

## Trends in Rates of Herpes Zoster–Related Hospitalizations: Are They Real, Are They Costly, and Are They Linked to Varicella Vaccination?

*To the Editor*—We read with interest the article by Patel et al.,<sup>1</sup> who argue that their data suggest an increase in the incidence of herpes zoster (HZ) in the US population, as signaled by increases in rates of HZ-related hospital discharges; that the increase in the incidence of HZ is attributable to reduced circulation of the varicella zoster virus after initiation of varicella vaccination in children; and that the savings from the reduction in the number of hospitalizations due to varicella that is attributable to the varicella-vaccine program is more than offset by increased costs from HZ-related hospitalizations. We do not believe the data support any of these conclusions.

HZ-related hospital discharge rates were derived from non-validated claims data. While such data can be useful in epidemiologic research, they are generated for billing purposes and prone to biases and random error, and they should be interpreted cautiously. In this study, the authors found a sought-for increase in just 1 of 6 age strata (persons aged 65 and older).

Furthermore, the authors defined HZ-related hospital discharge as hospitalization with an HZ code in any of 15 discharge diagnostic code fields; HZ was not the principal diagnosis in most instances. This is a very nonspecific definition. Using chart reviews, Jackson et al.<sup>2</sup> found that only 33% of such hospitalizations are attributable to HZ; remaining cases involved HZ or postherpetic neuralgia incidental to the hospitalization or a history of HZ not even present upon hospitalization. Trends detected through such nonspecific definitions are imprecise and prone to bias, especially given that there was a large expansion in the study population during the observation period, increasing it from 17 to 37 states. At a minimum, the authors should have provided trend data defining HZ-related hospital discharge specifically with HZ as the principal discharge code.

With fewer than 3% of patients with HZ requiring hospitalization,<sup>2</sup> HZ-related hospital discharge is a poor surrogate for the incidence of HZ. Both immunosuppression and increasing age among the cohort of persons aged 65 and older raise the risk of HZ-related hospital discharge by 300%–500%.<sup>2–4</sup> The authors did not adjust for either confounder; their report of a 23% increase in the HZ-related hospital discharge rate over 12 years could be explained fully by the aging of the population and by increases in the use of immunosuppressive medications, particularly because the effect was not seen in other age cohorts less affected by these confounders. This lack of adjustment is even more serious be-

cause their study population expanded so substantially during the study period.

In the absence of supporting information, it is unreasonable to attribute causality on the basis of a single ecologic observation. If an increase in HZ rates is, in fact, due to reduced exposure to varicella zoster virus, it is hard to understand why this effect is seen only in the 1 cohort (those 65 and older) least likely to encounter children with varicella and thus least likely to be affected by the reduced circulation of the varicella zoster virus. The authors allude to this paradox but provide no explanation.<sup>5</sup>

Studies have provided conflicting data with regard to secular trends in the incidence of HZ.<sup>3,6–8</sup> Notably, several studies have shown age-specific increases occurring in the absence of a varicella-vaccine program.<sup>9–11</sup> These published findings do not rule out the possibility that varicella vaccination can cause an increase in HZ rates, but they suggest one needs to be cautious in attributing causality on the basis of limited data.

A majority of the patients Patel et al.<sup>1</sup> defined as having HZ-related hospital discharge would not have been hospitalized at all for HZ had they not experienced a severe concurrent primary illness.<sup>2,3</sup> Neither is it possible without chart reviews to know the small portion of hospital charges attributable to incidental HZ for those patients hospitalized for other concurrent severe illnesses.<sup>2,3</sup> Indeed, the nonspecific HZ-related hospital discharge definition introduces a large bias into the analysis, since the risk of incidental HZ occurring during hospitalization is directly related to the duration of the hospitalization and the severity of the primary illness. For these reasons, it is not valid to use this study design to calculate the burden of severe HZ or of HZ hospitalization in the United States or to calculate unit costs for such HZ-related hospitalization. It is certainly not possible to use these data to make inferences with regard to the cost-effectiveness of HZ vaccine, to generate national estimates of hospitalization costs attributable to HZ, or to apply such exaggerated national costs to draw conclusions with regard to the cost-benefit of the varicella-vaccine program.

The theory that reduced exposure to varicella zoster virus due to the successful varicella-vaccination program may be reducing immunologic boosting and thereby increasing HZ rates is biologically plausible and supported by some empirical data.<sup>5</sup> This issue is very important because it can guide decisions with regard to adoption or design of varicella-vaccination programs, and we are most eager to see a clarification of the data to inform the debate. Unfortunately, the information provided by Patel et al.<sup>1</sup> does not contribute to this discussion: the authors expect too much from claims data, and they overinterpret these limited data to make far-reaching and inappropriate conclusions.

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Sample can be useful for epidemiologic research but have limitations, and that trends from such data should be interpreted cautiously. As we stated in our article,<sup>2</sup> we could not definitively draw a causal link between varicella-vaccination efforts and trends in HZ-related hospital discharges. Rather, we emphasized that the population-adjusted rate of HZ-related hospital discharges has changed significantly relative to past trends, and that the majority of these cases are among the HZ-vaccine-eligible group, which is meaningful for ongoing HZ-vaccination efforts.

After our article was accepted for publication, Jackson et al.<sup>3</sup> published an important study with regard to the accuracy of using discharge data to identify hospitalizations attributable to HZ. They found that 33% of hospitalizations were directly because of HZ or a complication of HZ treatment. They also found that, in another 52% of cases, HZ or post-herpetic neuralgia was present but was not the primary reason for hospitalization<sup>3</sup>—that is, HZ was a secondary issue. Thus, 85% of hospitalizations in their study were HZ-related. If that adjustment factor is applied to our study, in which we measured HZ-related hospital discharges via primary and secondary diagnoses, the relative increase in HZ-related hospital discharges from 2000 through 2004 remains significant.

We agree with Harpaz and Yawn<sup>1</sup> that both the increasing age of the population and the changing immunosuppression patterns can affect the rate of HZ-related hospital discharges. However, it is unlikely that either of these factors played a significant role in the trends we reported. In 1996, the proportion of the overall population that was 65 years of age or older was 12.7%.<sup>4</sup> By 2000, this proportion had declined to 12.4%, and it remained unchanged through 2004.<sup>4</sup> Therefore, increasing age was not likely to play a role in the growth of HZ-related hospital discharges from 2000 through 2004. In our article,<sup>2</sup> we identified the top 10 most common primary diagnoses among HZ-related hospital discharges in 1994, 1999, and 2004. We found that the vast majority of primary diagnoses were not immunocompromised conditions. For instance, human immunodeficiency virus accounted for less than 2% of primary diagnoses in 1994, 2.50% in 1999, and 2.46% in 2004—substantially less than primary diagnoses such as viral infections, pneumonia, and cardiac conditions, which accounted for nearly 30% of primary diagnoses. Although we are not aware of national estimates of immunosuppression status, we doubt that population-level immunosuppression increased enough from 2000 through 2004 to explain the increase in HZ-related hospital discharges.

We also agree with Harpaz and Yawn<sup>1</sup> that, if an increase in HZ-related hospital discharge rates were due to reduced exposure to wild-type varicella, the effect should be seen across multiple age groups. They note our finding that, among persons aged 65 and older, the rate of HZ-related hospital discharges grew 23% (from 11.30 to 13.89 HZ-related hospital discharges per 10,000 population) during the study period. While not easily seen within the second figure in our article,<sup>2</sup> the rate of HZ-related hospital discharges grew 40% (from

### Reply to Harpaz and Yawn

*To the Editor*—We welcome the comments of Harpaz and Yawn<sup>1</sup> regarding our article<sup>2</sup> on herpes zoster (HZ)-related hospitalizations and expenditures. We agree with Harpaz and Yawn<sup>1</sup> that the data we used from the Nationwide Inpatient