Is there any evidence that syphilis epidemics cycle?

Romulus Breban, Virginie Supervie, Justin T Okano, Raffaele Vardavas, Sally Blower

We re-examine the evidence behind the controversial hypothesis that syphilis epidemics cycle. We used the same methods (spectral analysis) used by the proponents of this hypothesis to reanalyse a longitudinal dataset provided by the US Centers for Disease Control and Prevention (CDC). We also analysed a longitudinal CDC mortality dataset. To investigate the theoretical results generated by the transmission model that was used to support the hypothesis, we simulated the model and predicted the expected dynamics of syphilis epidemics. By contrast with previous findings, we found that neither of the CDC’s datasets provides compelling evidence that syphilis epidemics cycle, and the transmission model (if more reasonable parameter values are used) does not predict cycling behaviour. We explain the possible reasons for the previous proposal that syphilis epidemics cycle. Our findings imply that it is quite possible that the CDC could be successful in eliminating syphilis within the next few decades.

Introduction

Epidemics of certain infectious diseases (eg, influenza) can rise and fall with a well-defined periodicity. This cycling behaviour is important because it can have significant implications for the design and effectiveness of control strategies. For example, effectiveness can be increased by intensifying interventions at the low point in the cycle. Recently, Grasley and colleagues have proposed, based on a statistical analysis of a US Centers for Disease Control and Prevention (CDC) dataset, that syphilis epidemics cycle and that these cyclic dynamics are a result of innate immunity rather than treatment or behavioural changes. This novel hypothesis is controversial. If it is correct, it could have important implications for the CDC’s plan to eliminate syphilis in the USA. It could potentially reduce the likelihood that the plan will be successful because it implies that treatment and other interventions are relatively unimportant in affecting the transmission dynamics of syphilis. To accept the hypothesis that syphilis epidemics cycle, strong evidence needs to be presented to support this assertion. Therefore, we have reanalysed the CDC’s datasets and the transmission model that was used to support the hypothesis. We compare the results of our reanalysis with the previous findings, and then briefly discuss the implications for the CDC’s current syphilis elimination plan.

Distinguishing between outbreaks and epidemic cycling

The dynamics of an infectious disease can be identified by examining longitudinal datasets. Not all infectious diseases show cycling behaviour (eg, tuberculosis and HIV). Therefore, when analysing a longitudinal dataset of any infectious disease, it is very important to distinguish whether any temporal changes in the data indicate a series of continuous periodic oscillations (as seen for influenza) or whether they simply indicate that several outbreaks have occurred (as has been seen for tuberculosis). The distinction between outbreaks and cycles can be made by using statistical analyses to determine whether any significant long-term periodicity is present in the data. If continuous periodic oscillations are identified, then a disease-specific transmission model should be able to predict, and explain, this cycling behaviour in terms of exogenous (ie, extrinsic) or endogenous (ie, intrinsic) factors. Exogenous factors are environmental factors (eg, temperature) that affect the host and the pathogen separately (eg, they might drive the abundance of pathogens or the density of hosts). They periodically perturb the epidemic from outside the system and cause cycling. By contrast, endogenous factors (eg, immunity) affect the host–pathogen interaction exclusively. They periodically perturb the epidemic from inside the system, and cycling occurs (through a Hopf bifurcation) in the absence of any external perturbation. The periodicity of an epidemic might be driven by a combination of exogenous and endogenous factors. For example, the immune status of the host population (an endogenous factor) and increased host density during school terms (an exogenous factor) can explain the biannual cycle of measles in England. The annual cycle of cholera in Bangladesh can be explained by the immune status of the local population (an endogenous factor), and the El Niño southern oscillation and the Indian Ocean temperature (both exogenous factors). The endogenous and exogenous factors that cause epidemic cycling can thus be independently isolated.

Certain infectious diseases do not cycle (eg, tuberculosis), as can be seen by the examination of longitudinal datasets, but they can show occasional outbreaks, particularly when incidence is low. The series of tuberculosis outbreaks that have occurred over the past few decades have been investigated by use of molecular epidemiological techniques and shown to be the result of reduction in treatment programmes, the HIV epidemic, and immigration of latently infected individuals. The mathematical analysis of transmission models of so-called “non-cycling” diseases have provided explanations as to why they do not cycle, and has identified the conditions that generate occasional outbreaks. For example, tuberculosis epidemics do not cycle because of the presence of a large number of latently infected individuals, but a high prevalence of HIV or low treatment rates, or both, can cause outbreaks to occur. Although several outbreaks of tuberculosis have occurred over the past two decades, infectious disease experts do not claim that tuberculosis epidemics cycle.
Multiple cycles have been observed in the incidence of childhood diseases (eg, measles and chickenpox; figure 1), faecal–oral infections (eg, cholera), vector-borne diseases (eg, malaria, dengue), respiratory infections (eg, influenza, pertussis, smallpox), and even some sexually transmitted diseases (eg, gonorrhoea). Epidemic cycles of various lengths have been observed for these diseases. The duration of an epidemic cycle (ie, period) is 1 year for diseases such as chickenpox, influenza, and gonorrhoea. Other infectious diseases, such as measles (figure 1), pertussis, and smallpox, have cycles of 2–3 years. An even longer cycle of 3–4 years has been documented for dengue.

Epidemic cycling is detected, and the periodicity of epidemic cycles calculated, by analysing longitudinal datasets by use of spectral techniques, wavelet techniques, and time-series models. Periodicity of multiple measles outbreaks (between 1703 and 1917) was investigated as early as 1918. More recently, spectral techniques (see webappendix) have been used to explore the periodicity of smallpox and cholera. Wavelet analysis has been used to study epidemiological time-series for measles, pertussis, and cholera.

Spectral analysis of longitudinal syphilis datasets The controversial hypothesis that syphilis epidemics cycle was based on a spectral analysis done by Grassly and colleagues on a short time series (1960–93) selectively sampled from a longer time series (1941–2002) of syphilis incidence data collected by the CDC in the USA (figure 1).

To do their analysis, they aggregated data over race, sex, and geographical regions. Based on the results of their
spectral analysis, they concluded that syphilis epidemics cycle with an approximate period of 8–11 years in the general population in the entire USA, and in large (eg, New York and Houston) and small (eg, Birmingham and Rochester) cities. Because of the controversial nature of this hypothesis, the results need to be carefully evaluated before it is widely accepted. Therefore, we have analysed the same CDC dataset and used the same methods (ie, spectral analysis) so that our results can be directly compared.

Grassly and colleagues' conclusion that syphilis epidemics cycle every 8–11 years might be an artifact of aggregating syphilis incidence data from men and women. To investigate this possibility, we stratified the CDC data for New York City by sex. If syphilis epidemics cycle in an aggregated dataset, then epidemic cycles should also be apparent if these data are stratified. Furthermore, if any interaction occurs between the two sexes (which obviously happens through the sexual transmission of syphilis), then, if cycles occur, they would have the same periodicity in the sex-stratified data as in the aggregated data. However, we find that the pattern in the female incidence data over the period 1960–93 does not increase every 8–11 years and does not match the pattern in the male incidence data (figure 2). Therefore, the sex-stratified data do not support the hypothesis that syphilis epidemics in the general population cycle every 8–11 years.

Since 1960, several large-scale well-documented changes in sexual behaviour have occurred, and these changes are highly correlated with the series of outbreaks of syphilis shown in figure 1 and figure 2. The rise of syphilis in the 1970s coincided with the sexual revolution, the rise in the 1980s with the beginning of the HIV epidemic in men who have sex with men, and the rise in the 1990s with the beginning of the HIV epidemic in heterosexual men and women. As syphilis rates increased, treatment rates intensified and led to decreases in incidence. The sex-stratified data (figure 2) are in agreement with the hypothesis that a series of sex-specific outbreaks, caused by large-scale changes in sexual behaviour followed by intensified treatment, caused temporal changes in aggregated syphilis incidence data (figure 1). Recent analyses of trends in syphilis incidence in subpopulations (defined on the basis of geography, sex, race, sexual orientation, etc) by Peterman and colleagues have also found that outbreaks occurred, but found no evidence that syphilis epidemics cycle.

Temporal variations in longitudinal incidence data can indicate epidemic cycles or simply show that several outbreaks have occurred. Spectral analysis can only reliably identify epidemic cycling behaviour, if it occurs, if the time series analysed is significantly longer than the period of the cycles. If the time series is too short relative to the cycle then a bias, known as aliasing, can occur and any apparent periodicity observed in the data can be spurious (see webappendix for details). Furthermore, if the incidence of an infectious disease actually cycles then the spectral density of a subset of the data, if it is significantly longer than the period of the cycle, should match the spectral density of the entire dataset. For example, because measles epidemics cycle, there is no significant difference (Wilcoxon test, p=0.23) between the spectrum calculated from a 16-year time series of measles incidence and the spectrum calculated from a subset of the data (indicated by dotted lines in figure 1). A relatively short time series (~10 years) can be used to reliably identify cycles of measles epidemics because they cycle every 2 years, as shown by the highest peak in the spectral density plot in figure 1.
Grassly and colleagues\(^1\) concluded that syphilis epidemics cycle, and have a periodicity of 8–11 years, by analysing a selected 33-year time series (1960–93) from the CDC syphilis incidence dataset. To determine whether spectral analysis of this 33-year period can reliably determine whether syphilis cycles and to identify cycles with a periodicity of 8–11 years, we compared the spectrum of the entire CDC syphilis dataset (1947–2002) with the spectrum of the subset of the dataset selected by Grassly and colleagues (figure 1).\(^1\) We found there is a significant difference between the long and the short selected time series (Wilcoxon test, \(p=0.009\)), implying that the cycling of syphilis epidemics is unlikely. Furthermore, to reliably identify cycles with a periodicity of 8–11 years, the time series analysed would need to be significantly longer than this period. If it is too short (relative to the cycle), periodicity can be observed, but it is likely to be the result of aliasing and hence spurious. To calculate whether a 33-year time series is too short to reliably identify cycles with an 8–11-year periodicity, we did a spectral analysis of a 33-year time series of a constant incidence (ie, when no cycles are present). We found that, as a result of aliasing, the spectrum indicates the existence of cycles with a periodicity of 13·5 years, 9·5 years, and 7·4 years (see weblappendix). Consequently, a 33-year time series is too short to reliably identify cycles with a periodicity of 8–11 years, as Grassly and colleagues\(^1\) assumed that the average number of new sex partners acquired per year is 14·5 (based on a transmission probability per partnership of 0·62), which corresponds to an average of 479 lifetime sex partners. We varied their parameter values and found that sustained cycles in incidence do not always occur. Specifically we found that cycling does not occur unless individuals acquire at least 9·8 new sex partners per year (which would result in an average of 323 lifetime sex partners), all other parameters held constant. Therefore, our results imply that if Grassly and colleagues\(^1\) had used more reasonable behavioural parameter values, they would not have concluded that syphilis epidemics cycle. More biologically realistic models of syphilis also show that epidemics are not expected to cycle.\(^35\)

**Conclusions**

The CDC is currently attempting to eliminate syphilis in the USA. They launched a syphilis elimination plan in 1999, which was redesigned in 2006.\(^4\) Their interim elimination targets are to reduce incidence of primary and secondary syphilis cases, by 2010, to less than 2·2 per 100000 population, congenital syphilis to less than 3·9 per 100000 livebirths, and black–white racial disparities to a ratio of less than 3·1. The CDC has specified three goals for reaching their elimination targets: enhancement of public-health services; evidence-based interventions that are culturally appropriate; and accountability. Their plan is intended to guide and assist local, state, and national health agencies to focus on achieving syphilis elimination in the most cost-effective, ethical, and acceptable way. The success of the CDC’s elimination plan will be greatly affected by the transmission dynamics of syphilis. Clearly, outbreaks of syphilis have occurred over recent decades, but occasional outbreaks are very different from cycling behaviour. These syphilis outbreaks can be explained by various factors: changes in sexual behaviour; the gay liberation movement in the 1970s; the HIV epidemic; the sexual revolution; and changes in the intensity of syphilis control programmes.\(^35\) By understanding the different factors that have caused each outbreak, appropriate interventions have been developed.

If, instead of occasional outbreaks, an infectious disease shows continuous periodic oscillations, intensified interventions can be focused on different stages of the cycle to increase effectiveness. For example, vaccination programmes are targeted to dampen down influenza epidemics before they begin. Thus, it is important to know whether the epidemics of an infectious disease do cycle. If syphilis epidemics do cycle approximately every 8–11 years, as Grassly and colleagues\(^1\) claim, then
interventions should be intensified every 8–11 years to increase the effectiveness of control. However, if syphilis epidemics cycle because of natural immunity, as they also propose, independently of behavioural changes and mass treatment, it is unclear what interventions will be effective. The natural immunity cycling hypothesis implies that current CDC control strategies may be relatively ineffective and that syphilis epidemics may continue to cycle.

On the basis of our analyses, we find that the evidence presented is not strong enough to support the claim that syphilis epidemics cycle. Furthermore, the syphilis transmission model that was used to provide a theoretical basis for the cycling hypothesis, when correctly parameterised, does not show cycling behaviour. Since mass treatment has been shown to be extremely effective in reducing syphilis incidence, it is quite possible that the CDC could be successful in eliminating syphilis within the next few decades. To achieve this goal, it will be necessary to increase case identification rates, strengthen behavioural and educational interventions, and intensify treatment.

Conflicts of interest
We declare that we have no conflicts of interest.

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References