Mathematical Models of the Ebola Epidemic in West Africa:
Principles, Predictions, and Control

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Ebola virus disease (EVD):

*Zaire ebolavirus*
- Causative agent of the current outbreak is *Zaire ebolavirus*, of the family Filoviridae.
- ssRNA enveloped virus, ~19,000 bp in length

**Outbreaks**
- >30 years of documented outbreaks, largely in Central Africa
- These outbreaks begin with infections arising from a zoonotic reservoir (e.g., bats, monkeys).

**Effects**
- Infected individuals are symptom-free for ~11 days
- ~50%-70% of infected individuals die
- Secondary transmission via body fluids, both pre- and post-death
The world's largest Ebola outbreak rages in West Africa, unprecedented in duration and spatial spread. The emergence of this disease invites many questions—most of which remain unresolved—notably: Why now and why in West Africa? While containment of the West African Ebola outbreak is the most pressing, immediate need, advancing our understanding of this outbreak remains critical to present health care interventions as well as preventing importation or emergence of this disease elsewhere. We review the sociological, ecological, and environmental drivers that could have influenced the emergence of EBOV in West Africa at this time and in this manner. Given these factors, we explore the lessons of this outbreak and how we might manage future threats from Ebola across the complex urban and rural landscapes that now define modern Africa.

Introduction

On December 6th, 2013, the world's largest Ebola epidemic began when a two-year-old in Guéckédou, Guinea, a small village bordering Sierra Leone and Liberia, became infected ([1,2] Figure 1).

Figure 1. Map of Ebola outbreaks in Africa.

The outbreak in West Africa is unprecedented in its scope and duration occurring for the first time in urban centers. Historically, Ebola viral outbreaks (stars, timeline

PLOS Neglected Tropical Diseases | www.plosntds.org

Figure 1 of Alexander et al. (2014), PLoS Neglected Tropical Diseases
Clinical Manifestations and Case Fatality Rate

Table 1 provides information on demographic characteristics and symptom frequency in patients with confirmed or probable EVD with a definitive outcome in Guinea, Liberia, Nigeria, and Sierra Leone. The most common symptoms reported between symptom onset and case detection included fever (87.1%), fatigue (76.4%), loss of appetite (64.5%), vomiting (67.6%), diarrhea (65.6%), headache (53.4%), and abdominal pain (44.3%). Specific hemorrhagic symptoms were rarely reported (in <1% to 5.7% of patients). "Unexplained bleeding," however, was reported in 18.0% of cases. These patterns are similar in each country (see Supplementary Appendix 1).

Assessing the case fatality rate during this...
CDC EbolaResponse tool:
Meltzer et al., MMWR, 9/26/2014

Prediction:
1.4 million cases by January 2015

WHO Model

Prediction:
12,000 - 60,000 cases in November 2014 (increasing beyond that)
In practice, the actual number of cases, though significant and striking, are well below predictions.

Data from Caitlin Rivers: https://github.com/cmrivers/ebola

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Models overestimate Ebola cases

Rate of infection in Liberia seems to plateau, raising questions over the usefulness of models in an outbreak.
To construct an illustrative control scenario in Liberia, an intervention modeling scenario was created in which, starting on August 24, 2014, the percentage of patients at home or in a community setting such that there is a reduced risk for disease transmission (including safe burial when needed) was increased from 8% of all patients to 25% and left at that level for the remainder of the period covered by the model (Figure 8). Starting on August 24, 2014, the percentage of patients in Ebola treatment units (ETUs) increased from 10% of all patients to 17%. In the subsequent 30 days (starting September 21, 2014), that percentage was increased to 20%. Additional increases were included so that by December 22, 2014, a total of 70% of patients were in either one of those two settings (25% in ETUs + 45% at home or in a community setting such that there is a reduced risk for disease transmission (including safe burial when needed)).

To summarize – initial models included predictions of $>10^6$ cases without interventions and $\sim10^4$ cases with interventions.

This difference raises questions at the center of today’s seminar.
What are the principles that mathematical models of EVD utilize to make near- and long-term predictions?

What are the assumptions made when considering interventions?

What are the challenges, unknowns and uncertainties?
Part 1 of 2: Mathematical principles underlying predictions of the epidemic spread of Ebola

Part 2 of 2: Challenges and opportunities for control of the Ebola outbreak in West Africa.
Part 1 of 2: Mathematical principles underlying predictions of the epidemic spread of Ebola

Part 2 of 2: Challenges and opportunities for control of the Ebola outbreak in West Africa.
Population “Classes”

$S$ – The number of susceptible individuals

$I$ – The number of infectious individuals

$R$ – The number of “removed” individuals (through recovery or, possibly, death)

Mechanisms

**Infection:** Requiring contact between a $S$ and a $I$ individual at rate $\beta$.

**Recovery:** After a period of infectiousness of average duration $T_I$. 
SIR Model - Basics

Population “Classes”

$S$ – The number of susceptible individuals

$I$ – The number of infectious individuals

$R$ – The number of “removed” individuals (through recovery or, possibly, death)

\[
\begin{align*}
\dot{S} &= -\beta \frac{I}{N} S \\
\dot{I} &= \beta \frac{I}{N} S - \frac{I}{T_I} \\
\dot{R} &= \frac{I}{T_I}
\end{align*}
\]
Consider a “small” number of infected individuals in an otherwise susceptible population.

Q: What determines whether the infection will spread or decline with time?

A: Intuitively, whether each infected individual infects at least one new individual, on average before they recover.
Consider a “small” number of infected individuals in an otherwise susceptible population.

Q: What determines whether the infection will spread or decline with time?

\[
\dot{I} = \beta S \frac{I}{N} - \frac{I}{T_I}
\]
Consider a “small” number of infected individuals in an otherwise susceptible population.

Q: What determines whether the infection will spread or decline with time?

\[
\dot{I} = \beta S \frac{I}{N} - \frac{I}{T_I}
\]

\[
\dot{I} \approx I \left( \beta - \frac{1}{T_I} \right)
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\[
\dot{I} \approx I \left( \beta - \frac{1}{T_I} \right)
\]

\[
\dot{I} \approx \frac{I}{T_I} (\beta T_I - 1)
\]
The expected number of cases, initially changes like:

\[ \frac{\dot{I}}{I} = \frac{I}{T_I} (R_0 - 1) \]
The expected number of cases, initially changes like:

\[ \dot{I} = \frac{I}{T_I} (R_0 - 1) \]

where

\[ R_0 \equiv \beta \times T_I \]

infections per time \hspace{1cm} infectious period
The expected number of cases, initially changes like:

\[ \dot{I} = \frac{I}{T_I} (\mathcal{R}_0 - 1) \]

where

\[ \mathcal{R}_0 \equiv \underbrace{\beta}_{\text{infections per time}} \times \underbrace{T_I}_{\text{infectious period}} \]

such that

1. Disease spreads whenever the average number of new cases exceeds unity, i.e: \( \mathcal{R}_0 > 1 \)

2. The increase is exponential
Conditions for epidemic growth

\[ R_0 \equiv \beta \times T_I \]

Where infections per time, \( \beta \), is a product of:

- Contacts by infectious individuals per unit time
- Probability of contact with a susceptible (\( S_0/N \))
- Probability that the contact transmits the disease
Conditions for epidemic growth also suggest opportunities for control.

\[ R_0 = \beta \times T_I \]

Where infections per time, \( \beta \), is a product of:

- Contacts by infectious individuals per unit time
- Probability of contact with a susceptible \( (S_0/N) \)
- Probability that the contact transmits the disease

<table>
<thead>
<tr>
<th>Hospitalization &amp; treatment</th>
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<tbody>
<tr>
<td>Contact tracing &amp; targeted isolation</td>
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<tr>
<td>Vaccination (herd or ring)</td>
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<tr>
<td>Process engineering &amp; PPE</td>
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Strategies for containing Ebola in West Africa

Abhishek Pandey,1* Katherine E. Atkins,1* Jan Medlock,2 Natasha Wenzel,1 Jeffrey P. Townsend,3 James E. Childs,4 Tolbert G. Nyenswah,5 Martial L. Ndeffo-Mbah,1 Alison P. Galvani1,4†

Science express // http://www.sciencemag.org/content/early/recent //

30 October 2014/ Page 2 / 10.1126/science.1260612

Factors considered

- Transmission precautions for healthcare workers
- Reducing general-community transmission
- Sanitary burial
- Isolation of Ebola patients
- Contact tracing and quarantine
- General quarantine

But how much reduction is needed for each factor alone or in combination depends on the value of $R_0$. 

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$R_0 = 1.5$

Days, $t$

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$R_0 = 2.0$

$R_0 = 1.5$
The diagram shows the spread of an infectious disease over time for three different values of the reproduction number \( R_0 \): 2.5, 2.0, and 1.5. The y-axis represents the number of infected individuals \( I(t) \) over time, while the x-axis represents the number of days, \( t \). For each value of \( R_0 \), the graph illustrates how the number of infected individuals grows over time, with \( R_0 = 2.5 \) showing the fastest growth, followed by \( R_0 = 2.0 \), and then \( R_0 = 1.5 \) with the slowest growth.
Question: consider data on an epidemic in which $\lambda = 1/4$ weeks where

- Disease 1: $T_I = 1$ week
- Disease 2: $T_I = 4$ weeks

Which disease has the higher $R_0$?
**Question:** consider data on an epidemic in which $\lambda = 1/4$ weeks where

- Disease 1: $T_I = 1$ week
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Which disease has the higher $R_0$?

**Answer:** Disease 2

**Algebra:** $R_0 = 1 + T_I \lambda$

- Disease 1: $R_0 = 1.25$
- Disease 2: $R_0 = 2$
**Question:** consider data on an epidemic in which $\lambda = 1/4$ weeks where
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**Answer:** Disease 2

**Algebra:** $R_0 = 1 + T_I \lambda$
- Disease 1: $R_0 = 1.25$
- Disease 2: $R_0 = 2$

**Intuition:**
Disease 1 takes 4 infectious periods to “double” the case count.
Disease 2 takes only 1 infectious period to “double” the case count.
Hence, disease 2 has a higher average number of secondary infections per average infectious period (the definition of $R_0$).
Significant difference between forward and inverse problems in epidemiology

Take-away points:

Whether a disease spreads or not, depends on whether $R_0 > 1$ or not.

Factors that affect transmission rate or infectious period represent opportunities for control.

In practice, an estimate of the epidemic growth rate $\lambda$ can be used to infer the unknown value of $R_0$.

Yet: many combinations of infectious period and the basic reproductive number yield the same apparent growth rate.

This can be problematic when there is uncertainty, as is the case for Ebola and other emerging infectious diseases.
Part 1 of 2: Mathematical principles underlying predictions of the epidemic spread of Ebola

Part 2 of 2: Challenges and opportunities for control of the Ebola outbreak in West Africa.
The West African nation of Mali, which just beat its first outbreak of Ebola, has confirmed a second one that is larger and more threatening, global health authorities said on Wednesday.

The victim who apparently began the new outbreak was an imam who fell ill in Guinea and traveled to Mali for better treatment at a major private clinic in Bamako, the capital.

The imam died at the Pasteur Clinic in Bamako on Oct. 27. Because of his status, his body was washed at a large mosque and returned to Guinea for burial after a funeral at another mosque.
Factors to consider in extending the SIR model for Ebola

**Disease characteristics**

- Individuals are initially latently infected, i.e., exposed but not yet infectious.
- The latent period can be up to 21 days.
- The period of infectiousness is ~6 days.
- Infectious individuals can transmit EVD when alive.
- Individuals who have died from EVD are still infectious after death.

**Other complexities**

- Hospitalization changes survival.
- Many countermeasures being applied at once.
- Behaviors change as information spreads.
- Spatio-temporal complexity
  - …
SEIR-D Model of Ebola Dynamics

A subset of recent models (e.g., Legrand et al. Epidemiol Infect, 2007; Lewnard et al., Lanc. Inf. Dis. 2014; Pandey Science 2014; … )

Working Assumptions: Similar to SIR model, except:

There is an exposed (E) class, that are non-infectious.

A fraction 1-f of infected individuals recover and are moved into the R class.

A fraction f of infected individuals die and are moved into the D class.

Dead (but as yet unburied) individuals can transmit disease to S individuals.

Dead individuals are buried with a characteristic time $T_D$. 
Consider an SEIR-D model in which

Latent period: \( T_E = 11 \) days
Infectious period: \( T_I = 6 \) days
Probability of death: \( f = 0.7 \)

Given a characteristic time of \(~3\) weeks for the spread of disease...

For which we do not know the transmission rates and the time of infectiousness after death:

\[ \beta_I \quad \beta_D \quad T_D \]
Consider an SEIR-D model in which

Latent period: \( T_E = 11 \) days
Infectious period: \( T_I = 6 \) days
Probability of death: \( f = 0.7 \)

Given a characteristic time of \(~3\) weeks for the spread of disease...

What combinations of parameters yield the same epidemic growth rate?

Approach:
Moment-generating function methods of Wallinga and Lipsitch (PRSB, 2007), that connects observed epidemic growth rate and unknown \( R_0 \)
Consider an SEIR-D model in which

Latent period: \( T_E = 11 \) days
Infectious period: \( T_I = 6 \) days
Probability of death: \( f = 0.7 \)

Given a characteristic time of \( \sim 3 \) weeks for the spread of disease...

Multiple “scenarios” \( \bigcirc, \bigcirc, \bigcirc \) and \( \bigcirc \) all yield the same predicted epidemic growth rate (using moment-generating function approach).

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Consider an SEIR-D model in which

Latent period: \( T_E = 11 \) days
Infectious period: \( T_I = 6 \) days
Probability of death: \( f = 0.7 \)

Given a characteristic time of \(~3\) weeks for the spread of disease...

These “scenarios” \( \bullet, \bullet, \bullet \) and \( \bullet \) all have a higher \( R_0 \) due to post-death transmission when compared to a SEIR model prediction.
SEIR-D model dynamics
Weitz & Dushoff, arXiv:1411.3435

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Inference of epidemiological parameters from cumulative case data

Take-home messages:

Multiple “scenarios” ○, ○, and ○ all yield the same predicted epidemic growth rate.

For a given growth rate, a larger proportion of post-death transmission implies a larger value of $R_0$.

Optimistically, the effect on $R_0$ is modest, generally <10%, so long as post-death transmission is relatively short in duration compared to total period.
How well can a SEIR-D model “fit” the early exponential increase in EVD cases?

**Data source:**

Caitlin Rivers’ public datasets: https://github.com/cmrivers/ebola

Guinea
Liberia
Sierra Leone
Model fits to case data: Guinea

\[ R_0 = \frac{\rho_D}{R_0(\text{dead}) / R_0} \]

- \( T_D = 2 \)
- \( T_D = 4 \)
- \( T_D = 6 \)
Model fits to case data: Liberia
Model fits to case data: Sierra Leone

\[ R_0 = \frac{R_0(\text{dead})}{R_0} \]

\[ T_D = 2 \quad T_D = 4 \quad T_D = 6 \]

\[ \frac{\beta_I}{0.1} \]

\[ \frac{\beta_D}{1.5} \]

\[ \frac{R_0}{1.75} \]

\[ \frac{T_D}{50} \]

\[ \frac{\text{Total cases}}{5000} \]

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Strategies and Thoughts Related to Post-Death Transmission of Ebola

Contact-tracing of ~700 cases suggests that between 10%-30% of transmissions are due to transmission via contact with dead individuals (see WHO-NEJM, SI).

Post-death transmission implies a longer “effective” infectious period and, in turn, a modestly larger value of $R_0$.

But, improvements in burial practice may also lead to substantial reductions in $R_0$ via:

- Reduction in post-death transmission rate
- Reduction in delay to burial
Benefits of Control of Post-death transmission (before/during burials)

Case 1: Infectious (I) and dead (D) periods are exponentially distributed.

Case 2: Infectious and (I) and dead (D) periods are peaked (i.e., most infectious at death and at burial)
Benefits of Control of Post-death transmission (before/during burials)

**Case 1:** Infectious (I) and dead (D) periods are exponentially distributed & 3 week characteristic growth rate.

\[ I - \text{exponential} \]
\[ D - \text{exponential} \]
\[ \lambda = 1/21 \]

**Case 2:** Infectious and (I) and dead (D) periods are peaked & 3 week characteristic growth rate.

\[ I - \text{delta} \]
\[ D - \text{delta} \]
\[ \lambda = 1/21 \]
Benefits of Control of Post-death transmission (before/during burials)

Case 1: Infectious ($I$) and dead ($D$) periods are exponentially distributed & 4 week characteristic growth rate.

\[ I - \text{exponential} \]
\[ D - \text{exponential} \]
\[ \lambda = 1/28 \]

Case 2: Infectious and ($I$) and dead ($D$) periods are peaked & 4 week characteristic growth rate.

\[ I - \Delta \]
\[ D - \Delta \]
\[ \lambda = 1/28 \]
Summary of analysis of post-death transmission of Ebola

Take-home message 1:
Estimates of $R_0$ for Ebola that focus on transmission while alive will necessarily be under-estimates, when inferences are made given the same epidemic growth data.

Take-home message 2:
Reduction of post-death transmission of Ebola may be substantial (e.g., one-half) of the necessary reduction in secondary transmission to stop epidemic spread (drop $R_e$ below 1).
Implications of analysis on post-death transmission
Weitz & Dushoff, arXiv:1411.3435

**Action item 1**: Continue to prioritize safe funeral/burial/grieving practices as key element of control & allocate resources for improvements in practices (e.g., burial teams).

**Action item 2**: Update contact tracing estimates on fraction of cases due to post-death transmission (see WHO-NEJM SI).

**Action item 3**: Evaluate whether serologically positive individuals can comprise burial teams (see Bellan et al., Lancet 2014).

**Action item 4**: Include the “identifiability” problem of post-death transmission risk in sensitivity analyses of current large-scale Ebola epidemiological models.
Ongoing challenge: connecting math models to support teams making decisions regarding control.

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Ebola control: effect of asymptomatic infection and acquired immunity
*Steve E Bellan, Juliet R C Pulliam, Jonathan Dushoff, Lauren Ancel Meyers

Dynamics and control of Ebola virus transmission in Montserrado, Liberia: a mathematical modelling analysis

Ebola cases and health system demand in Liberia
John M. Drake, RajReni B. Kaul, Laura Alexander, Suzanne M. O’Regan, Andrew M. Kramer, J. Tomsin Pulliam, Matthew J. Ferrari, and Andrew W. Park

Assessing the International Spreading Risk Associated with the 2014 West African Ebola Outbreak
September 2, 2014 · Research
Marcelo F. C. Gomes3, Ana Pastore y Piontti3, Luca Rossi3, Dennis Chao3, Ira Longini3, M. Elizabeth Halloran3, Alessandro Vespignani3
**Questions?**

\[ \beta_I, \quad \lambda = 1/21, \quad \text{Post-death control} \]

\[ \beta_D, \quad \lambda = 1/21, \quad \text{Other interventions} \]

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**Acknowledgments**

Jonathan Dushoff, McMaster  
Bradford Taylor, GT  
Hayriye Gulbudak, GT  
Yao-Hsuan Chen, CDC  
Brian Gurbaxani, CDC  
John Glasser, CDC  
Andrew Hill, CDC

**Funding**

BURROUGHS WELLCOME FUND
