incidence among children aged 3–6 years (who have the highest varicella age-specific incidence) was 10–14% and by age eight years, only 20% of children were still susceptible to varicella[2]. Using the life-tables method, we calculated incidence among susceptible 3–6-year-old children from Finger's data to be 16–26% per year not including subclinical infections, which approximates the 32.2%-per-year rate of infection plus boosting among children with the lowest anti-VZV titers described by Krause and Klinman.

Secondly, the colorimetric detection system used in ELISA produces data that are linear only over a short range of optical density values; as such, the four-fold increases in antibody titer reported by the authors are inherently more difficult to obtain among persons with a high initial titer than among those with a low or negative titer.

We do not agree that the lack of similar serologic findings among children vaccinated with hepatitis-B vaccine rules out the possibility that the VZV findings were an artifact of the analysis method. Compared with varicella, hepatitis B is an uncommon disease with minimal risk of exposure and boosting of immunity for pre-adolescent children in the United States.

The authors conclude, on the basis of one unpublished report of isolation of vaccine VZV in a healthy vaccine recipient five months after vaccination, that breakthrough disease is caused by the vaccine strain VZV. They neglect to cite extensive published data that have documented the exclusive association of wild-type VZV with breakthrough disease[3–5]. Other evidence contrary to the authors' conclusion comes from studies of immunocompromised children among whom reactivation of the vaccine virus as herpes zoster, not as varicella, has been correlated with cell-mediated immunity, not with antibody titers[6].

Certainly, vaccine strain VZV could potentially reactivate given that it is a viable herpes virus but we disagree that these data provide evidence for this phenomenon. Our interpretation of these data is that antibody boosting reflects exposures to wild-type VZV, that the risk of breakthrough disease is related to antibody titers after vaccination[3,4,7] and that vaccinees with high titers are unlikely to develop a four-fold boost on subsequent exposure. The varicella vaccine trials were conducted when varicella disease was common. The authors' hypothesis will be best tested when, through widespread vaccination, exposure to VZV becomes rare.

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To the editor—Krause *et al*.[1] have suggested that subclinical and possibly clinical reactivation of VZV serves to boost the humoral immune response in previously immunized healthy children.

We reviewed our prior experience and that from two ongoing prospective studies[8–10] of rashes occurring more than six weeks after varicella vaccination of healthy subjects. All 72 vaccinees (9 leukemic children, 6 healthy adults, 57 healthy children) with breakthrough varicella, characterized by a generalized maculopapular or vesicular rash, in whom VZV DNA was amplified, the wild-type virus was identified. In the two prospective studies, there were 57 vaccinees who had rashes caused by wild-type VZV, but in addition there were 36 vaccinees with rashes who were PCR-negative for VZV, and 19 vaccinees with rashes whose results were indeterminate. The second two groups indicate that some of the rashes were caused by something other than VZV and that some samples were not properly obtained. The sensitivity of the assay as determined by serial dilutions of extracted VZV Oka & wild-type DNA was previously found to be approximately 100 femtograms[10b]. In 38 patients with zoster, the vaccine strain was identified in 25 (3 leukemic and 22 healthy children) and the wild-type strain in 13 (2 leukemic and 10 healthy children, 1 healthy adult).

Our results are consistent with those from other studies. Watson[3] identified the wild-type virus in five of five cases of breakthrough varicella. In another study, in all cases where an isolate was identified from a vaccinee with a generalized rash beyond the six-week post-vaccination period, it was identified as wild-type VZV.[4]

Although it has been suggested that reactivation of VZV occurs in the setting of low levels of VZV-specific antibodies, this concept is not in keeping with data from our laboratory or that of others. VZV reactivates in the setting of low cell-mediated immunity.[6,11] Low antibody levels are not associated with reactivation,[6, 12] but are associated with reinfection.[6,13] The geometric mean FAMA titer[14] of vaccinees who developed breakthrough varicella (9 children with leukemia, 6 healthy adults) at a mean of 5.3 months before rash was 2. That of vaccinees who developed zoster (5 children with leukemia, 1 healthy adult) at a mean of 2.8 months prior to zoster was 5.7 (P = 0.01, Student's t-test).

To our knowledge, there has been only one documented generalized rash in a recipient of varicella vaccine due to vaccine strain VZV.[15] This child developed a rash about two weeks after a household exposure to his brother, who had zoster at the time of exposure. Both received the varicella vaccine five months previously. In a personal communication, Brunell proposed that the boy with the generalized rash was re-infected by the vaccine virus following exposure to his brother with zoster (Brunell, personal communication).

The available evidence indicates that generalized rashes due to VZV in previously vaccinated individuals are the result of re-infection with the wild-type virus. Vaccinated individuals with low antibody titers to VZV are at increased risk to become re-infected. In contrast, localized, unilateral rashes are due to reactivation of latent VZV, either wild or vaccine strain. Reactivation occurs in the setting of a low cell-mediated immune response to the virus. If reactivation of the vaccine virus resulting in generalized rash were to occur, it would be expected to occur particularly in immunocompromised vaccinees. It has been our experience (see above) that even in these vaccinees, generalized rash is caused by the wild-type virus.

Whether subclinical reactivation of vaccine strain occurs and boosts immunity to VZV requires further study. As more children are vaccinated, there will be fewer cases of varicella and therefore fewer opportunities for boosting of VZV-specific antibody titers in vaccinees due to exposure to wild-type virus. We would therefore predict that in the absence of subclinical reactivation of the vaccine virus mean antibody titers would decline.

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