MODELING THE DYNAMICS OF ENTEROVIRUS-71 IN TAIWAN

AN APPLICATION OF THE TSIR MODEL

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BACKGROUND

Human Enterovirus-71 (EV-71) is an emerging pathogen that has become a novel target for disease control efforts in the Asia-Pacific region. EV-71 is a major causative agent of **Hand, Foot & Mouth Disease (HFMD)**, normally a self-limiting childhood infection transmitted via the fecal-oral route that causes a rash of vesicular lesions on the hands, feet and oral mucosa. The majority of individuals infected with HFMD require little to no medical attention; in some cases, however, enterovirus infection leads to **severe neurologic complications** like encephalitis, meningitis, myocarditis and acute paralysis [1].

In 1998 in Taiwan, an epidemic of enteroviral infection saw an estimated 1.5 million cases of HFMD. 405 of those cases manifested severe symptoms, and 78 resulted in death. The vast majority of those affected were young children. EV-71 was identified as the primary etiologic agent behind the epidemic [2].

EV-71 has gone on to cause outbreaks of HFMD across the Asia-Pacific region. With candidate vaccines currently rushing to safety trials, a novel opportunity for disease modeling has emerged. Can existing models for childhood infections capture EV-71 dynamics? And what are the possibilities for control?

RESEARCH GOALS & HYPOTHESES

EV-71 poses a disease modeling challenge, as existing data captures only severe cases and not the true burden of infection. The goals of this thesis project were:

1. to elucidate key epidemiological parameters from available data using a stochastic, discrete-time modeling approach,
2. to use mathematical models to derive the true burden of EV-71 infection in Taiwan,
3. to use derived parameters to model the potential impact of vaccination, and to derive a value for R_0

I hypothesized that:

1. the weekly course of transmission parameter (β) would follow seasonal trends in disease incidence [3], with peaks in the summer and autumn seasons and troughs in the winter,
2. severe cases would represent less than 1/1000 infections,
3. R_0 for EV-71 would be approximately equal to that of related enterovirus polio, for which R_0 = 5-7 [4].

METHODS

DATA: The Taiwan CDC's Notifiable Infectious Diseases Surveillance System has published reported cases of severe enterovirus infection, 1999-2013.

MODEL: This project used the Time series-Susceptible-Infected-Recovered (TSIR) model, a stochastic variant of the traditional SIR in discrete time [5].

$$S_{t+1} = S_t + B_t - I_t$$
$$\Lambda_{t+1} = \beta S_t I_t^{\alpha}$$
$$I_t = \rho_t C_t$$

S = susceptibles class
B = births
I = true infecteds class
Λ = predicted infecteds class
β = transmission parameter
α = contact mixing parameter
ρ = reporting parameter

I is assumed to follow a negative binomial distribution around Λ.

KEY RESULTS

THE DATA

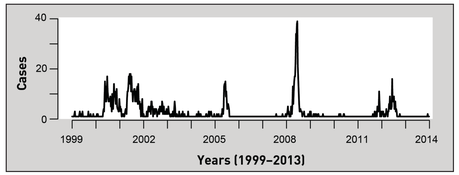


FIGURE 1: TIME SERIES OF REPORTED CASES OF SEVERE ENTEROVIRUS INFECTION, 1999-2013

TABLE OF KEY RESULTS

PARAMETER	VALUE
Transmission parameter (β)	See Fig. 3
Contact parameter (α)	0.8316127
Mean reporting coefficient (ρ)	1492
Model fit	m=1.000025
Critical vaccination threshold (p_c)	99.95% coverage
R_0	2000

1. UNDERREPORTING

ρ is given by regressing cumulative reported cases vs. cumulative births:

$$\sum_{i=1}^{t} B = \rho \sum_{i=1}^{t} C_i + D_t - D_0$$

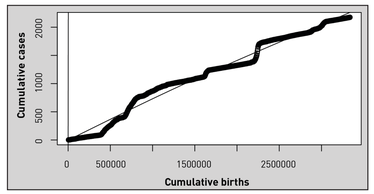


FIGURE 2: REGRESSION OF CUMULATIVE REPORTED CASES AGAINST CUMULATIVE BIRTHS

Based on the slope of the regression, the mean ρ = 1492.

2. TRANSMISSION PARAMETERS (β)

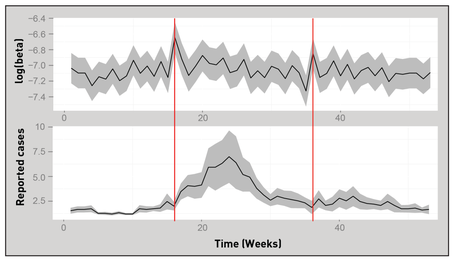


FIGURE 3: DERIVED βs. Top: Derived transmission parameters. Bottom: Avg course of reported cases. Red lines denote peaks in transmission, at around April and September.

3. MODEL FIT

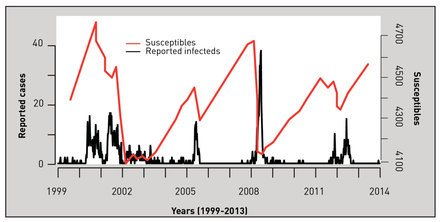


FIGURE 4: RECONSTRUCTED SUSCEPTIBLES. Susceptibles predicted by the model (red) plotted against reported infecteds (black).

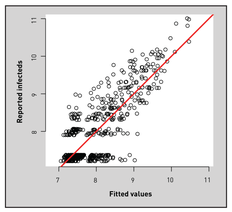


FIGURE 5: REGRESSION OF REPORTED INFECTEDS VS FITTED VALUES. The regression indicates goodness of fit. m=1.000025. R^2 = 0.7215.

Taken together, Fig. 3-5 show the model fits well to the data, but the derived transmission parameters display only some seasonality, indicating the model is still just a rough approximation.

4. SIMULATIONS

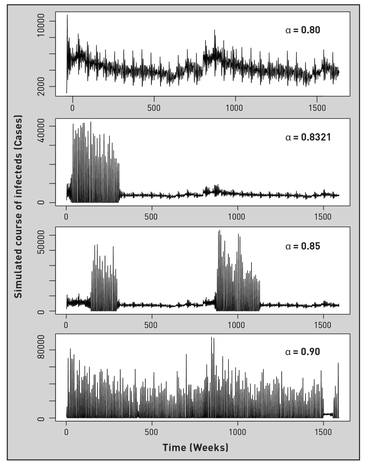


FIGURE 6: SIMULATED INFECTEDS COURSES AT VARYING CONTACT PARAMETERS. Each simulation was run at the corresponding α.

For the purposes of vaccine simulation, a regularly oscillating simulation was needed. Births were set at a constant rate representing the mean, with β & α as their derived values. Vaccination was modeled as:

$$S_{t+1} = S_t + \sigma B_t - I_t$$

σ = vaccination coverage as a proportion of the population removed from the births to become susceptibles.

5. VACCINATION & R_0

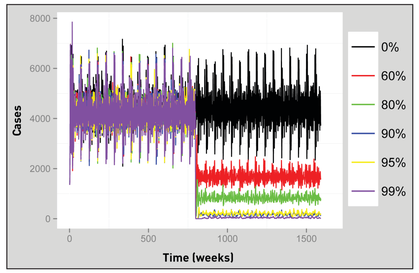
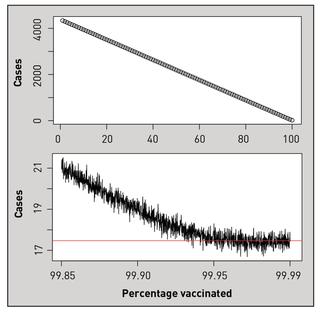


FIGURE 7: EFFECT OF VARYING VACCINATION COVERAGE ON INFECTEDS COURSE. Baseline is shown in black. Inputs: Constant births at mean; derived β & α.

FIGURE 8: EFFECT OF INCREASING VACCINATION COVERAGE ON MEAN NUMBER OF INFECTEDS AT ENDPOINT. The asymptotic behavior beginning at 99.95% coverage can be taken to indicate the critical population coverage (p_c).

$$p_c = 1 - \frac{1}{R_0}$$

Thus it follows that R_0 = 2000.



DISCUSSION

The model was successful in fitting to the data, but better data is necessary to elucidate more complex & meaningful control simulations & conclusions.

1. Derived transmission parameters (β) appear to map onto the reported infecteds course (Fig. 3), and the model fit demonstrated by Fig. 4 & 5 is encouraging. But **the transmission course lacks true seasonality**, which can be attributed to the weakness of the dataset.

   Derived contact parameter (**a=0.8316127**) has a t-value of 40.63. Thus the result may indicate the presence of a degree of homogeneity in the contact process of transmission, but this is again merely a rough approximation.

2. Derived reporting parameter (ρ = 1492) shows that **just one severe case out of every 1493 cases of infection is reported.**

3. Derived R_0 = 2000. This should not be construed as a realistic estimation of the basic reproduction number of EV-71. This interpretation would mean one enterovirus-infected child is able to infect 2,000 close contacts. The model fit here is a rough approximation. It can be taken as an indication, however, that the **R_0 of the virus is likely high.**

FUTURE DIRECTIONS & RECOMMENDATIONS

This study utilized an underreported dataset of case counts to extrapolate parameters then used to theoretically simulate what might be the true, underreported burden of infection. Through the course of this project, a number of directions for research emerged.

Existing datasets must be improved if modeling efforts are to continue. More stringent surveillance & reporting programs and more publicly available data are needed. A modeling effort on a dataset that includes all EV-71 infections, not just those manifesting severe symptoms, might yield more realistic results.

Better data would yield more malleable models & more realistic vaccine simulations. While the stochastic, discrete-time model utilized in this project was able to characterize the existing data to a degree of success, the limitations of the model were such that vaccination was modeled with a grossly oversimplified scheme.

Finally, research on EV-71 in Taiwan would benefit from a clarification of the spatial dynamics of contact and transmission on the island. Such research could **characterize heterogeneities in transmission that would be vital to effective control measures** [6]. Network-based models identifying target populations might prove more useful for a childhood illness known to spread most effectively through schools.

ACKNOWLEDGEMENTS & REFERENCES

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