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The epidemiology of varicella–zoster virus infections: the influence of varicella on the prevalence of herpes zoster

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SUMMARY

This paper uses mathematical models and data analysis to examine the epidemiological implications of possible immunologically mediated links between patterns of varicella and herpes-zoster incidence in human communities. A review of previously published reports does not clarify whether or not there is a relationship between the incidence of varicella and the incidence of zoster. However, new analysis of data collected by the Royal College of General Practitioners provides indirect evidence for the hypothesis that a high intensity of varicella transmission suppresses viral reactivation. The significance of this finding for proposed varicella vaccination campaigns is explored by a review of published data on the use of the vaccine. No significant difference is shown to exist between the risk of zoster caused by the vaccine and the wild virus. A mathematical model is then developed to take into consideration the influence of the prevalence of varicella on viral reactivation and the impact of vaccination with attenuated virus, which may be able to recrudesce. Under some conditions, mass application of such vaccines may have the impact of increasing zoster incidence. The results presented here indicate that, before starting any vaccination programme against varicella, its consequences need to be assessed in much more depth.

INTRODUCTION

The development of a vaccine against varicella–zoster virus (VZV) lends urgency to the need to understand the exact relationship between the incidence of its two disease manifestations, varicella (chickenpox) and zoster (shingles) [1–4]. It is important to establish whether or not there is a correlation in levels of incidence of the two diseases. If a reduction in varicella incidence were to change levels of zoster incidence then the implications of vaccination require careful consideration. For instance, a reduction in morbidity caused by varicella–zoster virus in children could be offset by an increase in morbidity in adults. To understand what may happen after the start of a vaccination programme we need to know what the role of challenges by exogenous virus is in the reactivation of

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zoster. Virus shed from varicella cases may or may not stimulate or inhibit the reactivation of latent virus.

In this paper an attempt is made to determine which of these three possibilities is present in the population dynamics of VZV. It is divided into two main sections, which respectively consider the relationship between varicella and zoster incidence, and explore the implications of these results for proposed varicella vaccination strategies. The paper reviews published data on the incidence of the two diseases to determine how varicella appears to influence zoster. The implications of these results are analysed using a mathematical model for the incidence of varicella and zoster [5], which is refined to allow for the influence of contact with varicella on the probability of viral reactivation as zoster. The second section begins with a quantitative review of research on the reactivation of varicella vaccine in immunocompromised children. Our mathematical model of VZV population dynamics is then used to assess the implications of vaccination against varicella with respect to the incidence of zoster. These results of the paper are then brought together in a conclusion which discusses the use of the vaccine.

INCIDENCE AND REACTIVATION OF VARICELLA

Records of disease incidence

Varicella has been a nationally notifiable disease in the USA since 1972 [6]. When this nationwide information is coupled with information from other more local studies [7, 8] it is possible to obtain a clear picture of how the incidence of varicella varies through time. The variation of zoster incidence with time is more difficult to assess. Because zoster has never been a nationally notifiable disease (Cochi and Wharton, 1988 pers comm), one is dependent for epidemiological data upon cases recorded by specific general practitioners and hospitals. This means that the available records are small in scale and are subject to under-reporting. However, because such records are the sole source of information they should be fully utilized in addressing what the role of virus shed from varicella patients is in the reactivation of zoster.

In principle, contact with varicella cases could either stimulate or inhibit the re-emergence of latent virus in its hosts. Both alternatives have been considered in the past.

Varicella induces reactivation

Local connections in the occurrence of varicella and zoster and clusters of zoster cases [9–13] have led to the inference that challenge with virus from varicella or zoster precipitates the emergence of latent virus. McNamara and colleagues [14] found one such case of zoster to be due to reinfection of an immunocompromised patient, suggesting that cases of disease which were thought to be zoster induced by challenge are in fact a second episode of varicella. However, in cases observed by Straus and colleagues [13] the virus responsible for the zoster was clearly different from the exogenous virus. All the published reports of clusters of cases describe small outbreaks and no mechanism has been proposed to explain their connection. It would not, therefore, be unreasonable to view such episodes as coincidence.

Varicella inhibits reactivation

The opposite relationship between varicella and zoster incidence, where challenges prevent viral reactivation, has also been considered. In a seminal study, Hope-Simpson [15] suggested that exogenous VZV, through it subclinical influence on the immune system, could delay the opportunity for reactivation of the latent virus. Arvin and colleagues [16] recorded subclinical increases in antibody levels in people in contact with varicella cases, which lends indirect support to this hypothesis. There are also papers which point to an inverse relationship between varicella and zoster incidence. Only two local studies of case reports, one from a general practice in England [12] and the other from a hospital in Sweden [13], describe a peak in the incidence of zoster in the summer months, which coincides with the yearly trough in varicella incidence, which has a seasonal peak in the winter months [6–8]. Neither analysis is particularly convincing. Other studies hint at a negative correlation between varicella and zoster incidence [15, 18] but do not produce statistically significant results. None of the data sets referred to is large and they are consequently inconclusive. In addition other studies have found that the overall incidence of varicella has no influence on the incidence of zoster [19–22]. However, these studies also use very small sample sizes.

To examine the possible influences of varicella on the reactivation of zoster, we require time series of case reports for the two diseases recorded in parallel for the same population. Such records are rare. Here we analyse the most detailed such data set for England and Wales, which is collected by the Royal College of General Practitioners (RCGP). These consist of weekly rates of both varicella and zoster incidence collected from the records of 106 doctors [22]. The records for zoster and varicella incidence are divided into the age categories 0–4, 5–14, 15–44, 45–64 and > 65 years. In an analysis of these data Joseph and Noah [23] noticed a change in the incidence of varicella with age taking place in the 1980s, following a large varicella epidemic in the winter of 1980. If there is any detectable relationship between varicella incidence and zoster incidence then it should be apparent after such a major epidemic. The weekly incidence of each disease was examined using the standard time series techniques of auto-correlation and spectral analysis [24, 25]. Cross correlation and multivariate spectral analysis were used to examine the relationship between the incidence of one disease and the other [25].

A model of viral reactivation

The initial model

A basic model representing the progress of varicella–zoster virus through the host population is described in Garnett and Grenfell [5]. This age-structured compartmental model describes varicella infections in a standard way and has the addition of virus carriage and zoster categories where the probability of viral reactivation is described by a function of age, the reactivation function. Possible forms of this reactivation function are described in Garnett and Grenfell [5].

Modelling the situation where varicella induces or inhibits reactivation in the model

These two alternative possibilities are represented in the model as follows.

(*a*) *Exogenous virus induces reactivation.* This hypothesis can be examined

simply by making the reactivation function an increasing function of the age specific force of infection. $\lambda(a,t)$, as well as of age. This is because the force of infection is a measure of the amount of infective contact each age group has with the varicella virus, irrespective of whether they are susceptible or immune. The reactivation function $\rho(a,\tau)$ [5] are therefore multiplied by $1+\mathbb{C}_2\lambda(a,t)$, where $\mathbb{C}_2\lambda(a,t)$ determines the number of cases of zoster (which would not otherwise have occurred) caused by contact with varicella. $\mathbb{C}_2$ is a scaling constant controlling the importance of this mechanism. If exogenous virus has no effect then $\mathbb{C}_2$ is zero which removes the infleunce of the force of infection from the reactivation function.

(*b*) *Exogenous virus inhibits reactivation.* Once again, because the age specific force of infection is a measure of the contact each age group has with exogenous varicella virus, the history of the age-specific forces of infection experienced by individuals is used in the model to assess the relative magnitude of any subclinical strengthening of VZV-specific immunity by contact with exogenous virus. In general reconstitution of specific immunity would reduce the probability of viral reactivation. The reactivation function $\rho(a,\tau)$, is therefore altered to allow for past transmission intensities of primary infection. In particular it is reduced to a proportion $1-\Omega(a,t,\tau)$, where $\Omega(a,t,\tau)$ is the proportion of zoster cases prevented through the influence of boosting of specific immunity by subclinical infection. $\Omega(a,t,\tau)$ controls the reduction in the probability of reactivation for all age groups and all times at which initial infection took place. Because of this an integral is necessary determining the cumulative effect of the forces of infection experienced from the present, back to the time of initial infection (τ years ago). The value of $\Omega(a,t,\tau)$ is defined as:

$$\Omega(a,t,\tau) = \mathbb{C}_2 \int_0^\tau (\lambda(a-s,t-s)\exp^{-\kappa(a)s})\,ds, \tag{1}$$

where $\lambda(a\text{–}s,t\text{–}s)$ is the transmission intensity of varicella at a period s years in the past. The formula used for $\Omega(a,t,\tau)$ is justified as follows.

(i) The integral from 0 to τ sums all the values of $\lambda(a,t)$ experienced by an individual since initial infection (when $s=\tau$) up to the present day (when $s=0$) providing a measure of past experience of varicella transmission intensities.

(ii) In general the effect of boosted immunity may be expected to fade with time (here measured by s). This is modelled in equation (1) by an exponential decay, $e^{-\kappa(a)s}$. Here $\kappa(a)$ is a general function which allows for a decline in immune competence with increasing age. A simple formulation of $\kappa(a)$ is used here: $\kappa(a) = \mathbb{C}_1(e^{(\phi a)}-1)$ allowing for the possibility that the decline is non-linear. ϕ controls the influence of age on the competence of the immune system and $\mathbb{C}_1$ is simply a scaling constant.

(iii) The influence of subclinical reconstitution of specific immunity is also scaled by $\mathbb{C}_2$. Exogenous virus being without effect is the case when $\Omega(a,t,\tau)$, the proportion of people protected from zoster, is zero, which is achieved by assigning $\mathbb{C}_2$ a value of zero.

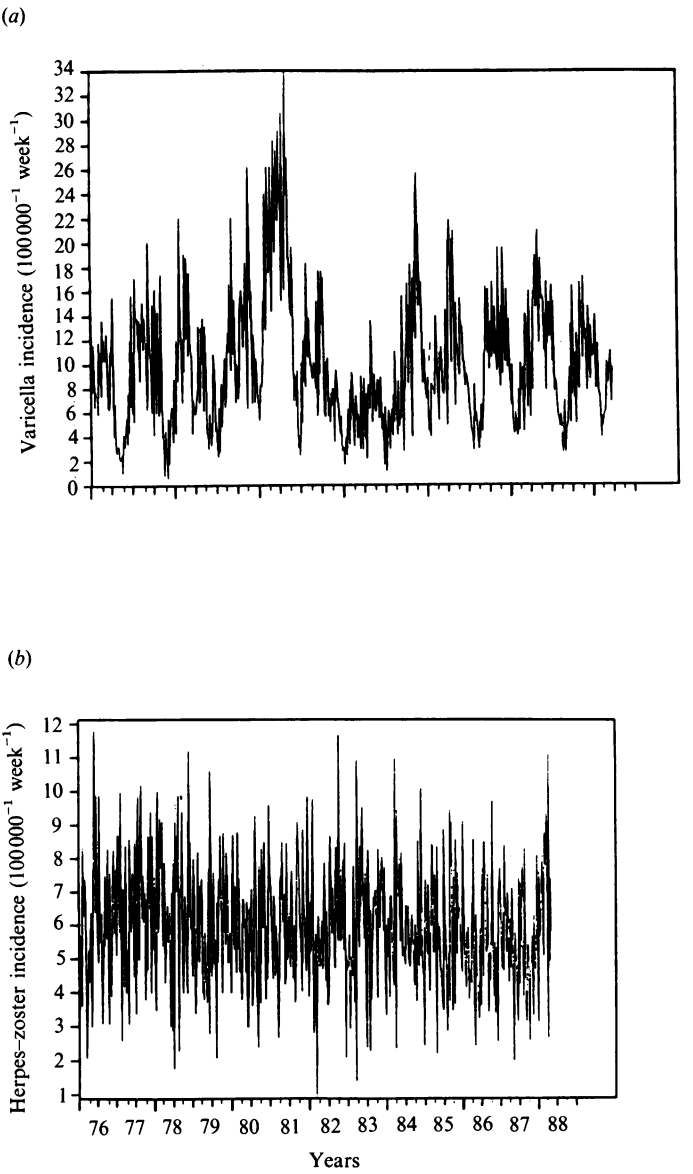

Fig. 1. The incidence of (*a*) varicella and (*b*) herpes-zoster reported to the Royal College of General Practitioners for each week from 1976 to 1987.

RESULTS

Analysis of data

The weekly incidence of varicella and zoster reported to the RCGP from 1976 to 1987 was examined for cyclical patterns using standard time series techniques. The raw data are shown in Fig. 1. In all age categories varicella incidence shows a significant annual cycle (auto-correlation coefficient $r_{52} = 0{\cdot}28$; $P < 0{\cdot}05$) which agrees with previous observations [6–8]. In contrast, no regular periodicity was detectable in the incidence of zoster, and there are no immediately apparent correlations between the dynamics of varicella and zoster in the time series. No

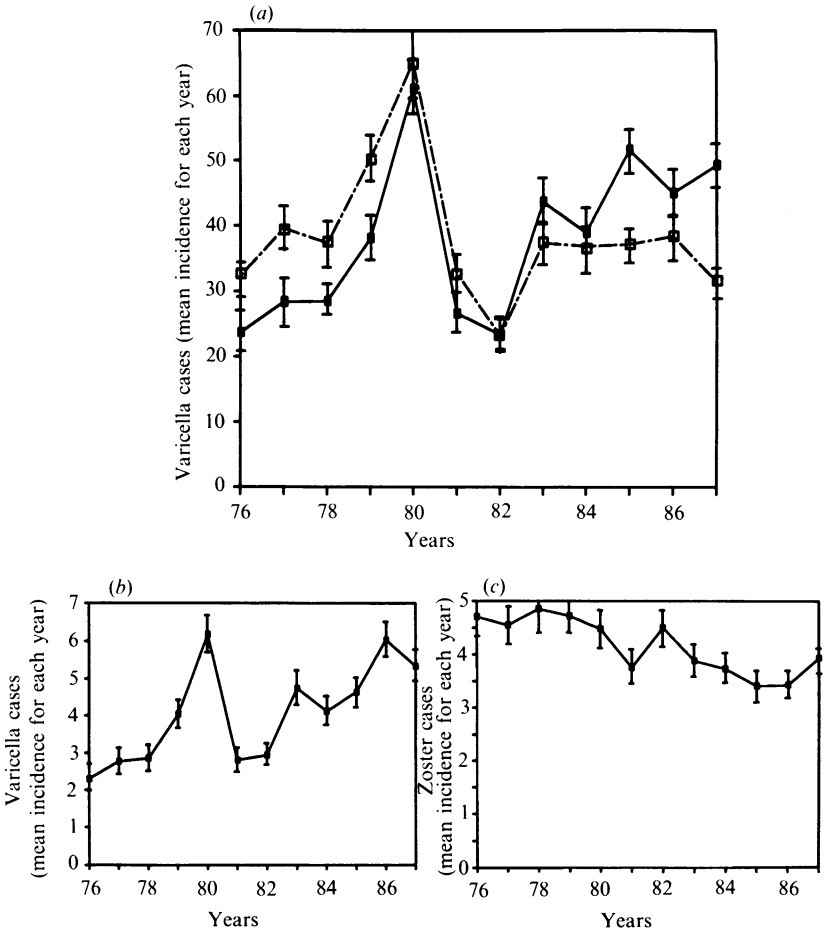

Fig. 2. The mean varicella and zoster incidence (per year per 100000) for 1976–87 calculated from the records of the RCGP. (*a*) Varicella incidence in children 0–4 years old, (–) and 5–14 years old (--). (*b*) Varicella incidence in young adults (15–44 years old). (*c*) Zoster incidence in young adults (15–44 years old). (Bars show standard errors.) The epidemic of varicella in 1980 is evident for all age groups, after 1982 the incidence of varicella rises in under 5 while remaining the same in 5–14 year-olds [27]. At the same time in 'young adults' there is an increase in varicella incidence and a decrease in herpes-zoster incidence.

overall relationship in the incidence of the two diseases was detectable at the weekly scale, either between overall rates or between specific age class rates. This suggests that the incidence of varicella has no immediate impact on observed levels of zoster.

In order to examine whether there were any long-term effects of incidence of varicella on the incidence of zoster the average incidence per year of the two diseases in the period 1976–87 were examined. After the 1980 epidemic, a change in the age structure of the incidence of varicella in children was observed by Joseph and Noah (23). The incidence of varicella in children under 5 years of age increased dramatically (Fig. 2; Wilcoxon Mann Whitney Test, $P < 0{\cdot}001$). This is possibly a consequence of the increase in the numbers of under fives attending school and preschool classes between 1981 and 1985 [26]. Changes in the pattern

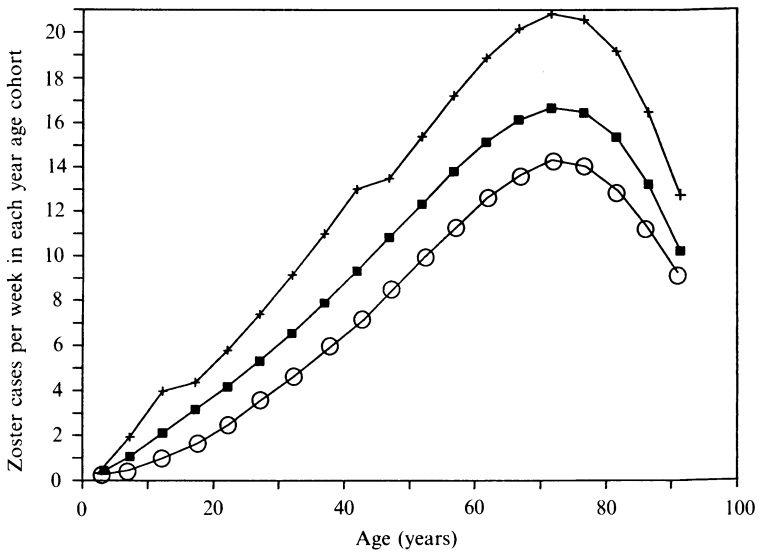

Fig. 3. The steady-state age at which zoster cases occur in model simulations. In these examples the underlying reactivation function increases exponentially with age. ■ = number of cases of zoster when varicella has no influence on the reactivation function; × = results when varicella induces viral reactivation; ○ = results when varicella inhibits viral reactivation. These results can be compared with the observed pattern determined in Garnett and Grenfell [5].

of reporting are another possible explanation, but there is no evidence to support this possibility. In 5–14-year-old children the incidence of varicella fell slightly (Fig. 2; $P < 0{\cdot}01$). This is probably a consequence of a reduction in the number of susceptibles in the age class following the epidemic and as a result of the increased incidence in the younger age group. The shift in the mean age of varicella incidence in children coincides with a slight, but significant, decrease in the overall incidence of zoster (Fig. 2; $P < 0{\cdot}05$), caused mainly by a significant decrease in the incidence of zoster in those aged 15–44 years (Fig. 2; $P < 0{\cdot}001$). There is also a significant increase in the number of cases of varicella in this 'young adult' age class (Fig. 2; $P < 0{\cdot}001$). As discussed below, if an increase in varicella amongst very young children increases the probability that young adults come into contact with the virus, then the reconstitution of specific immunity during challenges from exogenous virus is one explanation of these results.

Model results

Changes in the equilibrium results for the model caused by the inclusion of mechanisms whereby contact with exogenous virus alters the probability of reactivation of endogenous virus were examined. Solutions were calculated for the three reactivation functions, a linear, an exponential and a delayed increase with age, described by Garnett and Grenfell [5], under the two hypotheses (*a*) exogenous virus induces zoster and (*b*) exogenous virus inhibits zoster. The results were then compared with the base case where exogenous virus has no effect on the observed age at which zoster occurs. For illustration the results where varicella induces and inhibits reactivation of zoster are shown in Fig. 3. Here only for the sake of illustration there is assumed to be an exponential increase of the underlying reactivation function, other assumptions about the underlying

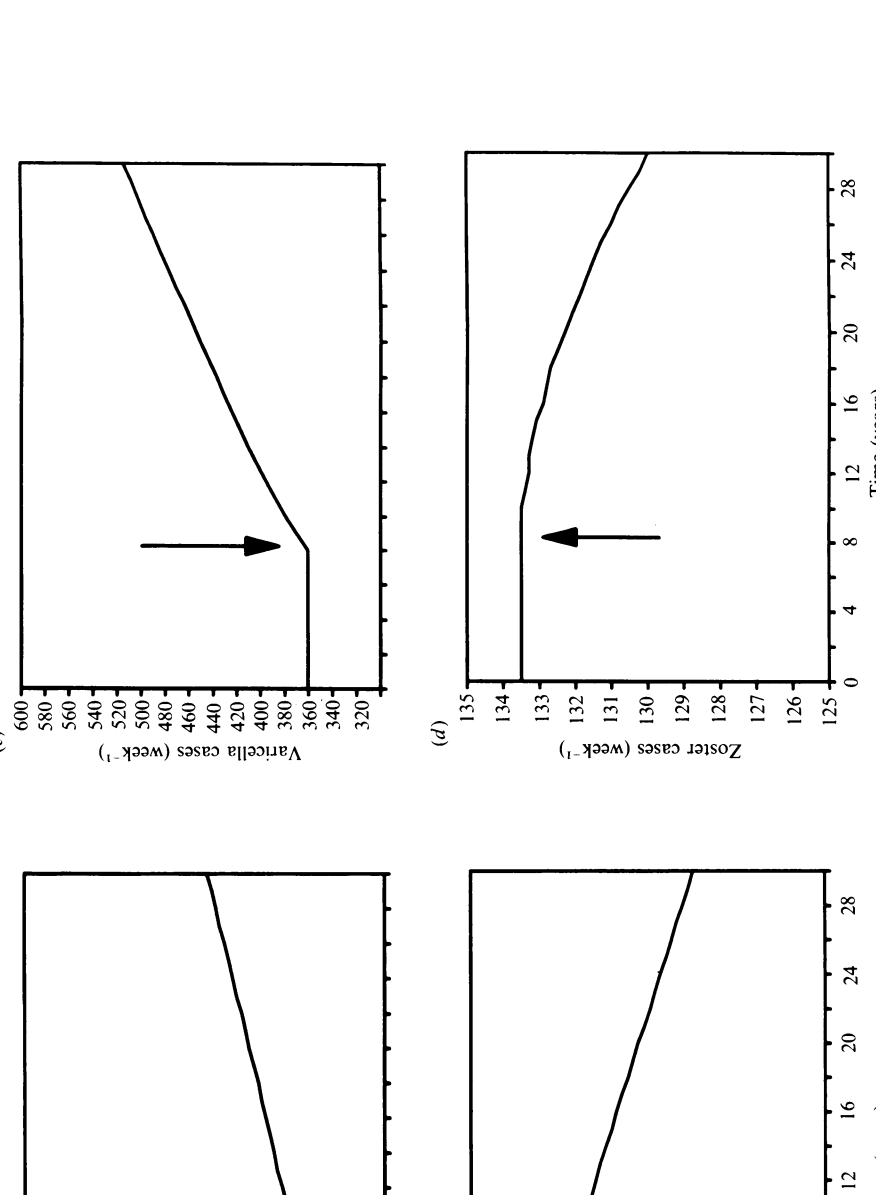

Fig. 4. Changes in the incidence of varicella and zoster (for a population of 50 million) caused by stimulating changes in the transmission intensity of varicella. The graphs represent the incidence of varicella amongst (*a*) 0–4-year-olds, (*b*) 5–14-year-olds, (*c*) 14–44-year-olds, and (*d*) the incidence of zoster amongst 15–44-year-olds. Arrows indicate the point at which the changes in transmission coefficients commence. In order to simulate the qualitative change in the observed incidence of varicella and zoster (Fig. 2) it is necessary to increase the transmission of varicella amongst pre-school-children and concurrently decrease transmission amongst school-children. This leads to an increase in transmission amongst young adults. These three changes are effected by (i) increasing the transmission coefficient amongst 0–4-year-olds by 1% of its original value each year; (ii) decreasing the transmission coefficient amongst 5–14-year-olds by 0·5% of its original value each year; and (iii) increasing the transmission coefficient from 0–4-year-olds to 15–44-year-olds by 0·5% of its original value each year.

function produce similar results. As would be expected, the prevalence of infection is increased by contact with virus inducing reactivation and decreased when it inhibits reactivation. Additionally, the force of infection for varicella in a population is greatest amongst children [5], which causes a slight alteration in the age of infection with both of these effects. However, the influence of varicella does not appreciably alter the qualitative pattern of disease occurrence with age, and the quality of both observed data and parameter estimates does not allow quantitative comparisons. We cannot, therefore, rule out either influence of varicella and must take into account proposed mechanisms and the existence of any other evidence in drawing conclusions about how varicella prevalence effects the reactivation of latent virus.

Simulating the dynamics of varicella and zoster

The parallel time series collected by the RCGP provide an indication of how the observed age structure of zoster incidence may be influenced by the incidence of varicella. The data describing zoster incidence are insufficient to warrant the formulation of a dynamic model including seasonality. However, changes in the steady state caused by changes in the transmission intensity of varicella were examined in the age structured VZV model. This simplified representation is to examine possible trends underlying detailed dynamics. The values of transmission coefficients in the model were changed to simulate an increase in the exogenous virus circulating amongst young adults. (The details of these changes are described in the legend to Fig. 4.) In this instance the reactivation function which increases exponentially with age [5] is multiplied by $1-\Omega$ where Ω is described in equation (1). Their impact accumulates with time to generate significant alterations in the rate of zoster reactivation (Fig. 4). The number of cases of zoster in 15–44-year-olds falls and there is a corresponding small rise in the number of cases in those over 45. At the same time the number of cases of varicella in 15–44-year-olds increases.

The analysis indicates that the observed relationship between varicella and zoster apparent in the RCGP data can be explained by a model in which the decrease in the incidence of zoster and increase in the incidence of varicella in 15–44-year-olds is a direct result of an increase in circulating virus. However, the results do not establish whether this is the correct interpretation and should be viewed with caution. Other possibilities are reviewed in the discussion. The implications of these results for proposed vaccination strategies, which aim to reduce the impact of varicella, are explained below.

VACCINATION

Reactivation of the varicella vaccine

On the basis of trials carried out in Japan and the USA, varicella vaccine appears to be efficient in protecting immunocompromised and healthy children from varicella [27–29]. However, it also has the potential to cause zoster [28]. The amount and severity of zoster caused by the vaccine virus, in comparison with the wild-type virus, has yet to be ascertained. Trials which involve immunocompromised children suggest that the vaccine virus will reactivate less often, and cause less serious disease [30, 31]. However, this reduction in the risk of zoster

Table 1. *The risk of zoster for immunocompromised children where latent virus is vaccine derived compared with risk of zoster following infection with wild-type virus*

	Without zoster	With zoster	Per cent without	Per cent with
Vaccinated group	40 (37·5)	4 (6·5)	90·0 (84·7)	9·1 (15·4)
Natural varicella group	29 (31·5)	8 (5·5)	78·4 (84·7)	21·6 (15·4)
	$\chi^2 = 2{\cdot}5$	$P > 0{\cdot}05$ Correct result	$\chi^2 = 6{\cdot}01$	$P < 0{\cdot}05$ Incorrect result

From Yabuuchi and colleagues [32]. In their analysis a significant result is generated using percentages, which more than doubles the effective sample size. The correct analysis using raw data is not significant. The expected values are presentedin parentheses.

(*b*)

Source	CI Vaccine	CI Wild	Duration of follow up	χ^2	$\approx$ P	ln($\approx$ P)
Baba, 1981 [33]	0·140	0·128	Not stated*	0·657	0·4	−0·92
Kamiya, 1982 [33]	0·094	0·222	Not stated*	0·036	0·85	−0·16
Yabuuchi et al. 1984 [32]	0·091	0·216	7 years*	2·5	0·15†	−1·9
Takahashi et al. 1985 [28]	0·104	0·158	Not stated*	1·342	0·25	−1·39
Brunell et al. 1986 [30]	0·283	0·0	5 years	7·15	0·075	−2·59
Kamiya et al. 1988 [34]	0·154	0·175	3 years*	0·09	0·975	−0·025
Lawrence et al. 1988 [31]	0·012	0·031	Value per year	3·818	0·05	−3·0

$-2.\Sigma \ln(P) = \chi^2 = 19{\cdot}962$ d.f. = 2. $N = 14$ $P < 0{\cdot}2$ N.S.

Published data on the difference in zoster incidence for wild type and vaccine virus analysed using Fisher's Combined Probability test, which shows that although the risk is always greater for wild type virus it is not significantly so.

* The number of withdrawals of subjects was not stated so could not be taken into account when calculating the cumulative incidence.

† The correct value was substituted for the analysis.

is not as significant as Yabuushi and colleagues [32] and Takahashi and colleagues [33] state. The results they quote are only significant if percentages are used in a χ^2 test (Table 1a), which is statistically invalid. Using Fisher's combined probability test, several studies (Table 1b) show no significant reduction in the incidence of zoster in vaccinated subjects in comparison with naturally infected people. It is important to note that studies of immunocompromised patients do not necessarily indicate what will happen in healthy individuals over a period of many more years.

This caveat is especially true when complications arise. The chance of virus reactivation is less in leukaemia patients if they contract varicella after the diagnosis of leukaemia [30]. Vaccine trials where the incidence of zoster has been assessed have mostly used leukaemia patients as subjects. It is most likely that these subjects are chosen for the study after their diagnosis of leukaemia. In trials with immunocompromised patients vaccine will have been administered after the start of the illness for which the subject is being treated. If vaccine is less likely to reactivate because of the stage in the immunocompromising illness rather than

because the virus is attenuated then the results of the trials are inconclusive. Use of the vaccine has only been possible for the last 10 years, so because the virus has a potential latency spanning decades, it will be many more years before it is known how frequently vaccine virus will cause subsequent disease. If programmes to vaccinate all healthy children are started their effect on the natural history of zoster should be seriously considered.

The inclusion of vaccination in the model of infection with VZV

For simplicity, vaccination is assumed to occur at one instant, at the age of 1 year. In the model this is achieved by the removal of the proportion vaccinated from the susceptible category (S) and their addition to the immune category (R). The number of vaccinated children in which the live vaccine virus has the potential to reactivate are also entered into the virus carriers category $V(a,t,\tau)$ at age 1 year, time t and delay 0. The possibility that attenuated vaccine virus is less likely to reactivate is allowed for by reducing the proportion (θ, $0 < \theta < 1$) of vaccinated individuals who enter the virus carriers class. This formulation produces essentially the same outcome as assuming that the probability that the vaccine can reactivate is lowered but that all the vaccine virus can become latent.

After the start of a vaccination programme, the force of infection will fall sharply, because of the fall in the prevalence of varicella in the population [34]. New equilibrium values for the force of infection can then be calculated, following the iterative method of Grenfell and Anderson [35], from the transmission coefficients derived from the steady state results without vaccination. The new steady-state levels of disease prevalence were calculated, and the ratio of the number of varicella and zoster cases following various vaccination strategies, relative to the number of varicella and zoster cases prior to vaccination, was also estimated. This generates a risk function for the impact of vaccination on disease incidence – a risk function value of less than one signifies a net benefit and a value of greater than one signifies a detrimental impact.

The impact of vaccination on the number of cases of varicella and zoster

Varicella. Following vaccination the equilibrium level of varicella is always reduced, with eradication in this very simple model at 85% vaccine uptake [36]. However, this is based on an assumption of 100% vaccine efficacy, which is clearly too high, and the model fails to take account of the re-introduction of infection into small pockets of susceptibles from index cases of zoster.

Zoster. Fig. 5 shows the risk function for zoster prevalence following vaccination. If it is assumed that the vaccine virus does not result in zoster ($\theta = 0$), then in the long term it would dramatically reduce the occurrence of zoster. Both those vaccinated and those protected from infection by the effects of herd immunity would not suffer from viral reactivation. This would apply, in the long term, whether or not contact with varicella helps delay the reactivation of latent virus.

However, the assumption that no vaccine virus reactivates is an extreme case, which goes against the empirical evidence, as reviewed above. If vaccine virus can reactivate to produce zoster, then there is a risk of vaccination producing an increase in equilibrium levels of zoster. This increase will only occur either if vaccination increases the proportion of the population carrying virus, or if contact

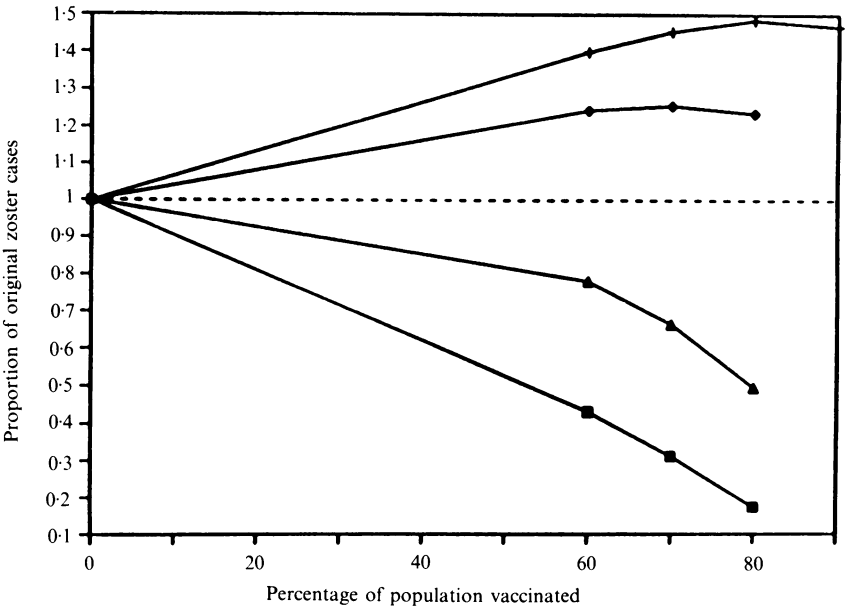

Fig. 5. The impact of vaccination on equilibrium zoster incidence in the VZV model. The proportions of the original steady-state number of zoster cases before vaccination which still occur after the inclusion of vaccination are shown. A value of this risk function below 1 indicates a reduction in the number of cases and a value above 1 and increase in the number of cases. ■, Values calculated when the vaccine virus does not recrudesce and when varicella does not boost specific immunity. The other values are the results of calculations where varicella does act to boost specific immunity, and where in 0 (△), 75 (◇) and 100% (+) of those vaccinated the vaccine virus has the potential to recrudesce.

with exogenous virus does boost specific immunity against latent virus. In the latter case, vaccination reduces the prevalence of varicella, which reduces the probability of people coming into contact with exogenous virus. This allows an increase in the number of people passing the lower threshold for specific immune resistance and consequently increases the probability of their suffering a case of zoster. The worst case, where 100% of vaccine virus has the potential to reactivate and where high varicella transmission intensities do normally lower the incidence of zoster is shown in Figure 5 along with the risk value if vaccine is less prone to reactivate.

DISCUSSION

From our analysis of the endemic pattern of zoster prevalence with age, it is not possible to test the hypotheses that contact with varicella induces or inhibits zoster. While some reports show clusters of cases of zoster [9–13], these are small and usually in a hospital setting where diseases related to old age are perhaps more likely to occur. Time series analysis shows no inverse correlation between varicella and zoster incidence, and zoster does not appear to be seasonal. These observations along with the lack of evidence of an appropriate mechanism suggest that varicella does not induce the reactivation of zoster. The mechanism proposed for varicella inhibiting zoster is that it boosts specific immunity [15]. The influence of such an effect would not necessarily be seen immediately, so the lack of seasonal changes

in the incidence of zoster cannot be used to falsify the hypothesis. The parallel time series for both diseases, collected by the RCGP in England and Wales, provided a unique opportunity to look at the relationship between varicella and zoster over a relatively long period of time in comparison to other time series for the two diseases. This generated some indirect evidence that viral reactivation may be inhibited by contact with varicella.

At the same time as incidence of varicella increased significantly in 'toddlers' and 'young adults' the incidence of zoster decreased significantly in 'young adults'. There are several possible explanations to account for the changes in the median yearly incidence of the diseases varicella and zoster in the young adult age class (14–44-year-olds as defined by the data collection methods employed by the RCGP). These changes may or may not be linked to the change in the incidence of varicella in pre-school and school children. The main hypotheses are as follows.

(*i*) *An increase in susceptible adults.* The changes in both varicella and herpes-zoster incidence amongst 15–45-year-olds could be the consequence of a large number of new susceptibles entering the age class. The decrease in the proportion of immune individuals could lead to the increase in the number of new cases of varicella. It would also mean that fewer people are carrying latent virus; this then decreases the number of potential zoster sufferers. This situation would be the outcome of a depressed incidence of varicella at some time in the previous 20 years. To correspond with the magnitude of the change in varicella incidence in young adults the lower incidence would have to be in the region of over 100000 fewer cases per year across the country. No other evidence suggests that the rate of varicella incidence has altered to such an extent.

(*ii*) *Changes in the pattern of reporting efficiency.* The change in zoster and varicella incidence observed could be due to changes in reporting efficiency. For example, changes in the perceived severity of cases of varicella and zoster would alter reporting efficiency. However, there seem to be no indications of a change in the severity of disease or any other factor which would influence reporting efficiency.

(*iii*) *The effect of subclinical reconstitution of specific immunity on contact with exogenous virus.* One hypothesis can tie all the changes together in a causal way. It seems most likely that the increase in varicella in young adults is a consequence of the increase in the incidence of varicella in young children. The transmission potential of varicella is greatest within families [37] and contact between parents and children is at its closest when those children are very young [38]. The increase in the incidence of varicella in 0–4-year-olds would cause an increase in the circulation of varicella virus amongst young adults. This would, in turn, lead to more cases of varicella as susceptible young adults are more likely to be challenged by infection, and fewer cases of zoster as the specific immunity is more likely to be exogenously stimulated. The possibility that specific immunity is being reinforced, which is not observable on a weekly scale, could well have an impact on the number of cases each year. It is not surprising that no effect corresponding to that in 15–45-year-olds occurs in the over-45 age group. Generally, people over 45 years old are less involved in very close contact with children with the virus [38]. Also, older people may not be able to respond to the stimulation from subclinical infections if they are less immunocompetent [39]. This second difference

in older patients is emphasized by the common severity of zoster in aged patients [40]. If the patient cannot mount a sufficient immune response, dissemination of the zoster lesions cannot be prevented. That this unified hypothesis provides the best explanation for the observed changes furnishes us with indirect support for the hypothesis that contact with varicella reduces levels of reactivation of latent virus.

Vaccination

The extensive pain caused by zoster [13, 40], and the morbidity produced in some of the most vulnerable members of society affect cost-benefit arguments for the use of the vaccine [3, 41]. These arguments would be greatly strengthened by the prospect of a reduction in the levels of zoster through vaccination. Conversely, they would be severely weakened by any increase in the incidence of zoster produced by such control programmes. The results presented here indicate that the latter worrying possibility, that high incidence of varicella in a community can keep the level of zoster low, is in fact the case. This effect is only of concern if the vaccine is to be used on all healthy children, thus reducing general levels of varicella. As illustrated above the danger involved in this depends very much on how likely the vaccine virus is to reactivate. This probability and the strength, if any, of inhibition of reactivation caused by varicella infection are two unknown factors. They make it impossible, at present, to predict with any confidence how a vaccination programme would influence the incidence of zoster in a community. It would be safer to wait until trials can tell us for certain that the vaccine is going to cause less zoster. The wait for this information will be a long one. An ideal solution to the problem would be the development of a subunit vaccine.

Future work

In the absence of any firm contradictory evidence on the immuno-epidemiology of viral reactivation, the hypothesis that exposure to varicella does reduce the probability of reactivation should be considered further. Future empirical data should be analysed for any observable influence of the incidence of varicella on the incidence of zoster.

The most appropriate policy for the use of vaccine needs more detailed consideration. In future work it would be useful to include more detailed information about the effectiveness and cost per dose of the vaccine and the relative levels of morbidity caused by varicella and zoster and the relative economic costs of disease. Varicella increases in severity with age [42], therefore, the effect of vaccination on the average age of infection and its consequences are also of interest.

The most important problem not discussed here is the possibility that the immunity to primary infection wanes with time after vaccination [27]. Any need for immune boosters would greatly increase the costs of what would, in any case, be an initially expensive vaccination programme [41]. This should be a key element of future work in assessing the impact of vaccination.

The use of vaccine in immunocompromised people susceptible to varicella would not be wise because of adverse responses to vaccination [27]. However, in children about to undergo immunosuppression vaccination could well prevent subsequent

severe varicella infections. If the licensing of vaccine for this reason also allows healthy children to be vaccinated then the use and impact of the vaccine should be carefully monitored. The recommendations for the vaccine's general use [2–4] may well prove correct, and the potential benefits of vaccination are greater than allowed for by just considering varicella. However, much more work needs to be done to elucidate the relationship between vaccination and reactivation, before the vaccine's widespread use in healthy children can be unequivocally advocated.

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