



Validity of a reported history of chickenpox in targeting varicella vaccination at susceptible adolescents in England[☆]



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ABSTRACT

Introduction: In the UK, primary varicella is usually a mild infection in children, but can cause serious illness in susceptible pregnant women and adults. The UK Joint Committee on Vaccination and Immunisation is considering an adolescent varicella vaccination programme. Cost-effectiveness depends upon identifying susceptibles and minimising vaccine wastage, and chickenpox history is one method to screen for eligibility. To inform this approach, we estimated the proportion of adolescents with varicella antibodies by reported chickenpox history.

Methods: Recruitment occurred through secondary schools in England from February to September 2012. Parents were asked about their child's history of chickenpox, explicitly setting the context in terms of the implications for vaccination. 247 adolescents, whose parents reported positive (120), negative (77) or uncertain (50) chickenpox history provided oral fluid for varicella zoster virus-specific immunoglobulin-G (VZV-IgG) testing.

Results: 109 (90.8% [85.6–96.0%]) adolescents with a positive chickenpox history, 52 (67.5% [57.0–78.1%]) with a negative history and 42 (84.0% [73.7–94.3%]) with an uncertain history had VZV-IgG suggesting prior infection. Combining negative and uncertain histories, 74% had VZV-IgG (best-case). When discounting low total-IgG samples and counting equivocal as positive (worst-case), 84% had VZV-IgG. We also modelled outcomes by varying the negative predictive value (NPV) for the antibody assay, and found 74–87% under the best-case and 84–92% under the worst-case scenario would receive vaccine unnecessarily as NPV falls to 50%.

Conclusion: Reported chickenpox history discriminates between varicella immunity and susceptibility in adolescents, but significant vaccine wastage would occur if this approach alone were used to determine vaccine eligibility. A small but important proportion of those with positive chickenpox history would remain susceptible. These data are needed to determine whether reported history, with or without oral fluid testing in those with negative and uncertain history, is sufficiently discriminatory to underpin a cost-effective adolescent varicella vaccination programme.

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1. Introduction

Primary varicella infection (chickenpox) is an acute illness caused by varicella-zoster virus (VZV), which is characterised by a generalised vesicular rash, fever and malaise. [1] In the UK, most chickenpox occurs in children under 10 years old and is mild. Seroprevalence data suggest 80% of 11-year-olds in England and Wales

have previously been exposed to varicella infection. [2] Serious illness mainly occurs in immunocompromised individuals and the remaining susceptible adults, which is of particular concern in pregnancy, and may lead to maternal complications (e.g. varicella pneumonia) and severe foetal consequences (e.g. congenital varicella syndrome). When VZV reactivates from dorsal root ganglia in later life, this causes a painful dermatomal rash known as herpes zoster or shingles.

Universal varicella immunisation has not been introduced in the UK, in part due to concerns that this may shift the burden of primary disease to susceptible adults, who are at higher risk of complications, [3–5] and increase shingles reactivations, due to reduced natural boosting in those previously exposed [4,5]. A recent review by the Joint Committee on Vaccination and Immunisation (JCVI) concluded that a two-dose childhood varicella vaccination schedule was not cost-effective, but JCVI did recommend a single-dose herpes zoster vaccine for adults aged 70–79 [6].

To prevent severe primary infections among adults, alternative approaches to routine childhood varicella vaccination are being considered in the UK [7]. In particular, the introduction of a selective adolescent varicella vaccination programme may be cost-effective [5]. Given that most adolescents will have acquired natural immunity, the cost-effectiveness of this approach will largely depend upon accurate pre-immunisation identification of susceptibles to minimise vaccine wastage in those already immune. Two screening methods are available: reported chickenpox history, or laboratory testing for VZV-specific immunoglobulin G (IgG) antibody, which is significantly more expensive, more time consuming and likely to involve higher dropout rates.

Understanding the validity of reported chickenpox history in the target group is essential to inform this decision, and to model the impact and cost-effectiveness of the overall approach. Oral fluid (gingivocrevicular fluid) is simple and non-invasive to collect, and with appropriately sensitive assays can be used for the detection of viral antibodies for seroprevalence studies [8]. This study estimates the proportions of adolescents already immune to VZV, by reported chickenpox history, using detection of VZV-specific antibodies in oral fluid as a serological correlate suggesting previous infection.

2. Methods

Recruitment occurred during February to September 2012. The study aimed to recruit a group broadly representative of the British general population, where approximately 15% of adolescents are of non-white ethnicity, [9] because differences in the predictive value of chickenpox history by ethnicity have been reported. [10,11] Adolescents were therefore recruited through two secondary schools in South London to increase the number of non-white participants, and two other regions of England (Hertfordshire and Gloucestershire). Participating schools provided all students aged 11–15 with study information packs to take home to their parents. Individuals with any serious health condition causing immune dysfunction, who would be ineligible to receive a live vaccine, and those who had previously received a varicella vaccine were excluded.

Study packs asked parents to return a short questionnaire by post, including their child's ethnicity and the following question about chickenpox history: "Most children will have had chickenpox by the time they are 10 years old. Chickenpox infection provides long-term protection against future infection and there is no need for vaccination if someone has already had chickenpox. We want you to think about your child's history of chickenpox in this context. Has your child had chickenpox?" Answers were: (1) "Yes (If yes, your child does not need chickenpox vaccine)", (2) "No" or (3) "I don't know". To increase the number of negative and uncertain responses towards the end of the study, after receiving over 500 positive responses,

the question was altered to, "Has your child had chickenpox? (If you answer yes, we do NOT need you to complete or return this form as we have now received enough replies from this group)".

Parents who returned the questionnaire were sent a consent form and a kit to collect oral fluid, with clear instructions on how to obtain a sample from their child, which they were asked to return to the Health Protection Agency (HPA). Approximately 7000 introductory letters were distributed by schools; 550 questionnaires were returned with a positive history of chickenpox, 84 with a negative history, and 56 with an uncertain history, and 1 was incomplete. We posted 268 oral fluid kits, including 128 to respondents with a positive history of chickenpox and all those with negative or uncertain histories.

Families were informed at the outset in the initial study information pack that, as a token of appreciation, a voucher for £10 would be sent to them once a sample was received in the laboratory. Children found to be susceptible to varicella were offered two doses of varicella vaccine without charge.

2.1. Laboratory procedures

Oral fluid samples and consent forms were received by the HPA Virus Reference Department, MS-Colindale, and processed to extract VZV-IgG using standard methods and diluents. Oral fluid samples were stored at -30°C prior to batch testing. For semi-quantitative determination of IgG antibodies to VZV, the in-house VZV-IgG time resolved fluorescence immunoassay, (TRFIA), [12] was modified for testing oral fluid. Testing of paired serum and oral fluid samples, had previously established that measurements above a cut-off of 0.35 mIU/mL should be considered positive, below a cut-off of 0.25 mIU/mL as negative, with an equivocal range between 0.25 and 0.35 mIU/mL. [HPA unpublished data] Samples testing negative or equivocal were also tested for total IgG to determine whether the sample had been taken appropriately and contained sufficient total IgG, using a cut-off of greater than 2.5 mg/L.

2.2. Data analysis

Data were analysed using Stata v12 (Stacorp, TX, US). For each chickenpox history group, we aimed for a sample size of 100, to estimate with reasonable precision the proportion with VZV-IgG (95% confidence interval within $\pm 10\%$). The study was not designed or powered to detect differences by ethnicity. Exact 95% confidence intervals for proportions were calculated and proportions compared according to history using two-sided Fisher's exact tests. We also undertook a sensitivity analysis to investigate the impact of using the oral fluid assay in populations with different VZV-IgG prevalence by modelling the effect of different values for the negative predictive value (NPV) of the assay.

3. Results

120 oral fluid samples were received from respondents with a positive history of chickenpox, 77 with a negative history and 50 with an uncertain history. The average age of respondents was 13 years, and 85% were white, 6% mixed ethnicity, 6% Asian, 3% Black, and 1% Chinese. The groups with different history responses were not significantly different with respect to age or ethnicity (data not shown).

Overall, 109 (90.8% [95% CI 85.6–96.0%]) with a positive history of chickenpox, 52 (67.5% [57.0–78.1%]) with a negative history and 42 (84.0% [73.7–94.3%]) with an uncertain history had VZV-IgG antibodies indicating previous varicella infection (Table 1). 16 oral fluid samples were found to have insufficient total IgG for reliable detection of specific VZV-IgG, including 13 (81%) from respondents with a negative or uncertain history, suggesting these

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