

Compassionate drug (mis)use during pandemics: lessons for COVID-19 from 2009.

Supplementary materials

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Appendix 1 – Compliance to MOOSE and PRISMA guidelines for reporting of systematic reviews

MOOSE GUIDELINES	
Reporting background should include	
Problem definition	Yes
Hypothesis statement	N/A
Description	Yes
Type of exposure or intervention used	Yes
Type of study designs used	Yes
Study population	Yes
Reporting of search strategy should include	
Qualifications of searches (e.g. librarians and investigators)	Yes
Search strategy, including time period included in the synthesis and keywords	Yes
Effort to include all available studies, including contact with authors	No, discussed
Databases and registries searched	Yes
Search software used, name and version, including special features	Yes
Use of hand searching (e.g. reference lists of obtained articles)	No
List of citations located and those excluded including justification	Available on request
Method of addressing articles published in languages other than English	Yes
Method of handling abstracts and unpublished studies	No
Description of any contact with authors	No, discussed
Reporting methods should include	
Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested	Yes
Rationale for the selection and coding of data (eg, sound clinical principles or convenience)	Yes
Documentation of how data were classified and coded (eg, multiple raters, blinding, and interrater reliability)	Yes
Assessment of confounding (eg, comparability of cases and controls in studies where appropriate)	N/A
Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results	N/A
Assessment of heterogeneity	N/A
Description of statistical methods (eg, complete description of fixed or random effects models, justification of whether the chosen models account for predictors of study results, dose-response models, or cumulative meta-analysis) in sufficient detail to be replicated	Yes
Provision of appropriate tables and graphics	Yes
Reporting of results should include	
Graphic summarizing individual study estimates and overall estimate	Yes, as appropriate

Table giving descriptive information for each study included	Yes
Results of sensitivity testing (eg, subgroup analysis)	Yes
Indication of statistical uncertainty of findings	Yes
Reporting of discussion should include	
Quantitative assessment of bias (eg, publication bias)	Yes
Justification for exclusion (eg, exclusion of non-English-language citations)	Yes
Assessment of quality of included studies	N/A
Reporting of conclusions should include	
Consideration of alternative explanations for observed results	Yes
Generalization of the conclusions (ie, appropriate for the data presented and within the domain of the literature review)	Yes
Guidelines for future research	Yes
Disclosure of funding source	Yes

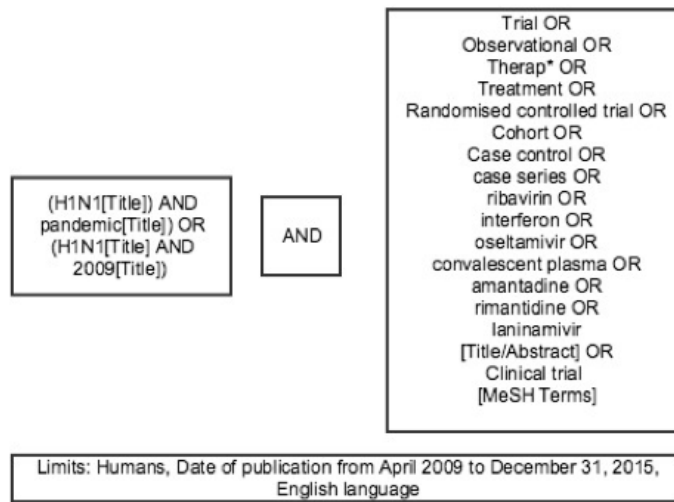
N/A: This is a bibliometric review and is not undertaken to assess a treatment effect, and so this item is not applicable.

PRISMA GUIDELINES			
Section/topic	#	Checklist item	Reported on page #
Title			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	N/A
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	3
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	3
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	3
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	N/A
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	3
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix 4

PRISMA GUIDELINES			
Section/topic	#	Checklist item	Reported on page #
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	5-6 as appropriate
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Appendix 2
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	7-8
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	9
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	9
Funding			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	10

N/A: This is a bibliometric review and is not undertaken to assess a treatment effect, and so this item is not applicable.

Appendix 2 – Search Strategy



Appendix 3: Details of clinical registry search strategy and data extraction

Search 1: Search of clinical trial records for A(H1N1)pdm09 influenza records.

We searched clinicaltrials.gov using the term “H1N1”. We included submissions submitted after the date of onset of the pandemic, and that began recruitment during the pandemic period, and were available on the database as of the 31st of December 2015. We included clinical trials and observational research enrolling patients with confirmed A(H1N1)pdm09. Trials must have reported on one or more outcomes of drug safety, efficacy, pharmacokinetics, or patient clinical outcomes. There was no minimum anticipated, or actual sample size. We excluded submissions where A(H1N1)pdm09 influenza was not specifically identified as a strain of interest. Registration records infrequently defined the hospitalisation status of patients, and so a subgroup analysis limiting enrolment to when records were explicit about enrolling only ‘severe’ or hospitalised patients is found in appendix 3 (supplementary figure 1).

Search 2: Search of clinical trial records for influenza records

We searched clinicaltrials.gov using the term “influenza” with Boolean operators to exclude “vaccine”, “vaccination”, “prophylaxis”, and “diagnostic”. We included submissions if they began recruitment before or during the pandemic (so long as they remained open to enrolment for some period during the pandemic period) and were available on the database as of the 31st of December 2015. We included clinical trials and observational research enrolling patients with confirmed influenza. Trials must have reported on one or more outcomes of drug safety, efficacy, pharmacokinetics, or patient clinical outcomes. There was no minimum anticipated, or actual sample size. Analysis is stratified as to whether the studies were ongoing at the time of the pandemic onset (April 1 2009).

Details of data extraction

For published literature, we extracted the type of research, the location of research, patient outcome measure(s) described, the number of patients, the dates that patients were enrolled, the number of patients receiving A(H1N1)pdm09 specific treatments, reporting of adverse events, reporting of drug resistance, the dates for manuscript submission, acceptance and first publication (including e-publication), and information on inclusion of some high-risk groups - pregnant women, the elderly (defined as older than 65 years), and children (defined as younger than 18 years). Where dates were only described to the closest month, the first day of the month was entered.

For registered clinical trials, we included the type of study, date of submission to the registry, predicted dates of enrolment and sample size (and then actual values when known), whether high-risk groups (as defined above) were included, the geographical location of the research, the completion status of the work, and the date of first publication (including e-publication). These details were cross checked against any corresponding publications.

Appendix 4 – Details of literature included in this systematic review

First author name	Study name	n
Prospective research		
Al-Tawfiq	Pandemic influenza A (2009 H1N1) in hospitalized patients in a Saudi Arabian hospital: Epidemiology and clinical comparison with H1N1-negative patients	47
Beutel	Virus-associated hemophagocytic syndrome as a major contributor to death in patients with 2009 influenza A (H1N1) infection.	25
Champunot	Impact of Pandemic Influenza (H1N1) Virus Associated Community Acquired Pneumonia among adults in a tertiary hospital in Thailand	24
Chitnis	Epidemiologic and clinical features among patients hospitalized in Wisconsin with 2009 H1N1 influenza A virus infections, April to August 2009.	252
Cordero	Immunosuppressed patients with pandemic influenza A 2009 (H1N1) virus infection	559
Cordero	Pandemic influenza A(H1N1) virus infection in solid organ transplant recipients: impact of viral and non-viral co-infection	51
Denholm	Hospitalised adult patients with pandemic (H1N1) 2009 influenza in Melbourne, Australia	112
Diaz	Impact of Obesity in Patients Infected With 2009 Influenza A(H1N1)	416
Giannella	Prolonged viral shedding in pandemic influenza A(H1N1): clinical significance and viral load analysis in hospitalized patients	64
Hung	Convalescent Plasma Treatment Reduced Mortality in Patients With Severe Pandemic Influenza A (H1N1) 2009 Virus Infection	93
Hung,	Hyperimmune IV immunoglobulin treatment: a multicenter double-blind randomized controlled trial for patients with severe 2009 influenza A(H1N1) infection	35
Kirakli	Survival from severe pandemic H1N1 in urban and rural Turkey: a case series	18
Koegeleneg	High mortality from respiratory failure secondary to swine-origin influenza A (H1N1) in South Africa	19
Lee	Complications and Outcomes of Pandemic 2009 Influenza A (H1N1) Virus Infection in Hospitalized Adults: How Do They Differ From Those in Seasonal Influenza	382
Ling	Effects of Early Oseltamivir Therapy on Viral Shedding in 2009 Pandemic Influenza A (H1N1) Virus Infection	70
Lucker	Clinical features and outcomes of hospitalised adults and children with the 2009 influenza A H1N1 infection at Geneva's University Hospital	85
Martin - Loeches	Severe pandemic (H1N1)v influenza A infection: report on the first deaths in Spain	131
Martin - Loeches	Pandemic and post-pandemic Influenza A (H1N1) infection in critically ill patients	648
Ploin	Complications and factors associated with severity of influenza in hospitalized children and adults during the pandemic wave of A(H1N1)pdm2009 infections--the Fluco French cohort	40
Poepl	Clinical aspects of 2009 pandemic influenza A (H1N1) virus infection in Austria	450
Riquelme	Characteristics of hospitalised patients with 2009 H1N1 influenza in Chile	100
Rodriguez	Impact of early oseltamivir treatment on outcome in critically ill patients with 2009 pandemic influenza	657
Stein	Hospitalization of Children With Influenza A(H1N1) Virus in Israel During the 2009 Outbreak in Israel	478
Suarez-Varela	Pandemic influenza A (H1N1) infection in pregnant and nonpregnant women in Spain (2009-2010).	219
Viasus	Factors associated with severe disease in hospitalized adults with pandemic (H1N1) 2009 in Spain	585

First author name	Study name	n
Viasus, Pano-Pardo	Effect of immunomodulatory therapies in patients with pandemic influenza A (H1N1) 2009 complicated by pneumonia	197
Wang	Adjuvant Treatment with a Mammalian Target of Rapamycin Inhibitor, Sirolimus, and Steroids Improves Outcomes in Patients with Severe H1N1 Pneumonia and Acute Respiratory Failure	38
Wu	Severity of pandemic H1N1 2009 influenza virus infection may not be directly correlated with initial viral load in upper respiratory tract	18
Yates	Influenza A/H1N1v in pregnancy: an investigation of the characteristics and management of affected women and the relationship to pregnancy outcomes for mother and infant	241
Yung	Pandemic H1N1 in children requiring intensive care in Australia and New Zealand during winter 2009	83
Retrospective research		
Al-Lawati	Hospitalised patients with Influenza A (H1N1) in the Royal Hospital, Oman: Experience of a tertiary care hospital, July-December 2009	131
Altmann	Severe Cases of Pandemic (H1N1) 2009 in Children, Germany	93
Asselet	Clinical, virological and epidemiological assessment of 2009 influenza A (H1N1) pandemic in a Belgian university hospital	28
Bagdure	Hospitalized Children with 2009 Pandemic Influenza A (H1N1): Comparison to Seasonal Influenza and Risk Factors for Admission to the ICU	307
Balanzat	An analysis of 332 fatalities infected with pandemic 2009 influenza A (H1N1) in Argentina	332
Baltagi	Neurological sequelae of 2009 influenza A (H1N1) in children: A case series observed during a pandemic	1
Brandsaeter	Hospitalised patients with suspected 2009 H1N1 influenza A in a hospital in Norway, July - December 2009	64
Calitri	Clinical features of hospitalised children with 2009 H1N1 influenza virus infection	63
Camous	Clinical features of H1N1 2009 infection in critically ill immunocompromised patients	10
Campbell	Respiratory Failure Caused by 2009 Novel Influenza A/H1N1 in a Hematopoietic Stem-Cell Transplant Recipient: Detection of Extrapulmonary H1N1 RNA and Use of Intravenous Peramivir	1
Cao	Clinical Features of the Initial Cases of 2009 Pandemic Influenza A (H1N1) Virus Infection in China	426
CDC	Neurologic complications associated with novel influenza A (H1N1) virus infection in children - Dallas, Texas, May 2009	4
Chacko	Cardiac manifestations in patients with pandemic (H1N1) 2009 virus infection needing intensive care	37
Chan	Pandemic (H1N1) 2009: clinical and laboratory findings of the first fifty cases in Singapore	50
Chan	Distinguishing characteristics between pandemic 2009-2010 influenza A (H1N1) and other viruses in patients hospitalized with respiratory illness.	291
Cheng	Clinical and epidemiological profile of patients with severe H1N1/09 pandemic influenza in Australia and New Zealand: an observational cohort study	478
Chien	Predictors and outcomes of respiratory failure among hospitalized pneumonia patients with 2009 H1N1 influenza in Taiwan	96
Chiu	Age-matched comparison of children hospitalized for 2009 pandemic H1N1 influenza with those hospitalized for seasonal H1N1 and H3N2	99
Choi	Critically Ill Patients with Pandemic Influenza A/H1N1 2009 at a Medical Center in Korea	27
Chong	Risk Factors for Complicated Influenza A (H1N1) 2009 Disease in Children	143

First author name	Study name	n
Chowell	Risk factors for mortality among 2009 A/H1N1 influenza hospitalizations in Maricopa County, Arizona, April 2009 to March 2010	546
Chudasama	Hospitalizations associated with 2009 influenza A (H1N1) and seasonal influenza in Saurashtra region, India	274
Chudasama	Characteristics of Fatal Cases of Pandemic Influenza A (H1N1) from September 2009 to January 2010 in Saurashtra Region, India	71
Chudasama	Correlates of severe disease in patients admitted with 2009 pandemic influenza A (H1N1) infection in Saurashtra region, India	274
Clay	Postpartum pharmacokinetics of peramivir in the treatment of 2009 H1N1 influenza	1
Creanga	Severity of 2009 Pandemic Influenza A (H1N1) Virus Infection in Pregnant Women	136
Cui	Factors associated with death in hospitalized pneumonia patients with 2009 H1N1 influenza in Shenyang, China	68
Da Dalt	Oseltamivir-resistant pandemic (H1N1) 2009 treated with nebulized zanamivir	1
Da Dalt	Pandemic influenza A (H1N1v) infection in pediatric population: a multicenter study in a north-east area of Italy	200
del Rosal	Pandemic H1N1 influenza-associated hospitalizations in children in Madrid, Spain	517
Delgado-Rodriguez	Prognosis of hospitalized patients with 2009 H1N1 influenza in Spain: influence of neuraminidase inhibitors	813
Dubar	French Experience of 2009 A/H1N1v Influenza in Pregnant Women	151
Dulek	Use of intravenous zanamivir after development of oseltamivir resistance in a critically ill immunosuppressed child infected with 2009 pandemic influenza A (H1N1) virus	1
Englund	Oseltamivir-resistant novel influenza A (H1N1) virus infection in two immunosuppressed patients - Seattle, Washington, 2009	2
Enstone	Nosocomial Pandemic (H1N1) 2009, United Kingdom, 2009–2010	30
Ergin	Clinical and epidemiological features of Turkish children with 2009 pandemic influenza A (H1N1) infection: Experience from multiple tertiary paediatric centres in Turkey	821
Esposito	Oseltamivir-induced resistant pandemic A/H1N1 influenza virus in a child with cystic fibrosis and Pseudomonas aeruginosa infection	18
Fraaij	Evaluation of the Antiviral Response to Zanamivir Administered Intravenously for Treatment of Critically Ill Patients With Pandemic Influenza A (H1N1) Infection	13
Fuhrman	Adult intensive-care patients with 2009 pandemic influenza A(H1N1) infection	1065
Fujikura	The (H1N1) 2009 Pandemic Influenza Pneumonia among Adult Patients in Japan	346
Gaur	Intravenous zanamivir for oseltamivir-resistant 2009 H1N1 influenza	1
Ghosh	Efficient control of pandemic 2009 H1N1 virus infection with intravenous zanamivir despite the lack of immune function	1
Gonzalez-Velez	Factors associated to admission to Intensive Care in patients hospitalized due to pandemic Influenza A/H1N1 2009	100
Hagerman	Clinical characteristics and outcomes in children hospitalised with pandemic influenza A/H1N1/09 virus infection – a nationwide survey by the Pediatric Infectious Diseases Group of Switzerland	326
Harter	Intravenous zanamivir for patients with pneumonitis due to pandemic (H1N1) 2009 influenza virus	226

First author name	Study name	n
Hasegawa	Characteristics of atopic children with pandemic H1N1 influenza viral infection: Pandemic H1N1 influenza reveals 'occult' asthma of childhood	33
Hasegawa	Pandemic (H1N1) 2009-associated Pneumonia in Children, Japan	80
Heninger	Comparative Analysis of Clinical Characteristics of Pandemic Influenza A/H1N1 and Seasonal Influenza A Infections in Hospitalized Children	57
Hernandez	Clinical Experience in Adults and Children Treated with Intravenous Peramivir for 2009 Influenza A (H1N1) Under an Emergency IND Program in the United States	42
Hiba	Benefit of early treatment with oseltamivir in hospitalized patients with documented 2009 influenza A (H1N1): retrospective cohort study	502
Hong-Ryang Kil	Early corticosteroid treatment for severe pneumonia caused by 2009 H1N1 influenza virus	32
Iglesias	Reducing occurrence and severity of pneumonia due to pandemic H1N1 2009 by early oseltamivir administration: a retrospective study in Mexico	442
Ismail	Characteristics of Children Hospitalized for Pandemic (H1N1) 2009, Malaysia	1321
Jain	Hospitalized Patients with 2009 H1N1 Influenza in the United States, April–June 2009	272
Kang	Virological Clearance Rate of High-Dose Oseltamivir or Triple-Combination Antiviral Therapy in Complicated 2009 Pandemic Influenza A (H1N1) Infection	14
Kar-Hui	Benign Clinical Course in H1N1 2009 Influenza Infection in Young Oseltamivir-treated Immunocompromised Patients With Kidney Disease in Singapore	38
Kedia	Pediatric neurological complications of 2009 pandemic influenza A (H1N1)	23
Kendirli	Critically ill children with pandemic influenza (H1N1) in pediatric intensive care units in Turkey	83
Khandaker	Nosocomial vs community-acquired pandemic influenza A (H1N1) 2009: a nested case-control study	188
Kim	Triple-combination antiviral drug for pandemic H1N1 influenza virus infection in critically ill patients on mechanical ventilation.	127
Kim	Fatal cases of 2009 pandemic influenza A (H1N1) in Korea	115
Kinikar	Predictors of mortality in hospitalized children with pandemic H1N1 influenza 2009 in Pune, India	92
Ko	Characteristics of hospitalized children with 2009 pandemic influenza A (H1N1): a multicenter study in Korea	804
Kusznierz	Clinical features of the hospitalized patients with 2009 pandemic influenza A (H1N1) in Santa Fe, Argentina	242
Kute	High mortality in critically ill patients infected with 2009 pandemic influenza A (H1N1) with pneumonia and acute kidney injury	20
Lam	Severe cases of pandemic H1N1 pneumonia and respiratory failure requiring intensive care	18
Larcombe	Pandemic (H1N1) 2009: a clinical spectrum in the general paediatric population	43
Launes	2009 Influenza A H1N1 infections: delays in starting treatment with oseltamivir were associated with a more severe disease	127
Law	Severe refractory hypoxaemia in H1N1 (2009) intensive care patients: initial experience in an Asian regional hospital	12
Lee	Fatalities associated with the 2009 H1N1 influenza A virus in New York city	123
Li	Clinical features of 2009 pandemic influenza A (H1N1) virus infection in chronic hemodialysis patients	15

First author name	Study name	n
Liang	New influenza A (H1N1) 2009 in Singapore: the first ten adult imported cases	10
Liu	Sixty-two severe and critical patients with 2009 influenza A (H1N1) in Shanghai, China	62
Low	Epidemiological and Clinical Features of 308 Hospitalized Patients with Novel 2009 Influenza A (H1N1) Virus Infection in China during the First Pandemic Wave	22
Mady	Clinical experience with severe 2009 H1N1 influenza in the intensive care unit at King Saud Medical City, Saudi Arabia	86
Memoli	Rapid selection of oseltamivir- and peramivir-resistant pandemic H1N1 virus during therapy in 2 immunocompromised hosts	2
Mickiene	Hospitalized adult patients with 2009 pandemic influenza A (H1N1) in Kaunas, Lithuania	121
Miller	Clinical Findings and Demographic Factors Associated With ICU Admission in Utah Due to Novel 2009 Influenza A(H1N1) Infection	47
Minnema	Comparison of Hospitalized Solid Organ Transplant Recipients and Nonimmunocompromised Patients With Pandemic H1N1 Infection: A Retrospective Cohort Study	17
Minnema	Clinical characteristics and outcome associated with pandemic (2009) H1N1 influenza infection in patients with hematologic malignancies: a retrospective cohort study	64
Moore	Evidence of Person-to-Person Transmission of Oseltamivir-Resistant Pandemic Influenza A(H1N1) 2009 Virus in a Hematology Unit	10
Moral	Burden of Severe 2009 Pandemic Influenza A (H1N1) Infection in Children in Southeast Spain	82
Nassar	Influenza A (H1N1) patients admitted to intensive care units during the 2009 pandemics: clinical features and outcomes	22
Nermin	A retrospective evaluation of critically ill patients infected with H1N1 influenza A virus in Bursa, Turkey, during the 2009–2010 pandemic	23
No authors	Human infection with new influenza A (H1N1) virus: clinical observations from a school-associated outbreak in Kobe, Japan, May 2009	49
Noun	Pandemic (H1N1) 2009 influenza in pediatric hematology/oncology units in Lebanon	14
O'Riordan	Risk factors and outcomes among children admitted to hospital with pandemic H1N1 influenza	58
Oh	A Prediction Rule to Identify Severe Cases among Adult Patients Hospitalized with Pandemic Influenza A (H1N1) 2009	709
Okada	Characteristic findings of pediatric inpatients with pandemic (H1N1) 2009 virus infection among severe and nonsevere illnesses	46
Owayed	Epidemiology and clinical presentation of pandemic influenza A (H1N1) among hospitalized children in Kuwait	197
Parakh	Pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1): an experience from a tertiary care center in north India	25
Park	Successful salvage therapy with inhaled zanamivir in a patient with peramivir-resistant pandemic influenza A (H1N1) 2009 virus	1
Perez - Padilla	Pneumonia and respiratory failure from swine-origin influenza A (H1N1) in Mexico	18
Petersen	Failure of combination oral oseltamivir and inhaled zanamivir antiviral treatment in ventilator- and ECMO-treated critically ill patients with pandemic influenza A (H1N1)v	21
Peterson	Failure of combination oral oseltamivir and inhaled zanamivir antiviral treatment in ventilator- and ECMO-treated critically ill patients with pandemic influenza A (H1N1)	21

First author name	Study name	n
Regan	Epidemiology of influenza A (H1N1)pdm09-associated deaths in the United States, September–October 2009	323
Rello	Intensive care adult patients with severe respiratory failure caused by Influenza A (H1N1)v in Spain	32
Rhim	Pandemic 2009 H1N1 virus infection in children and adults: A cohort study at a single hospital throughout the epidemic	373
Rhim	Epidemiological and clinical characteristics of childhood pandemic 2009 H1N1 virus infection: An observational cohort study	217
Rojas Suarez	Maternal mortality due to pandemic influenza A H1N1 2009 virus in Colombia	23
Schellongowski	A surge of flu-associated adult respiratory distress syndrome in an Austrian tertiary care hospital during the 2009/2010 Influenza A H1N1v pandemic	17
Sertogullarindan	Clinical and prognostic features of patients with pandemic 2009 influenza A (H1N1) virus in the intensive care unit	20
Shetty	Oseltamivir-resistant 2009 H1N1 influenza pneumonia during therapy in a renal transplant recipient	1
Siau	Influenza A H1N1 (2009): clinical spectrum of disease among adult patients admitted to a regional hospital in Singapore	153
Siau	Severe refractory hypoxaemia in H1N1 (2009) intensive care patients: initial experience in an Asian regional hospital	12
Soonhak	Neurologic Complications and Outcomes of Pandemic (H1N1) 2009 in Korean Children	23
Sorbello	Emergency use authorization for intravenous peramivir: evaluation of safety in the treatment of hospitalized patients infected with 2009 H1N1 influenza A virus	344
Souza	H1N1pdm Influenza Infection in Hospitalized Cancer Patients: Clinical Evolution and Viral Analysis	24
Sugaya	Efficacy, Safety, and Pharmacokinetics of Intravenous Peramivir in Children with 2009 Pandemic H1N1 Influenza A Virus Infection	106
Suhalia	Mixtures of oseltamivir-sensitive and -resistant pandemic influenza A/H1N1/2009 viruses in immunocompromised hospitalized children	1
Surana	Neurological complications of pandemic influenza A H1N1 2009 infection: European case series and review	1
Tabarsi	Factors associated with death or intensive care unit admission due to pandemic 2009 influenza A (H1N1) infection	46
To	Concurrent comparison of epidemiology, clinical presentation and outcome between adult patients suffering from the pandemic influenza A (H1N1) 2009 virus and the seasonal influenza A virus infection	69
van Zwol	Clinical Features of a Dutch Cohort of Critically Ill Children Due to the 2009 New Influenza A H1N1 Pandemic	13
Venkata	Hospitalized patients with 2009 H1N1 influenza infection: the Mayo Clinic experience	66
Webster	Oseltamivir-resistant pandemic H1N1 influenza	1
Wieching	Clinical characteristics of pediatric hospitalizations associated with 2009 pandemic influenza A (H1N1) in Northern Bavaria, Germany	94
Wijaya	Intravenous zanamivir in critically ill patients due to pandemic 2009 (H1N1) influenza A virus	5
Wolfé	Pandemic (H1N1) 2009 and Oseltamivir Resistance in Hematology/Oncology Patients	1
Xi	Hospitalized adult patients with 2009 influenza A(H1N1) in Beijing, China: risk factors for hospital mortality	155

First author name	Study name	<i>n</i>
Xiao	Hospitalized patients with novel influenza A (H1N1) virus infection: Shanghai, June–July 2009	156
Yang	Antiviral therapy and outcomes of patients with pneumonia caused by influenza a pandemic (H1N1) virus.	1461
Yu	Risk factors for severe illness with 2009 pandemic influenza A (H1N1) virus infection in China	9966
Yu	Effectiveness of oseltamivir on disease progression and viral RNA shedding in patients with mild pandemic 2009 influenza A H1N1: opportunistic retrospective study of medical charts in China	1291
Zhang	Risk factors for adult death due to 2009 pandemic influenza A (H1N1) virus infection: a 2151 severe and critical cases analysis	2151
Zhang	Clinical features and risk factors for severe and critical pregnant women with 2009 pandemic H1N1 influenza infection in China	394
Zhang	Epidemiological and Clinical Features of 308 Hospitalized Patients with Novel 2009 Influenza A (H1N1) Virus Infection in China during the First Pandemic Wave	308
Zheng	Hospitalized children with 2009 influenza A (H1N1) infection in Shenzhen, China, November-December 2009	148
Zhou	Clinical features of initial cases of 2009 pandemic influenza A (H1N1) in Macau, China.	72
Mixed prospective and retrospective research		
Prerna	Neurology of the H1N1 pandemic in Singapore: a nationwide case series of children and adults	98

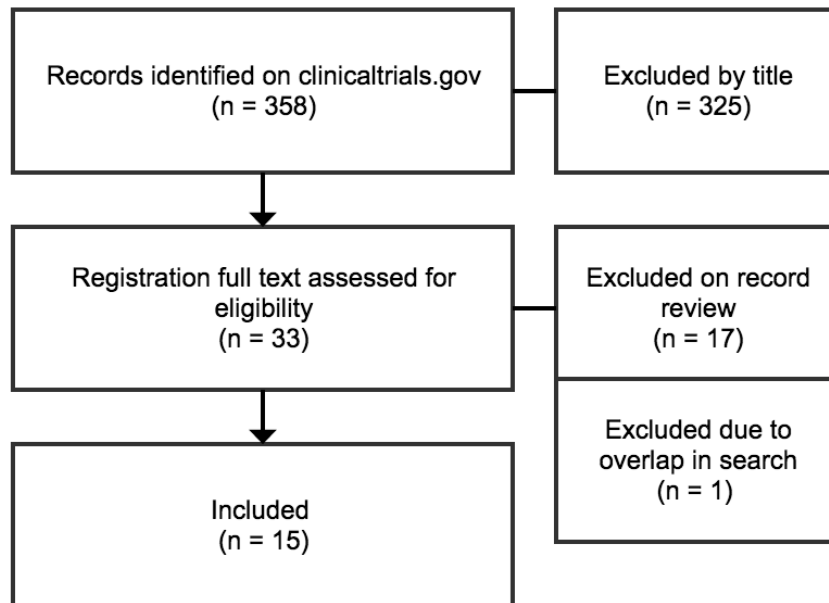
Appendix 4: Studies included in systematic review. *n* is the number of patients with laboratory confirmed influenza A(H1N1) pdm09 included in analysis. This excludes oseltamivir use when fewer than ten patients were treated.

Country reporting data	Number of treatment courses described in literature (by study enrolment type)			Total number of papers published	Date of first patient enrolment in prospective research
	Prospective	Retrospective	Total		
Argentina		517	517	2	
Australia	95	126	221	3	01/05/2009
Australia and New Zealand	67	390	457	2	01/06/2009
Austria	355	9	364	2	20/09/2009
Belgium		27	27	1	
Brazil		17	17	1	
Canada		98	98	4	
Chile	97		97	1	29/05/2009
China	384	14296	14680	16	01/06/2009
Colombia		26	26	1	
Denmark		84	84	2	
France	38	770	808	4	30/11/2009
Germany	39	79	118	5	05/10/2009
Holland		39	39	2	
Hong Kong	217	50	267	3	01/01/2009
India		813	813	7	
Iran		51	51	1	
Israel	262	449	711	2	12/07/2009
Italy		158	158	4	
Japan		670	670	6	
Korea		2451	2451	10	
Kuwait		196	196	1	
Lebanon		14	14	1	
Lithuania		69	69	1	
Malaysia		1306	1306	1	
Mexico		456	456	2	
Norway		63	63	1	
Oman		125	125	1	
Saudi Arabia	47	83	130	2	18/07/2009
Singapore	70	538	608	12	27/04/2009

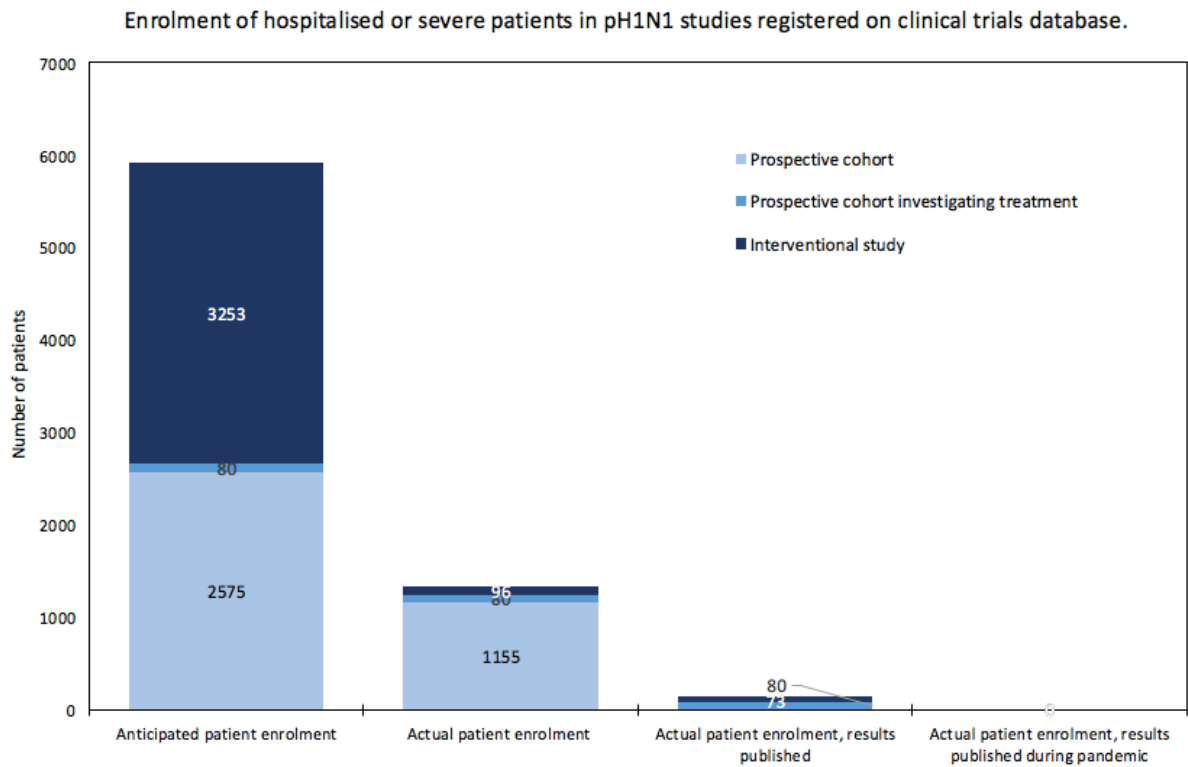
Country reporting data	Number of treatment courses described in literature (by study enrolment type)			Total number of papers published	Date of first patient enrolment in prospective research
	Prospective	Retrospective	Total		
South Africa	19		19	1	17/08/2009
South Korea		20	20	1	
Spain	2942	1156	4103	16	23/04/2009
Sweden		108	108	1	
Switzerland	78	11	89	2	01/10/2009
Taiwan	75	99	174	3	15/07/2009
Thailand	24		24	1	08/07/2009
Turkey	18	874	892	5	01/11/2009
UK	200	44	244	4	01/09/2009
USA	251	2308	2555	25	23/04/2009
Total	5278	28599	33869		

Appendix 5: Country level data demonstrating number of treatment courses described in the literature, and date of first enrolment in prospective research, where relevant. Date in DD/MM/YYYY format.

Appendix 6 –Prisma flow diagram describing screening, eligibility and inclusion for clinical trial registration records for studies aimed at enrolling A(H1N1)pdm09 patients.



Appendix 7: Enrolment metrics for studies enrolling A(H1N1)pdm09 patients, when analysis is restricted to ‘serious’ and hospitalized patients.



Enrolment metrics for studies enrolling A(H1N1)pdm09 patients, when analysis is restricted to ‘serious’ and hospitalized patients. 10 records are eligible for inclusion. This includes 6 interventional trials and 4 prospective observational studies. Registered trials intended to assess the following treatments: convalescent plasma, IVIG, Chinese medicines, rosuvastatin, and rapamune. Together, the trials intended to enrol 5908 patients, 1331 patients were actually enrolled, results are publicly available for 153 patients, and for no patient were the trial results available before the end of the epidemic. Results are now available for three studies

Appendix 8: Prisma flow diagram describing screening, eligibility and inclusion for clinical trial registration records for studies aimed at enrolling influenza patients, that were open during the pandemic period.

