Birth outcomes in Aboriginal mother–infant pairs from the Northern Territory, Australia, who received 23-valent polysaccharide pneumococcal vaccination during pregnancy, 2006–2011

The PneuMum randomised controlled trial

McHugh, Lisa; Binks, Michael; Ware, Robert S.; Snelling, Tom; Nelson, Sandra; Nelson, Jane; Dunbar, Melissa; Mulholland, E. Kim; Andrews, Ross M.

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Abstract

Background

Pregnant women and infants <6 months old have a high baseline risk for pneumococcal disease compared to the general population, particularly among Indigenous populations living in poverty and low-resource settings. Efficacy trials of pneumococcal vaccination in pregnancy examining adverse birth outcomes are lacking.

Aims

We report adverse birth events as secondary outcomes from the 'PneuMum' randomised controlled trial of 23-valent pneumococcal polysaccharide vaccination (23vPPV) in pregnancy (August 2006-January 2011).

Materials and methods

Australian Aboriginal women aged 17-39 years with singleton uncomplicated pregnancies were randomised (1:2 ratio) to receive 23vPPV or no 23vPPV in pregnancy at 30-36 weeks gestation. We compared risks of stillbirth, preterm birth, low birthweight (LBW), and small for gestational age (SGA) between vaccinated and unvaccinated pregnant women. Cox proportional-hazard ratios (HRs) were calculated on an intention-to-treat basis.

Results

Among 227 enrolled participants, 75 (33%) received 23vPPV in pregnancy. Risk differences in adverse birth outcomes between 23vPPV vaccinated and unvaccinated pregnant women were: preterm birth 9% vs 4% (HR 2.79; 95%CI 0.94-8.32)p=0.07; LBW 9% vs 5% (HR 2.09; 95%CI 0.76-5.78)p=0.15; and SGA 15% vs 17% (HR 1.02; 95%CI 0.50-2.06)p=0.96. There were no stillbirths.

Conclusions

We found a numerically higher rate of preterm births among women who received 23vPPV in pregnancy compared to unvaccinated pregnant women. Although further investigation with

larger participant numbers is needed to better evaluate this safety signal, the contribution of safety results from smaller studies using appropriate data analysis methodologies are critical, particularly as more clinical trials in pneumococcal vaccination in pregnancy are progressing.

Introduction

The pneumococcus is the dominant cause of severe respiratory infections worldwide, with disease most prevalent among disadvantaged populations.[1] Pregnant women and infants younger than six months of age have a high baseline risk for pneumococcal disease compared to the general population, [2, 3] and the risk is particularly high among Indigenous populations living in poverty and in low-resource settings. [4] In the Northern Territory (NT) of Australia, more than 75% of Aboriginal and Torres Strait Islander (hereafter respectfully referred to as 'Aboriginal'[5]) infants have nasopharyngeal pneumococcal carriage, [6] and over 20% of these infants are hospitalised with an acute lower respiratory infection in their first year of life. [4] Australian Aboriginal children consistently have the highest reported rates and severity of ear disease in the world, contributing to numerous poor health and educational outcomes, particularly hearing loss and difficulties reading. [7]

In an attempt to reduce the burden of respiratory disease in infants, clinical trials of pneumococcal vaccination given in pregnancy have been conducted worldwide, particularly in low-resource settings where the burden is greatest. [8-11] Outcomes have described immunogenicity and impact on infant clinical disease with mixed findings, [12, 13] however these efficacy trials have not reported detailed safety data for birth outcomes. The safety profile of maternal pneumococcal vaccination in pregnancy has not been rigorously examined in the general population, nor specifically amongst Australian Aboriginal mother-infant pairs, who are a high risk population in terms of both increased perinatal morbidity and mortality rates, [14, 15] as well as childhood respiratory infections. [16] If the safety and efficacy of

[5] 'Aboriginal' is the preferred official term for inclusively referring to both Aboriginal and Torres Strait Islander peoples from the Northern Territory. This respectfully acknowledges the relatively small percentage of the population who identify as Torres Strait Islanders and the greater proportion of these people who also identify as Aboriginal.

pneumococcal vaccination in pregnancy can be demonstrated, this population would benefit the most.

The World Health Organization (WHO) have recommended that large scale safety studies examining maternal and infant birth outcomes following pneumococcal vaccination in pregnancy should be conducted, and that smaller studies to test the safety and efficacy of maternal pneumococcal vaccination should continue to be supported. [17] Further, international experts in maternal vaccination stress that including both date of vaccination and gestation at time of vaccination in pregnancy in analytic models is critical in order to minimise immortal time bias when performing analyses with time-dependent variables. [18] Failure to use time-varying analyses in trials of vaccination in pregnancy have drawn methodological concern regarding the possible underestimation of adverse events in vaccinated women. [19]

We aimed to investigate the association between receipt of a 23-valent pneumococcal polysaccharide vaccine (23vPPV) in pregnancy and adverse birth outcomes for a group of Australian Aboriginal pregnant women.

Materials and methods

Trial design

The 'PneuMum' study was an open-label, allocation concealed, outcome-assessor blinded, community stratified, randomised controlled trial (RCT) of 23vPPV in pregnancy, where the primary outcome was middle ear disease amongst Australian Aboriginal infants. [20] Eligible participants were enrolled from 28 weeks gestation and randomly assigned to one of three parallel arms with an allocation ratio of 1:1:1; 23vPPV in pregnancy from 28-36 weeks

gestation (inclusive), 23vPPV within 72 hours of the birth of their infant, or 23vPPV offered at study exit, seven months post-partum.

The trial had a limited assessment of safety as a secondary outcome that did not adequately account for immortal time bias. We have re-analysed the data using the latest gold standard methodology recommended by WHO experts on the safety of vaccination in pregnancy. For these secondary outcomes of safety in pregnancy, the period of observation ceased at the birth of the infant, so the data were analysed as two arms with a randomisation schedule of 1:2 (23vPPV in pregnancy: no 23vPPV in pregnancy).

Participants

Aboriginal mother-infant pairs were recruited from urban and remote communities in the NT of Australia between August 2006 and January 2011. Inclusion criteria, eligibility and randomisation methods have been published. [20] Participants were excluded if they had received 23vPPV within the previous three years, intended to leave the study area during the follow-up period, were carrying a multiparous pregnancy, had a known congenital anomaly or were considered high-risk (described in Supplementary box 1). Participants were admitted into the study once only. A date for the last normal menstrual period (LNMP) was collected from the participants' antenatal records. Seasonal inactivated influenza vaccine (IIV) is routinely recommended in pregnancy, and IIV status was ascertained through self-report by study participants and verified by visual documentation in participants' medical records, then validated through the NT adult immunisation register. Maternal demographic characteristics were collected directly from participants by a member of the study team. Birth outcome data were ascertained from the participant's hospital records by a member of the study team in the week after the birth of the infant.

Interventions

The primary exposure of interest for assessment of adverse outcomes was the receipt and timing of 23vPPV in pregnancy. Participants were considered unvaccinated in pregnancy if they received no pneumococcal vaccines from the first date of their last normal menstrual period (LNMP) until the birth of their infant. All pregnant women received the same vaccine-23vPPV (PNEUMOVAX®23,Merck, USA) with batch numbers recorded at the time of vaccine administration. [20] Vaccine batch numbers were not available for women who received an IIV in pregnancy. Validation methods for IIV ascertainment, demographic data and IIV uptake in pregnant PneuMum study participants have been published. [21]

Outcomes

The outcomes of interest were; preterm birth, stillbirth, low birthweight (LBW), low birthweight at term (LBWT) and small for gestational age (SGA) infants. All outcome measures were assessed at the time of infant birth. Infants born before 37 completed weeks' gestation were defined as preterm, [22] stillborn infants were defined as showing no signs of life after a pregnancy of at least 20 weeks gestation or weighing 400g or more. [23] Infants with a birthweight of <2500 grams(g) were defined as LBW and infants with a birthweight of <2500g at >37 completed weeks gestation as LBWT. [24] Small for gestational age was defined as birthweight lower than the 10th percentile for the gestational age at birth asper Australian national birthweight data. [25]

Sample size

We expected the incidence of preterm births among Aboriginal pregnant women living in the Northern Territory, Australia, would be ~15%. [22] Given that there were 225 participants (75

vaccinated, 150 unvaccinated), our study would have 80% power to detect a relative increase in preterm births in the vaccinated group of ≥2.1 times (alpha=0.05).

Statistical analysis

All data were analysed using Stata statistical software v.14.1 (StataCorp, College Station, Texas). Summary statistics were calculated to describe demographic characteristics of mother-infant pairs. Means and medians were calculated for continuous variables depending on the distribution of data, presented with 95% confidence intervals (95%CIs) or ranges. To minimise immortal time bias for the adverse birth outcomes, we conducted time-dependent analyses, by maternal vaccination status. We used the continuous variable 'weeks gestation at delivery' as the time scale variable and results are presented as Cox proportional-hazard ratios (HR) with 95% CIs. All analyses were conducted on an intention-to-treat basis, with participants analysed in the group they were allocated to regardless of treatment compliance.

Ethics approvals

Human Research Ethics Committee approval was granted by Menzies School of Health Research; Reference number 05/52, and the trial was registered at clinicaltrials.gov (NCT007 14064). The PneuMum study was endorsed by the Cooperative Research Centre for Aboriginal Health, and received in-principle support from the WHO and the Centre for Disease Control of the Northern Territory Department of Health and Community Services. An Indigenous Reference Group (IRG) was established for the purposes of this study, and one member of the IRG was also a member of the Data Safety Monitoring Board.

Results

There were 11 withdrawals in the original PneuMum study,[20] two occurred during the antenatal period and nine during the postnatal period from birth through until infant age seven months. Therefore, for the purposes of our study, there were two withdrawals by the time our period of observation ceased at the birth of the infant. Following the two antenatal withdrawals, there were 225 Aboriginal women who gave birth to a live singleton infant during the PneuMum study. Compliance with the intended treatment allocation matched the actual assigned groups, with 33% of mothers (75/225) receiving the 23vPPV in pregnancy and 67% (150/225) who did not (Figure 1). The median gestational age at time of 23vPPV administration was 32 weeks (range 28-36 completed weeks).

Maternal demographic characteristics

The median maternal age of all study participants at birth of their infant was 24 years (range 17-39yrs) and 84% were multiparous. Most women (97%) were regular antenatal care attendees; 49% self-reported smoking during pregnancy; 69% were urban dwelling women and 53% of infants born were male. Comparisons between the 23vPPV vaccinated and unvaccinated groups showed maternal demographic characteristics were similar (Table 1).

Birth outcomes

There were no maternal deaths or stillbirths. Median gestational age at birth of the infant was 39 weeks for both groups, with a range of 34-42 weeks gestation in the unvaccinated group and 35-41 in the 23vPPV group. The mean birthweight of infants of unvaccinated pregnant women was 3358g (range 2080-4620g), and 3293g (range 2060-4425g) in infants from the 23vPPV group; a mean difference of 65 grams (95%CI -82, 212), p=*0.38*.

Cox proportional HR analysis found no statistically significant difference in the risk of any adverse birth outcome between those who received 23vPPV in pregnancy and those who did not (Table 2). Compared to infants born to unvaccinated pregnant women, a numerically higher proportion of infants born to women who received 23vPPV in pregnancy were preterm; 7/75 (9%) vs 6/150 (4%) (HR 2.79; 95%CI 0.94-8.32, p=0.07) and LBW; 7/75 (9%) vs 8/150 (5%) (HR 2.09; 95%CI 0.76,5.78, p=0.15). Accounting for the effect of preterm birth on LBW, the proportions of infants born LBWT in both groups were similar; 2/68 (3%) 23vPPV vs 6/144 (4%) unvaccinated (HR 0.77; 95%CI 0.16-3.83, p=0.75), as were the proportion of infants born SGA in both groups; 11/75 (15%) 23vPPV vs 26/150 (17%) unvaccinated (HR 0.98; 95%CI 0.48-1.99, p=0.96).

Discussion

We aimed to evaluate the safety of 23vPPV in pregnancy among Aboriginal women. Although there was no statistically significant differences in adverse birth outcomes between women who received a 23vPPV in pregnancy compared to unvaccinated pregnant women, the rate difference of preterm births and LBW among infants born to mothers who received 23vPPV in pregnancy was numerically higher than that observed among those born to unvaccinated women. We were therefore not able to confirm nor deny the safety of the vaccine. Preterm birth is a major reason for LBW, [26] and the rate of LBW among infants born *at term* (LBWT) was no different between the two groups. Given SGA is a reliable indicator of compromised intrauterine growth, [27] the rate difference of SGA between the 23vPPV and unvaccinated group was also not clinically nor statistically significant.

Strengths and limitations

Few RCT's have examined the safety of vaccination in pregnancy using methodologically sound analytic approaches, and ours is the only RCT to examine adverse birth outcomes in Australian Aboriginal mother-infant pairs following 23vPPV in pregnancy. Our RCT study design ensured maternal demographic characteristics between those who received 23vPPV in pregnancy were very similar to those who did not receive 23vPPV in pregnancy, with excellent compliance and retention. Our results are reflective of the wider Aboriginal population with respect to maternal demographic characteristics. The median age of Aboriginal mothers at infant birth was 24 years in our study compared to 24.8 years (median) in the wider Aboriginal population, [22] and proportions of maternal smoking in pregnancy in our study (48%) were also comparable with other Aboriginal pregnant women (47%).[22] Our power calculations for this secondary analysis (see sample size) accounted for a magnitude of effect (HR >2.1) that was similar to that detected for preterm birth (HR 2.79) and LBW (HR 2.09). The reason that we failed to detect a difference was not the magnitude of the effect, instead it was because the actual prevalence in the unvaccinated group was substantially lower (4-5%) than we had assumed (15%). The selection criteria for participants in the original study may have contributed to a relatively healthier pregnancy cohort than would otherwise have been expected. Our study participants were low-risk, predominantly urban living pregnant Aboriginal women who were >17 years old. This eligibility criteria excluded a demographic of very young, remote living Aboriginal mothers from the study – a group who experience greater levels of poverty, overcrowding in households, and infectious diseases, as well as higher rates of stillbirths, preterm births, LBW and SGA infants compared to non-Aboriginal women. [14, 28, 29] Proportions of preterm births and LBW infants were also lower in our study population compared to other Aboriginal mother-infant pairs in Australia. [22] Proportions of infants born SGA were the same in our *vaccinated* study

population (15%) compared to other Aboriginal infants in Australia, [22] although slightly more infants born SGA in our study were born to *unvaccinated* pregnant women (18%). [22]

As participants were recruited from 28 weeks gestation and therefore did not receive 23vPPV prior to this time, it was not possible to assess adverse outcomes that occurred earlier in pregnancy such as miscarriages, late spontaneous abortions, early stillbirths and extremely preterm births, and this is where the international evidence on the safety of vaccination in pregnancy is lacking. The sample size also lacked power to compare rarer birth outcomes such as congenital anomalies by vaccination status in pregnancy.

The WHO have recommended the safety of maternal vaccination research be ongoing, and to be conducted in diverse populations, in order to provide additional local representative data specific to that country or region. [30] Although a relatively small trial, our re-analysis among a group of Australian Aboriginal women points to potential increased risks that should be in the public domain as a call for careful examination of the evidence before proceeding to consider routine use in pregnancy. Much larger numbers of mother-infant pairs are required to demonstrate the safety and effectiveness of 23vPPV in pregnancy in urban and remote-living Aboriginal populations.

Conclusion

We contribute methodologically robust data on the safety of 23vPPV among pregnant Aboriginal women from the NT. Whilst no statistically significant increase was observed in risk, we found a numerically higher rate of preterm births among women who received the 23vPPV in pregnancy compared to unvaccinated pregnant women. Although further investigation with larger participant numbers is needed to better evaluate this safety signal,

the contribution of safety results from smaller studies using appropriate data analysis methodologies are critical, particularly as more clinical trials in pneumococcal vaccination in pregnancy are progressing.

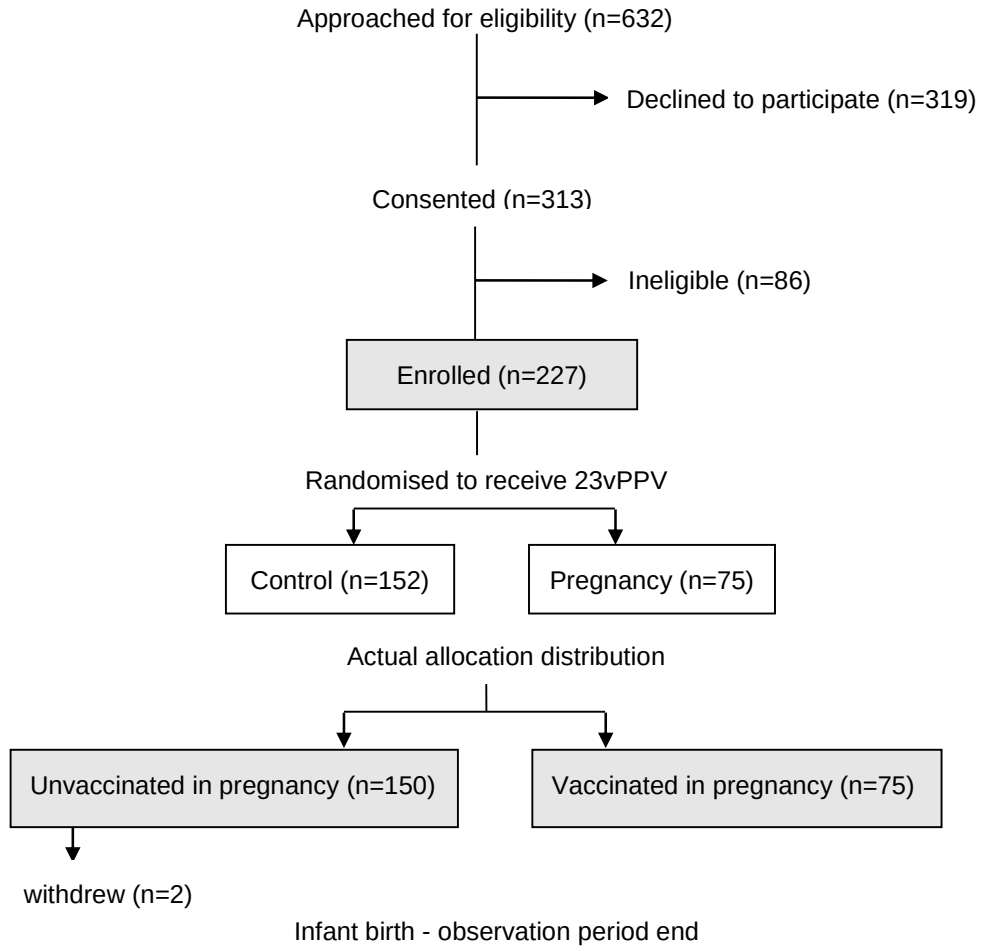

Figure 1: PneuMum study participant cohort, Northern Territory Australia, 2006-2011.

Tables

Table 1: Demographic characteristics of PneuMum study participants (n=225), by maternal ***pneumococcal*** vaccination status, Australia 2006-2011.

Characteristic or Outcome	**Unvaccinated (Referent group)** n=150 (67%)	**23vPPV in pregnancy*** n=75 (33%)
n/N (%)		
Women		
Median age at infant birth in years (range)	24.2 (17- 38.3)	23.5 (17.5- 39.3)
Living in remote Indigenous community	46/147 (31%)	23/75 (31%)
Maternal education (certificate or higher)	72/145 (50%)	41/75 (55%)
Median no. household members living in one house (range)	4 (2-11)	4 (2-15)
Pregnancy		
Attended antenatal care in 1st trimester	125/128 (98%)	67/69 (97%)
Smoking in pregnancy (self report)	73/150 (48%)	36/75 (48%)
Exposed to indoor smoke in pregnancy	45/150 (30%)	18/75 (24%)
Received influenza vaccine in pregnancy	25/125 (20%)	9/61 (15%)

Note: denominators differ due to missing data, results not shown for n=2 participants who withdrew from the study

* 23-valent polysaccharide pneumococcal vaccine given in the third trimester of pregnancy

Table 2 : Birth outcomes and time-dependent analyses in PneuMum study participants, Australia 2006-2011.

VARIABLES	**Unvaccinated**	**Vaccinated 23vPPV***	**HR† (95% CI) *P***
N (%)	N= 150 (67%)	N=75 (33%)	
Preterm birth‡	6/150 (4%)	7/75 (9%)	2.79 (0.94,8.32) *0.07*
LBW (<2500g)	8/150 (5%)	7/75 (9%)	2.09 (0.76,5.78) *0.15*
LBW at term§ (<2500g)	6/144 (4%)	2/68 (3%)	0.77 (0.16,3.83) *0.75*
SGA (<10th percentile)	26/150 (17%)	11/75 (15%)	0.98 (0.48,1.99) *0.96*

Abbreviations: 95% CI, 95% confidence interval; HR, hazard ratio; LBW, low birthweight; SGA, small for gestational age.
Note: denominators differ due to missing data for birthweight
* 23-valent polysaccharide pneumococcal vaccine given in the third trimester of pregnancy
† HR results comparing outcome variable in vaccinated group to referent (unvaccinated) group
‡ <37 completed weeks gestation at infant birth
§ Low birthweight at term (<2500 grams and ≥37 completed weeks gestation at birth)

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Supplementary data

Supplementary box 1: High-risk factors for exclusion criterion for PneuMum study participants

Significant previous poor obstetric history
Cardiac disease
Unstable diabetes requiring insulin
Severe or moderate liver or renal disease
Haematological diseases
Severe respiratory illnesses requiring hospitalisation (asthma, bronchitis, pneumonia)
Chronic respiratory conditions (Chronic obstructive pulmonary disease and chronic emphysema)
Chronic neurological conditions
Chronic metabolic diseases
Immunosuppressive conditions including HIV/AIDS