UK National Screening Committee

# Evidence map: Antenatal screening for Varicella-zoster virus susceptibility

## A literature search to outline the volume and type of evidence related to antenatal screening for varicella-zoster virus susceptibility for the UK National Screening Committee

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**The UK National Screening Committee secretariat is hosted by Public Health England.**

# About the UK National Screening Committee (UK NSC)

The UK NSC advises ministers and the NHS in the 4 UK countries about all aspects of population screening and supports implementation of screening programmes.
Conditions are reviewed against evidence review criteria according to the UK NSC's evidence review process.

Read a complete list of UK NSC recommendations.

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# Summary

This document discusses the findings of one evidence map on antenatal screening for varicella zoster virus susceptibility.

Evidence maps are a way of scanning published literature to gauge the volume and type of evidence which is available on a specific topic. They inform whether there is enough evidence to commission a more substantial rapid review on the topic under consideration.

Based on the findings of this evidence map a more comprehensive rapid review on antenatal screening for varicella zoster virus susceptibility should not be commissioned at the present time.

The UK National Screening Committee (UK NSC) will return to antenatal screening for varicella zoster virus in 3-years' time.

# Introduction and approach

## Background & Objectives

The UK National Screening Committee (UK NSC) external reviews (also known as evidence summaries or rapid reviews) are developed in keeping with the UK NSC evidence review process to ensure that each topic is addressed in the most appropriate and proportionate manner. Further information on the evidence review process can be accessed online.

Antenatal screening for varicella zoster virus (VZV) susceptibility is a topic currently due for an update review.

The UK NSC currently recommends against antenatal screening for VZV susceptibility. The Committee based this recommendation on the evidence provided by the review carried out by Bailey (2015). The review highlighted that:

- there is a lack of evidence about varicella zoster exposure in susceptible pregnant women.
- there is no agreed cut-off point for the screening test and ethnicity and age were considered factors that would affect the cut-off which would indicate immunity.
- there were no studies indicating the effectiveness of Varicella Zoster Immunoglobulin (VZIG) for preventing or reducing the severity of maternal symptoms reducing the risk of vertical transmission and fetal infection severity.
- it was uncertain whether screening would offer any benefits for the mother/infant above current management recommendations set out by Joint Committee on Vaccination and Immunisation (JCVI) and the Royal College of Obstetricians and Gynaecologists.

Preliminary work was undertaken to gauge whether this situation had changed.  This took the form of an evidence map.

Evidence maps are rapid evidence products which aim to gauge the volume and type of evidence relating to a specific topic. This approach has been used for this topic to support decision making on whether or not the evidence is sufficient to justify commissioning a more sustained review of the evidence.

It should be noted that screening for susceptibility to infectious diseases presents a number of conceptual and practical challenges. For example, unlike screening for the early signs of disease or for markers of risk, screening for susceptibility to infectious disease aims to identify a low level or absence of protective antibodies. Individuals identified in this way would require practical measures to avoid infection and to be aware of exposure should this occur. Intervals for subsequent, repeat, testing would also need to be established to ensure that the screening programme promptly identifies individuals who seroconvert but are not aware they have acquired the infection. Mechanisms such as these would need to be in place to ensure that an intervention can be offered at an appropriate point.

This document discusses the findings of the evidence map. This evidence map will focus on 2 key questions: the diagnostic accuracy of VZV screening tests in pregnant populations and the effectiveness of VZV immunoglobulin treatment in pregnancy when VZV susceptibility is determined before VZV exposure versus when it is determined after exposure. These are essential pre-requisites of a screening programme but do not, in themselves, address all the challenges of a varicella susceptibility screening programme.

The aim of this document is to present the information necessary for the UK NSC to consider whether an evidence summary on antenatal screening for VZV susceptibility should be commissioned in 2019.

## Previous review on screening for antenatal screening for varicella zoster virus susceptibility

The UK NSC previously reviewed antenatal screening for varicella susceptibility in 2015 (Bailey 2015) and assessed 3 evidence gaps: the prevalence of VZV susceptibility and the proportion expected to be exposed to VZV infection during pregnancy in the UK, the accuracy of VZV susceptibility tests and acceptable testing standards, and the effectiveness of VZIG treatment.

Natural history: The UK NSC review described studies reporting that 95% of pregnant women who grew up in the UK were likely to be seropositive for VZV but this proportion was significantly lower in women who were born in countries with a tropical climate and migrated to the UK in adulthood. The review also reported a paucity of evidence on virus exposure in susceptible women.

Screening test: The performance of commercially available VZV screening tests were described as significantly reduced in women who have been vaccinated compared to those who have a natural history of infection. Optimum cut-off points for the VZV screening test had not been agreed and it was thought that the cut-off point indicating immunity varied according to ethnicity and age. No studies examining the optimum cut-off points for the VZV screening test in the general pregnant population were identified.

Treatment: The UK NSC review did not find evidence for the effectiveness of VZIG for preventing or reducing severity of maternal symptoms or reducing the risk of vertical transmission and fetal infection severity. The review concluded that it remained uncertain if screening would offer any benefits for the mother and /or infant above the current management recommendations set out in JCVI and RCOG.

The 2015 review concluded that the body of evidence identified by the literature search was insufficient to change the recommendation not to offer antenatal screening for VZV.  Consultation responses agreed with the conclusions of the UK NSC review that VZV screening should not be recommended.

## Outcomes

On the basis of the evidence map, it is recommended that evidence summaries on antenatal screening for varicella zoster virus susceptibility should not be commissioned at the present time.

The Committee will return to antenatal screening for varicella zoster virus susceptibility in 3-years' time.

# Evidence maps

The evidence map has been developed as part of a process to assess whether an update review on antenatal screening for varicella zoster virus susceptibility should be commissioned in 2019 and to establish the volume and type of evidence on key issues related to this topic.

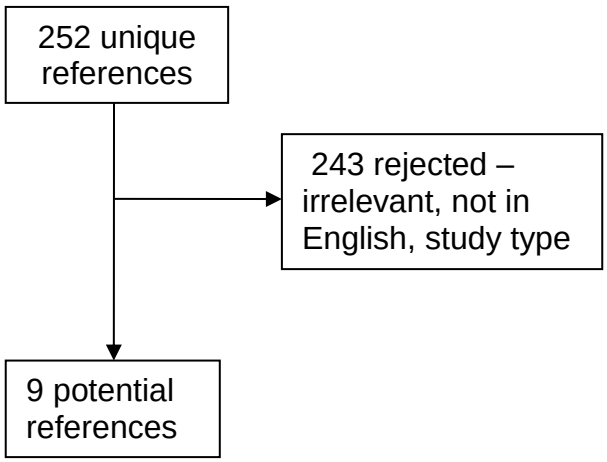
The evidence map aims to address the following questions:

1. What is the evidence on the diagnostic accuracy of tests available for population screening to determine varicella zoster virus?
2. What is the evidence on the effectiveness of varicella-zoster immunoglobulin (VZIG) when varicella zoster virus (VZV) susceptibility is determined before exposure through an antenatal screening programme compared with current practice?

This evidence map will provide the basis for discussion on whether evidence summaries in these areas are justified.

## Summary of the evidence map findings

The search for the evidence map was conducted on 25th February 2019 on 3 databases: Medline, Embase, and the Cochrane Library. The time period was restricted to January 1st 2014 – 25th February 2019. A detailed search strategy including exclusion and inclusion criteria is available in appendix 1. The search returned 252 references. After automatic and manual de-duplication, 243 unique references were sifted for relevance to the key question and 9 references were included in the final evidence map. All references were reviewed at abstract level, though in some cases full texts were reviewed to clarify uncertain pieces of information.



## Question 1: What is the evidence on the diagnostic accuracy of tests available for population screening to determine varicella zoster virus (VZV) susceptibility?

Of the 9 potential references identified from the search, 4 related to question 1 about tests available to determine VZV susceptibility. However none of the references directly addressed this question of test accuracy:

- 2 references reported the outcomes of the implementation of the Canadian prenatal infectious disease guidelines in respect to VZV but did not report the accuracy of the test. The guideline does not recommend population screening in the general pregnant population.
- 1 reference reviewed evidence about the management of pregnant women in respect to VZV.
- 1 reference reported the outcomes of a study to determine maternal antibody decay in babies to determine the mean duration of passive immunity conferred by the mother.

No further evidence has been identified in respect to the accuracy of the VZV antibody test in the general pregnant population or VZV exposed populations since the previous review in 2015. This includes a lack of new evidence about the performance of the test in women who may have been previously vaccinated or exposed to VZV. The test may not detect VZV antibodies in women previously vaccinated who are nevertheless not susceptible to the virus and there is no agreement about the cut-off point that is accurate in determining VZV susceptibility in women of different ages and ethnicities.

In summary, at present there is an insufficient volume of evidence in this key area to justify commissioning an evidence summary.

## Question 2: What is the evidence on the effectiveness of varicella-zoster immunoglobulin (VZIG) when varicella zoster virus (VZV) susceptibility is determined before exposure through an antenatal screening programme compared with current practice?

Of the 9 potential references identified from the search, 5 related to question 2 about the effectiveness of VZIG when VZV susceptibility is determined through an antenatal screening programme. However none of the references directly addressed the question of treatment effectiveness in women whose VZV susceptibility was determined through screening before exposure:

- 2 references are retrospective studies of the outcomes of VZIG vaccination in 215 and 104 pregnant women following VZV exposure from Italy and Denmark respectively.
- 2 references reported retrospective mortality and morbidity burden from VZV infection in mothers and babies,
- 1 reference is a correction to a publication unrelated to evidence of effectiveness of VZIG.

No further evidence has been identified in respect to the effectiveness of VZIG when VZV susceptibility is determined before exposure through an antenatal screening programme.

In summary, at present there is an insufficient volume of evidence in this key area to justify commissioning an evidence summary.

## Conclusions

The findings of this evidence map is unlikely to impact on current the recommendation on antenatal screening for varicella zoster virus susceptibility as no new evidence was identified that would change those conclusions.

## Recommendations

- The volume and type of evidence related to antenatal screening for varicella zoster virus susceptibility is currently insufficient to justify an update review at this stage and it should be re-considered in 3-years' time.

# Appendix 1 — Search strategy for the evidence map

**SOURCES SEARCHED**: Medline, Embase and Cochrane Library

**DATES OF SEARCH**: Medline, Embase and Cochrane 2014-25th February 2019

**SEARCH STRATEGIES**:

| **Medline Question 1: screening** | | | **Embase Question 1: screening** | | |
|---|---|---|---|---|---|
| 1 | exp Varicella Zoster Virus Infection/ | 17344 | 1 | exp varicella zoster virus/ or varicellovirus/ | 13299 |
| 2 | varicellovirus/ or herpesvirus 3, human/ | 6997 | 2 | chickenpox/ or exp herpes zoster/ | 31002 |
| 3 | (chickenpox or "chicken pox").ti,ab. | 2922 | 3 | (chickenpox or "chicken pox").ti,ab. | 3431 |
| 4 | (varicella or VZV or "herpesvirus 3" or "Herpes zoster Virus" or HHV-3).ti,ab. | 14265 | 4 | (varicella or VZV or "herpesvirus 3" or "Herpes zoster Virus" or HHV-3).ti,ab. | 17884 |
| 5 | 1 or 2 or 3 or 4 | 24963 | 5 | 1 or 2 or 3 or 4 | 41237 |
| 6 | exp pregnancy/ or pregnant women/ | 854193 | 6 | exp pregnancy/ or pregnant woman/ | 656491 |
| 7 | exp fetus/ | 153103 | 7 | exp fetus/ | 181486 |
| 8 | (pregnan$ or f?etal or f?etus or FVS).ti,ab. | 647136 | 8 | (pregnan$ or f?etal or f?etus or FVS).ti,ab. | 787381 |
| 9 | prenatal care/ | 25298 | 9 | exp prenatal care/ | 140398 |
| 10 | (prenatal or pre-natal or antenatal or ante-natal or perinatal or peri-natal or postnatal or post-natal or postpartum or post-partum).ti,ab. | 298788 | 10 | (prenatal or pre-natal or antenatal or ante-natal or perinatal or peri-natal or postnatal or post-natal or postpartum or post-partum).ti,ab. | 376050 |
| 11 | 6 or 7 or 8 or 9 or 10 | 1218079 | 11 | 6 or 7 or 8 or 9 or 10 | 1220474 |
| 12 | Mass Screening/ | 96384 | 12 | Mass Screening/ | 51462 |
| 13 | screen*.ti,ab. | 670829 | 13 | screen*.ti,ab. | 928768 |
| 14 | exp Population Surveillance/ | 64161 | 14 | screening/ or screening test/ | 235227 |
| 15 | Self Report/ | 25701 | 15 | Self Report/ | 107340 |
| 16 | (selfreport* or self-report* or ((oral or tak*) adj3 history)).ti,ab. | 146079 | 16 | (selfreport* or self-report* or ((oral or tak*) adj3 history)).ti,ab. | 194899 |
| 17 | Hematologic Tests/ or Diagnostic Tests, Routine/ | 19333 | 17 | blood examination/ or diagnostic test/ | 88134 |
| 18 | ((h?ematolog* or blood or serum or serologic*) adj3 (test* or assay*)).ti,ab. | 109543 | 18 | exp immunoassay/ | 517934 |

| | | | | | |
|---|---|---|---|---|---|
| 19 | exp immunoassays/ | 479536 | 19 | ((h?ematolog* or blood or serum or serologic*) adj3 (test* or assay*)).ti,ab. | 157968 |
| 20 | (immuno-assay* or immunoassay* or elisa or eia or Fluorescent antibody to membrane antibod* or fama or trfia).ti,ab. | 213571 | 20 | (immuno-assay* or immunoassay* or elisa or eia or Fluorescent antibody to membrane antibod* or fama or trfia).ti,ab. | 320847 |
| 21 | (test* or diagnos* or assay*).ti. | 1024241 | 21 | (test* or diagnos* or assay*).ti. | 1132825 |
| 22 | 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 | 2428348 | 22 | 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 | 2823719 |
| 23 | 5 and 11 and 22 | 255 | 23 | 5 and 11 and 22 | 389 |
| 24 | Prenatal diagnosis/ | 35570 | 24 | prenatal screening/ | 8069 |
| 25 | ((prenatal or pre-natal or antenatal or ante-natal or perinatal or peri-natal or postnatal or post-natal or postpartum or post-partum) adj5 (screen* or diagnos* or test*)).ti,ab. | 44653 | 25 | ((prenatal or pre-natal or antenatal or ante-natal or perinatal or peri-natal or postnatal or post-natal or postpartum or post-partum) adj5 (screen* or diagnos* or test*)).ti,ab. | 58421 |
| 26 | 24 or 25 | 63940 | 26 | 24 or 25 | 62229 |
| 27 | 5 and 26 | 91 | 27 | 5 and 26 | 121 |
| 28 | exp Varicella Zoster Virus Infection/di | 2946 | 28 | chickenpox/di or exp herpes zoster/di | 3793 |
| 29 | ((chickenpox or chicken pox or varicella or VZV or "herpesvirus 3" or "Herpes zoster Virus" or HHV-3) adj5 (screen* or diagnos* or test*)).ti,ab. | 1213 | 29 | ((chickenpox or chicken pox or varicella or VZV or "herpesvirus 3" or "Herpes zoster Virus" or HHV-3) adj5 (screen* or diagnos* or test*)).ti,ab. | 1738 |
| 30 | 28 or 29 | 3830 | 30 | 28 or 29 | 5180 |
| 31 | 11 and 30 | 333 | 31 | 11 and 30 | 401 |
| 32 | 23 or 27 or 31 | 488 | 32 | 23 or 27 or 31 | 667 |
| 33 | limit 32 to (english language and yr="2014 - Current") | 42 | 33 | limit 32 to (english language and yr="2014 -Current") | 124 |

| **Medline: Question 2 treatment** | | | **Embase: Question 2 treatment** | | |
|---|---|---|---|---|---|
| 1 | exp Varicella Zoster Virus Infection/ | 17344 | 1 | exp varicella zoster virus/ or varicellovirus/ | 13299 |
| 2 | varicellovirus/ or herpesvirus 3, human/ | 6997 | 2 | chickenpox/ or exp herpes zoster/ | 31002 |
| 3 | (chickenpox or "chicken pox").ti,ab. | 2922 | 3 | (chickenpox or "chicken pox").ti,ab. | 3431 |

| | | | | | |
|---|---|---|---|---|---|
| 4 | (varicella or VZV or "herpesvirus 3" or "Herpes zoster Virus" or HHV-3).ti,ab. | 14265 | 4 | (varicella or VZV or "herpesvirus 3" or "Herpes zoster Virus" or HHV-3).ti,ab. | 17884 |
| 5 | 1 or 2 or 3 or 4 | 24963 | 5 | 1 or 2 or 3 or 4 | 41237 |
| 6 | exp pregnancy/ or pregnant women/ | 854193 | 6 | exp pregnancy/ or pregnant woman/ | 656491 |
| 7 | exp fetus/ | 153103 | 7 | exp fetus/ | 181486 |
| 8 | (pregnan$ or f?etal or f?etus or FVS).ti,ab. | 647136 | 8 | (pregnan$ or f?etal or f?etus or FVS).ti,ab. | 787381 |
| 9 | prenatal care/ | 25298 | 9 | exp prenatal care/ | 140398 |
| 10 | (prenatal or pre-natal or antenatal or ante-natal or perinatal or peri-natal or postnatal or post-natal or postpartum or post-partum).ti,ab. | 298788 | 10 | (prenatal or pre-natal or antenatal or ante-natal or perinatal or peri-natal or postnatal or post-natal or postpartum or post-partum).ti,ab. | 376050 |
| 11 | 6 or 7 or 8 or 9 or 10 | 1218079 | 11 | 6 or 7 or 8 or 9 or 10 | 1220474 |
| 12 | Immunoglobulins/ | 42710 | 12 | (immunoglobulin? or immuno-globulin? or immuneglobulin? or immune globulin? or vzig).ti,ab. | 178809 |
| 13 | (immunoglobulin? or immuno-globulin? or immuneglobulin? or immune globulin? or vzig).ti,ab. | 148780 | 13 | herpes zoster immunoglobulin/ or immunoglobulin/ | 110328 |
| 14 | 12 or 13 | 170585 | 14 | 12 or 13 | 238439 |
| 15 | 5 and 11 and 14 | 150 | 15 | 5 and 11 and 14 | 397 |
| 16 | limit 15 to (english language and yr="2014 -Current") | 16 | 16 | limit 15 to (english language and yr="2014 -Current") | 57 |

| | **Cochrane** | |
|---|---|---|
| 1 | “chickenpox “ or chicken pox or varicella or VZV or herpes virus 3 or HHV-3 or herpesvirus | 693 |
| 2 | (prenatal or pre-natal or antenatal or ante-natal or perinatal or peri-natal or postnatal or post-natal or postpartum or post partum; ti,ab,kw OR (pregnan* or fetus or foetus or fetal or foetal or fvs) ti,ab,kw | 48468 |
| 3 | 1 and 2 | 13 |

### Results by database

| | |
|---|---|
| **Medline** | **58** |
| **Embase** | **181** |
| **Cochrane Library** | **13** |
| **Total** | **252** |

### Inclusions and exclusions

Publications not in the English language, case studies, conference reports and comment/letters were excluded.

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**Introduction**

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2. Royal College of Obstetricians and Gynaecologists. Chickenpox in Pregnancy: Green-top Guideline No. 13. 2015

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