Antenatal Screening for Susceptibility to Varicella Zoster Virus (VZV) in the United Kingdom

A REVIEW COMMISSIONED BY THE NATIONAL SCREENING COMMITTEE

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Evaluation of antenatal screening for Susceptibility to Varicella Zoster Virus infection (VZV) against NSC Criteria

EXECUTIVE SUMMARY

1. ***Approximately 90% of pregnant women in the UK are immune to chicken pox (caused by the Varicella Zoster Virus) so infection during pregnancy is relatively uncommon. However, when it does occur it can result in rare but potentially serious consequences for both the mother and her fetus. Women born and living in tropical climates are more susceptible to chicken pox during adult life than those born in the UK. The risk of acquiring chicken pox during pregnancy is therefore higher amongst women migrating to the UK from these countries in adult life.***

2. ***We estimate that 12-24% of the antenatal population in England and Wales are exposed to chicken pox each year. However, a paucity of high quality data means that estimates are uncertain and not available for the whole of the UK. Based on 2006/07 figures for issuing Varicella Zoster Immunoglobulin (VZIG) to susceptible pregnant contacts, we estimate that approximately 1318 women per year are exposed and assumed to be susceptible to chicken pox in England and Wales.[1]***

3. ***The true incidence of chicken pox in pregnancy is not known but we estimate that 362 - 435 women develop clinical chicken pox during pregnancy each year in England and Wales.***

4. ***Although complications for the mother such as pneumonia occur at a similar frequency in both the pregnant and non-pregnant women, disease severity is increased in pregnancy. An estimated 36-61 pregnant women with chickenpox each year in England and Wales develop pneumonia. The last published maternal death from chicken pox in the UK was recorded in 2002.***

5. ***Maternal infection can have serious consequences for the fetus. In early pregnancy, it can lead to the rare but devastating complication of fetal varicella syndrome (FVS), the highest risk (2%) occurring in women infected between 13-20 weeks. Exposure to chicken pox late in pregnancy***

(1 week either side of delivery) can result in life threatening disseminated neonatal varicella infection. We estimate that 2 cases of FVS and 6-7 severe neonatal cases occur in England and Wales each year. There is little evidence to suggest that pregnancies complicated by chicken pox are more likely to result in spontaneous abortion, stillbirth or prematurity.

6. ***Universal childhood vaccination against chicken pox has not been introduced in the UK due to concerns that this could result in an increased age of acquisition of infection (when disease is more severe), a rise in cases of shingles in later life (and its attendant morbidity) and a lack of evidence to support its cost effectiveness. Current UK vaccination policy - targeted vaccination to high risk groups - is currently under review by the Joint Committee on Vaccination and Immunisation (JCVI), in light of the lessons learnt from the introduction of a universal two dose vaccine schedule for children in the USA.***

7. ***The JCVI has asked the National Screening Committee to evaluate the role antenatal screening might play in the control of VZV infection in the UK. There are two objectives for identifying VZV susceptible women through antenatal screening:***

Primary Objective

- ***To prevent serious maternal, fetal and newborn complications due to VZV infection in future pregnancies by offering post partum vaccination to women identified as susceptible through screening in the current pregnancy***

Secondary Objective

- ***To optimise management following exposure to VZV infection in the current pregnancy***

8. ***Two screening methods are considered in this review, namely a history of chicken pox and serological assays to test for VZV IgG antibodies. The positive predictive value of a history of chicken pox is between 95-99% amongst pregnant women[2-6] although the reliability of history has been shown to be lower in ethnic minority populations.[7] A negative or uncertain history is less reliable (negative predictive value 6.8-35%) in determining susceptibility.[2-6]***

9. ***A number of commercially available serological assays are in use across the UK. Commercially available ELISAs are a practical and reliable screening method. However, recent studies[8,9] highlight the variability in test characteristics of commercially available assays (sensitivity ranging from 68.5%-98.4%).***

10. ***UK guidance[10] recommends the timely use (within 10 days of exposure) of VZIG for susceptible pregnant women exposed to chicken pox, the rationale being to reduce the severity of maternal disease and reduce the risk of fetal infection. Prior knowledge of the immune status of pregnant women in contact with chickenpox would enable VZIG to be given without delay. VZIG does not prevent but attenuates maternal infection thereby reducing severity of maternal disease and materno-fetal transmission from 12.3% in infants of unprotected women to 1.1% in those given post exposure VZIG.[11] However, VZIG is expensive costing £1120 for each adult course of treatment.***

11. ***Post partum vaccination of susceptible women is effective in preventing subsequent chicken pox. Successful implementation of a two dose vaccination policy would require clear guidelines on the roles and responsibilities of health professionals in both hospital and community settings.***

12. ***There has only been one UK study to investigate the cost effectiveness of introducing an antenatal screening programme to identify susceptible women who can be offered post partum vaccination.[12] It concluded that it was cost effective to screen UK born women by serological testing of those reporting a negative or uncertain history of chicken pox. However, a further analysis using population data from pregnant Bangladeshi born women residing in Tower Hamlets suggested that serological testing of <u>all</u> these women would be cost effective given their increased susceptibility as well as the reduced reliability of verbal screening. This would suggest a more complex screening pathway according to maternal country of birth. The generalisability of this study is limited, as is the feasibility and reliability of ascertaining such high risk groups within the UK antenatal population.***

13. ***This review has highlighted a number of key areas where there is a paucity of information. These include: data on the number of women booking for antenatal care in the UK, their risk of exposure and infection during pregnancy; the cost effectiveness of introducing antenatal screening in the UK; the feasibility of implementing a 2 dose post partum vaccination policy, pivotal to its success.***

14. ***The risk of maternal VZV infection is heterogeneously distributed amongst the UK antenatal population. We suggest that the adverse effects associated with infection during pregnancy are low. Countries such as the USA have introduced an antenatal screening programme offering post partum vaccination to women identified as susceptible to chicken pox. However, this has been done as part of an overall policy to control VZV infection, which is predominantly centred on universal childhood vaccination. Such primary prevention interventions are essential to the success of any control policy; other strategies such as screening newly arrived immigrants have been shown to be cost effective outside the UK.[13] In conclusion, we suggest that efforts to maximise effective primary prevention interventions and explore alternative screening strategies should be undertaken in the UK given the low levels of adverse effects associated with infection during pregnancy.***

INTRODUCTION

This report has been commissioned by the National Screening Committee [NSC] to inform a review of strategies to prevent Varicella Zoster Virus (VZV) infection in pregnancy and its consequences. The key objectives for identifying VZV susceptible women through antenatal screening are:

Primary Objective

- To prevent serious maternal, fetal and newborn complications due to VZV infection in future pregnancies by offering post partum vaccination to women identified as susceptible through screening in the current pregnancy

Secondary Objective

- To optimise management following exposure to VZV infection in the current pregnancy

We have structured the report using the current NSC criteria for a screening programme[14] based on a review of relevant literature (See Appendix for search strategy).

THE CONDITION

1. ***The condition should be an important health problem***

- ***90% pregnant women in the UK are immune to chicken pox so infection during pregnancy is relatively uncommon. However, infection during pregnancy can have rare but potentially serious consequences for both the mother and her fetus.***

Chickenpox is an acute infectious disease caused by the varicella-zoster virus (VZV). In the UK chickenpox mostly occurs in children less than 10 years of age, causing a mild infection. A more serious infection is seen in adults and those who are immunosuppressed. Although only 14% of cases in the UK occur in adults of child-bearing age (15-44yrs)[15], this group comprises 35% of all chicken pox deaths with a case fatality of 9 per 100 000 cases[15].

Contact with chickenpox in pregnancy is relatively common, particularly among women with small children. However, as 90% of pregnant women in the UK and

Ireland have serological evidence of previous infection, chicken pox is relatively uncommon in pregnant women. [16-18]

i. Exposure during pregnancy

- ***We estimate that 12-24% of the antenatal population in England and Wales are exposed to chicken pox each year. However, a paucity of high quality data means that estimates are uncertain and not available for the whole of the UK.***

Current UK guidelines recommend the administration of Varicella Zoster Immunoglobulin (VZIG) to susceptible pregnant women exposed to chicken pox within 10 days of exposure.[10] Using data on supplies of VZIG issued for pregnant women exposed to chicken pox, exposure during pregnancy can be estimated.

Data from the Health Protection Agency (HPA) for supplies of VZIG issued to pregnant contacts as post exposure prophylaxis in England and Wales[1] reveal that 1318 women were issued VZIG during the financial year 2006/07. If this figure represents the 5-33%[1][19] of pregnant contacts who report no history of chicken pox and are susceptible to chicken pox, an estimated 3994-26360 pregnant contacts give no history of chickenpox and require testing each year. The wide range of values highlights the degree of uncertainty in these estimates.

Studies outside the UK suggest that between 16-27% of pregnant women report a negative or uncertain history of chicken pox[2,3]. Data from pre-employment screening of health care workers in Northern Ireland [20] identified 30% of the adult population with no history of chicken pox. However, there have been no equivalent studies conducted on UK antenatal populations. Assuming a 90% sensitivity and 50% specificity of verbal screening[12] and a seroprevalence amongst the UK antenatal population of 88.7%[21], an estimated 15%[2] pregnant women in the UK would give a negative or uncertain history of chicken pox.

If it is assumed that the 26 360 women (using upper end of range of estimated values to measure maximum exposure) represent between 15- 30% of the total exposed

[1] Unpublished data provided by Dr. Elizabeth Boxall (HPA Birmingham Heartlands): Audit of 119 pregnant contacts with negative / uncertain history of chicken pox; 39 (33%) women were susceptible.
[2] Probability of a negative or uncertain history can be estimated using Bayes theorem.

cohort, then between 87 867 – 175 733 pregnant women are likely to be in contact with chickenpox. In 2007 an estimated 724 626 women booked for antenatal care in England and Wales[3]. This provisional figure is based on the number of antenatal screening tests for rubella which may underestimate the number of women booking for antenatal care. (In 2007 there were 690 013 live births across England and Wales published by the Office of National Statistics.) Based on the provisional antenatal booking figures, between 12%- 24% of the antenatal population are likely to be exposed to chicken pox (Figure 1). This figure is likely to be an underestimate as it assumes all pregnant women exposed to chicken pox seek medical advice.

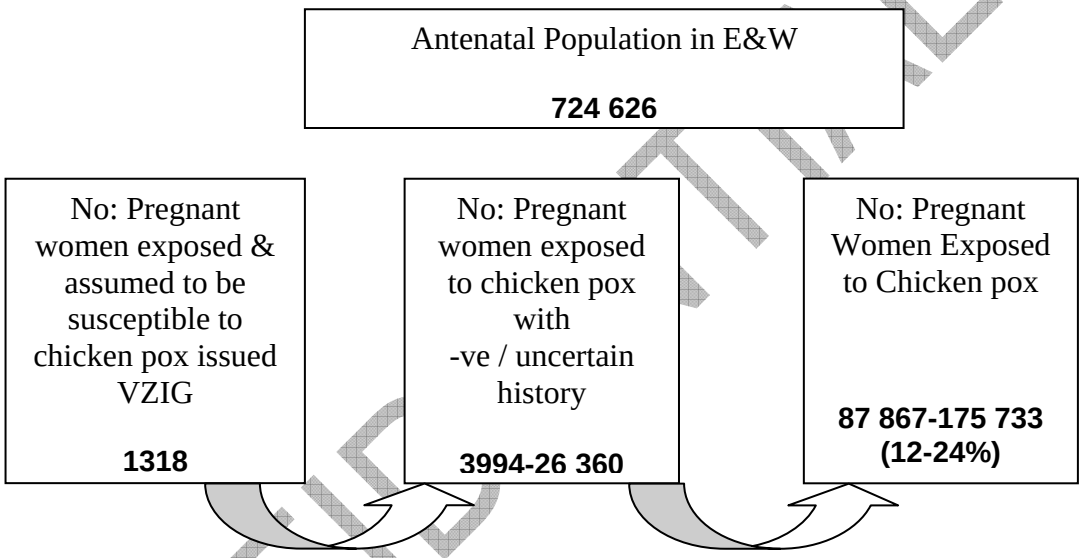

Figure 1: Estimated number of pregnant women exposed to chicken pox in England and Wales in 2007

ii. Infection during pregnancy

- ***The true incidence of chicken pox in pregnancy is not known but we estimate that between 362 and 435 women develop clinical chicken pox during pregnancy each year in England and Wales. A paucity of high quality data means that estimates are subject to wide variation.***

The true incidence of chicken pox in pregnancy is not known. Based on the proportion of women of child bearing age who are susceptible to chicken pox and

Probability of positive history = [p(pos|immune)*p(immune)] + [p(pos|not immune)*p(not immune

[3] Based on provisional data for number of antenatal screening tests for rubella in England (HPA Antenatal Infection Surveillance Scheme) and Wales (provided by Regional Antenatal Screening co-ordinator for Wales) in 2007. Equivalent data for Scotland and Northern Ireland was not available.

their risk of exposure during pregnancy, Miller *et. al.* estimated that 20-30 per 10 000 women acquire chicken pox during pregnancy in England and Wales each year.[22,23] This would equate to between 1450 and 2174 infected pregnant women in England and Wales each year.

However, more recent UK studies have suggested considerably lower estimates. For example in a Scottish study,[24] the incidence of chicken pox in pregnancy was estimated at 1 in 2000 (5 per 10 000) deliveries using information from questionnaires sent to all hospital based obstetricians. This may have underestimated the true incidence as all milder cases may not necessarily attend hospital. In Scotland chicken pox has been a notifiable disease since 1989, unlike the rest of the UK. However active surveillance of chicken pox infection acquired during pregnancy is not undertaken.

In a retrospective review (1997-2002) 19 pregnant women were admitted to a Sheffield maternity department with chicken pox (6 per 10 000 deliveries), although it is not clear how many of these women received VZIG following exposure.[16] Approximately a quarter (26%) of women were in their first pregnancy and antenatal screening with post partum vaccination would not have prevented these infections.

The influence of parity on estimating risk of infection in the UK has been investigated. Overall fertility amongst women in the UK has been increasing (total fertility rate 1.90 in 2007), mostly attributable to rising fertility rates amongst UK born women (TFR 1.79 in 2007). Although fertility rates are higher amongst non-UK born women (TFR 2.54 in 2007), they have remained relatively stable (ONS 2007). In one study of an antenatal population in the London Borough of Tower Hamlets, parity did not appear to influence the rate of susceptibility to VZV infection. The overall proportion immune was 86.8% amongst primiparous women and 88.4% amongst multiparous women (OR 1.16 [95% CI; 0.79, 1.71]) and amongst a sub-population of Bangladeshi born women, 81.0% of primiparous women and 86.1% of multiparous women were immune (OR 1.45 [95% CI; 0.94, 2.24]).[25]

Based on figures from these more recent studies[16,24], we estimate that between 362 -435 pregnant women in England and Wales are infected with chicken pox each year, which is consistent with the number of women exposed, assumed to be susceptible and issued VZIG each year (Figure 1). Data from the HPA suggest that

between 211-273 neonates in England and Wales were issued with VZIG as post-exposure prophylaxis. (Table 4) Issuing is likely to be a result of either maternal exposure 7 days before or after delivery or post-natal exposure from other contacts such as siblings or visitors at the Special Care Baby Unit.

The risk of acquiring chicken pox during pregnancy appears to be highest amongst women with young children. The force of infection (a measure of the incidence of infection in a susceptible population) for parous women in the UK has been reported at 0.15 per year for adults living with children in the household double that for non-parous women. [26]

iii. Consequences of VZV infection acquired in pregnancy

a. for mothers

- ***Although complications for the mother such as pneumonia occur at a similar frequency in both the pregnant and non-pregnant adult women, disease severity is increased in pregnancy. It is estimated that each year between 36-61 pregnant women infected with chicken pox in England and Wales develop pneumonia. The last published maternal death from chicken pox was recorded in 2002.***

Although chicken pox is much less common in adults than in children, it is associated with significant morbidity, namely pneumonia, hepatitis and encephalitis. Chickenpox is thought to be more severe during pregnancy due to an increased morbidity from varicella pneumonia due to both immunological and mechanical factors.

Pneumonia occurs in about 10-14% of pregnant women with chickenpox[27-31] the severity increased in later gestation.[32,33] This equates to between 36-61 pregnant women infected with chicken pox developing pneumonia in England and Wales each year.

Although pneumonia occurs in the pregnant population with the same frequency as in the general population, its course is often more virulent. The associated mortality and morbidity of pneumonia in pregnancy is up to 45%, particularly in the third trimester, compared with 10-20% in non-pregnant adults.[24,32-34] This leads to a higher incidence of hospitalisation and increased requirement for mechanical ventilation.[27,35] Pregnant women with chicken pox are more likely to develop pneumonia if they smoke or have at least 100 skin vesicles.[27]

In a UK retrospective review[24] of 164 000 pregnancies occurring during a 2 year period, there were seven (7%) cases of severe maternal illness reported amongst 98 patients with chicken pox in pregnancy including two maternal deaths(2%).

Of 19 pregnant women (26% in their first pregnancy) admitted to a hospital in Sheffield with chicken pox during a 5 year period (mean duration of stay 3 days), 3 (16%) had pneumonia (compared with 12 (25%) of 49 women who were not pregnant).[16] However, these results should be interpreted with caution as the higher rate in non pregnant women may reflect admission policies and not the risk of pneumonia per se.

In a US retrospective review[36] varicella pneumonia affected a similar proportion of pregnant and non-pregnant women (3.6% of 28 pregnant women [95% CI: 0.1%,18.3%] compared with 11.8% of 102 non-pregnant adults [95% CI: 5.5%, 18.0%]). In the largest study[28] to date 4 out of 43 pregnant women with chicken pox developed pneumonia (9.3%, 95% CI 2.6%, 22.1%), a figure comparable to that in non-pregnant adults.

No cases of pneumonia or death were recorded between 1980 and 1993 amongst 1373 pregnant women with chicken pox in the UK and Germany.[11]

Assuming an incidence of chicken pox of 20 per 10 000 pregnancies (not accounting for impact of VZIG),[37] the estimated case fatality in pregnancy is 1 per 2000[22] equivalent to one death per year in England and Wales. Based on ONS death certification data this appears to be five times higher in pregnant than in non-pregnant women.[22]

Maternal mortality due to chicken pox appears to have declined over time. From 1985 to 2002, ten deaths associated with VZV in pregnancy were reported to the UK Confidential Inquiry into Maternal Deaths, all occurring in the second half of pregnancy, equivalent to an average mortality rate of 1 per million pregnancies.[22] No deaths have been reported since then.

Whilst two maternal deaths were reported from three prospective studies[28,38,39] between 1966-1986, there were no maternal deaths in a more recent study (1980-1993) involving 1373 pregnant women infected with chicken pox.[11] This fall in

maternal mortality may be attributed to antiviral therapy and/or improved intensive care. In the pre-antiviral era between 11.4%-15%[40,41] of non-pregnant adults and 36%-41% of pregnant women with viral pneumonia died.[41,42] Following the widespread introduction of antiviral therapy, mortality among both pregnant and non-pregnant woman has declined to 13%-14%.[33,34,42]

b. for her fetus/infant

Chicken pox occurring in early pregnancy can lead to the rare but devastating complication of fetal varicella syndrome (FVS), the highest risk (2%) following fetal exposure to maternal chickenpox between 13-20 weeks gestation. Infants exposed to maternal infection (1 week either side of delivery) can develop disseminated neonatal varicella infection, which can be life threatening. We estimate that there are 2 cases of FVS and 6-7 children with severe neonatal infection in England and Wales each year. There is little evidence to suggest that pregnancies complicated by chicken pox are more likely to result in spontaneous abortion, stillbirth or prematurity.

When chicken pox occurs during pregnancy, the risk of adverse consequences for the fetus depends on the stage of pregnancy at which infection occurs.[37] Chicken pox during the first two trimesters of pregnancy may result in intrauterine infection in up to a quarter of cases.[43] There is little evidence to suggest that pregnancies complicated by chicken pox are more likely to result in spontaneous abortion, stillbirth or prematurity.[28,35,43] Fetal infection acquired in early pregnancy can result in the birth of an infant with clinical signs and symptoms, including skin lesions alone or in combination with the more severe form of fetal varicella syndrome (FVS). This is characterised by developmental delay, dermatomal skin scarring, eye defects and/or limb hypoplasia. The estimated risk of fetal damage following exposure to maternal infection acquired in the first 12 weeks of pregnancy is 0.4%, rising to 2% in those infected between weeks 13-20.[11]

Neonatal varicella can occur in infants born within 5 days of maternal illness. Perinatally acquired infection can result in disseminated neonatal varicella. The severity of neonatal chicken pox is related to the time of onset of maternal infection (transplacental antibodies may reduce severity) and the time of onset of neonatal illness. A fatal outcome is more likely if the neonatal disease occurs between 5 and 10 days after delivery. Those infected late in pregnancy may develop herpes zoster of infancy or early childhood (0.8 – 1.7% risk in first 2 years of life).

Modelling work[12] has suggested an overall incidence of 262 chicken pox cases per 100 000 parous women aged 15-44 years, with 10 of these occurring during pregnancy and resulting in 0.06 cases of fetal varicella syndrome and 0.16 cases of neonatal varicella. Assuming between 362 and 435 women in England and Wales are infected during pregnancy each year, this would equate to approximately 2 cases of FVS and between 6-7 infants with severe neonatal infection.

In the first UK prospective epidemiological study for varicella in childhood, the estimated incidence of cases of varicella requiring hospitalisation reported through the British Paediatric Surveillance Unit (BPSU) system in 2002-03 was 0.82 per 100 000 children per year. Of the 112 cases reported during the 13 month study period, 3 cases of neonatal varicella infection were reported, all of whom survived.[44]

2. i) The epidemiology of the condition should be known

- ***An estimated 90% of pregnant women in the UK are immune to chicken pox. However, the age of acquiring chicken pox has increased over time. Women born and living in tropical climates are more susceptible to chicken pox during adult life than those born in the UK. The risk of acquiring chicken pox during pregnancy is therefore higher among women migrating to the UK from these countries in adult life.***

In temperate climates, in the absence of vaccine, the lifetime risk of chicken pox is over 95%. Over 90% cases occur during the first 15 years of life and the burden of illness is predominantly borne by otherwise healthy children; in the UK, more than 60% of chickenpox transmission occurs in children less than 9 years old.

Estimating the incidence of chicken pox in England and Wales is limited as it is not a notifiable disease. Data on GP consultations available for England and Wales suggests an overall incidence of chicken pox of 1,290 cases per 100 000 person years between 1991 and 2000, with 435 cases per 100 000 person years for adults aged 15-44 years.[15] In Scotland, where notification data is available, the incidence of chicken pox has fallen from 3.6 per 1000 population in 2004 to 2.9 per 1000 population in 2006.[45]

There is some evidence to suggest that the age of acquisition of infection is increasing, especially among women aged 15-44 years in the UK.[46] In a recent seroprevalence study in England and Wales (2004), 30% of children showed

evidence of infection by 3 years, rising to around 85% in those aged 15-20 years with no significant differences between sexes or regions across the UK. Between 1966 and 1992, VZV seroprevalence amongst UK adults aged 20-29 years fell from 98% in 1970 to 92% in 1992[47] (Figure 2). This decline may partly reflect an increase in susceptible immigrant adults in the population over time.

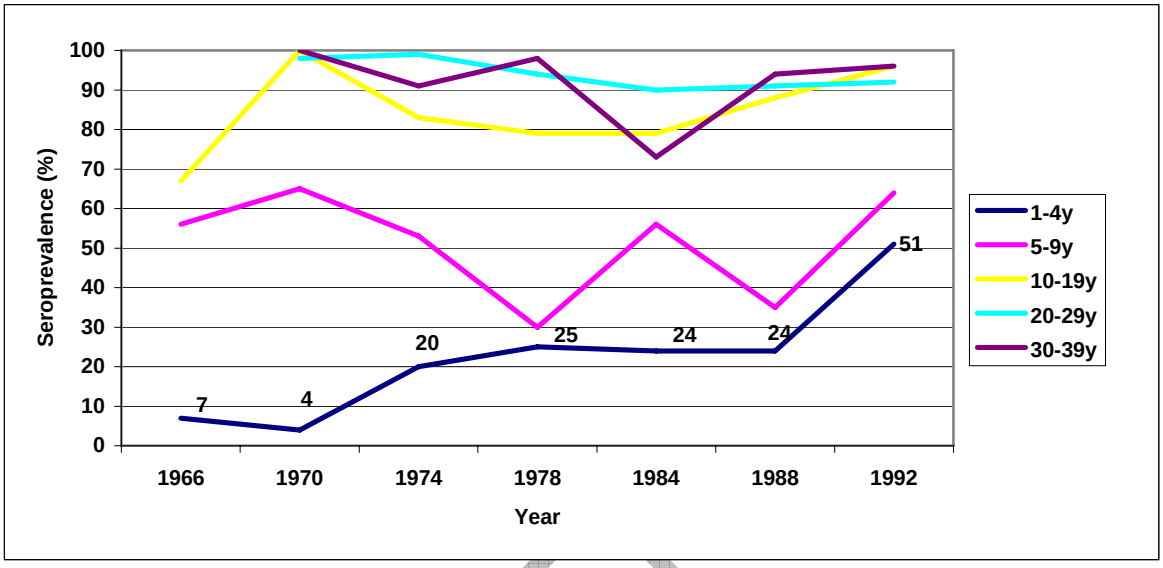

Figure 2: Age related VZV antibody seroprevalence in the UK 1966-1992 (adapted from Kudesia *et al* 2002)[47]

There are considerable geographical differences in the sero-epidemiology of VZV infection across Europe. (Table 1) The proportion of 20-29 year olds susceptible to VZV varies from 0% in the Netherlands, 7.1% in England and Wales to 11.2% in Italy.[48]

Of 1522 pregnant women in Spain 94% of those aged 15-24 years and 95% of those aged 25-29 years were reported to have VZV antibodies.[49] 11.3% of 7980 pregnant women from diverse geographical regions in Ireland were susceptible to chicken pox, 6.9% of women from Irish and other Western European countries were susceptible compared with 17.8%-21.7% women from Central and Eastern Europe, sub-Saharan Africa and Asia ($p<0.001$). [21]

Table 1: Percentage sero-negative for VZV by age group in the 11 European countries, 1995–2003[48]

Source:Nardone *et al.[48]*The Comparative sero-epidemiology of varicella zoster virus in 11 countries in the European region. 2007

	Percentage sero-negative for VZV by age group (*n*)				
	<5 years (%)	**5–9 years (%)**	**10–14 years (%)**	**15–19 years (%)**	**20–29 years (%)**
Belgium	48.8 (377)	12.6 (467)	5.8 (466)	5.1 (643)	3.2 (404)
England and Wales	**52.4 (580)**	**21.7 (452)**	**10.3 (476)**	**8.1 (484)**	**7.1 (99)***
Finland	69.1 (375)	22.9 (437)	6.9 (393)	3.3 (518)	3.0 (400)
Germany	67.4 (457)	13.8 (668)	4.4 (661)	5.9 (630)	2.3 (400)
Ireland	58.7 (271)	18.3 (240)	8.1 (297)	5.7 (314)	6.2 (453)
Israel	51.0 (198)	9.4 (277)	4.7 (300)	10.8 (241)	4.9 (203)
Italy	78.3 (443)	38.9 (543)	18.3 (519)	18.1 (524)	11.2 (448)
Luxembourg	27.0 (37)**	9.9 (425)	3.4 (532)	2.8 (387)	3.2 (379)
Netherlands	49.3 (286)	2.2 (317)	1.2 (333)	1.3 (80)	0.0 (160)
Slovakia	67.1 (456)	30.1 (538)	8.8 (524)	4.9 (531)	3.7 (462)
Spain	66.8 (322)	24.1 (585)	8.3 (484)	6.2 (535)	6.9 (1106)

* Samples tested for 20-year-olds only.

** Samples tested for 4-year-olds only.

Based on seroprevalence studies, women born and living in tropical and subtropical areas are more susceptible to chicken pox in adult life than those born in the UK [50-52]. In countries such as the West Indies, the Indian sub-continent and Singapore, susceptibility in adults is higher, with 20-40% at risk of acquiring chicken pox.[12] This has important implications for women migrating to the UK from these countries as they are likely to be at increased risk of acquiring chicken pox as adults, reflecting country of origin rather than ethnicity.[25]

In a study of women attending antenatal clinics in the London Borough of Tower Hamlets, Bangladeshi women were more likely to be susceptible to chicken pox and twice as likely to acquire infection during the child-bearing years than age-matched UK-born women.[25] VZV antibody prevalence for British and Bangladeshi women was 93.1% [95% CI 89.4–95.8] and 86.0% [95% CI 83.3–88.4] respectively.

Susceptibility was highest in women born in Bangladesh and migrating to the UK after 15 years of age. Of note, 22.7% of mothers giving birth in England in 2006 were born overseas many from countries where the prevalence of VZV immunity is lower than in UK born women [Office of National Statistics 2006].

ii) The natural history of the condition should be understood.

- ***A woman, who acquires chicken pox in pregnancy, has a 10-14% risk of developing pneumonia which has an increased morbidity and mortality compared with the general adult population. A fetus exposed to maternal infection in early pregnancy has 0.4-2% risk of damage due to fetal varicella syndrome and if exposed in late pregnancy or around the time of delivery, disseminated neonatal infection may occur. The timely administration of VZIG is effective in reducing the severity of maternal infection and neonatal chicken pox.***

This has already been discussed in previous sections of the review. To summarise, an estimated 362-435 pregnancies in England and Wales are complicated by chickenpox each year despite the current policy of using VZIG as post exposure prophylaxis.[16,24] Although the incidence of maternal complications such as pneumonia occurs at a similar frequency amongst pregnant and non-pregnant women, the associated morbidity and mortality is higher.

The consequences of maternal infection for the fetus depends on the stage of pregnancy at which maternal infection occurs.[37] These can include no fetal infection, fetal infection with no adverse sequelae or fetal infection with clinical signs of congenital chicken pox. The latter can present as a mild form of the illness with skin lesions alone or as the more severe “fetal varicella syndrome”. The estimated risk of adverse sequelae is 0.4% following infection acquired in the first 12 weeks of pregnancy, rising to 2% in those infected between weeks 13-20.[11]

In infants born within 5 days of maternal illness, neonatal chicken pox can occur and those infected late in pregnancy may develop herpes zoster of infancy or early childhood. The severity of neonatal chicken pox is related to the time of onset of maternal infection (transplacental antibodies may reduce severity) and the time of onset of neonatal illness. A fatal outcome is more likely if the neonatal disease occurs between 5 and 10 days after delivery.

Varicella Zoster Immunoglobulin (VZIG) is recommended for susceptible women exposed to chicken pox, to modify disease and reduce the risk of mother-to-child transmission should it occur. To be effective it must be given within 10 days of exposure.[10] VZIG may reduce transmission for mothers exposed during the first 36 weeks of gestation, by attenuating maternal disease. In one study transplacental transmission fell from 12.3% amongst infants of unprotected mothers with serological evidence of infection to 1.1% in infants born to mothers receiving post-exposure prophylaxis.[37,53] However, protection from fetal damage is not complete. A case of congenital varicella syndrome has been reported in the infant of a woman exposed at the 11th week of pregnancy and who developed clinical varicella despite post exposure prophylaxis with VZIG.[54] VZIG is effective in reducing the severity of neonatal varicella.[11,55] The protective efficacy against clinical chicken pox for pregnant women has been calculated as 53% in 44 seronegative pregnant women in the UK given VZIG within 10 days of exposure.[37]

iii). There should be a recognised latent period or early symptomatic stage.

- ***A 10 day window period exists to offer effective post exposure prophylaxis with VZIG prior to the onset of symptoms.***

Identification of susceptible women before exposure to chickenpox will benefit those who are subsequently exposed to infection as it will speed up the delivery of VZIG which needs to be given to susceptible women within 10 days of exposure.

Women identified as susceptible during pregnancy should be offered post partum vaccination with two doses of vaccine, administered 3 months apart. It is advised that pregnancy is avoided for 3 months after the second immunisation.

3. All cost-effective primary prevention interventions should have been implemented as far as practicable.

- ***Universal childhood vaccination against chicken pox has not been introduced in the UK due to concerns over a possible increase in the age of acquiring infection, a rise in cases of shingles in later life (with its attendant morbidity) and a lack of evidence to support its cost effectiveness. UK vaccine policy which offers targeted vaccination to high risk groups is currently under review by the JCVI in light of the***

lessons learnt from the introduction of a universal two dose vaccine schedule for children in the USA.

- ***Alternative strategies such as screening newly arrived adult immigrants have been shown to be cost effective outside the UK and warrant further investigation in a UK setting.***

A live attenuated vaccine against chicken pox was developed in the 1970s,[56] and this was introduced into the routine immunisation schedule in the USA in 1995 for children aged 12-18 months.[57]. The initial policy advised a single dose of vaccine for children aged 12 months – 12 years and two doses, 4-8 weeks apart for those over 12 years (either as part of the catch up programme or susceptible contacts of persons at high risk of serious complications). However, in 2006 this was replaced with a routine 2 dose schedule following outbreaks of breakthrough disease amongst vaccinated populations. The revised schedule recommends the first dose be administered at 12-15 months and the second at 4-6 years. In addition the revised guidelines include a recommendation that prenatal assessment and post partum vaccination should be introduced.[57] The USA and Germany (only European country to advise universal childhood varicella vaccination) are the only two countries where vaccination of women of child bearing age has been recommended.[58]

In contrast the UK has not adopted a policy of universal childhood vaccination to date. Current Department of Health[10] policy for the UK is to offer targeted varicella vaccination to non-immune healthcare workers to protect them from infection and to prevent subsequent transmission to patients, and to children aged 1 to 12 years to prevent transmission to close contacts of those at high risk of severe chickenpox or shingles infection. These include immunocompromised individuals such as individuals with leukaemia or those on chemotherapy.

Routine childhood immunisation has not been introduced in the UK to date due to specific concerns which include the increased risk of serious infections among older age groups arising from a resultant shift in age of infection [59-61] as well as a potential increase in shingles reflecting the impact of a decline in circulating virus in the community on maintenance of natural immunity. Economic evaluations in the UK[62] and Canada[63] suggest that if the potential increase in shingles is taken into account, a universal infant chicken pox immunisation programme would not be cost effective. However, the Joint Committee on Vaccination and Immunisation (JCVI)

which advises UK health ministers on matters relating to immunisation is currently undertaking a policy in light of the US experience.[64]

In the USA since 1995, the single dose vaccination programme has reduced disease incidence by 57%-90%, hospitalizations by 75%-88% and deaths by >74%[65] The impact of the two dose schedule, introduced following outbreaks amongst highly vaccinated populations is too early to examine. The effect of the programme on shingles epidemiology has been inconclusive and requires further investigation. However, in June 2008 the US Advisory Committee on Immunisation Practices (ACIP) recommended the introduction of a single dose of herpes zoster vaccine to all adults aged 60 years and above in an attempt to mitigate the potential increase in cases of shingles following the introduction of a universal childhood varicella vaccination programme. [66]

In addition to this primary prevention intervention, alternative screening strategies have been explored. The results from a Canadian study[13] investigating a strategy of vaccinating newly arrived adult immigrants suggest that routine serological testing of young adult immigrants in Montreal without a self-reported history of varicella, followed by vaccination of susceptible individuals, would prevent an estimated 37% of cases and would be the most cost-saving intervention from a societal perspective. However, these results are strongly dependent on key assumptions, which are subject to considerable uncertainty. Although there has been interest in screening for other infections among newly arrived immigrants to the UK including TB and HIV, these are not necessarily comparable with screening for VZV susceptibility. TB and HIV are chronic illnesses, screening aims to identify those who are already infected, who pose a risk to others and who require treatment themselves. However, there may be merit in undertaking more formal evaluation of strategies to ascertain varicella susceptibility in this group.

THE TEST

4. There should be a simple, safe, precise and validated screening test

- ***A history of chicken pox and serological assays to test for VZV IgG antibodies are potential screening tools.***
- ***The positive predictive value of a history of chicken pox is between 95-99% amongst pregnant women although the reliability of history is lower***

in ethnic minority populations. A negative or uncertain history is less reliable (6.8-35%) in determining susceptibility.

- ***A number of different commercially available serological assays are in use across the UK. Many commercially available ELISAs provide a practical and reliable screening method. Recent studies highlight the variability in test characteristics of assays. Establishing clear guidelines and criteria for serological assays (in terms of minimum sensitivity and specificity) is essential to ensure consistency, accuracy and reliability across the whole country.***

Screening in pregnancy

Screening in pregnancy has two aims:

I. To identify susceptible women not exposed during pregnancy, who can be offered post partum vaccination.
II. To identify susceptible women who can be offered VZIG at the earliest opportunity if exposed to chicken pox during pregnancy.

Screening in the first pregnancy is logical as most pregnant women acquire infection from contact with children, which is more likely in second and subsequent pregnancies.[16] However, reports have suggested that up to one quarter of infections that occur in pregnancy take place in primiparous women.[16] A number of strategy options need to be considered.

Screening Strategy Options

i. Maintain status quo i.e. no routine screening but testing women with a negative history who are in contact with chicken pox, as per UK guidelines[10]
ii. History and serological testing of those unsure or reporting a negative history with post partum vaccination of susceptible women.
iii. Serological testing of all women with post partum vaccination of susceptible women.

Reliability of history

The reliability of a history of chicken pox is important to establish. The sensitivity and specificity of verbal screening has been reported at 90% and 50% respectively.[12]

The predictive value of a positive history is a more meaningful measure in establishing whether a screening tool would be useful in practice. The positive predictive value amongst antenatal populations has been studied in different settings but has been found to be consistently high between 95%-99%. [2-6] In contrast the negative predictive value is significantly lower reported at between 6.8-35%[2-6] suggesting a negative or uncertain history cannot be reliably extrapolated to assume susceptibility.

It is important to recognise that the predictive value varies according to age and ethnicity. Whilst the negative predictive value is affected by sub-clinical infection, the positive predictive value is likely to be influenced by misdiagnosis, quality of the gold standard assay as well as age and region of origin.

In ethnically diverse populations the accurate identification of susceptible women is particularly relevant given the increased risk of susceptibility amongst women born overseas.[25] A history of chickenpox is a less reliable predictor of immunity in individuals born and raised overseas.[7,67] Thus verbal screening in these groups may fail to correctly identify susceptible women for post partum vaccination. The Royal College of Obstetrics and Gynaecology (RCOG) 2007 Green Top Guidelines[18] recommend routine testing of all individuals born overseas.

Following the introduction of universal immunisation and widespread vaccine coverage in the USA, self reported history of chicken pox has continued to be a strong predictor of immunity in pregnant women whilst negative or uncertain history remains a poor predictor of susceptibility.[4] This suggests that even if a chicken pox immunisation programme was introduced into the routine infant schedule in the UK, verbal screening is likely to remain a reliable antenatal screening tool in UK born women who report a history of chickenpox.

Serological Screening

A number of tests have been developed to determine the presence of VZV antibodies thereby indicating immunity to chicken pox and protection from disease. Antibody tests with low sensitivity may result in unnecessary post partum vaccinations and undue anxiety for women during pregnancy who think they are susceptible. Screening assays with low specificity can produce false positive results and identify

women as immune who are at risk of infection.[68] For the purposes of screening, reduced assay sensitivity is therefore less critical than lower assay specificity.

Diagnostic methods to establish serological status include the fluorescent antibody to membrane antibody (FAMA), latex agglutination (LA), enzyme linked immunoassorbent assay (ELISA or EIA) and a recently developed time-resolved fluorescence immunoassay test (TRFIA).

The FAMA is the most extensively validated assay and correlates best with susceptibility and protection against clinical disease.[69-77] Hence, it is widely regarded as the reference against which other assays should be measured. However, FAMA has some disadvantages which have precluded its widespread use. It is labour intensive, not amenable to automation and its interpretation requires experienced staff[68]

Other tests including LA have been shown to correlate with FAMA although false positive results have led to failures to vaccinate with development of chicken pox in healthcare workers incorrectly identified as immune.[73,78] LA results seem to correlate better with FAMA than some commercial ELISAs[69] but the drawbacks regarding the false positive and negative rates for this method raises serious questions about its value as a screening tool.

Many laboratories in the UK use automated assays for the detection of VZV IgG with ELISA or latex agglutination providing results on the same day or within 48 hours. A number of different commercially available assays are in use and their characteristics have been compared (table 2). As there is currently no consensus on a gold standard assay, different reference assays have been used in studies, leading to some contrasting findings.

Information from the Quality Assurance Laboratory, HPA Centre for Infections 2005 report suggests that the most popular assays in the UK were Biomerieux VIDAS assay (51.3% of UK laboratories) followed by Diamedix microtitre plate based EIA (26.6%) with 3.1% of UK laboratories using DiaSorin LIAISON assay.[8]

The cost of these assays is likely to vary according to the quantity purchased from the manufacturer. The manufacturers (Labmedics Ltd and Inverness Medical Ltd)

supplying Diamedix and Captia VZV IgG kits (each kit comprising 100 tests) in the UK provided quotations for the cost of their kits. (Table 3) The cost per test varies from between £1.04 to £2.77 depending on the assay and quantity purchased. This compares with £12 per test for the Dade Behring VZV IgG assay quoted in the only UK economic evaluation of universal antenatal screening for VZV susceptibility.[12]

STUDY	Name of Commercial Assay	Type of Assay	Reference Assay	Sensitivity (%)	Specificity (%)
Maple *et al.*[9] (2008)	LIAISON	ELFA	TRFIA	67	100
	VIDAS*	ELFA		54.5	97.9
Maple *et al.[8]* (2008)	Dade Behring	EIA	TRFIA	97.4	69.9
	"In house"	Indirect IF		95.2	84.6
	Becton Dickinson	LA		94.1	90.4
	Human	EIA		92.3	94.1
	Seraquest	EIA		88.6	98.5
	Novatec	EIA		83.5	99.3
	Trinity	EIA		83.5	100
	Biotest	EIA		83.2	93.4
	Meriflour	Indirect IF		82.4	88.8
	Diamedix	EIA		81.3	99.3
	Ridascreen	EIA		81.3	100
	VIDAS*	ELFA		80.4	92.4
	Panbio	EIA		80.2	99.3
	Virion	EIA		69.6	99.3
	Diesse	EIA		68.9	100
	Diasys	EIA		68.5	100
Ory *et al.[79]* (2006)	Dade Behring	EIA	FAMA	66.6	100
Sauerbrei *et al.[80]* (2006)	Dade Behring	EIA	FAMA	83	100
	Virion	EIA		100	100
LaRussa *et al.[81]* (1987)	In house	Membrane ELISA	FAMA	97	84
	In house	Dot- ELISA		95	87
	Whittaker	Indirect IF		94	84
	Electro-nucleics	Indirect IF		93	82
	Litton	Indirect IF		55	100

Table 2: Characteristics of commercially available assays to test for VZV IgG

Quantity of kits (1 kit = 100 tests)	Price per test (incl VAT) Diamedix VZV IgG	Price per test (incl VAT) Captia VZV IgG
0-500	£1.47	£2.77
0-1500	£1.37	£1.90
0-3500	£1.28	£1.79
0-10 000	£1.04	£1.57

Table 3: Cost of Diamedix (Labmedics Ltd)and Captia (Inverness Medical Ltd) VZV IgG kits in UK

Maple *et al*. in 2008 compared 15 different commercial assays and found considerable variation in the their sensitivity and specificity; sensitivity varied between 68.5% (Diasys EIA) up to a maximum of 97.4% (Dade Behring EIA) and specificity varied between 69.9% (Dade Behring EIA) and 100% (Diasys EIA).[8] These findings suggest that the least sensitive assays (<70%) all had >99.0% specificity whereas the most sensitive assays has lower specificities.[8] The most commonly available assay in the UK (VIDAS) had a sensitivity and specificity of 80.4% and 92.4% respectively. The discrepancy between estimations in two studies by Maple *et al.*[8,9] were due to differences in cut off criteria and types of samples used e.g. antenatal sera with few negative samples in one study[9] and a large number of VZV IgG negative sera in the other.[8] However, as these two studies used TRFIA as the reference assay rather than the widely accepted gold standard FAMA, test sensitivity and specificity estimates need to be interpreted with caution.

A number of different commercially available serological assays are in use across the UK and many commercially available ELISAs provide a practical and reliable screening method. However, recent studies highlight the variability in test characteristics of assays. Establishing clear guidelines and criteria for serological assays (in terms of minimum sensitivity and specificity) is essential to ensure consistency, accuracy and reliability across the whole country.

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

- ***There are no standard criteria for determining the antibody level which correlates with susceptibility to chicken pox in adults.***

There are currently no standard criteria for determining the level at which a woman would be considered susceptible. As far as markers for correlates of protection, vaccine studies or skin test measurements of cell mediated immune response have demonstrated varicella susceptibility among persons with FAMA titers <2. FAMA remains the only assay that has been evaluated in such longitudinal studies.[82]

Each of the commercially available kits have their recommended cut-off levels. For example with the Biomerieux VIDAS assay a test value of <0.6 is VZV IgG negative. Those test values above 0.9 are IgG positive and those in between equivocal .[9] For the DiaSorin LIAISON assay, the cut-off recommended for the test is 150mIU/ml, although in Germany the recommended level is 100mIU/ml.[9]

In order to allow comparison between test results obtained with different assays, a WHO VZV IgG antibody standard has been developed to which international units have been assigned. A UK standard, calibrated in international units, has been prepared and is available from the National Institute of Biological Standards and Control.[37]

6. The tests should be acceptable to the population.

- ***Acceptability of history and serological testing for susceptibility to chicken pox during pregnancy requires further investigation.***

There is no evidence that screening for chicken pox in pregnancy through history or by serological testing would not be acceptable to the antenatal population. However, attitudes amongst women regarding the risks associated with infection during pregnancy and their attitudes towards introducing a universal antenatal screening programme have not been investigated.

7. There should be an agreed policy on the further diagnostic investigation of individuals with a positive test and on the choices available to those individuals.

- ***No further diagnostic tests are required if susceptibility to chicken pox has been established, unless there is evidence of infection during pregnancy.***

There are no further diagnostic tests for women identified as susceptible through screening. Should known susceptible women become exposed to chickenpox, screening would enable the prompt administration of VZIG.

For pregnant women with chicken pox infection, diagnostic procedures cannot assess the risk or severity of fetal infection.[83] Prenatal diagnosis is based on detection of VZV DNA by polymerase chain reaction (PCR) in amniotic fluid and fetal blood as well as by ultrasound (however, the risk of varicella damage is low and if ultrasound shows no abnormalities it may not be appropriate to carry out amniocentesis with its attendant risks).

THE TREATMENT

8. There should be an effective treatment or intervention for patients identified through early detection.

- ***Early detection of susceptible women will enable the prompt administration of VZIG in the event of exposure. Pregnant women need to be aware of the risks of exposure during pregnancy.***
- ***VZIG is costly but effective in attenuating maternal disease. There is conflicting information on the protection VZIG confers to the fetus.***
- ***Oral acyclovir should be considered for women who develop signs and symptoms of chicken pox to reduce disease severity.***
- ***Post partum vaccination of susceptible women with 2 doses of varicella vaccine is highly protective.***

Effective treatment involves the management of a susceptible pregnant woman exposed to chickenpox with VZIG and the use of acyclovir should symptoms arise. In addition, as a result of screening, there is an effective management to prevent further cases arising through post partum vaccination.

Susceptible women who have had significant exposure (Significant exposure is defined as household contact, face to face contact with an index case for at least 5 minutes, having indoor contact for more than one hour or sharing the same hospital room with a contagious

patient) to chicken pox during pregnancy are offered post exposure prophylaxis with varicella zoster immunoglobulin (VZIG).[10]

This poses several issues.

- Pregnant women need to be aware of risks of exposure during pregnancy (in one UK retrospective review 60% delayed seeking health advice[16])
- In the event of exposure, susceptibility needs to be established– if there is a definite history of chicken pox the woman can be reassured – this is based on the wealth of evidence highlighting the reliability and high predictive value of a positive history in UK born women.
- In those with a negative or uncertain history serological testing is required– this needs to be performed in a timely manner as there is only a small window of 10 days following exposure for VZIG to be of benefit.
- In cases where the exposure has been more than 10 days, VZIG is of no benefit and advice needs to be offered if a woman develops symptoms.
- The administration of VZIG requires trained healthcare staff and appropriate health care facilities.

Women with significant exposure to chicken pox during pregnancy

Varicella zoster Immunoglobulin (VZIG) is a blood product derived from pooled plasma. It is used for susceptible pregnant women and neonates as post exposure prophylaxis within 10 days of exposure.

The rationale for use of VZIG includes reducing the severity of maternal disease and reducing the risk of fetal infection.[10] About 50% of susceptible pregnant women given VZIG after a household exposure to chicken pox will develop clinical varicella, although the disease may be attenuated.[10] However, severe maternal varicella may occur despite VZIG prophylaxis. The protective efficacy against clinical chicken pox has been calculated as 47% in 44 seronegative pregnant women in the UK given VZIG within 10 days of exposure.[37] Studies have also shown that it has some effect in reducing the severity of neonatal varicella.[11,55] VZIG is reported to reduce materno-fetal transmission of chicken pox from 12.3% in infants of unprotected women to 1.1% in infants of women given post exposure VZIG.[11]

VZIG is expensive (£280 per 250g vial – 1 adult dose requires 4 vials) and costs £1120 per adult. VZIG supplies in England and Wales are prepared by Bio Products Laboratory (BPL) which is sourced from US donors, and available on request through the Health Protection

Agency (HPA). In Scotland, VZIG is supplied by the Scottish National Blood Transfusion Service. The BPL product has been shown to attenuate chicken pox when given up to 10 days post exposure and is as effective when given later or earlier in the 10-day period.[84] With the advent of universal immunisation in the USA, antibody titres from paid donors are likely to fall (natural immunity induces higher antibody levels compared with vaccine induced immunity) thereby limiting its availability. In fact following the discontinuation of production of varicella zoster immunoglobulin by the sole US manufacturer and rapidly depleting supplies, the American Food and Drug Administration provided an investigational drug license in 2006 for VariZIG™ (a purified human immune globulin preparation which differs from the previous product in that it is lyophilised) to be administered within 96 hours of exposure in susceptible pregnant contacts.[85] The use of immunoglobulin remains first line treatment in susceptible pregnant contacts in the USA, with the recognition that intravenous immunoglobulin may be an alternative where supplies of varicella zoster immunoglobulin are unavailable.[82] The scarcity of supplies and high cost means that not only should varicella zoster immunoglobulin be reserved for those likely to benefit the most, but it also has important policy implications for the UK in the future.

YEAR	Northern Ireland[86]	Scotland*	England and Wales[1]		
	Number of pregnant contacts	Number of pregnant contacts	Number of pregnant contacts	Number of vials issued for pregnant women (% total)	Number of vials issued for neonates (% total)
2001/02	N/A	N/A	1051	4207 (73.2%)	228 (4.0%)
2002/03	N/A	N/A	1346	5386 (73.5%)	265 (3.6%)
2003/04	N/A	N/A	1216	4865 (75.6%)	211 (3.3%)
2004/05	N/A	N/A	1226	4904 (75.1%)	273 (4.2%)
2005/06	62	294	1145	4583 (78.7%)	213 (3.7%)
2006/07	105	283	1318	5273 (77.4%)	241 (3.5%)
2007/08	70	282	N/A	N/A	N/A

Table 4: Issuing of VZIG for pregnant women and neonates in the UK
Source: *Issuing of VZIG to pregnant contacts: 2005-2008, Regional Virus Laboratory, Royal Victoria Hospital, Belfast[86]*
Issue of Immunoglobulins by the HPA Colindale: Report for the financial year 2006/07[1]
***Figures for Scotland estimated from total number of VZIG vials issued annually from Scottish National Blood Transfusion Service, assuming 80% total vials issued to pregnant contacts.*

Approximately three quarters of all VZIG in England and Wales is issued to pregnant contacts(table 4).[1] In 2007, an estimated 1706 pregnant women across the UK were issued with VZIG at a cost of approximately 1.9 million pounds. This does not take account of staff and material costs to administer the VZIG. The 2006/07[1] report predicted the future

demand for VZIG supplies in England and Wales. Comparing the first quarter issuing in 2006/07 with 2007/08, the report highlighted a significant increase (499 extra vials used). Although there was an unexpected increase of chicken pox cases leading to greater demand for VZIG it is possible that this could lead to a greater demand for supplies in the future.

Although the outcome for pregnant women and neonates given VZIG as post exposure prophylaxis have been reported in the literature, these studies are small and were carried out around 20 years ago and provide limited evidence of the maternal outcome following VZIG given as post-exposure prophylaxis. Currently there is no systematic follow up of women and neonates given VZIG in the UK, despite the relatively large number treated each year in the UK. The findings of the three published studies are summarised here.

Evans *et al.* suggested that although immunoglobulin was largely ineffective in preventing infection in 43 high-risk contacts (clinical attack rate of 56%) it appeared to attenuate disease.[87] This group included 15 neonates whose mothers developed chickenpox shortly before or after delivery, nine of whom developed chickenpox despite post-exposure prophylaxis (clinical attack rate 60%) and 9 pregnant women, one of whom had asymptomatic infection.

Data from 44 seronegative pregnant household contacts showed no extra benefit of giving VZIG within 72 hours compared with 4 days and the overall protective efficacy from clinical disease was calculated at approximately 48%.[37] In a study of 280 neonates receiving VZIG following maternal chickenpox during the perinatal period, 169 (60%) were infected including 134 (48%) with chickenpox and 35 (13%) without symptoms.[84] 19 infants developed severe disease. The clinical attack rate (60%) was highest in those born to mothers developing chickenpox one week either side of delivery.

Women infected with chicken pox during pregnancy

Acyclovir has been considered for the treatment of severe complications of chicken pox in pregnancy, such as varicella pneumonia in the second half of pregnancy and has been shown to be clinically effective in reducing mortality .[24] Although acyclovir has not been approved for use in pregnancy by the manufacturer, the consensus of a working group of obstetricians in the UK was that oral acyclovir should be considered for women in the second half of their pregnancy because of the risk of pneumonia.[24] This is thought to be effective if administered within 24 hours of the onset of the rash, but in women with respiratory involvement, intravenous acyclovir is advised.[24] In the US, acyclovir is

classified as a Category B drug in the Food and Drug Administration use-in-pregnancy rating. Although US guidance does not recommended the routine use of oral acyclovir for pregnant women, in instances of serious, viral-mediated complications (e.g., pneumonia), it does recommend that intravenous acyclovir should be considered.[58] The US based acyclovir prospective pregnancy registry[88] has shown no increase in the risk of congenital malformations amongst 596 infants whose mothers were exposed to systemic acyclovir during the first trimester of pregnancy. There is no well controlled study for the prophylactic use of acyclovir for maternal chicken pox exposure near term or in exposed neonates to prevent neonatal varicella.

Neonates

The attack rate in healthy newborns exposed to chicken pox in utero or within 5 days of delivery is 30-40% and this is not substantially different for newborns treated with VZIG. However, the occurrence of complications and fatal outcomes is substantially lower in those treated with VZIG.[89] VZIG is also recommended for neonates whose mothers develop a chicken pox rash up to and including 7 days before delivery or up to a week after delivery.[10] Neonatal infection should be treated with acyclovir following discussion with a neonatologist and virologist.[18]

Vaccinating women of child bearing age

The Oka vaccine is a live attenuated vaccine developed in the 1970s[56] and has been tested in several trials in healthy adults and shown to be highly immunogenic.[90] In adults the efficacy in terms of immunity protection is 78% with one dose and 99% with two does of vaccine.[91]

In contrast to children whose VZV antibody titre increases over time, immunity has been shown to wane in adults with VZV antibodies detectable in approximately 80% after 1 year, and 70% from 2 to 6 years after vaccination.[90] Of 40 healthy adult vaccinees tested 7-13 years after immunisation, 18% were found to be seronegative by FAMA.[92] This compares with only 5% in a study of children following a similar interval. [93]

Protective efficacy from 2 doses of vaccine in household exposure studies has been estimated at between 65% - 75% in adults[90,94]; however, when breakthrough (i.e., in those who have seroconverted) illness has occurred, it has invariably been mild, so that its efficacy in preventing severe disease has been estimated at 100%.[90]

9. There should be agreed evidence based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

- ***UK guidance[10] clearly state the indications for the administration of VZIG for susceptible women exposed during pregnancy.***
- ***Successful implementation of a two dose post partum vaccination policy requires the development of clear guidelines on the roles and responsibilities of health professionals in both hospital and community settings.***
- ***The feasibility and acceptability of post partum vaccination is not yet certain as evidenced by the current rubella programme.***

Women shown to be susceptible and exposed to chickenpox should be offered VZIG as per UK guidance.[10]

Women identified as susceptible during pregnancy and not exposed should be offered post partum vaccination using the recommended schedule. This involves two doses of vaccine, to be administered 3 months apart, which does not fit into any existing schedule. UK guidance recommends that pregnancy be avoided for 3 months after the second immunisation, although in the USA, a one month interval is advised.[58]

The difficulties experienced in ensuring that women identified as susceptible to rubella through antenatal screening, attend for post partum vaccination may be replicated if a screening programme for chicken pox was introduced as there are many similarities, particularly as 2 doses of vaccine are required.

A number of different systems have been put in place across the country to ensure that rubella susceptible women receive post partum vaccination with contrasting results. In London, recent audits have shown that between 50-75% susceptible women receive MMR vaccine prior to discharge from hospital (personal communication Nadia Permalloo, London Regional Antenatal screening co-ordinator). In Harrogate for example, the local antenatal screening co-ordinator, is responsible for ensuring all susceptible women are informed of their need to be vaccinated post-partum and follows all cases up with the GP. This system has improved uptake from 56% to 97% over a 5 year period. (personal communication Tracy Thirwell local antenatal screening co-ordinator, Harrogate District Hospital).In a 2007 audit of the local NHS Trusts in Surrey (personal communication, Elizabeth Brutus, SpR Public Health) although there was some variation in practice few women received MMR vaccine if it

was not administered prior to hospital discharge. There is difficulty auditing rubella post partum vaccination as a model and hence only anecdotal data is presented here for this review.

There are certainly important lessons to be learnt from the rubella experience which has direct relevance to any proposed introduction of a screening programme for chicken pox. Ensuring rigorous systems are in place for informing women of the need for vaccination and establishing clear roles and responsibility for the administration of 2 doses of varicella vaccine post partum are essential for success.

10. Clinical management of the condition and patient outcomes should be optimised by all health care provides prior to participation in a screening programme.

There are no specific implications for women being susceptible to chicken pox unless they are exposed during pregnancy. However, it is essential that the risks of chicken pox during pregnancy are communicated effectively so that there are no delays in seeking health advice should exposure occur.

THE SCREENING PROGRAMME

11. There should be evidence from high quality Randomised Controlled Trials that the screening programme is effective in reducing mortality or morbidity.

No evidence

12. There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/ intervention) is clinically, socially and ethically acceptable to health professionals and the public.

- ***There is a lack of evidence on the acceptability of a screening programme for chicken pox for both health professionals and the public***

Although studies[95,96] have investigated parental attitudes to post partum vaccination and varicella vaccination specifically, there is no published evidence of mothers' knowledge and attitudes of the risk of chicken pox in pregnancy and the acceptability of post partum varicella vaccination for susceptible women. In the USA, parental perceptions following the introduction of a universal varicella vaccination programme, suggested that the ubiquitous nature of chicken pox in childhood may play a role in decreasing the perceived necessity for the vaccine and the seriousness of the disease.[96] However, there is a distinct lack of evidence on this particular issue.

13. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

- ***The adverse effects of testing and treatment with VZIG are minimal. However, the effectiveness of early treatment with VZIG for susceptible women exposed to chicken pox during pregnancy is well documented. Varicella vaccine is a highly effective and safe vaccine. Further information on the optimum timing for post partum vaccination is needed given concerns about its administration to breast feeding mothers.***

The commercially available kits to test for VZV immunity have no known side effects or associated complications.

VZIG has been shown to be effective as post exposure prophylaxis as previously discussed and is not associated with any significant side effects. As with all blood products VZIG supplies are screened for blood borne infections and having been sourced from US donors the theoretical risk of vCJD transmission is thought to be minimised.

Varicella vaccine has been shown to be highly effective. Vaccinating susceptible women of child bearing age with a two dose schedule given 4-8 weeks apart, induces IgG antibodies in 95% and these persist for 3-6 years.[22] Varicella vaccine is safe in adults with only mild side effects reported. These include a transient local reaction which occurs in 10% to 21% and a mild rash in 6% to 8%.[90] Approximately 5% adults develop a post vaccine rash from which vaccine virus rarely has been cultured[97] with a theoretical risk of transmission.

Pregnancy is a contra-indication for the administration of this live vaccine, but as the virulence of the vaccine virus is less than that of the wild type strain, the risk to the fetus of inadvertent administration should be lower and is not considered a reason for termination of the pregnancy.[22] A 10 year review of a US pregnancy registry which records inadvertent vaccination during pregnancy found no evidence to support a relationship between the occurrence of fetal varicella syndrome or other birth defects and varicella vaccine exposure during pregnancy.[98]

Varicella immunisation is not generally recommended for breast feeding mothers by the vaccine manufacturer. However, a US study showed no evidence of virus in breast milk or transmission to breast feeding babies from mothers receiving a 2 dose schedule at least 6 and 10 weeks after birth[99]. US guidance from the Centre for Disease Control, Atlanta states that vaccination is not contra-indicated in breastfeeding mothers and should not be

delayed.[58] In fact UK national guidance[10] also states that breast feeding women can be vaccinated if indicated. (This has been an issue with rubella and a note has recently gone out to say it is not of concern and women should be vaccinated prior to hospital discharge)

The benefits of vaccinating a susceptible mother to prevent illness in the mother and infant in a subsequent pregnancy should be considered. Further information is needed on the optimum timing for vaccinating women post partum.

14. The opportunity cost of the screening programme (including testing, diagnosis and treatment) should be economically balanced in relation to expenditure on medical care as a whole

- ***There has only been one UK study to investigate the cost effectiveness of introducing an antenatal screening programme to identify susceptible women who can be offered post partum vaccination.***
- ***It concluded that it was cost effective to screen UK born women by serological testing of those reporting a negative or uncertain history of chicken pox. However, a further analysis using population data from pregnant Bangladeshi born women residing in Tower Hamlets, suggested that serological testing of <u>all</u> these women would be cost effective given their increased susceptibility as well as the reduced reliability of verbal screening.***
- ***This would suggest a more complex screening pathway according to maternal country of birth. The generalisability of this study is limited, as is the feasibility and reliability of ascertaining such high risk groups within the UK antenatal population.***

There has only been one study in the UK that has investigated the cost effectiveness of introducing an antenatal screening programme with post partum vaccination of susceptible women.[12] It compared two screening strategies against current care (no active screening but post exposure prophylaxis with VZIG for susceptible women within 10 days of exposure). The two screening strategies were:-

I. History with serological testing of those women with a negative /uncertain history
II. Serological testing of all pregnant women

The study concluded that it was cost effective to screen UK born women by serological testing of those reporting a negative or uncertain history of chicken pox. However, a further analysis using population data from pregnant Bangladeshi born women residing in the

London Borough of Tower Hamlets, suggested that serological testing of all these women would be cost effective given their increased susceptibility as well as the reduced reliability of verbal screening. Although a sensitivity analysis was performed around a number of assumptions, including assay cost, vaccine uptake and estimates for the risk of infection during pregnancy were not considered. The analysis assumed 100% vaccine uptake and given the experience of the rubella programme, this appears highly optimistic. In addition, it is uncertain whether these estimates influence the cost effectiveness of the screening programme.

Based on the authors' findings however, the paper suggests a more complex screening pathway according to maternal country of birth. The generalisability of this study is limited, as is the feasibility and reliability of ascertaining such high risk groups within the UK antenatal population.

In an unpublished Irish study[100] the authors concluded that compared with current care, verbal screening and serological testing those with a negative history would save £34 350 pa whilst a strategy of serological testing of all pregnant women would save £15 100. However, only the cost of VZIG was included in the analysis. Indirect costs including staff costs and the costs for treating women with chicken pox and those with neonatal varicella were not included.

A US study performed in the pre-vaccine era based on data up to 1996 concluded that routine antenatal screening for all pregnant women with negative or indeterminate chicken pox histories was not cost effective.[101] The authors suggested that screening was not cost effective unless the cost of screening was decreased six-fold, chicken pox exposure rates were greater than 6%, or there was a greater than three-fold decrease in chicken pox exposure in women testing non-immune compared with unscreened women.[101] The risk of exposure estimated in the UK is well above the 6% level described in this paper.

In a second US economic evaluation[102] comparing no screening or vaccination, selective serotesting in those without a prior history of chickenpox and serotesting all women, selective serotesting was considered favourable by preventing nearly half of all chickenpox cases in women of reproductive age and being favourable from both the societal and health payer's perspective.

These studies were performed prior to the introduction of the universal infant immunisation programme. However, the results are sensitive to the prevalence of seronegativity (assumed at 9%) and the costs used are not generalisable to a UK setting. Interestingly in the second analysis[102] the strategy of serotesting all women became cost effective when at least 15% population were susceptible, which is likely to occur amongst some immigrant populations in the UK.

15. There should be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

- ***No quality assurance standards have been developed to date***

In the absence of national screening for chicken pox in the UK, no quality assurance standards have been agreed. The development of quality assurance standards is necessary to ensure laboratories across the UK are purchasing commercially available kits that meet nationally agreed standards.

16. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme

- ***Training clinical staff to communicate risks and appropriately treat susceptible women exposed during pregnancy is needed. Serological testing requires adequate laboratory facilities and trained staff.***

Training staff with respect to effectively communicating the risks associated with exposure to chicken pox during pregnancy, the method of testing and the need to vaccinate susceptible women post partum would need to be undertaken prior to the commencement of a screening programme. Appropriate laboratory facilities, equipment and trained staff would be required to undertake serological testing.

17. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services).

- ***A review of national vaccine policy on chicken pox is currently underway***

Current UK vaccine policy for chicken pox is under review by the Joint Committee on Vaccination and Immunisation (JCVI) to consider alternative approaches including the introduction of universal childhood immunisation. Countries, such as the USA have introduced an antenatal screening programme offering post partum vaccination to women identified as susceptible to chicken pox. However, this has been done as part of an overall policy to control VZV infection, which is predominantly centred on universal childhood

vaccination. Such primary prevention interventions are essential to the success of any control policy; other strategies such as screening newly arrived immigrants have been shown to be cost effective outside the UK[13] and need to be investigated in a UK setting.

*Boxes filled in red: estimates based on poor quality data

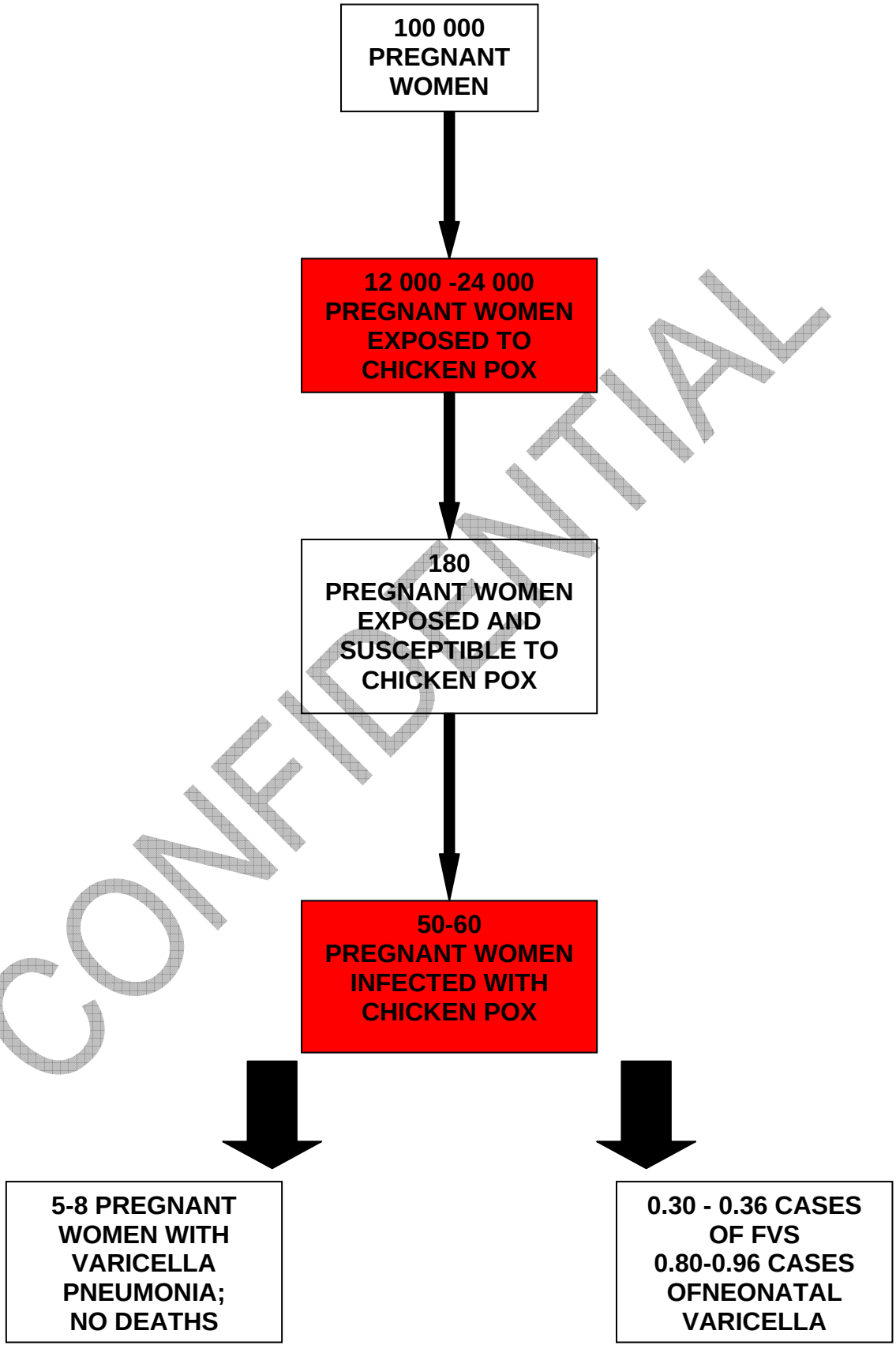

Figure 3: Flow Chart of 100 000 pregnant women in the UK

KEY FINDINGS

1. An estimated 90% of the UK antenatal population are immune to chicken pox. Susceptibility to chicken pox amongst adults shows considerable geographical variation with immigrants from tropical climates having significantly higher susceptibility than UK born adults. There is very limited evidence on the influence of parity on the risk of susceptibility amongst pregnant women.
2. Although the incidence of complications from chicken pox for the mother e.g. pneumonia is similar in pregnant and non-pregnant adults, the morbidity and mortality is higher amongst the pregnant population.
3. The consequences of chicken pox in pregnancy for the fetus can be severe particularly if infection occurs during the first two trimesters. This can lead to the development of fetal varicella syndrome. Perinatally acquired infection can cause disseminated neonatal infection, which can be fatal.
4. The ability to identify susceptible women by screening has two key objectives. Firstly it provides an opportunity to offer women identified through screening as susceptible, post partum vaccination to prevent serious maternal, fetal and newborn complications due to VZV infection in future pregnancies. A secondary objective is to allow the administration of VZIG at the earliest opportunity for those exposed during pregnancy. The rationale for VZIG prophylaxis is to reduce severity of maternal disease and reduce materno-fetal transmission in women infected during the first 20 weeks of pregnancy. However, VZIG only has a protective efficacy against clinical chicken pox of 53%, in pregnant women.
5. Two screening methods are considered in this review, history and serological assays that measure VZV IgG antibodies. The positive predictive value of a history of chicken pox is between 95-99% amongst pregnant women, although the validity of history has been shown to be lower in ethnic minority populations. A negative or uncertain history is less reliable (6.8-35%) in determining susceptibility.
6. Although a number of commercially available serological tests are available in the UK, there appears to be considerable variation in their sensitivity and specificity; many being of low sensitivity. There are no standard criteria for determining the antibody level which correlates with susceptibility to chicken pox in adults.
7. Establishing clear guidelines and criteria for serological assays (including minimum sensitivity and specificity) is essential to ensure consistency, accuracy and reliability across the whole country.

8. A 2 dose varicella vaccine schedule appears to be both safe and effective in the post partum period for those women identified as susceptible through screening, although further work is required to establish the optimum timing for vaccination, given some concerns regarding its administration to breast feeding mothers. The feasibility and logistics of implementing a 2 dose schedule is not yet certain as evidenced by the current rubella programme. Given the UK recommendation to avoid pregnancy for 3 months following the second vaccine dose, the acceptability of a post partum vaccination programme is critical for success.
9. At present there is a lack of evidence on both the public and health professionals' attitudes to a screening programme for chicken pox.
10. This review has highlighted a number of limitations with respect to current data collection systems, which should be strengthened
    i. There is a paucity of data on the number of women booking for antenatal care in the UK and their risk of exposure and infection during pregnancy, which needs addressing.
    ii. Data collection and surveillance systems vary widely across the UK. These should be aligned to allow meaningful comparisons to be made. For example whilst data is collected on the indication for issuing VZIG in England, Wales and Northern Ireland, this information is not currently collected in Scotland.
    iii. Current practice recommends the use of VZIG as post exposure prophylaxis, but there is a lack of current follow up data examining the outcome for the mother and her pregnancy.
11. There is limited evidence for the cost effectiveness of introducing antenatal screening with post partum vaccination in the UK. This needs to be addressed once we have better data on clinical effectiveness.

APPENDIX: SEARCH STRATEGY

Sources Searched: Medline, Embase, Cochrane Library

Dates of search: Medline1965-October 2008; Embase 1995-2008, Cochrane Library 2008 Issue 3.

Search strategies.
Medline (OVID interface)

1 Chickenpox/
2 exp pregnancy/
3 exp fetus/
4 exp pregnancy complications/
5 exp "congenital, hereditary, and neonatal diseases and abnormalities"/ or infant, newborn, diseases/
6 exp Chickenpox Vaccine/
7 exp herpes zoster/
8 perinatal care/ or postnatal care/ or preconception care/ or prenatal care/
9 exp Mass Screening/
10 exp prenatal diagnosis/
11 medical history taking/
12 (1 or 6 or 7) and (2 or 3 or 4 or 5 or 8 or 9 or 10 or 11)
13 limit 12 to yr="1995 - 2008"
14 Postpartum Period/
15 midwifery/ or obstetrical nursing/ or nurse midwives/
16 exp Immunization/
17 (1 or 6 or 7) and (14 or 15) and 16 (2)
18 13 or 17

Embase (OVID interface)

1 Chickenpox/
2 herpes zoster/ or herpes zoster encephalitis/ or herpes zoster ophthalmicus/ or herpes zoster oticus/
3 chickenpox measles mumps rubella vaccine/ or chickenpox vaccine/ or varicella zoster vaccine/
4 exp pregnancy/
5 Fetus/
6 exp pregnancy complications/
7 newborn disease/ or newborn infection/ or congenital infection/
8 prenatal screening/
9 exp obstetric care/
10 puerperium/
11 exp midwife/
12 exp immunization/ or exp genetic immunization/ or vaccination/ or revaccination/
13 (1 or 2 or 3) and (4 or 5 or 6 or 7 or 8 or 9)
14 (1 or 2 or 3) and (10 or 11) and 12
15 13 or 14
16 limit 15 to yr="1965 - 2008"

Cochrane Library (Wiley Interscience interface)

#1 chickenpox or varicella or (herpes near zoster)
#2 pregnan* or fetus or fetal or foetus or foetal or congenital or newborn or neonat*
#3 (#1 AND #2)
#4 MeSH descriptor Chickenpox explode all trees
#5 MeSH descriptor Herpes Zoster explode all trees
#6 MeSH descriptor Chickenpox Vaccine explode all trees
#7 MeSH descriptor Pregnancy explode all trees
#8 MeSH descriptor Fetus explode all trees
#9 MeSH descriptor Pregnancy Complications explode all trees
#10 MeSH descriptor Congenital, Hereditary, and Neonatal Diseases and Abnormalities explode all trees
#11 (postpart* or post-part* or puerper* or midwif* or midwiv*)
#12 (vaccin* or immuni*)
#13 MeSH descriptor Perinatal Care explode all trees
#14 MeSH descriptor Postnatal Care explode all trees
#15 MeSH descriptor Preconception Care explode all trees
#16 MeSH descriptor Prenatal Care explode all trees
#17 MeSH descriptor Mass Screening explode all trees
#18 MeSH descriptor Prenatal Diagnosis explode all trees
#19 MeSH descriptor Medical History Taking, this term only
#20 MeSH descriptor Postpartum Period, this term only
#21 MeSH descriptor Midwifery explode all trees
#22 MeSH descriptor Nurse Midwives explode all trees
#23 MeSH descriptor Obstetrical Nursing explode all trees
#24 MeSH descriptor Immunization explode all trees
#25 ((#4 OR #5 OR #6) AND (#7 OR #8 OR #9 OR #10 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19))
#26 ((#4 OR #5 OR #6) AND (#20 OR #21 OR #22 OR #23) AND #24)
#27 (#1 AND #11 AND #12)
#28 #3 or #25 or #26 or #27
#29 (#3 OR #25 OR #26 OR #27), from 1995 to 2008

Results.
All results were downloaded into an Access database, and 201 duplicates removed. A total of 843 citations remained.

Database	**No. citations retrieved**	**Exclusive**
Medline	492	478
Embase	529	358
Cochrane Library	60	44

1081 Total = 880

The title, abstracts and index terms of these citations, and where necessary and available the full text, were examined for relevance to antenatal varicella screening. 261 citations remained, and have been classified as follows.

Category	No. of citations
Editorials	2
Non-systematic reviews	61
Guidelines	7
Incidence	25
Transmission	20
Prevention – vaccination	15
Prevention – screening	19
Identification	3
Management	28
Case reports	81
Total	261

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