 2008-09 and 2017-18 influenza season. Results from surveys conducted by the VENICE network

MD ARIFUL ISLAM - International Centre for Diarrhoeal Disease and Research, Bangladesh (icddr,b)

Post-discharge mortality among patients hospitalized with severe acute respiratory infection in Bangladesh, 2011- 2018

HENRY LAURENSEN-SCHAFFER - World Health Organization

A tool to set thresholds on influenza surveillance data

TOOMAS TIMPKA - Lingöping University, Sweden

Real-time nowcasting (integrated detection and prediction) of influenza epidemics in local settings: prospective evaluation in Östergötland County, Sweden

DWI AGUSTIAN - Universitas Padjadjaran, Bandung-Indonesia

Geographical Clustering of Human Influenza A Virus Infections in Two Communities in Indonesia

16:00 - 16:30 COFFEE BREAK

16:30 - 18:00 SCIENTIFIC COMMITTEE MEMBERS

Reporting back on the 6 key topics - Panel discussion.

18:00 +

Poster Reception & Poster Presentations

8:30 – 10:00 **TOPIC 1** Linking clinical research and surveillance networks

Chair: GAIL CARSON

- 1.1 GAIL CARSON (Univ Oxford, UK, ISARIC)
Clinical research networks: recent advances
- 1.2 BENJAMIN COWLING (Univ Hong Kong; ISIRV)
Transmission dynamics at the individual level with disease burden, severity and dynamics at the population level
- 1.3 DEEPALI KUMAR (Univ. Toronto)
Influenza disease severity in high-risk and transplant populations

10:00 - 10:30 COFFEE BREAK + POSTER VIEWING

10:30 – 12:00 **TOPIC 2** What happens outside the hospital?

Chair: TIM UYEKI

- 2.1 TIM UYEKI (US CDC)
What are the gaps in current knowledge on influenza severity outside the hospital?
- 2.2 JESUS CASTILLA (Instituto de Salud Pública, Navarra)
Detection of influenza and other respiratory viruses in deceased persons swabbed in funeral parlours, Navarra, Spain
- 2.3 ANDREW HAYWARD (University College London, UK)
The spectrum of influenza virus infection in the community – findings of the UK Flu Watch study.

12:00 - 12:30 **ORAL SESSION 2** Presentations on Topics 1 and 2

- 12:00 - 12:15 SIRI HELENE HAUGE (Norwegian Institute of Public Health)
Medically attended influenza like illness in Norway, 2008-17
 - 12:15 - 12:30 EDGAR MOJICA (Universidad Nacional Autonoma De Mexico)
Use of space-time cubes to detect influenza patterns in Mexico
- 12:30 - 13:30 LUNCH

13:30 – 15:00 **TOPIC 3** Learning from real-world clinical and patient data

Chair: BARBARA RATH

- 3.1 BARBARA RATH (ViVi, Germany/USA; ISIRV)
Partnering for Enhanced Digital Surveillance of Influenza Disease and the Effect of Antivirals and Vaccines (PEDSIDEA)
- 3.2 DANIELA PAOLOTTI (ISI Foundation, Italy)
Influenza and self-reporting: modelling challenges in participatory surveillance
- 3.3 ELEKTRA PAPADOPOULOS (FDA, US)
Clinical Outcomes Assessment: measuring vaccine and drug effectiveness

15:00 - 15:30 COFFEE BREAK + POSTER VIEWING

15:30 – 17:00 **TOPIC 4** Predicting outcomes on the individual and population level

Chair: YUELONG SHU

- 4.1 YUELONG SHU (School of Public Health Shenzhen, China)
Predicting disease severity using biomarkers
- 4.2 MATT BIGGERSTAFF (US CDC)
Forecasting influenza in the United States
- 4.3 GIDEON EMUKULE (CDC Kenya)
Burden of severe influenza disease in the context of competing priorities in Sub-Saharan Africa

17:00 - 17:30 **ORAL SESSION 3** Presentations on Topics 3 and 4

- 17:00 - 17:15 **GEORGE MILNE** (University of Western Australia)
Population-wide effectiveness of enhanced influenza vaccines use for Older Adults
- 17:15 - 17:30 **MOHAMED ELHAKIM** (World Health Organization, EMRO, Egypt)
Severe cases of influenza reported to EMFLU Network in the Eastern Mediterranean Region of WHO, influenza seasons 2016/17 and 2017/18

8:30 – 10:00 **TOPIC 5** Advancing public health surveillance of severity

Chair: PASI PENTTINEN

5.1 PASI PENTTINEN (ECDC)

Surveillance of influenza severity in EU, (EuroMomo, iMove, ICU surveillance); lessons learnt and needs for the future

5.2 CARRIE REED (US CDC)

Burden, Incidence and prescriptions: The CDC's approach to population-based severity assessment burden estimates

5.3 CHERYL JONES (Univ Melbourne, Australia)

Assessing non-respiratory complications of influenza disease – the Australian PAEDS System

10:00 - 10:30 COFFEE BREAK + POSTER VIEWING

10:30 – 12:00 **TOPIC 6** What happens outside the hospital?

Chair: CHERYL COHEN

6.1 CHERYL COHEN (National Institute for Communicable Diseases, South Africa)

Conducting epidemiological research in underserved and vulnerable populations (incl. HIV/AIDS)

6.2 ZIAD MEMISH (Prince Mohammed bin Abdulaziz Hospital, Saudi Arabia)

Mass gatherings and the epidemiology of acute respiratory viral infections: an overview of the literature

6.3 ALICE WIMMER (International Organisation for Migration, UN)

Ensuring migrant inclusion in National Pandemic Influenza Preparedness Plans

12:00 - 12:30 **ORAL SESSION 4** Presentations on Topics 5 and 6

12:00 - 12:15 JEAN-MICHEL HERAUD (Institut Pasteur de Madagascar)

Assessing severity and impact of influenza in Madagascar: insight from biological surveillance to mortality data and economic burden.

12:15 - 12:30 JENS NIELSEN (Statens Serum Institut)

European all-cause excess and influenza-attributable mortality in the 2017/2018 season: Should the burden of influenza B be reconsidered?

12:30 - 13:30 Closing Statements

JULIA FITZNER (WHO): Take-away messages

BARBARA RATH (ISIRV) & PASI PENTTINEN (ECDC):

Needs Statement - Planning next steps incl. joint publications

ORAL SESSION 1

JOLITA MERECKIENE

Seasonal influenza vaccination recommendations, vaccination coverage and payment mechanisms in EU EEA countries, between 2008-09 and 2017-18 influenza season. Results from surveys conducted by the VENICE network

JOLITA MERECKIENE, Kari Johansen, Pasi Penttinen, Svetla Tsoлова, Maria Cristina Rota, Daniel Levy-Bruhl, Ole Wichmann, Luca Demattè, Palle Valentiner Branth, Iwona Stankiewicz, Suzanne Cotter

Health Protection Surveillance Centre, Dublin Ireland - European Centre for Disease Prevention and Control, Stockholm, Sweden - Istituto Superiore di Sanità, Rome, Italy, - Institut de Veille Sanitaire, Saint-Maurice, France - Robert Koch Institute, Berlin, Germany - CINECA Consortium of Universities, Bologna, Italy - Statens Serum Institut, Copenhagen - Denmark, National Institute of Public Health - National Institute of Hygiene, Warsaw, Poland - Health Protection Surveillance Centre, Dublin, Ireland

Background

In the European Union (EU) and European Economic Area (EEA) Member States (MS) seasonal influenza occurs in regular annual winter epidemics. The disease is associated with significant morbidity and mortality, varies in number of cases, affected age groups and dominating circulating influenza viruses. Severe illness and complications are more common in those with chronic medical conditions, individuals ≥ 65 years and pregnant women. The most effective public health intervention to prevent influenza and its complications is vaccination. To protect vulnerable individuals and reduce transmission, vaccination is also recommended for healthcare workers (HCWs).

Since 2008 VENICE project has conducted surveys to follow-up on vaccination policy and to identify compliance with the EU Council recommendation to achieve the goal of 75% coverage in older age and risk-groups.

Methods

In January 2018 a survey was done across EU/EEA MS. Vaccination policy data were collected for 2017-18 and coverage for 2015-16, 2016-17 and 2017-18 (if available at the time of survey) seasons. These data were compared between countries using data obtained from previous surveys. The questionnaire was completed on-line by MS gatekeepers. The questionnaire for United Kingdom was completed separately for England, Northern Ireland, Scotland and Wales.

Results

Of 30 responding MSs, all recommend seasonal influenza vaccines to older age-groups: 22 for individuals aged ≥ 65 years and eight with lower age cut-offs (ranging from ≥ 50 to ≥ 60 years of age). Six MSs recommend vaccination of healthy children. All MSs recommend influenza vaccine for clinical risk groups ($n=30$) and most for pregnant women ($n=28$), and HCWs ($n=29$).

Reported vaccination coverage varied by country and targeted group in 2016-17, ranging from 2.0%-72.8% (median 47.1%) for older age-groups ($n=19$) and 0.4%-73.0% for healthy children ($n=4$). Coverage in clinical risk-groups ($n=7$), HCWs ($n=12$) and pregnant women ($n=9$) ranged between 15.7%-57.1% (median 44.9%), 15.6%-63.2% (median 30.2%) and 0.5%- 58.6% (median 25.0%), respectively.

The predominant payment mechanism for influenza vaccinations was national health services or a combination of several mechanisms for vaccine targeted population groups and employer for HCWs.

Conclusions

Most MS recommend influenza vaccination for the known risk-groups. However, few MSs have achieved the recommended vaccination coverage among the elderly, and coverage is not available in most MS for clinical risk-groups, HCWs and pregnant women. Additional work is needed to improve coverage and respective data across the EU region, and lessons learnt in countries with high coverage should be utilized.

MD ARIFUL ISLAM

Post-discharge mortality among patients hospitalized with severe acute respiratory infection in Bangladesh, 2011- 2018

MD ARIFUL ISLAM, Md Zakiul Hassan, Mohammad Abdul Aleem, Md Mustafizur Rahman, Mohammed Ziaur Rahman, Zubair Akhtar, Mohammad Abdullah Heel Kafi, A. Danielle Iuliano, Eduardo Azziz-Baumgartner, Fahmida Chowdhury

International Centre for Diarrhoeal Disease and Research, Bangladesh (icDDR,b) - Centers for Disease Control and Prevention (CDC), Atlanta, Georgia, USA

Background

Severe acute respiratory infection (SARI) is one of the leading causes of morbidity and mortality worldwide. Annually, it causes 4.25 million deaths with 40% of deaths occurring in four Asian countries, including Bangladesh. While in-hospital SARI mortality is well-characterized in Bangladesh, there is limited information about post-discharge mortality.

Methods

We analyzed hospital-based influenza surveillance data from WHO defined SARI patients admitted to 14 tertiary level hospitals in Bangladesh from October 2011 to August 2018. Study physicians at each surveillance hospital identified SARI cases on weekdays throughout the year. We collected data about demographics, clinical characteristics, outcome at discharge, and survival 30 days after discharge. Influenza vaccination data was not collected because it was not part of the routine immunization program. We compared the data, including influenza virus PCR results, between decedents and survivors using Chi-square tests and t-tests.

Results

The median age of the 17,813 SARI patients was 20 years (IQR 1–46) and 66% were male. Fewer cases died during hospitalization (289, 1.6%) than after discharge (482, 2.7%; $p=0.001$). Persons who died at post-discharge were more likely to be adults aged ≥ 65 [9% (166/1,851) vs 2% (208/10,550), $p=0.001$] among those ≥ 5 years or to be infants aged <1 year [2.5% (94/3,813)] vs 1% (14/1,310) among children <5 years. Among the 482 post-discharge deaths, 235 (49%) died within 7 days, 81 (17%) within 8–14 days and 166 (34%) within 15–30 days of discharge. Of the post-discharge decedents, 195 (41%) patients left the hospital fully recovered, 144 (30%) patients were partially recovered, 79 (16%) patients requested to be discharged, and 64 (13%) patients were referred to specialized hospitals. Compared to the survivors, a higher proportion of post-discharge death cases had difficulty breathing (84% vs 60%, $p=0.001$), received oxygen (49% vs 23% $p=0.001$), had at least one co-morbid condition (44% vs 20%, $p=0.001$), and stayed longer in hospital [5 (SD ± 3.45) vs 4 (SD ± 2.97) days, $p=0.001$]. Influenza was detected in 17% (2,880) of survivors, 13% (37) of in-hospital deaths and 10% (47) of post-discharge deaths. Only five survivors and one decedent received oseltamivir.

Conclusions

Two-thirds of SARI deaths occurred after discharge, suggesting that post-discharge mortality after inpatient care is common in Bangladesh. Formative studies to better understand the underlying factors of in-patient treatment continuation and co-morbid conditions are required to inform effective intervention and to improve the survival of patients after discharge.

HENRY LAURENSEN-SCHAFFER

A tool to set thresholds on influenza surveillance data

HENRY LAURENSEN-SCHAFFER, Aspen Hammond, Katelijjn Vandemaele, Julia Fitzner

World Health Organization

Background

Following the recommendations of an independent report on the response to the 2009 pandemic, WHO, with the input of technical experts, developed the Pandemic Influenza Severity Assessment (PISA) methodology to provide a standardised framework for assessing pandemic and epidemic influenza severity using existing surveillance data and parameters to inform three indicators (transmissibility, seriousness of disease and impact). Historical data is used to calculate country- and parameter-specific threshold levels of activity; current activity is explained in relation to these categorical levels. This allows for comparison of influenza severity levels across countries and regions despite country-specific differences in surveillance systems and capacities. Among the different methods used to determine seasonal and intensity thresholds are the moving epidemic method (MEM) or the average curve method (WHO method). There are challenges when applying these methods on data from use this in some countries, especially those with non-temperate climates where influenza activity may peak more than once per year.

Methods

To address these challenges, a further work on the averaging method was undertaken. An automated algorithm was developed which first identifies numbers of peaks per year and then determines thresholds, either for each peak or for a single peak. To evaluate this method, country-specific influenza surveillance data reported to WHO via FLUID and FLUNET was extracted and seasonal and intensity thresholds for an initial selection of 13 countries were determined. These thresholds were compared to the those determined using the moving epidemic method (MEM). Both methods rely on R scripts to load data and run the calculations.

Results

For the countries analysed, the algorithm determined if influenza activity follows a one or two-peak per year pattern. Thresholds based on the average method and the MEM were determined. While the intensity thresholds determined by both methods were similar, the epidemic threshold calculated was very different for several countries examined.

Conclusions

Either method can be applied to determine intensity levels of influenza activity. Epidemic thresholds determined with the averaging method differed from those determined with the MEM method, specifically for countries where multiple peaks may occur in a year. Next steps include validating the methods and creating visualizations and a user-interface to ease interpreting data and assessing severity indicators.

Real-time nowcasting (integrated detection and prediction) of influenza epidemics in local settings: prospective evaluation in Östergötland County, Sweden

TOOMAS TIMPKA, Armin Spreco, Olle Eriksson, Örjan Dahlström, Benjamin Cowling

Linköping University, Hong Kong University

Background

The growing availability of health data opens possibilities for highly reactive influenza control in local settings. Although methods for local detection and prediction of influenza epidemics have been developed, few studies have evaluated these using rigorous evaluation protocols. The aim of this study was to prospectively evaluate a previously published method for integrated local detection and prediction (nowcasting) of influenza epidemics over 5 years in Östergötland County, Sweden (pop. 440.000).

Methods

We used syndromic telenursing data and routine health information system data on influenza-diagnosis cases for July 2009–June 2014 to evaluate epidemic detection, peak-timing prediction, and peak-intensity prediction. Nowcasting performance was defined to be excellent if the absolute value of the timeliness error was <3 days, good if it was 4–7 days, acceptable if it was 8–11 days and poor if it was >12 days. For peak intensity predictions, we used the epidemic thresholds and intensity level categories used for reporting by the ECDC. The prediction was considered successful only if the predicted peak intensity fell into the same category as the actual peak intensity.

Results

Detection performance was satisfactory throughout the period, except for the 2011–12 influenza A(H3N2) season, which followed a season with influenza B and pandemic influenza A(H1N1) pdm09 virus activity (Table 1). Peak-timing prediction performance was satisfactory for the 4 influenza seasons but not the pandemic (Table 2). Peak-intensity levels were correctly categorized for the pandemic and 2 of 4 influenza seasons (Table 2).

Conclusions

This prospective evaluation supports the application of locally adapted versions of the nowcasting method in comparative multi-center studies.

Table 1. Performance of detection algorithm.

Influenza activity	Timeliness*	Interpretation
2009 (pandemic) A (pH1N1)	-5	Good
2010-11 B & A (pH1N1)	-5	Good
2011-12 A (H3N2)	15	Poor
2012-13 A (H3N2), B & A (pH1N1)	3	Excellent
2013-14 A (H3N2), B & A (pH1N1)	-3	Excellent

*Value>0, alarm issued before start of epidemic; value<0, alarm issued after start of epidemic.

Table 2. Performance of peak timing and peak intensity predictions.

Influenza activity	Peak timing (days*)		Peak intensity category
	Prediction error	Interpretation	Interpretation (Predicted: Factual)
2009 (pandemic)	-28	Poor	Successful (Medium:Medium)
2010-11	0	Excellent	Successful (Medium:Medium)
2011-12	7	Good	Unsuccessful (Medium:Very high)
2012-13	-7	Good	Successful (Very high:Very high)
2013-14	-8	Acceptable	Unsuccessful (Non-epidemic:Medium)

*Value>0, peak predicted to be reached before the actual peak occurs; value<0, peak predicted to be reached after the actual peak.

DWI AGUSTIAN

Geographical Clustering of Human Influenza A Virus Infections in Two Communities in Indonesia

DWI AGUSTIAN, Elisabeth D. Root, Kuswandewi Mutyara, Chrysanti Murad, Cissy B. Kartasasmita, Eric A.F. Simoes

Universitas Padjadjaran Bandung, Indonesia, The Ohio State University USA, University of Colorado School of Medicine USA,

Background

Influenza pandemic is a global threat and it is predicted that if it occurred, most burden will be from developing country such as Indonesia. Therefore, understanding the geographical clustering of human influenza A in this setting is crucial for pandemic preparedness. To examine geospatial clustering of human influenza A in rural Indonesia, influenza A cases and all households in two rural communities were geocoded through passive surveillance and a population census in 2008-2011.

Methods

A spatial scan statistic using a Poisson discrete model, with and without covariate adjustment, was utilized to evaluate the geographic location and statistical significance of influenza A(H3N2) and A(H1N1pdm09) clusters in the community and the possible environmental determinants.

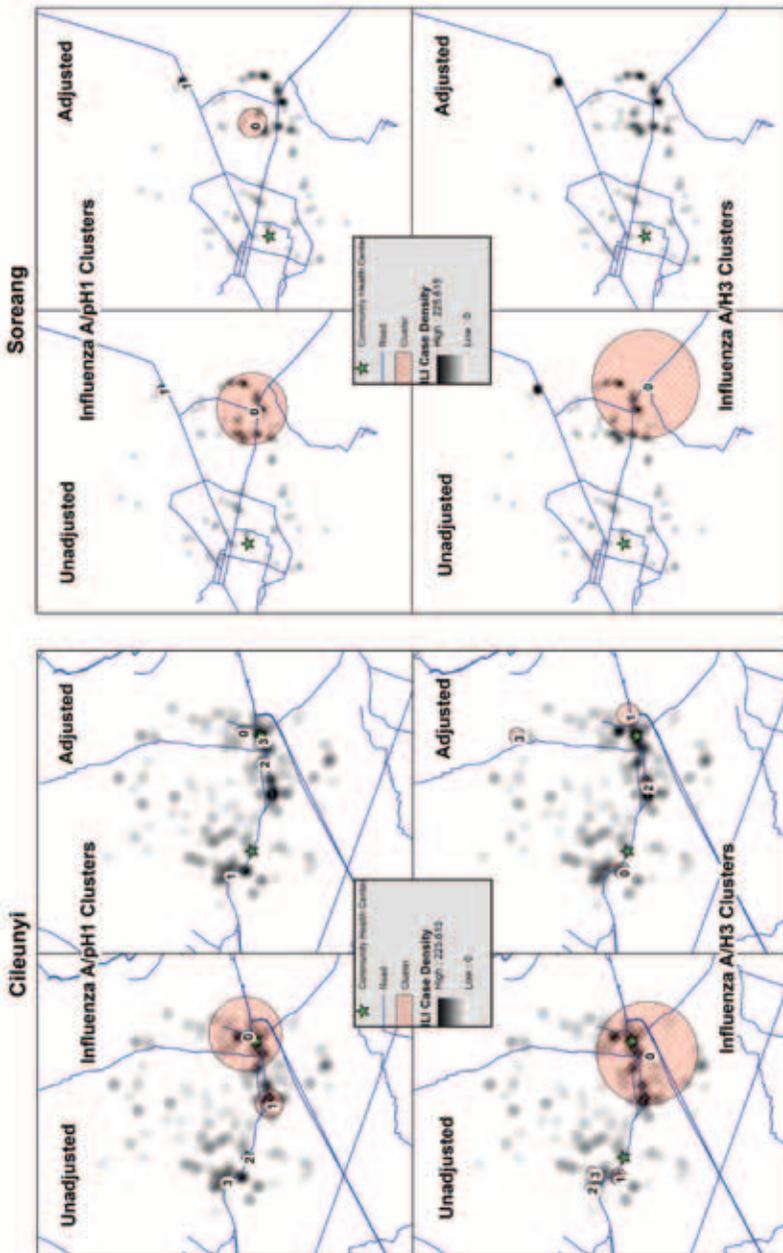
Results

Results indicate distinct clusters of influenza A(H3N2) and A(H1N1pdm09) infection in both communities. Altogether young children, birds kept by the house, and neighborhood community health care utilization explained approximately 97% and 81% of households contribute to the A(H3N2) and A(H1N1pdm09) clusters, respectively.

Conclusions

This study demonstrates human influenza A case clustering in two rural communities in rural Indonesia and household characteristics related to the number of children aged <5 years, and the number of birds are associated with these clusters after adjusting the health care utilization

for influenza like illness. Cluster detection methods can be adopted for influenza surveillance programs which monitor emerging outbreaks and focus on prevention and local containment in Indonesia, as well as other regions where novel influenza A viruses are likely to emerge.



ORAL SESSION 2

SIRI HELENE HAUGE

Medically Attended Influenza-like Illness in Norway, 2008-17

SIRI HELENE HAUGE, Inger Johanne Bakken, Birgitte F. de Blasio

Norwegian Institute of Public Health

Background

Despite yearly outbreaks, the burden of influenza in Norway remains unknown and data on seasonal variations and differences by age groups are needed. We aimed to describe influenza consultations by season, including the 2009-10 pandemic, using Norwegian national data.

Methods

We had access to registry data on all influenza diagnoses from primary care in Norway, coded according to the International Classification of Primary Care (ICPC). The study period, 2008 through 2017, included nine influenza seasons. We calculated seasonal rates, compared age groups within seasons and by seasons. We also compared seasonal influenza outbreaks with the 2009-10 pandemic outbreak. During the study period the population in Norway increased from 4 737 171 to 5 258 317.

Results

We identified in total 836 224 patients with an influenza diagnosis. The number of influenza diagnoses showed a clear seasonal pattern. Most outbreaks peaked in terms of weekly influenza diagnosis during the winter months, but the 2009-10 pandemic had the highest number of weekly influenza diagnosis in November. On average, 1.7 % (range 1.0 – 3.9) of the population was diagnosed with influenza each season. During the 2009-10 pandemic, we observed the highest rates with 3.9 % diagnosed with influenza. The average patient age was 36 years (median 36) and 55 % were female. The highest age-specific rates were seen in people aged 20-39 years, with an average of 2586 influenza diagnoses per 100 000 population for all seasons combined. The age-specific rates were lowest in those above 80 years (532 per 100 000 population).

Conclusions

Influenza outbreak cause a substantial disease burden in primary health care. Outbreaks occur during winter months and infection rates vary between seasons and between age groups. Young adults are those most frequently diagnosed with influenza in primary health care in Norway.

EDGAR MOJICA

Use of space-time cubes to detect influenza patterns in Mexico

EDGAR MOJICA

Universidad Nacional Autonoma De Mexico

Background

After the influenza H1N1 pandemic event, Mexico changed its methodology in epidemiological surveillance of influenza and the consequences of that was the creation of a unique data base type. This data base is known as SISVEFLU (Epidemiological surveillance System of Influenza), In

this data base can find detailed information of each suspicious cases of influenza in Mexico and allows to perform temporal space analyst. However, it's unknow if this method can be use in monitoring and epidemiological surveillance.

Methods

It was analyzed the SISVEFLU data base in search of temporary space patterns in Mexico between 2010 and 2015; For this, I was created a temporary space cube and it applied the Mann-Kendall statistic to detect a trend (increase or decrease) for: all suspicious cases of influenza, influenza type A, B (Yamagata and Victoria), H1N1 pmd and AH3. For those cases who shown a trend I applied an analysis of emerging hot spots using the GI of Getis-Ord, to detect specific locations.

Results

The results showed the existence of increasing patterns for all cases suspected of influenza and for confirmed cases of influenza type B and H3N2; only a decreasing pattern was detected in cases of type A influenza; no patterns were detected in confirmed cases of H1N1 and in cases not subtyped.

Conclusions

The methodology facilitates the location of specific places that present an increase in the number of cases for a specific type of influenza. Changing the scale of the analysis does not significantly alter the results or behavior patterns.

ORAL SESSION 3

GEORGE MILNE

Population-wide effectiveness of enhanced influenza vaccines use for Older Adults

GEORGE MILNE, Joel Kelso, Simon Xie, Sheena Moore, Sheena Sullivan

University of Western Australia, Telethon Kids Institute, Perth, WHO Collaborating Centre for Reference and Research on Influenza, Melbourne

Background

Following high mortality rates in the 2017 flu season enhanced influenza vaccines for those aged 65 and older were added to the Australia-wide free vaccination program in 2018. Individual-based simulation models were used to compare enhanced vaccine use with previous QIV.

Methods

Population-wide vaccine effectiveness determined by: simulating influenza transmission and health outcomes using QIV; repeated using enhanced vaccines; comparing outcomes. Models capture ages, household/workplace/school structure and individual-to-individual contact patterns (1). Three community models with different demographics then scaled for Australia as a whole.

Results

Benefit enhanced influenza vaccines for elderly: 7.4% reduction in hospitalisations and 11.4% reduction in deaths. Due to increased protection in 65+ cohort, little indirect protection. Similar benefits achieved by increasing QIV coverage to 80% in same age group, logistically difficult requiring 544,000 extra vaccinations.

Conclusions

Measurable reduction in health burden using enhanced influenza vaccines in the elderly.
No additional administration costs. Possible issue with missing B lineage in vaccine.

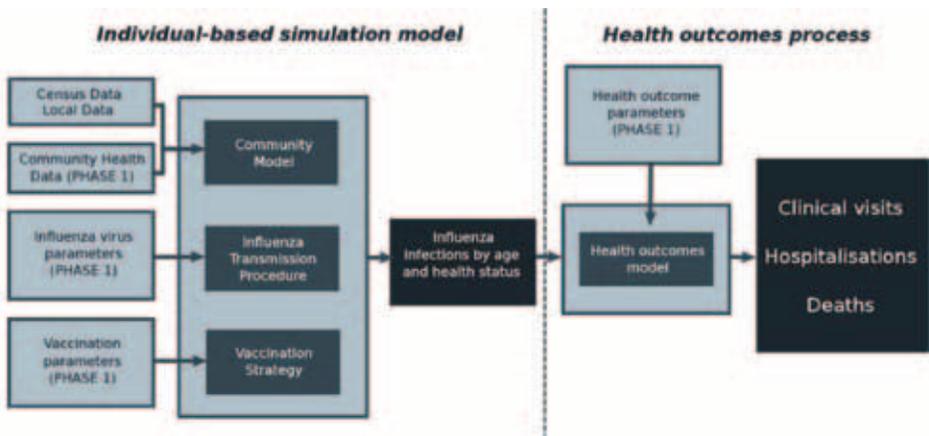


Figure 1: Simulation Model Framework

Table 1: Enhanced vaccine in older adults, for Australian population 24.7 million

	Extra vaccines required (1000's)	Health Outcomes								
		Symptomatic illness		GP visits		Hospitalisations		Deaths		
		Total (1000's)	% averted	Total (1000's)	% averted	Total	% averted	Total	% averted	
QIV to all ages	-	995	-	167	-	13,433	-	501	-	
enhanced TIV (≥65 years), all others QIV										
	0	954	4.1%	160	4.2%	12,445	7.4%	444	11.4%	

Benefit enhanced influenza vaccines for elderly: 7.4% reduction in hospitalisations and 11.4% reduction in deaths. Reduction in deaths from enhanced vaccines due to increased protection in 65+ cohort; little indirect protection.

Table 2: Increased QIV coverage for 65 years and older

Increased coverage level	Extra vaccines required (1000's)	Health Outcomes								
		Symptomatic illness		GP visits		Hospitalisations		Deaths		
		Total (1000's)	% averted	Total (1000's)	% averted	Total	% averted	Total	% averted	
Baseline	-	995	-	167	-	13,433	-	501	-	
Older adults; current coverage 66.9%										
70%	135	976	1.9%	164	1.9%	13,045	2.9%	480	4.2%	
80%	544	942	5.4%	158	5.4%	12,413	7.6%	448	10.5%	
90%	959	910	8.5%	153	8.6%	11,660	13.2%	405	19.1%	

1. Milne GJ, Halder N, Kelso JK, Barr IG, Moyes J, Kahn K, et al. Trivalent and quadrivalent influenza vaccination effectiveness in Australia and South Africa: results from a modelling study. *Influenza and other Respiratory Viruses*. 2016;10(4):324-32

Severe cases of influenza reported to EMFLU Network in the Eastern Mediterranean Region of WHO, influenza seasons 2016/17 and 2017/18

MOHAMED ELHAKIM, Abdinasir Abubakar, Amgad Elkholy, Amal Barakat, Bhagawan Shrestha, Sk Md Mamunur Rahman Malik

World Health Organization, Eastern Mediterranean Regional Office, Cairo, Egypt

Background

Influenza viruses represent a significant public health concern that leads to year-round severe morbidity and mortality. Influenza surveillance systems in the Eastern Mediterranean Region (EMR) of WHO have been strengthened in the past decade and 17 out of the 19 countries in the Region with functional influenza surveillance systems report their influenza data to the EMFLU Network, Regional platform for SARI and ILI data collection and analysis, officially launched in May 2016. This study aims to investigate the epidemiology of severe cases of influenza viruses reported to the EMFLU during the past two influenza seasons 2016/17 and 2017/18.

Methods

Data included in this study was collected by 17 countries in the EMR from 202 SARI sentinel surveillance sites over the previous two influenza seasons.

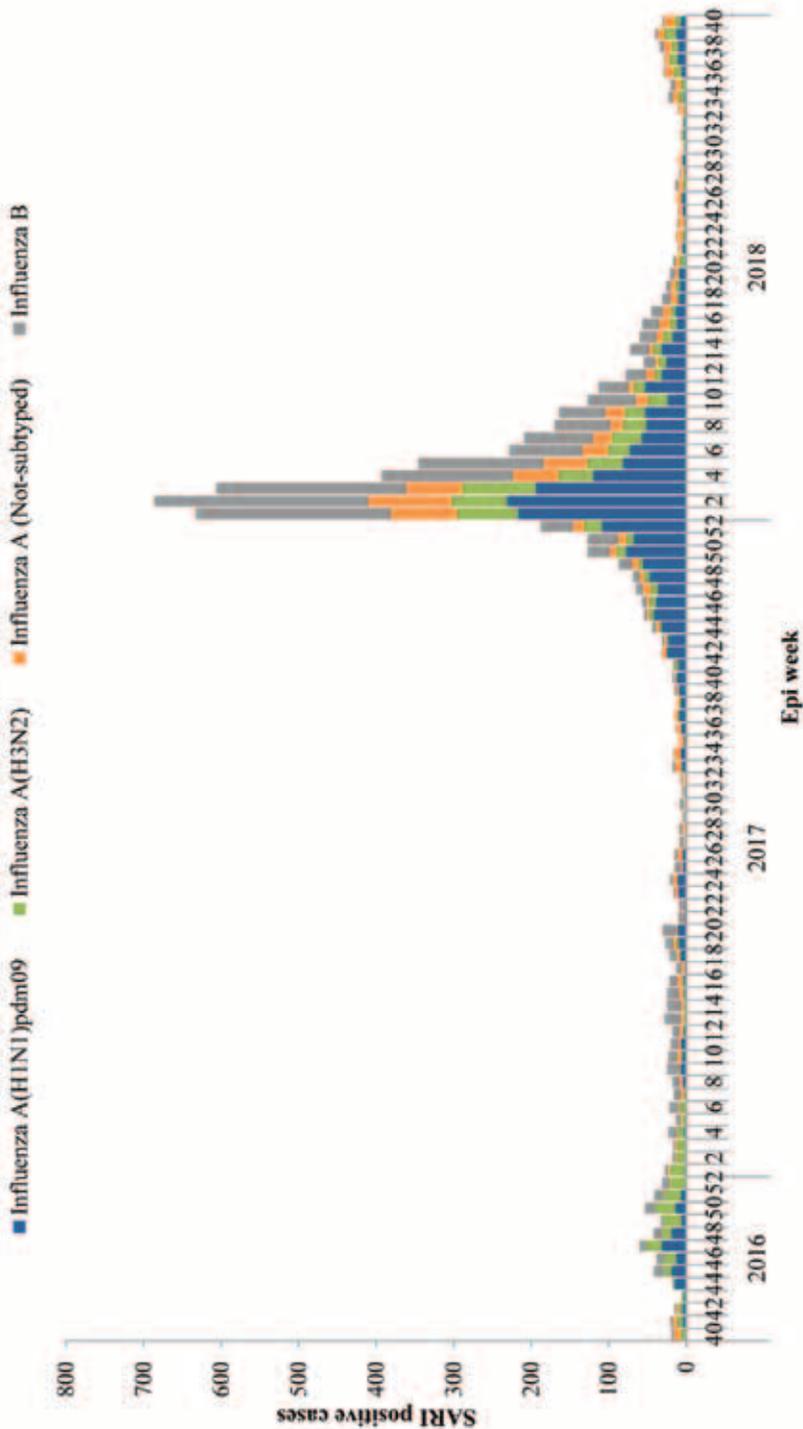
Results

A total of 72,526 cases of SARI were included in the study. Most cases 21,059 (29.04%) were less than 5 years of age. Influenza virus was detected in 6445 patients (please refer to figure 1), 4208 (65.29%) were influenza A and 2237 (34.71%) were influenza B. Influenza A(H1N1)pdm09 was the predominant circulating subtype with 2272 cases (53.99%).

Conclusions

Influenza viruses cause a high number of severe respiratory infections in the EMR. The WHO Regional Office of the Eastern Mediterranean Region continues to support countries through different workshops and trainings to calculate their Burden of Disease (BoD) and the baselines and thresholds for the Pandemic Influenza Severity Assessment (PISA). It is highly recommended for the countries in the EMR to understand the severity of influenza viruses in the Region and to continue enhancing their influenza surveillance capacity in order to be able detect any unusual influenza activity or new strain and be adequately prepared for the upcoming pandemic.

Figure 1. Severe Acute Respiratory Infection (SARI) positive cases reported to EMFLU Network from 17 countries in the EMR, epi week 40/2016 to epi week 40/2018



ORAL SESSION 4

JEAN-MICHEL HERAUD

Assessing severity and impact of influenza in Madagascar: insight from biological surveillance to mortality data and economic burden.

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Background

Lessons from the 2009 influenza A(H1N1) pandemic showed the need to establish surveillance of influenza severity. Madagascar has set up multidisciplinary approach including register of economic charge due to influenza disease, region wide mortality surveillance as well as routine biological surveillance to evaluate indicators of influenza severity and impact associated to influenza infections.

Methods

Routine biological influenza hospital surveillance (SARI) provides insights into the circulating virus types and subtypes in Antananarivo, the capital city of Madagascar. Association with clinical and demographic data as well as mortality curve also gives information about severity of infection according to the circulating strains. Contrasting economic charge is useful to assess the impact of influenza diseases.

Results

Between September 2016 and August 2018, 280 samples from SARI patients hospitalized in Cenhosoa hospital of Antananarivo were enrolled for biological analysis. About 21% (n=58) of tested patients were laboratory-confirmed influenza positive of which 13% (n=36) were positive for influenza type A and 10% (n=27) positive for influenza type B. The highest rate of infection was obtained in patients aged less than 5 years ($p<0.05$). Among positive patients, 97% (n=56) presented at least one severe clinical symptom at admission. Wheezing was significantly relatively more common during influenza infection linked to SARI ($p=0.02$). Considering age, patients aged between 3 and 5 years were less at risk to develop severe influenza compared to the other age groups ($p=0.03$). The total charge relative to SARI hospitalization is estimated at 1 849 070 ariary (\$ 536). Moreover, the total annual cost caused by SARI to the Malagasy health system is estimated at 18 billion ariary (\$ 5 217 275), representing 0.1% of nominal GDP in 2016. In terms of mortality surveillance, the number of deaths tends to increase with the number of influenza-associated SARI during specific periods, and for patients aged less than 5 years and more than 60 years.

Conclusions

Despite the fact that SARI and mortality surveillance is only active in Antananarivo, these findings highlight the need to maintain active surveillance and extend in the whole country in order to evaluate the real impact of influenza among the Malagasy population. Moreover, these results have important implications for implementing national vaccination policy in low-income countries like Madagascar.

European all-cause excess and influenza-attributable mortality in the 2017/2018 season: Should the burden of influenza B be reconsidered?

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Background

Marked increased all-cause excess and influenza-attributable mortality was observed amongst the elderly in many European countries during the 2017/18 influenza season, dominated by influenza B/Yamagata, but with co-circulation of both A(H3N2) and A(H1N1)pdm09 influenza subtypes.

Methods

For the European winter season 2017/18 we estimated excess mortality using the EuroMOMO model, and mortality attributable to influenza using the FluMOMO model. We used data from 24 European national or sub-national states on number of deaths, influenza indicators from clinical and virological surveillance, and ambient temperatures.

Results

The increased excess mortality was mainly attributable to influenza activity from December 2017 to April 2018, but partly also due to exceptionally cold temperatures in February-March 2018. The pattern and extent of mortality excess was similar to the two A(H3N2) dominated seasons 2014/15 and 2016/17. For the 2017/18 season the overall all-cause mortality attributable to influenza was estimated to be 25.4 (95%CI 25.0-25.8) per 100,000 population for all ages based on data from 24 European countries or sub-national regions representing 49% of the whole European population. Extrapolating the estimated mortality attributable to influenza to the entire European continent translates into nearly 190,000 deaths attributable to influenza.

Conclusions

Season 2017/18 was dominated by influenza influenza B and associated with a significant mortality burden. Even though A(H3N2) also circulated and may have contributed to the excess mortality among the elderly, the common perception that influenza B has a limited impact on excess mortality in the older population may need to be reconsidered

P1

Surveillance of severe influenza cases in France, 2009-2018: strengths, limits and perspectives

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Background

A comprehensive national surveillance system for severe influenza cases has been set up in France during the 2009-10 pandemic. Severe probable and confirmed influenza cases admitted to intensive care units (ICU) are reported to Santé publique France every season ever since.

Methods

A descriptive analysis of the epidemiological and virological characteristics of the influenza cases admitted to ICU reported during 9 seasons was conducted. The exhaustiveness of the surveillance during the period 2009-2013 was evaluated by a capture-recapture analysis, based on 2 independent data sources. A multivariate analysis was conducted to identify factors associated with the exhaustiveness of the surveillance. An evaluation of the surveillance was conducted in 2018.

Results

A total of 11,043 severe cases have been reported since 2009, with a minimum of 323 cases (2011-12) and a maximum of 2,933 (2017-18) per season. More than 95 % were biologically confirmed. The median age varied between 44 and 70 years (2009-10 and 2016-17 respectively). Twenty percent of cases had no risk factors of flu complications. Among the cases targeted by the French vaccination policy for which the information on vaccination status was available, 38% in people aged 65 years or older and 16% in those under 65 years were vaccinated. The exhaustiveness of the surveillance system was estimated at 47% at national level, with wide variations between regions (from 28% to 74%) and between the beginning and the end of the season (from 52% in November to 20% in April). An active animation of the network was associated with higher exhaustiveness, especially when weekly surveillance bulletins were sent to the ICU clinicians (relative risk of 1.37, 95% CI: 1.05-1.80). Eighty percent of the cases were reported by 20% of the ICU participating to the surveillance, which displayed a higher exhaustiveness rate (72%).

Conclusions

The French national surveillance system for severe influenza cases has provided valuable information on the severity of influenza epidemics since the 2009 pandemic. This study identified several areas for improvement in this surveillance system, including an evolution towards a sentinel system, an optimization of surveillance methods and a routine analysis of the exhaustiveness of the system at the end of the season. Those changes have been implemented for the current influenza season.

Characterizing healthcare-seeking behavior of the general population with influenza-related symptoms in Hong Kong

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Background

Healthcare-seeking behavior can affect health outcomes of individual patients and understanding of disease burden and severity at the population level. Many previous studies examined healthcare-seeking behavior according to the diagnosed disease. However, for patients, it was the symptoms or discomfort rather than the diagnosed diseases which determine their healthcare seeking decisions. Our study described the likelihood and type of healthcare utilization, and time from symptom onset to consultation due to different influenza-related symptoms. We also identified factors associated with healthcare-seeking behavior.

Methods

We conducted a 4-round longitudinal telephone survey, on multiple symptoms related to common infectious diseases in Hong Kong. We examined their healthcare-seeking behavior triggered by influenza-related symptoms (fever, cough, runny nose, sore throat, headache, chills, and fatigue) and by influenza-like illness (ILI) and acute respiratory infection (ARI). Post-stratification and multiple imputation were used to account for non-response and handle missing/right-censored healthcare-seeking behavior due to the short time interval between symptom onset and the interview. We further explored factors associated with healthcare-seeking behavior by using generalized estimating equation model.

Results

91% and 64% of subjects having ILI and ARI, respectively sought medical consultation. Considering specific influenza-related symptoms, among the subjects with fever, 78% sought medical consultation due to the symptom. The proportions dropped to 47%, 32% and 14% for cough, chills and fatigue respectively. Among those who have sought medical consultation, 84% of them visited a doctor within 3 days of symptom onset (91% and 85% for those with ILI and ARI respectively). Subjects who sought medical consultation due to fever and chills tend to have a shorter onset-to-consultation duration. Based on the multivariable GEE model, we found that people having fever (adjusted odds ratio aOR=5.4, 95% CI=3.4–8.8) were most likely to seek medical consultation, followed by cough and runny nose (aORs=1.6). There was no significant difference in healthcare-seeking behavior during or out of the influenza season.

Conclusions

Fever was the strongest driver for subjects having influenza-related symptoms to seek healthcare services. Among those subjects who have sought consultation, the majority of them visited doctors within 3 days. The findings could inform estimation of influenza disease burden and confirm that fever and cough are crucial for ILI syndromic surveillance. The findings are applicable to the Hong Kong general population but generalizability to other places has to be further assessed.

Assessing severity of seasonal influenza using proportions of hospitalisations, Denmark 2010-2018

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Background

Seasonal influenza is associated with significant morbidity and mortality. Understanding the severity of influenza across different seasons is essential in order to guide public health actions such as vaccination of risk groups. However, comparing the severity of influenza between countries with different surveillance systems can be challenging. In Denmark, we use data capture from existing registers for the surveillance of severe influenza. Here, we describe all influenza hospitalisations, influenza intensive care unit hospitalisations (ICU) and 30-day mortality as proportions of hospitalisations in order to compare severity of the influenza seasons 2010-2018 in Denmark.

Methods

Patients with laboratory-confirmed influenza were identified in the Danish Microbiology Database. Hospitalisations and intensive care procedures were captured from the Danish National Patient Register and 30-day mortality from the Civil Registration System. We calculated proportions of influenza hospitalisations (number of influenza hospitalisations/total number of hospitalisations), influenza ICU (number of influenza ICU/number of influenza hospitalisations) and influenza 30-day mortality (influenza 30-day mortality/number of influenza hospitalisations).

Results

Proportions of influenza hospitalisations, ICU and 30-day mortality varied across influenza seasons with different circulating influenza strains. The proportions of influenza hospitalisations ranged from 0.03% of all hospitalisations in the 2011/12 season to 1.63% in the 2017/18 season. The proportion of ICU ranged from 7.1% in the 2011/12 season to 19.4% in the 2013/14 season. This proportion was higher in adults compared to children especially in those ≥ 65 years of age. The 30-day mortality ranged from 4.2% in the 2011/12 season to 8.3% in the 2017/18 season. In children, the 30-day mortality was very low. In adults 15-64 years of age it ranged from 2.1% to 6.4% and from 10.1% and 18.1% in adults ≥ 65 years of age. The highest ICU proportions in adults 15-64 and ≥ 65 years of age were observed in the seasons 2010/11 and 2013/14 dominated by influenza A(H1N1) that also led to the highest 30-day mortality. The highest overall proportion of hospitalisations and 30-day mortality was observed in the 2017/18 season dominated by influenza B/Yamagata.

Conclusions

The 2017/18 season dominated by influenza B/Yamagata caused the highest proportion of hospitalisations and 30-day mortality overall, which was unexpected for influenza B. Proportions of hospitalisations provide a useable measure of severity of influenza and allows for comparison across seasons and potentially between countries with different influenza surveillance systems.

Global seasonal influenza mortality estimates: a comparison of three different approaches.

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Background

Prior to the publication of updated global influenza-associated mortality estimates, the World Health Organization convened an expert consultation on methods to estimate influenza mortality burden. The objectives were to understand the differences in approaches and implication on results of the three most recent influenza mortality projects from 1) United States Centers for Disease Control and Prevention (CDC), 2) the Netherlands institute for Health Service Research (GLaMOR), and 3) the Institute for Health Metrics and Evaluation (IHME).

Methods

The expert panel, which also included representatives from each research group, reviewed and compared methodologies and estimates. We explored differences in data sources, analyses, and model assumptions of each project. We performed a comparison analysis of the estimates from CDC, GLaMOR, and IHME for 183 countries and by three age groups (<65 years, ≥65 years and all ages).

Results

Annual influenza respiratory death counts were similar between CDC (409,111) and GLaMOR (389,213), while the IHME estimate was considerably lower (58,193). The lowest mean fold differences comparing pairwise influenza mortality rate estimates were between CDC and GLaMOR estimates. The highest country-specific influenza mortality rate fold differences were between CDC and IHME estimates and between GLaMOR and IHME estimates were in the Southeast Asia and Eastern Mediterranean regions. CDC and GLaMOR estimated Excess Mortality Rates starting from vital records mortality data for all respiratory causes of death and used the same input data for 30 out of 33 countries included in the analysis. IHME estimated influenza-attributable deaths in the envelope of lower respiratory infection (LRI) mortality starting from a total of 515,000 data points including data from vital records, verbal autopsy and surveillance systems. No overlapping covariates were found across the three models. Elements contributing to the population attributable fraction in the IHME modeling approach might have contributed to a lower influenza mortality estimate.

Conclusions

There is no standard approach to estimate the global influenza mortality burden. The envelope of data used for the calculation is one of the major differences identified (CDC and GLaMOR: all respiratory deaths; IHME: LRI deaths). With the assumption that there is only one cause of death for each death, the IHME estimate represents a fraction of the full influenza-associated respiratory mortality that is measured by the other two groups. There was wide variability of parameters to understand which model features were most likely driving differences. Future collaboration among groups could lead to improvements in modelling methodology and convergence of global estimates.

P5

How much did influenza contribute to the very high excess all cause mortality observed in the 2017/18 season?

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Background

Scotland experienced the highest number of excess all cause mortality deaths during the 2017/18 season since the 1999/2000 season. The mortality occurred in a season dominated by influenza A (H3N2) which disproportionately affected the elderly in a season of low vaccine effectiveness.

Methods

AI.I cause mortality alignment of EuroMOMO, FluMOMO and data linkage of end of season National Records of Scotland (NRS) data will be presented in the context of the correlated Scottish surveillance data to infer the contribution of seasonal influenza to the excess mortality observed

Results

Early warning of the impact of the season was given by the early and increased seasonal outbreaks in care homes. EuroMOMO data revealed consistent z-scores in excess of 10 for those over the age of 65. FluMOMO data suggested that almost all of the excess could be explained by influenza with no contribution of temperature and at most a 20% contribution by unknown confounders. End of season NRS data was data linked revealing the strong correlation of peak influenza surveillance with hospitalisation and mortality but only a minority of deaths had a flu clinical or laboratory diagnosis.

Conclusions

The observational data reveals the strength of association of flu with excess mortality and provides an indicator for future impact of the revised flu vaccine policy implemented in those age 65 or more in future seasons

Pandemic Influenza Severity Assessment (PISA)

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World Health Organisation

Background

The 2009 A(H1N1) pandemic revealed that WHO and national organizations did not have a robust and standardized method for timely assessment of the severity of pandemic influenza. In 2011, the World Health Assembly adopted a report by the Review Committee on the Functioning of the International Health Regulations (2005) and on Pandemic Influenza (H1N1) 2009. The committee recommended that WHO should develop and apply measures that can be used to assess the severity of every influenza epidemic (whether seasonal or pandemic) as part of pandemic preparedness. A severity assessment provides the scientific evidence needed to determine the timing, scale, emphasis, intensity and urgency of response actions. The Global Influenza Programme, with a group of experts, developed the Pandemic Influenza Severity Assessment (PISA) framework. PISA is intended for use by public health professionals at the national level, who plan to perform national influenza severity assessments, and who can contribute to global influenza severity assessments.

Methods

The process of assessing severity at the national level is detailed in the PISA guidance. Influenza severity is defined in terms of three indicators: transmissibility, seriousness of disease and impact. Each indicator is derived from parameters collected by routine surveillance systems (e.g. weekly ILI rate can be used for the transmissibility indicator). Once a country selects appropriate parameters for each indicator, thresholds of activity (low, moderate, etc.) for each are developed using historical data. Current activity is compared to these thresholds to arrive at a qualitative assessment for each indicator. The use of qualitative severity assessments using a country's own historical data allows for comparisons of severity between countries, given differences in surveillance systems.

Results

Anonymized country severity assessments for seasonal influenza epidemics will be graphically presented in several formats, including a heatmap and a map.

Conclusions

In 2017, there was consensus among experts and users that the tool should be rolled out for use in countries and the group identified key priorities: developing a communications strategy to address the need for messages tailored to specific audiences, developing and disseminating training materials to increase country engagement, and refining threshold setting methods for non-temperate countries.

Contribution of influenza to all-cause mortality in Scotland

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Health Protection Scotland

Background

In 2017/18, whilst we saw moderate levels of influenza activity in Scotland overall, a significant increase in all-cause excess mortality was seen during the winter months. To help better understand the contribution of influenza and other respiratory pathogens to the excess mortality seen last season we investigated whether there was a temporal association between the routine respiratory surveillance indicators for respiratory illness and death trends

Methods

Analysis of a temporal relationship between all-cause mortality and influenza activity was undertaken using routine influenza surveillance data described in our weekly HPS Respiratory Reports (<https://www.hps.scot.nhs.uk/resp/seasonalinfluenza.aspx?subjectid=00#report>). We looked at the number of laboratory positive samples for a range of respiratory pathogens (including influenza A & B, streptococcus pneumoniae, streptococcal group A, rhinovirus, adenovirus, coronavirus and respiratory syncytial virus) to compare their relative contribution to winter mortality. We stratified the data into age group with a particular focus on those aged 65-74 years and those aged 75 years above.

Statistical analysis was done using the Pearson's correlation and level of significance was defined at the 0.01 level (2-tailed).

Results

Of those respiratory pathogens reviewed that largest number of deaths were associated with influenza, particularly in those aged 75 years and over. Overall, there was evidence of a statistically significant correlation between the number of deaths due to all-causes and each of the influenza activity indicators reviewed. The number of influenza positive samples correlated best with the number of deaths each week (0.8) closely followed by the number of hospitalisations (0.79). Looking at the relationship between individual influenza types and the number of deaths, the best correlation with number of deaths was for any type of influenza (0.79), followed by Influenza A (0.77) and Influenza A H3N2 (0.74).

Conclusions

The significant temporal association between the different influenza surveillance indicators strongly supports a role of influenza in contributing to the excess all-cause mortality observed last winter in the elderly. The use of laboratory positive influenza detections to predict the number deaths each week during the winter is currently being investigated.

Acute respiratory infections in secondary care versus influenza-like illness in primary care in the Netherlands: hospital incidence peaks first

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Background

Surveillance of acute respiratory infections (ARI) in the Netherlands and other European countries is based mostly on primary care data, with little insight into the severe spectrum of the disease. We analyzed time-trends for ARI in secondary care and influenza-like illness (ILI) in primary care in order to assess the potential value of hospital data for surveillance.

Methods

We calculated the incidence of ARI in secondary care (Leiden University Medical Center) and ILI in primary care (NIVEL Primary Care data base) using two historical databases (2008-2016).

Results

Over eight years, the seasonal incidence peaks of ARI in secondary care occurred earlier than ILI incidence peaks, except during the influenza pandemic season of 2009/2010 and the post-pandemic season of 2010/2011. In the six seasons in which the ARI peak preceded the ILI peak, the median time-lag was eight weeks.

Conclusions

In most seasons, the incidence peaks for ARI in secondary care preceded the peaks for ILI in primary care with a considerable time-lag. This is crucial information for preparedness and emergency control. Adding microbiological test results to these incidence data would be of great value in explaining the whole spectrum of ILI in primary care and ARI in secondary care.

(File attachment not printed - available online)

Screening of Neuraminidase Inhibitor Resistance Markers among Avian Influenza Viruses N3-N9 subtypes

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Background

Several subtypes of avian influenza viruses (AIVs) are emerging as novel human pathogens, and the frequency of related infections has increased in recent years. Although neuraminidase (NA) inhibitors (NAIs) are the only class of antiviral drugs available for therapeutic intervention for AIV-infected patients, studies on NAI resistance among NA subtypes of AIVs other than N1 and N2 have been limited, and markers of resistance are poorly understood.

Methods

We screened NAI resistance substitutions in NA genes of group 1 (N4, N5, and N8) and 2 (N3, N6, N7, and N9) and identified NA substitutions that confer NAI resistance using gene-fragmented random mutagenesis method. We generated libraries of NA mutant influenza viruses in the genetic background of A/Puerto Rico/8/1934 (H1N1) virus using reverse genetics (RG) and selected resistant variants in the presence of the NAIs, oseltamivir carboxylate (OS) and zanamivir (ZA), in MDCK cells. All of 72 substitutions found via OS and ZA screening were evaluated for susceptibility to available NAIs including OS, ZA, peramivir, and laninamivir. In addition, two substitutions, H274Y and R292K (N2 numbering), were introduced into each NA gene for comparison.

Results

We identified three categories of NA substitutions associated with reduced inhibition by NAIs (oseltamivir, zanamivir, and peramivir): (i) novel subtype-specific substitutions in or near the enzyme catalytic site (G/N147V/I, R152W, A246T, A246V, D293N, and I427L N2 numbering), (ii) subtype-independent substitutions (E119G/V and/or D and R292K in group 2), and (iii) substitutions previously reported in other subtypes (Q136K, I222M, R371K and E276D).

Conclusions

Our data show that although some markers of resistance are present across NA subtypes, other subtype-specific markers can only be determined empirically. Therefore, knowledge of these substitutions in AIVs is important in facilitating antiviral susceptibility monitoring of NAI resistance in AIVs.

P10

Rapid and simple colorimetric detection of multiple influenza viruses infecting humans using a Reverse Transcriptional Loop-mediated Isothermal Amplification (RT-LAMP) diagnostic platform

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Background

In addition to the seasonal influenza viruses recently circulating in humans, avian influenza viruses (AIVs) of H5N1, H5N6, and H7N9 subtypes have also emerged and demonstrated human infections with high mortality rates. Although influenza viral infections are usually diagnosed using viral isolation and serological/molecular analyses, the cost, accessibility, and availability of these methods may limit their utility in various settings.

Methods

We have developed and optimized a multiplex detection system for most influenza viruses currently infecting humans including two type B (both Victoria lineages and Yamagata lineages), H1N1, H3N2, H5N1, H5N6, and H7N9 using Reverse Transcriptional Loop-mediated Isothermal Amplification (RT-LAMP) technology coupled with a one-pot colorimetric visualization system facilitating direct determination of results without additional steps. We also evaluated the multiplex RT-LAMP for clinical use using total 135 clinical and spike samples (91 influenza viruses and 44 other human infectious viruses).

Results

We achieved rapid detection of seasonal influenza viruses (H1N1, H3N2, and Type B), and avian influenza viruses (H5N1, H5N6, H5N8, and H7N9) within an hour. The assay can detect influenza viruses with high sensitivity (ie, from 100 to 0.1 viral genome copies) comparable to conventional RT-PCR-based approaches which typically take several hours and require expensive equipment. The assay was capable of specifically detecting each influenza virus (Type B, H1N1, H3N2, H5N1, H5N6, H5N8, and H7N9) with no cross-reactivity to other subtypes of AIVs or other human infectious viruses. Furthermore, 91 clinical and spike samples confirmed by qRT-PCR were also detected by the multiplex RT-LAMP with 98.9% agreement which is also more sensitive than one-step RT-PCR approach (92.3%).

Conclusions

This study suggests that our multiplex RT-LAMP assay may provide a rapid, sensitive, cost-effective and reliable diagnostic method for identifying recent influenza viruses infecting humans, especially in locations without access to large platforms or sophisticated equipment.

C-reactive protein as a biomarker of severe H1N1 influenza

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Background

C-reactive protein (CRP) is an acute-phase reactant downstream of the pro-inflammatory cytokines released during influenza infection. However, the role of this inflammatory marker in influenza severity and complications is yet to be elucidated. We aim to systematically review and evaluate the levels of CRP in severe and non-severe H1N1 influenza cases and assess its utility as a biomarker in predicting the severity of infection.

Methods

We conducted a comprehensive search in Ovid MEDLINE, Ovid MEDLINE (R) Epub ahead of Print, Embase and Embase Classic to identify human studies reporting measurements of CRP levels in patients infected with H1N1 influenza at various levels of disease severity.

Results

Our search identified ten studies eligible for inclusion in this systematic review. The results of the data analysis show that the average CRP levels upon diagnosis were significantly higher ($P < 0.05$) in patients who developed severe H1N1 influenza compared to their counterparts with a no severe disease. Furthermore, levels of CRP were associated with the degree of H1N1 severity. Subjects with H1N1-related pneumonia and patients who were hospitalized or died of the disease complications, respectively, had 1.4- and 2.5-fold significantly higher CRP levels ($P < 0.05$) than those with no severe disease outcome.

Conclusions

CRP levels have been consistently shown to be significantly higher in H1N1 influenza patients who develop a severe disease outcome. The results of the present study suggest that serum CRP can be employed—in combination with other biomarkers—to predict the complications of H1N1 influenza.

The epidemiological and etiological characteristic of influenza and ARVI in the Russian Federation in recent years

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The First I.M. Sechenov Moscow Medical University

Background

Influenza and acute respiratory viral infections (ARVI) owing to their high distribution continue to remain in the center of attention of health care worldwide, including Russia.

Methods

Data of official statistics (form No. 2, form No. 5) and also materials of various publications on influenza problem. The descriptive epidemiological retrospective research is conducted

Results

Annually in Russia 30-34 million cases of influenza and ARVI diseases are registered. Average annual rate of incidence of a ARVI in Russia in 2007 – 2017 have made 0,4%, and the moderate tendency to decrease in incidence with the average annual speed of -2,3% is characteristic of Moscow. The incidence of influenza as in general in Russia, and in Moscow from 2007 to 2017 had the expressed tendency to decrease with the average annual speed of -24,5% and – 27,7% respectively. The coverage vaccination against influenza was 46,6% during an epidemic season of 2017-2018. It is noted that seasonal rise in incidence of ARVI and influenza in Moscow begins for 10-12 weeks earlier, than in Russia in general. The most relevant agents of ARVI are parainfluenza viruses (1-3 types) and adenoviruses. During the last epidemic seasons change of the circulating influenza viruses is observed. So during epidemic seasons of 2009-2010, 2010-2011, 2012-2013 and 2015-2016 the main share was made by a virus of influenza A(H1N1)pdm09 (>50%). During epidemic seasons of 2011-2012, 2014-2015, 2016-2017, 2017-2018 in circulation viruses of influenza A(H3N2) which made more than 50% of the influenza cases confirmed laboratory in different years prevailed (67,8% in 2018). During a season of 2017-2018 among the viruses of influenza characterized at scientifically research institute of the Russian Ministry of Health (1019 strains) 33% were the share of influenza A(H1N1)pdm09, 23% - A(H3N2) and 44,2% of influenza B. All viruses of influenza A(H1N1)pdm09 and A(H3N2) were closely related to vaccinal strains. From all identified influenza B strains 97,8% belonged to the line Yamagata which wasn't a part of vaccines for 2017-2018. And only 10 strains of influenza B (2,2%) have been carried to the Victoria line and were close related to vaccinal strain B/Brisbane/60/2008. Clinical displays of influenza B on severity didn't differ from the diseases caused by a influenza A virus.

Conclusions

In July, 2018 in Russia the domestic quadrivalent influenza vaccine developed by NPO «Petrovaks Pharm» is registered. According to pharmaco-economic studies when replacing 3-valent vaccine on the 4th-valent the predicted number of the prevented cases of influenza for a season of 2018-2019 will be 265,8 thousand cases, the volume of the prevented expenses — more than 2,5 billion rubles.

Estimated type and subtype-specific benefits of influenza vaccination during the 2017-2018 influenza season in the United States

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Centers for Disease Control and Prevention

Background

The severity of the 2017–2018 influenza season in the U.S. was high. Influenza A(H3N2) viruses predominated, but influenza A(H1N1)pdm09 and B viruses also circulated. We estimated the number of vaccine prevented illnesses, medical visits, hospitalizations, and deaths associated with each influenza type and subtype for the 2017–2018 influenza season.

Methods

We used national age-specific estimates of 2017–2018 influenza vaccine coverage, vaccine effectiveness (VE), and burden. We estimated influenza burden using multipliers applied to population-based rates of influenza-associated hospitalizations. We estimated type and subtype-specific burden using virologic data in the inpatient and outpatient setting. We used a compartmental model to estimate numbers, with 95% credible intervals (CrI), of influenza-associated outcomes prevented by vaccination.

Results

Of an estimated 48 million influenza-associated illnesses in 2017–2018, 58% were due to A(H3N2), 10% due to A(H1N1)pdm09, and 32% due to B viruses. A(H3N2) viruses accounted for 67% of hospitalizations and deaths in those ≥ 65 years, but 45–52% of hospitalizations in those aged < 65 years. Overall, we estimate that influenza vaccination prevented 7.1 million (95% CrI: 5.4 million–9.3 million) illnesses, 3.7 million (95% CrI: 2.8 million–4.9 million) medical visits, 109,000 (95% CrI: 39,000–230,000) hospitalizations, and 8,000 (95% CrI: 1,100–21,000) deaths. Vaccination prevented 10% of expected hospitalizations overall, 6% of hospitalizations related to A(H3N2), 16% of hospitalizations related to A(H1N1)pdm09, and 16% related to B. Among young children (aged 6 months–4 years) who had the highest VE against each influenza virus (sub) type, vaccination prevented 31% of hospitalizations related to A(H3N2), 51% related to A(H1N1)pdm09, and 50% related to B.

Conclusions

Despite suboptimal VE, we estimate that influenza vaccination reduced a substantial burden of illnesses, medical visits, hospitalizations, and deaths associated with multiple influenza (sub) types in the U.S. during the 2017–2018 season. Given the co-circulation of multiple influenza viruses and the variable VE against each (sub)type, our results demonstrate the benefit of annual influenza vaccination.

Influenza Monitoring and Forecasting Using Participatory Web-based Data

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Background

Monitoring and forecasting the evolution of influenza activity can help in early detection and early response to minimize the impact of seasonal influenza epidemics. However, the traditional practices of influenza surveillance are generally affected by several issues, which contribute to hinder the potential impact of many studies. On the other hand, the recent availability of novel digital data streams has fuelled the emergence of non-traditional approaches to complement the traditional surveillance by capturing a high-resolution digital signal of the influenza activity in the population. In this context, a participatory Web-based surveillance system called Influenzanet monitors seasonal influenza epidemics in Europe in a cohort of individuals who self-report their health status through Internet-based surveys. Here we propose an overview of previously published studies in which we showed how Influenzanet represents a powerful tool for monitoring, modelling and forecasting the epidemic spread of seasonal influenza in near real-time.

Methods

Firstly, the data collected by Influenzanet are assessed in terms of representativeness of the participants compared to the general population and quality of the influenza-like illness (ILI) indicators compared to the traditional surveillance data. Then, the Influenzanet data are employed as input of both statistical and mechanistic models to provide real-time predictions of seasonal influenza activity up to four weeks in advance for several countries in Europe.

Results

Influenzanet counts about 35 thousand participants every influenza season, allowing to compute the weekly ILI incidence in good agreement with the traditional surveillance data and thus representing a powerful and innovative seasonal influenza monitoring system. The integration of Influenzanet data into linear autoregressive models allows to improve real-time forecasts of seasonal influenza activity, by increasing the Pearson's correlation up to 30% and by reducing the Mean Absolute Error up to 43% for the four weekly time horizons. In addition, our computational framework based on a mechanistic model called GLEAM and initialized with Influenzanet data, allows to provide quantitative projections of the spatio-temporal evolution of seasonal influenza epidemics and accurate predictions up to two weeks ahead the peak of the influenza season. Furthermore, in 2014 we launched a Web-platform called FluOutlook (www.fluoutlook.org) as a tool to disseminate to public health agencies the real-time influenza forecasts based on both forecasting approaches.

Conclusions

Our studies highlight the benefits of harnessing participatory Web-based surveillance data to significantly improve influenza monitoring and forecasting.

Understanding respiratory syncytial virus disease burden and mortality to inform future vaccination strategies

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Background

With the development of effective vaccines against respiratory syncytial virus (RSV) disease on the horizon, understanding the disease burden and mortality associated with this severe illness is critical in informing future vaccination strategies and their potential public health impact. The aim of this analysis was to review RSV disease and mortality patterns in Scotland during the period of 2009/10 to 2017/18.

Methods

Data for laboratory positive detections for RSV were reviewed using routine surveillance outputs from ECOSS (Electronic Communication of Surveillance in Scotland). Through linkage of laboratory positive detections with death information from the National Records for Scotland, 30-day crude mortality rates were calculated.

Results

RSV disease trends showed a distinct seasonal pattern with the peak week varying between week 46 and 52. The age group most affected was those aged under 5 years of age, however, increases were seen in older age groups, particularly those aged 65 years and over. The 30-day crude mortality rate varied over time, peaking at 23.4% in 2014/15 and falling thereafter to between 10-15%.

Conclusions

These results are important in informing future vaccine strategies for RSV illness. Further analysis undertaking linkage of laboratory detections with hospitalisation data is important to quantify RSV disease burden in secondary care and inform the potential public health impact of RSV vaccination.

Measuring the impact of influenza vaccination programmes among the elderly population in Spain, the Netherlands and Portugal, 2015 – 2018

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Background

Little is known about the number of influenza-associated events prevented by influenza vaccination among the elderly in the European Union. Measuring these would allow a better understanding of the overall impact of influenza vaccine programme, particularly in seasons with low influenza vaccine effectiveness (IVE). We measured the number of medically attended influenza-confirmed cases primary care (MAICC) among the ≥ 65 years averted by influenza vaccination programmes in Spain, the Netherlands and Portugal, from 2015 to 2018.

Methods

A common protocol was developed for measuring influenza vaccine programme impact in the elderly. In each season we compared the number of observed MAICC events (n) to the estimated number that would have occurred without the vaccination programme (N). To estimate N , we used: 1) Number of MAICC estimated from national influenza sentinel surveillance systems; 2) Influenza vaccination coverage (VC) ; 3) Type/subtype-specific IVE estimates from MOVE+ multicentre primary care studies, pooled across the 2015–18 influenza seasons, and weighted by country-specific type/subtype distribution of circulating seasonal virus. We estimated number of MAICC averted events ($NAE = N - n$), number needed to vaccinate (NNV) to prevent one MAICC, and MAICC prevented fraction (PF).

Results

The season average number of MAICC was 6,000, 42,000 and 43,000 MAICC in Portugal, the Netherlands and Spain, respectively. Influenza VC in the elderly was 50% in Portugal, 51–56% in Spain and 60–66% in the Netherlands. IVE was between 34% and 41% in 2015–16 (A(H1N1)pdm09 predominant season), 8% and 10% in 2016–17 (A(H3N2) predominant season) and 19% and 24% in 2017–18 (B predominant season with co-circulation of A(H3N2) and A(H1N1)pdm09). The NAE annual average was 29, 61 and 204 MAICC per 100,000 elderly population in Portugal, Spain and the Netherlands, respectively, with some seasonal variation. The NNV annual average ranged between 458, 741 and 1824 doses in the Netherlands, Spain and Portugal, respectively. On average, influenza vaccination prevented each season 9%, 12% and 14% of potential influenza MAICC in Portugal, Spain and the Netherlands, respectively.

Conclusions

Even with low IVE and suboptimal VC uptake among the elderly, our results suggest that influenza vaccine programmes could reduce influenza-related outcomes. These results, together with ongoing studies on hospitalisations and deaths averted by the influenza vaccination programme, will be determinant to evaluate the impact of national vaccination strategies and strengthen public health communication with the general public and policy makers.

Hospitalisation of adult influenza patients costs the Dutch healthcare system annually 28 million euros

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Background

Influenza virus infections cause a high disease and economic burden during seasonal epidemics. However, there is still a need for reliable disease burden estimates to provide a more detailed picture of the impact of influenza. Therefore, the aim of this study is to estimate the incidence of hospitalisation for influenza virus infection and associated hospitalisation costs in adult patients in the Netherlands during one influenza season.

Methods

We conducted a retrospective study in adult patients with a laboratory-confirmed influenza virus infection in three Dutch hospitals during respiratory season 2014-2015. Incidence was calculated as the weekly number of hospitalised influenza patients divided by the total population in the catchment populations of the three hospitals. Arithmetic mean hospitalisation costs per patient were estimated and included costs for emergency department consultation, diagnostics, general ward and/or intensive care unit admission, isolation, antibiotic- and/or antiviral treatment. These hospitalisation costs were extrapolated to national level and expressed in 2017 euros.

Results

The study population consisted of 249 hospitalised adult influenza patients. The seasonal cumulative incidence was 3.5 cases per 10,000 persons in respiratory season 2014-2015. The arithmetic mean hospitalisation cost per influenza patient was €6,128 per patient in 2014-2015, resulting in total hospitalisation costs of €28 million in 2014-2015.

Conclusions

For the first time, we provide seasonal cumulative incidence of adult hospitalised influenza patients in the Netherlands. Hospitalisation costs of adult influenza patients, estimated at 28 million euros annually, constitute a considerable economic burden for the Dutch healthcare system.

(File attachment not printed - available online)

Predictors and Outcomes of Hospitalization for Influenza among High Risk Patients: Real World Evidence from the United States Medicare Population

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Background

Because treatment of influenza may be more effective if initiated sooner, it is important for healthcare providers to identify appropriate patients for treatment at time of diagnosis. This study identifies predictors of initial hospitalization and describes outcomes of high-risk (HR) patients hospitalized with influenza.

Methods

Data were from years 2010-2015 of the US Medicare 5% national sample administrative database. Patients had ≥ 1 diagnosis of influenza, were aged ≥ 13 years, and had continuous health plan enrollment for 6 months before (baseline) and 3 months after influenza diagnosis (follow-up). Patients who died in the follow-up period were included. HR was defined as aged ≥ 65 years or having chronic lung disease, cardiovascular or cerebrovascular disease, or weakened immune system during baseline. Predictors of initial hospitalization vs. not hospitalized in the follow-up period were determined with logistic regression.

Results

Among HR patients, 8127 were initially hospitalized and 16,784 were not hospitalized. HR patients were more likely to be hospitalized if diagnosed in an emergency room (59%) vs. physician's office (4%). Of HR patients initially hospitalized, 40% had chronic obstructive pulmonary disease (COPD), 29% had congestive heart failure (CHF), and 23% had chronic kidney disease. These comorbidities were among the strongest predictors of hospitalization [COPD (OR: 2.05; 95% CI: 1.87-2.23), CHF (OR: 1.76; 95% CI: 1.61-1.92), and CKD (OR: 1.60; 95% CI: 1.44-1.76)]. Other significant predictors included older age, being male, greater comorbidity burden, and higher baseline healthcare resource use. Among HR patients initially hospitalized with influenza, 30% received care in the ICU, 6% received invasive mechanical ventilation, and 6% received non-invasive mechanical ventilation. Median length of stay was 5.0 days. All-cause mortality was 5.1% during inpatient stay and 9.2% within 30 days of diagnosis. At discharge, 25% were transferred to a skilled nursing facility. Thirty-day readmission rate was 14%.

Conclusions

To obtain the best outcomes, it is important that healthcare providers identify patients with influenza who need more than current standard of care at time of diagnosis. Emergency departments are likely to be the first point of care for HR patients. Predictors that can help identify these patients are older age, greater comorbidity burden, and diagnosis of COPD, CHF, or CKD.

Interim results from a large, European, multi-centre study of community-acquired acute respiratory infections

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Background

Acute respiratory infections are considered the most likely candidates to cause the next pandemic. To strengthen preparedness for a respiratory pandemic the EU-funded Platform for European Preparedness Against (Re-) emerging Epidemics (PREPARE) has established the Multi-centre, European study of MAJOR Infectious Disease Syndromes - Acute Respiratory Infections (MERMAIDS-ARI). To improve our ability to assess disease severity, MERMAIDS-ARI recruits ARI patients simultaneously from primary and secondary care.

Methods

The MERMAIDS-ARI study runs from 2014 – 2019 and is currently recruiting adults presenting with ARI in primary care and hospitals across eight European countries (Croatia, Germany, Ireland, the Netherlands, Poland, Romania, Spain, UK). Main study objectives are to identify host and pathogen related determinants of severity of ARI and describe the aetiology, clinical management and outcomes.

Results

Recruitment (as of 30 Sept 2018): n=1,110, primary care (n=447), hospital (n=663) sites. Female: Male ratio 0.9:1, Age, median: 54 (18-93) years. Antibiotics were given to 34% (n=153/447) of primary; 88% (n=582/663) of hospital patients, antivirals to 6% of primary (n=29/447); 29% (n=191/663) of hospital patients and corticosteroids to 7% (n=30/447) of primary; 43% (n=283/663) of hospital patients. CRB65 scores ranged from 0 to 2 in primary care vs. 0 to 4 in hospital patients; PSI risk scores ranged from I to IV in primary vs. I to V in hospital patients. Preliminary data shows that of 889 patient samples analysed, 51% (n=452) were diagnosed with viral infections, of which 48% (n=215/452) were diagnosed with influenza (Infl. A: 52% (n=112/215); Infl. B: 48% (n=103/215)). Detailed data on demographics, severity, clinical management and outcomes in patients presenting with influenza and other pathogens will be presented.

Conclusions

MERMAIDS-ARI is a multi-country, prospective research study that uniquely recruits patients simultaneously from both primary and secondary care. MERMAIDS-ARI is a potential platform for real-time evaluation of ARI and influenza severity in Europe.

VUMC and AMC.

Influenza pandemic preparedness in South Africa (SA) in context of the International Health Regulations (IHR) - Joint External Evaluation (JEE)

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Background

Influenza ranks among the top 5 in the disease prioritization list in SA. However, due to other diseases such as HIV and TB, influenza is not prioritized. In 2011, a WHO IHR Review Committee concluded that the world is ill-prepared to respond to a severe influenza pandemic. Therefore, WHO launched the JEE for countries to systematically evaluate their preparedness and response capacities and address the gaps identified.

We aimed to describe pandemic preparedness in SA, in context of the JEE, conducted in December 2017.

Methods

A national team conducted an internal assessment of the country's core capacities using a score range of 1 to 5 (1= no capacity, 2=limited capacity, 3=developed capacity, 4=demonstrated capacity and 5=sustained capacity); all responses were supported by evidence. This was followed by the JEE, led by WHO.

We report on technical areas considered most relevant for pandemic preparedness: coordination, zoonotic diseases, laboratory, surveillance, preparedness, medical countermeasures, risk communication and points of entry (POEs).

Results

Coordination scored 4; this mechanism was tested through actual events and simulation exercises. Zoonotic diseases scored 4; collaboration between human and animal health was recognised as a best practice. Laboratory testing for detection scored 4; SA has advanced human and animal health laboratory systems with the only BSL-4 laboratory on the continent. The national laboratory supports several countries in diagnosis, training etc. Indicator and event based surveillance systems scored 3; linking human and animal health surveillance systems need strengthening. Preparedness and response plans scored 2; SA has several structures for preparedness with strong stakeholder engagement incorporating One Health concepts. For Emergency Response Operations: Activation scored 2, Emergency Operations Centre (EOC) Plans scored 2, Emergency Operations Programme scored 4 and Case Management Procedures scored 4. The EOC needs devolution and needs to include all hazards.

Medical countermeasures scored 2; SA needs a comprehensive plan especially for pandemic preparedness where drugs and vaccines need rapid deployment. Risk communication scored 3 and need strengthening through training and simulation exercises. POE scored 4; designation of ground crossings was recognised as a best practice.

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