

Varicella vaccine in post-exposure prophylaxis

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Abstract

Evidence concerning the effectiveness of Oka-based varicella vaccines when administered following exposure to varicella zoster virus in domestic and hospital settings is reviewed. The evidence appears to support post-exposure use of Oka-derived varicella vaccines in children within 3 days of rash onset in the index case. Despite vaccination, a small proportion will develop mild, but infectious, chickenpox, especially if they have been exposed in the household setting. Controlled studies of post-exposure prophylaxis in adults using both Varilrix and Varivax II are still needed. The applicability of this approach to disease control in health care facilities and in community settings warrants wider discussion. *Commun Dis Intell* 2001;25:13-15.

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Background

Two live, attenuated, varicella vaccines derived from the Oka strain of varicella-zoster virus (VZV) Varilrix (Glaxo Smith-Kline Beecham) and Varivax II (Merck/CSL) received Australian marketing approval during 2000. The indication for their use is the prevention of chickenpox in healthy individuals of 12 months of age or older. This paper reviews evidence concerning the effectiveness of Oka-based vaccines when administered following exposure to VZV. Use of the vaccines in Australia for post-exposure prophylaxis is not currently approved by the National Health and Medical Research Council; this is reflected in the 2000 edition of the *Australian Immunisation Handbook* and approved product information.

Theoretical basis for post-exposure prophylaxis

The development and use of Oka-based vaccines was first reported by Takahashi and colleagues in Japan in 1974.¹ Since that time several reports have referred to post-exposure prophylaxis in hospital or household settings using experimental or production lots of vaccine of varying composition and infectivity/virus dose. The theoretical basis for post-exposure prophylaxis relates to the ability of Oka-derived vaccines to induce cell-mediated and antibody responses within 5 to 7 days^{2,3} and the relatively prolonged incubation period of 10 to 18 days of primary VZV infection, ie chickenpox. The pathogenesis of chickenpox follows the general scheme for viral exanthems proposed by Fenner.⁴ Respiratory tract inoculation allows initial viral replication in regional lymph nodes. Primary viraemia leads to replication in the liver and spleen, and secondary viraemia disseminates virus (within infected mononuclear cells) to various organs including the skin leading to the characteristic rash. An immune response mounted prior to the secondary viraemia may abort or ameliorate clinical disease.

Post-exposure prophylaxis in the hospital setting

In their original report, Takahashi and colleagues described 23 children seronegative by complement fixation titre who received vaccine with 500 plaque forming units (PFU) of infectious virus 'immediately' (not otherwise defined) after

diagnosis of the index case. Two children developed low-grade fever and a mild vesicular rash attributed to the vaccine.¹

Katsushima and colleagues first reported in 1982 administration of experimental vaccines containing between 250 and 3,000 PFU to children with no history of chickenpox after hospital exposure and extended their findings in a later report. None of 149 children receiving 250-3,000 PFU within 3 days of exposure and none of 15 who received 1000 PFU at 100 hours (ie 4 days, rather than 5) became ill.^{5,6}

A further Japanese report found that 41 of 46 child contacts given 'emergency vaccination' with 300-2,000 PFU were protected from disease, but gave no details of timing.⁷

Post-exposure prophylaxis in the household setting

Asano and colleagues reported a controlled trial using experimental vaccines of varying infectious doses in which none of 17 seronegative children vaccinated within 3 days of onset of chickenpox rash in a sibling developed illness compared with 19 of 19 unvaccinated household contacts who developed chickenpox.⁸ The same group reported their experience with 43 child contacts in the absence of controls: 4 of 10 given 300-600 PFU, but all of 30 given 800-15,000 PFU within 3 days of household exposure were protected, whilst none of 3 given 1,500-4,000 PFU at 5 days were protected (no subjects were vaccinated at 4 days).⁹ Naganuma and colleagues also found that 30 of 40 sibling contacts were protected by 'emergency vaccination' with 300-2,000 PFU, but details of vaccination timing were not provided.⁷

An extensive US dose-ranging study incorporated a small randomised double blind, placebo-controlled trial of post-exposure prophylaxis using a pre-production 4,350 PFU Oka-Merck vaccine.¹⁰ Of 13 placebo recipients, 12 developed chickenpox. In the active group, only one of 10 vaccinated within 3 days of exposure developed mild chickenpox (20 lesions) whilst all 3 vaccinated at 4 to 5 days developed mild disease.¹⁰

Only 2 English-language reports evaluating standard production lots of vaccine for this purpose have been published, both US studies of the licensed Oka/Merck

vaccine containing no less than 1350 PFU. In the first, 10 children without a history of chickenpox were vaccinated within 3 days of rash onset in a sibling; of these, 5 developed mild illness with 5 to 83 skin lesions and 5 remained well.¹¹

In the most recent study, residents of a women's refuge with a negative chickenpox history were offered vaccination within 3 days of onset of rash in a mother and her child. The authors argued that this setting was equivalent to a household. None of 25 adults and only 2 of 42 children developed illness. However, the 2 children with chickenpox were members of the family of (and were housed in the same room as) the index case and both developed a brief, afebrile illness characterised by fewer than 20 lesions.¹²

Summary of results

The studies described above lend credence to the view that post-exposure prophylaxis with Oka-derived varicella vaccine is feasible. In relation to the hospital setting, one uncontrolled study of experimental vaccine batches suggested that vaccination within 3 days (and possibly within 4 days) prevented illness.⁶

More, and more recent, data are available regarding vaccination of children following household exposure. A controlled study demonstrated that early, Japanese experimental vaccine batches were protective when given within 3 days of exposure,⁸ as did a double-blind, randomised, control trial of Oka/Merck vaccine containing three times the infectious virus of the current vaccines.¹⁰ The only 2 studies using licensed vaccine, both uncontrolled, showed protection against moderate-to-severe disease, but some occurrence of mild disease (mostly fewer than 20 lesions) following household exposure.^{11,12}

Reliable data are not available in relation to contact with zoster, a far less infectious condition than chickenpox, although in theory prompt post-exposure prophylaxis should also offer protection.

There is minimal and conflicting evidence regarding protection when vaccine is received 4 to 5 days after exposure.^{6,9,10} In interpreting the data, it should be borne in mind that all of the Japanese studies refer to days after exposure, whilst the US studies refer to days after onset of lesions. However, it is probable that all studies counted the first day of exposure as the day of onset of the varicella rash. Variation in vaccination effectiveness between studies may be explained by the more intense exposure in the household setting and the greater likelihood of exposure to the index case in the 2 days before rash onset.

Caveats and discussion

Scientific issues affecting the applicability of these studies include the small numbers of subjects, variety of vaccine formulations and infectivity, and paucity of data relevant to current commercial vaccines (and absence of data relating to the 2,000 PFU Varilrix vaccine). Most studies used inadequate assessment of susceptibility, based on history; a negative history, especially in adults,¹³ is poorly predictive of VZV susceptibility. The study in the women's refuge found that no vaccinated adult contacts developed chickenpox,¹² but it is likely that the majority were immune, and in the absence of a control group the true effect of vaccination cannot be determined.

Subjects in all other studies were children, rather than adolescents or adults in whom 2 doses of varicella vaccine

are recommended for reliable pre-exposure protection. Thus, the feasibility and effectiveness of post-exposure prophylaxis in those aged 13 years and older is unknown.

The final consideration is the interpretation of, and response to, the individual who develops a papular or vesicular rash following post-exposure varicella vaccination. A mild rash occurs 7 to 28 days after vaccination in approximately 5 per cent of recipients, so that a rash developing within a week of vaccination is most likely to be a result of natural infection. However, the individual is considered potentially infectious whether the rash is vaccine-induced or associated with natural VZV infection, and should be isolated from non-immune contacts in accordance with accepted practice for the particular setting. Vesicular fluid should be collected and sent to a virology laboratory for virus strain identification by polymerase chain reaction.

Conclusions

Theoretical considerations and experimental evidence appear to support the post-exposure use in children of Oka-derived varicella vaccines within 3 days of rash onset in the index case. Despite vaccination, a small proportion will develop mild, but infectious, chickenpox, especially if they have been exposed in the household setting. Controlled studies of post-exposure prophylaxis in adults using both Varilrix and Varivax II are still needed, whilst the applicability of this approach to disease control in health care facilities and in community settings warrants wider discussion.

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