Does Monastic Life Predispose to the Risk of Saint Anthony’s Fire (Herpes Zoster)?

Jacques Gaillat,1,a Vincent Gajdos,2,3,a Odile Launay,4,5 Denis Malvy,6 Bruno Demoures,7 Lucie Lewden,8 Sybil Pinchinat,9 Tarik Derrough,8 Claudine Sana,4,6 Evelyne Caulin,8 and Benoît Soubeyrand 8

1Department of Infectious and Tropical Diseases, Annecy General Hospital, Pringy, France; 2Department of Paediatric, APHP, Hôpital Antoine Béclère, Clamart, France; 3Reproduction and Child Development, CESP Inserm UMRS, Inserm, Univ-Paris Sud 11. UFR Kremlin Bicêtre, Le Kremlin Bicêtre; 4Université Paris Descartes, Faculté de Médecine, Inserm CIC BT505, Paris, France; 5Assistance Publique-Hôpitaux de Paris, Hôpital Cochin, CIC de Vaccinologie Cochin Pasteur, Paris, France; 6Department of Internal Medicine and Tropical Diseases, Saint André Hospital, Bordeaux, France; 7Ocso Abbaye de Tamié, Albertville, France; 8Department of Medical, Sanofi Pasteur MSD, Lyon, France; and 9Biostatem, Castries, France

(See the Editorial Commentary by Crumpacker II on pages 411–412.)

Background. The consequences of the epidemiology of varicella for zoster epidemiology are still debated. We therefore compared the frequency of herpes zoster in an adult population with virtually no varicella zoster virus (VZV) exposure with that in the general population (GP).

Methods. We performed a national, multicenter, observational, exposed versus nonexposed, comparative study. The nonexposed population consisted of members of contemplative monastic orders (CMO) of the Roman Catholic Church living in 40 isolated monasteries in France. The exposed population consisted of a sample of the GP representative of the French population in terms of age group, sex, socio-occupational categories, and regions.

Results. The primary analysis population comprised 920 members of CMO (41.5% nuns; mean age, 64.2 years) and 1533 members of the GP (51.9% women; mean age, 64.6 years). The reported frequency of zoster was 16.2% among CMO and 15.1% in the GP ($P = .27$, adjusted for sex and age). The reported mean age of onset of zoster was 54.8 and 48.6 years, respectively ($P = .06$).

Conclusions. This study failed to demonstrate an increased risk or earlier onset of zoster in members of CMO not exposed to VZV, compared with that in the GP. Although adults highly exposed to VZV could have a reduced risk of zoster, compared with the GP, our results suggest that the opposite is not true: adults not exposed to VZV are not at increased risk of zoster when compared with the GP, challenging the relevance of the assumptions and forecasts of current epidemiological models.

The consequences of the epidemiology of varicella for zoster epidemiology are still debated. Varicella zoster virus (VZV) causes 2 diseases: varicella and zoster. Varicella is highly contagious [1] and occurs predominantly in children. In France, 90% of children have developed chickenpox by the age of 10 years [2]. Herpes zoster, sometimes known as St Anthony’s fire (St Anthony is a founder of monastic life in Christianity), is caused by reactivation of VZV. It occurs once (rarely twice), essentially in adults >60 years of age [3, 4].

Control of VZV reactivation depends on the maintenance of an adequate level of cell-mediated immunity (CMI) to VZV, which explains why the 2 risk factors for developing zoster are aging and CMI deficiencies [4, 5]. The reasons why young healthy adults rarely develop zoster are not entirely clear. Two hypotheses that are not mutually exclusive are advanced. The first is that of exogenous boosting, which postulates that adults in contact with children with chickenpox reinforce their anti-VZV CMI and, thereby, reduce their risk of zoster [3]. This commonly accepted hypothesis of exogenous boosting, which was initially proposed by Hope-Simpson on the basis of studies conducted in England in the 1960s, was...
recently supported by the results of 4 epidemiological studies showing that repeated familial or occupational exposure is associated with a reduced risk of zoster [6–9].

All epidemiological models designed to predict the consequences of a routine childhood vaccination program incorporate exogenous boosting. This means that all consider that repeated contacts with varicella reduces the risk of zoster to be equivalent to the unproven assumption that the absence of contact with varicella causes an increased risk of zoster [10–14]. Thus, all of these models predicted that high childhood varicella vaccine coverage would be responsible for the prompt disappearance of cases of chickenpox and, as a consequence, an increasing number of cases of zoster in young adults. This outcome is one of the arguments for the lack of a childhood varicella vaccination program in a number of European countries, including France [15–20].

The second hypothesis is that of endogenous boosting, which holds that anti-VZV CMI is maintained by asymptomatic endogenous reactivation of VZV. In this case, not only would varicella vaccination not induce an increase in the number of cases of zoster in adults, but on the contrary, it would reduce the total number of cases of zoster because vaccinees have a reduced risk of developing zoster [4, 21].

In the United States, childhood varicella vaccination has been generalized since 1995. Vaccine coverage of children aged 19–35 months was 87% in 2004 and has been ≥90% since 2008 [22]. To date, 8 population studies have been conducted in the United States, with contradictory results that neither validate nor invalidate the predictions of the epidemiological models [23, 24]. In this context, we tested the hypothesis of the potential increased risk of zoster in the absence of contact with varicella by comparing the frequency and age of onset of zoster in monks and nuns not exposed to children and in the general population (GP).

OBJECTIVES

The primary objective was to evaluate the frequency of zoster in a population not exposed to children, (ie, members of contemplative monastic orders [CMO] of the Roman Catholic Church), in comparison with that in the GP. The secondary objectives were to compare the reported age of onset of zoster in members of CMO with that in the GP and to describe the frequency and age of onset of zoster in monks, compared with nuns.

METHODS

This was a national, multicenter, observational, comparative, epidemiological study with an exposed versus nonexposed design that was conducted using questionnaires. Data were collected from November 2008 through June 2009. The study was performed in accordance with Good Epidemiology Practice Guidelines and the procedures of French law. This study did not require formal approval from the Data Protection Committee.

Questionnaires were sent to members of CMO in 40 monasteries (20 with monks and 20 with nuns) located in France. A return sheet indicating the number of questionnaires returned and the reason for any refusals was completed. Lack of fluency in French and being a postulant or novice (present for <2 years) constituted exclusion criteria. Members who had had zoster before entering the monastery or at an indeterminate date and those who came into regular contact with groups of children <10 years of age were excluded from the primary analysis population.

The GP sample was constituted from a pre-established file based on the quota method, representative of the French population (by age, sex, socio-occupational categories, and regions) and matching the characteristics of the religious population. Persons who did not return the questionnaire within 15 days were contacted by telephone (up to 7 attempts). Those who were not fluent in French and/or who lived in an institution were not included in the primary analysis population.

The CMO numbers likely to participate in the study were estimated as 1000. With a set number of 1000 participants per group and power of 80% and taking into account the expected frequency of zoster based on the literature, the estimated odds ratio (OR) was 1.47 for a 10% frequency. A total of 1128 questionnaires were sent to all monasteries.

As predefined, 3000 questionnaires were sent to the GP. The following data were collected: date of birth, sex, history of zoster, age or year of onset of zoster, confirmation of the diagnosis at the time by a health care professional consulted for the zoster episode, localization of the zoster, presence of other diseases at the same time as zoster, and pain after the disappearance of the zoster rash. Additional data were collected according to the study groups.

For members of CMO, date of entry to the monastery, activity in the monastery, and history of regular contact with groups of children <10 years of age were recorded.

For the GP, socio-occupational category and activity, and when applicable, date of start of retirement or of living in an institution were recorded.

Analyses

Quantitative variables were described (distribution) by their number, mean, standard deviation (SD), median, and range. The results are expressed as means. Qualitative variables were described (distribution) by their frequency and the percentage in each category.

Frequency of zoster in the 2 populations was compared, first, by a univariate analysis using the $\chi^2$ test and, then, by adjusting the analyses for prognostic baseline covariates (sex and age), using a multivariate logistic regression model.
To test for a memory bias an additional predefined analysis including only events occurring during the 10 years before the study was performed, comparing the mean age at onset of zoster with use of a covariance analysis. We tested the hypothesis of increasing risk of zoster with age with use of the \( \chi^2 \) test for trend. The relationship between sex and onset of zoster in the populations was analyzed using a univariate logistic model and then a bivariate logistic model, taking into account age at onset. All statistical tests were 2-tailed with a type I error of 0.05. Analyses were performed using SAS software, version 9.1 (SAS Institute).

RESULTS

The primary analysis population was composed of 920 members of CMO and 1533 of the GP. Figure 1 shows the reasons for exclusion from the primary analysis populations, and Tables 1 and 2 show the characteristics at inclusion. Women were more numerous in the GP than in the religious population (51.9% vs 41.5%; \( P < .001 \)).

Table 1. Demographic Characteristics of Both Populations (Primary Analysis Populations)

<table>
<thead>
<tr>
<th>Group</th>
<th>Monks/nuns n = 920</th>
<th>General population n = 1533</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Wilcoxon ( P = .683 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>n 920</td>
<td>1532*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>64.2</td>
<td>64.6</td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>66.1</td>
<td>66.2</td>
<td></td>
</tr>
<tr>
<td>Min; Max</td>
<td>21.9; 101.9</td>
<td>16.4; 99.9</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>( \chi^2 P = .001 )</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male 538 (58.5%)</td>
<td>737 (48.1%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female 382 (41.5%)</td>
<td>796 (51.9%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NOTE. * One missing datum.

For the monks, the monasteries belonged to the Benedictine order in 55% of cases and the Cistercian order in 45% of cases; for the nuns, these 2 orders accounted for 30% of cases, and the Clarissa and Carmelite orders accounted for 20% of cases each.

Figure 1. Reasons for exclusion from primary analysis population.
Overall, 8.2% of nuns and 7.1% of monks were excluded because they came into regular contact with children <10 years of age. Monks accounted for 58.5%. The mean age was 64.2 years. A mean of 29 monks or nuns (median, 25; range, 9–63) lived in each monastery. Members of CMO had entered the monastery at the age of 27 years and had lived there for \(24/38\) years. The nuns were 10 years older than the monks (70 years vs 60 years; \(P < .001\)); had entered the monastery at the age of 28 years, as opposed to 26 years (\(P < .001\)); and had 8 years more of monastic life than the monks (\(P < .001\)).

Overall, the geographical distribution and socio-occupational categories of members of the general study population were representative of the French population aged \(\geq\)40 years. The women were aged 5 years older than the men (67 years vs 62 years; \(P < .001\)). More than 70% of persons reported that they had regular contact with children aged <10 years over the past 10 years.

Overall, 43.3% of members of CMO and 44.6% of the GP were aged \(\geq\)70 years, and 23.6% and 22.4%, respectively, were aged \(\geq\)80 years.

### Principal Analyses

The reported frequency of zoster in the primary analysis populations was 16.2% (149 of 920) among members of CMO and 15.1% (231 of 1533) in the GP (OR, 1.14; 95% confidence interval [CI], 0.91–1.44; \(P = .27\), adjusted for sex and age) (Table 3). The results of the additional predefined analysis, focusing on only the 10 years before the study, showed a frequency of zoster of 6.4% among members of CMO, compared with 6.1% in the GP (OR, 1.12; 95% CI, 0.78–1.6; \(P = .54\), adjusted for sex and age) (Table 3).

### Secondary Analyses

The mean age at onset of zoster was 54.8 years in the CMO population and 48.6 years in the GP (\(P = .06\)). In both populations, zoster had been confirmed by a health care professional in 93% of cases, increased with age (\(F^2\) trend: \(P < .001\)), and was more frequent in women than in men (\(P = .002\)). The rash was localized predominantly on the chest and abdomen in both populations. Members of CMO with a history of zoster reported having more diseases at the time of onset of zoster than did persons from the GP (28.8% vs 16.8%; \(P = .007\)).

### DISCUSSION

We found no association between the frequency and age of onset of zoster and a lack of exposure to varicella when we compared the frequency of zoster in a population of monks and nuns (16.2%) who had virtually no contact with children with that in the GP (15.1%). To our knowledge, this is the first study designed to evaluate an association between an increased risk of zoster in adults and the absence of contact with children with varicella [6, 7]. By the nature of its design, this study, similar to others, did not consider actual exposure to VZV [6, 7, 21]. A lack of contact with children aged <10 years was used as a substitute for a lack of contact with patients with varicella. Monk monastic orders in France constitute a specific isolated population, compared with other Anglo-Saxon Benedictine and Cistercian monasteries. Our results and their scope may have been affected by the limits of the exposed versus nonexposed method used. In fact, studies conducted on the basis of population questionnaires may be the source of memory and selection bias. Nevertheless, we are confident in the reliability of our results. First, in France, seroprevalence of VZV disease is \(\geq\)90% at age 10 years, and children are not vaccinated against varicella. Second, the robustness of the results was enhanced by excluding postulants, novices, and members of CMO who reported contact with children. Third, the quasi-exhaustive nature of the collection of cases and noncases in the religious

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**Table 2. Demographic Characteristics of Religious Population (Primary Analysis Population)**

<table>
<thead>
<tr>
<th></th>
<th>Monks n = 538</th>
<th>Nuns n = 382</th>
<th>Total n = 920</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age on entry to monastery (years)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>537&lt;sup&gt;a&lt;/sup&gt;</td>
<td>382</td>
<td>919</td>
</tr>
<tr>
<td>Mean</td>
<td>25.9</td>
<td>27.5</td>
<td>26.6</td>
</tr>
<tr>
<td>SD</td>
<td>8.6</td>
<td>7.6</td>
<td>8.2</td>
</tr>
<tr>
<td>Median</td>
<td>23.9</td>
<td>25.3</td>
<td>24.5</td>
</tr>
<tr>
<td>Min; Max</td>
<td>11.0; 67.5</td>
<td>14.6; 64.2</td>
<td>11.0; 67.5</td>
</tr>
<tr>
<td><strong>Duration of monastic life (months)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>537</td>
<td>382</td>
<td>919</td>
</tr>
<tr>
<td>Mean</td>
<td>408.3</td>
<td>510.2</td>
<td>450.6</td>
</tr>
<tr>
<td>MS</td>
<td>231.8</td>
<td>208.2</td>
<td>227.8</td>
</tr>
<tr>
<td>Median</td>
<td>370.6</td>
<td>540.6</td>
<td>441.0</td>
</tr>
<tr>
<td>Min; Max</td>
<td>33.5; 976.6</td>
<td>34.0; 971.3</td>
<td>33.5; 976.6</td>
</tr>
</tbody>
</table>

**NOTE.** <sup>a</sup> One missing datum.
population allows a reliable denominator. Fourth, the risk of memory bias appears low: <1% of participants did not remember whether they had had zoster, and the results of the analysis covering only the 10-year period before the response to the questionnaire did not differ from those of the primary analysis. Fifth, >90% of the cases were declared to have been confirmed by a health care professional (ie, confirmed by a physician) minimizing the risk of specificity bias. Nevertheless, we were not able to exclude zosteriform eruption due to non-VZV-like herpes simplex virus. Finally, the established frequency of zoster and its increase with age were comparable to the literature data [25–27].

All studies supporting exogenous boosting showed a decreased frequency among adults exposed to childhood varicella. The results of a study based on general practice-based registers in the United Kingdom during 1991–1992 (National Survey of Morbidity in General Practice) comparing households with and without children <16 years of age showed that living with children had an age-independent protective effect against the onset of zoster (relative risk, 0.75; 95% CI, 0.63–0.89). Using these data in a natural history model of relations between varicella and zoster, the authors estimated the mean duration of protection conferred by exposure to varicella to be 20 years (95% CI, 7–41 years). Our results, based on almost twice the observation period, showed no increase in the risk of zoster in adults not exposed to VZV. Therefore, increasing risk of zoster with increasing age would be mainly attributable to immunologic senescence with decreasing cell-mediated immunity to VZV in aging people.

These contradictory results may be reconciled if it is considered that the GP would have a basic risk of developing zoster that was essentially dependent on endogenous boosting. Contacts by adults with childhood varicella are infrequent and play a minor role in the reinforcement of anti-VZV CMI. This would explain the lack of any difference or the difficulty of demonstrating a minimal difference in the risk of zoster between a non-varicella-exposed population and the GP; in the GP, there is a limited number of individuals highly exposed to varicella in whom it is possible to reveal a reduction in the basic risk of onset of zoster because of the additional protective effect of exogenous boosting. In these circumstances, we concur with Reynolds [28] that the reduction in the circulation of VZV would not entail an increase in the frequency of zoster in the GP. Our results challenge both the relevance of the assumption that the absence of contact with varicella causes an increased risk of zoster, and current VZV epidemiological model forecasts.

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**Potential conflicts of interest.** J. G. has participated in the steering committee of an expert group supported by Sanofi Pasteur MSD; has received consulting fees from Sanofi Pasteur MSD; has had board membership at Sanofi Pasteur MSD, Pfizer, and Roche; has received payment for lectures and speakers’ bureaus from Sanofi Pasteur MSD, Pfizer, and Sanofi Pasteur; and has received payment for travel/meeting expenses from BMS, Roche, and Abbott.

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V. G. has been an investigator on vaccine studies sponsored by Sanofi Pasteur MSD and other companies, has received consulting fees from Sanofi Pasteur MSD and GSK, and has received travel support to attend scientific meetings from Sanofi Pasteur MSD.

O. L. has been an investigator on vaccine studies sponsored by Sanofi Pasteur MSD, GSK Bio, and MSD and has received travel support to attend scientific meetings from Sanofi Pasteur, Pfizer, GSK Bio, MSD, Abbott, and Boehringer.
B. S., E. C., T. D., C. S., and L. L. were employees of Sanofi Pasteur MSD at the time the study was conducted.

B. D. reported no conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed in the Acknowledgments section.

References