

Predictive value of a history of varicella infection

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ABSTRACT

OBJECTIVE To determine whether a history of previous varicella infection provides a reliable marker for prior infection.

QUALITY OF EVIDENCE MEDLINE was searched from January 1996 to May 2002 using the MeSH headings "varicella," "chickenpox," and "medical history taking." Recommendations in this paper are based on evidence from well designed cross-sectional studies.

MAIN MESSAGE Serologic testing is advised, rather than presumptive vaccination, for those with a negative or uncertain history of varicella; most will be immune. For those with a positive history of varicella, the advice given depends on the population. For populations at higher risk of varicella infection (eg, health care workers, pregnant women), routine serum testing is recommended. For low-risk populations, physicians could accept a positive history of varicella as a reliable indicator of immunity.

CONCLUSION Most studies found that patients' history of varicella had a high positive predictive value and a low negative predictive value. These findings suggest that a positive history of varicella is a reliable marker of disease while a negative history does not predict lack of immunity.

RÉSUMÉ

OBJECTIF Déterminer si une histoire de varicelle est un marqueur fiable d'infection antérieure.

QUALITÉ DES PREUVES Une recherche a été effectuée dans MEDLINE entre janvier 1996 et mai 2002 à l'aide des rubriques MeSH «varicella,» «chicken pox» «medical history taking.» Les recommandations formulées dans cet article sont fondées sur des études transversales bien structurées.

PRINCIPAL MESSAGE En cas d'histoire de varicelle négative ou incertaine, il est préférable de demander un test sérologique plutôt que de présumer une vaccination. Devant une histoire positive de varicelle, la recommandation dépend de la population en cause. Pour les groupes à risque élevé de contracter l'infection (travailleurs de la santé, femmes enceintes, etc.), on recommande un test sérologique systématique. Dans le cas de populations à faible risque, une histoire positive de varicelle pourrait être acceptée comme un indicateur fiable d'immunité.

CONCLUSION La plupart des études ont trouvé qu'une histoire de varicelle possède une forte valeur prédictive positive et une faible valeur prédictive négative. Les présentes données suggèrent qu'une histoire positive de varicelle constitue un marqueur fiable de cette maladie tandis qu'une histoire négative n'indique pas un défaut d'immunité.

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Cet article a fait l'objet d'une évaluation externe.

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Varicella (chickenpox) is caused by primary infection with the varicella zoster virus (VZV), a member of the herpes family. The virus is highly contagious and is spread through respiratory droplets or direct contact. Varicella can infect non-immune adults; disease increases in severity with age, and often causes serious morbidity and absences from work.¹ In Canada from 1987 to 1996, 70% of reported deaths due to varicella were among adolescents and adults.² When acquired during pregnancy, varicella can cause serious perinatal morbidity.^{3,4} Following varicella infection, more than 95% of people develop antibodies against varicella (VZV IgG).⁵ These antibodies can be detected by serologic testing; they indicate lifelong immunity to varicella.

Clinicians face the dilemma of whether to rely on a history of varicella to identify susceptible patients or to do serum testing. This article examines whether a patient's history of previous varicella infection provides a reliable marker of prior infection.

Quality of evidence

MEDLINE was searched from January 1996 to May 2002 using the key words "varicella" or "chickenpox" for studies in which patients' history of chickenpox exposure was compared with VZV serology. The key words were exploded, and 2103 articles were found. After limiting the search to human studies and English language, 1716 articles remained. Combining these articles with the key word "medical history taking" identified five articles. When the abstracts of all 1716 articles were reviewed, six more relevant articles were identified. Bibliographies of these 11 articles were reviewed to obtain further references. One additional article was found. Thus, 12 articles were identified that examined the predictive ability of self-reported history of varicella.⁶⁻¹⁷ All 12 articles were cross-sectional studies

(level II evidence), one was a cost-benefit study,¹⁴ and one examined cost-effectiveness.¹³ **Table 1**⁶⁻¹⁷ summarizes the literature review.

Main findings

Study outcomes included one or more of sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) (**Table 2**). Six of the 12 studies included only patients with a negative or uncertain history of varicella^{8,10-14} so only the negative predictive value, and not the positive predictive value, could be determined.

Three studies included only health care workers,⁶⁻⁸ two studies included only pregnant women,^{9,10} two studies included only children,^{11,18} and four studies included only adolescents and young adults (three of these examined military populations).¹²⁻¹⁵ One study examined two populations: pregnant women and men and women of all ages.¹⁶

Health care workers. Alagappan et al⁶ determined the association of self-reported history of varicella infection with varicella serology in medical house officers. Only two of 119 house officers with a positive varicella history were nonimmune. Only one of 10 subjects who reported previously receiving varicella vaccine was nonimmune. Thus, a reported history of varicella or past varicella vaccination did not ensure the presence of protective varicella titres (PPV 98%, NPV 27%). The authors⁶ recommend documenting varicella titres in all house officers.

Gallagher et al⁷ confirmed that a reported history of chickenpox was not a reliable marker for immune status among health care workers (PPV 95%, NPV 11%). The authors⁷ concluded that all health care workers involved in caring for patients should be screened with VZV serology before taking up duty.

Coyle et al⁸ examined seroprevalence of VZV among female health care workers. An NPV of 6% was found. Based on extrapolation of results, the authors recommended asking women at their first antenatal visit whether they had had chickenpox and offering serologic testing to those who had not. The authors⁸ suggested that nonimmune pregnant

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Table 1. Summary of literature review

STUDY	SUBJECTS AND SETTING	TYPE OF STUDY	FINDINGS	AUTHORS' CONCLUSIONS
HEALTH CARE WORKERS				
Alagappan et al, 1999 ⁶	154 male and female house officers with a mean age of 30 in a university-affiliated teaching hospital	Cross-sectional	PPV 98%, NPV 27%, seroprevalence 96%	Recommended serologic testing for all house officers, regardless of self-reported history or previous vaccination
Gallagher et al, 1996 ⁷	206 health care workers attending an occupational health department in Ireland	Cross-sectional	PPV 95%, NPV 11%, sensitivity 61%, specificity 36%, seroprevalence 96%	Serologic testing for all health care workers involved in patient care
Coyle et al, 1997 ⁸	2884 female health care workers in Ireland aged 16-45 y with no history of chickenpox	Cross-sectional	NPV 6%, seroprevalence 94%	Offer serologic testing at first antenatal visit to women with negative or uncertain histories of varicella
PREGNANT WOMEN				
Karunajeewa and Kelly, 2001 ⁹	308 pregnant women at an antenatal clinic in Australia	Cross-sectional	PPV 95%, NPV 9%, sensitivity 65%, specificity 47%, seroprevalence 93%	Serologic testing advised for high-risk groups regardless of self-reported history
Silverman et al, 1996 ¹⁰	Group 1: 81 pregnant women with negative or uncertain histories of chickenpox. Group 2: 100 pregnant women with positive histories of chickenpox at an obstetric clinic in the United States; mean age was 28 y	Cross-sectional	NPV 35% (significantly lower NPV if uncertain history: 6% vs 53% if negative history), seroprevalence 84%	Pregnant women with negative histories of varicella might benefit most from routine serologic testing
Nordin et al, 1998 ¹¹	Group 1: 599 male and female subjects. Group 2: 403 pregnant women, with negative or uncertain histories of chickenpox in a community-based HMO in the United States	Cross-sectional	NPV decreased with increasing age. Group 1: NPV 87.5% at age 0-6 y and 5% at age >40 y. Group 2: NPV 19% at age <30 y and 10% at age >30 y	Serologic testing for all hospital workers with negative histories of varicella before immunization
CHILDREN AND ADOLESCENTS				
Lieu et al, 1998 ¹²	1177 children aged 7-12 y with negative or uncertain histories of chickenpox whose HMO clinicians had ordered varicella serum testing in the United States	Cross-sectional	NPV 32%-91% depending on age and clinical history (negative or uncertain), seroprevalence 31%	Most cost-effective to recommend serum testing before deciding about vaccination for children aged 9-12
Boulianne et al, 2001 ¹³	181 children with negative or uncertain histories of chickenpox and a mean age of 10 y in the region of Quebec city	Cross-sectional	NPV 37%, but significantly lower if uncertain history (18%) vs negative history (44%), seroprevalence 63%	Negative or unknown history of varicella is not well correlated with absence of immunity
Harel et al, 2001 ¹⁴	40 adolescents with a mean age of 15 y and negative or uncertain histories of chickenpox at a hospital-based adolescent clinic in the United States	Retrospective chart review	NPV 20%, seroprevalence 80%	Serologic testing advised for adolescents with negative or uncertain histories of varicella rather than presumptive vaccination
YOUNG ADULTS (MILITARY PERSONNEL)				
Wallace et al, 1997 ¹⁵	20 male military recruits with a mean age of 21.3 y with varicella and positive history of prior varicella infection in a military hospital in the United States	Cross-sectional	19 of 19 subjects' prebanked serum showed no antibodies to VZV	Positive history of previous varicella might not be reliable
Jerant et al, 1998 ¹⁶	1201 new soldiers aged 17-25 at a military training facility in the United States	Cost-effectiveness analysis	PPV 98.5%, NPV 23%, seroprevalence 96%	Positive history of varicella accurately predicts immunity in young adults. Serologic testing recommended for those with negative or uncertain histories
Burnham et al, 1998 ¹⁷	1400 cadets aged 18-24 y at a military university in the United States	Cost-benefit analysis. Cross-sectional	PPV 96%, NPV 44%, sensitivity 90%, specificity 70%, seroprevalence 90%	Serologic testing of all incoming cadets and vaccinating seronegative cadets is cost-beneficial

FN—false-negative result; FP—false-positive result; HMO—health maintenance organization; NPV—negative predictive value (proportion of those reporting a negative history of varicella who are seronegative [ie, TN/(TN+FN)]); PPV—positive predictive value (proportion of those reporting a positive history of varicella who are seropositive [ie, TP/(TP+FP)]; TN—true-negative result; TP—true-positive result; VZV—varicella-zoster virus.

Table 2. Two-by-two table illustrating sensitivity, specificity, and positive and negative predictive values

HISTORY OF VARICELLA	IMMUNE BY SEROLOGIC TESTING	NONIMMUNE BY SEROLOGIC TESTING
POSITIVE	TRUE POSITIVE (TP)	FALSE POSITIVE (FP)
NEGATIVE	FALSE NEGATIVE (FN)	TRUE NEGATIVE (TN)

Sensitivity is the proportion of seropositive people who report a positive history of varicella (TP/TP+FN)

Specificity is the proportion of seronegative people who report a negative history of varicella (TN/TN +FP)

Positive predictive value is the proportion of people who report a positive history of varicella who are seropositive (TP/TP+FP)

Negative predictive value is the proportion of people who report a negative history of varicella who are seronegative (TN/TN+FN)

women should be counseled on the risk of exposure to patients with active chickenpox.

Studies examining health care workers⁶⁻⁸ support serologic testing for all health care workers, regardless of self-reported history of varicella. Varicella, a recognized nosocomial infection, is an occupational hazard for susceptible health care workers. Workers could also spread the disease to patients under their care; immunocompromised patients are at particularly high risk of varicella-associated morbidity. It is perhaps even more important to determine varicella susceptibility among health care workers than in the general population.

Pregnant women. Karunajeewa and Kelly⁹ found that 5% of pregnant women who think they have had chickenpox are actually nonimmune (PPV 95%, NPV 9%). For high-risk groups, such as pregnant women, health care workers, and household contacts of immunocompromised people, the authors recommend serologic testing regardless of self-reported history of varicella infection. Despite studying only pregnant women, the authors⁹ have generalized their results to other high-risk groups.

Silverman et al¹⁰ studied women at their first prenatal visit who gave either a negative or uncertain varicella history and had VZV serologic testing. Women with negative varicella histories were significantly less likely to be immune to varicella than those with uncertain histories (NPV 53%, NPV 6%,

respectively). A comparison group of women with positive varicella histories were all found to be immune (PPV 100%). In contrast to the recommendations of Karunajeewa and Kelly,⁹ Silverman et al¹⁰ concluded that women with positive histories of varicella infection could be excluded from prenatal screening programs. They suggested it might be prudent to screen women with uncertain histories only as needed because most of them would be immune. They thought women with negative VZV histories might benefit most from routine prenatal screening because fewer than half would actually be nonimmune. The authors¹⁰ made no mention of the role of varicella vaccine.

Nordin et al¹¹ studied two series of patients, one consisting of pregnant women with negative histories of varicella infection. They found that the NPV decreased with increasing age. The authors¹¹ extrapolated their results to health care workers and advised serologic testing for all those with negative histories of varicella before immunization.

It is crucial to establish VZV immunity in women of childbearing age and pregnant women because of potential adverse fetal and perinatal sequelae.¹⁸ Two studies recommend that pregnant women have routine serologic testing for varicella, regardless of history.^{9,11} Coyle et al⁸ recommend routine testing for varicella immunity, but Silverman et al¹⁰ say that pregnant women with a positive varicella history can be excluded from routine VZV serologic testing.

Preconception testing would be beneficial; susceptible women could be vaccinated against varicella. Women should be advised to avoid pregnancy for 1 month following each dose of varicella vaccine.¹⁸ Pregnancy is a contraindication to the varicella vaccine, but breastfeeding is not, so women nonimmune to varicella should be vaccinated as early in the postpartum period as possible.¹⁸ Future studies should examine the PPV and NPV of a history of varicella among nonpregnant women of childbearing age.

Children and adolescents. Lieu et al¹² described varicella seroprevalence among children aged 7 to 12 years with a negative or uncertain history of chickenpox. Prevalence varied from 9% to 68%, depending on age and clinical history. More children with uncertain histories were seropositive, and prevalence of seropositivity increased with age. The authors found that it would be most cost effective to test serum samples before deciding about varicella vaccination for children aged 9 to 12 with uncertain chickenpox histories.

Boulianne et al¹³ also examined varicella immunity among 10-year-old children with negative or uncertain chickenpox histories. Prevalence of seropositive results was 63%. Again, more children with uncertain histories were seropositive, compared with children with negative histories. The authors¹³ concluded that a negative or unknown history is not well correlated with aphyllaxis.

Harel et al¹⁴ performed a retrospective chart review of adolescents reporting a negative or uncertain chickenpox history. They found a NPV of 20%. The authors recommended serum testing for a previously unnoticed varicella infection and subsequent vaccination of susceptible individuals.

Studies involving children and adolescents found a low NPV overall. The NPV was significantly lower ($P < .001$) among those with uncertain histories than among those with negative histories.¹²⁻¹⁴ Serum testing before vaccination is suggested for those with a negative or uncertain varicella history. Children and adolescents with a positive history of varicella were not studied, so clinicians are left with the question of whether to test or presumptively vaccinate them.

Young adults (military personnel). Three studies focused on military personnel only.¹⁵⁻¹⁷ Wallace et al¹⁵ evaluated young male military recruits with varicella, who claimed to have had varicella previously, to determine whether they had true second episodes of varicella. All prior serum samples of those with positive varicella histories were negative. Thus, history of previous varicella infection in adults with varicella might be unreliable; true second episodes of varicella are rare.

Two of the three studies examining military recruits found a high PPV and a low NPV for history of varicella infection.^{16,17} The authors drew varying conclusions from these results.

Jerant et al¹⁶ found that, among army recruits, the most cost-effective strategy was to test only those with a negative varicella history and vaccinate seronegative recruits (PPV 99%, NPV 23%). They note, however, that this strategy led to the lowest number of cases being prevented and that testing serum samples from all recruits regardless of history was nearly as cost effective and led to more cases being prevented. Burnham et al¹⁷ found that serologic screening of all cadets and vaccinating susceptible ones was cost effective (PPV 96%, NPV 44%).

An important limitation of many studies is that the PPV was not determined. Also, whether results of these studies can be generalized to primary care is uncertain.

Discussion

This study was done to determine the predictive value of a history of varicella. Findings suggest that a positive history of varicella is reliable, but a negative history is not.

Negative or uncertain history of varicella. Most studies in this review conclude that, for those with a negative or uncertain history of varicella, serologic testing is advisable, rather than presumptive vaccination, because most of these people will be immune.

Positive history of varicella. Advice differs for those with a positive history of varicella, depending on the particular risks of varicella infection among the population. Among those at higher risk of varicella infection, such as health care workers and pregnant patients, routine serum testing is recommended regardless of self-reported varicella history. It is important to consider the level of risk of exposure to varicella, however. For pregnant patients at low risk of exposure, a positive history of varicella might be sufficient. For those at high risk of exposure or transmission, routine serum testing for varicella is prudent.

High-risk groups include people who live or work in environments where transmission of varicella is likely (eg, teachers of young children, day-care employees, and residents and staff in institutions); people who live and work in environments where transmission can occur (eg, college students, inmates and staff of correctional institutions, and military personnel); non-pregnant women of child-bearing age; adolescents and adults living in households with children; and international travelers.¹⁸

Conclusion

Our findings indicate that a history of varicella has a high PPV and a low NPV for immunity. Serologic testing is advised, rather than presumptive vaccination, for those with a negative or uncertain history of varicella because most of these people will be immune. For those at increased risk of varicella infection, routine serum testing, regardless of self-reported varicella history, is recommended. For populations at lower risk, it might be reasonable to accept a positive history of varicella as a reliable indicator of immunity.

More investigation is needed to evaluate the PPV of a self-reported history of varicella, including further studies of primary care populations. Whether particular vaccination strategies are appropriate, cost-effective, or cost-beneficial depends on the unique circumstances of the population examined. Cost of serologic testing; cost of vaccination; and the potential financial, social, and medical consequences of developing varicella should be considered. ❁

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EDITOR'S KEY POINTS

- Can physicians trust a positive history of varicella or must they verify immunity through antibody testing?
- This update concludes that a positive history is a reliable marker of disease. A negative history, however, is unreliable, because most people who have not had varicella still have antibodies in their systems.
- Clinical management varies according to risk of exposure to varicella. For those at high risk (pregnant women, health care workers), routine vaccination is recommended. For those at low risk, physicians can consider a positive history of varicella as a reliable marker of disease.

POINTS DE REPÈRE DU RÉDACTEUR

- Peut-on se fier à une histoire clinique positive de varicelle ou doit-on vérifier l'immunité par un dosage des anticorps?
- Cet article de mise à jour conclut qu'une histoire clinique positive de varicelle est fiable. Par contre, une histoire négative n'est pas fiable car la plupart des individus n'ayant pas d'antécédent de varicelle ont des anticorps.
- La conduite clinique varie selon niveau de risque d'être exposé à la varicelle. Chez les individus à haut risque (p.ex. certains travailleurs, femmes en âge de procréer), il est prudent de faire une sérologie de routine même en présence d'une histoire clinique positive de varicelle. Chez les individus à faible risque, il est raisonnable de considérer qu'une histoire clinique positive de varicelle est fiable.

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