Why Here? Why Now?
Travel, Trade, and Emergence of Infectious Diseases

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Unprecedented Volume and Speed of Travel

Image: Dr. Kamran Khan, Bluedot
Origins of Quarantine

- Dubrovnik (Ragusa) emerged as a trading center in Middle Ages.
- 1377: Great Council of Dubrovnik introduces 30 day quarantine of newcomers to avoid importing plague (trentina).
- Subsequently adopted by other cities, and extended to 40 days (“quaranti giorni” → “quarantine”).

Sources: Mackowiak and Sehdev, Clin Infect Dis 2002; Emerg Infect Dis 2002
Politics

The U.S. cannot allow people back. People places to help out are the consequences!

• **Limitations of travel restriction/travel screening:** economic consequences, prolonged incubation, alternate modes of travel, third country travel, ethical considerations (stigma, privation), impedance of outbreak response, poor sensitivity/specificity, others.
Factors Driving Disease Emergence

• **How** do diseases emerge and spread?
  – Need a “**seed**” (novel pathogen, opportunity for human infection).
  – Need “**soil**” (environmental conditions for introduction, ongoing reintroduction, or person-to-person transmission).
    • $R$ can be $< 1$ (clusters) or $> 1$ (outbreaks and epidemics).
Increasing Reproductive Number in Humans

Outline: A Tale of Two Emergences

• **Cholera, North America, 1832.**
  • Importation followed by epidemics, likely high $R_0$.
  • Communicability dismissed as implausible (prior experience, culture).
    • Contrast with importations in 2010-2011.

• **Arboviral emergences/resurgences, South America, 2013-present.**
  • Focus on travel and trade as “reason” for Zika epidemic.
  • Ignores longstanding movements of people and goods.
  • Focus on dynamic $R_0$ for Zika and chikungunya viruses?
    • Climate change?
Part I: Cholera, Commerce and Contagion

Rediscovering Dr. Beck’s Report.  [Ashleigh Tuite, Christina Chan and David Fisman, J Public Health Policy 2011]
Cholera and Empire

• First western description by East India Company physicians, 1817.

• East Bengal hub of jute industry (manufacture in Dundee, Scotland).

• Timing of introduction of cholera to U.K. corresponds with expansion of British Raj (1755-1856).
First (Recognized?) Cholera Pandemic

Persia and Middle East, 1821

Astrakhan, 1823

Russia, 1829-30

Baltic Ports, 1831

Newcastle and Sunderland, 1831
Cholera in North America, 1832

- Initial appearance in Great Britain in 1831.
- First reports in North America:
  - Quebec and Montreal in June 1832 in Irish immigrants.
  - Philadelphia delegation visit Canada (Drs. Meigs, Harlan, and Jackson).
  - Cholera moves south and west along waterways, including Northern and Western (Erie) Canals.

Beck’s Report

• Cholera popularly perceived to be communicable.
  • Medical opinion: “miasma” acting on susceptible (“corrupt”) constitutions.

• New York State: should government restrict trade and travel?
  • Newly completed Erie Canal (1825).

• Dr. Lewis Beck (1798-1853) commissioned by Legislature and Gov. Throop to report on cholera.

• Documents dates and locales of outbreaks from June to late July 1832.
  • Circumstances surrounding outbreak (presence of immigrants, importation of cases, habits of stricken individuals, case-fatality).
Beck’s Interpretation

• Having documented epidemics that follow movement of (potentially infectious) individuals, Beck concedes cholera *looks* contagious:
  • “[This pattern] seem[s] at first sight to favor the idea that cholera is contagious, or directly communicable from man to man...[but] that cholera is not contagious can be proved by a multitude of facts.”

• (Spoiler: his arguments are unconvincing).
Factors Contributing to Mischaracterization of Cholera

• Medical dogma ("ignorant public" disparaged by physicians [Rosenberg, The Cholera Years, 1962]).

• High attack rates among impoverished: equation of prosperity and morality.
  • Interaction between corrupted atmosphere ("miasma") and predisposed ("corrupted") individual, (with "contingent contagion").
  • Ruth Richardson: “hardly regarded as a biological entity but a means of retribution upon the morally suspect”.

• Observed failure of quarantine and cordon sanitaire in Russia (and subsequent rioting).

• Low attack rates/case fatality in care providers, spatial heterogeneity (villages unaffected), “hardy” boatmen (constitutions).
Daniel Drake: A Dissenting Voice

- Contemporaries (e.g., Daniel Drake) able to recognize importance of marine commerce to spread.
  - Attribution to “a poisonous, invisible, aerial insects, of the same or similar habits with the gnat” as this explains movement with ships, outbreaks at sea.

[Dr. Daniel Drake, 1785-1852]
Engd. by A.H. Ritchie. Source: IHM collection, National Library of Medicine
Fast Forward to IMED, 2010.

[Source: Tuite A et al., Annals of Internal Medicine 2011]
$R_0 \sim \frac{\beta_H + \beta_W}{\gamma}$

Appendix Table 2. Best-Fit Parameter Values Based on Model Fit to MSPP Hospitalization Data

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Plausible Range</th>
<th>Best-Fit Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_t$</td>
<td>Transmissibility, case</td>
<td>0.010 to 0.100</td>
<td>0.010</td>
</tr>
<tr>
<td>$\beta_w$</td>
<td>Transmissibility, water</td>
<td>0.789 to 0.945</td>
<td>0.944</td>
</tr>
<tr>
<td>$\xi^{-1}$</td>
<td>Mean survival of pathogen in water (weeks)</td>
<td>2.743 to 5.949</td>
<td>5.949</td>
</tr>
<tr>
<td>$\gamma^{-1}$</td>
<td>Mean duration of infectiousness (days)</td>
<td>2.376 to 3.013</td>
<td>2.913</td>
</tr>
<tr>
<td>$\kappa$</td>
<td>Gravity constant</td>
<td>$6.76 \times 10^{-13}$ to $8.92 \times 10^{-12}$</td>
<td>$6.83 \times 10^{-12}$</td>
</tr>
<tr>
<td>$R_0$</td>
<td>Basic reproductive number</td>
<td>2.07 to 2.78</td>
<td>2.78</td>
</tr>
</tbody>
</table>

MSPP = Ministère de la Santé Publique et de la Population.

References: Tien and Earn, Bull Math Biol 2010; Tuite et al., Annals of Internal Medicine, 2011
Vibrio cholerae in Traveler from Haiti to Canada

To the Editor: A nationwide outbreak of cholera caused by Vibrio cholerae O1 serotype Ogawa began in Haiti in October 2010 and has since resulted in >200,000 illnesses and 4,000 deaths (1). Additional cases of cholera attributed to the outbreak strain have subsequently been
Basic Reproduction Number $R_0$

Fraction of Infectivity from Water ($\frac{\beta_w}{\beta_w + \beta_h}$)
Part II: Recent Arboviral Emergences

Trade and Travel Are Not Enough
2000-2015: The Era of Arboviral Emergence and Resurgence?

• Introduction, resurgence, or *de novo* recognition of numerous arboviral pathogens in the Western hemisphere since 2000.
  • Chikungunya, Zika, Mayaro, Oropouche, Itaqui, Heartland, Cache Valley, Powassan, West Nile, Bourbon, West Nile viruses.
• ~150% increase in dengue incidence 2005-2015 (GBDS).
Zika Emergence in South America: Emphasis on Introduction via Travel

[Source: Faria NR et al., Science 2016]
Anticipating the International Spread of Zika

Bogoch I.B. et al. Lancet 2016; 387(10016); 335-6
Brazil and Sub-Saharan Africa: Historical Linkages

Brazilian slave trade evolved primarily to support sugar production (1533 onwards). Authorized by Portuguese crown, Papal blessing (1452). 4 million slaves imported to Brazil from sub-Saharan Africa (~40% of trans-Atlantic slave trade) (USA ~ 3.5%). Last western country to abolish slavery (1888).

Multiple independent introductions of *Plasmodium falciparum* in South America

Erhan Yalcindag1,2, Eric Elguero1,2, Céline Arnathau3, Patrick Durand4, Jean Akiana5, Timothy J. Andersc Agnes Aubovb5, François Balleub5, Patrick Besnard5, Hervé Bogaudeau6, Pierre Carnevale6, Umberto D’Alessa Didier Fontenilla7, Dionicia Gamboa1, Thibaut Jombart8, Jacques Le Mire9, Eric Leroy4, Amanda Maestnow, Mayfong Mayxaym, Didier Ménardm, Lise Musseto, Paul N. Newtonm, Dieudonné Nkoghe9, Oscar Noya9, Benjamin Ollomo9, Christophe Rogier9, Vincent Veron9, Albina Wide9, Sedigheh Zakerir, Bernard Carne, Eric Legrand9, Christine Chevillon9, Francisco J. Ayala11, François Renaud12, and Franck Prugnolle12

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"Our estimates of divergence time between the South American populations and their likely sources favor a likely introduction from Africa during the transatlantic slave trade."

[Source: Yalcindaga E, et al., PNAS 2011]
Yellow Fever Importation

“[E]stimated mean divergence time of the West African and South American clades was approximately 470 years ago [1537]...while the mean time of origin of both South American genotypes was 306 years ago [1701]. Taken together, these analyses...provide compelling support for an initial introduction during the period of the slave trade and first contact between the two continents.”

[Source: Bryant JE et al., PLoS Pathogens 2007]

Table 2. Evolutionary Rates and Divergence Times of Yellow Fever Viruses

<table>
<thead>
<tr>
<th>Data Set (n)</th>
<th>Demographic Model</th>
<th>Epidemic Doubling Time (Years)a</th>
<th>Substitution Rate ($\times 10^{-4}$ subs/site/year)a</th>
<th>Age (Years)a</th>
<th>$d_N/d_S$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brazil (38)</td>
<td>Exponential</td>
<td>26 (12, 211)</td>
<td>6.7 (3.7, 9.6)</td>
<td>96 (65, 143)</td>
<td>0.130b</td>
</tr>
<tr>
<td>Peru (25)</td>
<td>Constant</td>
<td>NA</td>
<td>8 (3.4, 13.3)</td>
<td>58 (28, 107)</td>
<td>0.191b</td>
</tr>
</tbody>
</table>
Chikungunya and Zika Endemic Ranges

Chikungunya local transmission (as of May, 2018)

Zika local transmission (as of September, 2018)

What is $R_0$ in the Ross Model?

Humans infected by an infectious human

$$amb_H/r \times ab_M/\mu$$

$$R_0 = a^2mb_Hb_M/r\mu$$
Figure 2. Decadal trends in seasonally averaged temperatures for Brazil and surrounding regions over the period 1960 to 2010. Monthly mean anomalies from CRUTEM3 (Brohan et al. 2006) are averaged over each 3 month season (December-January-February – DJF and June-July-August - JJA). Trends are fitted using the median of pairwise slopes method (Sen 1968, Lanzante 1996). There is higher confidence in the sign of trends if the 5th to 95th percentiles of the pairwise slopes do not encompass zero. This is shown by a black dot in the centre of the respective grid-box.

[Source: SN Gosling et al., University of Nottingham. Available via the Internet at http://eprints.nottingham.ac.uk/2040/7/Brazil.pdf]
Temperature and $R_0$ for Vectorborne Disease
Thought experiment
BASIC REPRODUCTION NUMBER (R0)

BITING RATE (PER DAY)

Threshold for Epidemic Spread
Baseline Biting Rate = 0.2
Baseline R0 = 0.6
Baseline R0 = 0.75
Baseline R0 = 0.9
Effect of temperature on $R_0$. 

![Graph showing the effect of temperature on $R_0$. The graph compares the relative $R_0$ values for ZIKV and DENV across different temperatures. The peak of the ZIKV curve is higher and shifts to a higher temperature compared to the DENV curve.]
Conclusions

• Global trade and travel at unprecedented levels, enhance risk (certainty?) of introduction of EID into new geographies.

• ”Seed” is necessary but not sufficient.
  • Often forget about soil ($R$, or $R_0$) when analyzing risk.

• $R_0$ not a fixed property of communicable diseases: varies with time, space, environment, and resources.

• Don’t be Dr. Beck: believe the data.