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RESEARCH

THIS WEEK'S RESEARCH QUESTIONS

1290 In acute respiratory distress syndrome, does high frequency oscillation improve clinical outcomes when compared with conventional mechanical ventilation?

1291 What is the impact of monthly immunisation campaigns on low immunisation rates in poor Indian toddlers, and does giving food and plates act as an extra incentive?

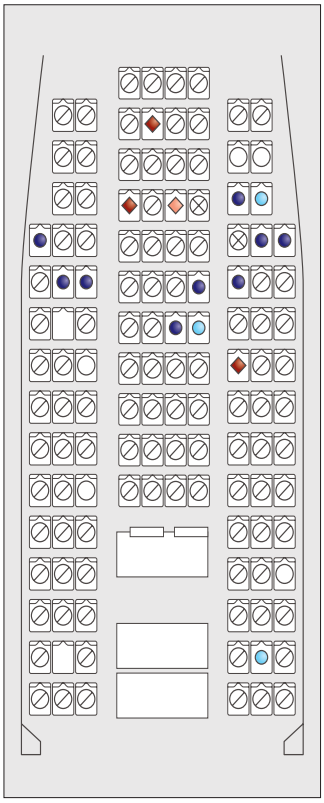
1292 How safe, reactogenic, and immunogenic were two novel swine flu vaccines in UK children aged 6 months to 12 years during the pandemic of 2009?

1293 What was the risk of transmission of pandemic swine flu on a long haul flight?

Swine flu on a plane

Pandemic A/H1N1 prompted a lot of unusual submissions to the *BMJ*. Michael Baker and colleagues' retrospective cohort study tells an epidemiological detective story (p 1293). On the day that WHO declared the outbreak pandemic A/H1N1 2009 influenza to be a "public health emergency of international concern" a general practitioner in New Zealand identified cases of influenza-like illness in a group of high school students just back from a trip to Mexico. Did the students infect anyone else on their long haul flight?

The authors report how the students, their teachers, and most of the 100-odd passengers sitting in the same section of the plane were contacted, surveyed, and swabbed. They conclude that the infection risk for passengers sitting within two rows of already infected passengers was about 3.5%. The plan of the cabin, right, shows the seats of people who had symptoms during the flight (denoted by circles) and after the flight (diamonds). So now we know whodunnit, or at least where.



Evaluation of two swine flu vaccines for UK children

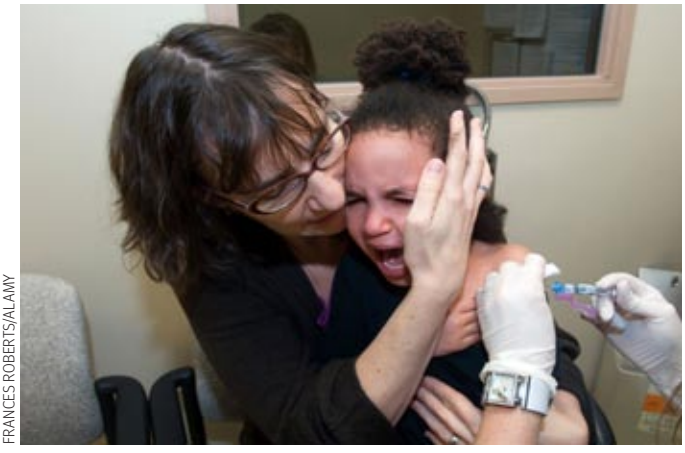
The trial by Claire Waddington and colleagues in the UKPVG H1N1 Influenza Vaccine Collaboration tested the safety, reactogenicity, and immunogenicity of two novel pandemic influenza A (H1N1) vaccines for children (p 1292). As this phase II study was conducted to choose a vaccine for urgent use, it wasn't designed or analysed to compare two means or the difference between the means and the confidence interval of the difference, as a large phase III trial would be. So it was not the kind of head to head trial the *BMJ* usually publishes which fully evaluates the overall benefit-risk of one intervention versus another. But we thought *BMJ* readers would value access to the data that explain the UK government's choice of vaccine.

More than 900 UK children without A/H1N1 pandemic influenza were enrolled into the trial during last year's pandemic (or non-demic, as one rapid responder calls it www.bmj.com/cgi/eletters/340/may25_3/c2792). They were randomised to receive two doses, three weeks apart, of either $AS03_B$ adjuvanted split virion H1N1 influenza vaccine (Pandemrix, GlaxoSmithKline) or whole virion vaccine (Celvapan, Baxter). Both vaccines were generally well tolerated, although the adjuvanted vaccine caused significantly more frequent severe local reactions and fever. As it also prompted significantly higher seroconversion rates, the adjuvanted vaccine won out.

When this paper appeared on bmj.com Bloomberg Businessweek quickly pointed out that "Glaxo said in April that sales of its pandemic flu vaccine helped it surpass expectations for first-quarter profit. The shot generated 698 million pounds ($1.02 billion) in revenue in the quarter. [GSK] agreed to cap its vaccine order from the British government at 34.8 million doses last month. The government canceled its contract with Deerfield, Illinois-based Baxter in February" (www.businessweek.com/news/2010-05-28/glaxo-beat-baxter-in-u-k-test-of-swine-flu-shots-in-children.html)

RESEARCH ONLINE: For new research articles see www.bmj.com/channels/research.dtl

Domhnall MacAuley's blog about the recent World Organization of National Colleges, Academies and Academic Associations of General Practitioners/Family Physicians (WONCA) world conference in Mexico has prompted some thought provoking comments, including from two giants of US primary care, Barbara Starfield and Larry Green (http://blogs.bmj.com/bmj/2010/05/26/domhnall-macauley-on-wonca-part-ii/). Both offer opinion on the paradox that the more education generalists in primary care receive, the more likely they are to refer to specialists. However, "The essence of primary care is person focused, not diseases or subspecialty focused," points out Professor Starfield. Larry Green's view is that we should "train family physicians so they can tell very well what most people have most of the time, close to where they live, and recognise 'can't miss and unusual but important stuff'."



FRANCES ROBERTS/ALAMY

High frequency oscillation in patients with acute lung injury and acute respiratory distress syndrome (ARDS): systematic review and meta-analysis

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STUDY QUESTION Among patients with acute lung injury/acute respiratory distress syndrome (ARDS), does high frequency oscillation improve clinical outcomes (including mortality) compared with conventional mechanical ventilation?

SUMMARY ANSWER High frequency oscillation reduces hospital or 30 day mortality, reduces risk of treatment failure, and improves oxygenation.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Some centres routinely use high frequency oscillation to support oxygenation in patients with ARDS, despite limited information on clinical outcomes. Our systematic review suggests that high frequency oscillation improves oxygenation and reduces the risks of treatment failure and hospital or 30 day mortality and therefore supports its use in patients with ARDS.

Selection criteria for studies

Included trials randomly assigned adults or children with acute lung injury or ARDS to receive either high frequency oscillation or conventional mechanical ventilation. To identify trials we searched Medline, Embase, CENTRAL, and ISI from inception to March 2010, article bibliographies, conference proceedings (1994-2009 or 2010), and clinicaltrials.gov and controlled-trials.com, and contacted clinical experts. We also contacted authors of all primary trials to clarify methods and/or provide additional unpublished data.

Primary outcomes

Hospital or 30 day mortality.

Main results and role of chance

The eight included trials enrolled 419 patients; essentially all had ARDS. The ratio of partial pressure of oxygen to inspired fraction of oxygen at 24, 48, and 72 hours was 24% (P<0.01), 16% (P=0.10), and 17% (P=0.02) higher in patients receiving high frequency oscillation. There were no significant differences in oxygenation index because mean airway pressure rose by 22-33% in patients receiving high frequency oscillation (P≤0.01). High frequency oscillation significantly reduced hospital (or 30 day) mortality (relative risk 0.77, 95% confidence interval 0.61 to 0.98; P=0.03; six trials, 365 patients, 160 deaths) and treatment failure (0.67, 0.46 to 0.99; P=0.04; five trials, 337 patients, 73 events). Treatment failure was defined as refractory hypoxaemia, hypercapnoea, hypotension, or barotrauma leading to crossover to the other treatment group. Other risks were similar.

Bias, confounding, and other reasons for caution

Blinding was not feasible. In three trials, patients assigned to conventional ventilation received higher tidal volumes than currently recommended, which might have biased results in favour of high frequency oscillation. In five trials, 4-52% of all randomised patients crossed over between study groups, which might have reduced the apparent benefit of high frequency oscillation. There was substantial heterogeneity between trials for physiological (I^2=21-95%) but not clinical (I^2=0%) outcomes. The quality of evidence was moderate for the most important clinical outcomes and low for others; pooled results were generally based on small numbers of trials, patients, and events.

Study funding/potential competing interests

This study received no specific funding. Some authors are either principal or site investigators for the ongoing Canadian Institutes of Health Research-funded multicentre OSCILLATE randomised trial of HFO in severe ARDS. CareFusion (formerly SensorMedics) is providing study oscillators to some of the hospitals involved in OSCILLATE. CIHR and CareFusion had no involvement in the design and conduct of this review; collection, management, analysis, and interpretation of the data; or preparation, review, or approval of the manuscript.

CLINICAL OUTCOMES AND ADVERSE EVENTS IN TRIALS OF HIGH FREQUENCY OSCILLATION

	No of trials	No of patients with event/ Total No of patients	Relative risk or weighted mean difference (95% CI), P value	Quality of evidence
Clincal outcomes				
Hospital (or 30 day) mortality	6	160/365	0.77 (0.61 to 0.98), 0.03	Moderate
Treatment failure	5	73/337	0.67 (0.46 to 0.99), 0.04	Moderate
Ventilator days	4	276*	−0.8 (−5.4 to 3.9), 0.75	Low
Ventilator free days to day 28	1	54*	2 (−0.7 to 4.7), 0.15	Low
Adverse events				
Barotrauma	6	41/365	0.68 (0.37 to 1.22), 0.2	Low
Hypotension	3	11/267	1.54 (0.34 to 7.02), 0.58	Low
Endotracheal tube obstruction	4	7†/246	1.3 (0.3 to 5.6), 0.73	Low

*Total number of patients.
†All events in one trial.

Improving immunisation coverage in rural India: clustered randomised controlled evaluation of immunisation campaigns with and without incentives

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STUDY QUESTION

What is the effect of improving the reliability of immunisation services in a low income setting with very low baseline immunisation rates, and what is the combined effect of reliable services with modest financial incentives?

SUMMARY ANSWER

Improving the reliability of services through the provision of reliable monthly immunisation camps had a modest impact on full immunisation rate among children aged 1-3. The addition of a small non-financial incentive led to larger improvement. Camps with incentives were more cost effective than camps without incentives.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Financial incentives, such as those used in conditional cash transfer programmes, are known to be effective in promoting the use of certain preventive healthcare services. This paper shows that modest incentives have a positive effect on immunisation in settings with very low immunisation rates.

Design

Villages were randomised with computer generated allocation into three groups. In one intervention (A), regular well publicised immunisation clinics (or "camps") were held, while in the second intervention (B), similar camps were held and parents were also offered small incentives (1 kg of dried beans at each immunisation and a set of plates on completion of the extended package of immunisation) to immunise their children. A third set of villages formed the control group.

Participants and setting

134 villages in Udaipur district, Rajasthan, India, were randomised. The villages were mostly poor tribal villages in the catchment area of our partner organisation, Seva Mandir. All children aged 0-5 were eligible to be immunised in the camp, and all children aged 0-2 at their first visit to the camps were eligible for the incentives.

Primary outcome

Our primary outcome was the receipt of all or part of the extended package of immunisation. Data were collected about 18 months after the start of the intervention in each village.

Main results and the role of chance

The highest rate of full immunisation was observed for intervention B (camps with incentives). In intervention B villages, 148/382 (39%) children were completely immunised compared with 68/379 (18%) in intervention A villages and 50/860 (6%) in control villages. The relative risk of being completely immunised was 3.1 (2.0 to 4.2) for intervention A versus control, 6.7 (4.5 to 8.8) for intervention B versus control, and 2.2 for intervention B versus intervention A (1.5 to 2.8). The average cost to Seva Mandir of fully immunising a child was $28 (£16, €19) in the reliable camp with incentives and $56 in the reliable camp without incentives.

Harms

There were no adverse events (severe reaction to immunisation) reported in either intervention group.

Bias, confounding, and other reasons for caution

Self reported immunisation status is a potential source of bias, though the differences between interventions A and B were similar when we used administrative data.

Generalisability to other populations

The study was conducted in a low density area where initial immunisation rates were extremely low. In areas where initial immunisation rates are higher similar interventions might not produce such a large increase.

Study funding/potential competing interests

This study was funded by the MacArthur Foundation. The intervention was funded by the Evangelischer Entwicklungdienst (Germany), Inter Church Cooperation for Development Cooperation (Netherlands), and Plan International, through Seva Mandir comprehensive plan.

Trial registration number

IRSCTN87759937.

MEAN (95% CI) EFFECTS ACCORDING TO GROUP ALLOCATION

	Control (n=860)	A-reliable immunisation (n=379)	B-reliable immunisation plus incentive (n=382)
% completely immunised	6 (3 to 9)	18 (11 to 25)	39 (30 to 47)
% with ≥1 immunisation	49 (40 to 57)	78 (70 to 85)	74 (67 to 82)
% with BCG scar*	28 (21 to 36)	50 (41 to 59)	50 (41 to 59)
No of immunisations	1.20 (0.94 to 1.46)	2.35 (1.99 to 2.71)	2.85 (2.44 to 3.25)

*N=790 in control group, n=334 group A, n=336 group B.

Safety and immunogenicity of AS03$_B$ adjuvanted split virion versus non-adjuvanted whole virion H1N1 influenza vaccine in UK children aged 6 months-12 years: open label, randomised, parallel group, multicentre study

UKPVG H1N1 Influenza Vaccine Collaboration

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The UKPVG H1N1 Influenza Vaccine Collaboration comprises the Oxford Vaccine Group (University of Oxford), Centre for Infections (Health Protection Agency), University of Southampton Wellcome Trust Clinical Research Facility, Royal Devon and Exeter Foundation Trust, St George's Vaccine Institute, and University of Bristol Children's Vaccine Centre. The individual members of the collaboration are listed in the full paper on bmj.com

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c2649

Response on bmj.com

"One group got an adjuvanted split virion vaccine derived from egg culture. The other got a non-adjuvanted whole virion vaccine derived from cell culture. So there are three variables . . . actually there is a fourth . . . the seed virus was different in each case . . . And yet the conclusion allocates all of the difference to the adjuvant . . . What is the scientific rationale for that?"
Ron Law, risk and policy adviser, Auckland, New Zealand

To submit a rapid response, go to any article on bmj.com and click "respond to this article."

STUDY QUESTION What is the comparative safety, reactogenicity, and immunogenicity of two novel pandemic influenza A (H1N1) vaccines in children?

SUMMARY ANSWER Compared with non-adjuvanted whole virion H1N1 influenza vaccine, AS03$_B$ adjuvanted split virion vaccine was more immunogenic in all age groups studied.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Previously used seasonal influenza vaccines have limited immunogenicity in young children. The AS03$_B$ adjuvanted vaccine used in this study was significantly more immunogenic than the whole virion vaccine, especially in younger children, but was also more reactogenic.

Design

In this open label, parallel group, phase II study children were randomised 1:1 to receive two doses of AS03$_B$ adjuvanted split virion H1N1 influenza vaccine or whole virion vaccine 21 days apart. Reactogenicity data were collected for one week after immunisation. Serum samples were collected at baseline and after the second dose.

Participants and setting

During the 2009 H1N1 pandemic, 942 children aged 6 months to 12 years were enrolled at five UK centres. Recruitment used web based screening after media advertising, direct mail, and email. Exclusion criteria were confirmed H1N1 (or antiviral treated) influenza, egg allergy, coagulation defects, immunocompromise, or recent receipt of blood products.

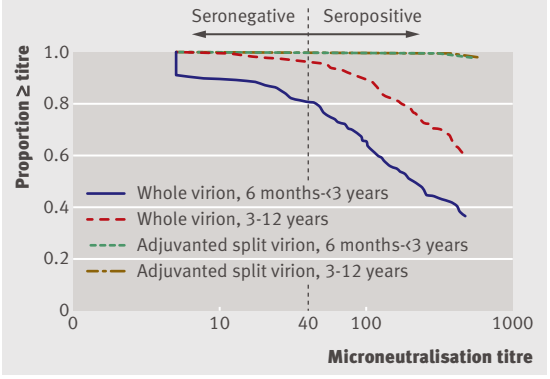
Primary outcome

Primary reactogenicity end points were frequency and severity of fever and injection site reactions. Immunogenicity was primarily assessed by the microneutralisation assay seroconversion rate.

Main results and the role of chance

937 children were included in a per protocol analysis (439 aged 6 months-<3 years, and 498 aged 3-12 years). Seroconversion rates were higher after the adjuvanted vaccine than the whole virion vaccine in children under 3 years (98.2% (95% confidence interval 94.8% to 99.6%) *v* 80.1% (73.8% to 85.5%), P<0.001) and in those over 3 years (99.1% (96.9% to 99.9%) *v* 95.9% (92.4% to 98.1%), P=0.03). The adjuvanted vaccine was more reactogenic than the whole virion vaccine with more frequent severe local reactions in those aged over 5 after dose one (7.2% (3.9% to 12%) *v* 1.1% (0.1% to 3.9%), P<0.001) and dose two (8.5% (4.8% to 13.7%) *v* 1.1% (0.1% to 4.1%), P<0.002), and after dose two in those under 5 (5.9% (3.3% to 9.6%) *v* 0.0% (0% to 1.4%), P<0.001).

ANTIBODY AS MEASURED BY MICRONEUTRALISATION CURVES



Harms

While both vaccines were generally well tolerated, dose two of the adjuvanted vaccine was more reactogenic than dose one, especially for fever ≥38°C in those aged under 5 years (22.4% (17.5% to 28.1%) *v* 8.9% (5.8% to 12.9%), P<0.001).

Bias, confounding, and other reasons for caution

Although we studied a two dose schedule, the UK programme was later changed to a single dose of the adjuvanted vaccine.

Generalisability to other populations

Like other oil in water adjuvanted vaccines, the AS03$_B$ adjuvanted vaccine was more reactogenic than the non-adjuvanted whole virion vaccine but was highly immunogenic. The high seroconversion rates achieved in young children with the adjuvanted vaccine indicates the potential for improved immunogenicity of pandemic and seasonal influenza vaccines in this age group.

Study funding/potential competing interests

Funded by a grant from the NIHR Health Technology Assessment Programme. Vaccines were manufactured and donated by GlaxoSmithKline vaccines and Baxter. The study investigators received no personal remuneration for any of this work, but acknowledge financial assistance to attend conferences, along with other financial links to vaccine manufacturers as members of advisory boards and receiving research grants and honorariums paid to their respective NHS Trusts or universities or independent charities (see full paper on bmj.com for details).

Trial registration number

Clinical trials.gov NCT00980850

Transmission of pandemic A/H1N1 2009 influenza on passenger aircraft: retrospective cohort study

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STUDY QUESTION

What is the risk of transmission of pandemic A/H1N1 2009 influenza (pandemic A/H1N1) on a long haul airline flight?

SUMMARY ANSWER

A low but measurable risk of pandemic A/H1N1 transmission exists during modern commercial air travel; this risk is concentrated close to infected passengers with symptoms.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Respiratory agents may be transmitted during airline travel, although the level of risk is poorly defined for most agents, including influenza viruses. Influenza may be transmitted to nearby passengers, even in modern well ventilated commercial aircraft.

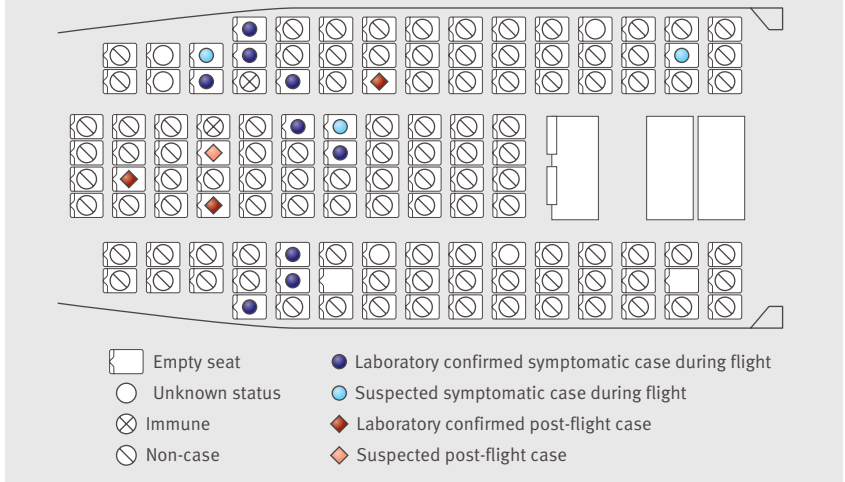
Participants and setting

We investigated passengers seated in the rear section of a Boeing 747-400 long haul flight that arrived in Auckland, New Zealand, on 25 April 2009. The passengers located and interviewed comprised a group of 24 students and teachers and a further 97 (out of 102) other passengers in the same section of the plane.

Design, size, and duration

This was a retrospective cohort investigation using a questionnaire administered to passengers to identify those with symptomatic illness. Nasopharyngeal swabs were obtained from passengers with symptoms, as well as from some who were asymptomatic. We tested these by real time polymerase chain reaction using primers that distinguished pandemic A/H1N1 from other influenza virus sequences.

SEATING PLAN OF REAR SECTION OF AIRCRAFT SHOWING PASSENGERS ACCORDING TO INFECTION STATUS



Main results and the role of chance

Nine laboratory confirmed symptomatic cases of pandemic A/H1N1 infection occurred in the school group during the flight. Two other passengers developed laboratory confirmed pandemic A/H1N1 infection, 12 and 48 hours after the 13 hour flight. The timing of their illness was consistent with exposure during the flight and the known incubation period for influenza A. They reported no other potential sources of infection and so were classified as cases of in-flight infection. Their seating was within two rows of infected passengers, implying an infection risk of about 3.5% for the 57 passengers in those rows. One other laboratory confirmed post-flight case developed illness 24 hours after the flight. Because he was a member of the school group and may have been infected before boarding, he was considered a case of possible in-flight infection.

Bias, confounding, and other reasons for caution

A limitation of the investigation is that passengers were interviewed by several personnel during the initial response phase, so this process was not as complete and consistent as would be desirable. Some characteristics, notably symptoms, may therefore have been under-reported, which could have reduced case ascertainment. Time delays in interviewing would have produced further recall bias, again probably lowering reporting of symptoms. Testing focused on passengers with symptoms and would have missed most asymptomatic infections. On balance, the sources of error in this investigation would tend to under-estimate the risk of in-flight transmission of pandemic A/H1N1.

Generalisability to other populations

Our findings are likely to apply to the risk of influenza transmission on modern passenger aircraft generally. However, the risk may be quite different in other forms of transport, and in non-transport settings in which people are close together, as ventilation and air humidity will differ from the conditions found in aircraft.

Study funding/potential competing interests

This investigation was largely funded by the internal resources of the investigators' employing organisations as part of the public health response to the A/H1N1 pandemic. MGB was partly supported by a grant from the Centers for Disease Control and Prevention (USA) for research on pandemic influenza (1U01CI000445-01). The WHO Collaborating Centre for Reference and Research on Influenza is supported by the Australian Government Department of Health and Ageing. The funding sources had no involvement with the decision to write this paper and submit it for publication.