Statistical challenges and opportunities in modelling coupled behaviour-disease dynamics of vaccine refusal

Modellazione del rifiuto vaccinale come interazione delle dinamiche delle malattie infettive e del comportamento individuale: sfide ed opportunità per le discipline statistiche

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Abstract Vaccine refusal has proven to be a persistent foe in efforts to protect populations from infectious diseases. One hypothesis about its origin posits a coupling between vaccinating behaviour and disease transmission: when infection prevalence is sufficiently low, individuals become complacent and vaccinating becomes less desirable, causing a decline in vaccine coverage and resurgence of the disease. This dynamic is being explored in a growing number of mathematical models. Here, I present a differential equation model of coupled behaviour-disease dynamics for vaccine-preventable paediatric infections, and I discuss previous research that has applied various statistical methodologies to parameterize and validate the model. I will show how methodologies such as model selection analysis and statistical learning, in conjunction with mechanistic modelling, can be used to test for the presence of phenomena related to coupled behaviour-disease dynamics during episodes of vaccine refusal. These phenomena include social learning and imitation, social norms, criticality, and coupling between vaccinating behaviour and disease prevalence. Some of these methodologies exploit new data sources such as online social media. I conclude that the study and modelling of vaccine refusal can greatly benefit from using mechanistic models informed by both traditional and state-of-the-art statistical methodologies.

Abstract *L'opposizione ai vaccini è un fenomeno persistente che indebolisce la capacità delle comunità di difendersi dalle malattie infettive. La spiegazione di base del rifiuto vaccinale postula l'esistenza di un'interazione tra decisione di vaccinare e trasmissione dell'infezione: quando la prevalenza di infezione è sufficientemente bassa il beneficio percepito dalla vaccinazione è a sua volta basso, il che a lungo andare causerà una discesa della copertura vaccinale, creando le premesse per una "risorgenza" della malattia. Queste dinamiche sono state analizzate in un numero crescente di studi modellistici. In questo lavoro presento un modello per in-*

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fezioni pediatriche prevenibili da vaccino, come il morbillo, che accoppia le dinamiche dell'infezione con quelle delle decisioni vaccinali, e discuto le ricerche di tipo statistico che si sono occupate della parametrizzazione e validazione di queste classi di modelli. In particolare cerco di mettere in luce il ruolo delle metodologie statistiche (p.e., teoria dell'informazione, statistical learning, etc) per verificare la presenza di fenomeni di interazione tra decisioni individuali e prevalenza dell'infezione durante epoche di rifiuto dei vaccini. Lo studio di questi fenomeni, che includono l'apprendimento via imitazione, il ruolo delle norme sociali, e la presenza di vari effetti "critici", ha potuto in tempi recenti sfruttare le potenzialità dei dati forniti dai "social". Concludo discutendo l'importanza di combinare le metodologie statistiche tradizionali con le nuove tecniche della "data science" nello studio dell'opposizione ai vaccini.

Key words: behavioural epidemiology, vaccine refusal, coupled behaviour-disease systems, statistical learning, model selection

1 Vaccine-preventable infectious diseases: some background

Infectious diseases have long imposed a considerable burden on human health [36]. Improvements in nutrition, sanitation, hygiene and vaccines have considerably reduced this burden [9]. Smallpox was globally eradicated largely due to use of ring vaccination [20]. Even measles–which is highly transmissible–has been eliminated through universal vaccination programs in many countries, and the elimination of measles from the WHO Region of the Americas raises the possibility that even measles could one day be globally eradicated [16]. As our vaccine technologies and ability to administer them improve, universal vaccine access could become replaced as the primary barrier to elimination and eradication by vaccine refusal. In high- and low-income countries alike, vaccine refusal has led to resurgence of previously eliminated diseases such as measles [28], and has even delayed the eradication of polio by at least a decade [33].

Vaccines provide direct protection to vaccinated individuals by stimulating their immune response to specific antigens, but most vaccines also provide indirect protection for unvaccinated individuals by interrupting pathogen transmission [1, 31]. The transmission of infectious diseases can be mathematically modelled through compartmental models, which assume that individuals are divided into mutually exclusive compartments based on their infection status, and which tracks the transitions between these compartments through linear or nonlinear processes [1, 31]. For instance, the classic Susceptible-Infectious-Recovered (SIR) deterministic model with vaccination, births and deaths assumes that the population is divided into susceptible, infectious and recovered (immune) individuals, and is represented by:

$$\frac{dS}{dt} = \mu(1-p\varepsilon) - \beta SI - \mu S, \tag{1}$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I, \tag{2}$$

$$\frac{dR}{dt} = \mu p\varepsilon + \gamma I - \mu R. \tag{3}$$

where S is the proportion of the population that is susceptible, I is the proportion infectious, R is the proportion recovered, $\mu > 0$ is the mean birth/death rate, $\beta > 0$ is the mean transmission rate, $1/\gamma > 0$ is the mean duration of the infectious period, $0 \leq p \leq 1$ is the vaccine coverage, and $0 \leq \varepsilon \leq 1$ is the vaccine efficacy [31]. We assume that a proportion p of individuals are vaccinated at birth and, moreover, a proportion ε of those individuals were efficaciously immunised, entering the R compartment. The remaining proportion $1 - p\varepsilon$ enter the susceptible compartment at birth. We also assume that the birth rate equals the death rate and hence the population size is constant. Note that the R equation does not appear in the S or I equations, and since birth and death rates are equal, $R = 1 - S - I$ therefore we can characterize the system entirely in terms of S and I. This system has two equilibria:

$$E_1 = (S_1, I_1) = (1 - p\varepsilon, 0) \tag{4}$$

$$E_2 = (S_2, I_2) = \left(\frac{\gamma+\mu}{\beta}, \frac{\mu}{\gamma+\mu} \left(1 - p\varepsilon - \frac{\gamma+\mu}{\beta} \right) \right) \tag{5}$$

It is possible to show that the elimination threshold–the proportion of individuals who should be vaccinated in order to eliminate the infection–is given by

$$p_{crit} = \frac{1}{\varepsilon} \left(1 - \frac{1}{R_0} \right) \tag{6}$$

where the basic reproductive ratio $R_0 = \beta/(\gamma + \mu)$ is interpreted as the average number of secondary infections produced by a single infected individuals in an otherwise susceptible population [1]. (In the absence of vaccination, when $R_0 < 1$, the *disease-free equilibrium* E_1 is stable, but when $R_0 > 1$, the disease-free state loses stability and the system converges instead to the *endemic equilibrium* E_2.) When $p \geq p_{crit}$, the disease-free state E_1 is globally asymptotically stable, hence the infection is eliminated [31]. However, when $p < p_{crit}$, E_2 is globally asymptotically stable and the infection is endemic [31].

2 Coupled behaviour-disease systems

The SIR model, equations (1)-(3), represents a world where vaccine coverage is fixed at a specified level p. This is probably applicable where a decision-maker can assume that all eligible individuals will receive a vaccine. However, as we have noted in the first few paragraphs of this paper, vaccine refusal is an increasing problem. Therefore, we cannot always take it for granted that p will be fixed at sufficiently high to eliminate an infection from a population.

Multiple factors influence vaccine decision-making. However, several lines of evidence indicate that individuals are more likely to get vaccinated if (1) they perceive a risk of becoming infected (either due to an ongoing outbreak, possible future outbreaks, or due to a personal history of infection), (2) they perceive a risk of serious complications due to infection, and/or (3) they believe that the vaccine is safe and effective [25, 15, 13, 10, 44]. Indeed, we might have predicted the first factor from the SIR model: once $p = p_{crit}$ is obtained, the infection has been eliminated. In that case, any small real or perceived risk of suffering an adverse effect from the vaccine appears large compared to zero risk of being infected, thus the vaccine becomes undesirable and vaccine coverage can fall back below p_{crit}. Hence, we have a situation where individuals influence disease prevalence through their decision to become vaccinated, but disease prevalence in turn influences vaccine decision-making through individuals' desire to avoid becoming infected. We can therefore conceptualize this as a coupled behaviour-disease system, where disease dynamics and behavioural dynamics are combined into a single coupled system (Figure 1). An increase in vaccine coverage reduces infection prevalence (negative feedback), whereas an increase in infection prevalence boosts perception of infection risk and therefore boosts vaccine coverage (positive feedback), hence together they form a negative feedback loop leading to a stable state of endemic infection and intermediate vaccine coverage. Similar approaches to coupling human and natural systems have been taken up by ecologists and environmental scientists studying terrestrial and other ecosystems [34, 32, 2, 8, 30].

The importance of this interaction between infection and behaviour was not lost on the mathematical epidemiologists of the late twentieth century. Perhaps the earliest work to incorporate behaviour into epidemic dynamics was by Capasso and Serio, who proposed a model where the infection incidence term βSI in the SIR compartmental model is modified to take into account behavioural reactions to changing infection incidence during an outbreak [14]. Year later, the HIV/AIDS pandemic stimulated research on modelling the dynamics of core groups in infection transmission models, where recruitment into the core group depends on infection prevalence [27]. Economists and epidemiologists studied the problem from the perspective conflicts between individual interest and socially optimal approaches starting in the 1980s and 1990s as well [21, 11]. Subsequently, models of coupled

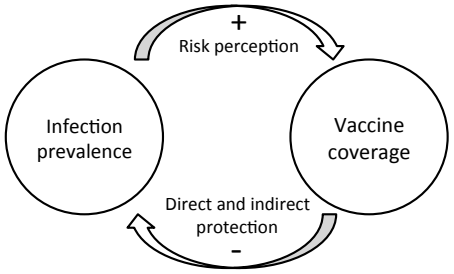

Fig. 1 Schematic diagram of a coupled behaviour-disease system. Increasing vaccine coverage reduces infection prevalence, which in turn causes a drop in vaccine coverage if the population becomes complacent due to lack of infections. The result is a negative feedback loop.

behaviour-disease interactions started becoming popular starting in the mid-2000s [7, 3, 26, 18, 19] (see Refs. [23, 6, 35, 45, 22, 46, 43] for reviews).

A game theoretical treatment of vaccine refusal provides a clear example of how adding adaptive human behaviour changes the predictions of epidemic models. For instance, following the approach of Ref. [5] for equations (1)–(3), it is possible to find the Nash equilibrium vaccine coverage p^* at which the payoff for an individual to vaccinate equals the payoff for an individual not to vaccinate. This turns out to be the vaccine coverage that should be exhibited by a population of rational, self-interested agents [5]. The expression is

$$p^* = \frac{1}{\varepsilon}\left(1 - \frac{1}{R_0(1 - r_v/r_i)}\right) \tag{7}$$

where r_v is the perceived risk of vaccine side effects and r_i is the perceived risk of infection complications. By comparing this expression to equation (6) for the elimination threshold, it is clear that $p^* < p_{crit}$ when $0 < r_v < r_i$. Due to the free-rider effect, it should therefore be impossible to eliminate an infection under a voluntary vaccination policy in a population of rational, self-interested agents [21, 5].

However, individuals are not rational self-interested agents when it pertains to vaccinating decisions [25, 15, 13, 10, 44]. For instance, peer imitation is an important feature of vaccinating behaviour that can be incorporated into epidemic models [17]. In the remainder of this paper we use a model that accounts for more realistic processes including imitation (social learning), social norms, and use of rule-of-thumb (heuristics) to determine infection risks [37]. The SIR equations are modified by replacing constant vaccine coverage p by a dynamic vaccine coverage x, where x is determined by a differential equation capturing how individuals learn vaccine opinions from others. A perfectly efficacious vaccine is assumed ($\varepsilon = 1$) which is a good approximation to the actual effectiveness for multi-course doses of most common pediatric vaccines. The model equations are:

$$\frac{dS}{dt} = \mu(1-x) - \beta SI - \mu S, \tag{8}$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \mu I, \tag{9}$$

$$\frac{dR}{dt} = \mu x + \gamma I - \mu R, \tag{10}$$

$$\frac{dx}{dt} = \kappa x(1-x)\left[-\omega + I + \delta(2x-1)\right]. \tag{11}$$

In these equations, x is the proportion of the population favouring vaccination; $\omega \equiv r_v/mr_i$ controls the relative effects of the perceived risk of vaccine complications r_v, the perceived risk of infection complications r_i, and a proportionality constant m determining the perceived probability of becoming infected as a function of current infection prevalence $I(t)$ (the 'rule of thumb' for determining individual risk of becoming infected); δ is the strength of social norms; κ represents the social learning rate; and other parameters and variables are as in equations (1)–(3). In this

model, individuals are either vaccinators or non-vaccinators and sample other individuals at a specified rate. If the other person being sampled is playing a different strategy and is receiving a higher utility, the given individual will change to that strategy with a probability proportional to the expected gain in utility (see Ref. [37] for details). When I is higher, more individuals will switch to a vaccinator strategy by imitating others. But when ω is higher due to higher perceived vaccine risk, or lower perceived risk of infection or infection complications, then more individuals will switch to a non-vaccinator strategy. The social norms term $\delta(2x-1)$ moves the population in the direction of whichever strategy is more popular, and thus captures peer pressure. We may remove the R equation since R does not appear in the other equations, hence dynamics can be described completely through (S,I,x).

The coupled behaviour-disease model, equations (8)–(11), exhibits a broad range of behaviour including 5 equilibria: a disease-free equilibrium where no one gets vaccinated, (1,0,0); a disease-free equilibrium where everyone gets vaccinated, (0,0,1); a disease-free equilibrium where part of the population are vaccinators; an endemic equilibrium where no one gets vaccinated; and an endemic equilibrium where part of the population are vaccinators. The model also exhibits stable limit cycles where x and I oscillate (Figure 2). The model is characterized in Ref. [37].

3 Challenges and opportunities for statistics in coupled behaviour-disease modelling

3.1 Parameterization and validation

Parameterizing and validating coupled behaviour-disease models present unique challenges on account of both their larger dimensionality and their coupling. Even with rich data on the epidemiological and sociological layers of the system in separation from one another (Figure 1), one is faced with the additional challenge of obtaining data on the coupling between the two layers–an aspect often ignored in

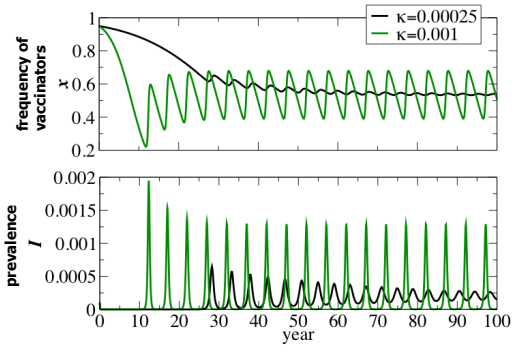

Fig. 2 Example dynamics of the coupled behaviour-disease model in equations (8)–(11). When κ is high, rapid social learning destabilizes the non-trivial equilibrium, causing infection prevalence and vaccine opinion to oscillats. Other parameters: $1/\mu = 50$ yrs., $1/\gamma = 10$ days, $\mathscr{R}_0 = 10$, $\kappa = 0.001$. Figure reproduced from Ref. [3].

traditional epidemiological and sociological studies. Accordingly, statistical inference [29], probabilistic uncertainty analysis [24], and model selection analyses such as use of information criteria [4, 37] are even more important for coupled behaviour-disease models than for sociological models or disease dynamic models in the absence of coupling. Information criteria can be particularly helpful because higher dimensionality and relative lack of data create hazards of over-fitting.

When the sample size n of a dataset is small compared to the number of parameters K being used to fit a model ($n/K < 40$), a variant of the Aikaike information criterion known as the corrected Aikaike information criterion (AICc) may be used (AICc = AIC + $2K(K+1)/(n-K-1)$) [12]. Using AICc, the baseline model in equations (8)–(11) has been compared to variant models lacking either the social learning mechanism (such that individuals switch opinions immediately as soon as the utility becomes more favourable, without learning the new opinion from peers); feedback from infection prevalence (such that infection prevalence is not a part of the utility function); or both mechanisms. The baseline model and its three variants were compared under five different forms for the possible time evolution of relative risk perception during a vaccine scare, $\omega = \omega(t)$ (see Figure 3, left-hand side). The $5 \times 4 = 20$ models were fitted using maximum likelihood to vaccine coverage and case notification data from the whole cell pertussis vaccine scare in the United Kingdom in the 1970s-80s (Figure 3) [4]. Comparing the AICc for these 20 models reveals interesting findings. Firstly, adding both social learning and prevalence feedback (i.e., using the baseline model) improved the AICc score and resulted in a better fit for most of the risk evolution curves (Figure 3, first column). (The comparison is worse under the bottom risk evolution curve, but this may be expected since an arbitrarily good AICc score can be obtained by adding enough degrees of freedom to the phenomenological curves that describes risk evolution.) Secondly, the variant model with infection prevalence feedback but no social learning (Figure 3, third column) exhibited highly unstable dynamics that both yields poor AICc scores and does not resemble vaccine coverage time series in any known system. This variant can be taken as a representative of *Homo economicus*–the idea that humans adopt Nash equilibria irrespective of social influences, while the baseline model including social learning could be taken as representative of *Homo socialis*–humans as social animals. Hence, this information theoretic exercise supports the notion that both infection prevalence feedback and social learning are important parts of explaining vaccine refusal in coupled behaviour-disease systems.

Model validation in coupled behavior-disease models can take the form of retrospectively testing of predictive power, for instance. For the pertussis vaccine scare, equations (8)–(11) were also fitted to the early years of the vaccine scare to see whether the model could predict the later years, and it was found that the first seven years of data provided enough information to predict the last ten years of the time series with good accuracy, despite the simplicity of the model [4]. However, the model did not show predictive power in retrospective analysis for the measles-mumps-rubella (MMR) autism vaccine scare in the UK during the 1990s-2000s. This might be due to the fact that measles dynamics were too irregular and stochastic throughout most of the MMR vaccine scare and thus a deterministic differential equation

model might not be the right model to use in that situation. This is in contrast to the pertussis vaccine scare where large 'deterministic' outbreaks occurred.

3.2 Applications of statistical learning

The previous section described the need for data on both sociological and epidemiological subsystems. However, acquiring data for social subsystems–or sometimes even epidemiological subsystems–can be a challenge. The advent of digital data from sources like online social media has provided an alternative data source that can complement existing methods such as social surveys and case notifications [39]. Digital social data have been used not only to study online sentiment relating to vaccinating behaviour [40] but also to predict the outbreaks themselves, such as through

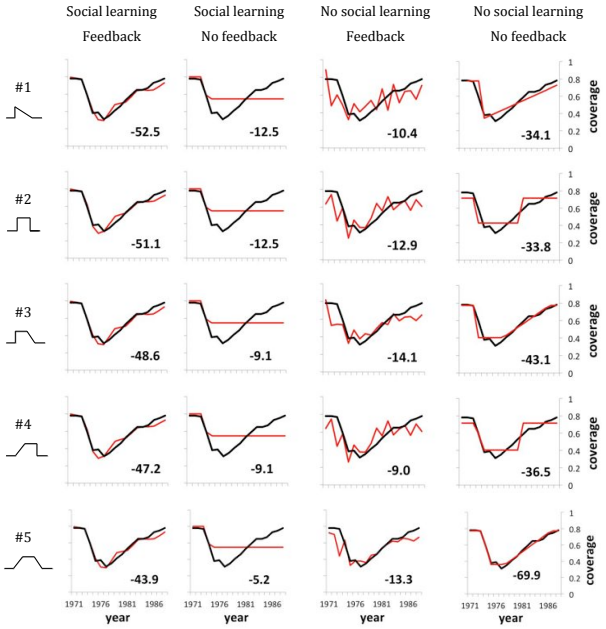

Fig. 3 Aikaike information criterion (AICc) scores and model fit of the coupled behaviour-disease model compared to variants for the UK whole pertussis vaccine scare. Pertussis vaccine coverage in the UK showed a steep decline over 5 years, from ∼80% to ∼30%, before commencing a slow return trajectory to high coverage levels (black lines). The red lines show best-fitting models for the baseline model (first column) and three variant models (second to fourth columns), for 5 risk evolution curves (rows, with form of curve shown on left). The numerical value in each subpanel is the AICc value for the fit: more negative AICc values correspond to better scores, i.e., the model exhibits a better balance of explanatory power with as few parameters as possible. Figure reproduced from Ref. [4].

symptom searches on the Internet [39]. Accordingly, it can help investigators obtain data on social dynamics, disease dynamics, and their coupled dynamics.

However, the amount of digital data is staggering compared to the size of most conventional epidemiological datasets and it cannot be manually processed. Hence, methods such as machine learning are required to analyze the data [42]. A particularly common type of machine learning is statistical learning, in which a computer is used to construct a probabilistic model of a dataset that exhibits statistical regularities. The statistical learning algorithm may use a training set in order to improve its probabilistic models. In Ref. [38], a statistical learning algorithm called a linear support vector machine (SVM) is used to study the 2014-15 California measles outbreak, in which vaccine refusal played a considerable role. The algorithm classified tweets about MMR vaccines into 'pro-vaccine', 'anti-vaccine', and 'other' categories. The number of pro-vaccine tweets were taken to correspond to x in equations (8)–(11) (see Ref. [38] for discussion of limitations of this assumption).

When the perceived vaccine risk ω increases sufficiently, equations (8)–(11) exhibit a tipping point beyond which vaccine uptake falls dramatically and the disease becomes endemic again [38]. The authors hypothesized that California was approaching this tipping point in the years before the relatively small Disneyland outbreak, and then receded from the tipping point afterward as vaccination became popular again. The approach and recession from a tipping point can be detected far in advance through changes in statistical indicators such as the lag-1 autocorrelation, coefficient of variation, and variance of a time series [41, 8]. The authors show that three empirical datasets based on SVM-classified tweets generally show expected trends, as predicted by equations (1)–(3) (Figure 4) [38].

This research suggests that vaccinating behaviour in coupled behaviour-disease systems can be classified as a critical phenomenon, and may exhibit early warning signals before widespread changes in behaviour such as the occurrence of large-scale vaccine scares. Interestingly, the coefficient of variation of the anti-vaccine time series of tweets shows a decline before the tipping point, instead of an increase as shown in all other time series tested and as might be expected from other research on tipping points in related systems [38]. The model predicts the same decline for the coefficient of variation of antivaccinators, however, illustrating the importance of using mechanistic models when interpreting statistical indicators.

4 Summary and Discussion

These examples illustrate the statistical challenges that emerge when parameterizing and validating coupled behaviour-disease models, as well as the synergies and opportunities that may arise when statistical and mechanistic approaches are used in conjunction. In the example of the model selection exercise, we saw how comparing the AICc scores of different models supported the notion that vaccinating behaviour is closer to the *Homo socialis* description than the *Homo economicus* description. In the example of using statistical learning to analyze tipping points, we saw how

algorithms like linear support vector machines can be used to analyze vast amounts of online social media data to look for early warning signals of tipping points. The need for using mechanistic models to help interpret statistical patterns was shown by the decrease in coefficient of variation near a tipping point for anti-vaccinators, instead of the increase that is more commonly expected.

This research also suggests a more general approach by which mechanistic models can help us to make sense out of the bewildering complexity of social data. Dynamics generally simplify near tipping points, such that different types of complex nonlinear systems with highly divergent dynamics generally exhibit only the same restricted set of possible dynamics near a tipping point [41]. Hence, looking for evidence of tipping points in social media data is one possible way to begin moving from current predominantly descriptive statistical approaches to social media data, to statistically-informed mechanistic theories of social interactions.

These cases are only two selection-biased examples from a vast array of published work on how statistics and mathematics can be used together to study coupled behaviour-disease systems. For instance, a further opportunity not addressed here is the use of stochastic models, which maybe be particularly relevant close to the disease elimination threshold, or when rare but scary events perceived to be associated with vaccines or diseases occur. Moreover, new data sources such as online social media are already generating new statistical methodologies, and will likely continue to do so in the future. In conclusion, mechanistic approaches to coupled behaviour-disease dynamics of vaccine refusal can benefit from close attention to use of rel-

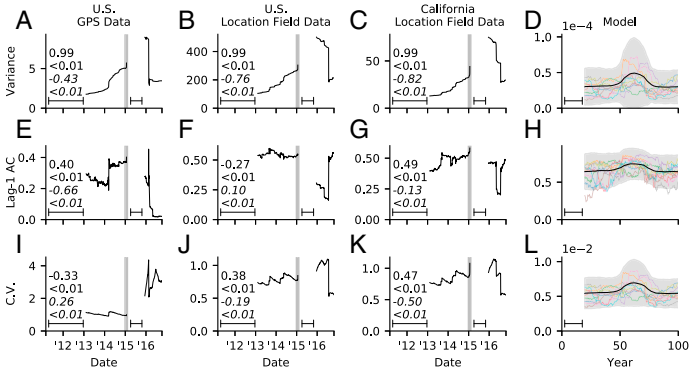

Fig. 4 Critical slowing down in pro-vaccine tweets near a tipping point, before and after Disneyland measles outbreak. (A-D) Variance, (E-H) lag-1 AC, and (I-L) coefficient of variation for (A, E, and I) US GPS-derived data, (B, F, and J) US Location Field-derived data, (C, G, and K) California Location Field-derived data data, and (D, H, and l) model predictions. The residual time series was used for variance and lag-1 AC. Kendall tau rank correlation coefficients are displayed before (regular font) and after (italic) the Disneyland peak with p values denoted by $<$. Window width used to compute rolling averages is indicated by line interval. Shaded region indicates outbreak time period. Model panels show indicators averaged across 500 stochastic model realizations (black), 2 SDs (shaded), and 10 example realizations (colored lines). Figure reproduced from Ref. [38].

evant empirical data for parameterization and validation, analyzed with both traditional and state-of-the-art statistical methods. Such empirically-driven modelling may help us tackle problems of vaccine refusal around the world, and perhaps even speed the global eradication of some vaccine-preventable infections.

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