CORE
Metadata, citation and similar papers at core.ac.uk
Provided by Edinburgh Research Explorer

THE UNIVERSITY of EDINBURGH

Edinburgh Research Explorer

Fear, Access, and the Real-Time Estimation of Etiological Parameters for Outbreaks of Novel Pathogens

Citation for published version:
Fefferman, NH, Lofgren, ET, Li, N, Blue, P, Weber, DJ & Yakubu, A-A 2020 'Fear, Access, and the Real-Time Estimation of Etiological Parameters for Outbreaks of Novel Pathogens' medRxiv. https://doi.org/10.1101/2020.03.19.20038729

Digital Object Identifier (DOI):
10.1101/2020.03.19.20038729

Link:
Link to publication record in Edinburgh Research Explorer

Document Version:
Early version, also known as pre-print

General rights
Copyright for the publications made accessible via the Edinburgh Research Explorer is retained by the author(s) and / or other copyright owners and it is a condition of accessing these publications that users recognise and abide by the legal requirements associated with these rights.

Take down policy
The University of Edinburgh has made every reasonable effort to ensure that Edinburgh Research Explorer content complies with UK legislation. If you believe that the public display of this file breaches copyright please contact openaccess@ed.ac.uk providing details, and we will remove access to the work immediately and investigate your claim.

OPEN ACCESS

Download date: 04. Jan. 2021

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY-NC-ND 4.0 International license .

Fear, Access, and the Real-Time Estimation of Etiological Parameters for Outbreaks of Novel Pathogens

Authors: Nina H. Fefferman[*1,2], Eric T. Lofgren[3], Nianpeng Li[4], Pieter Blue[5], David J. Weber[6] and Abdul-Aziz Yakubu[4].

[*] Corresponding Author: N.H. Fefferman, 447 Hesler Biology Building, Department of Ecology and Evolutionary Biology, University of Tennessee, Knoxville, TN, 37996, email: nfefferm@utk.edu

[1] Department of Ecology and Evolutionary Biology, University of Tennessee, Knoxville, TN, USA

[2] Department of Mathematics, University of Tennessee, Knoxville, TN, USA

[3] Paul G. Allen School for Global Animal Health, Washington State University, Pullman, WA, USA

[4] Department of Mathematics, Howard University, Washington, DC 20059, USA

[5] School of Mathematics, The University of Edinburgh, James Clerk Maxwell Building, The King's Buildings, Mayfield Road, Edinburgh, Scotland

[6] Division of Infectious Diseases, UNC School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Abstract:

Early analysis of outbreaks of novel pathogens to evaluate their likely public health impact depends on fitting predictive models to data gathered and updated in real-time. Both transmission rates and the critical R_0 threshold (i.e. the pathogen's 'reproductive number') are inferred by finding the values that provide the best model fit to reported case incidence. These models and inferred results are then the basic tools used for public health planning: how many people expected to be infected, at what scales of time and space, and whether potential intervention strategies impact disease transmission and spread. An underlying assumption, however, is that the ability to observe new cases is either constant, or at least constant relative to diagnostic test availability.
We present a demonstration, discussion, and mathematical analysis of how this assumption of predictable observability in disease incidence can drastically impact model accuracy. We also demonstrate how to tailor estimations of these parameters to a few examples of different types of shifting influences acting on detection, depending on the likely sensitivity of surveillance systems to errors from sources such as clinical testing rates and differences in healthcare-seeking behavior from the public over time. Finally, we discuss the implications of these corrections for both historical and current outbreaks.

Keywords: Mathematical Epidemiology, Observer Effects, Biosurveillance, Outbreak Modeling, H1N1 2009, COVID-19

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

Introduction:

Mathematical models of the progression of the spread of infectious disease provide the tools used for real-time decision making in public health planning and outbreak management. They allow us to predict the time course of spread within a population(Chowell et al. 2017; Perkins et al. 2016; van den Driessche and Watmough 2002) , provide critical cost-benefit estimates (Dasbach et al. 2006; Hayman et al. 2017; Keeling et al. 2017; Purdy et al. 2004), and evaluate best practices for particular interventions (Andrews and Basu 2011; Andrews and Bauch 2016; Ferguson et al. 2003; Kretzschmar et al. 2004). When confronted with a novel, potentially virulent pathogen, there is a rush to parameterize models appropriately (Capaldi et al. 2012; Farah et al. 2014; Sebrango-RodrÍGuez et al. 2017; Tizzoni et al. 2012), getting real-time case incidence data from surveillance sources and fitting the models to it to determine the likeliest estimates for probabilities of transmission (i.e. infectiousness) and the basic reproductive number, R_0, which provides a metric of epidemic potential (Anderson 1991; Chowell et al. 2006; Chowell et al. 2004). As a new outbreak unfolds, updated incidence data helps refine the parameter estimates, shifting our understanding of the nature of the threat in real time (Moore 2004; Sebrango-RodrÍGuez et al. 2017; Tizzoni et al. 2012). However, many of these models make an explicit assumption that detection of new disease incidence is a function of well-understood confounders that remain mostly invariant over the course of an outbreak, such as the probability of an infected person developing symptoms. There are known corrections for instances that violate this assumption of constant detectability, such as when clinical case definition criteria are

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

revised (Green 1998; Santermans et al. 2016; Thursky et al. 2003) or when new more sensitive and/or specific diagnostic tests become available (Nouvellet et al. 2015; Villela 2017). These confounders, however, are features of the surveillance process itself, and may therefore be understood so long as there is sufficient incorporation of medical and public health practice in the interpretation of the models (Villela 2017). Critically, these surveillance-based step-function changes may not the be the only meaningful factors confounding our ability to accurately estimate incidence data over time, and therefore accurately model the progression of an outbreak.

The importance of incorporating human behaviors into predictive epidemiological models has gained attention over the past decade (e.g. (Bansal et al. 2007; Del Valle et al. 2005; Fenichel et al. 2011; Funk et al. 2010; Perra et al. 2011)). Many models have now explored the potential impact of behaviors that directly impact transmission (e.g. school closures (Earn et al. 2012; Ferguson et al. 2006; Gemmetto et al. 2014; Lofgren et al. 2008), social distancing (Glass et al. 2006; Maharaj and Kleczkowski 2012; Reluga 2010; Valdez et al. 2012), use of personal protective equipment (PPE) (Anderson and Garnett 2000; Duerr et al. 2007)), etc.). However, the impact of human behavior within the context of epidemic outbreaks is not limited only to those that affect the transmission patterns of the pathogen. Our functioning societies enter into an epidemiological observer effect (cf. (Dirac 1947)) in which various behaviors are likely to confound both the sensitivity and specificity of surveillance detection of disease incidence.

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

Media-fanned public apprehension can create an over-demand for clinical testing (Sharma et al. 2003), even in the absence of clinical signs or symptoms and when transmission from asymptomatic persons does not occur (Baxter 2010). Social stigmatization associated with illness can conversely cause many with symptoms to avoid healthcare providers, and hence diagnosis, for as long as possible in order to avoid social repercussions (e.g. as with HIV/AIDS patients (Chesney and Smith 1999; Kalichman and Simbayi 2003). Even with fully rational and cooperative behavior on the part of the general public, public health directives and media attention will affect physicians themselves, potentially drastically altering rates at which physicians order tests to provide clinical diagnosis rather than relying on palliative treatment without the need for diagnosis (Barras 2020; Cowie et al.). This effect has already been shown to scale disproportionately with the actual rate of incidence (though not the focus of the study, this can be inferred from Fig 2 in (Iowa 1998 Annual Report)).

Further compounding the potential for these behavioral effects to mislead our models, the behaviors themselves are likely to depend on perceived epidemic status of the population. Individuals may shift their behaviors as reported prevalence rises and falls out of fear, or lack thereof, whether warranted by epidemiological truths or not. Case fatality rates are calculated based both on reported deaths and estimated case incidence, potentially amplifying the feedback since death may be considered an even greater motivator to action than illness. This implies that, not only do we may need to correct our predictive models for the pattern of surveillance sensitivity over time, but also to have sensitivity itself depend on the current perceived prevalence of the disease. This may be even more

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

117 critical in instances where estimated case incidence does not accurately reflect numbers
118 of infections (i.e. when case fatality rates and infection fatality rates differ significantly).
119 In effect, modeling efforts should be split into separate endeavors: one of curve fitting for
120 observed incidence, and one of inferring from those curves the likely underlying, actual
121 disease process.
122
123 To capture this coupled process of disease dynamics and disease detection, we consider a
124 standard, simple epidemiological model, but incorporate the potential for errors derived
125 from a variety of sources that confound our estimates of case incidence. We use these
126 models to demonstrate how these corrections would alter our understanding of historical
127 outbreaks, and then discuss some evidence that modern outbreaks are affected by the
128 types of behavioral shifts that we consider.
129
130
131 **Methods/ Model**
132 We begin with a standard Susceptible-Infected-Recovered (SIR) system, however, we
133 will examine both "real" process of actual pathogen spread (denoted by the subscript *a*),
134 and a "perceived" or "measured" process (denoted by the subscript *m*). For simplicity
135 sake, we will assume that correct diagnosis and treatment has no bearing on the duration
136 of illness/ recovery time, nor on the rates of transmission from infected to susceptible
137 individuals. Although both of these are obviously false for most outbreaks, they allow us
138 to highlight the processes and methods most relevant to our purpose here and are easily
139 corrected in specific application to particular outbreaks in the future. We therefore

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

assume that the recovery rate, γ, is the same in both the perceived and real processes (i.e. $\gamma_a = \gamma_m = \gamma$).

This therefore yields a "real" process of $\frac{ds_a}{dt} = -\beta_a s_a i_a$, $\frac{di_a}{dt} = \beta_a s_a i_a - \gamma i_a$, and $r_a(t) = 1 - s_a(t) - i_a(t)$, where $s_a(t)$, $i_a(t)$, and $r_a(t)$ are the fractions of the populations in the respective health categories at time *t*. To build the perceived disease process from this model, we then incorporate rates of testing for each fraction of the population, and the sensitivity and specificity of the test as follows.

Importantly, we will define as susceptible any person one who is not infected with our the pathogen of concern, despite possible infection with another illness. It is therefore not only reasonable but probable that "susceptible people" will seek out health care services and be tested for infection under our surveillance process, especially if the symptoms of their infection closely match those of the pathogen causing our focal outbreak. We therefore define α to be the rate at which susceptible people are tested for illness, call δ the rate at which infected people are tested for illness, and call λ the rate at which recovered people are tested for illness. (For purposes of this paper, we will assume $\alpha = \lambda$, however this assumption may be relaxed in future work if memory of recently resolved symptoms affects health care seeking behavior). We define the false positive rate of the diagnostic test ε_1 and the false negative rate of the test ε_2 (these may apply either to clinical diagnostic sensitivity and specificity, or else to error rates stemming from differences in physician opinion during syndromic surveillance).

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

Assuming that, at least initially, our surveillance cannot determine whether an uninfected person is susceptible or recovered, and therefore $s_m(t) + i_m(t) = 1$, we can define $s_m = s_a(1-\alpha) + s_a\alpha(1-\varepsilon_1) + i_a(1-\delta) + i_a\delta\varepsilon_2 + r_a(1-\lambda) + r_a\lambda(1-\varepsilon_1)$ and $i_m = s_a(\alpha\varepsilon_1 - \lambda\varepsilon_1) + i_a(\delta - \delta\varepsilon_2 - \lambda\varepsilon_1) + \lambda\varepsilon_1$. Defined in this way, if $\alpha = \delta = \lambda = 1$, and $\varepsilon_1 = \varepsilon_2 = 0$, and $r_a = 0$, then $i_m = i_a$ and $s_m = s_a$ (i.e. when there are no errors and the surveillance is perfect, then the measured case incidence will be equal to the corresponding real case incidence, as we would hope).

Using this definition, we then correct our understanding of any disease incidence curve once we have either measured or assumed appropriate functions/values for α, δ, λ, ε_1, and ε_2. While this might at first seem straightforward, there arises the complication that our health care seeking behavior functions are likely to be problematic in at least three separate ways: (1) they are likely to be functions of the current perceived prevalence of infection in the population (i.e. some function of i_m), (2) they are likely to be functions of time since the beginning of the perception of the current outbreak, (3) they are likely to be non-linear and, in some cases, not even continuous. We therefore propose the following algorithm to produce a system of SIR curves which reflect the underlying disease dynamics without the influence of behavioral shifts and/or testing inaccuracy; we will denote this system as "Testing Neutral", TN.

We start from the most conservative assumption: that only the epidemiological rates of β_m and γ for the outbreak curve of interest are known (i.e. that the raw data to which an

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

SIR model was fit to obtain those parameters is currently unavailable). We make this assumption to provide a method by which analysis of previously published rates for historical outbreaks could be analyzed without having to reanalyze the original outbreak data (should that data in fact be accessible, the correction can naturally be applied directly to the i_m data directly rather than to i^* curve described below). We, therefore, begin with an initially reconstructed SIR system (denoted by *) using only our measured β_m and γ: $\frac{ds^*}{dt} = -\beta_m s^* i^*$ and $\frac{di^*}{dt} = \beta_m s^* i^* - \gamma i^*$. We then compute the corrected curve for the infected population (which is no longer necessarily continuous) using the definition of i_m above and applying it to the i^* and i_{cor} instead of i_m and i_a (respectively), we obtain $i_{cor} = \frac{i^* - \varepsilon_1 \alpha}{\delta(1-\varepsilon_2) - \varepsilon_1 \alpha}$ so long as $\frac{\varepsilon_1 \alpha}{(1-\varepsilon_2)} \neq 1$ (note: if it is equal to 1, then $i^* = \alpha$, which implies that the surveillance process cannot accurately capture the underlying real disease dynamics; derivation of this equality can be found in ESM Appendix 1). We are then able to generate the TN system by finding a new value of β which minimizes the square of the distance between the $i_{cor}(t)$ curve and a new, hypothetical, standard continuous SIR system's infected curve, using the known value of γ. We call this new, corrected value the "Testing Neutral β" which we denote β_{TN}. So long as our assumed rates and behavior adjustment functions are reasonable approximations of the associated real-world values and behaviors, $\beta_{TN} = \beta_a$, and the TN system may reasonably approximate the real disease dynamics (i.e. $s_{TN} = s_a$, $i_{TN} = i_a$, using the rates β_{TN} and γ). These values of β_a and γ (and by extension, the R_0 computed either by fitting $i_{TN} = i_a$, or else computed as the ratio of these corrected

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

205 etiological rates) may then be compared to similarly corrected values for other outbreaks
206 without worry that differences in sensitivity or health-care seeking behavior will
207 influence the comparison.
208
209 **Results**
210
211 *Demonstration of Impact of Healthcare-Seeking Behavior, Clinical Testing Rates, and*
212 *Diagnostic Error Rates on Estimation of Outbreak Dynamics and Severity*
213
214 To demonstrate the potential of these types of confounding factors in incidence
215 estimation to influence our understanding of ongoing disease dynamics, we present the
216 i_m and i_a curves under a variety of values for ε_1, and ε_2, and function choices for α
217 and δ. Even under the simplest exploratory case, in which there are no ongoing
218 dynamics affecting the ability to estimate incidence over time and where also the rates of
219 testing for susceptible, infected, and recovered individuals are all held constant and
220 identical, we see that asymmetry in error type rates alone can drastically alter our
221 understanding of an ongoing outbreak (Fig. 1a). Extending this simple case to also
222 include behavioral responses that shift over the course of an outbreak (i.e. non-constant
223 testing rates), while still keeping all else the same, we see also that there can be drastic
224 errors, even in the understood shape of the incidence curve to match the cases observed
225 (Fig. 1b). (Again, for derivation of predictions for agreement/disagreement with real
226 disease process based on the direction of the inequality between A_ε and 1, and the
227 derivation of this example, see ESM Appendix 1).

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

Note that these calculations presented in Figure 1 are meant to be extremes to highlight the potential for confusion – we show a full range of values for ε_1, and ε_2 ranging from potentially realistic (A_ε =1) to dramatically inflated (both ε_1, and ε_2 are greater than 0.5, which would result in a more accurate test by simply negating the result). This is done to highlight the problem, though of course, real-world values are expected to be within a much narrower, more conservative range.

Data-Driven Case Studies

Historical Outbreaks of Pandemic Influenza

Employing this now demonstrated potential for mismatch in understood dynamics to more realistic outbreak scenarios, we see that when health-care seeking behavior is dependent on the perceived prevalence of disease, shifting at a set threshold, there is also the potential for drastic misunderstanding of the disease dynamics, even if the error rates in testing are realistically low (Ai et al. 2020; Chu et al. 2012) (Fig 2a). Further departing from an idealized instructional case, when we incorporate both testing rate dependence on perceived prevalence and the amount of time since surpassing the threshold for increased behavioral demand for testing (e.g. gradual relaxation in public risk perception over time), the differences between the reality of the disease dynamics and the understanding that would be provided by fitting a model to case incidence data is even greater (Fig 2b).

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

To demonstrate how these effects might impact current understanding of modern analyses, we construct a hypothetical scenario using results from an excellent paper comparing the severity of pandemic and epidemic outbreaks of influenza: Viboud et al. 2006 (Viboud et al. 2006). In this paper, the authors concluded (among other things) that the R_0 values for three pandemic years (1918, 1957, and 1968) were 2.1, 1.5 and 1.8 (respectively). However, while all three pandemic years of data were analyzed using transmission estimates inferred from influenza-attributed mortality data, the data for the 1957 and 1968 years were based upon WHO laboratory surveillance. For this reason, we can assume that the reported influenza attributed mortality was more accurate in representing only deaths from influenza (or associated pneumonia) than would have been possible for 1918. Entirely hypothetically, even if we assume that health care seeking behavior did not change at all between 1918 and 1957 (purely for demonstration, we assume $\alpha = \begin{cases} 0.01 if\ i_m \le 0.05 \\ 0.8\ if\ i_m > 0.05 \end{cases}$ and $\delta = \begin{cases} 0.5 if\ i_m \le 0.01 \\ 1.0 if\ i_m > 0.01 \end{cases}$ for all of these analyses), if we posit that the syndromic surveillance of 1918 led to error rates of $\varepsilon_1 = 0.1$ and $\varepsilon_2 = 0.005$, whereas the laboratory based testing was able to increase the specificity of the diagnosis (leaving the sensitivity the same) to $\varepsilon_1 = 0.01$, we already see a drop in the perceived vs TN estimates of R_0 for 1918 from 2.1 to 1.9, but no change (after rounding to the same number of digits) in the R_0 estimates for either 1957 or 1968. This leads to a substantial mismatch in the observed incidence curve for the 1918 pandemic and an understanding of the same outbreak under a Testing Neutral assumption (Fig 3a) while both the 1957 and 1958 outbreaks would already have been accurately understood (Fig 3b and 3c).

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

While we have no reason to suspect that our hypothetical error rates and assumed health care seeking behavioral functions reflect the reality of any of these three pandemics, they are clearly within realistic ranges and therefore demonstrate how dramatic the impact of even small differences in diagnostic sensitivity (whether due to changes in laboratory practice or to patient- or physician-driven behavior) can be on epidemiological estimates on which we base our public health strategies and policies.

Outbreak of Influenza H1N1-09

Whereas case studies of historical outbreaks of pandemic influenza allowed us to demonstrate the potential misestimate for R_0 and resulting disease dynamics in the absence of direct understanding of behavioral shifts in testing practices, the more recent "novel" (H1N1-09) provides instead real-world data on the shifting demand for clinical diagnostic testing. This pandemic was first brought to light by global media attention *in advance* of clinical diagnosis in many areas. This is made clear by considering a time-series of both ordered clinical tests and confirmed cases of H1N1 in the UNC healthcare system in 2009 in which testing started immediately after media attention to the virus, but significantly before any actual circulation was detected (Fig. 4a).

Using the actual sensitivity and specificity known for the H1N1 tests in use at the time (Ginocchio et al. 2009), and the UNC testing curve to parameterize demand, we see that the reported estimate of $R_0 = 1.58$ (Fraser et al. 2009), under correction, instead becomes and $R_0 = 1.64$ (Fig. 4b). Of potential note, if we restrict the window for curve fitting to

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

just the first weeks' worth of data, we instead get an estimated $R_0 = 1.66$ (Fig. 4c), meaning that, for this scenario, earlier estimates and projections were likely to overestimate the progression of the outbreak slightly. Depending on whether or not the UNC data is actually representative of broader patterns of test-seeking or test-ordering behavior this provides evidence that our understanding of the global dynamics of novel H1N1 in 2009 may be flawed.

Outbreak of COVID-19

While we have no way of currently estimating the rate of susceptible individuals seeking testing, we can make some generalizations given that the demand for testing in the United States as of 17 March well outstripped the supply of tests, and access to these tests was decidedly non-uniform (e.g. supplemental test availability from the Seattle Flu Study).

Analytic Condition for Accuracy in Estimated Case Incidence from Surveillance

In addition to these numerical examples, we provide a theoretical threshold condition, $\overline{A}_\varepsilon$, for the ability of a surveillance system to reflect actual disease incidence based on assumed relationships among the behavioral functions and error rates (much as R_0 provides a threshold condition for epidemics). Assuming that the behavioral health care seeking functions are independent of time, the effective ratio of error rates in the diagnostic tests, defined as $A_\varepsilon = \frac{\varepsilon_1}{(1-\varepsilon_2)\, j(i_m)}$, where $j(i_m) = \delta/\alpha$, can be used to define

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

316 $\overline{A}_\varepsilon = \begin{cases} A_\varepsilon, if \phi(i_m) - i_m \phi'(i_m) > 0; \\ \dfrac{1}{A_\varepsilon}, if \phi(i_m) - i_m \phi'(i_m) < 0 \end{cases}$ where $\phi(i_m) = \alpha$. This $\overline{A}_\varepsilon$ then provides a way to

317 determine whether the perceived or measured disease process may accurately reflect the
318 real, underlying disease process. In this case, when the ratio of the diagnosis test rates is
319 constant, if there are no errors in the diagnosis tests then the surveillance accurately
320 reflects the real disease process though it may overestimate or underestimate actual
321 incidence. If there are errors, the surveillance system accurately reflects the increasing or
322 decreasing nature of the real disease if $\overline{A}_\varepsilon < 1$, but can indicate increasing (resp.
323 decreasing) incidence while the actual incidence is decreasing (resp. increasing) when
324 $\overline{A}_\varepsilon > 1$. When the ratio of the diagnosis tests is non-constant the results are more
325 complicated, but some results are still accessible: without errors in diagnostic tests, a
326 surveillance system can wrongly report no disease incidence while actual case incidence
327 is either increasing or decreasing. Further, with small errors in the diagnostic tests it is
328 possible for a surveillance system to report decreasing incidence while the actual
329 incidence is increasing. (Proofs and characterizations of these relationships are provided
330 in ESM Appendix 1.)
331
332 **Discussion**
333
334 The ability to accurately infer epidemiological rates from outbreak data is critical to a
335 majority of our public health planning efforts. As our models demonstrate, the accuracy
336 of our estimates may be significantly compromised by our implicit assumption that
337 diagnostic error rates and health care seeking behavior remain constant over the course of

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

single, and even multiple, outbreaks, even as we know this assumption to be untrue. Regardless of the particular mechanism through which we attempt to characterize the changes in diagnostic sensitivity and specificity, our results demonstrate (in both theory and practice) how these dynamics may be incorporated into epidemiological modeling efforts and how the results may translate into a more accurate understanding of infectious disease dynamics.

Some studies have been able to assess the impact of public health announcement- or media-driven behavioral change with regard to disease risk and diagnosis (e.g. (Sharma et al. 2003)). It is clear that we will need to develop better models that explicitly capture the major factors that can effect change in public behavior regarding health care and diagnosis. While it may be impossible to accurately assess the impact of behavioral changes in health care seeking behavior for past epidemics, one possible course of action going forwards would be to ask physicians, hospitals and laboratories to record and report the number of tests performed in addition to merely the number of cases positively diagnosed, regardless of acknowledge threat of outbreaks.

These models and insights may also be of critical use our collective ongoing efforts to understand and predict the progression of COVID-19. Not only do we provide the obvious alternations to the standard epidemic predictions for error rates in testing, we also provide a mechanism by which to correct our understanding of R_0 based on changes in access to tests of various sensitivities and specificities over time. This is especially important given both the formulation of governmental responses to the pandemic (i.e.

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

"flattening the curve" or relying on community protection, *i.e.* 'herd immunity') and their subsequent evaluation hinge on accurate estimations of R_0. While presented here with constant rates to enable the analytic calculations, real-time estimations of R_0 are frequently based on numerical solutions, rather than analytic calculations. In this case, the expansion of precisely these equations to allow for α, δ, and λ to themselves be dynamic functions of public perception and disease prevalence will enable vastly more accurate understanding of real-time case incidence data. Work currently underway to try and capture the functional forms of these responses in observed behaviors in the US will hopefully allow us to extend these results very soon to the ongoing COVID-19 pandemic itself, but we provide this model in the meanwhile to allow others to work in parallel and improve our real-time decision-support capabilities.

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

Literature Cited

Ai, T., Z. Yang, H. Hou, C. Zhan, C. Chen, W. Lv, Q. Tao et al. 2020. Correlation of chest CT and RT-PCR testing in coronavirus disease 2019 (COVID-19) in China: a report of 1014 cases. Radiology:200642.

Anderson, R., May, R.M. 1991, Infectious disease of humans. Oxford, UK, Oxford University Press.

Anderson, R. M., and G. P. Garnett. 2000. Mathematical models of the transmission and control of sexually transmitted diseases. Sexually Transmitted Diseases 27:636-643.

Andrews, J. R., and S. Basu. 2011. Transmission dynamics and control of cholera in Haiti: an epidemic model. The Lancet 377:1248-1255.

Andrews, M. A., and C. T. Bauch. 2016. The impacts of simultaneous disease intervention decisions on epidemic outcomes. Journal of theoretical biology 395:1-10.

Bansal, S., B. T. Grenfell, and L. A. Meyers. 2007. When individual behaviour matters: homogeneous and network models in epidemiology. Journal of the Royal Society Interface 4:879-891.

Barras, C. 2020. Major testing issues in US, Pages 8, New Scientist, Elsevier.

Baxter, R. 2010. Surveillance lessons from first-wave pandemic (H1N1) 2009, Northern California, USA. Emerging infectious diseases 16:504.

Capaldi, A., S. Behrend, B. Berman, J. Smith, J. Wright, and A. L. Lloyd. 2012. Parameter estimation and uncertainty quantication for an epidemic model. Mathematical biosciences and engineering:553.

Chesney, M. A., and A. W. Smith. 1999. Critical delays in HIV testing and care - The potential role of stigma. American Behavioral Scientist 42:1162-1174.

Chowell, G., C. E. Ammon, N. W. Hengartner, and J. M. Hyman. 2006. Estimation of the reproductive number of the Spanish flu epidemic in Geneva, Switzerland. Vaccine 24:6747-6750.

Chowell, G., N. W. Hengartner, C. Castillo-Chavez, P. W. Fenimore, and J. M. Hyman. 2004. The basic reproductive number of Ebola and the effects of public health measures: the cases of Congo and Uganda. Journal of theoretical biology 229:119-126.

Chowell, G., C. Viboud, L. Simonsen, S. Merler, and A. Vespignani. 2017. Perspectives on model forecasts of the 2014–2015 Ebola epidemic in West Africa: lessons and the way forward. BMC medicine 15:42.

Chu, H., E. T. Lofgren, M. E. Halloran, P. F. Kuan, M. Hudgens, and S. R. Cole. 2012. Performance of rapid influenza H1N1 diagnostic tests: a meta□analysis. Influenza and other respiratory viruses 6:80-86.

Cowie, G. A., B. C. Cowie, and J. E. Fielding. Influenza testing trends in sentinel surveillance general practices in Victoria 2007 to 2014 The Victorian Sentinel Practice Influenza Network (VicSPIN) conducts surveillance for syndromic and laboratory confirmed influenza in approximately 100 general practices in Victoria each influenza season. Participating general practitioners test for influenza at their own discretion–the percentage of patients swabbed within and between seasons is evaluated. Page last updated: 30 March 2017.

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

418 Dasbach, E. J., E. H. Elbasha, and R. P. Insinga. 2006. Mathematical models for
419 predicting the epidemiologic and economic impact of vaccination against human
420 papillomavirus infection and disease. Epidemiologic Reviews 28:88-100.
421 Del Valle, S., H. Hethcote, J. M. Hyman, and C. Castillo-Chavez. 2005. Effects of
422 behavioral changes in a smallpox attack model. Mathematical Biosciences
423 195:228-251.
424 Dirac, P. A. M. 1947, The principles of quantum mechanics. Oxford, Clarendon Press.
425 Duerr, H. P., S. O. Brockmann, I. Piechotowski, M. Schwehm, and M. Eichner. 2007.
426 Influenza pandemic intervention planning using InfluSim: pharmaceutical and
427 non-pharmaceutical interventions. Bmc Infectious Diseases 7:13.
428 Earn, D. J. D., D. He, M. B. Loeb, K. Fonseca, B. E. Lee, and J. Dushoff. 2012. Effects
429 of school closure on incidence of pandemic influenza in Alberta, Canada. Annals
430 of internal medicine 156:173-181.
431 Farah, M., P. Birrell, S. Conti, and D. D. Angelis. 2014. Bayesian emulation and
432 calibration of a dynamic epidemic model for A/H1N1 influenza. Journal of the
433 American Statistical Association 109:1398-1411.
434 Fenichel, E. P., C. Castillo-Chavez, M. G. Ceddia, G. Chowell, P. A. G. Parra, G. J.
435 Hickling, G. Holloway et al. 2011. Adaptive human behavior in epidemiological
436 models. Proceedings of the National Academy of Sciences 108:6306-6311.
437 Ferguson, N. M., D. A. T. Cummings, C. Fraser, J. C. Cajka, P. C. Cooley, and D. S.
438 Burke. 2006. Strategies for mitigating an influenza pandemic. Nature 442:448-
439 452.
440 Ferguson, N. M., M. J. Keeling, W. J. Edmunds, R. Gant, B. T. Grenfell, R. M.
441 Amderson, and S. Leach. 2003. Planning for smallpox outbreaks. Nature 425:681-
442 685.
443 Fraser, C., C. A. Donnelly, S. Cauchemez, W. P. Hanage, M. D. Van Kerkhove, T. D.
444 Hollingsworth, J. Griffin et al. 2009. Pandemic potential of a strain of influenza A
445 (H1N1): early findings. Science 324:1557-1561.
446 Funk, S., M. Salathé, and V. A. Jansen. 2010. Modelling the influence of human
447 behaviour on the spread of infectious diseases: a review. Journal of The Royal
448 Society Interface 7:1247-1256.
449 Gemmetto, V., A. Barrat, and C. Cattuto. 2014. Mitigation of infectious disease at school:
450 targeted class closure vs school closure. BMC infectious diseases 14:695.
451 Ginocchio, C. C., F. Zhang, R. Manji, S. Arora, M. Bornfreund, L. Falk, M. Lotlikar et al.
452 2009. Evaluation of multiple test methods for the detection of the novel 2009
453 influenza A (H1N1) during the New York City outbreak. Journal of Clinical
454 Virology 45:191-195.
455 Glass, R. J., L. M. Glass, W. E. Beyeler, and H. J. Min. 2006. Targeted Social Distancing
456 Design for Pandemic Influenza. Emerging Infectious Diseases 12:11.
457 Green, T. A. 1998. Using surveillance data to monitor trends in the AIDS epidemic.
458 Statistics in medicine 17:143-154.
459 Hayman, D., J. Marshall, N. French, T. Carpenter, M. Roberts, and T. Kiedrzynski. 2017.
460 Cost-benefit analyses of supplementary measles immunisation in the highly
461 immunized population of New Zealand. Vaccine 35:4913-4922.
462 Iowa, S. H. L. a. U. o. 1998 Annual Report. Eastern Iowa Whooping Cough Outbreak.

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

Kalichman, S. C., and L. C. Simbayi. 2003. HIV testing attitudes, AIDS stigma, and voluntary HIV counselling and testing in a black township in Cape Town, South Africa. Sexually Transmitted Infections 79:442-447.

Keeling, M. J., K. A. Broadfoot, and S. Datta. 2017. The impact of current infection levels on the cost-benefit of vaccination. Epidemics 21:56-62.

Kretzschmar, M., S. van den Hof, J. Wallinga, and J. van Wijngaarden. 2004. Ring vaccination and smallpox control. Emerging Infectious Diseases 10:832-841.

Lofgren, E. T., J. Rogers, M. Senese, and N. H. Fefferman. 2008. Pandemic preparedness strategies for school systems: is closure really the only way? Annales Zoologici Fennici 45:449-458.

Maharaj, S., and A. Kleczkowski. 2012. Controlling epidemic spread by social distancing: Do it well or not at all. BMC Public Health 12:679.

Moore, K. 2004. Real-time syndrome surveillance in Ontario, Canada: the potential use of emergency departments and Telehealth. European Journal of Emergency Medicine 11:3-11.

Nouvellet, P., T. Garske, H. L. Mills, G. Nedjati-Gilani, W. Hinsley, I. M. Blake, M. D. Van Kerkhove et al. 2015. The role of rapid diagnostics in managing Ebola epidemics. Nature 528:S109.

Perkins, T. A., A. S. Siraj, C. W. Ruktanonchai, M. U. G. Kraemer, and A. J. Tatem. 2016. Model-based projections of Zika virus infections in childbearing women in the Americas. Nature microbiology 1:16126.

Perra, N., D. Balcan, B. Gonçalves, and A. Vespignani. 2011. Towards a characterization of behavior-disease models. PloS one 6.

Purdy, K. W., J. W. Hay, M. F. Botteman, and J. I. Ward. 2004. Evaluation of strategies for use of acellular pertussis vaccine in adolescents and adults: A cost-benefit analysis. Clinical Infectious Diseases 39:20-28.

Reluga, T. C. 2010. Game theory of social distancing in response to an epidemic.

Santermans, E., E. Robesyn, T. Ganyani, B. Sudre, C. Faes, C. Quinten, W. Van Bortel et al. 2016. Spatiotemporal evolution of Ebola virus disease at sub-national level during the 2014 West Africa epidemic: model scrutiny and data meagreness. PloS one 11.

Sebrango-RodrÍGuez, C. R., D. A. MartÍNez-Bello, L. SÁNchez-ValdÉS, P. J. Thilakarathne, E. Del Fava, P. Van Der Stuyft, A. LÓPez-QuÍLez et al. 2017. Real-time parameter estimation of Zika outbreaks using model averaging. Epidemiology & Infection 145:2313-2323.

Sharma, V., M. D. Dowd, D. S. Swanson, A. J. Slaughter, and S. D. Simon. 2003. Influence of the news media on diagnostic testing in the emergency department. Archives of Pediatrics & Adolescent Medicine 157:257-260.

Thursky, K., S. P. Cordova, D. Smith, and H. Kelly. 2003. Working towards a simple case definition for influenza surveillance. Journal of Clinical Virology 27:170-179.

Tizzoni, M., P. Bajardi, C. Poletto, J. J. Ramasco, D. Balcan, B. Gonçalves, N. Perra et al. 2012. Real-time numerical forecast of global epidemic spreading: case study of 2009 A/H1N1pdm. BMC medicine 10:165.

Valdez, L. D., P. A. Macri, and L. A. Braunstein. 2012. Intermittent social distancing strategy for epidemic control. Physical Review E 85:036108.

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

van den Driessche, P., and J. Watmough. 2002. Reproduction numbers and sub-threshold endemic equilibria for compartmental models of disease transmission. Mathematical Biosciences 180:29-48.

Viboud, C., T. Tam, D. Fleming, A. Handel, M. A. Miller, and L. Simonsen. 2006. Transmissibility and mortality impact of epidemic and pandemic influenza, with emphasis on the unusually deadly 1951 epidemic. Vaccine 24:6701-6707.

Villela, D. A. M. 2017. Imperfect testing of individuals for infectious diseases: Mathematical model and analysis. Communications in Nonlinear Science and Numerical Simulation 46:153-160.

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity. It is made available under a CC-BY-NC-ND 4.0 International license .

Figure Legends

Figure 1: Example Perceived and Infected Curves Representing the Same Outbreak Under Different Testing Rates/Functions. All curves: $\beta_a = 3$, $\gamma = 1$, $s_a(0) = 0.9$, $i_a(0) = 0.1$. **(a)** Constant Behavioral Responses. Black solid curve: real disease dynamics; Black ■: $\alpha = 0.65$, $\delta = 0.65$, $\varepsilon_1 = 0.2$, and $\varepsilon_2 = 0.1$; Dashed curve: $\alpha = 0.65$, $\delta = 0.65$, $\varepsilon_1 = 0.6$, and $\varepsilon_2 = 0.7$; Black ✕: when the effective ratio of errors in testing, A_ε =1 (for calculations, see Appendix 1). **(b)** Non-Constant Behavioral Responses: All curves: $\beta_a = 3$, $\gamma = 1$, $s_a(0) = 0.9$, $i_a(0) = 0.1$. Black curve: real disease dynamics; All other curves $\alpha = 0.65$, $\delta = \dfrac{0.65(1 + qi_m)}{pi_m}$, $p = q = 1$, (ε_1 and ε_2 for each curve as labeled).

Figure 2: Example Perceived and TN Infected Curves Representing the Same Outbreak. (a) Non-Constant Health Care Seeking Behavior Functions**.** All curves: $\gamma = 1$, $s_a(0) = 0.999$, $i_a(0) = 0.001$. Solid curve – Perceived Outbreak: $\beta_m = 1.15$, $\alpha = \begin{cases} 0.01 if\ i_m \le 0.003 \\ 0.8\ if\ i_m > 0.003 \end{cases}$, $\delta = \begin{cases} 0.5 if\ i_m \le 0.001 \\ 1.0 if\ i_m > 0.001 \end{cases}$, $\varepsilon_1 = 0.002$, and $\varepsilon_2 = 0.005$; Dotted curve – Testing Neutral Outbreak: $\beta_{TN} = 1.13$ **(b)** Healthcare Seeking Behavior Functions that Depend on Perceived Epidemic Severity and Time from first Outbreak Identification. All curves: $\gamma = 1$, $s_a(0) = 0.999$, $i_a(0) = 0.001$. Solid curve – Perceived Outbreak: $\beta_m = 1.15$, $\alpha = \{0.01$ if i_m has never exceeded 0.003, and 0.7 when i_m first exceeds 0.003, decreasing exponentially (by a factor of $e^{(x-t)}$) over time to 0.3$\}$, $\delta = \begin{cases} 0.5 if\ i_m \le 0.001 \\ 1.0 if\ i_m > 0.001 \end{cases}$, $\varepsilon_1 = 0.01$, and $\varepsilon_2 = 0.005$; Dotted curve – Testing Neutral Outbreak: $\beta_{TN} = 1.10$

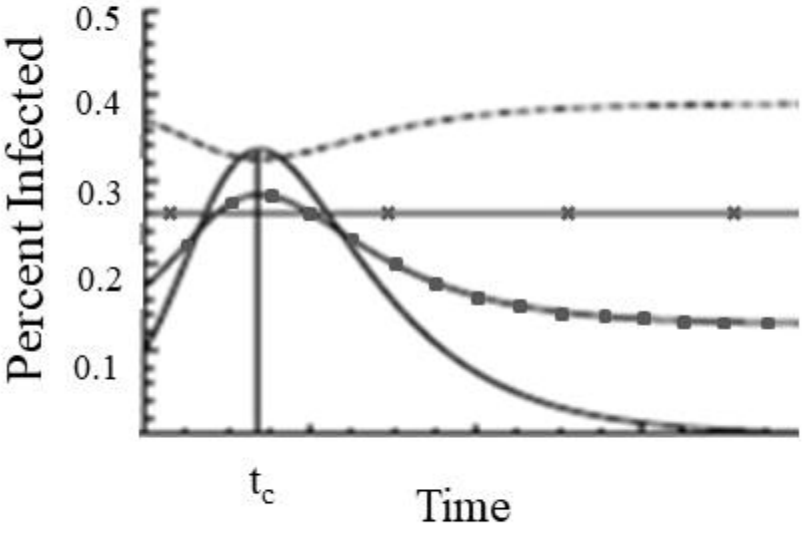
Figure 3: Differences in Estimates of R_0 for Three Pandemic Years Using Hypothetical Correction Rates. (a) Analysis of Influenza Pandemic of 1918, **(b)** Analysis of Influenza Pandemic of 1957, **(c)** Analysis of Influenza Pandemic of 1968.
For all panels – Solid line: Perceived/Reported pandemic incidence curve, reconstructed from reported R_0. Dotted line: TN pandemic incidence curves (1918 TN R_0 =1.9; TN 1957 R_0 =1.5; 1968 TN R_0 =1.8).

Figure 4: Testing Rates and Resulting Estimates of R_0 for Novel H1N1 2009. (a) Counts of influenza tests ordered and H1N1 positive tests from UNC, **(b)** Estimated epidemic curves from reported (solid line) and TN (dotted line) epidemic incidence curves using the full time series, **(c)** Estimated epidemic curves from reported (solid line) and TN (dotted line) epidemic incidence using

medRxiv preprint doi: https://doi.org/10.1101/2020.03.19.20038729.this version posted March 20, 2020. The copyright holder for this preprint
(which was not certified by peer review) is the author/funder, who has granted medRxiv a license to display the preprint in perpetuity.
It is made available under a CC-BY-NC-ND 4.0 International license .

only the first 7 days of data after the first reported case to approximate real-time parameter estimation and resulting prediction.

(a)


0.5
0.4
0.3
0.2
0.1
Percent Infected
t_c
Time

(b)

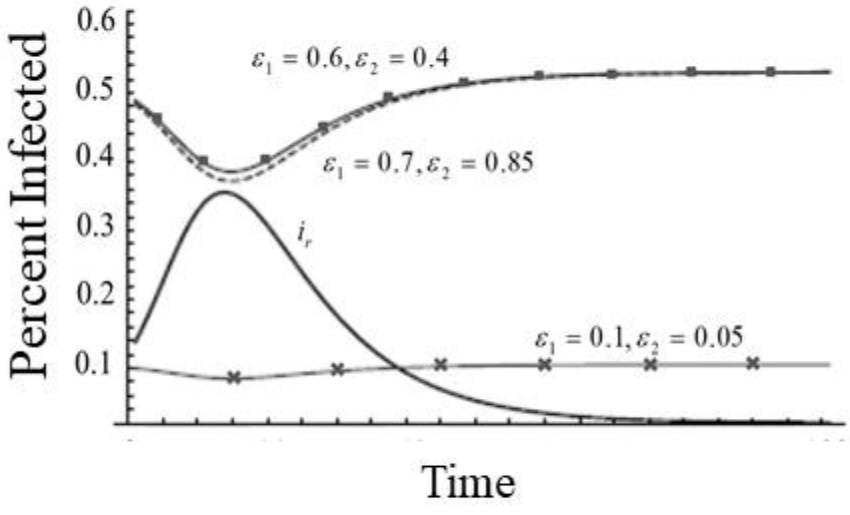
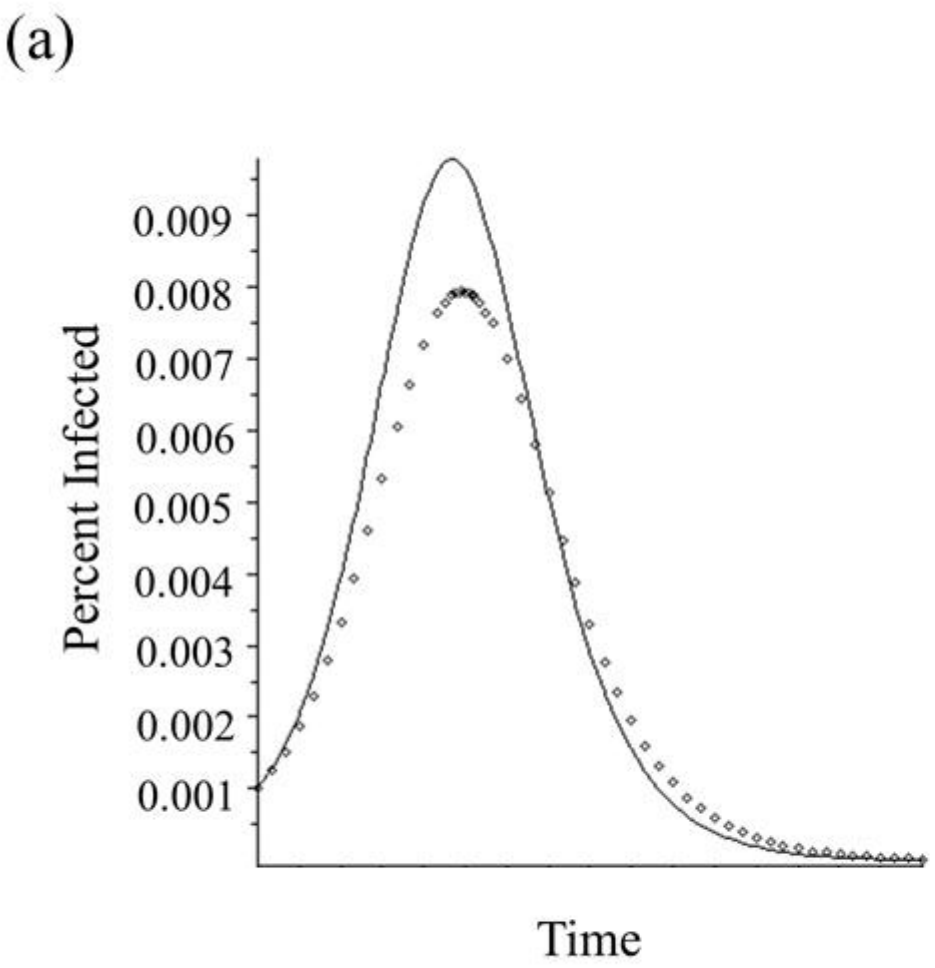

0.6
0.5
0.4
0.3
0.2
0.1
Percent Infected
$\varepsilon_1 = 0.6, \varepsilon_2 = 0.4$
$\varepsilon_1 = 0.7, \varepsilon_2 = 0.85$
i_r
$\varepsilon_1 = 0.1, \varepsilon_2 = 0.05$
Time

Figure 1


(a)
Percent Infected
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
Time

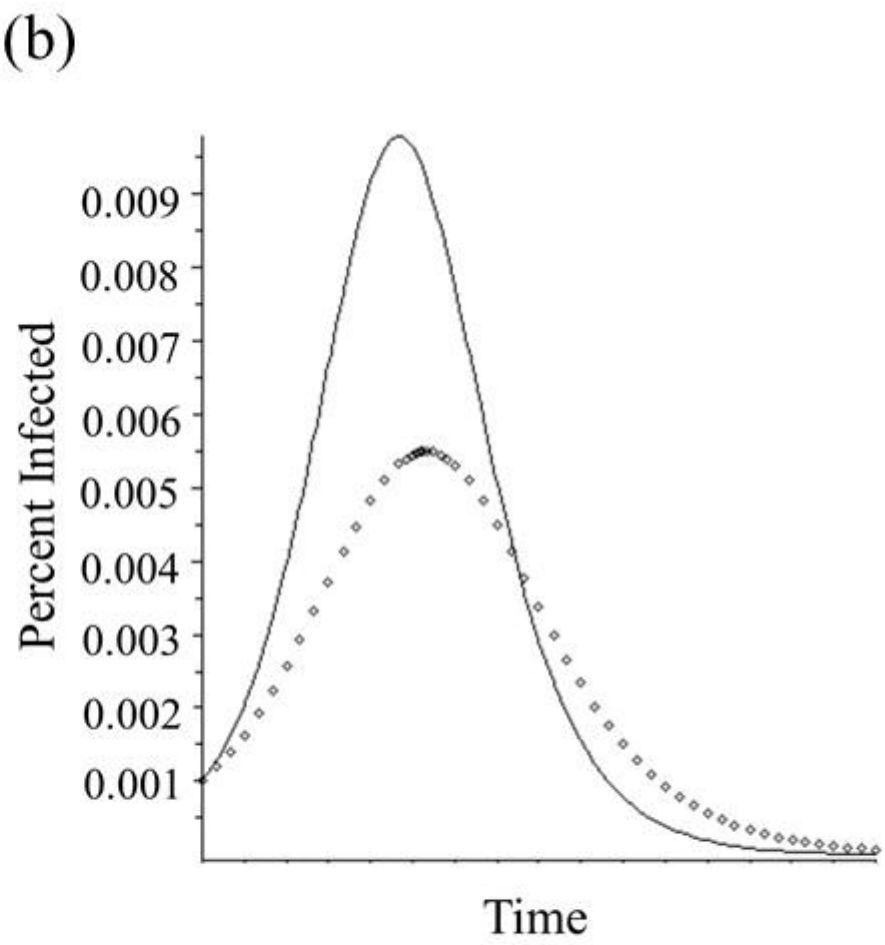
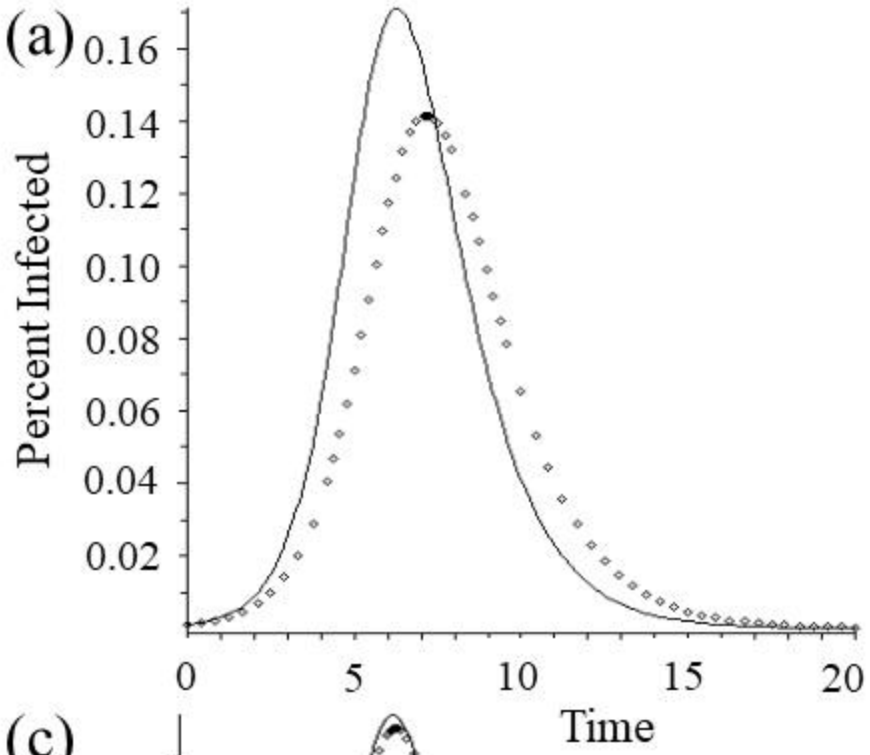
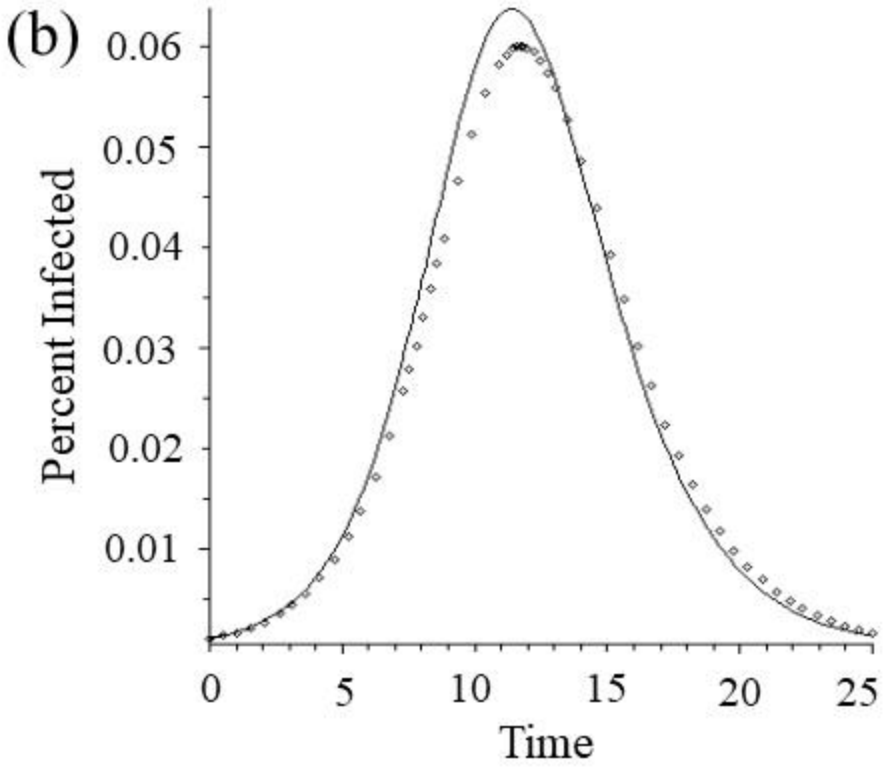

(b)
Percent Infected
0.009
0.008
0.007
0.006
0.005
0.004
0.003
0.002
0.001
Time

Figure 2


(a)
Percent Infected
0.16
0.14
0.12
0.10
0.08
0.06
0.04
0.02
0
5
10
15
20
Time


(b)
Percent Infected
0.06
0.05
0.04
0.03
0.02
0.01
0
5
10
15
20
25
Time

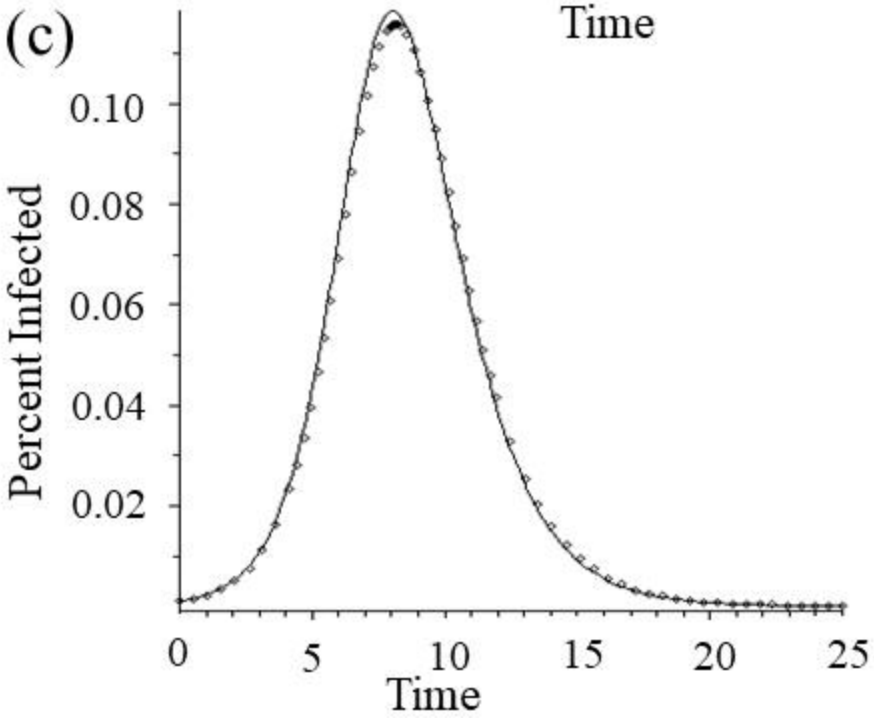
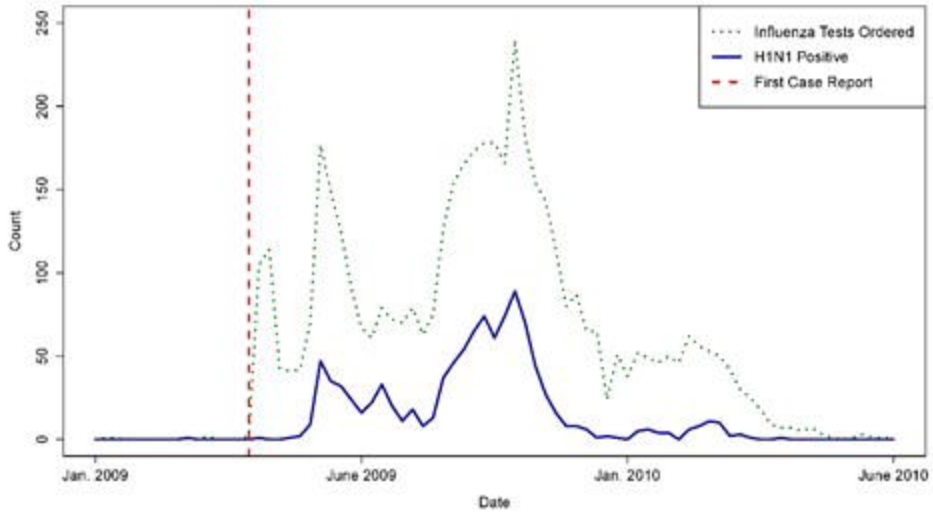
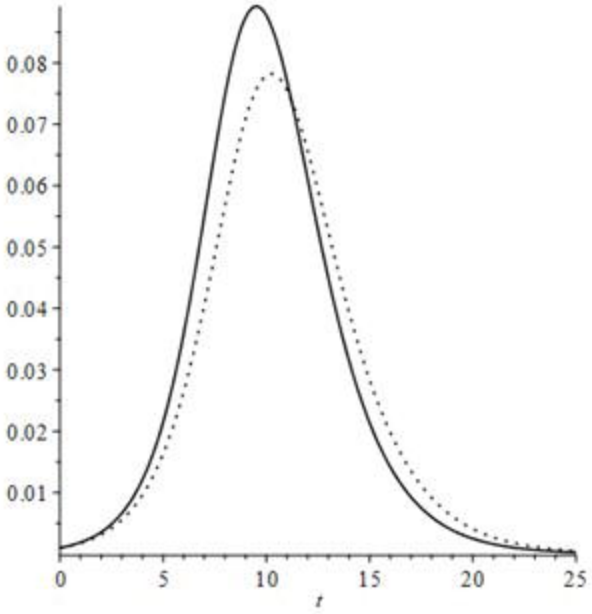

(c)
Percent Infected
0.10
0.08
0.06
0.04
0.02
0
5
10
15
20
25
Time

Figure 3

(a)


Influenza Tests Ordered
H1N1 Positive
First Case Report
Count
0
50
100
150
200
250
Jan. 2009
June 2009
Jan. 2010
June 2010
Date

(b)


0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0
5
10
15
20
25
t

(c)

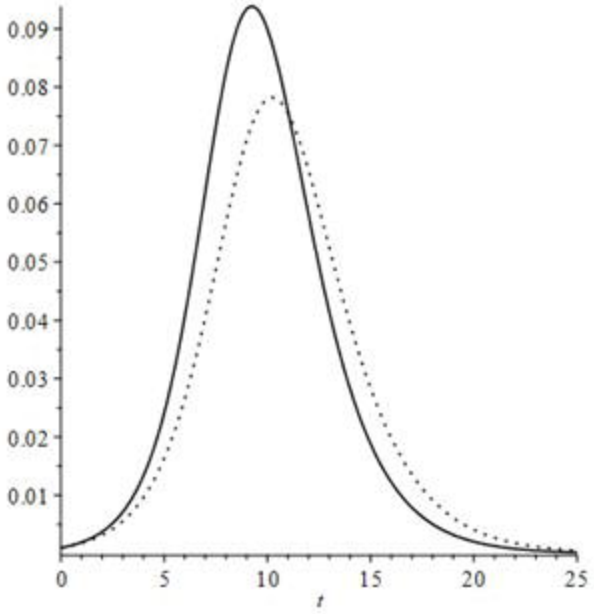

0.01
0.02
0.03
0.04
0.05
0.06
0.07
0.08
0.09
0
5
10
15
20
25
t

Figure 4