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Herpes zoster in Australia: evidence of increase in incidence in adults attributable to varicella immunization?

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SUMMARY

Rates of herpes zoster (HZ) hospitalizations, antiviral prescriptions, and New South Wales emergency-department presentations for age groups <20, 20–39, 40–59 and ⩾60 years were investigated. Trends were analysed using Poisson regression to determine if rates increased following funding of varicella immunization in Australia in November 2005. The regression analysis revealed significantly increasing trends of between 2% and 6% per year in both antiviral prescriptions and emergency-department presentations in all except the <20 years age group. When considered together, the differential changes in rates observed by age group provides preliminary evidence to indicate that HZ incidence is increasing in adults aged >20 years. However, it is not possible to attribute the increasing trends in HZ observed directly to the varicella immunization programme, and continued monitoring and analyses of data for a longer duration, both pre- and post-vaccine introduction, is required.

Key words: Vaccination (immunization), varicella zoster, zoster (shingles).

INTRODUCTION

Varicella zoster virus (VZV) causes both varicella (chickenpox) following primary infection and herpes zoster (HZ, shingles) associated with reactivation of latent VZV. Both illnesses are important causes of morbidity in Australia and represent a significant cost to the community [1–6]. A live attenuated varicella vaccine was introduced into the routine immunization schedule in the USA in 1995 and resulted in significant reductions in varicella incidence, hospitalizations, mortality, and associated healthcare costs [7–11]. However, it has been hypothesized that exposure to varicella naturally boosts VZV-specific immunity and reduces the risk of subsequent HZ reactivation [12], and several observational studies have supported this [13–15]. Based on these findings, modelling studies have suggested that the reduction in natural exposure to varicella resulting from immunization programmes with high coverage may increase susceptibility to reactivation of latent VZV infection and result in an increase in HZ in the unvaccinated population [16–19].

Zoster surveillance data from the USA has been inconclusive so far. Among patients enrolled in a large health maintenance organization (HMO) in Seattle, Washington, overall age-adjusted, and age-specific HZ incidence rates did not change between 1992 and 2002, while varicella incidence declined by 65% [11]. Similarly, no change in overall HZ incidence rates

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from 1997 to 2003 was observed in another study of HMO patients in Washington and Oregon [20]. However, in contrast, an annual state-wide telephone survey in Massachusetts determined that age-standardized rates of HZ incidence increased by 90% from 2·77 cases/1000 person-years in 1999 to 5·25 in 2003, whereas varicella incidence declined by 66% [21]. In addition, the age-adjusted HZ incidence rate increased from 3·2/1000 person-years to 4·1 from 1996 to 2001 in adults aged ⩾22 years in a population-based study in Minnesota [22]. Recent evidence has also emerged from a national sample of in-patients in the USA suggesting that HZ related hospitalizations and associated healthcare expenditure increased from 2000 to 2004, primarily in those aged ⩾65 years, but also in the 45–64 years age group [23]. Finally, the incidence of HZ decreased by 55% in children aged <10 years but increased by 63% in those aged between 10 and 19 years in California between 2000 and 2006 [24].

The varicella vaccine was licensed in Australia in 1999, recommended as a routine childhood vaccination in September 2003, but not government funded until November 2005 when it was included in the National Immunization Program for use for all children as a single dose at age 18 months and a school-based catch-up programme at age 10–13 years. Modelling of Australian data predicted an increase in HZ incidence would become evident almost immediately, peak at 10–15 years after initiation of universal varicella immunization with 90% coverage, and fall below pre-vaccination rates after 37 years, with adults aged >25 years accounting for the majority of the extra cases [25]. Zoster morbidity (annual in-patient days) was also predicted to increase, although at a slower rate over the first 59 years of the varicella immunization programme, driven primarily by the elderly (aged ⩾60 years) [25]. Recent modelling has also predicted a similar effect on HZ incidence and morbidity should Australia adopt a two-dose varicella immunization programme similar to that used in the USA [26].

Another live, attenuated Oka/Merck strain VZV vaccine has also recently been developed that has been demonstrated to be effective in reducing the incidence and morbidity associated with latent HZ reactivation [27]. Currently, in Australia, the vaccine is registered for use in individuals aged ⩾50 years for prevention of HZ, and indicated for HZ prevention and reduction of acute and chronic zoster-associated pain in individuals aged 60–79 years. An application to the federal government for the vaccine to be listed on the National Immunization Program is being considered [28]. If the predicted increase in HZ early in the varicella immunization programme does occur, this may strengthen the case for funding of the new vaccine.

Garnett & Ferguson [29] emphasized the need to look for 'early signs of an increase in the incidence of zoster … after the introduction of widespread use of varicella vaccine in healthy children'. Therefore the aim of this study was to undertake a preliminary investigation into trends in HZ incidence in Australia since the introduction of the universally funded varicella immunization programme in November 2005. The utility of data sources available for this purpose will be evaluated and implications for the new vaccine to prevent HZ reactivation in the elderly are discussed.

METHODS

Data sources

Hospitalization, emergency-department (ED) presentation, and pharmaceutical prescribing data were used to describe the secular trends in zoster incidence since the introduction of universal varicella immunization in Australia.

Hospitalization data were extracted from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database, an electronic collection of de-identified records of episodes of care in over 99% of public and private hospitals in Australia. All records with a primary diagnosis code for zoster (B02.0–B02.9) for the financial years July 1998/1999 to 2006/2007 were included in the analysis.

Pharmaceutical Benefits Scheme (PBS) prescriptions supplied for community (non-hospital) use of the antiviral drugs for the specific indication of HZ were also used to detect changes in disease incidence. The PBS schedule lists all pharmaceuticals that are government subsidized in Australia and includes three direct-acting prescription-only antiviral drugs at a dosage specific for the treatment of patients with HZ: acyclovir (PBS Item No. 01052J), famciclovir (08002E) and valaciclovir hydrochloride (08064K). Monthly numbers of prescriptions for acyclovir, famciclovir, and valaciclovir, by 10-year age group between November 2005 and March 2009 inclusive, were provided by Medicare Australia.

Monthly presentations between January 2001 and July 2009 at 51 hospital EDs in the state of New South

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Wales (NSW) assigned a diagnosis of HZ or shingles in the NSW Emergency Department Data Collection were provided by the Centre for Epidemiology and Research, NSW Department of Health. Finally, Australian population data by single year of age was obtained from the Australian Bureau of Statistics for the years 1999 to 2008 inclusive [30].

Statistical analysis

Age-specific rates for the <20, 20–39, 40–59 and ⩾60 years age groups were plotted for HZ hospitalizations, NSW ED presentations, and prescriptions.

Hospitalization, ED presentation, and prescribing data were analysed as a time series. For HZ hospitalizations, univariate Poisson regression was undertaken in Stata 9.2 (StataCorp, USA) for each of the above age-specific groups to quantify the changes over time. The number of hospitalizations per year was assigned as the dependent variable, the population estimate for that year as the offset variable and the year as the independent variable. A multivariate model was used for monthly ED presentations and antiviral prescriptions that was similar to the univariate model, with the addition of independent variables including a 1/12 increment per month to obtain an estimate of the annual rate of change, and four sin and cos functions with frequencies of 12, 6, 3 and 1·5 months to adjust for the seasonal component of the data. All trend parameter estimates were then exponentiated to generate an estimate of the percentage change in rate per year.

RESULTS

Hospitalizations

Annual age-specific hospitalization rates for HZ from 1998/1999 to 2006/2007 are shown in Figure 1. Univariate Poisson regression revealed no evidence of a trend in the <20 and ⩾60 years age groups, a significant decline of 3·7% ($P=0·001$) and marginally significant increase of 1·6% ($P=0·036$) per annum in the 20–39 and 40–59 years age groups, respectively.

NSW ED presentations

Monthly age-specific rates of ED presentations for HZ or shingles in NSW from January 2001 to July 2009 are shown in Figure 2, overlaid by predicted monthly rates from the multivariate Poisson regression model. No obvious trend was evident in the <20 and 20–39 years age groups while rates clearly increased in both the 40–59 and ⩾60 years age groups over the period of study. In both older age groups there was an increase in rates of ED presentations in early 2005 before the varicella vaccine was government funded in November of that year; however, the rate of change before and after appears to be fairly similar. The Poisson regression analysis revealed that ED presentations in NSW increased significantly by between 2·0% and 5·7% per year ($P<0·001$) between 2001 and 2009 in all age groups, except those aged <20 years for which a non-significant increase of 1·4% was observed.

HZ antiviral prescriptions

Monthly age-specific prescribing rates of HZ antivirals from November 2005 to March 2009 are shown in Figure 3, overlaid by predicted monthly rates from the multivariate Poisson regression model. Consistent with ED presentations, the regression analysis again revealed that significantly ($P<0·001$) increasing trends in prescribing were evident in all except the <20 years age group. The greatest increase of 3% per annum was observed in those aged ⩾60 years, compared to 2·6% for the 20–39 years age group and 1·7% for the 40–59 years age group. Goodness-of-fit testing indicated that the Poisson model was appropriate.

DISCUSSION

This is the first study to examine trends in HZ incidence following the introduction of universal funding for varicella immunization in Australia in November 2005. Hospitalizations, ED presentations, and prescriptions for HZ-specific antivirals were investigated and evidence of an increasing background trend in the latter two data sources was demonstrated for adults aged ⩾20 years as summarized in Figure 4, although we were not able to demonstrate a clear association with vaccine introduction. National notification data were also investigated, but are not reported here as the recent and staggered introduction of the requirement to notify HZ cases across jurisdictions in Australia does not permit meaningful interpretation at present.

This study is limited by the pattern of introduction of varicella vaccine in Australia and some limitations in the data sources available to assess population increases in the incidence of HZ. After the varicella vaccine was government funded in November 2005,

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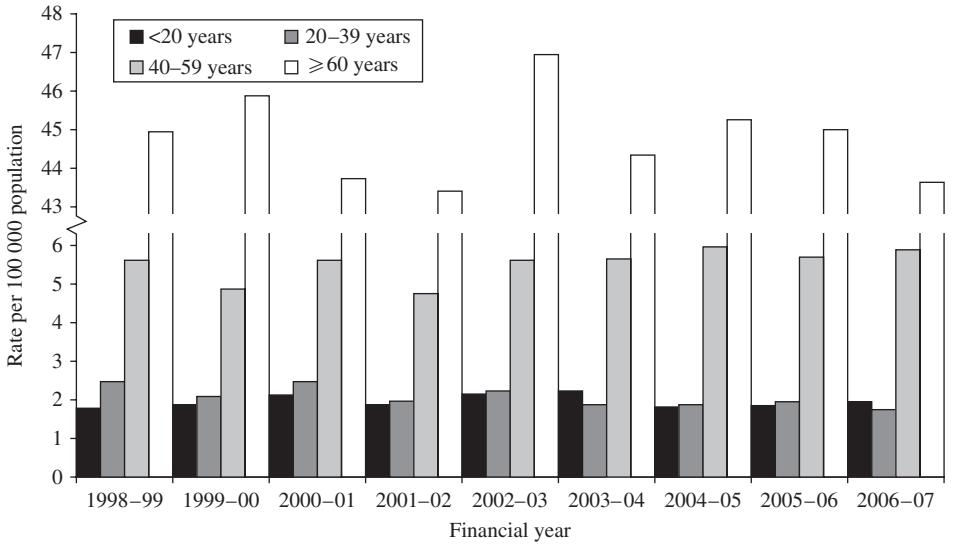

Fig. 1. Age-specific hospitalization rate of herpes zoster per 100 000 population in Australia by financial year and age group.

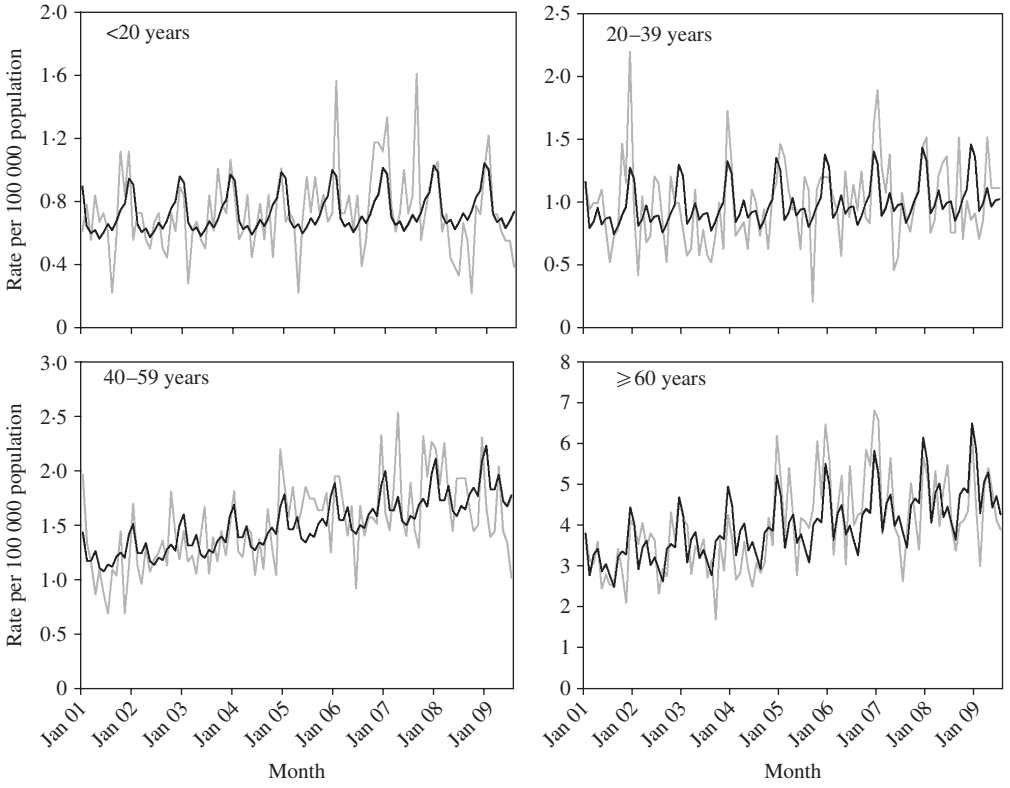

Fig. 2. Monthly age-specific rates of emergency-department presentations to 51 hospitals in NSW assigned a diagnosis of herpes zoster or shingles per 100 000 population, January 2001 to July 2009. Solid black lines indicate predicted rates from the multivariate Poisson regression modelling (note variation in y-axis scale). ——, Observed; ——, predicted.

coverage increased rapidly to ~80% by age 2 years in 2007 [31]. However, uptake is difficult to estimate during the period it was available in Australia but not funded. The Australian Childhood Immunization Register (ACIR) indicates that 6·4% and 15·8% of children aged <2 years had received varicella vaccine in 2004 and 2005, respectively [32, 33]. However, these are likely to be underestimates because being an

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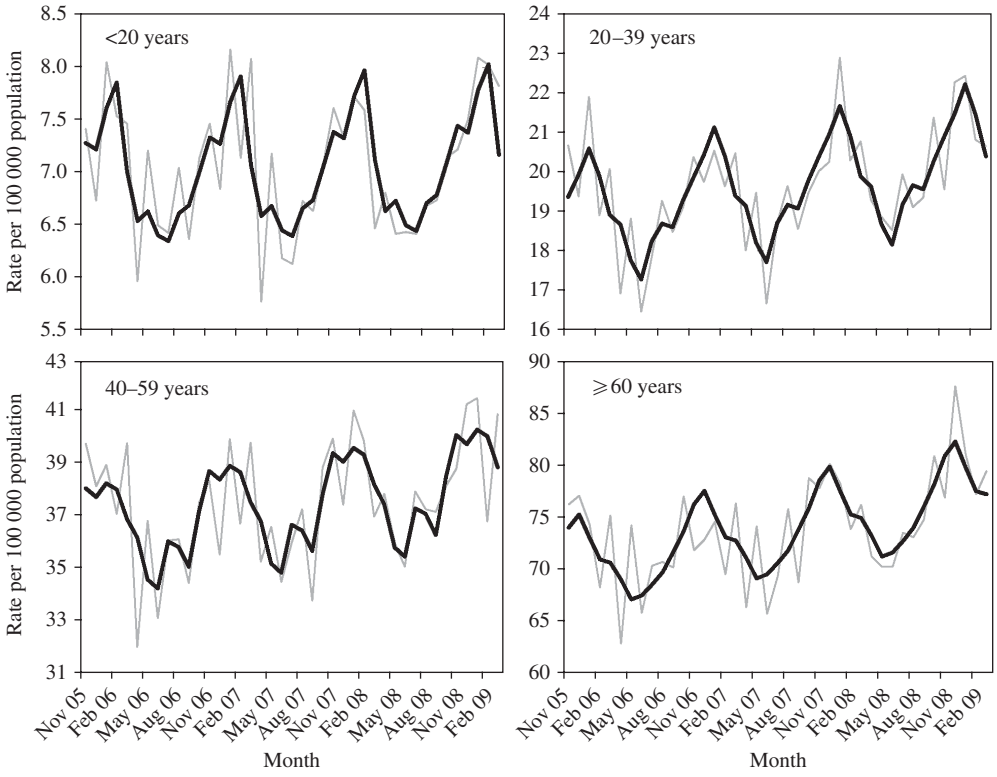

Fig. 3. Monthly age-specific rates of antiviral prescriptions to treat herpes zoster per 100 000 population in Australia, November 2005 to March 2009. Solid black lines indicate predicted rates from the multivariate Poisson regression modelling (note variation in y-axis scale). ——, Observed; ——, predicted.

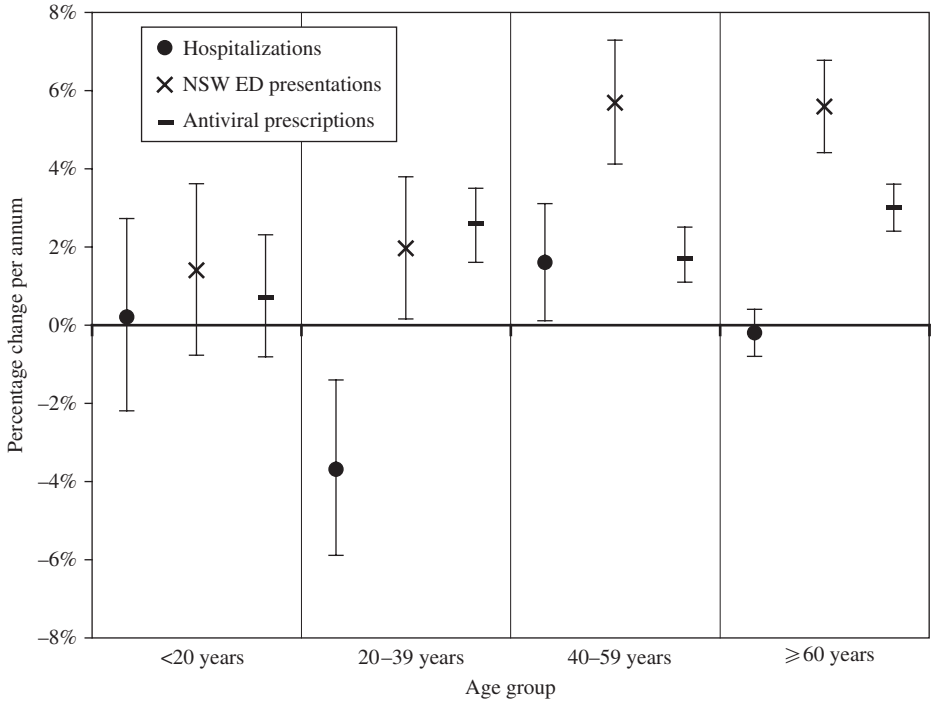

Fig. 4. Estimated age-specific annual percentage change in national hospitalizations, emergency-department (ED) presentations in NSW, and national antiviral prescriptions for treatment of herpes zoster.

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unfunded vaccine, there was no financial incentive for notifications to the ACIR. A study in South Australia in June 2004 involving telephone interviews of 613 households containing 294 children aged 9 months to 4 years indicated that 166 (48%) had a history of varicella immunization [34]. A subsequent survey of general practitioners (GPs) in mid-2005 indicated significant variability in prescribing practices for the non-funded varicella vaccine and only one quarter discussed it with parents [35].

A marked increase during summer months was noted in HZ-specific antiviral prescription data and to a lesser extent, ED presentations. Seasonality of varicella hospitalizations and notifications has previously been demonstrated in Australia, but not for HZ [36]. Suppression of cellular immunity by solar ultraviolet irradiation during summer has been suggested as a potential biological explanation for HZ seasonality [37]. However, a comprehensive review of HZ epidemiology concluded that there was little evidence of seasonal variation in the majority of studies reviewed [38].

Hospitalization data are released by AIHW annually in August for the financial year prior to the one just ended at 30 June. Currently, data were only available up until 2006/2007 and were therefore insufficient for the purpose of determining trends after varicella vaccine was funded in Australia. However, rates of hospitalization for HZ remained relatively stable during the period the vaccine was available in Australia, but not funded, and coverage was suboptimal. Additionally, hospitalizations only include more severe cases and may not be sensitive enough to detect relatively small changes in true disease incidence in the community. Further, admissions data are not incident data and trends are subject to changes in management.

The ED presentation data were available from the same 51 hospitals in NSW from 2001 to the present, overcoming some of the limitations of the notification and hospitalization data. Taking seasonal variation into account, there was evidence of a significant increase in the rate of HZ presentations in adults aged >20 years, but the temporal relationship between the observed increase in presentations and the introduction of the vaccine is unclear. In the 40–59 and $\geqslant 60$ years age groups, the increase appeared to occur in early 2005 before the varicella vaccine was funded and may be an artifact due to changes in data coding or some other form of confounding. Regardless, surveillance of varicella and HZ using ED presentation data only occurs in NSW, therefore this data source is limited by the fact that the trends observed are not necessarily representative of the rest of the country.

Prescriptions for antivirals specific for the treatment of HZ are the most stable and current data source available at a national level to evaluate trends in HZ incidence in the community. A standard process to collect PBS data has been in place at a national level since 1992, therefore time trends are likely to be reliable, and there is a much shorter delay in data availability compared to hospitalization data. Unfortunately one major limitation is that PBS data are only provided up to 5 years retrospectively, therefore we were not able to evaluate trends in prescribing data over a meaningful period of time before universal vaccine funding. MacIntyre *et al.* [2] evaluated trends in HZ hospitalizations and antiviral use before the vaccine was licensed in Australia and demonstrated that the increase in prescriptions from just over 250/100 000 population in 1995 to 329/100 000 in 1999, was consistent with trends in hospitalization rates that also increased from 1993/1994 to 1998/1999. However, the steady rate of hospitalizations for HZ in the early to mid 2000s demonstrated in the present study is perhaps an indication that zoster incidence was static during this period of low varicella vaccine coverage. Regardless, the differential increase by age in prescriptions for HZ-specific doses of acyclovir, famciclovir, and valaciclovir since November 2005 is worthy of note, as it corresponds with the prediction by Gidding *et al.* [25] that HZ incidence would increase in adults, but not children, following the introduction of a varicella immunization programme with high coverage.

In conclusion, when considered together, the data presented in this study provide preliminary evidence to suggest that HZ incidence is increasing in adults aged $\geqslant 20$ years. It is important to recognize that this study was an ecological design and that there were a number of limitations in the available data sources, and a lack of accurate coverage data during the period prior to universal varicella vaccine funding. Therefore it is not possible to directly attribute the increasing trends in HZ observed to the immunization programme, and alternative explanations such as changes in other non-immunization factors like greater parent–child contact or increasing health-seeking behaviour for HZ and treatment with antivirals cannot be ruled out. We are therefore unable to make recommendations regarding funding of the new vaccine to prevent HZ reactivation in the elderly at

present based on these trend data alone. Continued monitoring and analyses of data for a longer duration, both pre- and post-vaccine introduction, using multiple data sources are therefore vitally important to assess the impact of the varicella vaccine and various other contributing factors such as scheduling, coverage, and catch-up immunization.

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DECLARATION OF INTEREST

None.

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