



**UK National
Screening Committee**

Screening for varicella in pregnancy

External review against programme appraisal criteria
for the UK National Screening Committee (UK NSC)

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The UK NSC advises Ministers and the NHS in all four UK countries about all aspects of screening policy. Its policies are reviewed on a 3 yearly cycle. Current policies can be found in the policy database at <http://www.screening.nhs.uk/policies> and the policy review process is described in detail at <http://www.screening.nhs.uk/policyreview>

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Plain English Summary

Varicella, commonly known as chicken pox, is a very common infection in the UK. Most people growing up in the UK will have had an infection by the time they are an adult, the majority in early childhood. Chickenpox is less common in tropical or subtropical climates, and a larger proportion of the population will reach adulthood having never been infected. Almost all people who have had chicken pox are immune and protected from a second infection.

In children, chicken pox is usually mild and very rarely life threatening. In adults, the symptoms are usually worse, particularly in vulnerable people and pregnant women. If a pregnant woman becomes infected with chickenpox in the first or second trimesters, there is a small chance that this will cause congenital abnormalities in the baby. Later on in pregnancy, women are at increased risk of complications from pneumonia caused by chickenpox and there may be varicella in the newborn, which can be serious. In some cases, the baby may not survive the infection.

For pregnant women who have not had chicken pox before, there is already a process in place for them to receive medication if they come in contact with the infection. The medication, Varicella Zoster Immunoglobulin (VZIG), is given to prevent the mother and baby from getting the infection or to make the infection less severe.

A screening programme would aim to find pregnant women who have not had chicken pox before. These women would be “susceptible” to an infection in pregnancy. The aim of identifying susceptible women early in their pregnancy would be to speed up the delivery of VZIG should they come into contact with chicken pox later on. The current UK NSC recommendation is that screening should not be recommended. This update revisits some of the areas of concern found in the last review.

- Around 95% of pregnant women who have grown up in the UK have already had chicken pox and therefore they or their baby would not be at risk. There are slightly more women at risk in some migrant groups, particularly women born in and recently migrating from tropical and subtropical regions. There is very little information about the number of women who are at risk who then come into contact with chicken pox in their pregnancy.
- The best screening tests look for a history of infection in the mother's immune system. Unfortunately there is no one level of immunity that all the tests can use. This means that one test may say that a woman is immune and another may not.
- There was no evidence that finding women who are at risk of infection in pregnancy through screening would mean fewer women and babies get chicken pox, or that their infections would be less severe, compared with the processes that are currently in place.

The evidence considered in this update suggests that the recommendation not to screen should not be changed.

Executive Summary

Varicella Zoster Virus (VZV) infection, commonly known as chicken pox, is very common in childhood in the UK. It is estimated that over 90% of people growing up in the UK have had an infection by adulthood. Reinfection is uncommon and most seropositive people are not at risk of reoccurrence.

VZV infections are more severe in adults and can lead to serious complications in pregnant women. If acquired in the first or second trimesters, there is a risk that the infection could be passed to the fetus and cause congenital abnormalities. If chickenpox is acquired later on in pregnancy, women are at particular risk of complications from pneumonia and their babies are at risk of neonatal varicella. Varicella infections in newborns are very rare but have a significant risk of mortality and severe morbidity.

For susceptible (seronegative) pregnant women exposed to VZV and for neonates whose mothers develop chickenpox around the time of delivery, Varicella Zoster Immunoglobulin (VZIG) is indicated to prevent or attenuate severity of disease. VZIG can be used as post-exposure prophylaxis up to 10 days after an exposure has occurred.

The current UKNSC screening recommendation is based on a review produced on behalf of UKNSC in 2009. The review concluded that key evidence gaps remained around the proportion of women in the UK who are susceptible and, of these, the proportion who are exposed to VZV during pregnancy, test standards for identifying women at risk of VZV infection, and the effectiveness of a screening programme beyond the current management strategies recommended by the JCVI and RCOG.

This 2015 UKNSC update is a rapid review of the three main evidence gaps noted in the 2009 review. The review concludes that the volume, quality and consistency of the published evidence does not challenge the conclusions made in the 2009 review.

The findings for each of the key questions are as follows:

What is the prevalence of susceptibility to VZV among pregnant women in the UK? What proportion of women are expected to come into contact with VZV during pregnancy?

- Two studies conducted in small UK populations suggest that around 95% of pregnant women who have grown up in the UK are seropositive for VZV, but that this proportion is significantly lower among women who were born in countries with a tropical climate and migrated to the UK in adulthood.
- There is very little data on virus exposure in susceptible pregnant women. The number of VZIG prescriptions issued has not changed significantly since the last review; however there are some serious limitations that would preclude this information being used as a proxy for this outcome.

What is the most accurate screening test for determining VZV susceptibility, and is there an agreed standard for this test?

- Sub-group analysis in the included studies highlighted that the test performance of these commercially available tests is significantly reduced in women who have been vaccinated when compared to those who have a history of natural infection.
- The most commonly cited IgG test cut-off for differentiating between immune and susceptible individuals was an IgG level of <100 mIU/ml, some studies reported promising results using this cut-off. However, the cut-off indicating immunity is thought to vary according to the ethnicity and age of the individual. There is still no agreed standard that would allow a consistent screening test to be implemented.

What is the effectiveness of VZIG for preventing or reducing the severity of maternal symptoms, reducing the risk of vertical transmission and reducing foetal infection severity?

- No studies were identified that adequately answered the question.
- It remains uncertain if screening would offer any benefits, for mother and/or infant, above the current management recommendations (JCVI and RCOG).

Introduction

Varicella Zoster Virus (VZV) infection or chickenpox is a common childhood illness in the UK which is usually mild and self-limiting. Vaccination against Varicella is not currently part of the universal immunisation schedule in the UK. By adulthood, over 90% of the UK-born population are seropositive for VZV immunoglobulin G (IgG) indicating past infection with VZV and immunity, since re-infection is uncommon. VZV (a herpes virus) remains dormant in the dorsal root ganglia following primary infection and can reactivate, causing herpes zoster or shingles.

VZV infection is more severe in adults than in children and can cause serious complications during pregnancy. The most common maternal complication is varicella pneumonia, which occurs in 10-20% of pregnant women with chickenpox; up to 40% may require mechanical ventilation.[1] Fetal varicella syndrome (FVS) is a rare but serious complication of maternal chickenpox in the first and second trimesters, occurring in around 0.5% of pregnancies where maternal infection occurs before 13 weeks gestation and up to around 2% of pregnancies where maternal infection occurs between 13-20 weeks. Congenital abnormalities associated with FVS may affect the skin, limbs, eyes and nervous system; mortality in the first month of life is around 30%.[2]

If maternal infection occurs less than four weeks before delivery, around 50% of neonates will develop neonatal varicella. This is most severe if maternal infection occurs in the 7 days before or after delivery, as the baby is at risk of primary VZV in the first month of life in the absence of passively acquired maternal VZV IgG antibodies.[3]

For susceptible pregnant women exposed to VZV and for neonates whose mothers develop chickenpox around the time of delivery, Varicella Zoster Immunoglobulin (VZIG) is indicated to prevent or attenuate severity of disease. VZIG can be used as post-exposure prophylaxis up to 10 days after an exposure has occurred [3-5], but is not effective in treating symptomatic chickenpox; pregnant women who present with symptoms within 24 hours of rash onset may be treated with oral acyclovir (IV acyclovir is indicated if chickenpox is severe) and acyclovir is also indicated for neonatal varicella.

Routine identification of pregnant women susceptible to VZV (through self-reported history and/or serological testing) is considered here as part of a strategy to facilitate more complete or rapid administration of VZIG post-exposure prophylaxis should exposure to chickenpox occur during pregnancy. Identification of individuals in this way is conceptually distinct from a screening test for a disease, since the test is for susceptibility to a condition which presents clinically or via reported contact. Any benefit to the pregnancy of routine antenatal testing for susceptibility is dependent on subsequent presentation of susceptible women within 10 days of contact with a case, and more complete or effective use of VZIG than would be possible if susceptibility was only determined post-exposure, translating into better outcomes.

This report evaluates evidence published since the 2009 UK NSC-commissioned review on this topic [6] against NSC criteria for a screening programme [7], focussing on the following evidence-gaps identified in the last review:

- **The condition:** Prevalence of susceptibility to VZV among pregnant women in the UK, and the proportion of women expected to come into contact with VZV during pregnancy (*UK NSC criteria 1, 2*).
- **The test:** The accuracy of self-reported history of chickenpox and different antibody tests and availability of an agreed standard for the antibody level determining VZV susceptibility (*UK NSC criteria 5, 6*).
- **The treatment:** The effectiveness of VZIG for preventing or reducing the severity of maternal symptoms, reducing the risk of vertical transmission and reducing foetal infection severity (*UK NSC criteria 10*).

The aim of this update is to establish whether the quality, quantity and direction of the evidence published since the last review impacts on its conclusions and the current UK NSC recommendation that screening for VZV susceptibility should not be routinely offered in pregnancy.

Search methods

Medline (OvidSP), Embase, Cochrane bibliographic databases were searched to identify relevant citations published between January 2009 and mid-October 2014; a description of the full search strategy is given in Appendix 1. Of 5600 citations initially identified, 5020 remained after de-duplication. The titles and abstracts of these citations were appraised and 152 considered relevant to this review; this knowledge update is based on evidence available from these 152 publications.

Criteria 1 and 2:

The condition should be an important health problem

The epidemiology of the condition should be known

Introduction

This section addresses the key questions:

- What proportion of pregnant women in the UK are Varicella Zoster Virus (VZV) seronegative (i.e. susceptible to chickenpox)?
- How many seronegative women are expected to come into contact with chickenpox during pregnancy?

Evidence in these areas is needed to establish the proportion of pregnant women who could stand to gain from any potential benefits of an antenatal screening programme to determine VZV susceptibility.

Key conclusion(s) from 2009 evidence report

Around 10% of pregnant women in the UK and Ireland are thought to be susceptible to VZV (i.e. without antibodies indicating prior infection), but this proportion is higher among women from tropical climates who have migrated to the UK in adult life. There is substantial uncertainty around the proportion exposed to VZV during pregnancy; in the last review this was estimated to be 12-24% in England and Wales overall, via a back-calculation method from the number of women issued with Varicella Zoster Immunoglobulin (VZIG) over a one-year period (1318), to the number reporting an uncertain or no history of chickenpox and requiring testing (3,994-26,360), to the number exposed overall (87,867-175,733, representing 12-24% of pregnant women in England and Wales). As noted in the review, this figure does not take into account the proportion of women who do not seek medical advice following exposure or do not receive VZIG for other reasons, and so is likely to be an underestimate.

Evidence summary

VZV seroprevalence in antenatal UK population

Two studies of VZV seroprevalence among the antenatal population in the UK have been published since the last review. A further eight studies which included data on VZV seroprevalence among women in other European countries are also included in Table 1. Studies in women of reproductive age and particularly those living in the UK were prioritised.

Of note, the proportion of live births in England and Wales to non-UK born women has increased over recent years from 22.7% in 2006 (reported in the last review) to 26.5% in 2013; 9.5% of these live births were to women born in the Middle East and Asia, most commonly Pakistan, India and Bangladesh (accounting for 2.7%, 2.0% and 1.1% of total live births respectively) [8]. Given the importance of geographical differences in VZV seroprevalence, studies commonly disaggregated findings by maternal country or region of birth and ethnicity, or over-sampled women from the Indian subcontinent.

In the first study, information on VZV seroprevalence by country of birth was reported for a sub-set of 949 pregnant women enrolled in the Born in Bradford study, a longitudinal cohort study of 13,776 pregnancies in 12,453 women in Bradford between 2007 and 2010. Among these 949 women, 350 were White British, 300 UK-born of South Asian ethnicity and 299 were Asian and born in South Asia. VZV seroprevalence was high among UK-born pregnant women regardless of ethnicity (94.8% among White British and 94.8% among UK-born women of South Asian ethnicity) but lower at 89.6%

among women born in South Asia (90% of whom were Pakistani, 8% Indian and 2% Bangladeshi) [9]. VZV seroprevalence in the cohort overall increased with age, from 86.2% among women aged <20 years to 97.9% among those aged ≥35 years, and with parity from 90.6% among nulliparous women to 98.7% among women with at least three previous live or still births; women born in South Asia remained less likely to be VZV seropositive after adjusting for these two factors (adjusted risk ratio 0.93, 95% CI 0.89-0.97 vs. White British).

In a second study of 995 pregnant women receiving antenatal care in Tower Hamlets, East London in 2001-2004, VZV seroprevalence was 87.8% among 639 Bangladeshi-born Bangladeshi women (BBB), 96.8% among 94 UK-born Bangladeshi women (BUK) and 95.8% among 262 UK-born white women (WUK) [10]. Although the WUK group were older than BBB women, both UK-born groups remained more likely to be VZV seropositive than the Bangladeshi-born women after adjusting for age. The BBB women were 4% less likely to be VZV seropositive for each additional year spent in Bangladesh, and more likely to report having been infected with chickenpox at age >10 years compared with the other two groups.

Studies among women in other European countries reported varying VZV seroprevalence, for example 92.3% among women in Madrid [11], 97.8% in Slovenia [12] and 89.4% in Italy [13] (increasing from 62.5% in 15-19 year olds to 94.4% among 40-49 year olds, reflecting an older age of VZV acquisition in Italy compared with the UK). In a study among Pakistani migrants in Norway, 93% were seropositive (increasing from 87% among those who had lived in Norway for <5 years to 98% for those resident in Norway for ≥5 years) [14] (Table 1); meanwhile, VZV seroprevalence was only 72.3% among 494 young women in an Indian study [15]. The factors causing geographical variability in VZV seroprevalence are not well understood, however a study from Canada identified climate of the country of origin as the factor most strongly associated with VZV susceptibility among 1480 migrants in Montreal [16].

Table 1: Studies of VZV seroprevalence in Europe which included women of reproductive age

Author	Year(s) of study	Country	Population	Country of birth / ethnicity	Age	VZV seroprevalence
Ayres [10]	2001-04	UK	995 pregnant women in Tower Hamlets, East London	64% Born in Bangladesh 9% Bangladeshi UK-born 26% White UK-born	Mean 26 years Mean 24 years Mean 28 years	87.8% 96.8% 95.8%
Pembrey [9]	2007-10	UK	949 pregnant women in Bradford	37% White British 32% South Asian born in UK 32% Asian born in South Asia	Mean 26.6 years Mean 27.4 years Mean 28.1 years	94.8% 94.8% 89.6%
Gonzalez-Escalada [11]	2007-10	Spain	930 women	Not given	19-39 years	92.3%
Guido [13]	2008-09	Italy	539 pregnant women	90% (397/440) born in Italy, 8% in other European countries, 2% elsewhere	Median 31 years	89.4%
Rijckevorsel [17]	2004	The Netherlands	619 men, 717 women	39% born in the Netherlands. 33% Dutch, 21% Moroccan, 7% Surinamese or Antillean, 24% Turkish, 16% Other ethnicity.	Median age 52 years for men, 47 years for women	93% in both men and women in this sample; estimated to be 94% in Amsterdam population overall.
Rijckevorsel [18]	2007	The Netherlands	242 women (child day care personnel)	77% born in the Netherlands /other European countries, 23% outside of Europe	16-44 years; median 29 years	100%
Urbiztondo	2008-10	Spain,	493 women (healthcare	Not given	Not disaggregated by sex; 54% ≤44 years	95.3%

[19]		Catalonia	workers)		overall	
Socan [12]	2006	Slovenia	Around 750 women of childbearing age	Not given	15-49 years	97.2%
Vilibic-Cavlek[20]	2007-11	Croatia	638 women (12% pregnant)	Not given	16-45 years	84.3%
Bjerke [14]	2007-09	Norway	206 pregnant women	Pakistani, born in Pakistan	18-44 years, mean 27.3 years	93%

Footnote: Where a study presented VZV seroprevalence disaggregated by sex, the seroprevalence for women only is presented in the table

Exposure to VZV in pregnancy

Data on exposure to chickenpox in pregnancy are scarce; the only new study on this topic published since the last review, from Northern Ireland, used data on issues of VZIG in 2006 and concluded that 14.5% of pregnant women were exposed to VZV during pregnancy [21].

Data provided by Public Health England (PHE) indicate that, on average, approximately 1200 pregnant women received VZIG annually in England from 2008-13, equating to approximately 0.14% of conceptions in England over this time period [22]. The VZIG issue data for these years is similar to that used in the 2009 review, in which it was used to estimate that 12-24% of pregnant women were exposed to chickenpox during pregnancy [6].

Issues of VZIG to pregnant women give an indication of the number of pregnant women who present and are identified as being susceptible within 10 days of an exposure (the window in which VZIG can be effective), but will represent an underestimate of actual exposures because (i) some exposures will be unrecognised (ii) some exposed women may not seek medical attention or may present more than 10 days after contact (when VZIG is not of benefit) (iii) supplies of VZIG may be insufficient to meet all requests for supplies for pregnant women (iv) some women may decline the offer of VZIG. Furthermore, the true number of women who actually received VZIG may be higher than indicated above, as some women receive fewer than four vials which make up a typical dose. It is therefore not possible to estimate the overall proportion of pregnant women exposed to VZV with more precision.

Finally, differential VZV exposure by susceptibility is possible if susceptible migrant women are more likely to have susceptible contacts; however, the majority of contacts are likely to be with infected children rather than other susceptible adults [23] and the majority of susceptible, exposed women will be UK-born, since this group forms three-quarters of the antenatal population in the UK overall.

Updates since 2009 evidence review

Further studies on VZV seroprevalence in pregnant women published since the last review confirm that among UK-born women, the proportion already immune to chickenpox is high at around 95%. However seroprevalence is thought to be lower (<90%) among women from tropical and subtropical regions and may be particularly low among young nulliparous women and recent migrants. It is therefore likely that there is geographical variation in VZV susceptibility among pregnant women within the UK. The two studies found in UK populations were limited to antenatal populations in Bradford and East London; further studies are needed to accurately describe the nationwide seroprevalence.

Data on the proportion of women exposed to VZV during pregnancy remains very sparse. While useful, VZIG prescription information alone is not adequate to describe the number of women likely to be exposed to VZV during pregnancy in the UK.

Conclusion: criteria not met

Criteria 5 and 6:

There should be a simple, safe and validated screening test

The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed

Introduction

This section addresses two key questions:

- What is the most accurate screening test for determining VZV susceptibility?
- Is there an agreed standard for this test?

A test with low specificity will miscategorise susceptible women (who may benefit from VZIG if exposed) as being immune, while an assay with low sensitivity will miscategorise immune women as susceptible. The specificity of the test is important in ensuring that susceptible women are not missed; the sensitivity has important implications for service provision and potentially unnecessary administration of Varicella Zoster Immunoglobulin (VZIG), a blood product. In addition, VZIG is expensive and supplies are limited (due to limited availability of non-UK donors with high titres of Varicella Zoster Virus (VZV) antibody) [4]. A test with low sensitivity will not effectively identify women who should be given priority for the limited doses available, and impact on the cost-effectiveness of a potential screening programme.

In addition to data on the accuracy of VZV susceptibility tests, this review covers considerations of cost, operational expertise and availability where this information is available, and data on validation of antibody levels against risk of incident chickenpox among adults.

Key conclusion(s) from 2009 evidence report

The last review summarised the evidence available on the accuracy of self-reported history of chickenpox in determining VZV susceptibility and of commercially available serological assays, which are currently recommended for use in women with a negative or uncertain history of chickenpox to identify those requiring VZIG. [3,4] The positive predictive value of a self-reported history of chickenpox was found to be high at 95-99% in pregnant women, while the negative predictive value was much lower; with only around 6.8-35% of women with a negative or uncertain history found to be susceptible on serological testing. The reliability of chickenpox history in determining immunity varied by age and ethnicity, and was lower among people who had grown up abroad, who were also more likely to be susceptible.

The 2009 review summarised data from several studies validating enzyme immunoassays (ELISA or EIA) against either fluorescent antibody to membrane antibody (FAMA) or time-resolved fluorescence immunoassay test (TRFIA). These studies indicated that enzyme immunoassays provide a practical and reliable method for serological testing, but that there is variability in the test characteristics of the assays (and variation in gold standards used across studies), and a need for national guidelines and criteria for the sensitivity and specificity of assays for use in any potential future screening programme. Furthermore, there were no standard criteria for determining the antibody level which correlated with susceptibility to chickenpox in adults, with FAMA being the only assay to have been evaluated in longitudinal studies.

Evidence summary

Self-reported history of chickenpox

In the updated search, two studies were identified that were undertaken in a UK population; studies that compared the accuracy of a self-reported history against a gold standard diagnostic test were prioritised.

These studies confirm the high positive predictive value of self-reported history of chickenpox to determine VZV susceptibility, particularly in UK-born women. In one study of 995 pregnant women in East London, the positive predictive value of a history of chickenpox was 97.4% in white women, similarly high (96.1%) among Bangladeshi women born in the UK, but lower at 92.8% for Bangladeshi-born women [10], while sensitivity of self-reported history was 90.4%, 82.4% and 79.9% for determining seropositivity in these three groups respectively (when women with no or an uncertain chickenpox history were grouped together). Published data did not give sufficient information to determine the specificity or negative predictive value of chickenpox history.

A study of 247 adolescents in England of average age 13 years, purposively sampled to include 120 with a positive history, 77 with a negative history and 50 with an uncertain history of chickenpox, detected VZV IgG antibodies in 109 (90.8%) with a positive history of infection, 52 (67.5%) with a negative history and 42 (84%) with an uncertain history [24]. In this study, 6% of participants were Asian, 3% Black, 1% Chinese and 6% of mixed ethnicity, and results were not disaggregated by country of birth; the study focussed on the feasibility of a future VZV vaccination programme for susceptible adolescents, which may have influenced decisions to participate and responses to the chickenpox history question. The negative predictive value of history of chickenpox (when the participants with a negative or uncertain history of chickenpox were considered together) was 25.9%.

Serological assays: cut-offs indicating VZV susceptibility

The antibody titre cut-off which can most accurately discriminate between immune and susceptible individuals is population-specific, as the antibody titre of vaccinated individuals is estimated to be one log lower than that among individuals who are immune following natural infection, and antibody levels may also vary by ethnicity and age. A study of pregnant women in London found that the magnitude of the humoral immune response to VZV was lower among Bangladeshi women than among white women, irrespective of country of birth or age, and that antibody levels among Bangladeshi women remained stable or waned with age rather than increasing as in white UK-born women, possibly due to older age at primary varicella infection [10]. Some caution may therefore be needed to interpret data relating to assay cut-offs and sensitivity within the context of the population tested.

In the only study published since the last review which relates VZV IgG levels with risk of subsequent infection, information was sought on the outcomes of 209 pregnant women with a negative or uncertain history of chickenpox who were tested for VZV IgG antibody following exposure to VZV during pregnancy.[23] Samples were tested by LIAISON, an enzyme-linked fluorescence assay (ELFA), as well as by TRFIA. Overall, outcome information was available for 143 women of whom 14 (9.8%) had subsequently developed chickenpox. Serum samples were available for 13 of these 14 cases. Five women developed chickenpox despite receiving VZIG, with a mean VZV IgG level of 62 mIU/ml by TRFIA; all had a level <100 mIU/ml. Of the eight who developed chickenpox having not received VZIG, three had high VZV IgG levels (all ≥ 380 mIU/ml by TRFIA) and were considered to be possible "re-infections" due to high VZV IgG avidity of >80%; the remaining five had a mean antibody level very similar to the group with VZIG of 65.1 mIU/ml by TRFIA. Among 119 women who did not develop chickenpox, mean VZV IgG levels were 272 mIU/ml by TRFIA for 99 women who did receive VZIG and 866 mIU/ml among 20 women who did not. Of note, the sample included in this study may not be representative of the target population for a potential antenatal screening programme if outcome information was more likely to be reported for women who went on to develop chickenpox.

Although TRFIA gave higher IgG values than the LIAISON assay in this study due to greater sensitivity, the 100 mIU/ml cut-off was informative in both assays for indicating VZV susceptibility in this unvaccinated population. Ten of 32 women with an IgG level <100 mIU/ml via the LIAISON assay developed chickenpox compared with 3/100 with levels above (all possible re-infections), giving a relative risk of infection of 10.4 for women with IgG levels <100 mIU/ml, while for TRFIA there were 9 cases among 27 women with an IgG level <100 mIU/ml vs. 4/105 with levels above this value, giving a relative risk of 8.8. Most women who developed chickenpox in this study reported contact with an infection within the family or household; in some cases, chickenpox developed before VZIG could be administered and within a shorter time from first reported contact than the 2-3 week incubation period expected, probably indicating an earlier unrecognised exposure.

A second study examined antibody titre levels before and after vOka vaccination among 110 healthcare workers in the UK who had negative or repeatedly equivocal results for VZV IgG. [25] Avidity measures at 6 weeks after first vaccine dose were used to identify individuals without prior immunity, who had a primary response to the vaccine (61% of the group), and those with high avidity antibodies $\geq 60\%$, suggesting prior immunity (35% of the group). The TRFIA cut-off at baseline which discriminated best between the two groups was >130 mIU/ml; using the vaccine response as a gold standard, the sensitivity of this TRFIA >130 mIU/ml cut-off at baseline for identifying individuals with prior immunity was 90% (95% CI 79-96) and the specificity was 78% (95% CI 61-90).

Serological assays: accuracy and other characteristics

From the update search, three studies were included that reported outcomes on the accuracy of varicella susceptibility screening tests. One study compared the accuracy of an EIA test against TRFIA, the other two compared ELISA tests against FAMA. Studies including pregnant women were prioritised. No studies were identified that considered the accuracy of latex agglutination test. Five studies evaluating serological microarrays to simultaneously screen for antibodies against VZV and a range of other infections (measles, mumps and rubella [26-28], or others such as HSV-1, HSV-2 and CMV [29,30]) were excluded, as this review considers the feasibility of a programme to screen for VZV susceptibility only. Finally, a study reporting good agreement of results between standard FAMA and a flow cytometry-adapted FAMA, was excluded, as the flow cytometry-adapted FAMA is not commercially available. [31]

FAMA is an accepted gold standard for determining VZV IgG levels, however it is not suitable for widespread use in diagnostic laboratories because it is not suited to automation, requires specialist equipment and, as a semi-quantitative method, requires skilled interpretation. TRFIA is another highly sensitive method which is quantitative and has been calibrated with British Standard VZV antibody (an in vitro diagnostic prepared by the National Institute for Biological Standards and Control), allowing results to be expressed in mIU/ml and facilitating comparisons with other assays [32], but also requires specialist equipment. ELISAs are the most widely used assays and three studies published since the last review provide data on the accuracy of commercially available ELISAs evaluated against FAMA or TRFIA (details given in the Table 2, below, [33-35]).

The VaccZyme™ EIA demonstrated high sensitivity and specificity against the TRFIA in the only study using samples from pregnant women [35], particularly when results falling into the equivocal range (100-150 mIU/ml) were categorised as positive, in-line with the cut-off validated against the clinical outcome of incident cases in the study by Boxall et al, previously described [23]. In a study by Sauerbrei et al, the specificity of two assays tested on a heterogeneous group of sera ('Group 1', see Table) was 100% despite the use of lower cut-offs of <50 mIU/ml or <80 mIU/ml to indicate negative results. [33] The PPV or NPV of these tests would not be generalizable to a potential antenatal screening programme in the UK because, with the exception of the study by Maple et al [35], the populations included were not representative of the target population with regards VZV seroprevalence or vaccination history.

Sub-group analysis in the studies included in this review demonstrated that ELISA tests which have adequate sensitivity among individuals with history of natural infection may be insufficiently sensitive to reliably detect vaccine-induced immunity. For example, sensitivity of the VaccZyme™ EIA among vaccinated healthcare workers was 69.1%-71.6% at 6 weeks after the first vaccine and 80.4%-87.0% at 6 weeks after the second vaccine dose, compared with 97.8%-99% among unvaccinated pregnant women (Table 2) [35]. Another study using sera from vaccinated children found that the same EIA test had a sensitivity of only 31.4% (Table) [34] – sensitivity and specificity values of 88.9% and 95.1% were obtained using the lower cut-offs of FAMA <1:16 and EIA <49.7mIU/ml. Finally, in a study of 67 samples from vaccinated healthcare workers which were found to be negative or equivocal by ELISA assays, 47 (70%) were positive by the more sensitive VZV FAMA assay [36]. The large majority of pregnant women with VZV antibodies in the UK will have a history of natural infection, but it is important to note that an assay validated in this population may have low sensitivity among sub-groups, including migrants from countries with universal vaccination programmes.

Table 2 – characteristics of commercially available EIA / ELISA assays to test for VZV IgG

Author	Name of assay	Type of assay	Reference assay	Noted cut-offs	Population from which serum samples taken	Sensitivity	Specificity
Maple et al [35] (2012)	VaccZyme™ EIA	EIA	TRFIA	<100 mIU/ml considered negative, 100-150 mIU/ml equivocal, ≥150 mIU/ml positive (immune)	248 pregnant women (unvaccinated); 185 VZV IgG positive, 57 negative and 6 equivocal by TRFIA	100-150 mIU/ml treated as positive: 99% (95% CI 96.3, 99.9) 100-150 mIU/ml treated as negative: 97.8% (95%CI 94.6, 99.4)	100-150 mIU/ml treated as positive: 98.2% (95% CI 60.6, 100) 100-150 mIU/ml treated as negative: 96.8% (95% CI 89.0, 99.6)
Kim et al [34] (2014)	VaccZyme™ EIA	EIA	FAMA	<100 mIU/ml considered negative for EIA [†] , <1:4 for FAMA	305 vaccinated children (349 sera), 44 residual sera from 5-12 month olds without vaccination or chickenpox history	31.4%	100%
Sauerbrei et al [33] (2012)	Enzygnost anti-VZV/IgG	ELISA	FAMA	<50 mIU/ml considered negative	Group 1: 109 sera from VZV-seronegative children (by FAMA), 420 sera from blood donors (419 VZV-seropositive by FAMA), 57 sera from varicella vaccines, 52 sera showing seroconversions from 21 bone marrow transplant recipients. Group 2: 146 sera which were negative or borderline for VZV IgG by Enzygnost test	Group 1: 99.6% Group 2: 83.9%	Group 1: 100% Group 2: 86.7%
	Anti-VZV-ELISA (IgG) (Euroimmun)	ELISA		<80 mIU/ml considered negative, 80-<110 mIU/ml equivocal, ≥110 mIU/ml positive [†]		Group 1: 90.5% Group 2: 3.6%	Group 1: 100% Group 2: 100%
	Serion ELISA Classic VZV IgG	ELISA		<50 mIU/ml considered negative, 50-100mIU/ml equivocal, >100 mIU/ml positive [†]		Group 1: 99.2% Group 2: 89.3%	Group 1: 89.4% Group 2: 75.6%

[†]Equivocal and positive results both treated as positive for purposes of calculating sensitivity and specificity

Updates since 2009 evidence review

Limited new data on the predictive value of history of chickenpox to determine VZV susceptibility suggest that the current strategy (antibody testing for exposed women with no or an uncertain history of chickenpox, and possibly also of those born in tropical and subtropical regions [3,4]) continues to be appropriate.

While an oral history taking appears to be accurate in women who believe they have had an infection, the reliability of the response is significantly lower in women who are uncertain or believe that they have not had an infection before.

The accuracy of immunological screening tests appears to be higher than an oral history; however the amount of evidence undertaken in a potential UK screening cohort was limited. New published evidence that a VZV IgG level >100mIU/ml as measured by TRFIA or ELFA confers protection against subsequent chickenpox infection in pregnant women [23] is helpful in interpreting data from studies evaluating the sensitivity and specificity of other assays. Of the three studies published since the last review which evaluated ELISAs against FAMA or TRFIA, only one included unvaccinated pregnant women within the study population; in this sub-group, high sensitivity and specificity of the EIA was shown when values >100mIU/ml were considered to be positive.

The key conclusion from the evidence published since the last review is that, despite advances since the last review, there remains a significant degree of uncertainty about the correct cut-offs that can be used with an immunological screening test. Although >100mIU/ml appears to be a promising cut-off, the quantity of evidence does not support its widespread use. Furthermore, the cut-off indicating susceptibility may vary by vaccination history, ethnicity and age. The previous review highlighted the requirement for a validated standardisation of tests; the update search identified no evidence to suggest that this requirement has been met.

Conclusion: criteria not met

Criteria 10:

There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment

Introduction

Vaccination of women found to be susceptible to VZV is not an option during pregnancy as the varicella (vOka) vaccine is a live vaccine. Therefore, post-exposure prophylaxis with Varicella Zoster Immunoglobulin (VZIG) is the only intervention available for susceptible and exposed pregnant women.

This section addresses key questions about the effectiveness of VZIG for prevention or reduction of maternal symptoms, reduction of transmission risk to the fetus, and reduction of fetal infection severity, with a primary focus on whether there is a beneficial effect of VZIG for the fetus beyond prevention of infection in the mother.

With regards the timing of prophylaxis, VZIG is effective if given up to 10 days after exposure and current guidelines recommend that women with no or uncertain history of chickenpox should be tested for VZV IgG to establish susceptibility before VZIG is given. Serological testing is expected to be available within 24-48 hours (using a stored antenatal booking blood sample if available); for women presenting towards the end of the 10-day window following exposure, VZIG can be ordered at the same time as the serological test to expedite administration of VZIG if found to be seronegative [3-5]. To meet the second part of this screening programme criteria (that early treatment leads to better outcomes than late treatment), evidence is needed that prior determination of VZV susceptibility through an antenatal screening programme would result in better outcomes (via earlier administration of VZIG) than is possible when testing for susceptibility takes place only after a woman presents with an exposure, as is currently the case. A susceptible screening test result could also provide an opportunity for counselling on the importance of avoiding exposure to chickenpox during pregnancy, and what to do if this occurs; however, educational messages about exposure to rash-like illnesses in pregnancy are relevant for other infections, and therefore important for all women.

Key conclusion(s) from 2009 evidence report

The last review found that, although around 50% of susceptible pregnant women given VZIG still go on to develop chickenpox, VZIG is effective in attenuating maternal disease and also attenuates disease in neonates when given to exposed infants after delivery. Data on fetal outcomes were scarce; one study from 1994 reported that VZIG administered to pregnant women reduced maternal-fetal transmission of chickenpox from 12.3% to 1.1%, however there were no large or recent studies reporting outcomes of pregnant women given VZIG and their infants and no systematic follow-up of this group in the UK.

Evidence summary

No original research studies providing evidence on the effectiveness of VZIG for preventing or attenuating disease in the mother, fetus or neonate have been published since the last review.

Studies investigating the effectiveness of VZIG for maternal and fetal health would be problematic to conduct for several reasons. The existing evidence of the benefit of VZIG for susceptible pregnant women exposed to VZV means that studies in which VZIG is withheld from this group are unlikely to be ethical. Observational data may be available, for example through follow-up of women who present following exposure to chickenpox during pregnancy (as in the retrospective study by Boxall et al [23]); however, the use of these data to investigate the effectiveness of VZIG will be problematic due to

confounding by treatment indication, and data will be missing on susceptible women who do not receive VZIG, because many will not have presented for care following exposure.

Prenatal diagnosis of fetal varicella infection presents diagnostic challenges and therefore also challenges for determining the impact of VZIG on reducing fetal risk. Amniocentesis can be conducted to determine whether VZV DNA is present in amniotic fluid, but most infants infected with VZV in-utero will be healthy although may present with herpes zoster in the first years of life [37]. When maternal infection occurs in the first or second trimesters, VZV is transmitted to the fetus in around 25% of cases [1] but even in this high-risk sub-group, the proportion of babies affected by FVS is small. Evidence from a review of nine cohort studies included in the last review indicated an overall FVS incidence rate among women with chickenpox of 0.55% in the first trimester and 1.4% in the second trimester [38]. In the last review it was estimated that two cases of FVS occur in England and Wales annually, while the HPA Guidance on Rash in Pregnancy guidelines estimate that around 10 babies may be born with congenital damage from VZV each year [5]. Studies which are sufficiently powered to draw conclusions about the effectiveness of maternal VZIG for preventing FVS would be therefore very difficult to conduct, due to the rarity of the outcome.

There are no data available on the proportion of women who present on the 9th or 10th day following exposure to chickenpox, for whom there may be insufficient time to request serological testing before VZIG administration within the 10 day window, and for whom prior determination of VZV susceptibility through an antenatal screening programme could guide treatment response.

Updates since 2009 evidence review

There are no new data which alter the conclusions of the last review that VZIG has benefits for susceptible pregnant women exposed to VZV and can be given within 10 days of exposure. Although evidence of the effectiveness of VZIG in protecting the fetus is scarce, sufficiently powered studies would be very difficult to conduct due to the rarity of FVS. The opportunity to provide VZIG depends on a pregnant women presenting for care promptly following an exposure to chickenpox, regardless of whether or not her susceptibility to VZV is already known. As the evidence to date suggests that VZIG is beneficial when administered up to 10 days after exposure and serological testing should be available within 24-48 hours, the women for whom prior determination of VZV susceptibility could make a difference to the decision to provide VZIG are those presenting on the 9th or 10th day after exposure; however, there are no data on the proportion of susceptible, exposed pregnant women who fall into this group, for whom empirical VZIG could be an option. The potential benefits of an antenatal screening programme for VZV susceptibility are therefore unclear. Counselling of pregnant women on the importance of seeking prompt medical attention following contact with a rash-like illness during pregnancy is essential for timely administration of VZIG, and VZV susceptibility testing could present an opportunity for this; however, such guidance is also essential for timely interventions following exposure to other infectious diseases including parvovirus B19 and measles.[5]

Conclusion: criteria not met

VZIG is an effective intervention for susceptible pregnant women exposed to VZV, however evidence is lacking that an antenatal screening programme to determine maternal VZV susceptibility would result in its more effective use or better outcomes.

Summary

- Around 95% of UK-born pregnant women are already immune to chickenpox but this proportion is lower (<90%) among some migrant groups, particularly women born in and recently migrating from tropical and subtropical regions.
- Data on the proportion of pregnant women exposed to VZV during pregnancy are scarce. The use of VZIG issues as a proxy is subject to several limitations, and therefore the number of women who may be exposed to VZV during pregnancy is unclear.
- Limited new data on the predictive value of history of chickenpox in determining VZV susceptibility suggest that the current strategy (antibody testing for exposed women with no or an uncertain history of chickenpox, and possibly also of those born in tropical and subtropical regions) continues to be appropriate.
- There is some evidence that a VZV IgG level >100mIU/ml as measured by TRFIA or ELFA confers protection against subsequent chickenpox infection in pregnant women; published data suggest that EIA can have high sensitivity and specificity in pregnant women when this cut-off is used. Criteria for minimum sensitivity and specificity of assays used to determine VZV susceptibility in pregnant women are needed.
- No new data have been published since the last review on the effectiveness of VZIG in preventing or reducing the severity of maternal, fetal or neonatal symptoms when used as post-exposure prophylaxis. Benefits of VZIG in preventing FVS will be very difficult to ascertain in any future studies due to the rarity of this outcome. However, conclusions on the benefits of VZIG in attenuating maternal and neonatal disease remain unchanged.
- As VZIG can be given within 10 days of exposure to chickenpox and as serological testing is expected to be available within 24-48 hours for women presenting following an exposure, the benefits of an antenatal screening programme to determine VZV susceptibility at an earlier time point in the pregnancy are unclear.
- Guidance for pregnant women on the importance of seeking prompt medical attention following contact with a rash-like illness during pregnancy is essential, since post-exposure prophylaxis is the only intervention available for women found to be susceptible to VZV during pregnancy.

Recommendation

It is recommended that the current policy not to screen all pregnant women for VZV susceptibility is retained.

Further research is needed on the timing of presentation to medical care following exposure to chickenpox (or other rash-like illnesses) during pregnancy and on circumstances around missed opportunities for VZIG administration within ten days of exposure, to inform estimates of VZV exposure among pregnant women and efforts to optimise post-exposure prophylaxis where exposure occurs.

Appendix 1

NSC Antenatal Varicella Susceptibility Screening review Search record form 31 October 2014

Search/sifting results

Databases and sites searched	Dates searched	Number of hits
MEDLINE	2009-17/10/2014	4391
EMBASE	2009-17/10/2014	1030
Cochrane Database Syst Rev	2009-21/10/2014	8
Cochrane CENTRAL	2009-21/10/2014	142
CRD - DARE	2009-21/10/2014	7
CRD - HTA	2009-21/10/2014	3
Cochrane - NHS EED	2009-21/10/2014	19
Total number of hits		5600
Total number after de-duplication		5020
Total number after first appraisal		152

Search strategies

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>

- 1 Chickenpox/ (6741)
- 2 exp Herpes Zoster/ (10044)
- 3 Herpesvirus 3, Human/ (5574)
- 4 (chickenpox or "chicken pox").ti,ab. (2568)
- 5 (varicella or VZV or herpesvirus or "Herpes zoster Virus" or HHV-3).ti,ab. (29986)
- 6 exp Chickenpox Vaccine/ (2047)
- 7 (((Oka or varicella) adj3 vaccin*) or varivax).ti,ab. (2000)
- 8 "varicella zoster immune globulin".ti,ab. (71)
- 9 Varicella Zoster Immunoglobulin.ti,ab. (83)
- 10 (varicellon or VZIG or variZIG).ti,ab. (59)
- 11 or/1-10 (39507)
- 12 exp pregnancy/ (734058)
- 13 exp fetus/ (140557)
- 14 (pregnan\$ or f?etal or fetus or FVS).ti,ab. (541903)
- 15 exp pregnancy complications/ (350427)
- 16 exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or infant, newborn, diseases/ (991735)

17 perinatal care/ or postnatal care/ or preconception care/ or prenatal care/ (27523)
 18 (prenatal or antenatal or perinatal or postnatal or post-partum).ti,ab. (210026)
 19 (infant* or newborn* or neonat*).ti,ab. (531451)
 20 or/12-19 (2141882)
 21 11 and 20 (3487)
 22 limit 21 to (english language and yr="2009 -Current") (494)
 23 Epidemiology/ (11790)
 24 Incidence/ (184509)
 25 exp Mortality/ (291971)
 26 Population Surveillance/ (47679)
 27 exp disease progression/ (126189)
 28 (ep or tm or di or mi or mo or pc or sn).fs. (4863618)
 29 (incidence or prevalence or seroprevalence or epidemiolog* or mortality or prevention or transmission or surveillance or "natural history").ti,ab. (2063775)
 30 or/23-29 (5915088)
 31 11 and 30 (17808)
 32 limit 31 to (english language and yr="2009 -Current") (3683)
 33 exp "Sensitivity and Specificity"/ (440249)
 34 sensitivity.tw. (565616)
 35 specificity.tw. (342215)
 36 ((pre-test or pretest) adj probability).tw. (1401)
 37 post-test probability.tw. (380)
 38 predictive value\$.tw. (72548)
 39 likelihood ratio\$.tw. (9787)
 40 33 or 34 or 35 or 36 or 37 or 38 or 39 (1092032)
 41 (test or tests or testing or screen*).ti,ab. (1982525)
 42 exp Serologic Tests/ (168779)
 43 ("Fluorescent antibody to membrane antibody" or "Latex agglutination" or "Enzyme linked immunoassorbent assay" or ELISA or "Time-resolved fluorescence immunoassay").ti,ab. (120898)
 44 41 or 42 or 43 (2192008)
 45 11 and 40 (1850)
 46 11 and 44 (5224)
 47 45 or 46 (6383)
 48 limit 47 to (english language and yr="2009 -Current") (1306)
 49 22 or 32 or 48 (4391)

Database: Embase <1996 to 2014 October 16>

1 chickenpox/ (6454)
 2 exp herpes zoster/ (12261)
 3 Herpes virus/ (6520)
 4 (chickenpox or "chicken pox").ti,ab. (1894)
 5 (varicella or VZV or herpesvirus or "Herpes zoster Virus" or HHV-3).ti,ab. (22089)
 6 chickenpox vaccine/ (3348)
 7 (((Oka or varicella) adj3 vaccin*) or varivax).ti,ab. (1921)
 8 "varicella zoster immune globulin".ti,ab. (30)
 9 Varicella Zoster Immunoglobulin.ti,ab. (41)
 10 (varicellon or VZIG or variZIG).ti,ab. (48)
 11 or/1-10 (37397)

12 exp pregnancy/ (267917)
 13 fetus/ (68091)
 14 (pregnan\$ or f?etal or fetus or FVS).ti,ab. (386096)
 15 exp pregnancy complication/ (60550)
 16 exp newborn disease/ (576040)
 17 exp perinatal care/ (34288)
 18 exp postnatal care/ (60910)
 19 maternal care/ (11201)
 20 exp prenatal care/ (73818)
 21 (prenatal or antenatal or perinatal or postnatal or post-partum).ti,ab. (168810)
 22 (infant* or newborn* or neonat*).ti,ab. (359365)
 23 or/12-22 (1225405)
 24 11 and 23 (3344)
 25 limit 24 to (english language and yr="2009 -Current") (1275)
 26 epidemiology/ (65599)
 27 incidence/ (193406)
 28 exp mortality/ (543764)
 29 exp disease course/ (1762782)
 30 (di or ep or pc).fs. (2788820)
 31 (incidence or prevalence or seroprevalence or epidemiolog* or mortality or prevention or transmission or surveillance or "natural history").ti,ab. (1945748)
 32 or/26-31 (5153827)
 33 11 and 32 (21351)
 34 limit 33 to (english language and yr="2009 -Current") (8377)
 35 exp "SENSITIVITY AND SPECIFICITY"/ (201142)
 36 sensitivity.tw. (496958)
 37 specificity.tw. (290948)
 38 ((pre-test or pretest) adj probability).tw. (1959)
 39 post-test probability.tw. (448)
 40 predictive value\$.tw. (80821)
 41 likelihood ratio\$.tw. (10788)
 42 *Diagnostic Accuracy/ (3831)
 43 or/35-42 (768630)
 44 (test or tests or testing or screen*).ti,ab. (1892473)
 45 exp serology/ (99266)
 46 ("Fluorescent antibody to membrane antibody" or "Latex agglutination" or "Enzyme linked immunoassorbent assay" or ELISA or "Time-resolved fluorescence immunoassay").ti,ab. (139283)
 47 44 or 45 or 46 (2050172)
 48 11 and 43 (1562)
 49 11 and 47 (5759)
 50 48 or 49 (6660)
 51 limit 50 to (english language and yr="2009 -Current") (3014)
 52 25 or 34 or 51 (9893)
 53 limit 52 to exclude medline journals (1030)

Cochrane Library: CDSR, CENTRAL, DARE, HTA, NHS EED

ID	Search	Hits
#1	MeSH descriptor: [Chickenpox] this term only	136
#2	MeSH descriptor: [Herpes Zoster] explode all trees	359

#3	MeSH descriptor: [Herpesvirus 3, Human] this term only	126	
#4	(chickenpox or "chicken pox"):ti,ab	57	
#5	(varicella or VZV or herpesvirus or "Herpes zoster Virus" or HHV-3):ti,ab		464
#6	MeSH descriptor: [Chickenpox Vaccine] explode all trees	165	
#7	((Oka or varicella) near/3 vaccin*) or varivax):ti,ab	172	
#8	"varicella zoster immune globulin":ti,ab	4	
#9	"Varicella Zoster Immunoglobulin":ti,ab	0	
#10	(varicellon or VZIG or variZIG):ti,ab	4	
#11	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 Publication Year from 2009 to 2014		179

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