Clinical characteristics and severity of influenza infections by virus (sub)type: A systematic literature review

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INTRODUCTION

- Influenza illness is clinically characterized by nonspecific signs and symptoms that are common to other respiratory infections, such as sudden onset, fever, malaise, headache and cough.
- Influenza illness is usually short-lived (3-5 days) and severe outcomes are rare unless the person is elderly or has an underlying disease (such as chronic heart disease, diabetes, and cancer), a weakened immune system, or other medical conditions.
- Influenza has been described as "*an unvarying disease caused by a varying virus*" (Kilbourne 1975), suggesting that the illness caused by the different virus strains is clinically indistinguishable, both in terms of clinical presentation and course severity.
- However, two ground-breaking studies published by the US-CDC in 2003 and 2004 (Thompson 2003, Thompson 2004) found that the number of hospitalizations and influenza-associated deaths was highest during seasons in which A(H3N2) was the dominant subtype among the circulating viruses, followed by seasons in which influenza B or influenza A(H1N1) were dominant.
- These findings have led to the hypothesis that the clinical presentation, severity and risk of unfavourable outcomes of influenza illness may differ across virus types, subtypes and lineages.
- However, two ground-breaking studies published by the US-CDC in 2003 and 2004 (Thompson 2003, Thompson 2004) found that the number of hospitalizations and influenza-associated deaths was highest during seasons in which A(H3N2) was the dominant subtype among the circulating viruses, followed by seasons in which influenza B or influenza A(H1N1) were dominant.
- These findings have led to the hypothesis that the clinical presentation, severity and risk of unfavourable outcomes of influenza illness may differ across virus types, subtypes and lineages.
- In recent years, the hypothesis that influenza severity is dependent on the causal virus strain has been examined in a number of studies, whose results have been inconclusive.
- The question is of importance from both the clinical and public health perspective, as it may have implications for the management of influenza patients, preparedness and communication during seasonal epidemics, and accurate cost-benefit estimation of influenza vaccination campaigns and other control and prevention strategies.

STUDY OBJECTIVES

- We conducted a systematic and comprehensive review of published studies that compared the clinical presentation, course severity, and case-fatality ratio of influenza patients infected with different virus types, subtypes and lineages.

MATERIALS AND METHODS

We searched articles in PubMed, using the following search string:

influenza

AND

(sign(s) OR symptom(s) OR clinical OR comorbidity OR severity OR complication(s) OR death)

AND

(comparison OR compare/s/d).

We considered all papers published until January 31st, 2017, that were written in English, French, Spanish, Italian or Dutch.

- All retrieved entries were initially screened on the basis of their title and abstract: papers that were considered as potentially eligible for inclusion were obtained and read in full copy.
- The reference list of all retrieved papers (including those that were eventually not included in the literature review) was cross-referenced to find additional publications.

Papers were considered as eligible for inclusion if they compared:

- the clinical presentation (signs, symptoms, underlying conditions), and/or
- the disease severity (complications, hospitalization, admission to an intensive care unit [ICU], need for ventilation support, case-fatality ratio)

between laboratory-confirmed influenza patients infected with different influenza virus **types** (A, B), **subtypes** (pre-pandemic AH1N1, 2009 pandemic AH1N1 (in short referred to as AH1N1p), AH3N2) and lineages (B Victoria, B Yamagata).

We excluded studies:

- in which all study influenza cases were infected with only one influenza virus (sub)type (for instance, studies describing the disease severity of H1N1 influenza cases during the 2009 pandemic);
- focusing on avian influenza viruses (e.g. influenza AH7N9);
- carried out during the 2009 pandemic period (defined as 2009 to the summer of 2010).

When there was an overlap of influenza cases included in two papers, we included in the literature review the paper with the highest number of cases, or (in case of equal study size) the paper with the most adjusted statistics.

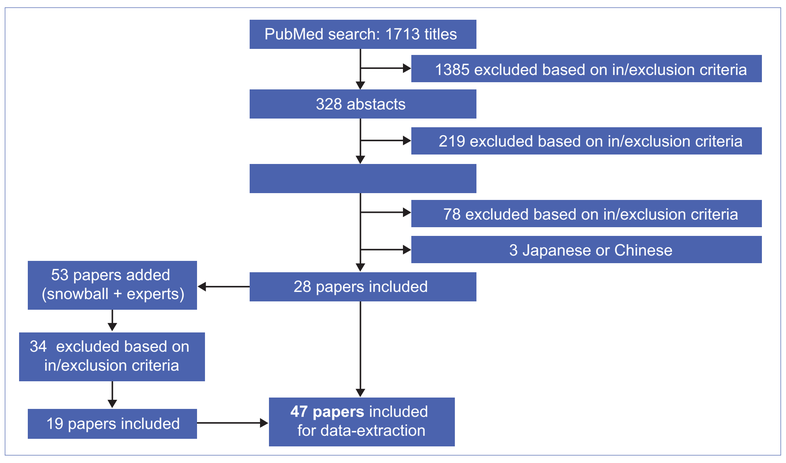
In addition to the main study findings, we extracted information on the **factors that were considered on an a priori basis to be relevant for the correct interpretation of the study findings**, namely:

- country, region and year(s) in which the study was conducted;
- criteria for inclusion of influenza patients (e.g. patients reported to national community-based surveillance system, sick individuals visiting the emergency room of hospitals and clinics, or inpatients) and whether the study was conducted among specific population subgroups (e.g. asthma patients, healthcare personnel, pregnant women, or HIV/AIDS patients);
- definition of influenza-like illness (ILI), acute respiratory infection (ARI) and/or severe acute respiratory infection (SARI);
- number of influenza cases included, broken down by virus type, subtype and lineage;
- age and gender distribution of influenza patients;
- exact definition of the signs and symptoms, underlying conditions, illness severity, complications, and of all the other outcomes being compared;
- statistical methods and variables used to adjust estimates (if any).

- The studies differed in the statistical methods that were used to compare the clinical presentation and/or severity of influenza illness between patients infected with different virus (sub)types.
- In a subset of papers a measure of relative risk (RR) (i.e. odds ratio, risk ratio) was calculated through regression models, with some adjustment performed (e.g. age, other).
- The small number of studies prevented us from pooling the study-specific RRs into a summary estimate using random effects meta-analysis models, as originally planned.
- The majority of studies performed no adjustment for the patient's age or other potential confounding variables (although some of them focused on specific age groups).
- In these studies, proportions (for binary variables e.g. presence/absence of symptoms) and mean/median values (for continuous variables e.g. length of hospital stay) were reported and, in most cases, compared using appropriate statistical tests.
- When no test was performed by the authors, we applied appropriate statistical tests provided that sufficient information was available in the text.

RESULTS

- The literature search in PubMed resulted in 1713 titles, of which 1685 were rejected based on the in- and exclusion criteria.
  This resulted in 28 included full papers.
- From these papers, the references were checked for relevant papers (and two experts were approached for suggestions for relevant papers).
- This resulted in 19 extra full papers and the literature review is therefore based on **47 papers**.



An overview of the included papers showed a lot of diversity in the populations studied.

- Data are presented in terms of hospitalized patients (n=22) or cover mainly outpatient settings (n=19), such as primary care (n=6) or community based (n=4) settings.
- Most studies were carried out in Asia (n=17), Europe (n=15) or North America (n=8).
- The majority of papers present data since 2000 (n=41).
- The number of subjects varied widely, from less than 100 to over 14,000.
- Patients of all ages were included in most papers (n=22); 15 studies addressed children and 10 studies adults only.
- The main inclusion criteria for the patients were respiratory infections and symptoms (n=15) or influenza-like illness (n=11).
- The virus strains that were most frequently compared were A(H1N1) versus A(H3N3) (n=27), influenza A versus B (18) and B/Victoria versus B/Yamagata (n=9).

- Only nine papers reported odds ratios or risk ratios for differences in the frequency of symptoms and signs.
- Overall hardly any significant differences were found between the different influenza viruses.
- Some evidence was found that patients infected with A(H1N1)p presented more frequently with fever (two studies) and rhinitis (two studies) compared to A(H3N2).
- Also, a larger proportion of patients with seasonal A(H1N1) presented with a sore throat compared to the pandemic H1N1 variant (two studies).

- A similar overall finding was found for the risk of complications and death and for the prevalence of underlying conditions, with the only significant differences reported in two studies for the pandemic H1N1 variant vs. A(H3N2), with different ICU admission or case fatality ratio (patients with the 2009 pandemic strain were admitted more often to the ICU and died more often).

- The assessment of the unadjusted differences in the frequency of symptoms and signs mainly showed no differences between the influenza viruses.
- There was some evidence that patients with influenza A less often presented with myalgia (4 papers out of 15), less often were admitted to the hospital (2 papers out of 14), and more often presented with cough (2 papers out of 9), compared to influenza B.
- Concerning the frequency of complications and underlying conditions, we also found very few significant differences between the influenza viruses in the unadjusted virus comparisons.
- There was some evidence that A(H1N1)p may result in more complications compared to other influenza virus (sub)types: people infected with A(H1N1)p
  - more often had pneumonia and were more frequently admitted in the ICU compared to influenza B
  - more often had upper respiratory tract infections and pneumonia, and were more frequently admitted in the ICU compared to A(H3N2).

First author, year	Country	Age group	Underlying conditions	Associated respiratory infections	Hospitalization, in-hospital complications, length of hospital stay, and mortality
A(H1N1)p vs. A(H3N2)					
Esposito, 2011	Italy	<14		URTI: NS LRTI: NS	Hospitalization: NS Length of hospital stay: 1.22 (1.03-1.97)
Yang, 2012	China	All ages		Pneumonia: NS	
Dangi, 2014	India	All ages	Any underlying condition: NS		
Chaves, 2013	USA	<18			ICU admission or death: 2.19 (1.11-4.33)
Chaves, 2013	USA	>= 18			ICU admission or death: 2.21 (1.66-2.94)
Kusznierz, 2016	Argentina	All ages			ICU admission or death: 2.6 (1.0-6.8)
Cohen, 2014	South Africa	All ages	Any underlying condition: NS		ICU admission: NS Mechanical ventilation: NS Oxygen supplementation: NS Length of hospital stay: NS Death: NS

Main characteristics of the included studies

First author, year	Country	Study period	Age group or range	A	B	A (H1N1)	A (H1N1)p	A (H3N2)	B Victoria	B Yamagata	Population studied (syndrome)
Children											
Weigl, 2002	Germany	1996-2001	≤16	122	14						ARI
Dawood, 2011	USA	2003-09	≤17		116		733[a]	494			children with asthma
Chiu, 2011	China	2009	<18			99	99[a]	99			respiratory symptoms
Daley, 2000	Australia	1997	children	64	27						any virus isolation from nasopharyngeal aspirates
Hu, 2004	Taiwan	2000-01	children	73	124						not specified
Meury, 2004	Switzerland	2001-02	children	45	15						respiratory symptoms
Guan, 2015	China	2010-12	children		59		26	131			lower RTI
Mancinelli, 2016	Italy	2012-13	children				54	8	6	65	RTI
Adults											
Yang, 2014	China	2010-11	≥14				58	30			pneumonia
Jennings, 2008	New Zealand	1999-2000	≥18	23	6						community acquired pneumonia
Loubet, 2016	France	2012-15	≥18	422	144		163	239			ILI
Seo, 2014	Korea	2009-12	adults	55	31						ARI
Drinka, 1999	USA	1988-99	elderly[b]	322	129						ARI
All ages											
Rahamat-Langendoen, 2012	Netherlands	2007-11	all ages		50	45	85[a]				ARI
Chaves, 201 Cohen, 2014	USA South Africa	2010-11 2009-12	all ages all ages		948 418		924 338[a]	1749 463			not specified SARI
Sočan, 2014	Slovenia	2010-13	all ages						150	114	Lower RTI
Ishiguro, 2016	Japan	2002-14	all ages		42		20[a]	34			Influenza-associated pneumonia
Kusznierz, 2016	Argentina	2013	all ages				46	54			not specified
Puig-Barberà, 2016	Four countries	2013-14	all ages				362	534	3	130	ILI
Puig-Barberà, 2016	Six countries	2014-15	all ages				121	1243	11	623	ILI
Tan, 2013	China	2009-10	all ages						139	43	ARI or community-acquired pneumonia

ARI: acute respiratory infection; ILI: influenza-like illness; RTI: respiratory tract infection; SARI: severe acute respiratory infection; [a]Pandemic detections (2009/2010 season only) were not included in the analysis. ; [b]All study participants were nursing home residents

Relative risk of main signs and symptoms among patients infected with different influenza virus types, subtypes and lineages

First author, year	Setting	Age group or range	Fever[a]	Cough[b]	Rhinitis[c]	Sore throat	Headache	Dyspnoea[d]	GI symptoms[e]	Myalgia	Age-adjusted
A vs B											
Hite, 2007	hosp	<19	ns	ns	ns	ns ns	ns	ns	0.34 (0.13-0.91)	unclear	
A(H1N1)p vs B											
Yap, 2012	non-hosp	young adults	0.51 (0.29-0.92)	2.10 (1.25-3.54)	0.54 (0.34-0.86)	0.44ns (0.24-0.80)			ns	yes	
Gutiérrez-Pizarraya, 2012	non-hosp	adults	2.5 (1.2-5.4)					ns		unclear	
A(H3N2) vs B											
Yap, 2012	non-hosp	young adults	ns	ns	ns	ns ns			ns	yes	
Cohen, 2014	hosp	all ages	ns	ns			ns			yes	
A(H1N1)p vs A(H3N2)											
Yap, 2012	non-hosp	young adults	0.33 (0.11-0.99)	ns	ns	ns ns			ns	yes	
Cohen, 201424	non-hosp	all ages	ns	ns			ns			yes	
Dangi, 20149	non-hosp	all ages				2.27 (1.22-4.22)	ns	ns	ns	ns	unclear
B Victoria vs B Yamagata											
Dangi, 201	non-hosp	all ages				ns ns	12.00 (2.42-59.8)	9.60 (0.97-19.40)	ns	unclear	
Sočan, 2014	non-hosp hosp	all ages	ns ns	ns ns	ns	ns ns	ns	ns	ns	yes yes	

ARI: acute respiratory infection; ILI: influenza-like illness; RTI: respiratory tract infection; SARI: severe acute respiratory infection; [a]Pandemic detections (2009/2010 season only) were not included in the analysis. ; [b]All study participants were nursing home residents

DISCUSSION

- Despite the common assumption that A(H3N2) infections result in more severe illness and that influenza B infections are usually milder, the current literature review did not reveal such differences.
- In particular, there were hardly any differences in signs/symptoms and underlying conditions, while there seemed to be some evidence that the 2009 pandemic A(H1N1) strain was more severe than the other influenza virus (sub)types, as it was more often associated with secondary bacterial pneumonia, ICU admission, and death.
- The papers included in our review showed a wide diversity in terms of:
  - age groups: children, adults, all ages
  - virus comparisons: multiple
  - population studied: ILI, respiratory infection, ARI, pneumonia, asthma, etc.
  - definitions of illness severity: ICU admission, length of hospital stay, complications, in-hospital death, etc.

  This large diversity made it difficult to compare studies, and may be a possible explanation of why significant results emerging from one study were very often not confirmed in subsequent studies.

  In particular, settings varied widely:
  - community based
  - primary care
  - patients visiting hospitals
  - hospitalized patients
  - military personnel
  - ...

  Moreover, even for similar health seeking settings, the characteristics of patients may vary as a result of differences in healthcare system (e.g. in countries were GPs have a gate-keeping function, another selection of patients may go the hospital compared to countries where patients have direct access).
- A very important shortcoming is that most papers failed in controlling for potential confounding factors such as age, underlying conditions, vaccine status or anti-viral treatment, as no multivariate analyses was performed.
- Frequently, this was not possible because of the relatively small numbers of included influenza cases.
- Some studies tried to overcome the lack of statistical power by combining all influenza A subtypes into one category, which may be not be an advisable strategy as there is some evidence that the clinical outcomes of influenza illness might be worse for the 2009 A(H1N1) pandemic strain.
- Likewise, combining different seasons may be helpful to increase the number of study participants; however, the comparison may be influenced in this case by the genetic drift of influenza viruses.
- Our review focussed on clinical presentation and illness severity, while the age signature of the different influenza viruses was not included.
- Some studies suggested that there is a difference between age groups affected by different influenza viruses: reviewing these data could provide additional knowledge, although the diversity of studies would still be a limitation difficult to overcome.
- Finally, we did not include in our literature review a comparison of laboratory data between patients infected with different virus types, subtypes and lineages.

DISCUSSION

- **We found very limited evidence that the different influenza virus (sub)types differ between one another in terms of clinical presentations, underlying conditions, illness severity or case-fatality ratio.**
- **By and large, Kilbourne's definition of influenza as "*an unvarying disease caused by a varying virus*" seems to be justified by the data.**
- **Critically, however, it needs to be emphasized that an important gap in knowledge still exists: drawing firm conclusions was made difficult by low comparability, limited sample size and methodological limitations of most studies that were included in our review.**

A minimum set of quality requirements for future studies in the topic should include:

- **a clear description of the study setting and inclusion/exclusion criteria;**
- **a follow-up of each patient during the entire illness course, i.e. from onset until recovery or death (and including details of in-hospital stay for hospitalized patients);**
- **the use of multivariate regression techniques providing relative risk estimates adjusted by (at least) patient's age, vaccine status and anti-viral treatment.**

Disclosures

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