Australian Government

Department of Health

Australian Technical Advisory Group on Immunisation

Public consultation on changes to the recommended use of pertussis vaccines in pregnant women

The Australian Technical Advisory Group on Immunisation (ATAGI) is consulting with stakeholders on proposed changes to maternal pertussis vaccination recommendations for inclusion in the Australian Immunisation Handbook, with an intention to submit the recommendation to the National Health and Medical Research Council (NHMRC) for its approval under section 14A of the NHMRC Act.

This draft includes new recommendations and the rationale for the proposed changes.

You are invited to make a submission on the draft recommendation by 9 February 2019.

In particular, ATAGI is seeking comments on the following:

- Are there additional potential benefits, risks or unintended consequences which could arise from the proposed changes to the use of pertussis vaccines in pregnant women, not already outlined and how likely are they to occur?
- Are there additional clinical or implementation considerations which need to be outlined?

Should you require additional information please contact ATAGI Secretariat on atagi.secretariat@health.gov.au.

Changes to the recommended use of pertussis vaccines in pregnant women

Plain-language summary

Pertussis (whooping cough) is a serious bacterial infection that can cause:

- pneumonia
- brain damage
- death

The bacteria affect the lungs and airways, causing violent and uncontrollable coughing. This can make it hard for the infected person to breathe.

Whooping cough can affect people at any age, but babies have the highest risk of serious disease. Babies are more likely to need to go to hospital or die from whooping cough. About 1 in every 200 babies under 6 months old who gets whooping cough develops brain damage or dies from pneumonia.

Vaccinating the mother against pertussis while she is pregnant can protect the baby as soon as it's born. This is because antibodies from the mother can cross the placenta into the baby. This gives the baby some protection against pertussis until it is old enough to receive its first pertussis vaccine at 6 weeks of age.

All pregnant women are recommended to have 1 dose of pertussis vaccine in every pregnancy. Research is still being done to find the best time to have the vaccine during pregnancy, and the latest evidence shows that it may be better to get vaccinated earlier than currently recommended. This would mean that:

- pregnant women have more chances to be vaccinated so they won't miss out
- if the mother is vaccinated earlier, the baby will still be protected if it's born early (preterm or premature)
- pregnant women can have pertussis vaccine at any time from their 20-week scan

Because of this, the recommendations for pertussis vaccination during pregnancy are changing to include information about the longer time window to get the vaccine, and to make it easier to update as new evidence becomes available.

For more information about pertussis and vaccination for pregnant women, see the Department of Health website.

Summary of revised recommendation

The Australian Technical Advisory Group on Immunisation (ATAGI) proposes the following changes to recommendations for the use of pertussis vaccines in pregnant women in Australia:

- broadening the optimal timing of vaccination from 28 to 32 weeks gestation to 20 to 32 weeks gestation (mid 2nd trimester to early 3rd trimester)
- incorporating advice on optimal timing of pertussis vaccination under the recommendation that women should be vaccinated in each pregnancy

This means that the standalone recommendation on optimal timing of pertussis vaccination would be removed.

Background

ATAGI advises the Australian Government on clinical recommendations for vaccinations. ATAGI is proposing changes to the recommendations for the use of pertussis vaccines in pregnant women.

The proposed changes reflect the current best clinical practice to prevent pertussis. The revised recommendations will be published online in the Australian Immunisation Handbook.

Pertussis vaccination in pregnancy boosts maternal antibodies against pertussis. These antibodies are transferred across the placenta to the fetus. This provides passive immunity to the infant until they can receive their 1st dose of pertussis-containing vaccine from 6 weeks of age.

Rationale

Currently, the Australian Immunisation Handbook recommends that pregnant women receive 1 dose of dTpa (diphtheria-tetanus-acellular pertussis) vaccine early in the 3rd trimester, at 28 to 32 weeks.

Recent studies show that antibody levels in cord blood are similar whether the mother was vaccinated in the 2nd trimester or the 3rd trimester. Earlier vaccination may also help protect preterm infants.

Broadening the time window of vaccination to include part of the 2nd trimester reflects the latest evidence on the effectiveness of pertussis vaccination during pregnancy. Removing the standalone recommendation for vaccination at 28 to 32 weeks allows ATAGI to update the optimal timing more easily as new evidence emerges.

New recommendation

ATAGI proposes the following changes to the recommendations for the use of pertussis vaccines in pregnant women in Australia.

Pregnant women are recommended to receive a single dose of pertussis-containing vaccine in each pregnancy

dTpa vaccine is recommended as a single dose in each pregnancy.

Vaccination during pregnancy reduces the risk of pertussis in pregnant women and their young infants.[1,2] This results from direct passive protection by transplacental transfer of pertussis antibodies from the mother to the fetus during pregnancy.

Vaccination is recommended with each pregnancy, including pregnancies that are closely spaced, to provide maximal protection to every infant. This is because:

- vaccine-induced pertussis antibody levels wane over time
- the antibody level needed in mothers to pass on immunity to newborn infants is unknown

The optimal time for pertussis vaccination in pregnancy is between mid 2nd trimester and early 3rd trimester (between 20 and 32 weeks gestation). This is because:

- levels of pertussis antibodies that are likely to be protective are detected in infants born to mothers vaccinated in the 2nd and 3rd trimesters
- maternal antibodies are transported to the fetus from 13 weeks, with maximum transfer from 30 weeks gestation onwards
- pertussis antibody levels do not peak until about 2 weeks after vaccination

Pregnant women typically have a routine morphology scan by ultrasound at around 20 weeks gestation. Most women present to an immunisation provider at this time in relation to the scan, and this may be an opportunity to vaccinate (if presenting at 20 weeks gestation or more) or schedule a vaccination visit (if presenting earlier than 20 weeks).

If pregnant women are not vaccinated between 20 and 32 weeks, they should receive pertussis-containing vaccine as soon as possible and at any time up to delivery. If given within 2 weeks of delivery, the newborn may not be adequately protected.[1]

If pregnant women receive the vaccine earlier than 20 weeks, they do not need a repeat dose during the same pregnancy. Evidence shows transfer of pertussis antibodies to the infant in women who received dTpa vaccine as early as 13 weeks gestation.[3]

Current recommendation

ATAGI currently recommends the following:

> **Pregnant women are recommended to receive a single dose of pertussis-containing vaccine in each pregnancy**
>
> dTpa vaccine is recommended as a single dose in each pregnancy.
>
> Vaccination during pregnancy reduces the risk of pertussis in pregnant women and their young infants.[1,4] This results from direct passive protection by transplacental transfer of pertussis antibodies from the mother to the fetus during pregnancy.

Vaccination is recommended with each pregnancy, including pregnancies that are closely spaced, to provide maximal protection to every infant. This is because:

- vaccine-induced pertussis antibodies wane over time
- the antibody level needed in mothers to pass on immunity to newborn infants is unknown

Optimal time for pertussis vaccination in pregnancy is early in the 3rd trimester

The optimal time for pertussis vaccination is early in the 3rd trimester (between 28 and 32 weeks gestation). This is because:

- pertussis antibody levels do not peak until about 2 weeks after vaccination[5]
- maternal antibodies are actively transported to the fetus from 13 weeks,[6] but mainly from 30 weeks gestation onwards[7]

If pregnant women are not vaccinated between 28 and 32 weeks, they can receive pertussis-containing vaccine at any time during the 3rd trimester up to delivery. The highest levels of infant pertussis antibodies occur when the interval between maternal vaccination and delivery is at least 4 weeks.[3]

If pregnant women receive the vaccine earlier than the 3rd trimester, they do not need a repeat dose during the same pregnancy. Evidence shows transfer of pertussis antibodies to the infant in women who received dTpa (diphtheria-tetanus-acellular pertussis) vaccine as early as 13 weeks gestation.[3]

Key differences

The new recommendation includes the information on optimal timing as supporting information under the recommendation for vaccination in every pregnancy, rather than as a separate standalone recommendation. This allows ATAGI to update the optimal timing more easily as new evidence emerges.

The optimal timing has also been revised to provide a longer time window for pregnant women to be vaccinated. In the new recommendation, pregnant women are recommended to receive pertussis vaccine up to 8 weeks earlier than the current recommendation, from 20 weeks gestation.

Evidence for the new recommendation

Pertussis antibody levels are similar whether the mother is vaccinated in the 2nd trimester or 3rd trimester

Pertussis antibodies can be measured in cord blood. This is the blood that is left in the umbilical cord and the placenta after childbirth. It indicates whether antibodies from the mother have crossed the placenta into the fetus. The antibodies measured include anti-pertussis toxin (PT) antibodies and anti-filamentous haemagglutinin (FHA) antibodies.

In two recent studies,[3,8] women who were vaccinated in the 2nd trimester had higher levels of pertussis antibodies in cord blood than women who were vaccinated in the 3rd trimester.

Two other studies showed no difference in antibody levels in cord blood between 2nd trimester and 3rd trimester vaccination.

Together, these studies indicate that 2nd trimester vaccination is at least as good as, or better than, 3rd trimester vaccination.

Full-term infants

One study in full-term infants compared cord blood from:[3]

- 122 infants born to mothers who were vaccinated between 13 and 25 weeks gestation (2nd trimester)
- 213 infants born to mothers vaccinated at ≥26 weeks gestation (3rd trimester)

Geometric mean concentrations (GMCs) of anti-PT and anti-FHA antibodies were significantly higher after vaccination in the 2nd trimester than in the 3rd trimester.[3]

The study calculated that 98% of infants in the 2nd trimester vaccination group would be seropositive, compared with 86% of the 3rd trimester vaccination group.[3]

This study was limited because it calculated seropositivity in infants, rather than measuring seropositivity directly. This means the true antibody levels in infants may have been different. On the other hand, the study was large enough to allow multiple types of analysis, which increases confidence in the conclusions.

Preterm infants

The other study in preterm infants compared cord blood from:[8]

- 37 infants born to mothers who were vaccinated in the 2nd trimester
- 48 infants born to mothers vaccinated in the 3rd trimester

Anti-PT and anti-FHA antibodies were significantly higher in the 2nd trimester group. The study calculated that 100% of infants in the 2nd trimester vaccination group would be seropositive, compared with 77% of the 3rd trimester vaccination group.

Rationale

It is not clear why antibody levels are higher after 2nd trimester vaccination than after 3rd trimester vaccination in these studies.

The study authors suggest that earlier vaccination means the fetus has longer exposure to antibodies, which results in higher antibody levels at delivery.[3,8] Even though transfer of antibodies across the placenta may be more efficient in the 3rd trimester and close to term, this longer exposure may provide better protection against pertussis in newborns.

Other studies

Other studies show there is no difference in antibody levels whether the mother was vaccinated in the 2nd trimester or 3rd trimester:

- A small study in Argentina found no relationship between timing of vaccination in pregnancy and antibody levels in maternal serum or cord blood.[9]
- Another study found no difference in antibody levels between late 2nd trimester and 3rd trimester vaccination – a similar proportion of infants had antibodies in their cord blood regardless of when their mothers were vaccinated.[10]

Broader window for vaccination may help protect preterm infants

Vaccinating women earlier in pregnancy could help protect preterm infants. Preterm infants have a higher risk of pertussis infection and complications.[11,12]

The World Health Organization's categories for preterm birth are:[13]

- less than 28 weeks gestation – extremely preterm
- 28–32 weeks – very preterm
- 33–36 weeks – moderately preterm

Pertussis antibody levels peak around 2 weeks after vaccination.[5] Infants born within 2 weeks of vaccination will not have had time to receive enough maternal antibodies through the placenta, and may not be protected. Earlier vaccination will allow enough time for antibodies to be transferred to the fetus even if it is born preterm.

A study of women who gave birth in the Northern Territory in 2016 found that, when women were recommended to receive pertussis vaccine from 28 weeks gestation, vaccination coverage was:[14]

- 48.9% for all mothers overall (full term and preterm births)
- 0% for mothers with extremely preterm births
- 14% for mothers with very preterm births
- 39.2% for mothers with moderate preterm births

Overall, 66.5% of mothers who delivered preterm infants had not received pertussis vaccine, compared with 49.4% of mothers with term births. Mothers of infants who were born at term were 1.9 times more likely to have received pertussis vaccine than mothers of preterm infants.[14] The mean time from vaccination to delivery was 59 days, but 10% of women gave birth within 14 days of receiving the vaccine. This means they would likely not have had enough time to mount a sufficient immune response to protect the infant.

A broader window for pertussis vaccination during pregnancy may particularly benefit Aboriginal and Torres Strait Islander women. This study noted that the rate of preterm births among Aboriginal and Torres Strait Islander women (14.5 per 100 live births, or 14.5%) was:[14]

- more than 2 times higher than for non-Indigenous women in this study
- higher than the national average (8.6%) and the global average (11.1%)

Pertussis vaccination during pregnancy is safe

Safety studies suggest that pertussis vaccination in the 2nd or 3rd trimester is not associated with clinically significant harms to either the fetus or the mother.[15-23] Very few studies have specifically analysed whether the timing of pertussis vaccination is associated with adverse events.

One study[17] (a retrospective observational cohort study) compared 123,494 vaccinated women with 29,261 unvaccinated women. It concluded that vaccination was not associated with an increased risk of selected adverse outcomes or high blood pressure in the mother (maternal hypertensive disorder). Vaccination before 20 weeks gestation was also not associated with maternal high blood pressure.

Vaccination has been associated with a small increased risk of chorioamnionitis[17] – infection and inflammation of the membranes around the fetus. However, there is no plausible biological mechanism for this. Chorioamnionitis is a risk factor for preterm birth, but there

was no increase in preterm birth among women in the study. The risk was relatively lower in the women who were vaccinated between 27 and 36 weeks.[17]

One other study compared 'earlier' vaccination (before 27 weeks) and 'later' vaccination (from 27 weeks onwards).[18] Earlier vaccination was not associated with an increased risk of adverse events for the infant, but it was associated with an increased risk for mothers of bleeding after birth (postpartum haemorrhage) and chorioamnionitis. These increased risks were small and may be due to unrelated factors (confounding).

2 smaller cohort studies that looked at the outcome of chorioamnionitis did not find an increased risk for vaccinated women.[24,25]

Recommendations in other countries

Most countries that recommend maternal pertussis vaccination recommend that:[26-29]

- women receive the vaccine at any point in pregnancy, but preferably from 27 or 28 weeks to 32 weeks
- vaccination after 32 weeks is preferable to no vaccination or vaccination after delivery

The UK's Joint Committee on Vaccination and Immunisation changed its recommendation in 2016 from vaccination at 28 to 32 weeks to vaccination at 16 to 32 weeks.[30] This was based on the evidence of higher antibody levels in cord blood.[3] There is an option for the vaccine to be offered at the same time as, or any time after, the routine 20-week morphology scan.

Canada's National Advisory Committee on Immunization notes that evidence supports vaccination from 13 weeks to account for individual and program characteristics.[27]

Benefits

There are 4 key benefits from the longer time window in the new recommendation:

- Providers will have more opportunities to vaccinate pregnant women.
- Pregnant women will be less likely to miss pertussis vaccination. This will likely increase vaccination coverage.
- Pregnant women who receive the vaccine earlier will maximise protection for their infant if it is born preterm.
- Pertussis vaccination can align with other key prenatal visits such as morphology scanning and gestational diabetes testing.

Potential risks

A perceived association between vaccination and adverse pregnancy outcomes could lead to concern among providers and the public. Vaccinating women earlier in pregnancy increases the potential for a chance association between vaccination and adverse pregnancy outcomes.

Preference and values

The proposed changes to the use of pertussis vaccines in pregnant women are in line with best clinical advice. It is expected that the changes will improve protection for newborn infants, a group that is particularly vulnerable to pertussis disease. This is consistent with

societal expectations of the best use of vaccines in Australia, including under the National Immunisation Program.

Glossary

A glossary of technical terms is available on the Australian Immunisation Handbook website.

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