

Original Contribution

Exploring the Seasonal Drivers of Varicella Zoster Virus Transmission and Reactivation

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Varicella zoster virus (VZV) is a herpesvirus that causes chickenpox and shingles. The biological mechanisms underpinning the multidecadal latency of VZV in the body and subsequent viral reactivation—which occurs in approximately 30% of individuals—are largely unknown. Because chickenpox and shingles are endemic worldwide, understanding the relationship between VZV transmission and reactivation is important for informing disease treatment and control. While chickenpox is a vaccine-preventable childhood disease with a rich legacy of research, shingles is not a notifiable disease in most countries. To date, population-level studies of shingles have had to rely on small-scale hospital or community-level data sets. Here, we examined chickenpox and shingles notifications from Thailand and found strong seasonal incidence in both diseases, with a 3-month lag between peak chickenpox transmission season and peak shingles reactivation. We tested and fitted 14 mathematical models examining the biological drivers of chickenpox and shingles over an 8-year period to estimate rates of VZV transmission, reactivation, and immunity-boosting, wherein reexposure to VZV boosts VZV-specific immunity to reinforce protection against shingles. The models suggested that the seasonal cycles of chickenpox and shingles have different underlying mechanisms, with ambient levels of ultraviolet radiation being correlated with shingles reactivation.

herpesvirus; modeling; reactivation; varicella; varicella zoster virus; zoster

Abbreviations: UV, ultraviolet; VZV, varicella zoster virus.

Herpesviruses are unique in that they are able to cause recurring disease due to cycles of latency and reactivation. Initial infection requires close contact, which typically occurs through salivary/respiratory or sexual transmission. Varicella zoster virus (VZV), one of the 8 herpesviruses that infects humans, presents as chickenpox during primary infection and causes shingles upon reactivation. Reactivation of herpesviruses is highly complex at the molecular level, and the conditions favoring reactivation remain relatively unknown, though ultraviolet (UV) radiation is suspected to induce suppression of VZV cellular immunity (1). In animal models, trauma and stress can induce reactivation (2), while human herpes simplex cold sores have been shown to correlate with fatigue and UV radiation levels (3, 4), and reactivation of Epstein-Barr virus from infected B-cells is thought to occur when the cells respond to unrelated infections (5).

Most countries do not include herpesvirus diseases within their disease notification systems, and those that do typically report only chickenpox. VZV transmission, in the form of chickenpox, is well studied relative to other herpesviruses and is known for its explosive annual springtime outbreaks worldwide (6). There have been recent advances in understanding VZV reactivation at the molecular level (7, 8); however, how this translates to the epidemiology of shingles reactivation remains unknown. Global VZV seroprevalence has been reported to be above 90% in children and adolescents (9–11), and nearly all individuals are infected with VZV in the absence of vaccination. Although latent VZV is highly prevalent, only 10%–30% of individuals will ever experience a symptomatic reactivation of VZV expressed as shingles (12, 13).

We aimed to shed light on herpesvirus transmission and reactivation by leveraging available data on chickenpox and

shingles. We used data from Thailand, where VZV is endemic, the VZV vaccine is not required, and concurrent chickenpox and shingles notifications exist. Such data are rarely available, and we know of no other such data set in existence. We obtained data on cases at the national and regional scales from publicly available monthly clinical case reports that were supplemented with annual age-specific incidence data, spanning 2003–2010 (14). These data allowed us to focus modeling efforts on understanding the temporal dynamics of transmission and reactivation in the absence of human intervention. Although a great deal is known about chickenpox seasonality, there has been little work examining the seasonal dynamics of shingles, particularly at the population level. We took advantage of simplifying modeling assumptions in order to focus attention on our main areas of interest: 1) the seasonality of VZV transmission and reactivation and 2) immune boosting. For chickenpox, age-stratified contact patterns play a role in structuring the age-specific incidence in vaccinated populations (15). However, because of the high rate of transmission of the pathogen and lifelong immunity against chickenpox, in the absence of vaccination (as in Thailand), simple models with homogeneous contact rates have been shown to be sufficient in capturing chickenpox dynamics (16). Immunity-boosting has been shown to be a vital component of understanding shingles dynamics in theoretical models (17).

In order to supplement our case notification data, we also collated data on national and regional UV radiation levels (18, 19). We did this because other herpesviruses have been identified that reactivate from latency when exposed to increased levels of UV radiation (3, 4). Here, we wanted to examine whether elevated UV radiation levels increased shingles incidence. In order to test hypotheses regarding seasonal transmission, boosting of immunity, and UV radiation exposure, we built a suite of 14 mechanistic models to test various drivers of VZV transmission and herpes zoster reactivation.

METHODS

We collated clinical case reports of chickenpox and shingles from Thailand (14) to examine varicella transmission and reactivation (see Figures 1 and 2 and Web Appendix 1 (available at <https://doi.org/10.1093/aje/kwab073>)). Provincially resolved monthly chickenpox and shingles case reports were downloaded and grouped into 4 regions spanning 2003–2010 (Web Figure 1). Nationwide age-specific annual incidence from this time period was also examined (Web Figures 2–6). We observed seasonal variation in the shingles data and tested whether there was a significant seasonal cycle using Morlet wavelet analyses (20) for each region (Web Figures 7 and 8). To test for potential relationships between ambient UV radiation levels and shingles, we also collated complementary UV covariate data from the US National Center for Atmospheric Research (Web Figures 8–10) (18, 19). Thailand demographic data were interpolated from annual population estimates (6). Case data and covariates were coupled with mechanistic transmission-reactivation models to test hypotheses regarding seasonality

of VZV transmission and reactivation, as well as immunological interactions between chickenpox and shingles.

Since the mechanisms driving the transmission and reactivation of herpesviruses are not fully understood, multiple biological hypotheses were considered (Web Figure 11 and Web Table 1). We developed a modular compartmental model by redeveloping the classical susceptible-infected-recovered model (Web Figure 11, Web Appendices 2–4) (21). Since the majority of VZV infections are symptomatic with classic chickenpox symptoms, in order to model the manifestation of symptoms, clinical visits, and subsequent reporting to the notification system, we assumed that reported cases were the number of infected individuals scaled by an estimated reporting rate and drawn from a normal distribution.

The model included 3 modular components: component 1, the seasonal driver for transmission/chickenpox; component 2, the seasonal driver for reactivation/shingles; and component 3, immunity-boosting. For components 1 and 2, we tested models with flexible seasonal transmission and/or reactivation using B-splines to capture seasonal variation due to an unspecified driver. We also alternatively tested seasonality driven by the timing of school terms, UV radiation exposure, and past UV radiation exposure. For component 3, we tested the presence/absence and amount of immunity-boosting. The combinations of these options resulted in 14 different model variants (detailed in Web Figure 11). Model variants included those that assumed chickenpox transmission and shingles reactivation had identical or independent seasonal drivers. For the models with B-splines, it is important to note that they were a semiparametric representation of seasonal forcing that could account for flexible seasonal patterns; however, because we implemented the B-splines for seasonal effects, they were unable to account for inter-annual variation in seasonality (22). All models were implemented in the R package “pomp” and fitted via maximization by iterated particle filtering (23, 24) using national-level chickenpox and shingles data from 2003–2010. Although the chickenpox data were available for 1985–2019, shingles data were only available for 2003–2010.

RESULTS

Using Thailand’s national-level disease data, we observed strong seasonal cycles in chickenpox outbreaks, which was expected based on observations from other countries (6, 16). Less expected, however, was the seasonal occurrence of shingles, which was less explosive than that of chickenpox but still prominent (Figures 1 and 2 and Web Figure 1). Chickenpox dynamics were characterized by outbreaks that began to take off each year during November and December, culminating with seasonal peaks in February or March. Peaks were followed by deep troughs that lasted from June to October. The observed national-level seasonal outbreak patterns also persisted at the regional (Web Figure 12) and provincial (Web Figure 13) levels, though amplitude decreased closer to the equator. The seasonality of shingles was more complicated. January consistently had a relatively high number of cases compared with other months; however,

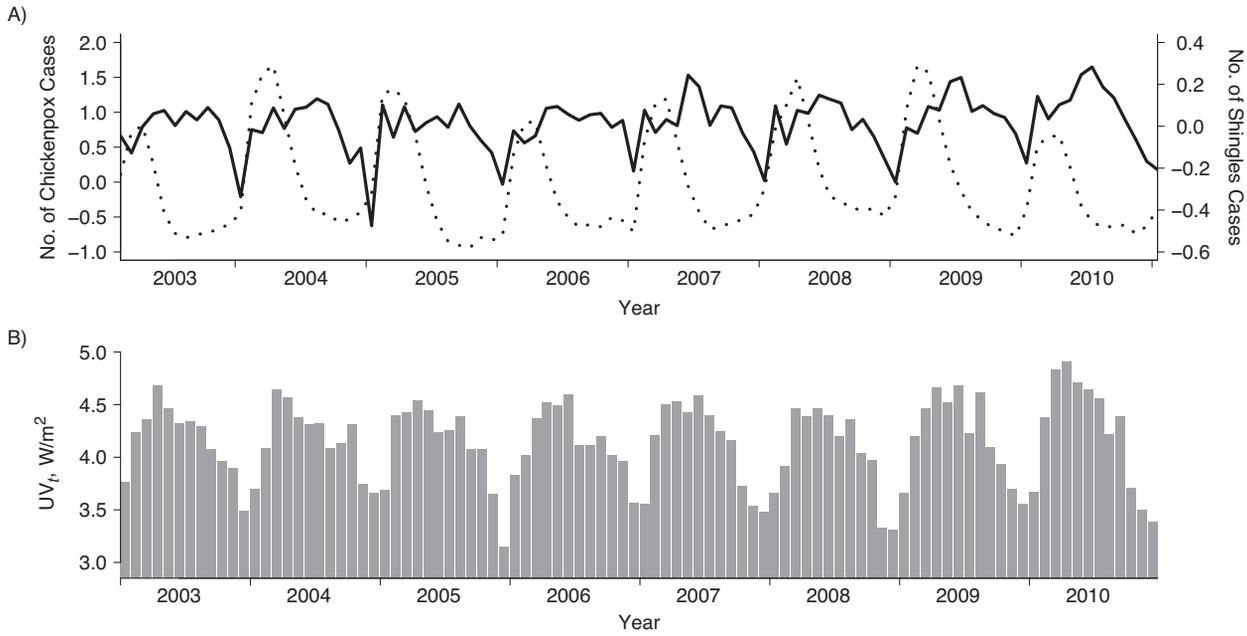


Figure 1. Numbers of chickenpox and shingles cases in Thailand, 2003–2010. A) Monthly log-detrended numbers of cases of chickenpox (dotted line) and shingles (solid line); B) ultraviolet (UV) radiation levels for the corresponding time period.

there were typically 2 annual troughs for shingles cases—a shallow trough and a deep trough. The shallow trough was not always present, but it was coincident with the peak in chickenpox (February–March). The deep trough was consistent and occurred in October–December. Shingles cases peaked in May–June, meaning that the shingles peak was delayed relative to the chickenpox peak. Importantly, a cross-wavelet analysis confirmed that both diseases displayed significant annual periodicity, with peak numbers of cases spaced 3 months apart (Web Figure 8).

The country-level shingles cases indicated a novel seasonal pattern; therefore, we investigated the possibility of spatial variation in shingles seasonality. We discovered a latitudinal gradient in shingles seasonality, since regions in higher latitudes had more pronounced seasonal cycles (Web Figures 1, 7, 9, 10, and 14), with diminished seasonal variation as populations approached the equator. The northern region, where the seasonal signal of both shingles and UV radiation was strongest, also had the highest shingles incidence in Thailand.

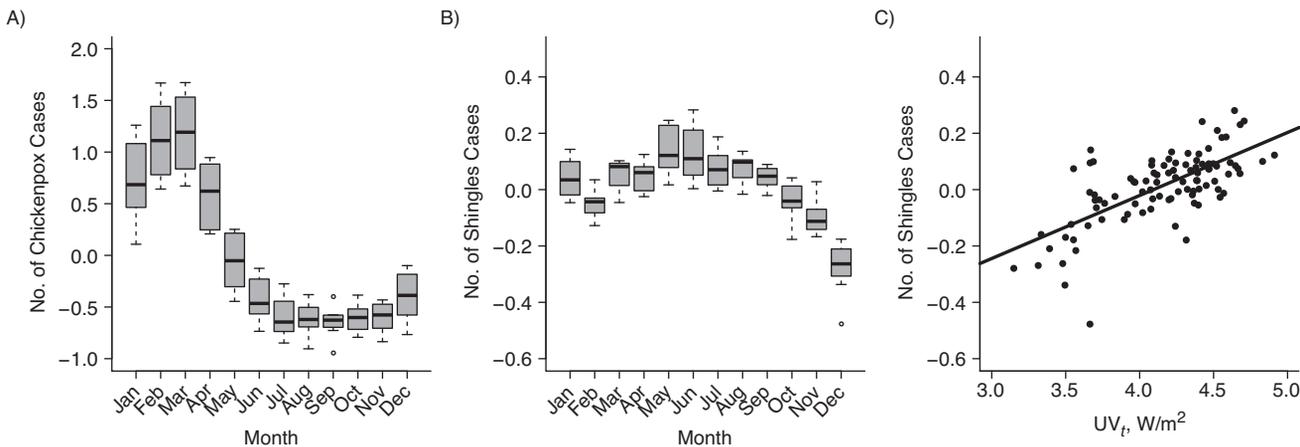


Figure 2. Numbers of chickenpox and shingles cases in Thailand and number of shingles cases according to ambient ultraviolet (UV) radiation levels, Thailand, 2003–2010. A) Box plot of monthly log-detrended numbers of chickenpox cases; B) box plot of monthly log-detrended numbers of shingles cases; C) correlation between monthly log-detrended shingles cases and monthly UV radiation levels ($R^2 = 0.467$, $P = 1.66e^{-14}$). Box plots: black line, median value; box borders, interquartile range; bars with dashed lines, 5th and 95th percentiles; open circles, outliers.

We observed a significant positive correlation between the monthly UV radiation index and monthly numbers of shingles cases in each region (Web Figures 9 and 10) and at the national level (Figures 1 and 2). At the national level, approximately 47% of the seasonal variation in shingles cases was explained by UV radiation exposure (Figure 2C). On a regional scale, the correlation between UV radiation and shingles was stronger in the north, northeastern, and central regions, relative to the southern region (Web Figures 9 and 10). This was at least partially due to the lack of seasonal cyclicality of shingles in the south (Web Figure 7). As a country, Thailand spans the latitudinal band from approximately 6°N to 21°N, with the northern region encompassing roughly 15°N–21°N and the southern region spanning 6°N–12°N. Throughout the study period, annual periodicity in both UV radiation levels and shingles was significant, with a 1/8-year (i.e., approximately 1.5-month) lag between the initial increase in UV radiation and the increased number of shingles cases (Web Figure 8).

We used the national-level data to test models representing different hypotheses regarding seasonal transmission, reactivation, and boosting of immunity. In total, we explored 14 mechanistic models and tested which of these models was most capable of capturing the observed data and seasonal patterns therein, using maximization by iterated particle filtering, a likelihood-based method for statistical inference of dynamical systems (23, 24). The best-fitting model (Web Tables 1 and 2, Web Figure 15, Web Appendix 5) had flexible seasonal components and fitted both chickenpox transmission and shingles reactivation (Figure 3). This model utilized separate B-splines for each chickenpox and shingles case, which allowed for a high amount of flexibility in fitting the shape of the seasonal processes. Although our models examining Thai school terms as a seasonal step function for chickenpox transmission and/or UV radiation as seasonal covariates for shingles reactivation were not the best-fitting, the parameters of the best-fitting model suggested that school terms and UV radiation are important in VZV transmission and reactivation, respectively. This is because the transmission spline estimated for the best-fitting model closely matched school terms (25) and the reactivation spline closely matched UV radiation data (Figures 3B and 3D). The splines afforded the model additional flexibility that may have allowed it to capture the nuance in school-term time forcing that a step function could not capture. Similarly, although there was a high correlation between numbers of shingles cases and UV radiation, the UV radiation data were unable to capture the entirety of the seasonal nuance of shingles reactivation. This could be due to a multitude of factors, including UV radiation not being the primary seasonal driver, UV radiation acting in combination with other seasonal drivers, or imperfect data—both in reporting and in aggregation at the national level. The B-splines estimated for our best-fitting model correlated with lagged UV radiation levels for shingles. We then used the best-fitting model to conduct 2,500 stochastic simulations to show how they compared with the chickenpox and shingles data (Figure 3). The model was able to capture the seasonal cycles of both chickenpox and shingles, but the shingles data had a high amount of interannual variation in its seasonal shape that

the model was unable to capture with its fixed seasonal spline.

DISCUSSION

Using population-level data in Thailand, we 1) revealed out-of-phase coseasonality of chickenpox transmission and shingles reactivation, 2) determined that chickenpox transmission and shingles reactivation are driven by separate processes, and 3) found a strong correlation between seasonal UV radiation and shingles incidence.

Thailand had seasonal peaks in both chickenpox and shingles, with a 3-month lag in peak incidence (Figures 1 and 2, Web Figure 8). Previous studies of shingles reactivation at smaller scales (i.e., hospitals and towns) indicated a lack of seasonality in reactivation (26–32). The absence of observed shingles seasonality in previous studies, and in the southern region in our study, may be due to multiple factors. There could be regional differences in seasonality, with some regions lacking seasonal variation in the reactivation rate. For example, if an environmental exposure, such as UV radiation, is the mechanism driving shingles reactivation, the exposure may not vary seasonally in all locations, and/or it may not affect a sufficiently large portion of the population. So if UV radiation was important but most people worked indoors, the seasonal variation in UV radiation would not have the same impact as it would in a population that primarily worked outdoors. Alternatively, it could be that seasonal variation in reactivation exists across regions but because of the low amplitude of the variation it is difficult to distinguish from noise in locations with low incidence, thus reducing the statistical power to detect seasonality. In our study, it became more difficult to identify seasonality as we broke the data into regions (Web Figures 1, 7, 9, 10, 13, and 14), which may have been due to demographic stochasticity.

Shingles seasonality displayed a latitudinal gradient (Web Figures 1, 7, 9, and 10), similar to other human diseases (6, 33–37). We identified a strong correlation between shingles reactivation and UV radiation (both lagged and unlagged), providing evidence that UV radiation may have a biological impact on shingles reactivation, similar to the effect it has on herpes simplex virus (Figures 1 and 2, Web Figures 8–10, Web Table 1) (38). If the positive correlation between UV radiation and shingles is due to UV effects on the immune system, then the observed lag could be due to the time it takes for UV radiation exposure to effect immunity (either systemically or locally in the skin and peripheral neurons where the virus is latent) and/or the time between the start of the cellular reactivation pathway and the appearance and reporting of symptomatic illness (Figure 3D) (39). There may also be a reporting lag between the time of reactivation, symptom appearance, and a clinic/doctor visit.

To better understand the dynamics of the VZV system, we fitted multiple transmission-reactivation models to the data from Thailand. The best-fitting model revealed distinct drivers of chickenpox transmission and shingles reactivation (Figure 3, Web Table 1). The fitted model had a major peak in VZV transmission from December to February and a smaller peak in August–September, both of which mirrored

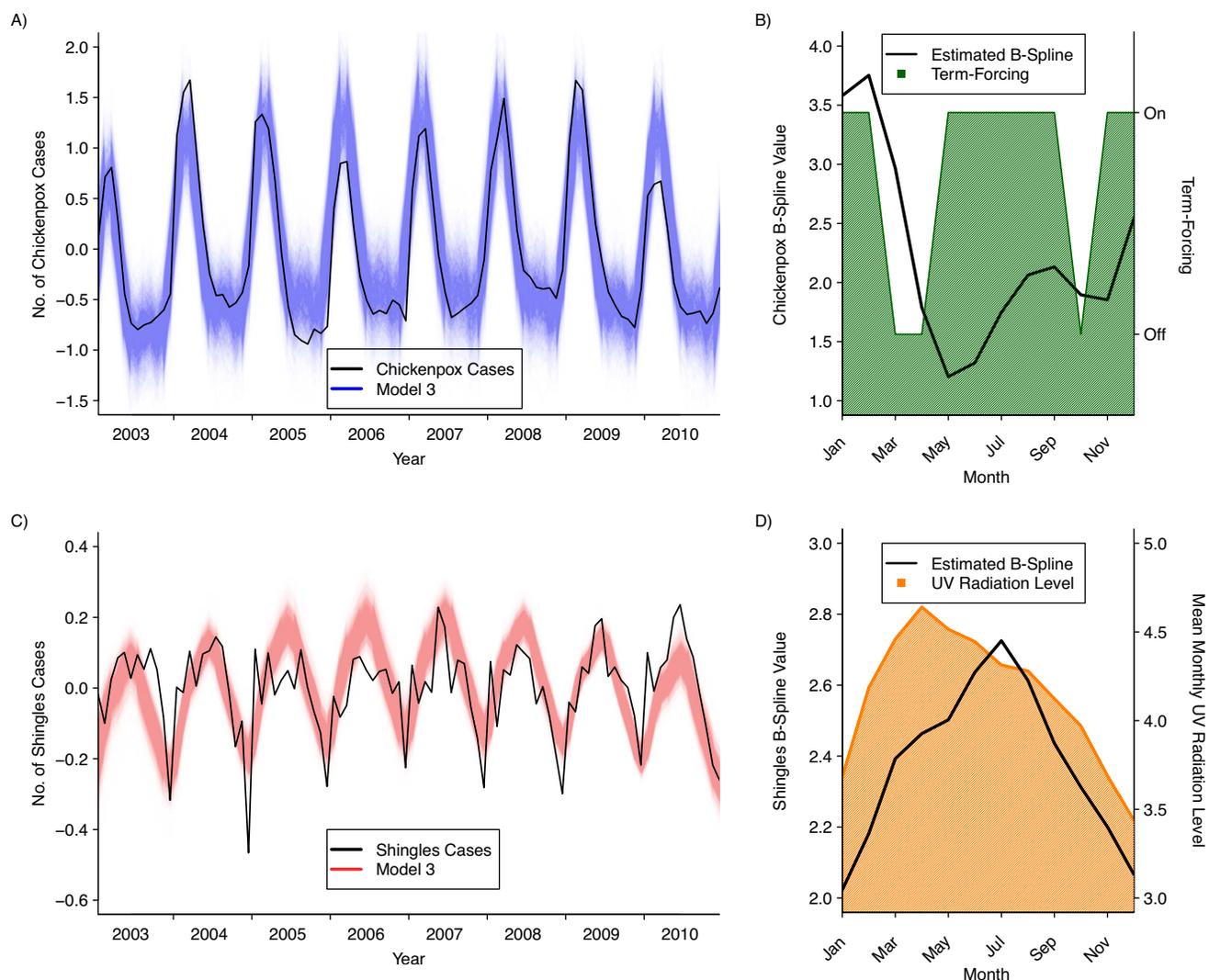


Figure 3. Comparison of simulated cases of chickenpox and shingles from the best-fitting model with monthly log-detrended numbers of clinical cases in Thailand, 2003–2010. A) Reported log-detrended numbers of chickenpox cases (black line) with 2,500 fitted simulations (blue) through 2010. B) Maximum likelihood (B-spline) estimate of the monthly seasonal forcing for chickenpox from the best-fitting model (black line) and school terms for Thailand (green). C) Reported log-detrended numbers of shingles cases (black line) with 2,500 fitted simulations (red) through 2010. D) Maximum likelihood (B-spline) estimate of monthly seasonal forcing for shingles from the best-fitting model (black line) and mean monthly ultraviolet (UV) radiation values for Thailand (orange).

Thailand's school terms. Low transmission was estimated in April–June and October–November, both of which were preceded by weeks when students were on vacation (Figure 3B). However, implementing the school terms as a step function for transmission did not improve model fits (Web Table 1). This is probably because the transmission rate varies among school sessions (i.e., the May–September session has lower transmission than the November–February session). There is also heterogeneity in school terms across Thailand that we were unable to capture. Students in many private international schools go to school year-round or have term breaks in different months than public schools. Additionally, school terms may not accurately

reflect contact patterns in Thailand because of heterogeneous social mixing patterns across this culturally and geographically diverse country.

Note that the best-fitting model did not include boosting of immunity by VZV transmission. This does not rule out the possibility that immunity-boosting exists; it simply shows that in our susceptible-infected-latent-reactivated model it was not required in order to capture the dynamics of chickenpox and shingles in Thailand. In fact, immunity-boosting may exist in our system and be captured by the model in the B-spline used to parameterize the reactivation rate. Thus, we must be careful when interpreting how VZV transmission affects shingles. Previous epidemiologic studies have shown

a decrease in immunity-boosting due to demographic shifts in the population structure via decreased birth rates (40, 41). In Thailand, a massive demographic shift has been occurring over the last 4 decades through a decrease in births, which has previously been shown to affect the epidemiology of other infectious diseases in the country (42). With a proven, safe, and effective VZV vaccine that protects against chickenpox and shingles and with clinical trials for other herpesvirus vaccines currently under way, an understanding of the biology underpinning herpesvirus reactivation may aid in the control of these diseases. We believe reactivation seasonality is an important phenomenon, because infectious disease transmission is largely assumed to be the driver of infectious disease seasonality. For shingles, however, the disease is not tied to a transmission event; it is due to reactivation of latent virus acquired decades in the past. We hypothesize that shingles seasonality is tied to an underlying seasonal susceptibility that may be important for public health more generally; but at the very least, these findings should inform shingles vaccination policy by identifying the “shingles season” as a time of vulnerability in the population.

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All data and software code are freely available at <https://www.kevinmbakker.com/data.html>.

Conflict of interest: none declared.

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