Infectious disease outbreaks recapitulate biology: they emerge from the multi-level interaction of hosts, pathogens, and their shared environment. As a result, predicting when, where, and how far diseases will spread requires a complex systems approach to modeling. Recent studies have demonstrated that predicting different components of outbreaks—e.g., the expected number of cases, pace and tempo of cases needing treatment, demand for prophylactic equipment, importation probability etc.—is feasible. Therefore, advancing both the science and practice of disease forecasting now requires testing for the presence of fundamental limits to outbreak prediction. To investigate the question of outbreak prediction, we study the information theoretic limits to forecasting across a broad set of infectious diseases using permutation entropy as a model independent measure of predictability. Studying the predictability of a diverse collection of historical outbreaks—including, chlamydia, gonorrhea, hepatitis A, influenza, Zika, measles, polio, whooping cough, and mumps—we identify a fundamental entropy barrier for infectious disease time series forecasting. However, we find that for most diseases this barrier to prediction is often well beyond the time scale of single outbreaks, implying prediction is likely to succeed. We also find that the forecast horizon varies by disease and demonstrate that both shifting model structures and social network heterogeneity are the most likely mechanisms for the observed differences in predictability across contagions. Our results highlight the importance of moving beyond time series forecasting, by embracing dynamic modeling approaches to
prediction\textsuperscript{15}, and suggest challenges for performing model selection across long disease time series. We further anticipate that our findings will contribute to the rapidly growing field of epidemiological forecasting and may relate more broadly to the predictability of complex adaptive systems.

“If we don’t have a vaccine—yes, we are all going to get it.”\textsuperscript{16} This dire assessment by a Canadian nurse in 2003 reflected the global public health community’s best understanding of the ongoing SARS outbreak\textsuperscript{17,1}. This understanding—for perhaps the first time in history—was partially derived from mathematical and computational models, which were developed in near real-time during the outbreak to forecast SARS transmission risk\textsuperscript{10,1}. However, the predictions for SARS failed to match the data\textsuperscript{18,1}. Over the subsequent fifteen years, the scientific community developed a rich understanding for how complex social contact networks, variation in health care infrastructure, the spatial distribution of prior immunity, etc., drive complex patterns of disease transmission\textsuperscript{19,13} and demonstrated that data-driven, dynamic and/or agent-based models can produce actionable forecasts\textsuperscript{20,6,21,22}. What remains an open question is whether the existing barriers to forecasting stem from gaps in our mechanistic understanding of disease transmission and low-quality data or from fundamental limits to the predictability of complex, sociobiological systems, i.e. outbreaks\textsuperscript{19,23,13}.

In order to study the predictability of diseases in a comparative framework, which also permits stochasticity and model non-stationarity, we employ permutation entropy as a model-free measure of time series predictability\textsuperscript{25,14}. This measure, i.e permutation entropy, is ideal because—in addition to being a model independent metric of predictability—recent work has demonstrated that it correlates strongly with known limits to forecasting in dynamical systems, e.g., models where we can measure Lyapunov stability\textsuperscript{25,14}.

Permutation entropy is conceptually similar to the well-known Shannon entropy\textsuperscript{25}. However, instead of being based on the probability of observing a system in a particular state, it utilizes the frequency of discrete motifs, i.e symbols, associated with the growth, decay, and stasis of a time series. For example, in a binary time series the permutation entropy in
Permutation entropy variability through time

Figure 1. We calculated the permutation entropy in windows of size 50 weeks across three time series of equal length: 1.) dark red: Gaussian–white–noise (μ = 0, σ = 1); 2.) gray: Measles cases reported to the CDC from the state of Texas between 1927 and 1965 (gray dashed line, lower panel) as digitized from MMWR reports by Project Tycho; and 3.) blue: a sine wave with Gaussian noise (μ = 0, σ = 0.01). The fluctuations in the permutation entropy calculated from the measles time series (gray dashed line) are larger than would be predicted by chance and result in periods of time being predictable (in the range of a noisy sine wave, blue shaded region) and periods of time being unpredictable (in the range of the white noise, red shaded region).

More formally, for a given time series \( \{x_t\}_{t=1}^{N} \) indexed by positive integers, an embedding dimension \( d \) and a temporal delay \( \tau \), we consider the set of all sequences of value \( s \) of the type \( s = \{x_t, x_{t+\tau}, \ldots, x_{t+(d-1)\tau}\} \). To each \( s \), we then associate the permutation \( \pi \) of order \( d \) that makes \( s \) totally ordered, that is \( \hat{s} = \pi(s) = [x_{t_1}, \ldots, x_{t_N}] \) such that \( x_{t_i} < x_{t_j} \forall t_i < t_j \), hence generating the symbolic alphabet. Ties in neighboring values, i.e. \( x_{t_i} = x_{t_j} \), were broken both
by keeping them in their original order in the time series and/or by adding a small amount of noise, the method of tie breaking did not affect the results.

The permutation entropy of time series \( \{x_t\} \) is then given by the Shannon entropy on the permutation orders, that is \( H_{d,\tau}^p(\{x_t\}) = -\sum_{\pi} p_\pi \log p_\pi \), where \( p_\pi \) is the probability of encountering the pattern associated with permutation \( \pi \). In this study, we select a conservative value of \( H^p \) by searching over a wide range of possible \((d, \tau)\) pairs and setting \( H^p(\{x_t\}) = \min_{d,\tau} H_{d,\tau}^p(\{x_t\}) \). To control for differences in dimension and for the effect of time series length on the entropy estimation, we normalize the entropy by \( \log(d!) \) (following\(^26\)), ensure that each window is greater in length than \( d! \), and confirm that the estimate of \( H^p \) has stabilized (specifically that the marginal change in \( H^p \) as data are added is less than 1%). To facilitate interpretation, we present results from continuous intervals by fixing \( \tau = 1 \). However, our results generalize to the case where we fix both \( d \) and \( \tau \) across all diseases and where we minimize over a range of \((d, \tau)\) pairs (see Supplement).

As defined above, permutation entropy does not require the \textit{a priori} specification of a mechanistic nor generating model, which allows us to study the predictability of -potentially very different- systems within a unified framework. What is not explicit in the above formulation is that the permutation entropy can be accurately measured with far shorter time series than Lyapunov exponents and that it is robust to both stochasticity and linear/nonlinear monotonous transformations of the data, i.e. it is equivalent for time series with different magnitudes\(^{25,27}\). Consider–for example–two opposite cases with respect to their known predictability, pure white noise and a perfectly periodic signal. We expect the former, being essentially random, to display a very high entropy as compared with the latter, which instead we expect to show a rather low entropy in consideration of its simple periodic structure.

In Figure\(^1\) we demonstrate that this is indeed the case, even when we allow the periodic signal to be corrupted by a small amount of noise. We track the short scale predictability of the time series by calculating the permutation entropy in moving windows (with width = one year, although the results are robust to variation in window size). For comparison, we calculate
the same moving window estimate of the permutation entropy for the time series of measles cases in Texas prior to the introduction of the first vaccine. The critical observation is that the moving-window entropy for the measles time series fluctuates between values comparable with that of pure random noise and, at times, values closer to the more predictable periodic signal, which suggests alternating intervals with different dynamical regimes and, thus, predictability. The magnitude of the entropy fluctuations for measles in Texas is statistically significant by permutation test, $p < 0.001$, as compared with simulated fluctuations obtained by building an estimated multinomial distribution over the symbols and repeatedly calculating the expected Kullback-Leibler divergence from simulations.

We now turn our attention to a broader set of diseases and ask how the predictability, defined as $\chi = 1 - H^p$ (where $H^p$ is the permutation entropy), scales with the amount of available data (i.e. the time series’ length). Specifically, we compute the permutation entropy across more than 25 years of weekly data at the US state-level for measles, whooping cough, polio, influenza, gonorrhea, chlamydia, hepatitis A, and mumps and weekly, country-level data for Zika from Colombia and Mexico and plot the predictability ($\chi = 1 - H^p$) as a function of the length of each time series. Focusing first on the predictability over short timescales (Figure 2), for each time series we average $H^p$ over temporal windows of width up to 100 weeks with 1000 random starting points each. We find that all diseases show a clear decrease in predictability with increasing time window width, which implies that accumulating longer stretches of time series data for a given disease does not translate into improved predictability. However, we also find strong evidence that the majority of single outbreaks –i.e. temporal horizons characteristic for each disease – are predictable. The confidence intervals in Figure 2 show that there can be large variation in predictability across across outbreaks of the same disease, providing a first indication of the presence of a changing underlying model structures and/or dynamics on the scale of months. By comparison, across all models with fixed structures studied to date, e.g., white noise, sine waves, and even chaotic systems, the predictability is constant in time or is expected to improve with increasing amounts of time
Figure 2. Single outbreaks are typically predictable. The average predictability ($1 - H^p$) for weekly, state-level (Zika data are country-level), data from nine diseases is plotted as a function of time series length in weeks. For each disease, we selected 1,000 random starting locations and calculated the permutation entropy in rolling windows between 2 - 104 weeks. The solid lines indicate the mean value and the shaded region marks the interquartile range. Although the slopes are different for each disease, in all cases, longer time series result in lower predictability. However, most diseases are predictable across single outbreaks. For reference, the black line is the median permutation entropy across 20,000 stochastic simulations of an SIR network model, as described below.

Zooming out, what is also conspicuous about the relationship between time series length and predictability is that diseases cluster together and show disease-specific slopes, i.e. predictability vs. time series length, which suggests that permutation entropy is indeed detecting temporal features specific to each disease, Figure 3A. After re-normalizing time for each disease by its corresponding $R_0$—we used the mean of all reported values found in a literature review (see Supplement)—we find that the best-fit mixed-effect slope on a log scale is one and that the residual effect is well predicted by the times series’ embedding dimension $d$ (see supplemental figures S1 and S2). Moreover, because the embedding dimension $d$ of a time
series is the length of the basic blocks used in the calculation of the permutation entropy,

![Figure 3. Permutation entropy and time series length show regularity by disease A.)](image)

**Figure 3.** Permutation entropy and time series length show regularity by disease *A.*

The predictability \((1 - H^p)\) for chlamydia, gonorrhea, hepatitis A, influenza, Zika, measles, polio, whooping cough, and mumps is plotted as a function of time series length in weeks. Although the slopes are different for each disease, in all cases, longer time series, i.e. more data, result in lower predictability. However, we again find that single outbreaks should be predictable and that diseases show a remarkable degree of clustering based on the slope of entropy gain. **B.)** We rescaled the time series length based on the mean published basic reproductive number, i.e. \(R_0\), from the literature (see Supplement) and plot the log of this quantity against the log of the permutation entropy.

It encodes the fundamental temporal unit of predictability in the form of an entropy production rate, thus implying that predictability decreases with time series data at a disease-specific rate determined to first order by \(R_0\), which is further modulated by \(d\). This result predictability depends on scale also suggests that the permutation entropy could be an approach for justifying the utility of different data sets, i.e. one could determine the optimal granularity of data by selecting the dimension that maximized predictability.

One might assume that this phenomenon, i.e. decreasing predictability with increasing time series length, could be driven purely by random walks on the symbolic alphabet used in the permutation entropy estimation. However, \(n\)-dimensional Markov chain models built from the time series embeddings \((n = d\) the time series’ embedding dimension) consistently produced stable and smaller predictability values in comparison with those obtained from
data, corroborating that the predictability behaviour we observe does not stem from random fluctuations but is an actual fundamental feature of spreading processes. This observation, that Markov chain models of the same embedding order do not reproduce the observed predictability, indicates that either the model structure is changing in time and/or the system has a very long memory, which is consistent with our current understanding of the entanglement between mobility and disease\supercite{30,111}. That the best-fit $n$-dimensional Markov chain models overpredict the amount of entropy in real systems, also supports our earlier results that predictable structure does exist in most outbreak time series.

**Figure 4. Permutation entropy detects changing model structure** A.) A rolling window estimate of the permutation entropy for weekly Measles cases reported to the CDC from the state of Texas between 1927 and 1983 (red dashed line). The vertical blue line indicates when the first measles vaccine was licensed for use in the United States. Shortly after the vaccine was introduced the permutation entropy increased significantly, which is expected after a system experiences a change to its model structure, in this case vaccination. B.) The Kullback-Leibler divergence of the symbol frequency distribution was calculated between all pairs of rolling one-year (52 week) windows for the measles time series in panel A (dark blue points) and for a noise-free sine wave (black points). The best-fit loess regression is plotted for both time series. Significance (red line) was determined by permutation test.

To gain insight into what mechanisms might be driving changes in the predictability, we take advantage of the repeated, “natural” experiment of vaccine introduction. For diseases, such as measles, where we have data from both the pre- and post- vaccine era, we ask whether the permutation entropy changes after vaccination begins. We consistently observe that predictability decreases after vaccination, again with significance determined by permutation test (see Figure 4A.). We also find that the Kullback-Leibler divergence of the symbol
frequency distribution changes significantly from year-to-year across the entire measles time series (see Figure 4B.). Critically, because—as stated earlier—permutation entropy is not affected by changes in magnitude, the difference in entropy cannot simply be accounted for by a reduction in cases. Instead, it means that the temporal pattern of cases changes. This leads us to the hypothesis that the distribution of secondary infections, its first moment or \( R_0 \) and its higher moments, drives predictable changes in the permutation entropy.

Figure 5. **Permutation entropy and contact network heterogeneity** We simulated outbreaks on social networks with increasing contact heterogeneity, as measured by the first two moments of the degree distribution, and calculated the resulting permutation entropy. We plot the permutation entropy on the ordinate axis as a function of the distance between the critical transmissibility for each simulation \( T_c = \frac{<k>}{<k^2> - <k>} \), where \( <k> \) is the mean degree and \( <k^2> \) is the mean square degree. The increase in transmissibility is dual to the network heterogeneity and distance from criticality, which are both decreasing along the x-axis, as indicated in the cartoon. We find a significant, non-linear relationship between contact heterogeneity and permutation entropy, which qualitatively matches the pattern seen in the real-world disease time series. Specifically, lower heterogeneity—or conversely larger distance from the critical transition point to an epidemic (i.e. a large-scale outbreak)—leads to higher permutation entropy (i.e. lower predictability).
phenomenon originally discovered in synthetic directed networks by Meyers et al.\cite{Meyers2007}.

To further evaluate the hypothesis that heterogeneity in social networks –and thus in the number of secondary infections– produces predictable changes in permutation entropy, we simulated data on social contact networks with varying degree distributions or, equivalently, critical transmissibilities $T_c$–the per contact probability of transmission required to cause a large-scale outbreak, i.e an epidemic\cite{VanKampen2007}–as measured by the first two moments of the degree distribution ($T_c = \frac{\langle k \rangle}{\langle k^2 \rangle - \langle k \rangle}$). More specifically, we simulated 100 iterations of a stochastic \textit{Susceptible, Infectious, Removed} (SIR) model on a social contact network, fixing the per-contact probability of transmission ($T$) and varied the amount of contact heterogeneity. From the resulting epidemic curves (the time series of infections) we calculated the permutation entropy.

We find that the distance of the actual transmissibility from the critical transmissibility ($\delta = T_c - T$) predicts the entropy of the outbreak time series, Figure\,5. This result demonstrates that, as the system gets closer to the critical transition point, from localized outbreaks to a large-scale epidemic, the predictability goes up exponentially fast. From this, we can draw three conclusions. First, coupled with our earlier results comparing diseases with different average reproductive numbers, heterogeneity in the number of secondary infections can drive differences in predictability, which is related to results on predicting disease arrival time on networks\cite{Ma2007} and to recurrent epidemics in hierarchical metapopulations\cite{Hufnagle2007}. Second, the permutation entropy could provide a model-free approach for detecting epidemics, which is related to a recent model-based approach based on bifurcation delays\cite{Berenkopf2007}. Finally, as outbreaks grow and transition to large-scale epidemics, they should become more predictable, which–as seen in Figures\,1 and 3–appears to be true for real-world diseases as well and agrees with earlier results on how permutation entropy relates to predictability of non-linear systems\cite{Pincus1991}.

Research in dynamical systems over the the past 30 years has demonstrated that prediction error increases with increasing forecast length\cite{Benjamin1960}. However, across that same body work, researchers typically find that predictions improve when they are trained on longer time series,
even for chaotic systems\textsuperscript{20}. Our data-driven results suggest that for infectious diseases the opposite is true, more time series data should most often lead to lower predictability. Then, by integrating our biological understanding of each pathogen and simulated outbreaks, we found that changing dynamics, e.g., the shifting number of secondary infections as a disease moves through a heterogeneous social network, can cause the prediction error to increase with increasing data, which is related to earlier findings on the role of airline travel networks and disease forecasting\textsuperscript{15}. What this implies is that different “models” generate data at different time points and suggests that the optimal coarse-graining of complex systems might change with scale and/or time\textsuperscript{36}.

The global community of scientists, public health officials, and medical professionals studying infectious diseases has placed a high value on predicting when and where outbreaks will occur, along with how severe they will be\textsuperscript{37,38,39}. Our results demonstrate that outbreaks should be predictable. However, as outbreaks spread--and spatiotemporally separated waves become entangled with the substrate, human mobility, behavioural changes, pathogen evolution, etc.–the system is driven through a space of diverse model structures, driving down predictability despite increasing time series lengths. Taken together, our results agree with observations that accurate long-range forecasts for complex adaptive systems, e.g., contagions beyond a single outbreak, may be impossible to achieve due to the emergence of entropy barriers. However, they also support the utility and accuracy of dynamical modeling approaches for infectious disease forecasting, especially those that leverage myriad data streams and are iteratively calibrated as outbreaks evolves. Lastly, our results also suggest that cross-validation over long infectious disease time series can not guarantee that the correct model for any individual window of time will be favored, which would imply a no free lunch theorem for infectious disease model selection, and perhaps for sociobiological systems more generally\textsuperscript{40}.

**Data Availability Statement**

Empirical data for all diseases–aside from Zika–were obtained from the U.S.A. National Notifiable Diseases Surveillance System as digitized by Project Tycho\textsuperscript{24}. Zika data were
obtained from public health reports from Colombia and Mexico as digitized by 28. All other data and code that support the plots and findings of this study will be available on github soon. In the interim, they are available from the corresponding authors upon reasonable request. The supplement is available at http://scarpino.github.io/files/supplementary-information-predictability.pdf.

Acknowledgements

We thank Joshua Garland for productive conversations on permutation entropy and helpful comments on an earlier version of the manuscript. S.V.S. received funding support from the University of Vermont. G.P. received funding support from Fondazione Compagnia San Paolo. S.V.S. and G.P. conducted performed the study as fellows at IMeRA.

Author contributions

Both authors conceived the project, performed the simulations and calculations, analyzed the empirical data, interpreted the results, and produced the final manuscript.

Conflicts of interest

The authors declare no conflicts of interest exist.

References

1. Colizza, V., Barrat, A., Barthélemy, M. & Vespignani, A. Predictability and epidemic pathways in global outbreaks of infectious diseases: the SARS case study. BMC medicine 5, 1 (2007).

2. Shaman, J., Karspeck, A., Yang, W., Tamerius, J. & Lipsitch, M. Real-time influenza forecasts during the 2012–2013 season. Nature Communications 4, 1–26 (2013).

3. Venkatramanan, S. et al. Using Data-driven Agent-based models for Forecasting Emerging Infectious Diseases. Epidemics (2017).
4. Johansson, M. A., Reich, N. G., Hota, A., Brownstein, J. S. & Santillana, M. Evaluating the performance of infectious disease forecasts: A comparison of climate-driven and seasonal dengue forecasts for Mexico. *Scientific Reports* **6** (2016).

5. Brooks, L. C., Farrow, D. C., Hyun, S., Tibshirani, R. J. & Rosenfeld, R. Flexible modeling of epidemics with an empirical Bayes framework. *PLoS Comput Biol* **11**, e1004382 (2015).

6. Funk, S., Camacho, A., Kucharski, A. J., Eggo, R. M. & Edmunds, W. J. Real-time forecasting of infectious disease dynamics with a stochastic semi-mechanistic model. *Epidemics* (2016).

7. Chowell, G. *et al.* Using phenomenological models to characterize transmissibility and forecast patterns and final burden of zika epidemics. *PLoS Currents* **8** (2016).

8. Zhang, Q. *et al.* Social data mining and seasonal influenza forecasts: the FluOutlook platform. In *Joint European Conference on Machine Learning and Knowledge Discovery in Databases*, 237–240 (Springer, 2015).

9. Nsoesie, E. O., Beckman, R. J., Shashaani, S., Nagaraj, K. S. & Marathe, M. V. A simulation optimization approach to epidemic forecasting. *PloS one* **8**, e67164 (2013).

10. Chretien, J.-P. *et al.* Advancing Epidemic Prediction and Forecasting: A New US Government Initiative. *Online journal of public health informatics* **7** (2015).

11. Biggerstaff, M. *et al.* Results from the centers for disease control and prevention’s predict the 2013–2014 Influenza Season Challenge. *BMC Infectious Diseases* **16**, 357 (2016).

12. Prediction, P., Science, F. & Group, T. W. Towards Epidemic Prediction: Federal Efforts and Opportunities in Outbreak Modeling. *National Science and Technology Council USA* (2016).
13. Gandon, S., Day, T., Metcalf, C. J. E. & Grenfell, B. T. Forecasting epidemiological and evolutionary dynamics of infectious diseases. *Trends in Ecology & Evolution* **31**, 776–788 (2016).

14. Garland, J., James, R. & Bradley, E. Model-free quantification of time-series predictability. *Physical Review E* **90**, 052910 (2014).

15. Colizza, V., Barrat, A., Barthélemy, M. & Vespignani, A. The role of the airline transportation network in the prediction and predictability of global epidemics. *Proceedings of the National Academy of Sciences of the United States of America* **103**, 2015–2020 (2006).

16. Shaw, J. The SARS Scare. *Harvard Magazine* **109**, 48 (2007).

17. Dye, C. & Gay, N. Modeling the SARS epidemic. *Science* **300**, 1884–1885 (2003).

18. Meyers, L. A., Pourbohloul, B., Newman, M. E., Skowronski, D. M. & Brunham, R. C. Network theory and SARS: predicting outbreak diversity. *Journal of theoretical biology* **232**, 71–81 (2005).

19. Perra, N. & Gonçalves, B. Modeling and predicting human infectious diseases. In *Social phenomena*, 59–83 (Springer, 2015).

20. Bansal, S., Chowell, G., Simonsen, L., Vespignani, A. & Viboud, C. Big Data for Infectious Disease Surveillance and Modeling. *Journal of Infectious Diseases* **214**, S375–S379 (2016).

21. Pastore-Piontti, A. *et al.* Real-Time Assessment of the International Spreading Risk Associated with the 2014 West African Ebola Outbreak. In *Mathematical and Statistical Modeling for Emerging and Re-emerging Infectious Diseases*, 39–56 (Springer, 2016).

22. Lofgren, E. T. *et al.* Opinion: Mathematical models: A key tool for outbreak response. *Proceedings of the National Academy of Sciences* **111**, 18095–18096 (2014).
23. Moran, K. R. et al. Epidemic Forecasting is Messier Than Weather Forecasting: The Role of Human Behavior and Internet Data Streams in Epidemic Forecast. *Journal of Infectious Diseases* **214**, S404–S408 (2016).

24. van Panhuis, W. G. et al. Contagious diseases in the United States from 1888 to the present. *The New England journal of medicine* **369**, 2152–2152 (2013).

25. Bandt, C. & Pompe, B. Permutation entropy: a natural complexity measure for time series. *Physical review letters* **88**, 174102 (2002).

26. Brandmaier, A. M. pdc: An R package for complexity-based clustering of time series. *Journal of Statistical Software* **67**, 1–23 (2015).

27. Zunino, L., Soriano, M. C. & Rosso, O. A. Distinguishing chaotic and stochastic dynamics from time series by using a multiscale symbolic approach. *Physical Review E* **86**, 046210 (2012).

28. Rodriguez, D. M. et al. 10.5281/zenodo.344913 (2017).

29. Farmer, J. D. & Sidorowich, J. J. Predicting chaotic time series. *Physical review letters* **59**, 845 (1987).

30. Szell, M., Sinatra, R., Petri, G., Thurner, S. & Latora, V. Understanding mobility in a social petri dish. *arXiv preprint arXiv:1112.1220* (2011).

31. Meyers, L. A., Newman, M. & Pourbohloul, B. Predicting epidemics on directed contact networks. *Journal of theoretical biology* **240**, 400–418 (2006).

32. Meyers, L. Contact network epidemiology: Bond percolation applied to infectious disease prediction and control. *Bulletin of the American Mathematical Society* **44**, 63–86 (2007).

33. Shu, P., Tang, M., Gong, K. & Liu, Y. Effects of weak ties on epidemic predictability on community networks. *Chaos: An Interdisciplinary Journal of Nonlinear Science* **22**, 043124 (2012).
34. Watts, D. J., Muhamad, R., Medina, D. C. & Dodds, P. S. Multiscale, resurgent epidemics in a hierarchical metapopulation model. *Proceedings of the National Academy of Sciences of the United States of America* **102**, 11157–11162 (2005).

35. Dibble, C. J., O'Dea, E. B., Park, A. W. & Drake, J. M. Waiting time to infectious disease emergence. *Journal of The Royal Society Interface* **13**, 20160540 (2016).

36. Wolpert, D. H., Grochow, J. A., Libby, E. & DeDeo, S. Optimal high-level descriptions of dynamical systems. *arXiv preprint arXiv:1409.7403* (2014).

37. Hufnagel, L., Brockmann, D. & Geisel, T. Forecast and control of epidemics in a globalized world. *Proceedings of the National Academy of Sciences of the United States of America* **101**, 15124–15129 (2004).

38. Altizer, S., Ostfeld, R. S., Johnson, P. T., Kutz, S. & Harvell, C. D. Climate change and infectious diseases: from evidence to a predictive framework. *Science* **341**, 514–519 (2013).

39. Myers, M. F., Rogers, D., Cox, J., Flahault, A. & Hay, S. Forecasting disease risk for increased epidemic preparedness in public health. *Advances in Parasitology* **47**, 309–330 (2000).

40. Wolpert, D. H. & Macready, W. G. No free lunch theorems for optimization. *IEEE transactions on evolutionary computation* **1**, 67–82 (1997).