FAST TRACK

Detection of mild to moderate influenza A/H7N9 infection by China's national sentinel surveillance system for influenza-like illness: case series

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STUDY QUESTION Does human infection by the influenza A/H7N9 virus always present with clinically severe illness, as most early reports suggest?

SUMMARY ANSWER As of 27 May 2013, patients with A/H7N9 infection detected through the routine sentinel surveillance system in China for influenza-like illness had mild or moderate disease.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Most reports of influenza A/H7N9 infection have so far presented a severe clinical picture. Our findings suggest the presence of a substantial proportion of milder cases, and support the existence of a "clinical iceberg" phenomenon.

Participants and setting

All individuals with laboratory confirmed A/H7N9 infection, detected through the sentinel surveillance system for influenza-like illness in mainland China, as of 27 May 2013. The surveillance system includes outpatient clinics and emergency departments of 554 sentinel hospitals across 31 provinces in the country. Patients meeting the World Health Organization's definition of influenza-like illness undergo weekly surveillance, and 10-15 nasopharyngeal swabs are collected each week from a subset of patients with influenza-like illness in each hospital for virological testing.

Main results

Of 130 people with laboratory confirmed A/H7N9 infection as of 27 May 2013, five (4%) were detected through the routine sentinel surveillance system for influenza-like illness. Four (80%) of these detected patients were male, with a mean age of 13 years (range 2-26), and none had any underlying medical condition. Exposure history, geographical location, and timing of symptom onset of these five patients were similar to the general cohort of patients with laboratory confirmed infection. All five patients presented with fever, and most with upper respiratory tract symptoms. By contrast with the generally severe clinical picture reported so far for A/H7N9 infection, all five patients had mild to moderate disease and have already recovered. Among them, three (60%) were managed only as outpatients without being prescribed antiviral drugs, and the other two (40%) were admitted to hospital and subsequently discharged. One patient had pneumonia without requiring intensive care.

Epidemiological and clinical characteristics of five patients with influenza A/H7N9 identified through routine surveillance for influenza-like illness in China

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age (years)	2	4	26	26	9
Sex	Male	Male	Female	Male	Male
Location	Shanghai	Shanghai	Jiangsu	Jiangsu	Fujian
Underlying medical conditions	None	None	None	None	None
Date of illness onset	17 March 2013	31 March 2013	8 April 2013	8 April 2013	26 April 2013
Presenting symptoms	Fever	Fever, rhinorrhoea	Fever, myalgia	Fever, productive cough	Fever, diarrhoea, malaise
Pneumonia	No	No	No	Yes (left sided)	No
Admitted to hospital	No	Yes	No	Yes	No
Admitted to intensive care unit	No	No	No	No	No
Mechanical ventilation	No	No	No	No	No
Received antiviral treatment	No	Yes	No	Yes	No
Recovered	Yes	Yes	Yes	Yes	Yes

Bias, confounding, and other reasons for caution

Although our study included all individuals with A/H7N9 infection detected by the sentinel surveillance system for influenza-like illness, the small number of cases is not definitive and thus requires confirmation by systematic seroepidemiological data. Viral genetic data were not available.

Generalisability to other populations

Because outpatient clinics or emergency departments in hospitals represent a typical first step for patients with influenza-like illness in China presenting to the healthcare system, the sentinel surveillance system is believed to capture typical patients with the illness in the community. Although the selection of patients with influenza-like illness for virology testing was not random, there should not have been any incentive for selection according to clinical severity, because results would not have been fed back to doctors for treatment purposes.

Study funding/potential competing interests

The study was funded by the US National Institutes of Health, the China-US collaborative programme on emerging and re-emerging infectious diseases, grants from the Chinese Ministry of Science and Technology, the Harvard Center for Communicable Disease Dynamics from the National Institute of General Medical Sciences, the Research Fund for the Control of Infectious Disease of the government of the Hong Kong Special Administrative Region, and the area of excellence scheme of the Hong Kong University grants committee. DKMI received research funding from Hoffmann-La Roche; BJC received research funding from MedImmune, and consults for Crucell NV; GML received speaker honoraria from HSBC and Credit Lyonnais Securities Asia.

Lithium in the prevention of suicide in mood disorders: updated systematic review and meta-analysis

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Clinical review: Bipolar disorder (*BMJ* 2012;345:e8508)

STUDY QUESTION Has lithium a specific preventive effect for suicide and self harm in unipolar and bipolar mood disorders?

SUMMARY ANSWER Lithium was more effective than placebo in reducing the number of suicides in patients with mood disorders and specifically in patients with unipolar depression only; less clear benefits were found with lithium than with placebo in preventing deliberate self harm. There were no statistically significant differences for suicide between lithium and each individual active treatment, but lithium was more effective than carbamazepine in reducing the number of episodes of deliberate self harm.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
All psychiatric disorders are associated with an increased risk of suicide, but the risk is highest in people with mood disorder. This meta-analysis of randomised evidence showed lithium to be protective against suicide in people with unipolar depressive disorder.

Selection criteria for studies
We searched Medline, Embase, CINAHL, PsycINFO, CENTRAL, web based clinical trial registries, major textbooks, and the websites of pharmaceutical companies that manufacture lithium or the comparator drugs, up to January 2013. We also contacted the authors of major papers and other experts in the discipline. All randomised controlled trials comparing lithium with placebo or active drugs in long term treatment (≥3 months) for mood disorders were included.

Primary outcomes
The number of people who died by suicide, engaged in deliberate self harm, and died from any cause.

Main results and role of chance
48 controlled trials (6674 participants, 15 comparisons) were included. Lithium was more effective than placebo in reducing the number of suicides (odds ratio 0.13, 95% confidence interval 0.03 to 0.66) and deaths from any cause (0.38, 0.15 to 0.95). No clear benefits were observed for lithium compared with placebo in preventing deliberate self harm (0.60, 0.27 to 1.32). In unipolar depression, lithium was associated with a reduced risk of suicide (0.36, 0.13 to 0.98) and also the number of total deaths (0.13, 0.02 to 0.76) compared with placebo.

Bias, confounding, and other reasons for caution
The main limitation of the review is the quantity of the primary evidence. The sample size of most included studies was fewer than 100 participants, with overall few suicide and deliberate self harm events. Publication bias might be particularly important in such a review, because just one or two moderately-sized trials with neutral or negative results could materially affect the estimates. Included trials were clinically heterogeneous in terms of patients, diagnoses, comparators, study durations and phase of illness.

Study funding/potential competing interests
This study received no funding. JRG currently receives research funding from the UK Medical Research Council, UK Economic and Social Research Council, the National Institute for Health Research, and the Stanley Medical Research Institute. He was expert witness for Dr Reddys Laboratories and is Chief Investigator on the CEQUEL trial to which GlaxoSmithKline have contributed and supplied investigational drugs.

Efficacy of lithium versus placebo in preventing suicide, deliberate self harm, and all cause mortality in people with mood disorders

Mood disorders	No of studies	No of participants	Odds ratio (95% CI)
Bipolar and unipolar disorders:			
Completed suicide	4	485	0.13 (0.03 to 0.66)
Deliberate self harm	3	1231	0.60 (0.27 to 1.32)
All cause mortality	8	782	0.38 (0.15 to 0.95)
Unipolar depression only:			
Completed suicide	3	280	0.13 (0.02 to 0.76)
Deliberate self harm	1	167	0.99 (0.33 to 2.94)
All cause mortality	7	577	0.36 (0.13 to 0.98)

Anaemia, prenatal iron use, and risk of adverse pregnancy outcomes: systematic review and meta-analysis

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Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality (*BMJ* 2008;337:a2001)

STUDY QUESTION Does an association exist between prenatal anaemia, use of iron, and maternal haematological and pregnancy outcomes, and is a dose-response relation apparent?

SUMMARY ANSWER Daily prenatal iron use improved maternal haematological outcomes and birth weight in a linear dose-response relation, and an improvement in prenatal mean haemoglobin concentration linearly increased birth weight.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Evidence on the association of prenatal anaemia and iron use with birth outcomes has been inconclusive. This comprehensive meta-analysis of randomised trials suggests that prenatal iron use is associated with a significant increase in birth weight and reduction in risk of low birth weight.

Selection criteria for studies
We identified randomised trials of prenatal iron use and prospective cohort studies of prenatal anaemia, by electronic literature searches of PubMed and Embase up to 31 May 2012.

Primary outcome(s)
We included maternal haematological and pregnancy outcomes.

Main results and role of chance
We included 48 randomised trials (17 793 women) and 44 cohort studies (1 851 682 women). Use of iron significantly increased maternal mean haemoglobin concentration and reduced the risk of anaemia, iron deficiency anaemia, and low birth weight. The effect of iron on preterm birth was not significant. Analysis of cohort studies of prenatal anaemia showed a significantly higher risk of low birth weight (adjusted odds ratio 1.29, 95% confidence interval 1.09 to 1.53) and preterm birth (1.21, 1.13 to 1.30) with anaemia in the first or second trimester. Exposure-response analysis indicated that for every 10 mg increase in daily dose of iron, up to 66 mg/day, the relative risk of maternal anaemia was 0.88 (0.84 to 0.92) (P for linear trend<0.001). Birth weight increased by 15.1 (6.0 to 24.2) g (P for linear trend=0.005) and risk of low birth weight decreased by 3% (relative risk 0.97, 0.95 to 0.98) (P for linear trend<0.001) for every 10 mg increase in dose/day. Duration of use was not significantly associated with the outcomes after adjustment for dose. Furthermore, for each 1 g/L increase in mean haemoglobin, birth weight increased by 14.0 (6.8 to 21.8) g (P for linear trend=0.002). However, mean haemoglobin was not associated with risk of low birth weight and preterm birth. We found no evidence of a significant effect on duration of gestation, small for gestational age births, or birth length.

Bias, confounding, and other reasons for caution
Several outcomes in this review were associated with significant heterogeneity. Although we did subgroup analysis and meta-regression to evaluate the sources of heterogeneity, it could not be explained substantially by the prespecified subgroups. This limits the understanding of the association in various study settings and restricts the generalisability of our findings. In the cohort studies analysis, although we used adjusted estimates available from studies, these results still could have been biased by residual confounding, in either direction depending on the nature of residual confounding. In the exposure-response analysis of cohort studies, we assumed mean haemoglobin concentrations for studies with missing values, which may have introduced bias towards the null due to random measurement error. We also could not evaluate associations with several outcomes owing to the paucity of data.

Study funding/potential competing interests
The study was funded by the Bill and Melinda Gates Foundation. Additional support was obtained from the Saving Brains Program, Grand Challenges Canada Grant Number 0073-03.

Effects of prenatal iron use on maternal haematological* and pregnancy outcomes

Outcomes	No of trials	Weighted mean difference or relative risk (95% CI)	P value
Haemoglobin (g/L)	36	4.59† (3.72 to 5.46)	<0.001
Anaemia	19	0.50 (0.42 to 0.59)	<0.001
Iron deficiency anaemia	6	0.40 (0.26 to 0.60)	<0.001
Birth weight (g)	19	41.2† (1.2 to 81.2)	<0.001
Low birth weight	13	0.81 (0.71 to 0.93)	0.001
Preterm birth	12	0.84 (0.68 to 1.03)	0.09

*Haematological outcomes measured in third trimester or at delivery.
†Weighted mean difference.

Analysis of the systematic reviews process in reports of network meta-analyses: methodological systematic review

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Research methods and reporting: The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions (*BMJ* 2009;339:b2700)

STUDY QUESTION Do network meta-analyses, increasingly used to assess comparative effectiveness of healthcare interventions, follow the key methodological recommendations for reporting and conduct of systematic reviews?

SUMMARY ANSWER Essential methodological components of the systematic review process (such as literature search, assessment of the risk of bias of individual studies) are frequently lacking in reports of network meta-analyses.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Network meta-analyses are primarily meta-analyses and should be conducted in accordance with the methodological rules of systematic reviews. Key methodological components of the systematic review process are frequently reported inadequately in publications of network meta-analyses.

Selection criteria for studies

We searched the Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Medline, and Embase from inception to 12 July 2012. The study included network meta-analyses comparing the clinical efficacy of three or more interventions based on randomised controlled trials, and excluded network meta-analyses with an open loop network of three interventions.

Primary outcome(s)

We assessed the reporting of general characteristics and key methodological components of the systematic review process. For some components, when reporting was adequate, we assessed their conduct quality. We used two composite outcomes. The first composite, inadequate reporting or conduct, meant that the authors either: (1) did not report a literature search, or reported an electronic search of only one bibliographic database and did not search for other sources; or (2) did not report an assessment of risk of bias of individual studies. The second composite was compliance with seven of the mandatory items of the methodological expectations of Cochrane intervention reviews.

Main results and role of chance

Of 121 network meta-analyses covering a wide range of medical areas, 100 (83%) assessed pharmacological interventions and 11 (9%) non-pharmacological interventions; 56 (46%) were published in journals with a high impact factor. The electronic search strategy for each database was not reported in 88 (73%) network meta-analyses. In total, 61 (50%) network meta-analyses did not report any information regarding the assessment of risk of bias of individual studies, and 103 (85%) did not report any methods to assess the likelihood of publication bias. Overall, 87 (72%) network meta-analyses showed inadequate reporting of key methodological components or inadequate conduct quality, based on the first composite. This proportion did not differ by the type of journal publishing the report (general journal 69% (95% confidence interval 57% to 81%), specialty journal 74% (63% to 85%); P=0.5) or the funding source (public funding 67% (74% to 79%), private funding 79% (67% to 90%); P=0.2). Based on the items in the second composite, almost all network meta-analyses (120 (99%)) showed inadequate reporting of key methodological components or inadequate conduct. These findings did not differ by journal type or funding source.

Reporting of key methodological components of the systematic review process in 121 network meta-analyses

Items and subcategory	No (%) of reports featuring item
Reporting of information sources searched	
Databases searched	118 (98)
Electronic search strategy for each database	33 (27)
Search for any other sources	79 (65)
Search for ongoing studies	19 (16)
Reporting of study selection and data collection process	
Process for selecting studies	79 (65)
Method of data extraction	89 (74)
Reporting of methods used for assessing risk of bias of individual studies	60 (50)
Reporting of methods used for assessing publication bias	18 (15)
Reporting of study characteristics in the results section	
Description of network	82 (68)
Characteristics of patients (for example, age, female:male ratio)	70 (58)
Description of interventions	64 (53)
Reporting of risk within studies in the results section	51 (42)
Reporting of publication bias in the results section	18 (15)
Reporting of limitations at review level (reporting or publication bias)	58 (48)

Bias, confounding, and other reasons for caution

Our study had some limitations. Assessing conduct quality from published reports alone could be unreliable, as has been shown for randomised trials. The authors of these reports may have used adequate methods but omitted important details from their reports, or key information was deleted during the publication process.

Study funding/potential competing interests

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