RESEARCH

The *BMJ* is an Open Access journal. We set no word limits on *BMJ* research articles, but they are abridged for print. The full text of each *BMJ* research article is freely available on bmj.com

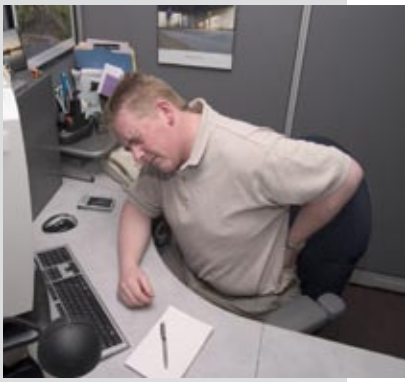
SATURN STILLS/SPL

THIS WEEK'S RESEARCH QUESTIONS

Child mortality after revaccination with BCG in Guinea-Bissau

Evidence suggests that BCG vaccination might reduce child mortality in less developed countries through nonspecific immune stimulation, prompting debate about whether toddlers who had the jab at birth should be revaccinated. So Adam Edvin Roth and colleagues set up a randomised controlled trial to test whether giving BCG again at 19 months—just after vaccination for diphtheria, tetanus, and polio (DPT)—altered mortality up to age five (p 749). They stopped enrolment to the trial suddenly when an informal interim analysis showed increased mortality in the revaccinated children, possibly owing to interactions between BCG, vitamin A supplements, and DTP. This early termination precluded firm conclusions, but as the paper raised important scientific and ethical questions we decided to publish it anyway, along with expert comment. Editorialist Frank Shann calls for review of the immunisation schedule in developing countries and recommends that in such regions all new vaccines are tested for their effects on total mortality (p 720). In an online commentary Charles Weijer considers the ethics of this trial and concludes that "While the conduct of vaccine trials in developing countries is challenging for many reasons, lack of funding is not an acceptable reason for a study not to have a data monitoring committee. If anything, the multidimensional vulnerability of trial participants in developing countries renders the need for such oversight more pressing" (doi:10.1136/bmj.c1373). Rapid responder and paediatrician David E Bratt from Trinidad and Tobago calls it "simply appalling that such a study was ever allowed without the required funding for a data monitoring committee and formal stopping rules. The excuse will be that the local Ministry of Health agreed. To those of us who work in developing countries, that is no excuse" (www.bmj.com/cgi/eletters/340/mar15_1/c671).

Occupational health for chronic low back pain



ISTOCK

Given that chronic low back pain often has clinical, psychosocial, and occupational implications, Ludeke Lambeek and colleagues decided to tackle all three dimensions in their randomised controlled trial in the Netherlands (p 750). They found that a combined intervention—which set a clear treatment plan with patients and healthcare teams, trained patients to adopt and embrace graded activity, and eased the return to work—reduced the duration of disability in both working and private life and got people back to work much more quickly than usual care. The new CONSORT 2010 statement asks authors to describe trial interventions in enough detail to allow replication (www.bmj.com/cgi/content/full/340/mar23_1/c332), and you can follow the detailed description of this trial's integrated care intervention at www.bmj.com/cgi/data/bmj.c1035/DC1/1.

LATEST RESEARCH: For these and other new research articles see http://www.bmj.com/channels/research.dtl

PICTURE PARTNERS/ALAMY

Outcomes of treatment for gestational diabetes

There's surprisingly little consensus on the specific maternal and neonatal benefits of treating women with gestational diabetes, so Karl Horvath and colleagues systematically reviewed trials in which women were rigorously screened and vigorously treated (doi:10.1136/bmj.c1395). They found that treatment reduced the risk of shoulder dystocia but had no significant effect on perinatal or neonatal death or on the number of babies small for gestational age.

Intensive care for swine flu in pregnancy

Swine flu hasn't gone yet: WHO is currently reporting active transmission with laboratory confirmation in West Africa and Southeast Asia, particularly Thailand (www.who.int/csr/don/2010_03_19/en/index.html). One of the first regions to see A/H1N1 pandemic flu was Australia and New Zealand, and intensive care specialists there had the foresight to set up a comprehensive binational prospective case registry. We already knew that pregnant women were particularly vulnerable to A/H1N1, and this registry now reports that women at 20 or more weeks' gestation were 13 times more likely than non-pregnant women of childbearing age to be admitted to intensive care, with 11% of mothers and 12% of babies dying despite highly specialist intervention (p 751).

Sutures versus staples for skin closure in orthopaedic surgery: meta-analysis

Toby O Smith, Debbie Sexton, Charles Mann, Simon Donell

EDITORIAL by Singh and Mcgarvey

Norfolk and Norwich University Hospital, Norwich NR2 7UY

Correspondence to: T O Smith
toby.smith@uea.ac.uk

Cite this as: *BMJ* 2010;340:c1199
doi: 10.1136/bmj.c1199

STUDY QUESTION Is there a difference in clinical outcomes with staples versus sutures in orthopaedic wound closure?

SUMMARY ANSWER A much higher risk of developing a wound infection exists where the wound is closed with staples rather than sutures. This risk is greater in patients who specifically undergo hip surgery.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Orthopaedic surgeons use both metallic staples and nylon sutures to close wounds. Controversy exists as to the best method of wound closure after orthopaedic procedures such as lower limb joint arthroplasty, reconstructive surgery, and trauma fixation. The risk of infection after staple closure is three times greater than suture closure after orthopaedic surgery. After hip surgery the risk of infection is four times greater with staples. To minimise wound infection orthopaedic surgeons should close wounds with sutures rather than staples.

Selection criteria for studies

We searched Medline, CINAHL, AMED, Embase, Scopus, and the Cochrane Library databases from 1950 to September 2009. Unpublished literature was assessed using the databases SIGLE, the National Technical Information Service, the National Research Register, and the Current Controlled Trials databases. Additional studies were identified from cited references and by contacting all corresponding authors. We sought all randomised and non-randomised controlled trials that compared the clinical outcomes with use of staples compared with sutures for wound closure after orthopaedic surgery procedures. Two authors independently reviewed all potential studies for eligibility, methodological quality using the Physiotherapy Evidence Database (PEDro) critical appraisal tool, and data extraction. Data were analysed with meta-analysis. Relative risk and mean difference with 95% confidence intervals were calculated and pooled with a random effects model. Statistical heterogeneity was assessed with I^2 and χ^2 statistical tests.

Primary outcome

The primary outcome measure was the assessment of superficial wound infection after wound closure with staples or sutures.

Main results and role of chance

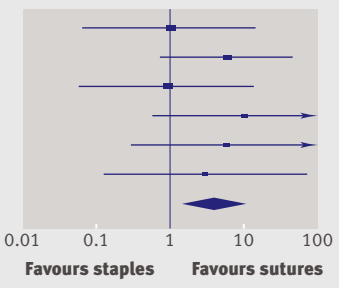
Of 195 citations retrieved, six papers were included, detailing 683 wounds. In total, 332 patients underwent suture closure and 351 staple closure. The overall risk of developing a superficial wound infection was more than three times greater after staple closure compared with suture closure, after orthopaedic procedures (relative risk 3.83, 95% confidence interval 1.38 to 10.68; P=0.01). In a subgroup analysis of hip surgery alone, the risk of developing a wound infection was four times greater after staple closure compared with suture closure (4.79, 1.24 to 18.47; P=0.02). There were no notable differences between sutures and staples for wound closure in respect to the development of inflammation, discharge, dehiscence, necrosis, and allergic reaction (P>0.05).

Bias, confounding, and other reasons for caution

The included studies poorly presented the characteristics of their cohorts, such as age, weight, or medical history. Accordingly, we could not determine whether these factors were important confounding variables to the findings. The studies reviewed were largely small and underpowered, allowing the potential for type I statistical error to impact on conclusions drawn. The potential for assessor and allocation bias was also evident as the papers reviewed poorly blinded patients and assessors to wound closure method.

INCIDENCE OF INFECTION FOR WOUNDS CLOSED WITH SUTURES OR STAPLES

Study	Staples	Sutures
Clayer and Southwood	1/33	1/33
Khan et al	6/63	1/64
Murphy et al	1/31	1/29
Shetty et al	5/54	0/47
Singh et al	3/40	0/31
Stockley and Elson	1/129	0/129
Total (95% CI)	17/350	3/333



Study funding/potential competing interests

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c1199

Local anaesthesia for pain control during outpatient hysteroscopy: systematic review and meta-analysis

Natalie A M Cooper, Khalid S Khan, T Justin Clark

University of Birmingham, Birmingham Women's Hospital, Birmingham B15 2TG

Correspondence to: T Justin Clark
justin.clark@bwhct.nhs.uk

Cite this as: *BMJ* 2010;340:c1130
doi: 10.1136/bmj.c1130

STUDY QUESTION

What is the effectiveness of local anaesthetic techniques for outpatient hysteroscopy?

SUMMARY ANSWER

Paracervical local anaesthetic injection provides better pain control than other methods during outpatient hysteroscopy.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Hysteroscopy, an accurate procedure for diagnosing intrauterine pathology, can be carried out with local anaesthesia. Injectable local anaesthetic, in particular paracervical administration, is the best way to reduce the pain of outpatient hysteroscopy.

Selection criteria for studies

We searched for randomised controlled trials on the effect of local anaesthetics on pain during outpatient hysteroscopy in Medline, Embase, CINAHL, and the Cochrane library. There were no limits or filters placed on the searches to ensure maximal sensitivity. We checked the reference lists for relevant papers. Our selection criteria captured studies on women undergoing outpatient hysteroscopy, the use of local anaesthetic versus a comparator, an assessment of pain, and randomised controlled trials.

Primary outcome

The primary outcome was pain experienced.

Main results and role of chance

From 245 citations, we selected 20 studies (2811 women) for review. Meta-analysis of 15 studies showed that local anaesthetic reduced pain during outpatient hysteroscopy (standardised mean difference −0.54, 95% confidence interval −0.86 to −0.23, I^2 = 91%) (figure). Paracervical injection greatly reduced pain (−1.28, −2.22 to −0.35, I^2 =97%) as did intracervical injection (−0.36, −0.61 to −0.10, I^2 = 0%). Intracavity instillation of local anaesthetic and anaesthetic applied topically to the cervix, however, did not substantially reduce the pain (−0.11, −0.31 to 0.10, I^2 =27%, and −0.32, −0.97 to 0.33, I^2 = 90%, respectively). Meta-regression analysis showed that paracervical injection was significantly more effective than the other methods (−1.02, −2.03 to −0.01).

Bias, confounding, and other reasons for caution

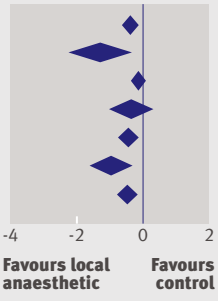
We did not seek any unpublished data and a funnel plot suggested the possibility of missing small negative studies. Meta-analysis of the studies grouped according to quality found that both the poor and the high quality studies showed a notable benefit of using local anaesthetic for outpatient hysteroscopy (−0.77, −1.45 to −0.08, I^2 = 95%, and −0.43, −0.73 to −0.12, I^2 = 83%, respectively). The heterogeneity observed between results was unexplained by our exploration. Our main inference was supported by the high quality subgroup of studies that had adequate randomisation and blinding. Not all studies selected for review could be included in meta-analysis, introducing some imprecision but our main inferences were drawn from results that were significant.

Study funding/potential competing interest

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

EFFECT OF LOCAL ANAESTHETIC ON PAIN SCORES IN WOMEN UNDERGOING HYSTEROSCOPY AS OUTPATIENTS

Study	Anaesthetic	Control	Standardised mean difference, random (95% CI)
Intracervical	123	116	-0.36 (-0.61 to -0.10)
Paracervical	335	337	-1.28 (-2.22 to -0.35)
Transcervical	276	270	-0.11 (-0.31 to 0.10)
Topical	312	306	-0.32 (-0.97 to 0.33)
Total	1046	1029	-0.54 (-0.86 to -0.23)
High quality studies	614	602	-0.43 (-0.73 to -0.12)
Low quality studies	432	427	-0.77 (-1.45 to -0.08)



This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c1130

Effect of revaccination with BCG in early childhood on mortality: randomised trial in Guinea-Bissau

Adam Edvin Roth,[1 2] Christine Stabell Benn,[3] Henrik Ravn,[3] Amabelia Rodrigues,[1] Ida Maria Lisse,[4] Maria Yazdanbakhsh,[5] Hilton Whittle,[6] Peter Aaby[1 3]

EDITORIAL by Shann

[1]Bandim Health Project, Indepth Network, Apartado 861, Bissau, Guinea-Bissau
[2]Department of Medical Microbiology, Lund University, 205 02 Malmö, Sweden
[3]Bandim Health Project, Danish Epidemiology Science Centre, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark
[4]Department of Pathology, Herlev University Hospital, 2730 Herlev, Denmark
[5]Department of Parasitology, Leiden University, Netherlands
[6]MRC Laboratories, Fajara, POB 273, Gambia
Correspondence to: P Aaby, Bandim Health Project, Statens Serum Institut, Artillerivej 5, 2300 Copenhagen S, Denmark
p.aaby@bandim.org

Cite this as: *BMJ* 2010;340:c671
doi: 10.1136/bmj.c671

bmj.com
Commentary: Ethics in conduct of trials in developing countries by Charles Weijer
Published 15 March 2010, doi:10.1136/bmj.c1373
Cite this as: *BMJ* 2010;340:c1373

This article is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c671

STUDY QUESTION Is intradermal BCG revaccination at 19 months of age after booster diphtheria-tetanus-pertussis (DTP) vaccination, usually administered at 18 months of age, associated with improved childhood survival?

SUMMARY ANSWER There was no overall beneficial effect of BCG revaccination on survival in children. The mortality of BCG revaccinated children increased significantly during a short period when many children received missing vaccinations or vitamin A or iron supplementation in campaigns.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS
BCG vaccination has stimulatory effects on the immune system, and previous studies have reported oral BCG revaccination to be associated with improved childhood survival. In this trial, BCG revaccination reduced mortality when given after booster DTP vaccination but mortality was increased among the children who were likely to receive DTP booster vaccination after BCG revaccination.

Design
Randomised controlled trial with block randomisation comparing BCG revaccination with no vaccine. No placebo or control vaccine was used.

Participants and setting
2871 children aged 19 months to 5 years registered in the study area of the Bandim Health Project in Bissau, Guinea-Bissau. Children with low or no reactivity to tuberculin and who were not severely sick on the day of enrolment were offered participation.

Primary outcome
Mortality hazard ratios of BCG revaccinated children compared with controls.

Main results and the role of chance
A total of 77 children died during follow-up. Compared with control children, the BCG revaccinated children had a hazard ratio of 1.20 (95% confidence interval 0.77 to 1.89). Some 250 children were admitted to hospital for the first time between enrolment and the end of the study: the incidence rate ratio for BCG revaccinated children versus controls was 1.04 (0.81 to 1.33). The trial was stopped prematurely because of a cluster of deaths in the BCG arm of the study, which occurred at a time when many children received missing vaccinations and vitamin A or iron supplementation. Throughout the trial, the effect of BCG revaccination on mortality was significantly different in children who had received DTP booster vaccination before enrolment (hazard ratio 0.36, 0.13 to 0.99) compared with children who had not received DTP booster before enrolment (1.78, 1.04 to 3.04) (P=0.006).

Harms
We observed a cluster of deaths in the BCG arm of the study. The hazard ratio for BCG revaccinated children compared with controls was 2.69 (1.05 to 6.88) in the period after campaigns in which children received missing vaccinations and vitamin A or iron supplementation.

Bias, confounding, and other reasons for caution
Because of the unexpected cluster of deaths we carried out many exploratory analyses to find possible causes. Fewer children than expected had received DTP booster before enrolment, and many were therefore likely to receive DTP booster after BCG revaccination. The level of mortality dropped significantly during the trial, and the study therefore did not have the power originally planned.

Generalisability to other populations
We could not find any similar studies of the impact of BCG revaccination on child survival. Several studies in Guinea-Bissau and elsewhere have suggested a negative effect when the sequence of vaccinations is changed and DTP is given as the last vaccination. Vitamin A supplementation has been found to enhance this negative effect in some situations.

Study funding/potential competing interests
The study was funded by the EU (ICA4-CT-2002-10053), the Danish National Research Foundation, DANIDA and the Novo Nordisk Foundation. The funding agencies had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. The authors have no competing interests.

Trial registration number
Register.clinicaltrials ICA4-CT-2002-10053-REVAC.
Accepted: 11 December 2009

MORTALITY RATES AND HAZARD RATIOS FOR CHILDREN REVACCINATED WITH BCG AND CONTROLS

	Mortality/100 person years (deaths/days)		
	BCG revaccination	Controls	Hazard ratio (BCG/no BCG)
Main result (total period)	1.2 (42/1 242 701)	1.0 (35/1 251 051)	1.20 (0.77 to 1.89)
Vaccination status (explorative analysis):			
Booster DTP before enrolment	0.4 (5/508 443)	1.0 (14/513 158)	0.36 (0.13 to 0.99)
No booster DTP before enrolment	1.8 (37/734 258)	1.0 (21/737 893)	1.78 (1.04 to 3.04)

Randomised controlled trial of integrated care to reduce disability from chronic low back pain in working and private life

Ludeke C Lambeek,[1] Willem van Mechelen,[1] Dirk L Knol,[2] Patrick Loisel,[3] Johannes R Anema[1]

[1]EMGO Institute for Health and Care Research, Department of Public and Occupational Health, VU University Medical Center, Amsterdam, Netherlands
[2]EMGO Institute for Health and Care Research, Department of Epidemiology and Biostatistics
[3]Dalla Lana School of Public Health, University of Toronto, Canada
Correspondence to: J R Anema
h.anema@vumc.nl

Cite this as: *BMJ* 2010;340:c1035
doi: 10.1136/bmj.c1035

STUDY QUESTION

To evaluate the effectiveness of an integrated care programme, combining a patient directed and workplace directed intervention, compared with usual care for patients sick listed due to chronic low back pain.

SUMMARY ANSWER

The integrated care programme substantially reduced disability due to chronic low back pain in working and private life.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Chronic low back pain is a clinical as well as psychosocial and work related problem. This study fills the gap in evidence for the effectiveness of combined workplace interventions and cognitive behavioural therapy on reduction of disability in working and private life for patients with chronic back pain.

Design

A population based randomised controlled trial comparing integrated care with usual care. Integrated care involved a medical specialist, clinical occupational physician, occupational therapist, and physical therapist. It was coordinated by a clinical occupational physician and consisted of a workplace intervention based on participatory ergonomics, and a graded activity programme (a time contingent programme based on cognitive behavioural principles). Usual care consisted of usual treatment from a medical specialist, occupational physician, general practitioner, and/or allied health professionals. Patients were randomised using block randomisation and computer generated allocation. Blinding was not possible.

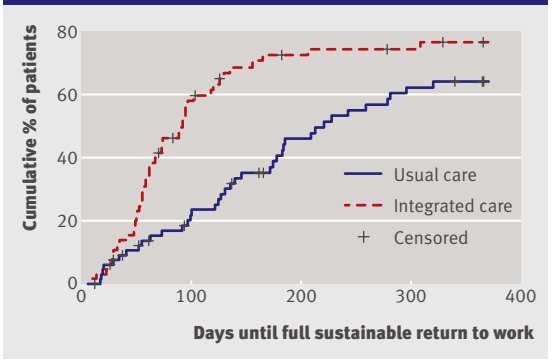
Participants and setting

Adults (n=134) aged 18-65 who were sick listed due to chronic low back pain for more than 12 weeks were randomised to integrated care (n=66) or usual care (n=68). These patients had visited an outpatient clinic of a participating hospital and were absent or partially absent from work. Integrated care was carried out in secondary care (five hospitals) and in primary care (10 physiotherapy practices, one occupational health service, one occupational therapy practice).

Primary outcome(s)

The primary outcome was sustainable return to work, defined as duration of work disability due to low back pain in calendar days from the day of randomisation until full return to work in own or other work, with equal earnings for at least four weeks without recurrence, partial or full. Patient reported data on sick leave were collected every month by means of a diary and after 12 months from the database of the occupational health services. In addition, we measured pain intensity (visual analogue scale) and functional status (Roland disability questionnaire) at baseline and at 3, 6, and 12 months.

KAPLAN-MEIER SURVIVAL CURVES OF ABSENCE FROM WORK FOR INTEGRATED CARE AND USUAL CARE GROUPS



Main results and the role of chance

After 12 months, the median duration from randomisation until sustainable return to work in the integrated care group compared with usual care group was 88 versus 208 days (P=0.003). Integrated care was effective on return to work (hazard ratio 1.9, 95% confidence interval 1.2 to 2.8, P=0.004). After 12 months, patients in the integrated care group improved significantly more on functional status compared with patients in the usual care group (P=0.01). Improvement of pain did not differ significantly between the groups.

Harms

No harms occurred.

Bias, confounding, and other reasons for caution

Baseline characteristics between the groups did not differ significantly.

Generalisability to other populations

The results of this study apply to a select group of patients with chronic low back pain, all of whom were judged suitable for this type of psychosocial treatment.

Study funding/potential competing interests

This study was supported by VU University Medical Center, TNO Work & Employment, Dutch Health Insurance Executive Council, Stichting Instituut GAK, and the Netherlands Organisation for Health Research and Development. This research was carried out within the framework of the Work Disability Prevention Canadian Institutes of Health Research strategic training programme, which supported LCL (grant FRN: 53909).

Trial registration number

Current Controlled Trials ISRCTN28478651.

This article is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c1035

Critical illness due to 2009 A/H1N1 influenza in pregnant and postpartum women: population based cohort study

The ANZIC Influenza Investigators and Australasian Maternity Outcomes Surveillance System

EDITORIAL by Lapinsky

Correspondence to: I Seppelt, Department of Intensive Care Medicine, Nepean Hospital, PO Box 63, Penrith, NSW 2751, Sydney, Australia
seppelt@med.usyd.edu.au

Cite this as: *BMJ* 2010;340:c1279
doi: 10.1136/bmj.c1279

This is a summary of a paper that was published on bmj.com as *BMJ* 2010;340:c1279

STUDY QUESTION

What were the maternal and neonatal outcomes of all pregnant and postpartum women admitted to intensive care with 2009 A/H1N1 influenza in Australia and New Zealand during June to August (winter) 2009?

SUMMARY ANSWER

Seven of 64 women (11%) admitted to intensive care died. Sixty births occurred after 20 weeks' gestation; four infants were stillborn, and three liveborn infants died.

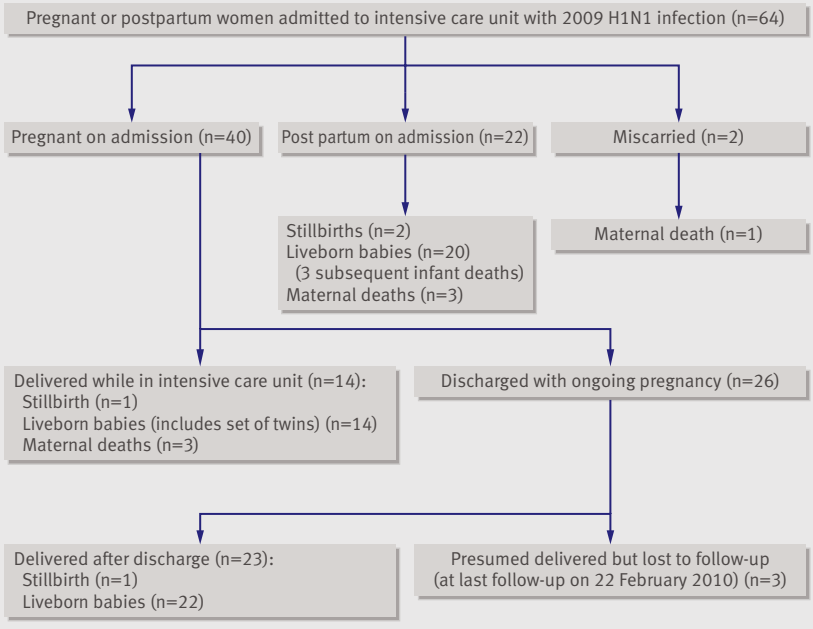
WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Pregnant women are at increased risk of the complications of influenza, particularly later in pregnancy. Intensive therapy for maternal hypoxia, including mechanical ventilation, caesarean section, and extracorporeal membrane oxygenation, led to better than expected outcomes.

Participants and setting

All 187 adult and paediatric intensive care units in Australia and New Zealand have been screening patients with confirmed influenza A for the Australian and New Zealand Intensive Care (ANZIC) Influenza Registry. Between June and August 2009 we identified 209 women aged 15-44 who were admitted to an intensive care unit with confirmed 2009 H1N1 infection. Of these women, 64 were pregnant or post partum within 28 days.

MATERNAL AND PAEDIATRIC OUTCOMES AFTER ADMISSION TO INTENSIVE CARE



Design, size, and duration

A population based cohort study. In addition to the prospectively collected registry data we collected data retrospectively on obstetric management and maternal and neonatal outcomes.

Main results and the role of chance

Sixty four pregnant or postpartum women admitted to an intensive care unit had confirmed 2009 H1N1 infection. Compared with non-pregnant women of childbearing age, pregnant or postpartum women with 2009 H1N1 infection were at increased risk of admission to intensive care (relative risk 7.4, 95% confidence interval 5.5 to 10.0). This risk was 13-fold greater (13.2, 9.6 to 18.3) for women at 20 weeks or more gestation. At the time of admission, 22 (34%) women were post partum and two had miscarried. Fourteen (22%) women gave birth during their stay in intensive care, and 26 (41%) were discharged with ongoing pregnancy. All subsequently delivered. Forty four (69%) women were treated with mechanical ventilation. Of these, nine (14%) were treated with extracorporeal membrane oxygenation. Seven (11%) women died. Of 60 babies born after 20 weeks' gestation, four were stillbirths and three were infant deaths. Twenty two (39%) of the liveborn babies were preterm and 32 (57%) were admitted to a neonatal intensive care unit. Of 20 babies tested, two were positive for 2009 H1N1.

Bias, confounding, and other reasons for caution

Overall numbers are small and caution is recommended to avoid over-interpreting the findings.

Generalisability to other populations

These results represent outcomes in one critical care system in the southern hemisphere in 2009, before the introduction of immunisation against 2009 H1N1 influenza. It is impossible to predict how the disease will change during a second wave in 2010, with widespread immunisation and antiviral drugs.

Study funding/potential competing interests

The ANZIC Influenza Investigators registry is supported by the Department of Health and Ageing, Commonwealth Government of Australia; New South Wales Health, Government of New South Wales; Department of Health, Government of Victoria; the Australian and New Zealand Intensive Care Research Centre; the Australian and New Zealand Intensive Care Society; and an unrestricted grant from CSL, Melbourne, Victoria. The Australasian Maternity Outcomes Surveillance System is supported by National Health and Medical Research Council (Australia) project grant, No 510298.