

BMJ Open FluMum: a prospective cohort study of mother–infant pairs assessing the effectiveness of maternal influenza vaccination in prevention of influenza in early infancy

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ABSTRACT

Introduction: Influenza vaccination in pregnancy is recommended for all women in Australia, particularly those who will be in their second or third trimester during the influenza season. However, there has been no systematic monitoring of influenza vaccine uptake among pregnant women in Australia. Evidence is emerging of benefit to the infant with respect to preventing influenza infection in the first 6 months of life. The FluMum study aims to systematically monitor influenza vaccine uptake during pregnancy in Australia and determine the effectiveness of maternal vaccination in preventing laboratory-confirmed influenza in their offspring up to 6 months of age.

Methods and analysis: A prospective cohort study of 10 106 mother–infant pairs recruited between 38 weeks gestation and 55 days postdelivery in six Australian capital cities. Detailed maternal and infant information is collected at enrolment, including influenza illness and vaccination history with a follow-up data collection time point at infant age 6 months. The primary outcome is laboratory-confirmed influenza in the infant. Case ascertainment occurs through searches of Australian notifiable diseases data sets once the infant turns 6 months of age (with parental consent). The primary analysis involves calculating vaccine effectiveness against laboratory-confirmed influenza by comparing the incidence of influenza in infants of vaccinated mothers to the incidence in infants of unvaccinated mothers. Secondary analyses include annual and pooled estimates of the proportion of mothers vaccinated during pregnancy, the effectiveness of maternal vaccination in preventing hospitalisation for acute respiratory illness and modelling to assess the determinants of vaccination.

Ethics and dissemination: The study was approved by all institutional Human Research Ethics Committees responsible for participating sites. Study findings will be published in peer review journals and presented at national and international conferences.

Strengths and limitations of this study

- The national approach, including women giving birth in six capital cities in Australia will provide broadly representative data on women and their infants.
- The large sample size, over 10 000 mother–infant pairs, with recruitment spread over four influenza seasons will provide sufficient power to detect a vaccine effectiveness of at least 40% against laboratory-confirmed influenza in infants.
- The primary outcome, laboratory-confirmed influenza in the infant is objective and is accessed from national notifiable diseases data sets.
- Ascertainment bias for the primary outcome of laboratory-confirmed influenza is likely to be minimal and non-differential.
- Loss to follow-up will occur if the mother withdraws from the study but will not affect ascertainment of the primary outcome.

Trial registration number: The study is registered with the Australia and New Zealand Clinical Trials Registry (ANZCTR) number: 12612000175875.

INTRODUCTION

Influenza infection during pregnancy and in the first 6 months of life is a substantial cause of morbidity. During pregnancy, reported cumulative incidence ranges from 4% to 22% in non-pandemic periods,^{1–4} and pregnant women are at an increased risk of severe disease and death,^{4–7} particularly during pandemic periods.^{8–10}

Consequences for the fetus of influenza infection during pregnancy are not well established.¹¹ An investigation of a cluster of 12 fetal deaths that occurred within 3 weeks

during the influenza season in the UK found the case pregnancies had an excess of recent flu-like illness, and were more likely than controls to have serological evidence of influenza A infection.¹² Observational studies have suggested maternal influenza infection during pregnancy may increase the risk of mental health illnesses in the offspring,^{13 14} although the evidence is weak and predominantly limited to animal models.

The impact of influenza infection during infancy, particularly in the very young with high-risk conditions, can be substantial, with higher hospitalisation rates than older children and increased likelihood of intensive care admission and respiratory failure.^{15 16} Influenza infection in infants can also increase the risk of serious secondary invasive bacterial infections, particularly *Streptococcus pneumoniae*.¹⁷

Given the impact of influenza in pregnancy, maternal influenza vaccination during pregnancy is now recommended in many countries.^{18 19} Pregnant women are not only considered a priority group for vaccination during influenza pandemics, they are also identified by the WHO as the priority for funded influenza vaccination programmes globally (reference SAGE report). Influenza vaccination during pregnancy is considered safe^{20 21} and there is some evidence that it may also decrease the likelihood of a baby being born premature or small for gestational age.²² Importantly, in recent years, data have emerged indicating maternal influenza vaccination during pregnancy may provide protection against influenza infection in their infants up to 6 months of age,^{23–26} a group for whom there are currently no licensed vaccines. Given the varying nature of study designs and relatively small sample sizes, larger studies are needed in a variety of populations to confirm these findings.

Uptake of vaccine during pregnancy is not systematically monitored and studies suggest uptake is suboptimal in many settings^{11 27–29} and there are few large studies that have examined the reasons why. A woman's perception of the benefits and risks of vaccine and whether or not their health service provider recommended and/or offered the vaccine appear to be key determinants.^{29–31} Large-scale prospective studies are required to monitor seasonal vaccine uptake and its determinants during pregnancy over time. Similarly, such studies are needed to also improve the evidence for the effectiveness of influenza vaccination during pregnancy in preventing influenza in young infants. We present the study protocol for a national prospective cohort study of Australian mother–infant pairs that aims to: (A) determine the effectiveness of influenza vaccine in pregnancy in preventing laboratory-confirmed influenza among infant offspring up to 6 months of age, and (B) monitor influenza vaccine uptake and its determinants over time.

METHODS AND ANALYSIS

Study design

FluMum is a 5-year prospective cohort study of 10 106 mother–infant pairs recruited between 38 weeks

gestation and 55 days postdelivery in six sites across Australia over a 4-year period. The six study centres are each affiliated with local public maternity units that collectively average over 20 000 births/year. Primary end-points are determined when the infant reaches 6 months of age. Recruitment is equal in all sites and is scheduled to be completed by 25 October 2015 for infants born up until 31 August (ie, within a 55-day post-delivery window period). The follow-up period of observation for the last enrolled mother–infant pair is scheduled to end on or before 31 March 2016.

Our primary objective is to assess the effectiveness of influenza vaccine during pregnancy against laboratory-confirmed influenza among infant offspring during the first 6 months of life. Our secondary objectives are to:

- Determine influenza vaccine uptake during pregnancy at each of six sentinel research centres during each of four consecutive years.
- Assess independent predictors of influenza vaccination in pregnancy, including: demographic factors; obstetric history; knowledge and attitudes surrounding influenza and influenza vaccine and access to influenza vaccination.
- Determine the incidence of laboratory-confirmed influenza infection during pregnancy.
- Estimate the effectiveness of maternal influenza vaccine in pregnancy against laboratory-confirmed influenza in the mother during pregnancy, and hospitalisation of the infant with acute lower respiratory infection during the first 6 months of life.

Study sample

Eligible participants are identified from maternity units and primary healthcare settings in the six cities. Participants are approached by study personnel who explain the study and obtain informed consent.

Women are eligible for the study if they are aged 17 years or more at the time of consent, are at least 38 weeks gestation or have delivered a live born infant who is no older than 55 days at enrolment and if the participant (mother) has sufficient verbal English to permit questionnaire completion at study entry and at the 6-month follow-up. For the purposes of the primary analysis, women are excluded from the study if they are (A) planning to move overseas before the infant reaches 6 months of age, or (B) have received influenza vaccination less than 14 days prior to delivery. Those participants who enrol but subsequently are lost to follow-up at age 6 months remain eligible for assessment of the secondary outcomes at the time of enrolment.

Once consent is obtained, an interviewer-administered questionnaire is completed that collects detailed information on maternal self-reported influenza and pertussis vaccination status, information relating to the barriers/influences of influenza and pertussis vaccination, contact details for the participant's usual medical practitioner, self-reported maternal medical/obstetric history and some sociodemographic indicators. An additional

telephone and/or email contact occurs once the infant reaches 6 months of age to seek parent-reported episodes of medically diagnosed influenza in the infant.

Outcomes to be measured

In Australia, influenza is a nationally notifiable disease with local notification requirements according to state public health laws. The uniform notification case definition requires laboratory confirmation. Hence, for our outcomes of laboratory-diagnosed influenza in the infant or in the mother from 12 months prior to delivery to 6 months postdelivery, individual data are obtained with consent from state/territory administered data sets of laboratory-confirmed influenza results. We match all notifications of episodes of laboratory-confirmed influenza and/or any other vaccine preventable diseases recorded by the notifiable diseases systems within each state/territory for infant (6 months postdelivery) and maternal influenza. Participant-reported episodes of medically diagnosed influenza where a specimen was collected from the mother or the infant but not notified will be followed up with the treating physician to establish if they were laboratory confirmed and had not been notified to the relevant public health authority.

Our secondary outcome of vaccine uptake in pregnancy requires a valid date of vaccination for a participant to be considered vaccinated. Each participant's usual medical practitioner/vaccine provider will be contacted to confirm the date of vaccination when a participant self-reports receipt of influenza vaccination but is unable to cite the date given from a written record, or where the participant is unsure of her vaccination history. Participants who state that they have not been vaccinated are considered unvaccinated.

Sample size and analysis plan

Accounting for a potential loss to follow-up of 10%, the sample size calculation requires 10 106 women to be recruited over the 4-year recruitment period. There will be power of 80% ($\alpha=0.05$) to detect vaccine effectiveness against laboratory-confirmed influenza in infancy of at least 40% assuming cumulative incidence among the unvaccinated cohort of 2.3% for laboratory-confirmed influenza in infants up to 6 months of age and average vaccine uptake in pregnancy of 30%, both calculated over the 4-year study period. Disease incidence and vaccine uptake are averaged over the 4-year study period as fluctuations are expected.

Estimates of vaccine uptake per year per site will be accurate to within $\pm 5\%$ with the proposed sample size of 422 participants per year per site, for example: 15% uptake (95% CI 11.9% to 18.7%); 25% uptake (95% CI 21.2% to 29.3%); 35% uptake (95% CI 30.6% to 39.5%); 45% uptake (95% CI 40.3% to 49.5%). Similarly, the study is well powered to monitor a range of predictors of influenza vaccination in pregnancy including changes over time and differences between sites,

particularly so for the pooled data from over 10 000 participants.

The *primary analysis* will be a comparison of the cumulative incidence of laboratory-confirmed influenza in infants aged <6 months by treatment group (vaccinated cohort vs unvaccinated cohort). Vaccine effectiveness will be calculated as $(1 - \text{relative risk}) \times 100$ and reported with 95% CIs. The relative risk is approximated by the OR from logistic regression. As noted previously, those women receiving influenza vaccine less than 14 days prior to delivery will be excluded in the primary analysis. A propensity score approach will be used to account for differences in baseline characteristics between groups.³² The propensity score, defined as the conditional probability of receiving the vaccine given the measured confounders,³³ will be estimated from a logistic regression model with receipt of vaccine as the dependent variable and including all variables considered to be potential confounders as independent variables. Participants will be weighted by a function of the propensity score in order to construct a pseudo population in which there is no confounding by observed variables. In particular, each mother–infant pair who receives the vaccine is weighted by the inverse of their estimated propensity score and each mother–infant pair who does not receive the vaccine is weighted by the inverse of 1 minus their propensity score. The relative risk of influenza associated with the vaccine will then be estimated using weighted logistic regression with vaccination being the sole independent variable. In 2014, the protocol was amended (and approved by the relevant ethics committees) to limit our analyses to the first-born infant only in cases of multiple births.

Control for potentially important confounding factors will be incorporated into the study. Consistent with previous studies, these will include maternal comorbidities, maternal influenza infection during pregnancy and potential influenza risk factors in infancy such as potential exposure to other individuals in the household, attendance of older siblings in day care or primary school, household smoking and breastfeeding. We will also consider the sensitivity of the results to a number of other potentially important factors that could be associated with the risk of influenza in infancy including the trimester of influenza vaccination, history of maternal influenza vaccination in previous years, severity of the influenza season, the infant's month of birth, indigenous status, gestational age and birth weight.

Maternal influenza infection during pregnancy will be ascertained using standard surveillance definitions of influenza-like illness derived from self-report and from medical record review and adjusted by state/territory. Assessment of the magnitude of the influenza infection risk in infancy within each state/territory will be made. This will be done through a comparison of influenza incidence in the unvaccinated cohort against data on the incidence of influenza among two slightly older infant cohorts for the same period (infants aged

6–12 months and those aged 12–18 months). The disease burden in these two older cohorts will be assumed to be similar to but not more than the expected disease burden in the younger cohort since this has been the pattern for some time (unpublished data, NCIRS). Western Australia (WA) is the only state that has an active infant influenza vaccination programme starting from 6 months of age. Vaccine uptake and disease incidence are already being carefully monitored in WA with respect to their childhood influenza vaccination programme.³⁴

Secondary analyses will incorporate multivariate logistic regression models to monitor changes in vaccine uptake by site and year and to identify independent predictors of vaccine uptake during pregnancy by study site and year. Subject to availability of outcome data, we have planned interim analyses of the primary objective on an annual basis using the pooled data to that point in time but with $\alpha=0.001$ so as not to adversely impact on the overall power of the study. The purpose of the interim analyses is to track annual progress towards demonstration of vaccine effectiveness over time. Potential benefits to the infant from maternal influenza immunisation may be highest in the first 3 months of life. We will therefore also analyse the time to first episode of laboratory-confirmed influenza infection in infants using survival analyses methods.

DISCUSSION

Influenza infections during pregnancy and early infancy are of global public health importance. Large population-based studies that account for seasonal variations in influenza incidence are needed to monitor public health recommendations and to determine the effectiveness of the vaccine in preventing laboratory-confirmed influenza. The FluMum study aims to address this need through a national cohort study of over 10 000 mother–infant pairs conducted over four influenza seasons.

The major strengths of our study are the national approach, the sample size and that the primary outcome can be determined through accessing information on laboratory-confirmed notifications of influenza from state/territory notifiable diseases data sets using individual consent obtained prior to occurrence of the outcome of interest. Influenza is a notifiable disease in Australia and that is a well-known requirement among physicians and laboratories. We believe the simplicity of the study design—incorporating recruitment at/near delivery, ascertainment of infant exposure status at day 0 (delivery) then ascertainment of the primary outcome from administrative data sets—will maximise maternal participation rates, minimise drop out and thus minimise the risk of response bias. Ascertainment bias for the primary outcome of laboratory-confirmed influenza is likely to be minimal and non-differential given that maternal vaccination is: (A) unlikely to influence care-

seeking behaviour for severe respiratory illness in early infancy; (B) unlikely to influence the healthcare provider's decision to submit a specimen for laboratory testing and (C) would not influence the laboratory undertaking the test since maternal vaccination history would be unknown to the laboratory undertaking testing of an infant's specimen.

We are cognisant of the risk of potential bias between the vaccinated and unvaccinated cohort and will account for key differences in baseline characteristics as mentioned previously. There is a risk that vaccinated mothers may be more willing to participate than unvaccinated mothers; while a high response rate will help mitigate this, we will also seek ethics approval to ask mothers who do not consent if we can record a brief reason why not, which will include the option that they have not received an influenza vaccine. Given the study is being conducted in urban centres, the generalisability of the findings will be limited to women and infants in those settings, although we will be able to determine how many participants were from rural and remote areas.

Loss to follow-up is a concern for any cohort study. Women may choose to withdraw or there may be a failure to contact them at the 6-month time period. This loss to follow-up will not affect ascertainment of the primary outcome (laboratory-confirmed influenza in the infant) given the sources of that information are notifiable diseases data sets, unless the infant has moved interstate or overseas. If that does occur, the effect on the primary analysis is likely to be non-differential as discussed previously. However, there are several strategies in place to minimise attrition. Study operating procedures for follow-ups include telephone, email and short message service (text messaging), with a minimum of three attempts required. Regular study newsletters are distributed to participants to keep them informed of the study progress and to remind them to contact study staff if their contact details change. Our data linkage to notifiable diseases data sets will still capture cases of laboratory-confirmed influenza among those who are lost to follow-up, unless the participant has moved interstate or overseas. Sensitivity analyses that account for missing data will be undertaken to determine the effect of loss to follow-up on our vaccine effectiveness estimates.

CONCLUSION

The FluMum study will be an important contribution to maternal and infant child health policy and practice in Australia, and potentially globally. Recruitment for the study started in March 2012 and will cease in December 2015. While some Australian states are currently considering incorporating maternal vaccination during pregnancy into perinatal data collections, that is likely to be some years away and hence the FluMum study will provide information critical to improving and maintaining influenza vaccine uptake in pregnancy. If we

determine that influenza vaccination during pregnancy is effective in preventing laboratory-confirmed influenza in infants, it will provide an additional incentive for women to be vaccinated.

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Contributors RMA was the study's principal investigator. RMA, KF, TN, SBL, NW, PR, HSM and MC developed the successful grant application and study protocol. LM was the National Study Coordinator until January 2014. KF and LM drafted the manuscript. All authors critically revised the manuscript and contributed to and approved the final version of the manuscript for publication.

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support from GSK, Wyeth and other vaccine companies to present scientific data and chair workshops. HSM's institution has received research grants from vaccine manufacturers GSK, Pfizer, Novartis and Sanofi Pasteur for investigator-led research. HSM has been an investigator for studies funded by pharmaceutical companies including Pfizer, GSK Sanofi-Pasteur, Novartis. Travel support has been provided to their institutions by GSK and/or Sanofi-Pasteur for HSM to present scientific data at international meetings. RA is the member of the Australian Government ATAGI (Australian Technical Advisory Group on Immunisation).

Patient consent Obtained.

Ethics approval The study has been approved by all institutional ethics committees at all participating sites around Australia.

Provenance and peer review Not commissioned; peer reviewed for ethical and funding approval prior to submission.

Data sharing statement The data collection form can be made available to researchers on request.

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