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The relationship between influenza medical risk factors and age

Technical report
March 2017

Public Health Ontario

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Disclaimer

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Executive summary

Purpose and methods

This technical report assesses the relationship between of medical risk factors for influenza complications and age. The information will assist with determining how to target promotional efforts within influenza immunization programs, specifically, whether to focus promotion to audiences based on age, medical risk factors or a combination of both. This report consists of three parts:

- An analysis of the prevalence of medical conditions that increase the risk for influenza complications in different age groups using administrative data from Ontario held by the Institute for Clinical Evaluative Science**.**
- An analysis of the relationship between influenza medical risk factors and age with respect to hospitalizations and deaths based on information from the integrated Public Health Information System (iPHIS).
- A literature review of the relationship between influenza medical risk factors and age with respect to hospitalizations and deaths.

The analyses were confined to adults; analyses of age and medical risk factors for children were out of scope for this review.

Results

The prevalence of medical risk factors in Ontario increases progressively with age as follows:

- 20-64 years: 30%
- ≥50 years: 53%
- ≥65 years: 70%

With regard to determining the relationship between age and medical risk factors for influenza complications, the iPHIS analysis and literature review both suggested that in older age groups, such as those 65 years of age and over, age itself appears to be a risk factor for influenza complications, in addition to underlying medical conditions. In younger age groups, medical risk factors are more important contributors to influenza complications.

Implications of the findings

Promotional efforts to prevent complications should be targeted both to those 65 years of age and older and those with medical risk factors. It is important to note that almost one-third of individuals 20 to 64 years of age have underlying medical risk factors for influenza complications.

Introduction

This technical report assesses the relationship of risk factors for influenza complications and age. The information provided in this report will assist with determining how to target influenza vaccination promotional efforts, specifically whether to focus on promotion by age, medical risk factors or a combination of both. This report consists of three parts:

- An analysis of the prevalence of medical conditions that increase the risk for influenza complications in different age groups based on Ontario data.
- An analysis of the relationship between influenza medical risk factors and age with respect to hospitalizations and deaths based on information from the integrated Public Health Information System (iPHIS).
- A literature review of the relationship between influenza medical risk factors and age with respect to hospitalizations and deaths.

The analyses in this report were confined to adults; analyses of age and medical risk factors for children were out of scope for this review.

Definition of medical conditions that increase the risk of influenza complications

Throughout this report, the following terms are used interchangeably in relation to medical conditions that increase the risk for influenza-related complication: risk factors, risk group, medical risk factors, high risk condition, underlying medical conditions, and comorbidities. In the first two sections, medical conditions that are considered risk factors for influenza complications are based on the recommendations of the National Advisory Committee on Immunization (NACI).[1] It is recognized that some medical risk factors are associated with higher risks of influenza complications than others; however for the purposes of this document, medical risk factors are considered as a group. The evidence for and the relative risk of each of the risk groups have not been reviewed.

An analysis of the prevalence of influenza and related complication risks

This section provides an analysis of the prevalence of medical conditions in different age groups that increase the risk for influenza complications based on Ontario data.

Methods

Using a standard SAS macro for randomly selecting records from a dataset, a random sample of 10% of people aged ≥20 years who were alive and eligible to receive publicly funded health insurance on July 1, 2013 was selected without replacement from Ontario's Registered Persons Database. This sample was linked to health administrative databases housed at the Institute for Clinical Evaluative Sciences (ICES) in order to identify individuals ≥20 years who had medical conditions that the National Advisory Committee on Immunization (NACI)[1] has deemed to be risk factors for serious influenza infections. The list of conditions, data sources, and definitions are outlined in Table 1. To correspond to the use of 10% of the Registered Person Database, 10% of the 2013 Census estimate was used as the denominator. The following adult age groups were considered: 20-29, 30-39, 40-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, and ≥85 years. Pregnancy and morbid obesity (BMI ≥ 40) are two high risk conditions designated by NACI that were not available through the databases used in this analysis and hence were excluded from the analysis.

Results

Results of the prevalence of medical conditions by age are provided in Table 2. A summary of selected medical conditions is also presented in Figure 1. Overall, 38.2% of adults aged ≥20 years in Ontario had at least one medical condition considered to be a risk factor for influenza complications. This percentage increased progressively with age and was 30.4% for those aged 20-64 years, 53.2% for those aged ≥50 years and 70.1% for those aged ≥65 years. The most prevalent risk factor was asthma for younger adults aged 20-64 years (13.8%) and diabetes (30.1%) for older adults aged ≥65 years. At least one cardiovascular condition occurred in 27.6% of older adults aged ≥65 years. With the exception of asthma, the prevalence of all risk factors increased with age.

Discussion

Just under one-third of individuals aged 20 to 64 years and just over half of those aged ≥50 years have a medical condition that puts them in a high-risk group based on NACI recommendations for influenza vaccination. This proportion increases to 70% for those aged ≥65 years.

The Centers for Disease Control and Prevention in the United States quoted a rate of medical risk factors for those 50 to 64 years of age of 34%, based on a study published in 2003[2], rates that are somewhat lower than those found in the ICES analysis of Ontario data. Additional validation of Ontario's results should be considered for future analyses.

This analysis did not include pregnancy or morbid obesity, two risk conditions for which NACI recommends vaccination. The Canadian Health Measures Survey from 2007 to 2009 estimated that 3.0% (95% CI: 2.3% to 3.7%)[3] of the population was morbidly obese (defined as Obesity Class III).[4] The prevalence of pregnancy during influenza season was estimated to be 1.1% of the population aged ≥12 years in a recent study.[5] Some individuals with morbid obesity may already be included in other medical risk factors for influenza complications captured by this analysis, so excluding this group from the analysis may not lead to considerable underestimation of the prevalence of medical risk factors. Pregnant women are less likely to have other medical risk factors for influenza complications; therefore, exclusion of pregnant women likely underestimates the prevalence of underlying risk factors for influenza complications for those aged 15 to 49 years.

Table 1: Databases and codes used to define medical conditions

Medical condition	Definition
Asthma	Asthma database was used to identify patients with asthma, based on 2 or more ambulatory care visits and/or 1 or more hospitalizations[6] OHIP OHIP diagnostic code: 493 CIHI-DAD ICD-9 diagnostic code: 493 ICD-10 diagnostic codes: J45, J46
Chronic obstructive pulmonary disease (COPD)	COPD database was used to identify patients with COPD, based on 1 or more ambulatory care visits and/or 1 or more hospitalizations. Algorithm to identify COPD patients were only validated in those ages 35 and over.[7] OHIP OHIP diagnostic codes: 491, 492, 496 CIHI-DAD ICD-9 diagnostic codes: 491, 492, 496 ICD-10 diagnostic codes: J41, J42, J43, J44
Diabetes	ODD was used to identify patients with diabetes, based on 2 OHIP diagnostic codes or 1 OHIP service code or 1 CIHI admission within 2 years[8]

Medical condition	Definition
	OHIP OHIP diagnostic code: 250 OHIP service codes: Q040, K029, K030, K045, K046 CIHI-DAD, CIHI-SDS ICD-9 diagnostic code: 250 ICD-10 diagnostic codes: E10, E11, E13, E14
Anemia	ACG macro was used to identify patients in OHIP, CIHI-NACRS, and CIHI-DAD with any mention of anemia in the 3 years prior to index date[9]
Cancer	OCR was used to identify patients with any cancer diagnosed in Ontario except for non-melanoma skin cancer[10]
Chronic kidney disease (CKD)	Patients with a diagnosis of CKD in the 5 years before index date, using the following diagnostic codes[11]: OHIP OHIP diagnostic codes: 403, 585 CIHI NACRS, CIHI-DAD ICD-10 diagnostic codes: E102, E112, E132, E142, I12, I13, N08, N18, N19
	Patients who were on chronic dialysis[12] in the year before index date, identified as those with at least 2 of any of the following codes in OHIP, CIHI-DAD, or CIHI-SDS separated by at least 90 days, but less than 150 days OHIP OHIP service codes: R849, G323, G325, G326, G860, G862, G865 G863, G866, G330, G331, G332, G333, G861, G082, G083, G085, G090, G091, G092, G093, G094, G095, G096, G294, G295, G864, H540, H740 CIHI-DAD, CIHI-SDS CCI procedure codes: 5195, 6698 CCP procedure code: 1PZ21 CORR Treatment codes: 060, 111, 112, 113, 121, 122, 123, 131, 132, 133, 141, 151, 152, 211, 221, 231, 241, 242, 251, 252, 311, 312, 313, 321, 322, 323, 331, 332, 333, 413, 423, 433, 443, 453 ORRS Patients included in ORRS

Medical condition	Definition
	Exclusion criteria: Patients with kidney transplants[13]: OHIP OHIP service codes: S435, S434 CIHI DAD CCP procedure code: 6759 CCI procedure code: 1PC85 CORR **Treatment code:** 171 plus one or more of Transplanted Organ Codes (1-3): 10, 11, 12, 18, 19 ORRS Type of event during patient care: Transplanted (tx) (Note: ORRS data only available for 2010 and onwards.)
Immuno-compromised	ACG macro was used to identify patients in OHIP, CIHI-NACRS, and CIHI-DAD with any mention of disorders of the immune system in the 3 years prior to index date[9] In addition, those identified using the following databases and definitions: ODB 30 days of oral corticosteroids in the past 6 months, antineoplastic use in the past 6 months, or use of another immunocompromising drug in the past 6 months CORRLINK CORRLINK is a dataset in ICES which links CORR and CIHI-DAD data. This database only includes patients that have received an organ transplant and does not include dialysis patients. HIV HIV database was used to identify patients with HIV, based on 3 physician claims in 3 years with OHIP diagnostic codes: 042, 043 or 044[14]
Dementia	1 hospitalization for dementia or 3 ambulatory visits for dementia, each separated by at least 30 days, within 2 years or 1 prescription from ODB[15] OHIP OHIP diagnostic codes: 290, 331 CIHI-DAD, CIHI-SDS

Medical condition	Definition
	ICD-10 diagnostic codes: F00, F01, F02, F03, G30 ODB 1 prescription for a cholinesterase inhibitor
History of congestive heart failure (CHF)	CHF database was used to identify patients with CHF, based on 1 CIHI NACRS, CIHI-DAD, CIHI-SDS, or OHIP claim and a second claim (from either) in 1 year. The CHF database is limited to those 40 years of age or older.[16] OHIP OHIP diagnostic code: 428 CIHI-DAD, CIHI-SDS ICD-9 diagnostic code: 428 ICD-10 diagnostic codes: I500, I501, I509
History of TIA or Acute Ischemic Stroke	Transient Ischemic Attack: CIHI-DAD and CIHI-NACRS were used to identify patients with a history of a transient ischemic attack, based on at least 1 hospitalizations or ED visit with a diagnosis coded with one of the following codes: ICD-9 diagnostic codes: 435, 3623 ICD-10 diagnostic codes: G450, G451, G452, G453, G458, G459, H340 Acute Ischemic Stroke:[17] CIHI-DAD was used to identify patients with a history of acute ischemic stroke, based on at least 1 hospitalization with a main diagnosis coded with one of the following codes: ICD-9 diagnostic codes: 434, 436 ICD-10 diagnostic codes: I63 (excluding 163.6), I 64, H34.1
History of cardiovascular (blockage) conditions or interventions	CIHI-DAD and CIHI-NACRS were used to identify patients with a history of a cardiovascular (blockage) condition or intervention, based on at least 1 hospitalizations or ED visit with a diagnosis or procedure coded with one of the following codes: Angina: ICD-9 diagnostic codes: 411, 413, 4298 ICD-10 diagnostic codes: I20, I2382, I24 Chronic Ischemic Heart Disease: ICD-9 diagnostic codes: 412, 4140, 4141, 4148,4149, 4292 ICD-10 diagnostic codes: I25 Myocardial infarction:

Medical condition	Definition
	ICD-9 diagnostic codes: 410 ICD-10 diagnostic codes: I21, I22 Coronary Artery Bypass Grafting:[18] CCI procedure codes: 1IJ76, 1IJ80 CCP procedure codes: 481, 4899 Percutaneous Coronary Intervention:[18] CCI procedure codes: 1IJ26, 1IJ50, 1IJ55, 1IJ57 CCP procedure codes: 4802, 4899, 4804
History of cardiovascular (rhythm) conditions or interventions	CIHI-DAD and CIHI-NACRS were used to identify patients with a history of a cardiovascular (rhythm) condition or intervention, based on at least 1 hospitalizations or ED visit with a diagnosis or procedure coded with one of the following codes: Atrial Fibrillation/Atrial Flutter: ICD-9 diagnostic codes: 4273 ICD-10 diagnostic codes: I48 Ventricular Arrhythmia & Tachycardia: ICD-9 diagnostic codes: 4271, 4274, 4276, 4278 ICD-10 diagnostic codes: I470, I472, I490, I493 Permanent Pacemaker:[19, 20] CCI procedure codes: 1HZ53GRNM, 1HZ53LANM, 1HZ53GRNK, 1HZ53LANK, 1HZ53GRNL, 1HZ53LANL CCP procedure code: 4971 Implantable Cardioverter- Defibrillator:[21] CCI procedure codes: 1HZ53GRFS, 1HZ53LAFS, 1HZ53SYFS, 1HZ53HAFS CCP procedure codes: 4974

Abbreviations:

OHIP – Ontario Health Insurance Plan

CIHI – Canadian Institute of Health

DAD – Discharge Abstract Database

NACRS – National Ambulatory Care Reporting System

SDS – Same Day Surgery

CCI – Canadian Classification of Health Interventions

CCP – Canadian Classification of Procedures

CORR – Canadian Organ Replacement Register

ORRS – Ontario Renal Reporting System

ODD – Ontario Diabetes Database

ACG – Adjusted Clinical Groups®

OCR – Ontario Cancer Registry

OMID – Ontario Myocardial Infarction Database

CHF – Ontario Congestive Heart Failure Database

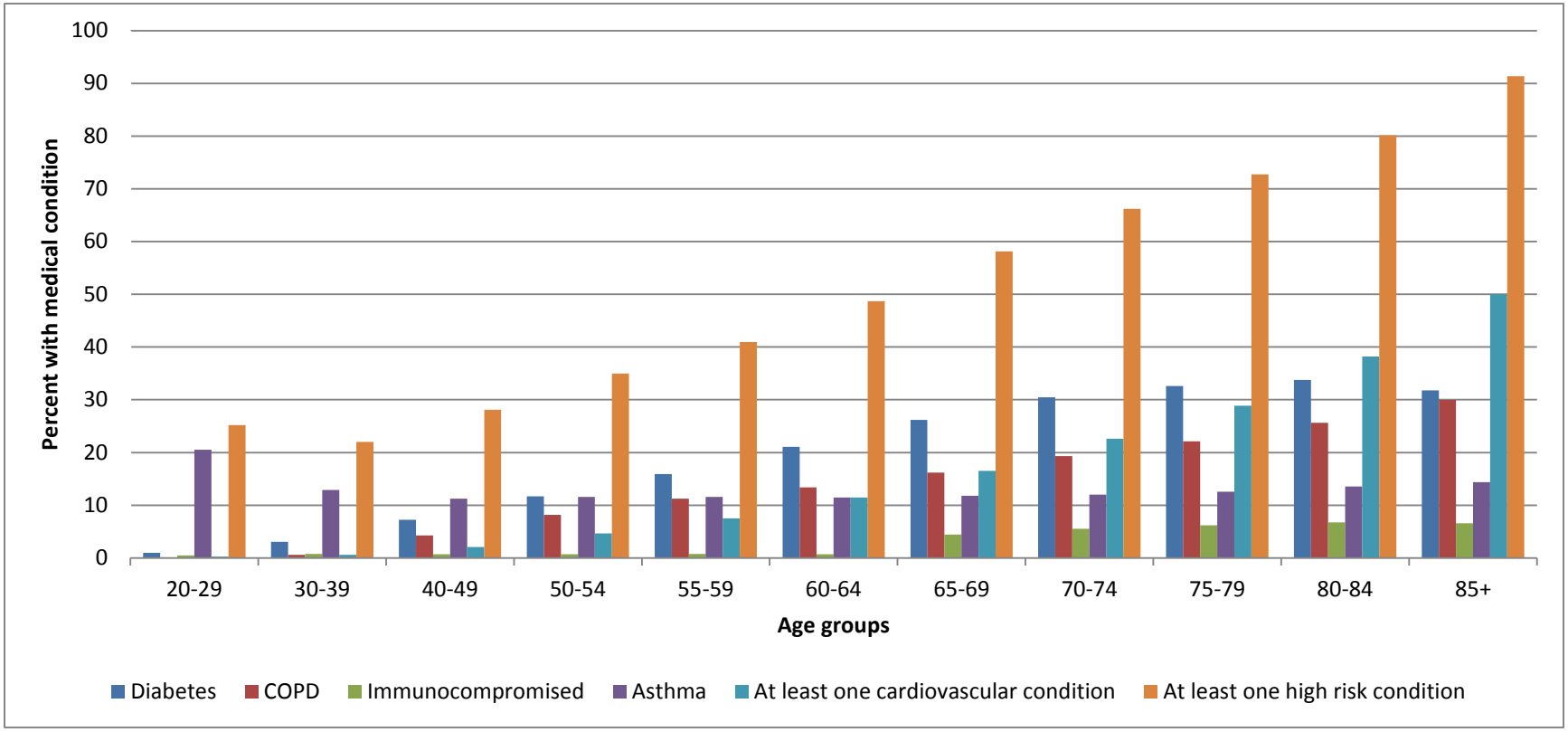
ODB – Ontario Drug Benefit

HIV – Ontario HIV database

Table 2: Prevalence of medical conditions by age of condition per 1,000 population

Age group	Asthma	COPD	Diabetes	Anemia	History of Cancer	Chronic Kidney Disease	Immuno-compromised	Dementia	History of Congestive Heart Failure	History of TIA or Stroke	Angina/Chronic Ischemic Heart Disease/ Myocardial Infarction/ CABG/PCI	Atrial fibrillation/ Atrial flutter/ Ventricular Arrhythmia & Tachycardia /PPM/ICD	At least one cardiovascular condition	At least one high-risk condition
20-29	205.0	N/A	9.9	38.2	3.6	2.7	4.9	0.1	N/A	0.4	0.5	1.8	2.6	252.1
30-39	129.0	5.7	30.7	52.6	9.4	4.6	7.7	0.4	N/A	0.8	1.9	3.8	6.2	220.3
40-49	112.7	42.5	72.5	60.9	20.7	7.4	7.3	0.7	2.7	2.4	11.2	6.9	20.6	280.8
50-54	115.9	81.9	117.0	51.0	36.9	11.0	7.2	1.3	7.8	5.8	29.9	12.1	46.7	349.5
55-59	114.5	112.3	159.1	43.3	55.1	15.9	7.5	2.1	15.0	9.2	50.8	18.5	75.3	409.7
60-64	118.0	133.9	210.6	51.3	80.0	23.9	7.2	4.3	24.8	14.9	78.0	30.6	114.9	486.9
65-69	120.4	161.8	261.7	69.4	117.1	34.2	44.6	10.6	40.0	24.4	110.1	48.3	165.3	581.5
70-74	125.8	193.2	304.5	91.3	154.1	55.2	55.6	24.4	63.8	34.1	148.9	76.4	225.9	662.3
75-79	128.8	221.0	326.0	118.0	182.4	77.7	62.2	58.5	91.5	50.5	182.9	108.1	288.8	727.6
80-84	135.5	256.5	337.4	151.2	214.9	106.6	67.5	124.1	144.6	75.1	225.0	166.5	381.8	801.5
85+	144.0	299.8	318.0	174.2	233.3	120.3	65.9	249.2	241.9	116.0	265.6	225.6	500.0	913.6
Total (20-64)	137.8	46.6	78.0	50.0	26.0	8.7	6.9	1.1	5.6	4.0	19.9	9.3	31.8	304.1
Total (50+)	121.3	150.9	218.3	73.8	102.2	38.3	28.1	30.9	49.3	26.9	100.5	55.8	160.2	532.2
Total (65+)	128.3	210.9	301.0	108.3	166.2	68.2	56.3	69.5	95.8	50.4	168.5	105.2	275.5	700.5
Total (20+)	136.0	78.9	121.8	61.4	53.5	20.4	16.6	14.5	23.4	13.1	49.1	28.2	79.7	382.0

Figure 1. Prevalence of selected medical conditions by age



The relationship between influenza medical risk factors and age with respect to hospitalizations and deaths

This section provides an analysis of the relationship between influenza medical risk factors and age on hospitalizations and deaths based on information from the integrated Public Health Information System (iPHIS).

Methods

Data source

The data source used for this analysis was the integrated Public Health Information System (iPHIS), the database populated by Ontario's 36 public health units to track and manage cases of reportable diseases. All laboratory-confirmed cases of influenza diagnosed in Ontario residents are reportable and therefore captured in iPHIS. iPHIS is a dynamic disease reporting system which allows ongoing updates to data previously entered. As a result, data extracted from iPHIS represent a snapshot at the time of extraction and may differ from previous or subsequent reports.

Inclusion criteria

Laboratory confirmed cases of influenza from iPHIS were included if:

- They were residents of Ontario;
- They were age 20 or older;
- Their symptom onset date was between September 1, 2010 and August 31, 2015 which spans the five influenza seasons from 2010-2011 to 2014-2015; and
- There was evidence they were followed up for risk factor information

Evidence of risk factor information was determined by including cases who had any response (i.e., "yes", "no", "unknown") for one or more risk factor fields in the iPHIS database. Anyone with no response (i.e., blank) for all risk factor fields was assumed to not have been followed up and was therefore excluded from the analysis.

Risk factors

There are many risk factor fields in iPHIS; only some were considered relevant for complications from influenza. Selected risk factors were generally consistent with those identified by National Advisory Committee on Immunization (NACI) in "Statement on Seasonal Influenza Vaccine for 2015-16."[1]

Selected risk factors include the following conditions, which are collectively referred to as "medical risk factors" in the results section of this document:

- Anemia
- Asthma
- Cancer
- Chronic kidney disease
- Dementia
- Developmental disability
- Diabetes
- History of cardiovascular disease
- History of stroke or transient ischemic attack (TIA)
- Immunocompromised
- Living in long-term care
- Neurological conditions
- Obesity
- Respiratory conditions
- Other chronic conditions

Complications

Influenza complications included in this analysis were: hospitalizations, deaths, and hospitalizations and/or deaths. Other complications from influenza were not available.

Statistical analysis

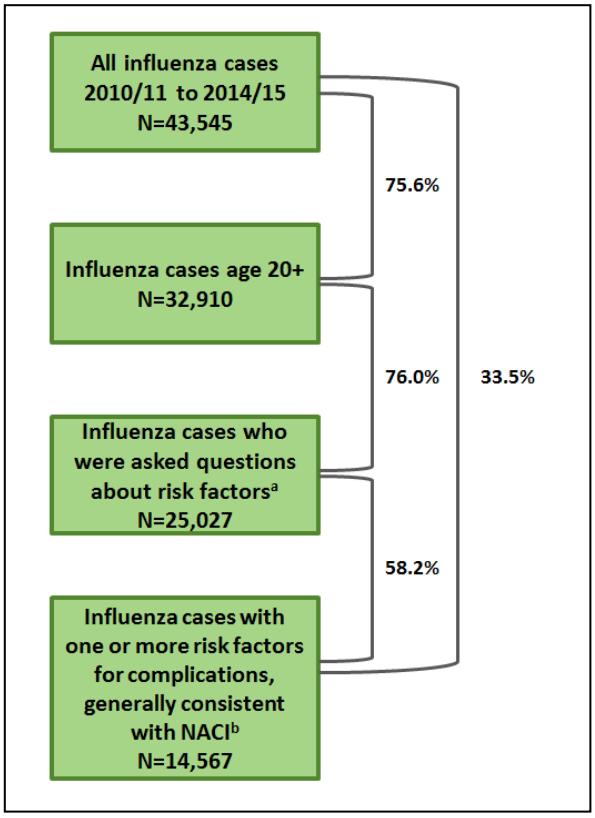
Descriptive analyses were performed and were carried out using SAS version 9.3.

Results

Cases

Figure 2 summarizes the numbers of influenza cases in iPHIS used for this analysis. A total of 43,545 cases of influenza with an onset date between 2010-2011 and 2014-2015 were extracted from iPHIS; 32,910 (75.6%) were age 20 or older. Of those, 25,027 had *any* risk factor information in iPHIS (i.e., a non-blank response for any risk factor). Considering only those risk factors generally consistent with NACI, 14,567 had one or more risk factors for complications from influenza.

Figure 2. Number of influenza cases in iPHIS retained based on the inclusion criteria



Notes for Figure 2:

a. Defined as cases who had a non-blank response (includes "yes," "no" or "unknown") for any risk factor. It was assumed that any non-blank response was an indication that the case was asked risk factor related questions.

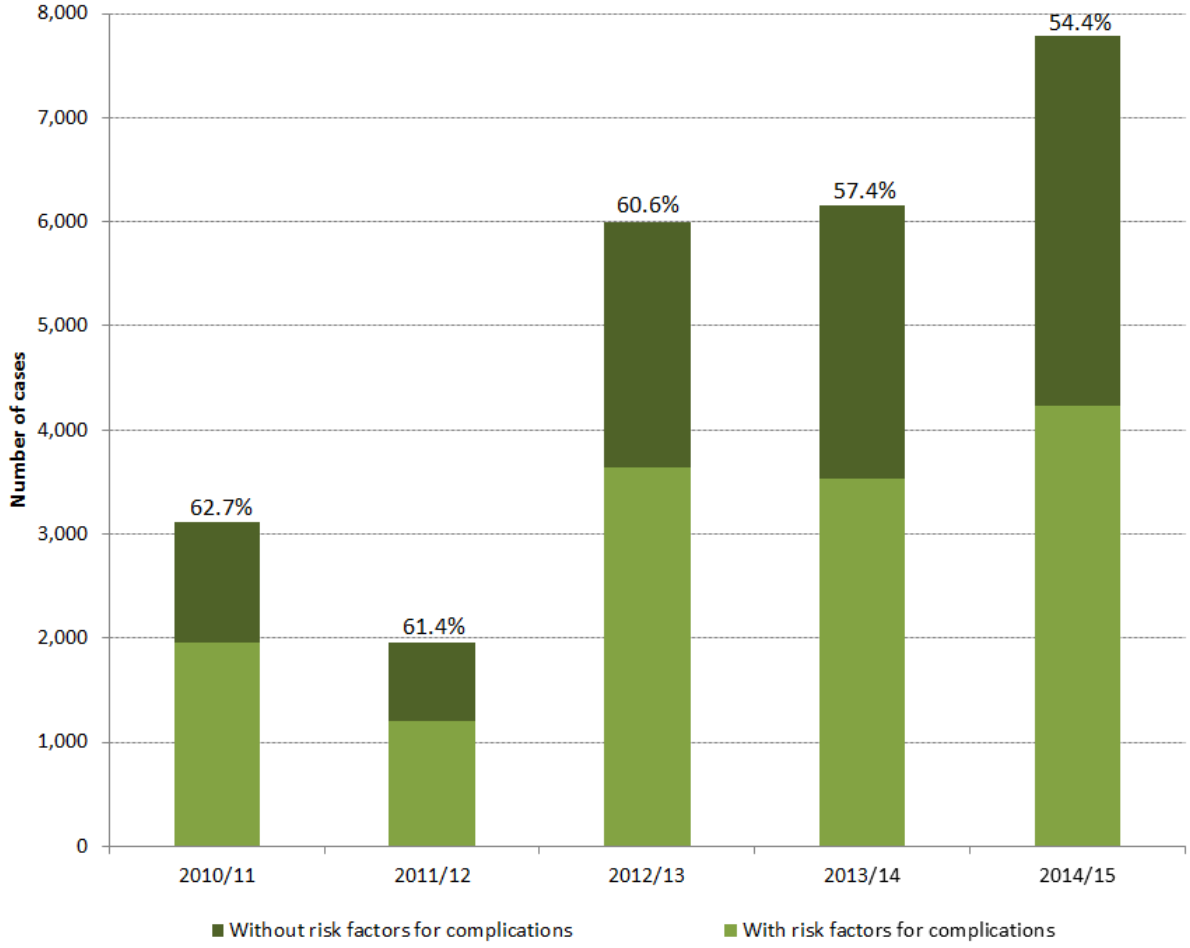
b. Defined as cases marked as "yes" for one or more medical risk factors for influenza complications generally consistent with those identified by NACI.

Note: Only those 25,027 cases with available risk factor information (i.e., those with non-blank responses for any risk factor) will be included in the remainder of this report. Those without any available risk factor information are not included in any calculations or figures reported below.

Influenza seasons and the proportion of cases with medical risk factors

Figure 3 indicates the number of included cases by influenza season, and the proportion who had medical risk factors generally consistent with NACI definitions. In total, 58.2% of included cases had one or more medical risk factors. The overall number of included influenza cases and the proportion with medical risk factors varied by season. The 2010-2011 and 2011-2012 seasons had fewer cases of influenza recorded in iPHIS than the following three seasons. The greatest number of cases (7,782) had an onset date during the 2014-2015 season, and the fewest (1,963) had an onset date during the 2011-2012 season. In 2010-2011 to 2014-2015, between 54.4% and 62.7% of cases had medical risk factors for complications.

Figure 3. Number of iPHIS influenza cases age 20+ (n=25,027) by influenza season and medical risk factors status; Ontario, 2010-2011 to 2014-2015



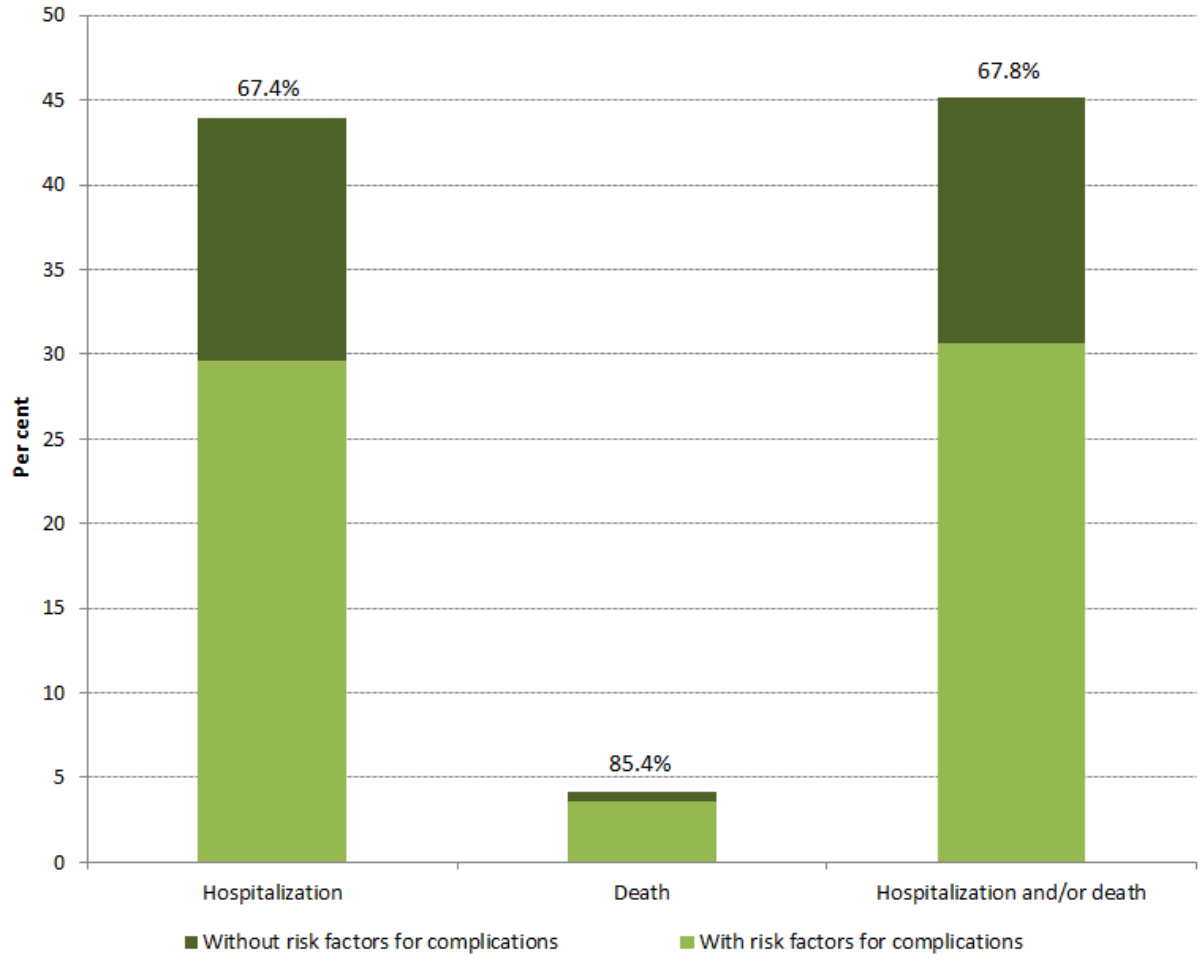
Notes for Figure 3:

- The percentages above the bars for each age group are the per cent with medical risk factors for complications (for example, 62.7% of cases in 2010/11 had risk factors for complications)
- "With risk factors for complications" is defined as cases marked as "yes" for one or more medical risk factors for influenza complications generally consistent with those identified by NACI.
- "Without risk factors for complications" is defined as cases who had a non-blank response (includes "yes," "no" or "unknown") for any risk factor but did not have a "yes" for any medical risk factors generally consistent with those defined by NACI. It was assumed that any non-blank response was an indication that the case was asked risk factor-related questions.

Complications and medical risk factors

During the seasons studied, 45.1% of the included cases had complications (hospitalization and/or death) recorded in iPHIS. Of those with complications, 67.4% had one or more medical risk factors. Considering complication types separately, 43.9% of cases were hospitalized, of whom 67.4% had one or more medical risk factors; and 4.2% of cases died, of whom 85.4% had one or more medical risk factors. This information is summarized in Figure 4.

Figure 4. Percent of included iPHIS influenza cases age 20+ (n=25,027) with complications from influenza, by complication type; Ontario, 2010-2011 to 2014-2015



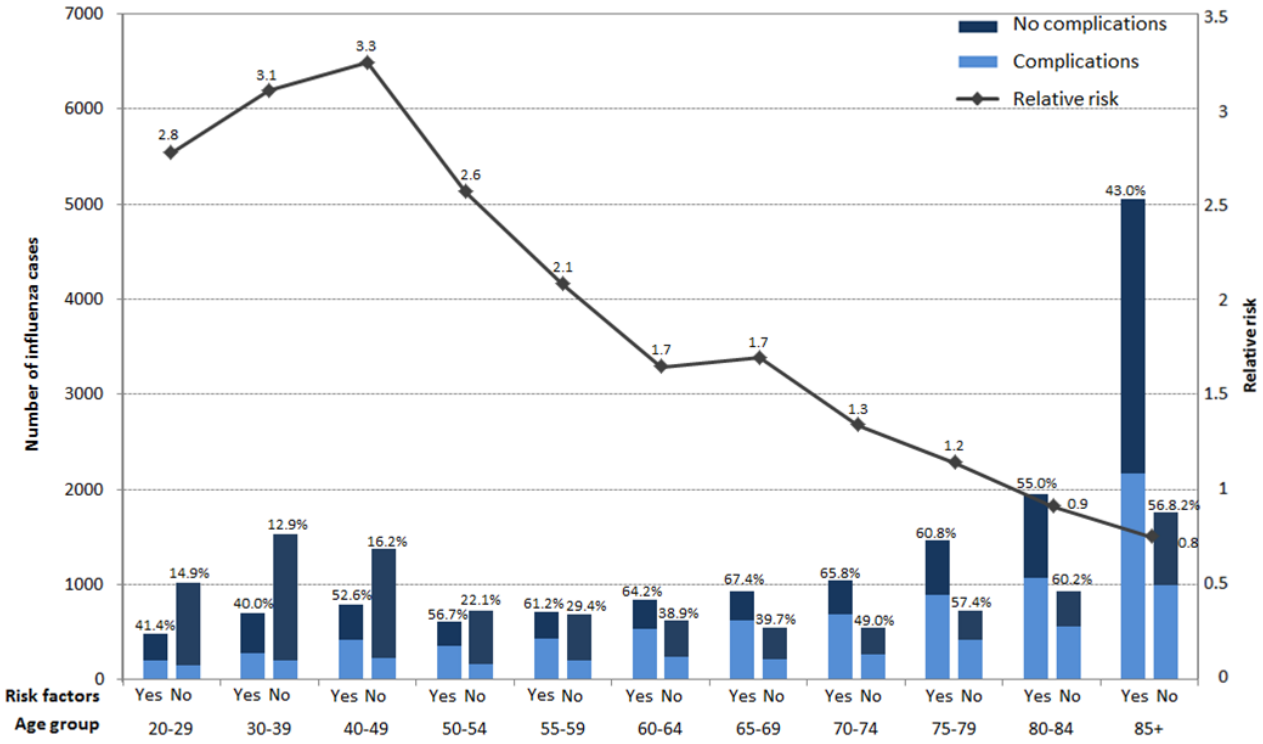
Notes for Figure 4:

- The percentages above the bars for each age group are the per cent with medical risk factors (for example, 67.4% of cases that were hospitalized had medical risk factors for complications)
- "With risk factors for complications" is defined as cases marked as "yes" for one or more medical risk factors for influenza complications generally consistent with those identified by NACI.
- "Without risk factors for complications" is defined as cases who had a non-blank response (includes "yes," "no" or "unknown") for any risk factor but did not have a "yes" for any medical risk factors generally consistent with those defined by NACI. It was assumed that any non-blank response was an indication that the case was asked risk factor-related questions.

Medical risk factors and complications by age

The relationship between medical risk factor status and complications (hospitalizations and/or deaths) in included iPHIS cases age 20 or older varies by age. For example, 41.4% of cases age 20-29 with medical risk factors had complications, compared to a complication rate of 14.9% for cases in the same age group without medical risk factors, for a relative risk of complications of 2.8. This relationship peaked in the 40-49 age group, where the relative risk of complications was 3.3, comparing those with and without medical risk factors. In those aged 70 years and older, the relative risk of complications for those with and without medical risk factors ranged from 0.8 to 1.3. This information is summarized in Figure 5.

Figure 5. Number, percent with complications, and relative risk of complications (hospitalizations and/or deaths) of iPHIS influenza cases age 20+ by medical risk factor status and age group Ontario, 2010-2011 to 2014-2015



Notes for Figure 5:

- The percentages above the bars for each age group are the percent with complications (hospitalizations and/or deaths) (for example, for those age 20-29, 41.4% of those with medical risk factors had complications and 14.9% of those without medical risk factors had complications)
- The relative risk (RR) for each age group is the percent with complications in those with medical risk factors divided by the percent with complications in those without medical risk factors (for example, for those age 20-29, RR= 41.9 / 14.9 = 2.8)
- "With risk factors for complications" is defined as cases marked as "yes" for one or more medical risk factors for influenza complications generally consistent with those identified by NACI.
- "Without risk factors for complications" is defined as cases who had a non-blank response (includes "yes," "no" or "unknown") for any risk factor but did not have a "yes" for any medical risk factors generally consistent with those defined by NACI. It was assumed that any non-blank response was an indication that the case was asked risk factor-related questions.

Data caveats

There are significant limitations associated with using iPHIS for this analysis, which are as follows:

1. **Only reported, laboratory-confirmed cases of influenza are represented:** The data only represent laboratory confirmed cases of influenza reported to public health and recorded in iPHIS. As a result, all counts will be subject to varying degrees of underreporting depending on factors such as severity of illness, healthcare seeking behaviours, health care provider testing practices, accuracy of laboratory tests and reporting behaviours.
2. **Risk factor information is not always collected:** Public health units are encouraged to enter at least one risk factor for each reported influenza case; however, this is not always implemented or feasible, particularly since the change in public health reporting requirements noted below. Data analysis indicates that individuals who experienced complications (i.e., hospitalizations and/or deaths) were more likely to be asked risk factor questions. For example, in the 2010-2011 to 2014-2015 seasons, 39% of all influenza cases age 20 or older in iPHIS had any risk factor information, compared to 45% in the same group considering only those who were hospitalized or died.
3. **Hospitalizations and deaths may be under-reported:** The numbers of hospitalizations and deaths reported in iPHIS may be an underestimation of the true experience in the Ontario population for many reasons, including undiagnosed infection and subsequent underreporting because influenza is not suspected as the source of the illness; public health follow-up of the case may not have occurred to determine if the case was hospitalized or died; or the public health follow-up may have occurred before the patient was hospitalized or died.
4. **Public health follow up requirements have changed:** In December 2014, public health units were advised that only 20% of laboratory-confirmed cases required follow-up, as opposed to all cases. Health units were advised to follow-up every fifth consecutive reported case, although some health units chose to do additional follow-up. All cases were to be entered into iPHIS based on information on the laboratory slip. Health units were encouraged to enter all available information, including hospitalizations or deaths if the information was provided. However, the extent to which this change in reporting requirements affected the reporting of risk factor information and hospitalizations and deaths is uncertain.
5. **Testing biases:** Cases in iPHIS are influenced by who is tested for influenza. Patients with risk factors or more severe outcomes (i.e., hospitalizations and deaths) are more likely to be tested for influenza and therefore captured in the iPHIS database. The number of tests done increases with age but the extent to which age itself influences the likelihood of being tested is uncertain.
6. **Deaths are not always attributable to influenza**: Deaths in any laboratory-confirmed influenza case are included if reported; however, it is not possible to determine the contribution of influenza to the death.

As a result of these limitations, this dataset should not be considered representative of the population of Ontario and results should be interpreted with caution.

Conclusions

In total 58.2% of cases included in this analysis had a medical risk factor consistent with NACI definitions, with a range of 54.4% to 62.7% per year. Of the included cases, 45.1% had a complication recorded in iPHIS (43.9% were hospitalized and 4.2% died). Of those who were hospitalized, 67.4% had medical risk factors; of those who died, 85.4% had medical risk factors.

The results suggest that in influenza cases reported through iPHIS, the presence of one or more medical risk factors led to a higher rate of complications (hospitalizations and/or deaths), particularly in persons under 70 years of age. In individuals under 70 years of age the relative risk of complications comparing those with and without medical risk factors ranged from 1.7 to 3.3. In adults 70 years of age and over the relative risk of complications ranged from 0.8 to 1.3. The findings support that age itself is a risk factor for influenza complications, consistent with the NACI high-risk group of 65 years of age and over. There are significant limitations to using iPHIS for this analysis and therefore these findings should be interpreted with caution.

A literature review of the relationship between influenza medical risk factors and age with respect to hospitalizations and deaths

This section outlines the methods and finding of a literature review on the relationship between influenza medical risk factors and age with respect to hospitalizations and deaths.

Background

Globally, influenza is a major cause of illness and death. In Canada, estimates of influenza-attributable hospitalizations range from 14,000 – 17,000 annually and influenza-attributable deaths have been estimated at approximately 4000 annually.[22,23] Although differences exist in the epidemiology of seasonal versus pandemic influenza infections, both age and underlying medical risk factors contribute to disease severity in both types of influenza infection.

Influenza-attributable hospital admissions and deaths are higher among the elderly compared with non-elderly people.[23-27] Approximately 90% of influenza deaths occur among those 65 years of age and over.[28] Seasons predominated by influenza A(H3N2) often result in more severe outcomes compared to seasons where other influenza types/subtypes predominate.[29] The relationship between pandemic influenza and age is somewhat more complex. During the 2009 H1N1 pandemic, seniors were at lower risk for influenza acquisition than younger adults, but as with non-pandemic H1N1 influenza, when seniors develop pandemic H1N1 influenza, they are at increased risk for complications.[25,31] This pattern of relative sparing of the elderly was also seen in the 1918 pandemic but not in the 1957 or 1968 pandemics. In all four pandemics, however, the epidemiological pattern differed from that of seasonal influenza in that typically relatively more severe disease and mortality occurred in the young and in persons without underlying health conditions compared to seasonal influenza where most severe outcomes occur in the elderly and persons with underlying health conditions.[31]

Underlying medical risk factors are also known to increase the risk for influenza-related complications, including hospitalizations and deaths. The National Advisory Committee on Immunization (NACI) lists a number of chronic conditions that are associated with an increased risk of influenza-related complications or hospitalizations. These conditions include: cardiac or pulmonary disorders, diabetes mellitus and other metabolic diseases, cancer and other immune compromising conditions, renal disease, anemia or hemoglobinopathy, conditions that compromise the management of respiratory secretions and are associated with an increased risk of aspiration, neurologic and neurodevelopmental conditions for children and adolescents, and morbid obesity (BMI≥40). Pregnant women, Aboriginal people, people living in long term care facilities, people age ≥65 and children younger than 59 months of age are also at increased risk for influenza complications.[1]

The prevalence of risk factors for influenza complications increases with age.[32] Therefore it is difficult to determine if increased risk of influenza complications with age is related to the presence of underlying

medical conditions or to age itself. The purpose of this review is to explore the relationship between age and risk factors in adults with respect to influenza-related hospitalizations and deaths.

Methods

Search methods for identification of studies

A literature search was conducted by Public Health Ontario Library Services on December 22, 2015 using the MEDLINE and Embase databases for studies which examined the risk of influenza-related hospitalizations or death in adult populations with and without medical risk factors. A detailed description of the search strategy can be found in Appendix A. Research articles of any study design were included and no time limits were applied to the search. The search was limited to English language articles and articles from developed countries. Articles were considered for review if they included:

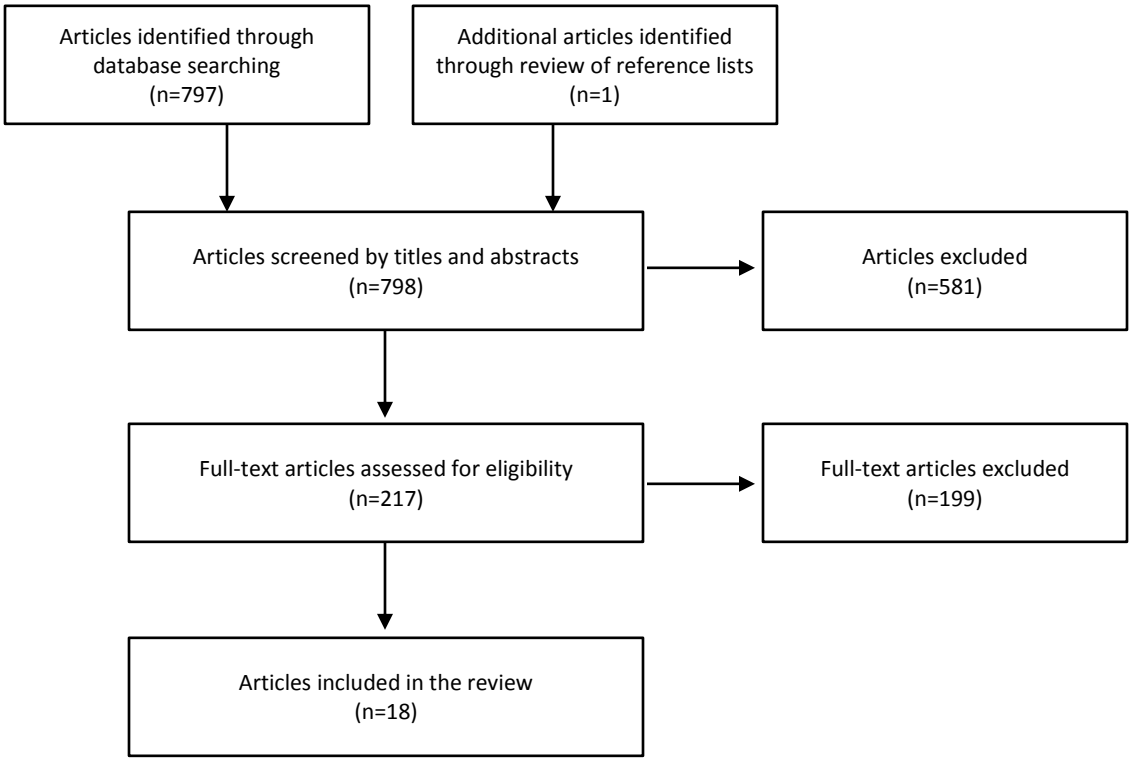
- influenza-associated hospitalization or mortality as an outcome;
- adult populations over the age of 18; and
- considered or controlled for both age and medical risk factors in the analysis.

Reference lists of all publications identified for final inclusion were also reviewed for relevant articles; one additional relevant article was identified using this method.

Study screening, data extraction and quality appraisal

A total of 798 articles were retrieved. One reviewer assessed titles and abstracts of all retrieved articles for relevance. A total of 217 articles were reviewed in full-text, of which 18 were identified for final inclusion. Throughout these processes, uncertainties about study selection were discussed between two reviewers to come to consensus. One reviewer carried out the data extraction for the 18 included studies, which was verified by a second reviewer. A study selection flow diagram can be found in Figure 6. Quality appraisal of the included studies was carried out by one reviewer using a modified version of Public Health Ontario's MetaQAT tool and subsequently verified by a second reviewer.

Figure 6. PRISMA flow diagram of included studies



Results

In total, 18 articles were included in this literature review. The studies were of varying designs as follows: cross sectional (n=8), cohort (n=1), statistical modelling to estimate the burden of influenza attributable complications (n=6) and case-control (n=3) studies. More than half of the studies were conducted during the 2009-2010 H1N1 pandemic (n=10). The findings of the literature review are summarized below in two subsections: the first summarizing articles from non-pandemic seasons and the second focusing on articles related to the 2009-2010 H1N1 influenza pandemic. It should be noted that an article that refers to the 1968-1969 pandemic is included in the non-pandemic section (Barker et al.[40]). A summary of key findings from each included article can be found in Table 3. Please see Table 4 for a detailed overview of the articles, including study methods, results and a summary of the critical appraisal of each article.

Articles assessing non-pandemic seasons

In total, eight studies were conducted during non-pandemic seasons (including an article by Barker et al.[40] which assessed the 1968-1969 season) which examined influenza-related hospitalizations and deaths in adult populations with and without medical risk factors.[33-40] Six of the studies used statistical modelling of administrative data to estimate the burden of complications attributed to influenza[33, 34, 36-39] and the other two studies were a retrospective cohort study[35] and cross sectional study.[40] In general, the studies that used statistical modelling of administrative data assessed influenza-attributed hospitalizations or deaths by analyzing rates of hospitalizations or deaths by week for International Classification of Diseases (ICD) codes possibly related to influenza (e.g., pneumonia and influenza, or

respiratory and circulatory disease) although in two studies[37,39] all-cause mortality was used. The studies compared these rates during times when influenza was known and not known to be circulating, or controlled for influenza circulation in the model. The timing of influenza circulation was generally based on positive laboratory-confirmed cases from a reportable disease database. Many of the studies also attempted to control for a variety of parameters including the circulation of other respiratory viruses such as respiratory syncytial virus (RSV). The results are presented below for hospitalizations and deaths.

Hospitalizations

Overall, the risk of influenza-attributable hospitalization was significantly increased for those with medical risk factors compared to those without risk factors.[33-37] In two studies, the impact of medical risk factors was more pronounced in adults under 65 years of age than in older adults.[33,34] A statistical modelling study by **Cromer et al**. found the effect of being in a clinical risk group increased the influenza-attributable hospital admission rate similarly for those aged 15-44 (RR = 4.9, 95%CI: 4.7 to 5.1) and aged 45-64 (RR = 4.5, 95% CI: 4.3 to 4.7) compared to those not in a clinical risk group; however the effect of risk factors on influenza-attributable hospitalizations was lower for those 65 years of age or older (RR=1.8, 95%CI: 1.7 to 2.0).[33] Similarly, a statistical modelling study by **Mullooly et al**. found that the proportional increases of influenza-associated hospitalization rates for high-risk adults compared to low-risk adults were greater in those under 65 years of age than they were in those 65 years of age and older. Using circulatory and respiratory diseases as an example, the rates of influenza-associated hospitalizations were as follows:

- low-risk individuals aged 18-49 had 0.5 hospitalizations per 10,000 person-periods (95%CI: -0.9 to 1.9) compared to 4.7 hospitalizations per 10,000 person-periods (95%CI: 0.5 to 9.0) for high-risk individuals;
- low-risk individuals aged 50-64 had 1.5 hospitalizations per 10,000 person-periods (95%CI: -0.9 to 3.9) compared to 23.2 hospitalizations per 10,000 person-periods (95%CI: 13.8 to 32.7) for high-risk individuals; and
- low-risk individuals aged 65+ had 28.3 hospitalizations per 10,000 person-periods (95%CI: 17.9 to 38.8) compared to 107.5 per 10,000 person-periods (95%CI: 87.1 to 127.8) for high-risk individuals.

Mullooly et al. also found significant rates of influenza-attributable hospitalizations in adults 65 years of age and older regardless of risk factor status; however the rates were highest in those with medical risk factors.[34]

In a cohort study by **Neuzil et al**. of women aged 15-64, the influenza-attributable risk for hospitalizations and deaths was higher in high-risk women compared to low-risk women. However, the authors noted that even among those without traditional risk factors, acute cardiopulmonary hospitalizations increased significantly during influenza season. By age and risk factor status, influenza-attributable events (hospitalizations and deaths) were as follows: for those 45-64 years of age - 26.4 events per 10,000 person-months (95%CI: 22.0 to 30.7) for high-risk women compared to 2.9 events per 10,000 person-months (95% CI: 0.58 to 5.2) for low-risk women; for those 15-44 years of age, influenza-attributable risk was determined to be 10.3 events per 10,000 person-months (95%CI 5.9 to 14.7) for

high-risk women compared to 2.0 events per 10,000 person-months (95% CI: 1.6 to 2.4) for low-risk women. Those 65 years of age and over were not assessed in this study.[35]

A statistical modelling study by **Pockett et al**. found that age and risk status (high-risk versus low-risk) were independently associated with increased risk of influenza-attributable hospitalization. Compared to individuals without high-risk conditions, individuals designated as high-risk had increased odds of influenza-attributable hospitalization (OR=3.23) in a logistic regression model that controlled for age.[36]

A statistical modelling study by **Jansen et al**. assessed influenza-attributable hospitalization in those 50-64 years of age and noted that influenza-associated hospitalization occurred among both low-risk 50-64 year olds, and those with risk factors, although at much higher rates in the latter (66.5/100,000 for those with risk factors compared to 12.8/100,000 for those without risk factors).[37]

Deaths

Studies found the risk of influenza-attributable death was highest in the elderly.[33, 36-40] Several studies found increased influenza-attributable mortality in adults with risk factors compared to those without risk factors; however there was mixed evidence regarding how this effect was influenced by age. [33, 36, 38-40] Similar to their findings with regard to hospitalizations, **Cromer et al.** found that the case-fatality rate (deaths/1,000 admissions) in patients with risk factors was higher than among non-risk group patients at every age, but that the impact of risk factors decreased with age. The relative risk (RR) of death among those with risk factors compared to those without risk factors decreased with age as follows: age 15-64, RR = 6.6 (95% CI: 6.0 to 7.3) and age 65+, RR =2.3 (95% CI: 2.1 to 2.6).[33] Other studies, such as the statistical modelling study by **Matias et al**., found a less clear age-related pattern with respect to the relative risk of influenza-attributable deaths in adults with high-risk conditions compared to those with low-risk status. They noted the following relative risks (RR) by age group: age 18-49, RR = 1.45; age 50-64, RR= 3.72; age 65-74, RR=5.84; and age 75+, RR = 2.75. The authors hypothesized that the lower relative risk between high and low risk groups in those 75+ may be related to an increase in susceptibility to complications with increasing age, independent of underlying chronic conditions.[38]

A statistical modelling study by **Schanzer et al**. found that age and medical risk factors contribute independently to increased risk of influenza-attributable mortality. An increased risk with age was found for all health status groups that were assessed. The authors noted that 3% of deaths attributed to influenza were among otherwise healthy seniors, primarily over the age of 80 years; deaths in those under 60 years of age occurred too infrequently to stratify by health status. Of interest, 2% of all deaths in those aged 65-69 year were attributed to influenza and 5% of all deaths in those 90 years of age and over were attributed to influenza.[39]

A cross sectional study by **Barker et al**. noted an increase in the rates of influenza-attributable mortality with increasing number of risk factors. In those 45 years of age and over, the risks of pneumonia and influenza mortality when one underlying condition and two or more underlying conditions were present were respectively estimated to be 39 and 202 times that for persons without underlying disease.[40]

Articles assessing the 2009-2010 H1N1 pandemic

In total, 10 studies were conducted examining influenza–related hospitalizations and deaths in adult populations with and without medical risk factors during the H1N1 influenza pandemic of 2009-2010.[41-50] Seven of the 10 studies used a cross sectional design[41, 44, 45, 47, 48, 49, 50] and three were case-control studies[42, 43, 46]. All assessed laboratory-confirmed pandemic H1N1 influenza. The results are presented below for hospitalizations, severe outcomes (e.g., intensive care admission, mechanical ventilation) and deaths.

Hospitalizations

The risk of pandemic H1N1 influenza-attributable hospitalization was greater for those with medical risk factors than for those without risk factors.[41-46] In a cross sectional study by **Campbell et al**., the effect of pre-existing conditions on hospitalizations with pandemic H1N1 influenza was greater for those under 65 years of age than for older individuals. The relative risk (RR) of hospitalization was 10.3 times higher (95%CI: 9.4 to 11.3) for those with pre-existing conditions than for those without pre-existing conditions. By comparison, in those over 65 years of age the RR was only 2.8 times higher (95% CI: 1.7 to 4.6) in those with pre-existing conditions compared to those without pre-existing conditions.[41]

Several studies found age and the presence of medical risk factors to be independently associated with increased risk of influenza-attributable hospitalization.[42-46] In a case-control study comparing laboratory-confirmed cases of pandemic H1N1 influenza who were hospitalized with laboratory-confirmed cases of pandemic H1N1 who were not hospitalized, **Gilca et al**. found that when controlling for age, the presence of at least one underlying chronic condition was significantly associated with influenza-attributable hospitalization (OR = 4.9, 95% CI: 1.2 to 2.9).[42] Similarly, a case-control study by **Ward et al.** comparing laboratory-confirmed cases of pandemic H1N1 influenza admitted to hospital and randomly selected community controls found that 86% of cases reported one or more independent medical risk factor compared to 52% of controls. In their multivariate analysis that controlled for age, various underlying chronic conditions were independently associated with hospitalization for pandemic H1N1 2009 as follows: lung disease (OR=6.6, 95% CI: 3.8 to 11.6); immunosuppression (OR=5.5, 95% CI: 2.8 to 10.9); asthma which regularly required medication (OR=4.3, 95% CI: 2.7 to 6.8); diabetes (OR=3.8, 95% CI: 2.2 to 6.5); and heart disease (OR=2.3, 95% CI: 1.2 to 4.1). The study also indicated the risk for hospitalization increased with increasing number of significant risk factors. When assessed by age, Ward et al. found that compared to the reference group (those age 65 and older), the multivariate analysis demonstrated that the odds of influenza-attributable hospitalization was highest for those aged 16-25 (OR=5.4, 95% CI: 2.5 to 11.4) and 46-55 (OR=5.1, 95% CI: 2.7 to 9.6).[43]

A cross sectional study by **Thompson et al**. found that, of hospitalized patients with pandemic H1N1 influenza, 62% had one or more high-risk medical conditions with the three most common conditions being asthma (27%), diabetes (16%) and other chronic lung disease (16%). In their multivariate analysis, compared to those 65 years of age and older, patients age 5-24 were 1.9 times more likely to be hospitalized (95%CI: 1.5 to 2.4); interestingly persons age 25-49 had a significantly lower rate of hospitalization (RR=0.8, 95%CI 0.6 to 0.96).[44]

Severe outcomes

The cross sectional study by Campbell et al. noted above found that medical risk factors contributed more to critical care admission at younger ages than at older ages, as 82% of those ≤ 64 years of age admitted to critical care had risk factors compared to only 60% of those ≥65 years.[41]

A cross sectional study by **Hlavinkova et al**. assessed risk factors for severe outcomes (admission to intensive care, development of pneumonia or death) among cases who were hospitalized with pandemic H1N1 influenza. Cases with severe outcomes were significantly older (median age 35 years) than cases with non-severe outcomes (median age 24 years). Patients with severe outcome were 3.28 times (95% CI: 1.01 to 10.66) more likely to have one risk factor and 8.58 times (95% CI: 4.80 to 15.32) more likely to have two or more risk factors compared to cases with non-severe outcomes. Although the number of risk factors was associated with severe outcomes, 35% of patients with severe outcomes had no risk factors.[45]

A case control study by **Zarychanski et al.** compared cases with pandemic H1N1 influenza admitted to the intensive care unit (ICU), to two control groups - those with pandemic H1N1 influenza admitted to hospital only and those who remained in the community. Comorbidities were present in 35% of the community cases, 57% of those admitted to hospital but not the ICU, and 76% of those admitted to the ICU. The mean age was 25.3 years for community cases, 23.0 years for those admitted to hospital but not the ICU, and 33.4 years for those admitted to the ICU. In their multivariate analyses, the authors found that relative to those not admitted to hospital, admission to the ICU was associated with the presence of a medical comorbidity (OR=3.19, 95%CI: 1.07 to 9.52). Similarly, when comparing hospital controls without admission to the ICU and community controls, medical comorbidities were significantly associated with admission to hospital (OR 3.36, 95% CI: 2.05 to 5.49). Age was not a significant risk factor in any of the multivariate analyses.[46]

In the cross sectional study by **Thompson et al.** noted above, two multivariate analyses assessed the association between age and mechanical ventilation among those hospitalized with pandemic H1N1 influenza. Compared to the reference group (age 5-24), patients aged 25-49 and those aged 50-64 were significantly more likely to require mechanical ventilation in both models.[38] Age over 65 was significantly associated with mechanical ventilation in one model but not the other; presence of any high-risk medical condition was not statistically associated with an increased risk of mechanical ventilation.[44]

Deaths

The risk of influenza-attributable death during the 2009-2010 H1N1 influenza pandemic was greater for those with medical risk factors than for those without medical risk factors.[44, 47-50] Age also appeared to be an independent risk for death among those who developed pandemic H1N1 influenza, however this relationship appears more complex than with seasonal influenza.

A cross sectional study by **Pebody et al**. found that both risk factors and age increased the risk of influenza-attributable death. The estimated case-fatality ratios (deaths with pandemic H1N1 divided by clinical cases) for those aged >6 months to 64 years who belonged to a risk group (excluding obesity and pregnancy) was 2 per 1,000 cases compared to 0.1 per 1,000 cases for those who did not belong to a risk group. For those aged 65+, the case-fatality ratio was 15 per 1,000 cases for those in a risk group

compared to 1.5 per 1,000 cases for those not in a risk group. The relative risk of death with pandemic H1N1 influenza for those with any risk factor compared to those who were not in a risk group was higher for those age >6 months to 64 years old (RR=17.9, 95% CI: 13.8 to 23.2) compared to those age 65 and older (RR=9.8, 95% CI: 3.5 to 27.4). The population attributable fraction for risk factors in fatal cases aged 65+ was 81.8% and was 64.7% for those age 6 months to 64 years.[47]

A cross sectional study by **Louie et al**. found the highest influenza fatality rates in adults age 50-59 (annualized rate of 2.6/100,000 population). Annualized fatality rates were somewhat lower in those 60-69 (annualized rate of 1.7/100,000). Eighty percent of people who died had a comorbid condition that increased their risk for influenza complications as defined by the Advisory Committee on Immunization Practices (ACIP) for seasonal influenza vaccine. Older fatal cases were significantly more likely to have an ACIP-defined high-risk medical condition than younger fatal cases.[48]

In a multivariate analysis, when compared to children under the age of 18, a cross section study by **Nickel et al**. found that the odds of critical illness (ICU admission) or death with pandemic H1N1 influenza were 4.44 times greater (95% CI: 1.97 to 10.02) among adults aged 18-49; 5.93 times greater (95% CI: 2.24 to 15.65) in adults aged 50-64; and non-significantly higher in those ≥ 65 (OR= 2.53, 95% CI: 0.55 to 11.57). ACIP defined risk factors were not associated with critical illness or death in this multivariate analysis.[49]

A cross sectional study by **Campbell et al.** found that among patients hospitalized for pandemic H1N1 influenza, those with one or more underlying medical conditions had an increased risk of severe outcomes even after adjusting for age and gender (OR=1.5, 95% CI 1.1 to 2.1). For patients with no underlying conditions and who were not pregnant, compared to those 10-19 years of age, the risk of severe outcome was greatest among those 30-39 years old (OR = 3.5, 95% CI 1.5 to 7.7) and those 60 years and older (OR = 3.2, 95% CI 1.2 to 8.4).[50]

Finally, the cross sectional study by **Thompson et al.** noted above found the odds of death in a multivariate analysis were increased for those with cancer (OR=6.1, 95% CI: 1.6 to 23.0) and those with a liver disorder (OR=7.3, 95% CI: 2.5 to 21.0). Age was not statistically associated with increased odds of death in this study.[44]

Table 3: Summary of key findings from included articles from literature review

Reference	Key findings
Articles assessing non-pandemic seasons	
Hospitalizations	
Cromer et al.	• The effect of being in a risk group increased the influenza-attributable hospitalization rate compared to those not in a risk group as follows: o RR=4.9 (95% CI: 4.7 to 5.1), for those age 15-44 o RR=4.5 (95% CI: 4.3 to 4.7), for those age 45-64 o RR=1.8 (95% CI: 1.7 to 2.0), for those 65+
Mullooly et al.	• Proportional increases in influenza-attributable hospitalization rates for high-risk adults compared to low-risk adults were greater in those under 65 years of age • Using circulatory and respiratory diseases, the rates of hospitalization were as follows: o Individuals age 18-49 ▪ Hospitalizations per 10,000 person-periods = 0.5 (95%CI: -0.9 to 1.9) for low-risk persons ▪ Hospitalizations per 10,000 person-periods = 4.7 (95%CI: 0.5 to 9.0) for high-risk persons o Individuals age 50-64 ▪ Hospitalizations per 10,000 person-periods = 1.5 (95%CI: -0.9 to 3.9) for low-risk persons ▪ Hospitalizations per 10,000 person-periods = 23.2 (95%CI:13.8 to 32.7) for high-risk persons o Individuals age 65+ ▪ Hospitalizations per 10,000 person-periods = 28.3 (95%CI: 17.9 to 38.8) for low-risk persons ▪ Hospitalizations per 10,000 person-periods = 107.5 (95%CI:87.1 to 127.8) for high-risk persons
Neuzil et al.	• Influenza-attributable risk for hospitalizations and deaths were higher in high-risk women compared to low-risk women o Women ages 15-44 ▪ Events per 10,000 person-month=10.3 (95% CI: 5.9 to 14.7), for those with risk factors ▪ Events per 10,000 person-month=2.0 (95% CI: 1.6 to 2.4), for those without risk factors o Women ages 45-64 ▪ Events per 10,000 person-month = 26.4 (95% CI: 22.0 to 30.7, for those with risk factors ▪ Events per 10,000 person-month= 2.9 (95% CI: 0.58 to 5.2),, for those without risk factors
Pockett et al.	• When controlling for age, individuals with medical risk factors had increased odds of influenza-attributable hospitalization (OR=3.23) compared to those without high-risk conditions

Reference	Key findings
Jansen et al.	• Influenza-attributable rate of hospitalization for lower respiratory tract infections and pulmonary disease was higher in those with risk factors compared to those without risk factors as follows: o Rate=66.5 (95% CI: 61.6 to 71.4)/100,000 for those with risk factors o Rate=12.8 (95%CI: 11.3 to 14.3)/100,000, for those without risk factors
Deaths	
Cromer et al.	• Case-fatality rate in patients with risk factors was higher among non-risk group patients at every age, but the impact of risk factors decreased with age as follows: o RR=6.6 (95% CI: 6.0 to 7.3), for those age 15-64 o RR=2.3 (95% CI: 2.1 to 2.6), for those age 65+
Matias et al.	• Relative risk of influenza-attributable deaths was higher in those with high-risk conditions compared to those with low-risk status as follows: o RR=1.45, for those age 18-49 o RR=3.72, for those age 50-64 o RR=5.84, for those age 65-74 o RR=2.75, for those age 75+
Schanzer et al.	• Age and medical risk factors contributed independently to increased risk of influenza-attributable mortality • An increased risk with age was found as follows: o Rate=23/100,000, for those age 65-69 o Rate=831/100,000 for those age 90+
Barker et al.	• Rates of influenza-attributable mortality increased with increasing number of risk factors, compared to those without underlying disease o Risk of pneumonia and influenza mortality= 39 times greater when one underlying condition was present o Risk of pneumonia and influenza mortality = 202 times greater when two or more underlying conditions present
Articles assessing the 2009-2010 H1N1 influenza pandemic	
Hospitalizations	
Campbell et al. (2011)	• The effect of risk factors on pandemic H1N1 hospitalization was greater for those under 65 compared to those 65 and older • Compared to those without a risk factor, the relative risks for hospitalizations with pandemic H1H1 for those with a risk factor were as follows: o RR=10.3 (95% CI: 9.4 to 11.3), for those under 65 o RR=2.8 (95% CI: 1.7 to 4.6), for those 65+
Gilca et al.	• When controlling for age, the presence of at least one underlying chronic condition was significantly associated with influenza-attributable hospitalization (OR=4.9, 95% CI: 1.2 to 2.9)

Reference	Key findings

Ward et al.	• When controlling for age, various underlying chronic conditions were independently associated with hospitalization for pandemic H1N1 2009
	  ○ OR=6.6 (95% CI: 3.8 to 11.6), for lung disease
	  ○ OR=5.5 (95% CI: 2.8 to 10.9), for immunosuppression
	  ○ OR=4.3 (95% CI: 2.7 to 6.8), for asthma which regularly requires medication
	  ○ OR=3.8 (95% CI: 2.2 to 6.5), for diabetes
	  ○ OR=2.3 (95% CI: 1.2 to 4.1), for heart disease
	• The risk for hospitalization increased with increasing number of significant risk factors
	• In a logistic regression model, the odds of influenza-attributable hospitalization compared to the reference group of 65+ were as follows:
	  ○ OR=5.4 (95% CI: 2.5 to 11.4), for those age 16-25
	  ○ OR=4.1 (95% CI: 2.0 to 8.3), for those 26-35
	  ○ OR=3.9 (95% CI: 2.0 to 7.6), for those 36-45
	  ○ OR=5.1 (95% CI: 2.7 to 9.6), for those age 46-55
	  ○ OR=1.9 (95% CI: 1.0 to 2.5), for those 56-65

Thompson et al.	• Using those 65+ as the reference group, the relative risks for hospitalizations were as follows:
	  ○ RR=1.9 (95% CI: 1.5 to 2.4), for those age 5-24
	  ○ RR=0.8 (95% CI: 0.6 to 0.96), for those age 25-49

Severe outcomes	
Campbell et al. (2011)	• Presence of medical risk factors was more important for critical care admissions at younger ages (≤ 64 years) than at older ages(≥65 years)
Hlavinkova et al.	• Compared to patients with non-severe outcomes, patients with severe outcomes were 3.28 times (95% CI: 1.01 to 10.66), more likely to have one risk factor and 8.58 times (95% CI: 4.8 to 15.32), more likely to have two or more risk factors

Zarychanski et al.	• In a multivariate analysis, compared to patients with pandemic H1N1 not admitted to the hospital
	  ○ Admission to the ICU with pandemic H1N1 was significantly associated with presence of a medical comorbidity (OR=3.19, 95% CI: 1.07 to 9.52)
	  ○ Admission to the hospital (but not the ICU) with pandemic H1N1 was significantly associated with presence of a medical comorbidity (OR=3.36, 95% CI: 2.05 to 5.49)

Thompson et al.	• Compared to patients 5-24 years of age, patients age 25-49 and 50-64 were significantly more likely to require mechanical ventilation
Deaths	

Pebody et al.	• The effect of risk factors on pandemic H1N1 mortality was greater for those under 65 compared to those aged 65 and older. Compared to those not in a risk group, the relative risks for death with pandemic H1N1 for those in a risk group were as follow:
	  ○ RR=17.9 (95% CI: 13.8 to 23.2), for those >6 months to 64
	  ○ RR= 9.8 (95% CI: 3.5 to 27.4), for those 65+

Louie et al.	• 80% of those who died with pandemic H1N1 had a high- risk condition • Older fatal cases were more likely than younger fatal cases to have a high-risk condition

Reference	Key findings

Nickel et al.	• Age was independently associated with critical illness (ICU admission) or death from pandemic H1N1
	• In a multivariate analysis, compared to children under the age of 18, the odds of critical illness with pandemic H1N1 were:
	  ○ OR=4.44 (95% CI: 1.97 to 10.02), for those age 18-49
	  ○ OR=5.93 (95% CI: 2.24 to 15.65), for those age 50-64
	  ○ OR=2.53 (95% CI: 0.55 to 11.57), for those age 65+
	• Presence of risk factors was not associated with critical illness or death

Campbell et al. (2010)	• Presence of one or more underlying medical conditions was independently associated with risk of severe outcome for pandemic H1N1 (OR=1.5)
	• Age was independently associated with risk of severe outcome for pandemic H1N1. Compared to those 10-19, the odds of severe outcomes in those with no underlying risk factors were as follows:
	  ○ OR=1.5 (95% CI: 0.6 to 3.4), for those age 20-29
	  ○ OR=3.5 (95% CI: 1.5 to 7.7), for those age 30-39
	  ○ OR=2.6 (95% CI: 1.1 to 6.1), for those 40-49
	  ○ OR=2.2 (95% CI: 0.9 to 5.6), for those 50-59
	  ○ OR=3.2 (95% CI: 1.2 to 8.4), for those age 60+

Thompson et al.	• In a multivariate analysis, various underlying medical conditions were independently associated with increased risk of death for pandemic H1N1
	  ○ OR=6.1 (95% CI: 1.6 to 23.0), for those with cancer
	  ○ OR=7.3 (95% CI: 1.2 to 8.4), for those with liver disease
	• Age was not statistically associated with increased odds of death

Discussion

In summary, both underlying medical conditions and increased age contribute to an increased risk of influenza-attributable hospitalization, severe outcomes including death. The relationship between these factors is discussed below; the strengths and weakness of the included studies are also reviewed.

Non-pandemic seasons

In non-pandemic seasons, several studies found that the relative risk for hospitalization comparing those with and without medical risk factors was greater at younger ages and decreased at older ages.[33, 34] This finding supports older age as a risk factor for influenza hospitalization even in the absence of comorbidities, which is consistent with 65 years of age and over being listed as a NACI risk factor for influenza complications.[1]

Most influenza-attributable deaths occur in those 65 years of age and older.[27, 28] The presence of medical risk factors also increases the risk of influenza-attributed deaths. Studies suggest a decrease in the relative contribution of risk factors with increasing age with respect to influenza-attributable mortality; however this relationship is less clear than the relationship observed from data related to influenza-attributable hospitalization. The risk of death was found to increase with increasing numbers of risk factors in one study.[40]

Most of the studies that assessed hospitalizations and deaths by age and risk factor for seasons other than the H1N1 pandemic used statistical modelling of administrative data to determine influenza-attributable complications. These studies are strengthened by the incorporation of data from multiple influenza seasons to reflect seasonal variation in influenza incidence and severity. Controlling for multiple circulating pathogens, especially respiratory syncytial virus (RSV), and including sensitivity analyses also strengthened these types of studies.

Several methodological challenges were noted in interpreting the studies that used statistical modelling of administrative data to determine the burden of complications attributable to influenza. Studies often differed on the ICD codes used to determine influenza-attributable hospitalizations and/or deaths as well as on the definition for the start and end of influenza seasons. Similarly, studies often differed on medical conditions used in the designation of risk group status and how these risk factors were determined. Many studies did not capture or analyse patient influenza vaccination status or provide details regarding circulating influenza types/subtypes. Some studies had limited statistical power due to small sample sizes and several studies may have had limited generalizability to the Ontario population due to the nature of the study population. Additionally, studies often used different referent groups within their regression analyses, making outcome comparisons between studies difficult. Outcomes used in modelling studies lacked direct evidence for the causative pathogen that led to hospitalizations and/or deaths and several lacked clearly defined model assumptions (e.g. definitions for pre-existing medical conditions, or definitions for risk status such as high risk and low risk). Other methodological issues included the potential for incomplete reporting of risk factors in studies that assessed hospitalization or deaths or in studies that relied on self-reporting of risk factors. Finally, individuals with underlying medical conditions may have been more likely to seek care and be tested for influenza, which may have overestimated the impact of risk factors on hospitalization and death.

2009-2010 H1N1 influenza pandemic

In studies of the 2009-2010 influenza pandemic, both age and medical risk factors were found to be associated with hospitalizations and deaths. Pandemic influenza was more likely to affect younger adults than older adults. This is hypothesized to be due to some residual immunity from past exposures in older individuals.[51] However, when older individuals were infected, they were more likely to become seriously ill. Comorbidities appeared to increase the risk of severe outcomes of pandemic influenza. However it is notable that severe outcomes occurred even in those without comorbidities in both younger populations and in the elderly.[41, 43, 44, 45, 46, 48] Two studies demonstrated an increased risk for pandemic H1N1 influenza complications with increasing number of risk factors.[43, 45]

Strengths of studies that looked at pandemic H1N1 influenza included the use of laboratory-confirmed outcomes. However, several methodological challenges were also noted with the pandemic H1N1 influenza studies. These studies had limited observation periods during the first season that pandemic H1N1 influenza circulated, some of which were only a few months. The pandemic H1N1 influenza studies also had different comparison groups such as community controls or non-hospitalized individuals with pandemic H1N1 influenza, making comparisons between studies difficult. Additionally, studies based on passive surveillance systems may be subject to underreporting and reporting bias. Finally, studies based on the 2009-2010 pandemic may not be generalizable to non-pandemic seasons.

Conclusions

Both age and medical risk factors increase the risk of influenza-attributable hospitalization and deaths. For seasons other than the 2009-2010 pandemic, medical risk factors have a greater impact on hospitalizations and deaths in younger adults and become relatively less important in older individuals. This suggests that age itself is a risk for complications in older individuals consistent with NACI's high risk groups. For the 2009-2010 H1N1 pandemic, older individuals were less likely to acquire infection compared to younger individuals. However, when older individuals became infected with pandemic H1N1 influenza, they were at increased risk for hospitalization and death compared to younger individuals. For pandemic H1N1 influenza, medical risk factors also contributed to hospitalization and death and the more medical risk factors, the greater the risk of complications; however, both younger adults and older adults without underlying risk factors were admitted to hospital or died.

Overall conclusions regarding influenza medical risk factors and age

The analysis of data from the Institute for Clinical Evaluative Sciences showed that the prevalence of medical risk factors for influenza complications increases with increasing age. Overall, 38.2% of adults in Ontario aged ≥20 had at least one medical condition considered to be a risk factor for serious influenza infection. This percentage increased progressively with age and was 30.4% for those aged 20-64, 53.2% for those aged ≥50, and 70.1% for those aged ≥65.

The analysis of iPHIS data indicated that risk factors were an important contributor to hospitalization and death at younger ages, while age itself appeared to be an important risk factor for complications at older ages. This finding is supported by the literature review that assessed seasons other than the 2009-2010 pandemic. In the 2009-2010 H1N1 influenza pandemic, age and medical risk factors increased the risk of hospitalization and deaths among those with influenza infection; however, it is notable that younger and older individuals without medical risk factors were also hospitalized and died from pandemic H1N1 influenza.

The analyses in this report would suggest that influenza immunization promotional efforts that are aimed at preventing influenza complications should be targeted both by age and medical risk factors. The National Advisory Committee on Immunization determined that those 65 years of age and over were at increased risk for influenza complications[1] and findings from this review support this conclusion. This age group also has a high rate of medical risk factors for influenza complications (70%) providing another reason to target this age group in promotional campaigns. Promotional campaigns for younger adults that target those with medical risk factors should recognize that approximately 30% of adults between 20 and 64 years of age have medical risk factors.

Table 4: Articles on influenza-attributable hospitalizations and/or deaths in adult populations with and without medical risk factors

Reference	Methods	Results	Study Authors' Comments	Quality assessment
Articles assessing non-pandemic seasons				
Cromer D, van Hoek AJ, Jit M, Edmunds WJ, Fleming D, Miller E. The burden of influenza in England by age and clinical risk group: a statistical analysis to inform vaccine policy. J Infect. 2014;68(4):363-71.	• Statistical modelling study using administrative data in order to estimate the number of influenza-associated healthcare outcomes in different age groups in those with and without high-risk conditions in England and Wales from 2000- 2001 to 2007-2008 • Weekly numbers of laboratory reports were obtained from a national database for the following pathogens: influenza A, influenza B, respiratory syncytial virus, parainfluenza, adenovirus, rhinovirus, invasive *S. pneumoniae*, invasive *Mycoplasma pneumoniae* and invasive *Haemophilus influenza* • Weekly inpatient admissions to National Health Service hospitals were obtained for patients if they had an acute respiratory illness code in any diagnosis field • Among these inpatients, the following conditions were identified as being in a clinical risk group: chronic respiratory disease, chronic heart disease, chronic kidney disease, chronic liver disease, chronic neurological disease, diabetes, immunosuppression, asplenia or dysfunction of the spleen, cochlear implants, cerebrospinal fluid leaks • Number of deaths in hospital was estimated based on inpatient admissions with an acute respiratory	• Among those not in a clinical risk group, there was an annual average of over 300,000 admissions for acute respiratory illness • Among those in a clinical risk group, there was almost 520,00 admissions for acute respiratory illness • *Streptococcus pneumonia* and respiratory syncytial virus (RSV) accounted for the largest number of hospital admissions and deaths, with influenza usually as the third most common pathogen • The effect of being in a risk group increased influenza attributable hospital admission rate compared to those not in a risk group [4.9 times (95% CI 4.7 to 5.1) for those 15-44 years of age, 4.5 times (95% CI 4.3 to 4.7) for those 45-64 and 1.8 times (95% CI 1.7 to 2.0) for those 65+] • Among those aged 15 years and older there was little contribution from influenza B to hospital admissions • The majority of annual deaths attributed to influenza occurred in those 65+ (93% of total deaths), particularly those 65+	• Those 65 years of age and over accounted for 93% of all influenza-attributable deaths in hospital, but only 29% of all admissions due to influenza • Among those 65 years of age and older, the effect of underlying comorbidities on hospitalization and case fatality rates was less marked • Vaccine coverage in England among those age 65+ has been approximately 75% since 2005-2006 • Vaccine coverage in high risk individuals under 65 is low and has remained around 50% since 2008-2009	**Strengths** • Sources of data, inclusion criteria and model construction detailed and clearly articulated • Supplementary material provided outlining details of model construction • Results consistently reported throughout • Eight years of consecutive data used to reflect potential variation in influenza incidence and severity between seasons • Laboratory confirmed data on pathogens likely to cause acute respiratory illness used as explanatory variables in the model • Negative binomial regression model accounted for over dispersion in outcome data and identity link function used to account for possible additive effects of different respiratory pathogens • Nine different models developed to determine best fit; sensitivity analysis performed • Model controlled for multiple circulating pathogens (including RSV) and temporal offsets between pathogen testing and onset of clinical effect

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	illness code and death recorded as the discharge method; only deaths within 30 days of admission were included in the analysis • An adapted generalised linear model for negative binomial outcome distribution with an identity link function was used to estimate the proportion of healthcare outcomes (hospital admissions and deaths) attributable to influenza; the weekly counts for pathogens potentially responsible for acute respiratory illness were used as explanatory variables • Model outcomes were stratified by age (<6 months, 6 months-4 years, 5-14 years, 15-44 years, 45-64 years and 65+ years) and clinical risk group	with underlying co-morbidities (72% of total deaths) • The influenza case fatality rate (deaths/1000 admissions) in risk group patients was higher than among non-risk groups patients with the relative risk decreasing with age [6.6 times higher (95% CI: 6.0 to 7.3) in those age 15-64 and 2.3 times higher (95% CI: 2.1 to 2.6) in those age 65+]		**Weaknesses** • Due to the use of only ICD codes for respiratory illness, not all influenza-attributed deaths and hospitalizations were captured (e.g. cardiovascular disease deaths would not have been captured) • Influenza-attributed deaths not occurring in hospital were not captured • Data on influenza vaccination status was not captured (or controlled for) and may differ between risk groups and for age categories • Influenza subtype not analyzed/presented in results which may influence age group affected • Clinical risk conditions may have been missed in hospitalization data resulting in individuals with these conditions being misclassified as low risk • Direct evidence lacking for causative pathogen that led to hospitalization/death
Mullooly JP, Bridges CB, Thompson WW, Chen J, Weintraub E, Jackson LA, et al. Influenza- and RSV-associated hospitalizations among adults. Vaccine.	• Statistical modelling study using administrative data from three large health maintenance organizations (HMO) to estimate the influenza attributable hospitalization rates by age and risk status in the US (Oregon, California, Washington) from 1996-2000 • Subjects were classified as high or low	• The proportional increases of outcome rates for high-risk persons versus low-risk persons were greater for age groups 18-49 and 50-64 than for those age 65+ • Using circulatory and respiratory diseases as an example, the rates of	• Healthy adults aged 50-64 years were not at increased risk for influenza-associated hospitalizations • One third of individuals 50-64 year of age have a high risk medical condition for	**Strengths** • Sources of data and inclusion/exclusion criteria detailed and clearly articulated • Outcomes and co-morbidities clearly defined using ICD codes • Rate difference calculations clearly articulated

Reference	Methods	Results	Study Authors' Comments	Quality assessment
2007;25(5):846-55	risk for influenza complications based on inpatient and outpatient healthcare encounters for specific conditions over the past 12 months • High risk conditions included: chronic cardiac, pulmonary, renal, metabolic, liver, neurological disease, diabetes mellitus, hemoglobinopathies, immunosuppressive conditions and malignancies • CDC surveillance systems provided weekly numbers of total respiratory specimens tested for influenza and respiratory syncytial virus (RSV) and the number of those that tested positive for each • Influenza period were defined as weeks during which more than 10% of specimens tested positive for influenza; RSV periods were defined as weeks during which more than 10% of specimens tested positive for RSV • Influenza-only periods were influenza periods that did not contain any RSV weeks (although analysis could not be done on influenza-only weeks); peri-season periods were defined as weeks during October through May that were neither influenza or RSV weeks • Study outcomes were hospitalizations with several primary discharge diagnoses that were aggregated as follows: pneumonia and influenza (P&I), cardiac disease, acute cerebrovascular disease (CVD), and circulatory and respiratory conditions (C&R); while the P&I, cardiac, and CVD diagnostic categories were mutually exclusive, C&R included all three	hospitalizations were as follows: low risk individuals age 18-49 had 0.5 hospitalizations per 10,000 (95%CI: -0.9 to 1.9) compared to 4.7 hospitalizations per 10,000 person-periods (95%CI: 0.5 to 9.0) for high-risk individuals; low-risk individuals age 50-64 had 1.5 hospitalizations per 10,000 person-periods (95%CI: -0.9 to 3.9) compared to 23.2 hospitalizations per 10,000 person-periods (95%CI: 13.8 to 32.7) for high-risk individuals; low-risk individuals age 65+ had 28.3 hospitalizations per 10,000 person-periods (95%CI: 17.9 to 38.8) compared to 107.5 hospitalizations per 10,000 person-periods (95%CI: 87.1 to 127.8) for high-risk individuals • For low-risk adults age 18-49 and 50-64, no statistically significant excess hospitalizations occurred during any influenza-periods or RSV-only periods • High-risk persons age 18-49, 50-64 and 65+ years had significant rates of P&I and C&R hospitalizations associated with influenza; these rates increased with age • For low-risk persons age 65+, significant influenza-associated rates of hospitalization for P&I and C&R were found	which influenza vaccination is recommended • No comments on vaccine match • During the study period, annual influenza vaccination was recommended for those aged ≥65 years but not for younger adults without risk factors • Rate difference approaches do not control for seasonal effects and are likely to over-estimate the effects of the circulation of influenza viruses.	• Results consistently reported throughout • Data from four consecutive influenza seasons used to reflect potential variation in influenza incidence and severity between seasons • Laboratory-confirmed data on influenza and RSV used to determine influenza/RSV periods • Influenza vaccination status captured and analysis confined to unvaccinated group • Model used to estimate impact of misclassification of vaccinated status if participants received vaccination outside of the HMO; vaccination misclassification had modest effects on modelled estimates **Weaknesses** • Study did not control for the circulation of multiple pathogens (other than RSV), gender or other seasonal factors • Could not do analysis for influenza-only periods because of the limited number of influenza-only weeks so used excess during any influenza period, therefore RSV effects may be confounding the influenza-associated impact • Small sample size for low-risk adults age 18-64 limits the statistical power • Unclear how generalizable the

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	categories and other cardiovascular and respiratory conditions. • Weekly excess hospitalization rates during influenza and RSV periods were measured relative to peri-season reference periods where neither virus was predominant; respiratory season (period) rates were calculated by multiplying weekly rates by the average length of the influenza and RSV periods • Rates of influenza-associated hospitalizations were compared among unvaccinated adults in three age groups (18-49, 50-64, ≥65)			HMO populations are to Ontario • Rational for percent positivity cut-off (>10%) to define influenza period not articulated • Sparse influenza viral surveillance data available for one HMO area • Direct evidence lacking for causative pathogen that led to hospitalization/death • Influenza subtype not analyzed/presented in results
Neuzil KM, Reed GW, Mitchel EF, Jr., Griffin MR. Influenza-associated morbidity and mortality in young and middle-aged women. JAMA. 1999;281(10):901-7	• Retrospective cohort study to identify hospitalizations for and deaths due to pneumonia, influenza and other selected acute cardiopulmonary conditions in Tennessee from 1974 to 1993 • Study population included all non-pregnant white or African American women aged 15-64 with at least 180 continuous days of enrollment in the Tennessee Medicaid program; men were excluded from this analysis because relative few men were covered by this program • Influenza season was defined each year as the period from November 1 to April 30 that included the dates of the first and last influenza viral isolation as determined by surveillance at Vanderbilt University; peri-influenza season was defined as each period from November 1 to April 30 where there was no influenza activity • Based on information present in the	• In high-risk women age 15-44 years, 10.3 events per 10,000 person-months (95% CI: 5.9 to 14.7) were estimated to be attributed to influenza viral infection; in high-risk women age 45-64 years, 26.4 events per 10,000 person-months (95% CI: 22 to 30.7) were estimated to be attributed • For low-risk women, rates of study events during influenza season were much lower than for women with high-risk conditions • In low risk women age 15-44 years, 2.0 events per 10,000 person-months (95% CI: 1.6 to 2.4) were estimated to be attributed to influenza viral infection; in low-risk women age 45-64 , 2.9 events per 10,000 person-months (95% CI: 0.58 to 5.2) can be attributed	• Excess hospitalizations and deaths attributed to influenza was most pronounced among high risk women • Even among women without traditional high-risk medical conditions, acute cardiopulmonary hospitalizations increased significantly during influenza season • Although hospitalization and death rates in low risk women were relatively low, this is a large population and so the public health impact of extrapolating these	**Strengths** • Sources of data and inclusion/exclusion criteria detailed and clearly articulated • Outcomes and co-morbidities clearly defined using ICD codes • Incidence rate and influenza attributable risk calculations clearly articulated; peri-seasonal rates used as the comparison, although summer rates also provided • Results consistently reported throughout • Data from 19 consecutive years used to reflect potential variation in influenza incidence and severity between seasons, although two of the seasons were defined as having no influenza activity • Lab confirmed influenza surveillance data used to determine influenza periods

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	Medicaid files, all person-time and study outcomes were classified into 1 of 4 mutually exclusive risk strata: high risk, recent hospitalization, blind/disabled, or low risk • High risk stratum included the following medical conditions based on ICD codes: chronic lung disease, diabetes, chronic heart disease, malignancy, long-term corticosteroid use, chronic renal disease, and HIV infection • Study outcomes included: acute cardiopulmonary hospitalizations and deaths for pneumonia and influenza, and for a broader range of acute cardiopulmonary conditions, including other acute respiratory conditions, other respiratory conditions, and heart failure/myocarditis • Incidence of study hospitalizations and deaths during influenza and peri-influenza seasons were calculated separately for each risk stratum; rates during the summer were also included but not used as the baseline • Influenza attributable risk was calculated by subtracting the rates during the peri-influenza season from adjusted rates during the influenza season	• Women in the recent hospitalization and blind/disabled strata had event rates and influenza attributable risk that were intermediate between the estimates for women in the low and high risk strata • The influenza-attributable mortality rate from cardiopulmonary causes for high-risk women age 45-64 was 1.8 deaths per 10,000 person-months (95% CI: 0.8 to 2.7) • Among low-risk women , deaths due to cardiopulmonary causes were rare and the rate attributable to influenza (0.02 per 10,000 person-months 95% CI: -0.01 to 0.05) was not statistically significant • Excess cardiopulmonary events in influenza season compared to per-influenza season were highest in those with HIV, followed by chronic renal disease, chronic heart disease, chronic lung disease and malignancy	rates to the entire population is substantial • Excess cardiopulmonary events varied markedly from season to season, with H3N2 seasons having the highest influenza attributed mortality	**Weaknesses** • Study did not control for the circulation of other pathogens, other seasonal factors or vaccination status • Study only investigated females 16 to 64 years of age, limiting generalizability to males or older age groups • Concerns regarding the generalizability of the Tennessee Medicaid population to Ontario, as the Medicaid population has high proportions of low income individuals and African Americans (47% African American) • Local surveillance data for influenza activity may not reflect broader influenza levels across the state/country • Direct evidence lacking for causative pathogen that led to hospitalization/death
Pockett RD, Watkins J, McEwan P, Meier G. Burden of illness in UK subjects with reported respiratory infections vaccinated or unvaccinated against	• Statistical modelling study using retrospective data to estimate influenza attributable general practitioner (GP) consultations, hospitalizations and deaths in the United Kingdom (UK) from January 21, 2001 to March 31, 2009	• Results from multivariate analysis showed high-risk patients and patients who had been vaccinated had a higher probability of >1 ILI related GP visit, compared with those who were not high-risk or had not	• Multivariate analysis indicated that patients categorised as high-risk had a disproportionate risk of hospitalization	**Strengths** • Sources of data and inclusion/exclusion criteria detailed and clearly articulated • Terms within regression model clearly defined

Reference	Methods	Results	Study Authors' Comments	Quality assessment
influenza: A retrospective observational study. PLoS ONE. 2015;10 (8):1-19	• For patients in a database that linked GP visits and hospitalizations, influenza cases were determined based on at least one GP consultation READ code describing influenza, acute upper or lower respiratory tract infection or influenza-like illness (ILI); hospitalizations within 14 days following the GP visit were monitored • Consultations with any of these READ codes that occurred during periods of peak influenza activity were attributed to ILI • Peak influenza periods were identified by regression analysis as weeks when influenza A and influenza B were circulating based on influenza and other respiratory pathogen surveillance data from the UK Health Protection Agency • Patients were stratified by age group (< 5, 5-18, 19-49, 50-64, and 65+ years of age), risk status and influenza vaccination status • Mortality data were identified by GP record or at hospital discharge from the linked data set • Primary outcome measures were mortality, resource use and cost associated with influenza in primary and secondary care, stratified by age group, complication status, vaccination status and risk status • Multivariable regression analysis was used to estimate the proportion of GP consultations, hospitalizations and deaths attributable to each pathogen • Independent variables included: weekly number of national laboratory	been vaccinated • The odds ratio (OR) for GP visits for vaccinated patients was 1.19 (95% CI 1.11 to 1.28); the OR for GP visits for high-risk patients was 2.16 (95% CI 2.02 to 2.28) • There was an interaction such that patients who were at high risk and vaccinated had a reduced risk of >1 GP visit, with an OR of 0.82 (95% CI 0.75 to 0.91); there was no apparent age interaction so these effects were relevant for all age groups • Based on the ORs derived from the logistic regression coefficients provided in the study, increased age and high risk conditions were associated with hospital admissions and deaths; the OR for hospitalization was calculated as 3.23 for those with high risk conditions compared to those without these conditions • High risk individuals who were vaccinated had a lower probability of ILI-related hospitalizations than individuals who were high-risk or vaccinated alone (OR = 0.59; 95% CI 0.46 to 0.75) • Individuals who were high-risk had a higher probability of ILI-related death during the study period (OR = 1.46; 95% CI 1.25 to 1.69)		• Results consistently reported throughout • Data from 9 consecutive years used to reflect potential variation in influenza incidence and severity between seasons • Laboratory-confirmed influenza surveillance data used to determine influenza periods • Model validity assessed • Model controlled for multiple pathogens, vaccination status and gender • Vaccine mismatch analysis performed **Weaknesses** • Outcomes defined, however specific ICD codes were only listed in supplementary material that was not accessible • Risk status not clearly defined; reference to other studies • Funding by GlaxoSmithKline; potential conflicts of interest • Overall methodology somewhat unclear; reference to other studies • Only regression coefficients presented in tables; OR presented in results section (difficult to verify consistency) • Unclear the type of regression model used • Model sensitivity analyses not explicit • Surveillance data from sentinel

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	reports for adenovirus, coronavirus, influenza A, influenza B, *Mycoplasma pneumoniae,* parainfluenza, respiratory syncytial virus and rhinovirus • A multiplying factor was calculated to extrapolate from the database sample to the total UK population			practices may not be generalizable • Direct evidence lacking for causative pathogen that led to hospitalization/death
Jansen AG, Sanders EA, Hoes AW, van Loon AM, Hak E. Influenza- and respiratory syncytial virus-associated mortality and hospitalisations. [Erratum appears in Eur Respir J. 2008 Mar;31(3):691]. Eur Respir J. 2007;30(6):1158-66	• Statistical modelling study using administrative data to estimate influenza- attributed mortality and hospitalizations in the Netherlands from 1997-2003, with a particular focus on low risk adults ages 50 to 64 years who are not covered by high risk influenza vaccination programs • Viral surveillance data for influenza and respiratory syncytial virus (RSV) was obtained from the Weekly Sentinel System of the Dutch Working Group on Clinical Virology • National weekly mortality figures were obtained from Statistics Netherlands • Weekly hospitalization rates were obtained nationwide; all hospitalizations with the following discharge diagnoses were included: acute upper respiratory disease, acute or chronic lower respiratory disease, cardiovascular disease, cerebrovascular disease, bacterial invasive disease, and other conditions possibly related to a respiratory infection • Hospitalizations were divided into upper respiratory tract infections (URTI), lower respiratory tract infections (LRTI) and pulmonary diseases (PD), cardiovascular	• A total of 839,303 all-cause deaths and 1,551,598 hospitalizations for URTI, LRTI, CVC and 'Others' were registered • 13% of influenza associated deaths occurred in those 50 to 64 years of age and 80% of these deaths occurred in those 65 years of age and older • No evidence of excess mortality was found in the age category 18-49 years during the influenza virus active periods; among those ≥50 years, significant influenza-associated excess mortality was recorded • Among 50-64 year olds, influenza associated mortality was highest for 60-64 year olds • In adults, significant excess hospitalization for LRTI and CVC was recorded during influenza virus active weeks • Excesses influenza-associated hospitalizations for all diagnosis categories (URTI, LRTI and PD, CVC and others) increased with age and was significant among low-risk 50-64 year olds which was the group that was the	• The study was not able to estimate which part of excess mortality occurred in low-risk individuals 50-64 years, as information about risk status was not available in the mortality figures. • Influenza-associated hospitalization was significant among low-risk 50-64 year olds, with hospitalization due to cardiovascular complications making up the largest part of influenza-associated hospitalization • The true influenza-associated excess mortality and hospitalization probably lies within estimations based on the peri-seasonal and summer baseline period. • All influenza seasons	**Strengths** • Sources of data and inclusion/exclusion criteria detailed and clearly articulated • Outcomes and co-morbidities clearly defined using ICD codes • Rate difference calculations clearly articulated • Results consistently reported throughout • Data from six consecutive influenza seasons used to reflect potential variation in influenza incidence and severity between seasons • Laboratory confirmed data on influenza and RSV used to determine periods where each was circulating and to separate the impact of each virus • Analysis conducted using both the summer season and peri-seasonal periods as baselines **Weaknesses** • Study did not control for the circulation of multiple pathogens, gender, vaccination status or

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	complications (CVC) and others • High risk conditions were extracted from the hospitalization data and consisted of at least one of the following: chronic respiratory disease, chronic cardiac disease, diabetes mellitus, renal insufficiency, haematological malignancy, or HIV/AIDS • Influenza virus active period was defined as the periods of at least 2 consecutive weeks in which each week accounted for ≥ 5% of the season's total number of laboratory confirmed influenza cases • The period of influenza predominance was defined as the influenza virus-active weeks with <5% of the season's total number of positive tests for RSV; • The peri-season baseline period was defined as periods of at least two consecutive weeks within winter (week 40 of one year and week 20 of the next year) in which each week accounted for <5% of the seasons total number of influenza and RSV-positive cases • The summer baseline period was defined as weeks 21-39 • Weekly excess mortality and hospitalizations associated with influenza virus and RSV were determined by subtracting summer and peri-seasonal baseline rates from rates during periods of influenza virus or RSV predominance • The cumulative annual winter excess influenza rate was the total average excess weekly rate during influenza	primary focus of the study • For adults 50-64 years of age, influenza-associated hospitalizations (using the summer baseline) for lower respiratory tract infection and pulmonary disease were much higher for those with risk factors (66.5/100,000) compared to those without risk factors (12.8/100,000). For those 65 years of age and older the rate was 115.2/100,000) and wasn't assessed by risk factors. • Similar differences in influenza-associated cardiovascular disease hospitalizations by risk factor was not noted for those 50-64 years of age when using a summer baseline (24.9/100,000 for high risk and 21.7/100,000 for those without risk factors); the rate in those 65 years of age and over was 81.1/100,000.	were A/H3N2 dominant, except 2000-2001, which was A/H1N1 dominant; no comments on vaccine match • Vaccination coverage among the elderly was 70-80%	other seasonal factors • Validity of using ≥ 5% of all positive cases for the season in two consecutive weeks to define influenza virus active period uncertain • High risk conditions may have been missed in hospitalization data resulting in individuals with these conditions being misclassified as low risk • Direct evidence lacking for causative pathogen that led to hospitalization/death

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	predominant weeks multiplied by the number of influenza active weeks • The proportion of the population with high risk condition for influenza complications was derived from the National Information Network Primary Care.			
Matias G, Taylor R, Haguinet F, Schuck-Paim C, Lustig R, Shinde V. Estimates of mortality attributable to influenza and RSV in the United States during 1997-2009 by influenza type or subtype, age, cause of death, and risk status. Influenza other respi. 2014;8(5):507-15	• Statistical modelling study using administrative data to estimate mortality attributed to influenza in the USA, stratified by age and risk status, for 12 influenza seasons from October 1, 1997 to March 31, 2009 • Weekly numbers of respiratory samples testing positive for influenza A and B in each of the 4 US census regions were obtained from FluView (CDC) • Weekly laboratory-confirmed regional and national respiratory syncytial virus (RSV) surveillance data was collected from laboratories that participate in national surveillance • Mortality data obtained from US National Vital Statistics System • Records were excluded if there was missing data on age, primary diagnosis, or month of death; the period April 2009 – September 2009 was excluded to avoid bias associated with circulation of 2009 A/H1N1 pandemic influenza • Records were classified as high risk if any of the following comorbidity diagnosis codes were listed under cause of death: COPD, cardiovascular disorders, kidney disorders, diabetes, immunosuppression, liver disorders, stroke, and central nervous system	• The distribution of influenza-attributable mortality across age groups was similar for P&I, respiratory broad and cardiorespiratory outcome definitions • The rates of death were highest in persons aged ≥ 75 years, accounting for 73% to 77% of the influenza-attributable deaths depending on the outcome used. • Those 65-74 years accounted for 10 to 14% of the deaths, depending on the outcome • Using the "respiratory broad" outcome, the risk of influenza-attributable death relative to the 50-64 year age was 22.7 in the 75+ age group and approximately 4.0 for the 65-74 year age group • Using the "respiratory broad" outcome, influenza A/H3N2 accounted for 71% of the deaths, influenza B for 29% and influenza A/H1N1 for 0.4% • The pattern of increasing mortality burden by age was consistent for influenza A/H3N2 and influenza B but not for influenza A/H1N1; deaths	• Comparisons provided with other models used during the same time period and explanations provided as to why there may be differences in findings • In addition to influenza, RSV is associated with substantial mortality in the elderly • An explanation in the lower relative risk between high and low risk groups in those 75+ is that frailty and susceptibility to complications increase with age independent of underlying chronic conditions	**Strengths** • Sources of data and inclusion/exclusion criteria detailed and clearly articulated • Results consistently reported throughout • Data from 12 consecutive influenza seasons used to reflect potential variation in influenza incidence and severity between seasons • Laboratory confirmed data on influenza and RSV used as an explanatory variable in the model • Influenza attributable mortality assessed against three different outcomes with varying sensitivity and specificity • Model goodness of fit assessed; sensitivity analysis performed • Model controlled for both influenza and RSV and included additional terms to adjust for possible influence of non-infectious factors and pathogens other than influenza and RSV on respiratory mortality • Influenza subtype analyzed/presented in results

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	disorders; if none of these conditions were listed, they were classified as low risk • Three mortality outcomes were defined: i) pneumonia & influenza (P&I), ii) respiratory disease broadly defined (respiratory diseases, cough, breathing abnormalities, fever and viral infection not otherwise specified) and iii) cardiorespiratory disease • A multiple linear regression model was developed • Model outcomes were stratified by age (0-4, 5-17, 18-49, 50-64, 65-74, 75+) and risk status	attributed to H1N1 were more common in children and young adults compared to older adults • In general, influenza-attributable mortality was higher for high-risk versus low-risk individuals • In adults, the relative risk of death for high versus low risk status for the 'respiratory broad' outcome definition was 1.45 in individuals aged 18-49; 3.72 in those 50-64; 5.84 in those age 65-74 years and 2.75 in those 75+		**Weaknesses** • Some terms within model not clearly described • Mortality data only available by month making it more difficult to ascertain the effect of influenza and RSV in some seasons where they circulated closely together • Virologic circulation was based on all ages combined, even though timing of influenza and RSV circulation may differ by age • Other potential drivers of mortality, including other pathogens were not included in the model • Data on influenza vaccination are not captured and may differ between risk groups and for age categories • Model did not control for gender • High risk conditions may have been missed in hospitalization data resulting in individuals with these conditions being misclassified as low risk • Direct evidence lacking for causative pathogen that led to death
Schanzer DL, Langley JM, Tam TW. Co-morbidities associated with influenza-attributed mortality, 1994-2000, Canada. Vaccine. 2008;26(36):4697-	• Statistical modelling study using administrative data to estimate influenza mortality based on age, health status and place of residence (i.e., community or long term care) in Canada from September 1994 to August 2000 • Discharge records of all persons who	• Over the study period approximately 4000 influenza attributable deaths occurred per year • Influenza-attributed mortality rates increased with age from 23/100,000 in persons aged 65-69 to 831/100,000 in persons	• Age, as well as co-morbidity, contribute independently to elevated risk of influenza associated mortality; increasing risk with age was apparent for all	**Strengths** • Sources of data and inclusion/exclusion criteria detailed and clearly articulated • Outcomes and co-morbidities clearly defined using ICD codes • Terms within model clearly

Reference	Methods	Results	Study Authors' Comments	Quality assessment
703.	died in hospital with any respiratory condition were extracted from the Hospitalization Database, aggregated to a weekly level and stratified by 5-year age groups and presence of co-morbidities • Co-morbidities included: chronic lung disease other than asthma, chronic heart conditions, asthma, diabetes, and chronic kidney disease • Patients admitted with only acute respiratory or acute heart conditions and with no other diagnosis were considered to be healthy, although their actual health status is unknown • Records extracted from the Discharge Abstract Database to identify patients transferred from a non-acute health care institution (excludes Quebec); population numbers of people living in health care related collective dwellings was obtained from the census • All cause deaths were extracted from the Canadian Vital Statistics Death Database and aggregated to weekly levels by 5-year age groups • Influenza-attributed deaths were estimated for 5-year age groups based on all-cause mortality from the Death Database, for age and health status cohorts from the Hospitalization Database and for age and place of residence from the Discharge Abstract Database • Measures of influenza activity included: influenza certified deaths, influenza certified admissions, weekly surveillance data on the number of tests performed and positive for	aged 90+ • Approximately 3% of deaths attributed to influenza were among otherwise healthy seniors, primarily over the age of 80 years • In persons under the age of 60, deaths were infrequent and of insufficient number to permit rate calculations stratified by health status • The proportion of annual all cause deaths attributed to influenza ranged from 2% in persons aged 65–69 years to 5% in persons aged 90 years and over, and was similar or slightly higher for institutional versus community dwelling elderly • The majority of hospitalized patients whose death was attributed to influenza had chronic heart or chronic lung conditions (80%) • For persons aged 65+, the risk for influenza-attributable death was 20 times higher for those with both chronic heart and chronic lung disease than for those with neither condition, and 12 and 5 times higher for persons with chronic lung disease and chronic heart disease respectively • The fatality rate for persons hospitalized due to influenza increased from 4% for persons aged 50-64 to 30% for persons aged 90+	health status groups • Regardless of health status, 90% of the mortality burden was in those 65 years of age and over, with a median age at death of 80-84 years • In Canada, vaccine coverage rate is 70% for persons over 65+ living in the community	defined in appendix • Data from 6 consecutive influenza seasons used to reflect potential variation in influenza incidence and severity between seasons • Laboratory confirmed data on influenza, RSV, parainfluenza, adenovirus and a surrogate for ILI used as variables in the model • Regression model accounted for possible additive effects of multiple respiratory pathogens and included additional terms to adjust for other secular and seasonal trends **Weaknesses** • Relevance of certain terms within the model are not presented • Goodness of fit testing or sensitivity analyses not detailed • Co-morbidity for deaths only available for those deaths that occurred in hospital; • Uncertainty regarding calculations of rates of risk conditions due to both numerator and denominator issues. • Use of mortality data associated only with respiratory conditions may have missed influenza attributed deaths coded with different ICD categories (e.g. cardiovascular, etc.), although authors noted that previous work and this study showed that influenza activity had a minimal

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	influenza. • Influenza test and tests for other viruses (respiratory syncytial virus (RSV) parainfluenza virus and adenovirus) were obtained from the *FluWatch* program • Poisson regression model was developed with a linear link function to maintain a linear relationship between viral activity and attributable deaths; proxies for RSV, parainfluenza, adenovirus and a surrogate for other influenza-like illness (ILI) were included in the model • Seasons were classified as mild, moderate or severe, according to their respective mortality burden • Influenza attributed deaths were calculated as the difference between model-predicted deaths and the model-predicted deaths under the hypothetical absence of influenza • Published prevalence estimates of chronic cardiac and pulmonary conditions by age provided denominators to calculate rates by health status, with an adjustment for those with chronic lung disease among those with chronic heart disease • Mortality rates by health status were adjusted for the age-specific proportion of influenza-attributable deaths occurring in hospital • Age specific estimates of influenza-attributed hospitalization rates provided the denominator to calculate fatality rates for hospitalized cases • Estimates of the case fatality rate for infected cases were based on a clinical			impact on admissions without any mention of respiratory conditions • Model did not control for gender or vaccination status • Some tables in results section a bit unclear with respect to how they were organized • Error noted in one table • Co-morbid conditions may have been missed in hospitalization data • Direct evidence lacking for causative pathogen that led to hospitalization/death • Influenza subtype not analyzed/presented in results, although analysis done by severity of the season

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	attack rate of 5-10%			
Barker WH, Mullooly JP. Pneumonia and influenza deaths during epidemics: implications for prevention. Arch Intern Med. 1982;142(1):85-9	• Cross sectional study to estimate absolute and relative risk of pneumonia and influenza (P&I) associated death among subgroups of the population in the Kaiser-Permanente Medical Care Program in Portland, Oregon during two epidemics of influenza A (H3N2) (December – March 1968-1969, 1972-1973) • Study is based on 38 of the 39 P&I associated deaths that occurred during the two epidemics (years with two to three fold excess hospitalization and death rates); one death was excluded based on missing medical records; these were compared with 38 consecutive P&I deaths occurring among adults between November through April of the three intervening non-epidemic years • Numbers of persons at risk for various categories of chronic disease was estimated from medical care records of a 5% probability sample of the health plan population • High-risk conditions, other demographic information including residence in a nursing home were obtained by reviewing the charts for those who died. Chronic high risk medical conditions were defined as: cardiovascular, pulmonary, renal, liver, central nervous system (CNS), diabetes, or cancer during the year before one of the epidemic periods • P&I associated hospitalizations were defined as: all medical admissions	• In both the epidemic and non-epidemic years, two-thirds of those who died were older than 65 years of age, there was a predominance of males, and greater than 90% of those who died had underlying chronic conditions, of which cardiovascular conditions were the most common followed by either chronic pulmonary conditions or malignant disease depending on seasons. Diabetes was also common. • More than 50% of the P&I associated deaths occurred in persons who were classified as being in good health or chronically ill but stable based on their medical records in the preceding year • Rates of deaths increased with the presence of risk factors and the number of risk factors. • Differences in rates between risk groups attained statistical significance when the experience of all persons older than 45 years was aggregated • In those 45 years of age and over, the risks of P&I mortality when one underlying condition and two or more underlying conditions were present were respectively estimated to be 39 and 202 times that for persons without underlying disease	• There was little difference in demographic or clinical features of the P&I associated deaths in epidemic and non-epidemic years. • The high proportion of deaths in those 65 years of age and over and those with chronic medical conditions are consistent with other observations/studies.	**Strengths** • Outcomes and high risk medical conditions clearly defined • Relative risk analysis performed; data stratified by age and high-risk medical condition **Weaknesses** • Small sample size • Sources of incoming data and statistical methods used for analysis unclear • Data collected for two non-consecutive influenza A (H3N2) epidemics • Study did not use laboratory confirmation to determine cases, so deaths may not have been due to influenza • No information on circulation of other viruses that could result in P&I associated deaths • Analysis did not give complete data on vaccination status or match between vaccine and circulating strain, although information was provided for one season • Only P&I outcomes analysed; may have missed influenza attributable fatalities with other diagnostic codes • Unclear how generalizable the Portland, Oregon Medical Care population would be to Ontario

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	during the epidemics in which either pneumonia or influenza was listed among the discharge diagnoses; those with fatal outcomes were defined as P&I associated deaths			• Limited information provided regarding vaccination status and vaccine match to circulating strain
ARTICLES ASSESSING THE 2009-2010 H1N1 INFLUENZA PANDEMIC				
Campbell CN, Mytton OT, McLean EM, Rutter PD, Pebody RG, Sachedina N, et al. Hospitalization in two waves of pandemic influenza A(H1N1) in England. Epidemiol Infect. 2011;139(10):1560-9	• Cross sectional study to investigate risks for hospitalization from pandemic influenza A(H1N1) in England at the population level and for individuals with pre-existing conditions from April 1, 2009 to January 6, 2010 • Data from hospital in-patients with pandemic influenza A(H1N1) were gathered from a hospital surveillance system; collected data included risk factors • Cases were defined as any person formally admitted to hospital who had laboratory confirmed pandemic influenza A(H1N1) during or prior to their hospital admission; additional cases were also identified through the Health Protection Agency's regional microbiology network • Estimated hospitalization rates for cases with symptomatic pandemic influenza A(H1N1) were calculated with a 1-week lag period assumed from disease onset to hospital admission using estimates of the number of symptomatic cases of pandemic influenza A(H1N1) as the denominator • Method for estimating the number of symptomatic cases incorporated the number of people consulting their GP	• 2416 hospitalized cases were reported from April 1, 2009 to January 6, 2010 • Hospitalization rates among cases were highest in the very young and very old • 58% of those hospitalized had one or more pre-existing conditions and the proportion increased with age • For patients age 6 months to 64 years , the age-adjusted relative risk of hospitalization was 10.3 (95% CI 9.4 to 11.3) times greater for those with a pre-existing medical condition compared to those without • For patients age 65+ years, the relative risk of hospitalization was 2.8 (95% CI 1.7 to 4.6) times greater for those with a pre-existing medical condition compared to those without • Pre-existing conditions conferring the highest relative risk for hospitalization in those age 6 months to 64 years were: immunosuppression, chronic renal disease, chronic neurological disease and chronic respiratory disease	• The study estimated that 0.31 % of pandemic A(H1N1) cases were hospitalized • Both the elderly and the young had high rates of hospitalization • Chronic kidney disease, chronic neurologic disease, chronic respiratory disease and immunosuppression are associated with 10-20 fold increased risk of hospitalization • England employed a targeted vaccination campaign; in the first phase vaccination was offered to those with pre-existing medical conditions, and in the second phase vaccination was offered to all children <5	**Strengths** • Sources of data and case definitions clearly articulated • Data collected for 10 consecutive months during pandemic influenza A(H1N1) outbreak; large sample size • Results consistently reported throughout • Lab confirmed data on pandemic influenza A (H1N1) used to define cases • Stratification by age and pre-existing condition • Took into account the prevalence of risk factors in the population when assessing the risk factor prevalence in cases **Weaknesses** • Some outcome terms (pre-existing medical conditions, critical care admissions, complications) not clearly defined • Gender and vaccination status not controlled for • Surveillance system likely to be incomplete in capturing cases; difficult to do quality assurance of

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	with influenza-like illness, the number using a national internet and telephone based system to obtain antiviral medication, the proportion of each of these groups with laboratory confirmed pandemic influenza A(H1N1) in a tested sample and an estimate of the proportion of those with symptomatic illness who do not seek medical attention via either of these routes • Risk factor prevalence for the general population was estimated from the influenza vaccine uptake monitoring system and it was assumed that the risk of acquiring pandemic influenza was the same in those with risk factors as in the general population • Pooled Mantel-Haenszel age-adjusted relative risks were calculated for each pre-existing condition; comparison group were those with no risk factors • The attributable fraction in the exposed and the population attributable fraction were estimated for each pre-existing condition	• The proportion of hospital patients admitted to critical care increased with age • Pre-existing conditions were significantly more common in patients admitted to critical care than in hospitalized patients as a whole (79% vs. 54%) • Of the 10.5% hospitalized patients admitted to critical care, the proportion with a pre-existing condition was similar across the age groups for those aged <65 years • A lower proportion of those aged ≥65 admitted to critical care had a pre-existing condition than those age ≤64 years (60% vs. 82%) • The case fatality in hospitalized cases was 3.5%; Hospital case fatality rate was highest in those age >64 (20%); significantly higher case fatality rates were found for those with pre-existing conditions compared to those without (5.1% vs 1.4%)		the surveillance system in an pandemic • Accuracy of mechanism to estimate total number of symptomatic cases uncertain • Possible calculation errors in table • Findings from H1N1 pdm09 may not be generalizable to other strains/seasons • Individuals with underlying medical conditions may be more likely to seek care and be tested for influenza and may be more likely to be admitted to hospital • It is uncertain if it is appropriate to assume that the risk of acquiring pandemic influenza was the same in those with risk factors as in the general population
Gilca R, De Serres G, Boulianne N, Ouhoummane N, Papenburg J, Douville-Fradet M, et al. Risk factors for hospitalization and severe outcomes of 2009 pandemic H1N1 influenza in Quebec,	• Case-control study to assess risk factors associated with hospitalizations and severe outcomes (ICU admission or death) among patients with confirmed pH1N1 in four regions in Quebec (Montreal, Monteregie, Laval, and Quebec City which accounted for the majority of cases in the province) from May 25, 2009 to July 1, 2009	• A total of 395 non-hospitalized patients and 321 hospitalized patients were included in the study • In multivariable analysis, age <5 years (OR = 5.5, 95% CI 2.1 to 14.3), consultation ≥ 5 days after illness onset (OR = 1.9, 95% CI 1.2 to 2.9) and presence of ≥1 underlying chronic	• Older individuals had a lower risk of infection but if they became infected they were more likely to get severe disease • The presence of underlying chronic conditions was the strongest contributing	**Strengths** • Relevant study setting/population, findings applicable to Ontario • Sources of data and inclusion/exclusion criteria detailed and clearly articulated • Outcomes and underlying medical conditions clearly defined

Reference	Methods	Results	Study Authors' Comments	Quality assessment
Canada. Influenza other respi. 2011;5(4):247-55	• All hospitalized and non-hospitalized cases with onset of laboratory confirmed pH1N1 during the study period from the registry of the provincial reference laboratory were considered eligible for the study • Cases were defined as patients with laboratory-confirmed pH1N1 illness admitted to hospital for ≥24 hours • Severe disease was defined as admission to ICU and/or death • Controls were defined as non-hospitalized patients with laboratory-confirmed pH1N1 illness • Trained interviewers called eligible patients to collect demographic and clinical data using standardized questionnaires; for deceased patients close family relatives were used • Odds ratios calculated to identify risk factors for hospitalization and severe disease were derived from univariate and multivariable logistic regression • Underlying medical conditions were analysed as a group (≥1 underlying medical condition) or individually for the most frequent categories (cardiac, pulmonary, diabetes mellitus, asthma, immunosuppression, neurological, and renal conditions); conditions such as anemia, cancer, liver and metabolic diseases were merged into an 'other' category • Final adjusted models included some or all of the following variables: gender, age, education, healthcare worker, smoking, seasonal influenza vaccination in 2008-2009, delay in consultation, antiviral use before	condition (OR = 4.9, 95% CI 3.2 to 7.3) were significantly associated with hospitalization • All underlying chronic conditions except immune-suppression were significantly associated with hospitalization • Among hospitalized patients, none of the examined factors further significantly increased the risk of admission to an ICU or death • In a separate model, the only significant association with death was observed for age ≥60 years (OR = 14.4, 95% CI 1.0 to 197.3) and immune suppression (OR = 7.3 , 95% CI 1.5 to 35.0)	factor to hospitalization, ICU admission and deaths.	• Terms within regression model clearly defined • Results consistently reported throughout • Laboratory confirmed influenza surveillance data used to determine cases/controls • Sensitivity analyses performed removing patients with missing data or health care workers, which did not alter results • Model controlled for gender, age, education, healthcare worker, smoking, seasonal influenza vaccination in 2008-2009, delay in consultation, antiviral use before hospital admission, pregnancy, obesity and sub-categories for underlying medical conditions **Weaknesses** • Data from only two months collected during the first part of the 2009 H1N1 pandemic • Findings from H1N1 pdm09 may not be generalizable to other strains/seasons • Only 43% of eligible non-hospitalized people reached compared to 81% of hospitalized cases • Information collected directly from patients or their proxy so subject to recall bias; proxy responses may differ from the rest of the population; hospitalized patients may respond

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	hospital admission, pregnancy, obesity and sub-categories for underlying medical conditions			differently than non-hospitalized patients • Individuals with underlying medical conditions may be more likely to seek care and be tested for influenza and may be more likely to be admitted to hospital • Small sample size for patients admitted to ICU/death limits power
Ward KA, Spokes PJ, McAnulty JM. Case-control study of risk factors for hospitalization caused by pandemic (H1N1) 2009. Emerg Infect Dis. 2011;17(8):1409-16	• Case-control study to identify independent risk factors for moderate to severe disease from pH1N1 infection among adults in Sydney from July 1, 2009 – August 31, 2009 • Moderate to severe disease was defined as requirement for hospital admission • Study population included persons age >16 years residing in metropolitan Sydney • A case was defined as a person with influenza-like illness admitted to a Sydney metropolitan hospital for a minimum of an overnight stay with laboratory confirmed pH1N1 during the study period • A control was defined as a person > 16 years residing in metropolitan Sydney who had not been hospitalized for influenza in 2009; telephone numbers were used to randomly select controls • Two households were selected per case matched on Area Health Services (of which there are four in Sydney) and a single control was randomly selected from within each household for interview • A telephone interview was performed;	• A total of 402 hospitalized cases were identified as eligible of which 302 (75%) cases agreed to participate; • Of 1,252 potential controls, 603 (48%) agreed to participated in the study • 86% of cases reported one or more independent risk factor compared to 52% of controls • No significant differences between cases and controls for receipt of 2009 seasonal influenza vaccination • In the logistic regression model, the following were independently associated with hospitalization: age, gender, smoking, asthma which regularly required medication, (OR= 4.3, 95% CI 2.7 to 6.8),heart disease (OR=2.3, 95% CI 1.2 to 4.1), immune suppression (OR=5.5, 95% CI 2.8 to 10.9), lung disease (OR=6.6, 95% CI: 3.8 to 11.6), diabetes (OR=3.8, 95% CI 2.2 to 6.5) and pregnancy (OR=22.4, 95% CI 9.2 to 54.5)	• Pregnancy, lung disease, immune suppression, asthma, diabetes, heart disease and smoking were associated with hospitalizations for pH1N1.	**Strengths** • Relevant study setting/population, findings applicable to Ontario • Sources of data and inclusion/exclusion criteria detailed and clearly articulated • Case and control definitions clearly defined • Outcomes and underlying medical conditions clearly defined • Terms within regression models clearly defined • Results consistently reported throughout • Laboratory confirmed influenza surveillance data used to determine cases • Model goodness of fit performed • Hospitalization model controlled for gender, age, underlying conditions, smoking status and number of significant risk factors • Mechanical ventilation model controlled for: gender, age, aboriginal status, BMI, underlying conditions, smoking status and receipt of seasonal influenza

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	if case patients were unable to complete the interview another household member completed it on their behalf • Information collected from cases and controls included: influenza symptoms, pregnancy, weight/height, smoking history, current/previous medications, past hospitalizations, general health conditions (asthma, lung disease, heart disease, diabetes, other metabolic disorders, kidney disease, liver disease, blood disorders, mental health diagnoses, neurologic conditions, immune suppression and sleep apnea) • Univariate analysis performed to compare cases and controls using X^2 tests • Multivariate analysis performed; independent risk factors for hospitalization were assessed through logistic regression • Mechanical ventilation was used as a measure of severity of illness instead of admission to an intensive care unit due to varying criteria for admission to intensive care	• In the logistic regression model, compared to those 65+, the odds of hospitalization by age were as follow: 16-25, OR=5.4 (95%CI 2.5 to 11.4); 26-35, OR=4.1 (95% CI 2.0 to 8.3); 36-45, OR=3.9 (95% CI 2.0 to 7.6); 46-55, OR=5.1 (95% CI 2.7 to 9.6); and 56-65 OR=1.9 (95% CI 1.0 to 2.5) • The risk for hospitalization increased with increasing number of reported significant risk factors • In the logistic regression model for case patients requiring mechanical ventilation, history of lung disease, diabetes, pregnancy, high BMI and smoking were independently associated with mechanical ventilation • There was no significant difference in underlying risk factors between controls who reported ILI and controls who did not report any respiratory symptoms • ILI was significantly more common among controls age 16-25 and 36-45 compared with controls age >65		vaccine for 2009 **Weaknesses** • Data collected from only two months • Hospitalization model did not control for vaccination status and mechanical ventilation model did not control for number of relevant risk factors • Patients information subject to recall bias; proxy responses may differ from the rest of the population • Self-reporting may have missed undiagnosed or unacknowledged risk factors • Individuals with underlying medical conditions may be more likely seek care and to be tested for influenza and therefore included as cases, potentially biasing the comparison between cases and controls; Additionally clinicians may have a lower threshold for hospital admission for certain medical conditions • Patients who died from pH1N1 were excluded (those with the most severe disease); this was not mentioned in the methods section, only in the discussion section • Compared to the average Sydney adult population, controls were older and more likely to be women; the analysis adjusted for

Reference	Methods	Results	Study Authors' Comments	Quality assessment
				these differences • The underlying reason for admission to hospital was not determined (i.e., was it due to the underlying condition, the infection or both?) • Findings from H1N1 pdm09 may not be generalizable to other strains/seasons
Thompson DL, Jungk J, Hancock E, Smelser C, Landen M, Nichols M, et al. Risk factors for 2009 pandemic influenza A (H1N1)-related hospitalization and death among racial/ethnic groups in New Mexico. Am J Public Health. 2011;101(9):1776-84	• Cross sectional study to analyse risk factors for pandemic H1N1 related hospitalizations, mechanical ventilation and deaths in New Mexico from September 14, 2009 to January 13, 2010 • Confirmed H1N1 related hospitalization was defined as illness in a New Mexico resident who had been admitted to hospital with a laboratory confirmed positive influenza test • Weekly reports were provided by hospitals of all laboratory-confirmed influenza hospitalizations • Data on influenza related deaths were collected from hospitals, the Bureau of Vital Records and Health Statistics and the Office of the Medical Investigator • Patient data was collected on: gender, age, race/ethnicity, county median household income, obesity, high-risk medical conditions, pregnancy status, antiviral treatment, distance to medical care and rural/urban residence • High–risk conditions included: asthma, chronic lung disease, chronic cardiovascular disease, diabetes, other chronic metabolic disease, renal	• A total of 926 laboratory-confirmed pandemic H1N1-related hospitalizations were reported during the study period • Of hospitalized patients, 62% had one or more high-risk medical conditions with the three most common conditions being asthma (27%), diabetes (16%) and other chronic lung disease (16%). • Patients aged 5-24 years were significantly more likely to be hospitalized for H1N1 illness than were those age 65+ (RR=1.9, 95% CI 1.5 to 2.4); persons age 25-49 had a significantly lower rate of hospitalization (RR=0.8, 95%CI 0.6 to 0.96) • In two multivariate models, patients age 25-49 and those 50-64 years were significantly associated with mechanical ventilation; age over 65 years was significantly associated with mechanical ventilation in one model but not the other • In both models, positive	• Younger age groups were associated with hospitalization, whereas older age groups were associated with mechanical ventilation • This analysis did not identify any high-risk conditions, other than age, as independently associated with mechanical ventilation • Cancer and liver disease were independently associated with death.	**Strengths** • Sources of data, case definitions, outcomes and high risk medical conditions clearly defined • Data collected for four consecutive months during pandemic influenza A(H1N1) outbreak • Laboratory confirmed data on pandemic influenza A (H1N1) used to define cases • Regression analysis for mechanical ventilation/death controlled for: race/ethnicity, gender, age, county median household income, obesity, high-risk medical conditions, pregnancy status, antiviral treatment, distance to medical care and urban/rural status **Weaknesses** • Unclear why certain independent variables were included in regression model for hospitalization outcome and not in model for mechanical

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	disease, cognitive or neurological disease, hepatic disease, immunosuppression and cancer • Poisson regression was used to estimate associations between independent variables and population-based incidence rates of H1N1-related hospitalization • Multivariate logistic regression was used to assess risk factors for mechanical ventilation and death among hospitalized H1N1-infected patients	associations between mechanical ventilation and chronic lung disease and immunosuppressive conditions were found but did not achieve statistical significance • In a multivariate logistic regression analysis the following characteristics were associated with death: male gender (OR = 2.2, 95% CI 1.003 to 4.9), cancer (OR = 6.1, 95% CI 1.6 to 23.0) or having a liver disorder (OR = 7.3, 95% CI 2.5 to 21.0) • Age of 65+ years had been significant in the univariate analysis but was no longer significant in the multivariate analysis.		ventilation/death • Individuals with underlying medical conditions may be more likely to seek care and be tested for influenza and may be more likely to be admitted to hospital • Surveillance data may be subject to underreporting or under-testing • Absence of documented underlying condition was recorded as absence of the condition • Unclear how generalizable New Mexico's population would be to Ontario • Findings from H1N1 pdm09 may not be generalizable to other strains/seasons
Hlavinkova L, Kristufkova MJ. Risk factors for severe outcome of cases with pandemic influenza A(H1N1) pdm09. Bratisl Lek Listy. 2015; 116 (6): 389-93	• Cross sectional study to analyze association between risk factors and severe outcome of cases with laboratory-confirmed pandemic influenza virus A(H1N1)pdm09 in Slovakia from May 28, 2009 to December 30, 2009 • Eligible cases included adults and children with clinical symptoms of influenza with laboratory-confirmed pandemic influenza virus A (H1N1)pdm09 • Data on pandemic influenza cases were reported by local epidemiologists to the Department of Epidemiology at the Public Health Authority of the Slovak Republic (PHA SR) • Risk factor for severe outcome was defined as: allergy, any pulmonary	• A total of 1014 cases of pandemic influenza were notified to the PHA SR; 12.9% of the cases were hospitalized, of which 4.2% required admission to the ICU. The case-fatality rate was 3.75%. • The most affected age group was 15-24 (29.3% of cases); least affected were cases aged 65 and older (0.8%) • 5.6% of cases had a severe outcome • Multivariate analysis found COPD (OR 9.16, 95% CI 1.42 to 59.98), cardiovascular disease (OR 14.97, 95% CI 5.49 to 40.79), malignancy (OR 7.58, 95% CI 1.95 to 29.37) and	• Cases with severe outcomes were significantly older (median age 35 years) than cases with non-severe outcome (median age 24 years) • COPD, cardiovascular disease, malignancy and pregnancy were associated with severe disease in the multivariate analysis • The number of risk factors was significantly associated with severe outcome, however 35% of	**Strengths** • Sources of data, case/control definitions, outcomes and comorbidities clearly defined • Data collected for seven consecutive months during pandemic influenza A(H1N1) outbreak • Laboratory confirmed data on pandemic influenza A (H1N1) used to define cases • Regression analysis controlled for: age, gender and comorbidities **Weaknesses** • During later stages of epidemic, only severe cases underwent laboratory testing and were

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	disease, asthma, COPD, cardiovascular disease, malignancy, neuromuscular disease, diabetes mellitus, chronic renal insufficiency, chronic hepatic disease, obesity (BMI 30-40), pregnancy, immunodeficiency (except HIV), HIV, leukopenia and hematuria • Outcome of a case was defined as severe when cases required hospitalization in the intensive care unit and/or the patient developed pneumonia and/or died • Odds ratios were used as the measure of association between risk factor and outcome of illness (severe versus non-severe outcomes) • Logistic regression was used to examine the relationship between severity of disease and variables found to be significant in the univariate analysis and age and gender	pregnancy (OR 22.17, 95% CI 4.36 to 112.64) to be independently associated with severe outcome • After adjusting for age and gender, the absence of risk factors had a protective effect on disease severity (aOR 0.08, 95% CI 0.04 to 0.15) • Study patients with severe outcome were 3.28 times more likely to have 1 risk factor (95% CI 1.01 to 10.66) and 8.58 times more likely to have 2 and more risk factors compared to study patients with non-severe outcome (95% CI 4.80 to 15.32)	people with severe outcomes had no risk factors • Vaccination against pandemic influenza was not available in Slovakia during the study period	reported • Presence of comorbid conditions may make presentation for care, virologic testing, admission to the hospital and admission to the ICU more likely • Unclear how similar Slovakia's population would be to Ontario and therefore how generalizable the results are • Findings from H1N1 pdm09 may not be generalizable to other strains/seasons
Zarychanski R, Stuart TL, Kumar A, Doucette S, Elliott L, Kettner J, Plummer F. Correlates of severe disease in patients with 2009 pandemic influenza (H1N1) virus infection. CMAJ. 2010; 182(3): 257-64	• Cumulative case-control study to identify factors that were correlated with severe disease in confirmed cases of pandemic H1N1 influenza in Manitoba from April 2, 2009 to September 5, 2009 • Study population consisted of all laboratory-confirmed cases of pandemic H1N1 influenza involving residents of Manitoba for whom the final location of treatment was: community, hospital or intensive care unit (ICU) • Data sources included surveillance data from Manitoba Health for all reported cases and the University of Manitoba's Section of Critical Care for those cases admitted to the ICU	• A total of 894 case of pandemic H1N1 influenza were confirmed among Manitoba residents • For patients with available information, 72% remained in the community, 23% were admitted to a hospital but not to an ICU and 6% were admitted to an ICU • The mean age was 25.3 years for community cases, 23.0 years for those admitted to hospital and not the ICU, and 33.4 years for those admitted to the ICU • Comorbidities were present in 35% of the community cases, 57% of those admitted to hospital and not the ICU, and	• Relative to those not admitted to hospital, severe disease, defined by admission to the ICU, was associated with a longer interval from onset of symptoms to treatment with antiviral therapy and with the presence of an underlying comorbidity. • First Nations ethnicity was also associated with severe disease	**Strengths** • Sources of data, case/control definitions, outcomes and comorbidities clearly defined • Data collected for five consecutive months during pandemic influenza A(H1N1) outbreak • Laboratory confirmed data on pandemic influenza A (H1N1) used to define cases • Regression analysis controlled for: age, gender, First Nations ethnicity, medical comorbidities, interval from onset of symptoms to initiation of antiviral therapy, urban versus rural status and income quintile group

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	• Severe cases were defined as those in which the patient was admitted to an ICU • Two control groups were defined: moderate cases were those in which the patient with pandemic H1N1 required admission to hospital but not to ICU; mild cases (also termed community cases) were those with pandemic H1N1 without admission to hospital • Self-reported ethnicity was defined as either First Nations or another ethnic group • The variable 'any comorbidity' was defined as any of the following: heart disease, diabetes mellitus, tuberculosis, asthma, smoking, neuromuscular disease, kidney disease, malignancy, immune suppression, lung disease, cognitive dysfunction, pregnancy, alcoholism, substance abuse and injection drug use • Overall differences between groups were analyzed using ANOVA, X^2 or Fischer's exact test as appropriate • Logistic regression was used to examine the relation between variables of interest and severity of disease; cases of severe disease (ICU admission) were compared to controls who remained in the community or those who were admitted to hospital but not to the ICU	76% of those admitted to the ICU. • In the multivariable logistic model for ICU cases versus community controls, treatment interval (OR 8.24, 95% CI 2.82 to 24.1), First Nations ethnicity (OR 6.52, 95% CI 2.04 to 20.8) and the presence of a medical comorbidity (OR 3.19, 95% CI 1.07 to 9.52) were associated with increased disease severity • In the multivariable analysis of hospital controls without admission to an ICU and community controls, treatment interval (OR 3.61, 95% CI 1.79 to 7.28) and presence of medical comorbidity (OR 3.36, 95% CI 2.05 to 5.49) were significantly associated with admission to hospital • In the multivariable analysis of ICU cases versus hospital controls, only First Nationals ethnicity was significantly associated with increased severity of disease (OR 3.23, 95% CI 1.04 to 10.1). • Age was not a significant risk factor in any of the multivariate analyses.		**Weaknesses** • Unclear how Manitoba Health received confirmed case information • Presence of comorbid conditions may make presentation for care, virologic testing, admission to the hospital and admission to the ICU more likely • Unclear how generalizable Manitoba's population would be to Ontario; Manitoba has a higher proportion of indigenous people compared to Ontario • Findings from H1N1 pdm09 may not be generalizable to other strains/seasons
Pebody RG, McLean E, Zhao H, Cleary P, Bracebridge S, Foster K, et al. Pandemic	• Cross sectional study to estimate mortality indicators by age and clinical risk group for cases of pandemic influenza A(H1N1) from April 27, 2009	• 440 fatal pandemic influenza cases were reported in the United Kingdom; 88% were laboratory confirmed and 12%	• The majority of pandemic influenza deaths occurred among young and	**Strengths** • Sources of data, case definitions and outcome calculations clearly

Reference	Methods	Results	Study Authors' Comments	Quality assessment
Influenza A (H1N1) 2009 and mortality in the United Kingdom: risk factors for death, April 2009 to March 2010. Euro Surveill. 2010;15(20):20	to March 12, 2010 in the United Kingdom (descriptive portion) and England (analytic portion) • Fatal case defined as a resident in the UK who died with laboratory confirmed pandemic influenza A(H1N1) or with any mention of pandemic influenza A(H1N1) on the death certificate • Fatal cases were ascertained by the Health Protection Agency from several sources including: local Health Protection Units (HPU), general practitioners, hospitals and the Office of National Statistics; risk factor information was collected from the clinical source or the death certificate • Seasonal influenza risk groups included: chronic respiratory disease, chronic heart disease, chronic liver disease, chronic renal disease, chronic neurological disease, stroke/transient ischaemic attack, immunosuppression • Death registrations between January 2, 2001 and February 2, 2009 with an ICD-10 code for influenza were also identified to compare fatal pandemic influenza with fatal seasonal influenza; these were compared using age-adjusted Mantel-Haenszel odds ratios • Prevalence of specific high risk conditions in the English population by age were derived from the influenza vaccine update monitoring system and it was assumed that the risk of acquiring pandemic influenza was the same in those with risk factors as in the general population • Case fatality ratios were calculated	were derived from the death certificate • For seasonal influenza, 69% of deaths occurred in those 65 years of age and over compared to 15% of deaths for pandemic influenza • Fatal cases of pandemic influenza were more likely to be associated with a risk factor (72% of cases with available information had a risk factor, not including obesity and pregnancy) than fatal cases of seasonal influenza (57% of cases with available information had a risk factor, not including obesity and pregnancy) • Higher case fatality ratio estimated for those age 65+ compared to those aged 6 months to 64 years (9.3 per 1,000 cases versus 0.4 per 1,000 cases) • Estimated case fatality ratios for those age 6 months to 64 years in a risk group (excluding pregnancy and obesity) weres higher than for those not in a risk group (2 per 1,000 cases versus 0.1 per 1,000 cases); this was also true for those age 65+ (15 per 1,000 cases versus 1.5 per 1,000 cases) • Much higher case fatality rates were observed for cases with underlying immunosuppression, chronic liver disease and chronic neurologic disease	middle-aged adults • Most fatal pandemic influenza cases had underlying risk factor • Vaccination program in the UK started in October 2009; initially targeted individuals at high risk for severe disease and subsequently included all children age 6 months to 5 years	defined • Data collected for 11 consecutive months during pandemic influenza A(H1N1) outbreak; large sample size • Laboratory confirmed data on pandemic influenza A (H1N1) used to define most cases • Stratification by age and risk factors **Weaknesses** • Included cases that mentioned pandemic influenza A (H1N1) on the death certificate with no laboratory confirmation • Age groups only broken down into two large categories (not very granular) • Gender and vaccination status not considered • Accuracy of estimated number of clinical cases uncertain • Accuracy of estimating number of deaths uncertain • Quality of data coded on death certificates may be questionable; risk factor information missing on 9% of pandemic cases • Deaths for pandemic influenza and seasonal influenza were obtained using different methods, requiring caution when making comparisons • One inconsistent result noted between tables and results section

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	overall and by age and risk group; estimated cumulative number of clinical cases in England from the beginning of the pandemic was used as the denominator which was estimated using data from several surveillance systems • Relative risk of fatal pandemic influenza for each risk group was calculated compared to those with no risk factors • Mantel-Haenszel age-adjusted relative risks were calculated for each risk group in those under 65 years of age; for those age 65+ only overall relative risk was calculated • Population attributable fraction of each risk group was estimated	• Relative risk of death for those with any risk factor compared to those not in a risk group was higher for ages >6 months to 64 years (RR=17.9, 95% CI 13.8 to 23.2) than in those age 65+ (RR=9.8, 95% CI 3.5 to 27.4) • Population attributable fraction for risk factor in fatal cases aged 65+ was 81.8% and 64.7% for those age 6 months to 64 years		• Individuals with underlying medical conditions may be more likely to seek care and be tested for influenza and may be more likely to be admitted to hospital • Findings from H1N1 pdm09 may not be generalizable to other strains/seasons • It is uncertain if it is appropriate to assume that the risk of acquiring pandemic influenza was the same in those with risk factors as in the general population is uncertain
Louie JK, Jean C, Acosta M, Samuel MC, Matyas BT, Schechter R. A review of adult mortality due to 2009 pandemic (H1N1) influenza A in California. PLoS ONE. 2011;6 (4)	• Cross sectional study to investigate epidemiologic and clinical characteristics of adults who died due to 2009 H1N1 in California from April 3, 2009 – August 10, 2010 • A case was defined as an adult ≥20 years of age who died with clinical illness consistent with respiratory infection and had laboratory confirmed 2009 H1N1 influenza • Hospitalized and fatal cases were reported by providers and hospitals to local health departments • Cause of death was determined by review of death certificates by the reporting clinician or local public health department • Data on demographics, clinical presentation, co-morbid conditions were abstracted from medical records and autopsy reports as appropriate	• 541 fatal cases were reported during the study period • Influenza fatality rates were highest in persons 50-59 years (annualized rate 2.6 /100,000) and 60-69 years (annualized rate 1.7/100,000) • ICU admission rates were highest in adults age 50-59 years (8.6/100,000) • Case fatality ratios were highest in those age 70-79 years (42.3%) • 80% of people who died had a co-morbid condition associated with severe seasonal influenza as determined by the Advisory Committee on Immunization Practice (ACIP) • Older fatal cases were significantly more likely than	• In contrast to seasonal influenza, adults aged 50–59 years in California had the highest fatality rate due to 2009 H1N1 • Adults over 60 years may have • been somewhat spared due to pre-existing relative immunity; however, once infected and hospitalized in intensive care, case fatality ratios in California were high for all adults, especially the elderly	**Strengths** • Relevant study setting/population • Sources of data, case definitions and outcome calculations clearly defined • Data collected for 16 consecutive months during declared period of the pandemic influenza A(H1N1) outbreak • Laboratory confirmed data on pandemic influenza A (H1N1) used to define cases • Stratification by age and co-morbid conditions **Weaknesses** • Clinicians may be more likely to test for influenza in those with

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	• Co-morbid conditions were considered absent in cases where records stated the patient was previously healthy or had no underlying medical conditions • Age –specific population-based fatality rates were calculated using all reported influenza deaths and age-specific population denominators; age-specific case-fatality ratios were calculated using age-specific reported deaths among cases that had been admitted to the ICU as the denominator • Significant trends among age groups were calculated using the Cochran-Armitage trend test	younger cases to have an ACIP defined high risk condition, including chronic lung disease, chronic cardiac diseases, immunosuppression, and chronic neurological diseases		ACIP risk factors, therefore leading to under diagnosis in those without risk factors; additionally Individuals with underlying medical conditions may be more likely to seek care and may be more likely to be admitted to hospital • Gender and vaccination status not considered • Quality of data coded on death certificates is uncertain, particularly for those not in hospital • California population may not be similar to Ontario, which would affect the generalizability of the findings • No exclusion criteria defined • Only looked at population who died of pandemic H1N1 so no comparison to general population with regard to prevalence of risk factors • Findings from H1N1 pdm09 may not be generalizable to other strains/seasons
Nickel KB, Marsden-Haug N, Lofy KH, Turnberg WL, Rietberg K, Lloyd JK, et al. Age as an independent risk factor for intensive care unit admission or death due to 2009 pandemic influenza A (H1N1) virus infection. [Erratum appears in Public Health Rep.	• Cross sectional study to investigate risk factors for intensive care unit (ICU) admission or death among patients hospitalized for pH1N1 infection in Washington state from April 27, 2009 to September 18, 2009 • Passive surveillance for laboratory confirmed pH1N1 infection resulting in hospitalization or death • Local health department staff reviewed medical records and/or interviewed patients or family	• Total of 189 hospitalized and/or fatal pH1N1 cases were reported during the study period; 184 had completed case reports; 33% were critically ill or died; 63% had at least one high-risk medical condition • Neither gender nor the presence of high-risk medical conditions was associated with severe outcomes in bivariate analysis	• Adults 18-64 years of age were more likely to be critically ill compared to children • The presence of any high risk medical condition was not found to be a risk factor for more severe outcomes • Studies looking at the independent impact	**Strengths** • Sources of data, case definitions, exclusion criteria, outcomes and high risk medical conditions clearly defined • Data collected for five consecutive months during pandemic influenza A(H1N1) outbreak • Laboratory confirmed data on pandemic influenza A (H1N1) used to define cases

Reference	Methods	Results	Study Authors' Comments	Quality assessment
2011 Sep-Oct;126(5):624]. Public Health Rep. 2011;126(3):349-53	members by telephone • A case was defined as a Washington resident reported between April 27 and September 18, 2009 who was hospitalized or died due to laboratory confirmed pH1N1 infection; cases were excluded if case report was incomplete • Two outcome groups defined based on severity of disease: i) patients who died or had a critical illness (admission to ICU) and ii) patients who were hospitalized but survived and did not become critically ill • High risk medical conditions were defined as those recognized by the Advisory Committee for Immunization Practices (ACIP) to increase the risk for severe or complicated influenza • Outcomes were assessed in relation to age, gender, presence of high-risk medical conditions and time from illness onset to hospital admission • Chi-square tests used for bivariate analysis; multivariable logistic regression performed with corresponding adjusted odds ratios calculated	• Using multivariable logistic regression, compared to hospitalized children < 18 years of age, the odds of critical illness or death were 4.44 times greater among adults age 18-49 years (95% CI 1.97 to 10.02) and 5.93 times greater among adults aged 50-64 years (95% CI 2.24 to 15.65) • A non-significant increase in critical illness or death was observed among cases ≥ 65 years compared with cases < 18 years (OR 2.53, 95% CI 0.55 to 11.57) • Using multivariable logistic regression, neither gender nor the presence of a high-risk medical condition was a significant risk factor for critical illness or death	of age and high risk medical conditions on pH1N1 have shown mixed results	• Regression analysis controlled for: age, gender, time from illness onset to hospital admission, and the presence of at least one high risk medical condition **Weaknesses** • Passive surveillance subject to under-reporting • Limiting to laboratory confirmed cases may bias towards hospitalized individuals with conditions/risk factors that would encourage clinicians to test them for influenza; additionally Individuals with underlying medical conditions may be more likely to seek care and may be more likely to be admitted to hospital • Classification of high risk medical conditions may vary across health departments • Unclear how many patients were telephoned and whether proxy respondents were used, both of which could affect the reliability of the risk factor and other information • Washington state population may not be similar to Ontario, which may affect the generalizability of the findings • Findings from H1N1 pdm09 may not be generalizable to other strains/seasons

Reference	Methods	Results	Study Authors' Comments	Quality assessment
Campbell A, Rodin R, Kropp R, Mao Y, Hong Z, Vachon J, et al. Risk of severe outcomes among patients admitted to hospital with pandemic (H1N1) influenza. CMAJ. 2010;182(4):349-5	• Cross sectional study to investigate risk factors for admission to intensive care unit (ICU) and death in patients admitted to hospital in Canada with A/H1N1 pdm2009 from April 26, 2009 to September 26, 2009 • All patients admitted to hospital or who died across 13 provinces and territories were captured through active surveillance and reported to the Public Health Agency of Canada • Patients admitted to hospital who subsequently were admitted to ICU or who died were defined as having a severe outcome • Patient data was collected on: age, gender, Aboriginal status, pregnancy status, presence or absence of underlying medical conditions known to predispose individuals to complications with influenza, mechanical ventilation, admission to ICU and death • Missing and unknown information was removed from calculations except for those on underlying medical conditions; it was assumed no information on underlying medical condition meant no underlying medical condition • Univariable analysis and multivariable logistic regression used to compare inpatients who had a non-severe outcome to those admitted to the ICU/died • Variables included in regression model included: gender, age and presence/absence of underlying medical conditions	• A total of 1479 patients admitted to hospital with laboratory confirmed pandemic H1N1 were reported during the study period of which 16% were admitted to the ICU and 5% died • On average, patients with a non-severe outcome were younger (18 years) than those admitted to the ICU (34 years) and those that died (51 years) • Compared to those 10-19 years, patients age 20-64 years were significantly more likely to be admitted to ICU and those age 45 years or older were significantly more likely to die, even after adjustment for gender and underlying medical condition • Patients age 65+ had the lowest incidence of hospital admission without a severe outcome but the highest rate and relative risk of death among those admitted to hospital • 48% of the hospitalized patients had one or more underlying medical conditions • Patients with one or more underlying medical condition had an increased risk of severe outcome even after adjusting for age and gender (OR=1.5, 95% CI 1.1 to 2.1) • The risk of severe outcomes was greatest among those with diabetes, heart disease and	• The risk of severe outcome was greatest among hospitalized patients with one or more underlying medical condition and those who were 20 years of age and older • Patients 65 years of age and older experienced the lowest incidence of hospital admission without a severe outcome but the highest population-based rate and relative risk of death among those admitted to hospital	**Strengths** • Relevant study setting/population, findings applicable to Ontario • Sources of data, case definitions, exclusion criteria, outcomes were clearly defined • High risk medical conditions were defined based on criteria set by the National Advisory Committee on Immunization • Information collected from health care providers so less subject to recall bias • Data collected for five consecutive months during pandemic influenza A(H1N1) outbreak • Laboratory confirmed data on pandemic influenza A (H1N1) used to define cases • Regression analysis controlled for: gender, age and presence/absence of underlying medical conditions **Weaknesses** • Probable or suspected cases were not included • Data on underlying conditions was missing from Ontario and Manitoba • Missing data on underlying conditions were coded as 'no underlying medical conditions' which may have underestimated their effect on severe outcomes

Reference	Methods	Results	Study Authors' Comments	Quality assessment
	• Aboriginal status was not included in the multivariate analysis due to a large amount of missing data	immunosuppression; lung disease, including asthma, was associated with an elevated risk of death • For patients with no underlying conditions and who were not pregnant, compared to those 10-19 years of age, the risk of severe outcome was as follows by age: 20-29, OR=1.5 (95% CI 0.6 to 3.4); 30-39, OR = 3.5 (95% CI 1.5 to 7.7); 40-49, OR=2.6 (95% CI 1.1 to 6.1); 50-59, OR=2.2 (95% CI 0.9 to 5.6); and 60+, OR = 3.2 (95% CI 1.2 to 8.4)		• Aboriginal status not collected from Ontario and Nova Scotia • Obesity not included as a risk factor • Information not collected on antiviral use • Individuals with underlying medical conditions may be more likely to seek care and be tested for influenza and may be more likely to be admitted to hospital • Findings from H1N1 pdm09 may not be generalizable to other strains/seasons

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Appendix A: Peer-reviewed literature search strategy

Databases

The bibliographic research databases MEDLINE and Embase were searched using relevant key words. Searches were done on December 22, 2015. Language limits were applied (English only); however, no date limits were applied.

Search strategy

Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to present

#	Searches	Results
1	Influenza, Human/ or exp Orthomyxoviridae/ or ((influenza or influenzalike or "influenza like" or flu).ti,kw,kf. and ("in data review" or in process or "pubmed not medline").st.)	71159
2	Hospitalization/ or Length of Stay/ or Patient Admission/ or Patient Discharge/ or Inpatients/ or ((hospitaliz* or hospitalis* or (hospital*or patient* adj3 (admi* or readmi* or discharg*)) or (hospital* adj3 stay*) or inpatient* or "in the hospital" or "in hospital*" or "hospital patient*").ti,kw,kf. and ("in data review" or in process or "pubmed not medline").st.)	186922
3	Mortality/ or Cause of Death/ or Fatal Outcome/ or Hospital Mortality/ or Mortality, Premature/ or Survival Rate/ or Survival Analysis/ or Survivors/ or mortality.fs. or ((mortality or death* or die or died or deceased or fatal* or surviv*).ti,kw,kf. and ("in data review" or in process or "pubmed not medline").st.)	706091
4	Adult/ or Aged/ or "Aged, 80 and over"/ or Frail Elderly/ or Middle Aged/ or Young Adult/ or ((adult* or elderly or "older people" or "older person*" or "middle age*" or geriatric* or seniors or "the? aged" or (age? adj3 ("18" or "19" or 2# or 3# or 4# or 5# or 6# or 7# or 8# or 9#)) or (year* adj3 ("18" or "19" or 2# or 3# or 4# or 5# or 6# or 7# or 8# or 9#) adj3 old)).ti,kw,kf. and ("in data review" or in process or "pubmed not medline").st.)	6086362
5	Aging/ or Age Factors/ or Age Distribution/ or Age Groups/ or (Risk Factors/ and (age or aging).ab.) or (age or aging).ti,kw,kf.	879562
6	1 and (2 or 3) and 4 and 5	652
7	limit 6 to English	572
8	7 not ((exp Africa/ or exp Caribbean Region/ or exp Central America/ or exp Latin America/ or exp South America/ or exp Asia/ or Mexico/ or Developing Countries/) not (North America/ or exp Canada/ or exp United States/ or exp Australia/ or New Zealand/ or exp Europe/ or exp Developed Countries/))	430
9	8 not (comment or editorial or letter or news).pt.	415

#	Searches	Results
10	remove duplicates from 9	395

Embase 1974 to 2015 December 21

#	Searches	Results
1	*influenza/ or *seasonal influenza/ or exp *influenza A/ or exp *orthomyxovirus/ or (influenza or influenzalike or "influenza like" or flu).ti,kw.	76310
2	hospitalization/ or hospital patient/ or aged hospital patient/ or hospital discharge/ or hospital admission/ or "length of stay"/ or hospital utilization/ or hospital bed utilization/ or (hospitaliz* or hospitalis* or (hospital*or patient* adj3 (admi* or readmi* or discharg*)) or (hospital* adj3 stay*) or inpatient* or "in the hospital" or "in hospital*" or "hospital patient*").ti,kw.	597890
3	mortality/ or death/ or cause of death/ or dying/ or fatality/ or lethality/ or sudden death/ or survival/ or survival factor/ or survival rate/ or survivor/ or (mortality or death* or die or died or deceased or fatal* or surviv*).ti,kw.	1462839
4	adult/ or young adult/ or adulthood/ or middle aged/ or aged/ or frail elderly/ or very elderly/ or aged hospital patient/ or (adult* or elderly or "older people" or "older person*" or "middle age*" or geriatric* or seniors or "the? aged" or (age? adj3 ("18" or "19" or 2# or 3# or 4# or 5# or 6# or 7# or 8# or 9#)) or (year* adj3 ("18" or "19" or 2# or 3# or 4# or 5# or 6# or 7# or 8# or 9#) adj3 old)).ti,kw.	6081330
5	aging/ or age/ or age distribution/ or groups by age/ or (risk factor/ and (age or aging).ab.) or (age or aging).ti,kw.	1050690
6	1 and (2 or 3) and 4 and 5	917
7	limit 6 to english language	827
8	7 not ((exp Africa/ or exp Asia/ or exp "South and Central America"/ or developing country/) not (North America/ or Canada/ or United States/ or exp "Australia and New Zealand"/ or exp Europe/ or developed country/))	632
9	8 not (conference proceeding or editorial or letter).pt.	626
11	remove duplicates from 9	620

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