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Author(s): Deshpande, Alina

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# RED Alert – Early warning or detection of global re-emerging infectious disease (RED)

July 6<sup>th</sup> and 13<sup>th</sup>, 2016

# Agenda

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- Overview of LANL biosurveillance tools
- About RED Alert
- Demonstration of a component prototype
- Q/A
- Open discussion

# LANL's suite of decision support tools

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- A suite of tools to enhance situational awareness during an unfolding infectious disease outbreak
  - Provide actionable information
  - Provide short term forecasts
  - Facilitate outbreak investigation



An app to provide context and a frame of reference for disease surveillance information about an unfolding event, through matching of user input to a library of global historical disease outbreaks (<http://swap.bsvgateway.org/>)



A tool to facilitate obtaining disease surveillance information. Contains information on disease surveillance resources worldwide (<http://brd.bsvgateway.org>)



A tool to rapidly select appropriate epidemiological models for infectious disease prediction, forecasting and monitoring (<http://brd.bsvgateway.org>)

**EPIDEMIOLOGICAL  
INFORMATION COLLECTION**



A data collection and visualization tool for notifiable disease data around the world (<http://epic.bsvgateway.org/>)

# Biosurveillance Gateway

*Diagnostics, predictive modelling, and decision support for global and national security*

ABOUT

RESOURCES

CAPABILITIES

NEWS

OUTREACH

Welcome to the  
**Biosurveillance Gateway**

The Biosurveillance Gateway serves as a centralized portal for all news, information, resources, and research related to biosurveillance at Los Alamos National Laboratory.

## Tweets





**LANL Health** @LANL\_Health

14 Oct

.@carlzimmer on ancient Siberian #viruses - read.bi/1Lu33sR via @businessinsider pic.twitter.com/6gNjFi3Jeo

↳ Retweeted by LANL Biosurveillance

- Decision support tools offered through LANL's Biosurveillance (BSV) gateway (<http://bsvgateway.org/>)

# RED Alert

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- An analysis tool that can provide early warning or detection of the re-emergence of an infectious disease at the global level, but through a local lens
  - tool that would alert a user of local re-emergence of a disease

# RED Alert inputs and outputs

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- A user will be asked to;
  - put in a time series of a local unfolding outbreak or a recently occurred outbreak
  - add in associated outbreak history together with auto-population of some data
  - select a historic duration of time to compare local disease incidence to
- RED Alert will;
  - Calculate a disease incidence for the unfolding/recent outbreak and the historic duration of time selected by user
  - Determine if there is increased incidence
  - Bin outbreak history into various categories of causes and determine most likely cause of increased incidence
  - Alert the user about a re-emergence and likely cause
  - Provide a visual of the global context for the local re-emergence

# Timeline

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- Prototype by December 2016
  - Proof of principle using two diseases;
    - Measles
    - Dengue
    - Case studies for demonstration of prototype
      - Measles in the US 2014
      - Dengue in Brazil 2010
  
- Final application: November/December 2017

# RED Alert primary components

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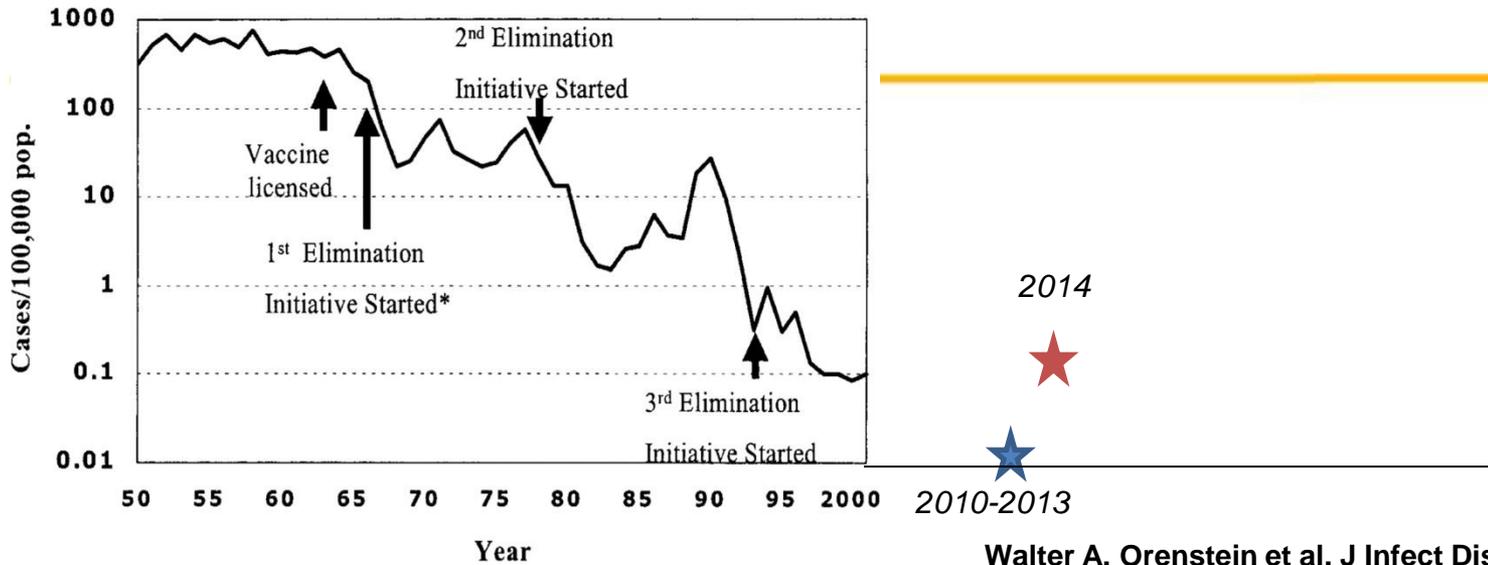
- Algorithm that generates an alert to indicate re-emergence if a calculated “re-emergence” threshold has been crossed for a *local* unfolding event
- Algorithm that provides the user with the most likely cause(s) of the re-emergence of an infectious disease at the *local* level
- To understand global re-emergence, a data visualization component to help the user rapidly understand the local outbreak in the context of global occurrence of the same disease

# The alerting algorithm

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- An algorithm with the following parts;
  - A disease incidence calculator for the time window specified by the user (cases/100,000 population)
  - Comparison to previous incidence for that location or area
    - Default comparison to past three years data if available
    - Custom comparison for user's preference of historical time window
  - **1st flag** if increased incidence

# Reported US measles incidence, 1950–2001. \*, First initiative was termed "eradication."



Walter A. Orenstein et al. J Infect Dis. 2004;189:S1-S3

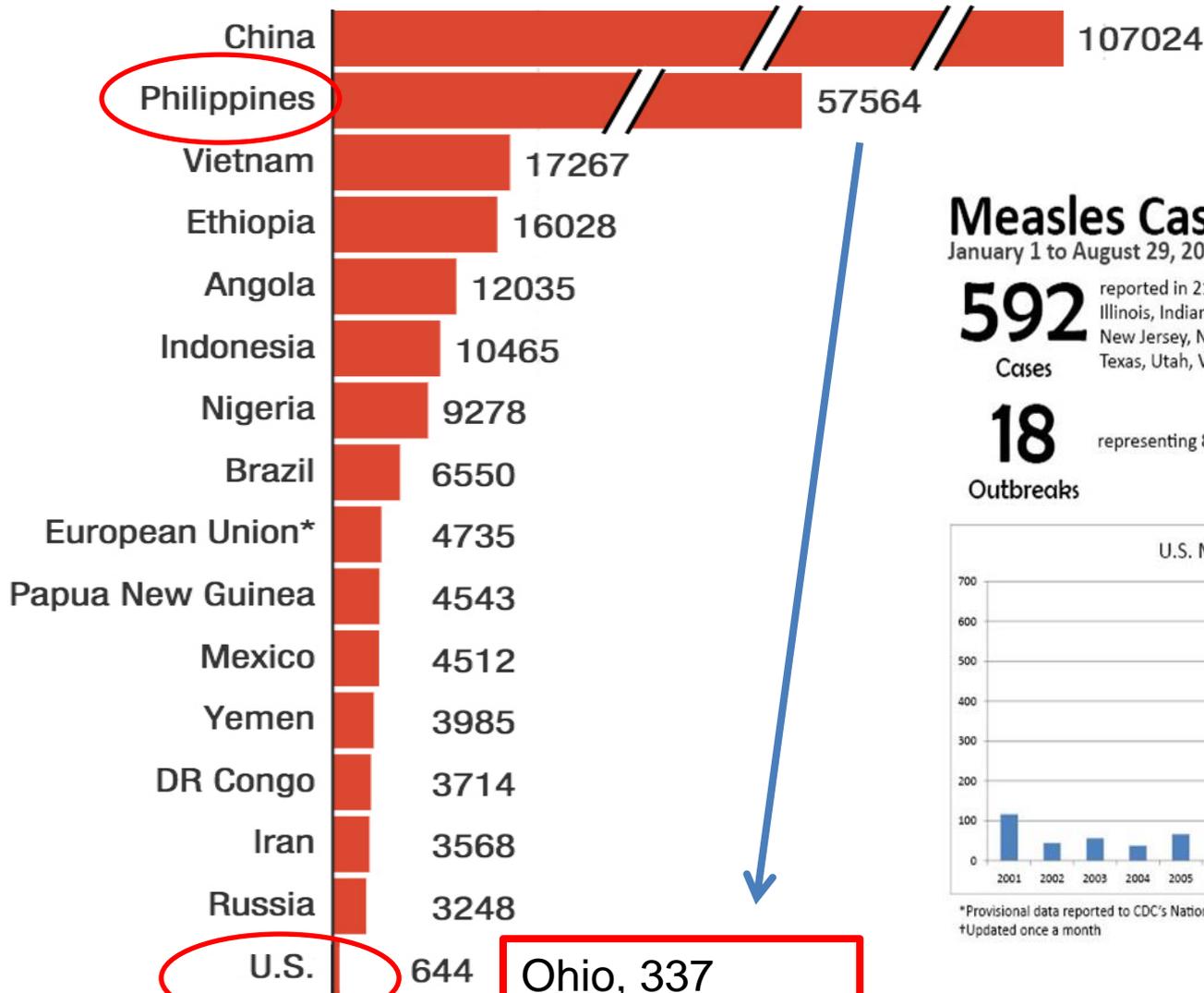
Year	Incidence
2010	0.012
2011	0.031
2012	0.002
2013	0.015
2014	0.131



UNCLASSIFIED

# Global context of local outbreak

## Reported Measles Cases In 2014



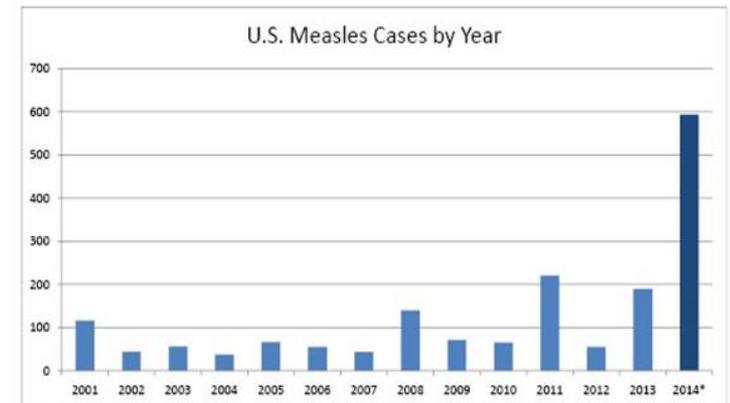
Ohio, 337 cases

## Measles Cases and Outbreaks

January 1 to August 29, 2014\*†

**592** Cases reported in 21 states: Alabama, California, Connecticut, Hawaii, Illinois, Indiana, Kansas, Massachusetts, Minnesota, Missouri, New Jersey, New York, Ohio, Oregon, Pennsylvania, Tennessee, Texas, Utah, Virginia, Washington, Wisconsin

**18** Outbreaks representing 89% of reported cases this year

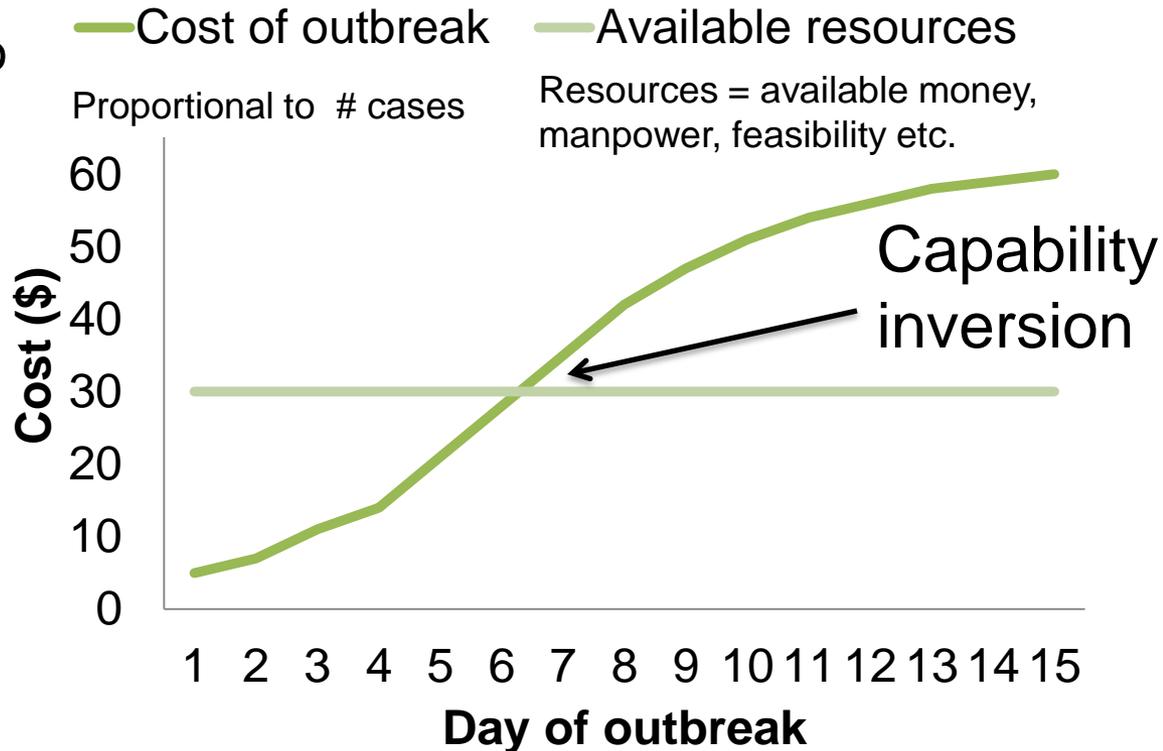


\*Provisional data reported to CDC's National Center for Immunization and Respiratory Diseases  
†Updated once a month



# The alerting algorithm

- Comparison of outbreak to local resource capacity
  - Hypothesis: outbreak or re-emergence means something different if you don't have the resources to handle it. *We want to know both*
- **2<sup>nd</sup> flag** if capability inversion seen



# Algorithm for most probable cause

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- Develop framework to understand disease specific causes of re-emergence
  - Causes of re-emergence binned into host, pathogen and environmental categories (sub categories)
    - Environmental factors include physical factors such as geology and climate, biologic factors such as insects that transmit the agent, and socioeconomic factors such as crowding, sanitation, and the availability of health services
- (<http://www.cdc.gov/ophss/csels/dsepd/ss1978/lesson1/section8.html>)
- Adapt Rothman's causal pie model for disease occurrence to determine most probable cause for re-emergence

# Framework for binning causes of re-emergence

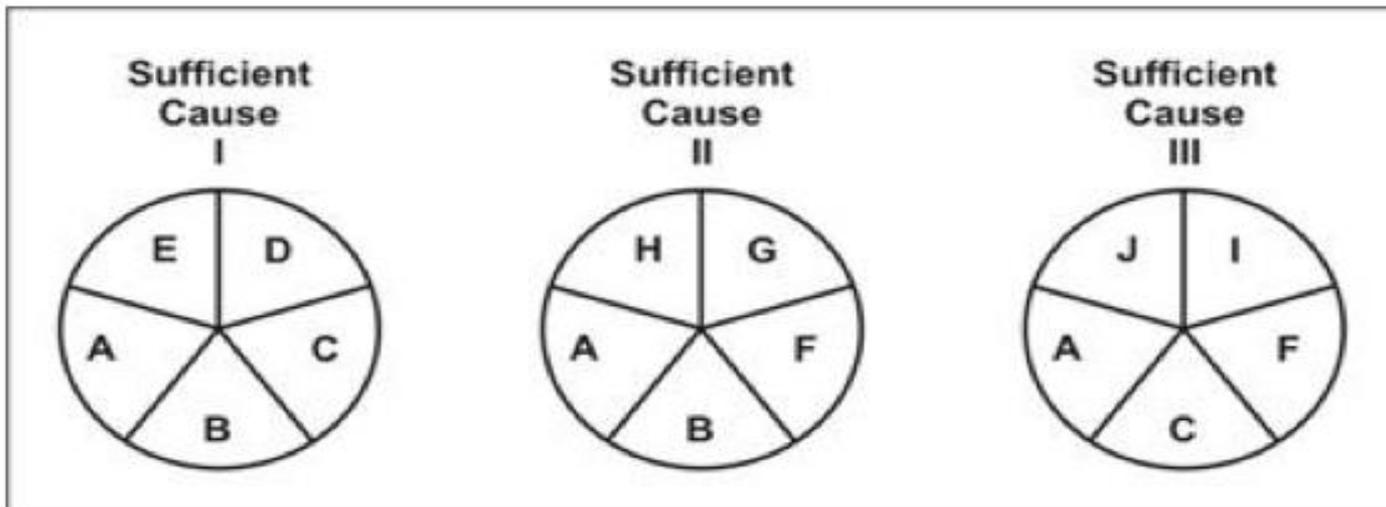
Microbial Agent	Human/Animal/Plant Host	Host Environment
Genetic adaptation and change	Susceptibility to infection	Climate and weather
Polymicrobial diseases	Demographics and behavior (human)	Changing ecosystems
	International trade and travel	Economic development and land use
	Occupational exposures	Technology and industry
	Antibiotic use	Poverty and social inequality
		Public health service quality and quantity
		Animal populations
		War and famine
		Political will

Adapted from Morens DM, Fauci AS. Emerging infectious diseases: Threats to human health and global stability. PLoS Pathog 9(7): e1003467. doi:10.1371/journal.ppat.1003467, 2013

# Features of sufficient-component cause model

- A sufficient cause is not a single component, but a minimal set of conditions or events that produces the outcome (disease occurrence) – sufficient causal pie
- Each component in a sufficient cause pie is called a “component cause” - the outcome will not occur by that pathway if any one of the components is missing (or prevented)
- There may be a number of sufficient causes (and therefore pies) for a given disease or outcome
- A component cause that must be present in every sufficient cause of a given outcome is referred to as a “necessary cause”. For example, HIV exposure is necessary for AIDS to occur, and TB exposure is necessary for TB infection to occur.

**Figure 1.17 Rothman's Causal Pies**



[Image Description](#)

Rothman and Greenland. Causation and Causal Inference in Epidemiology. American Journal of Public Health:2005, 95(S1): S144-S150. doi:10.2105/AJPH.2004.059204  
**Cited 563 times. Original paper cited 655 times**

# Further.....

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- The probability of the presence of all component causes (or risk factors) of a pie chart is the product of the probabilities of the presence of each individual component cause
- If A–D are all the component causes of causal pie I,  
$$P(I) = P(A)P(B)P(C)P(D).$$
- If there are more than one sufficient causes I–III (causal pies) for outcome  $\Omega$ ,  
$$P(\Omega) = P(I) + P(II) + P(III).$$
- A strong cause is a component cause that plays a causal role in a large proportion of the cases, whereas a weak cause would be a causal component in a small proportion of cases

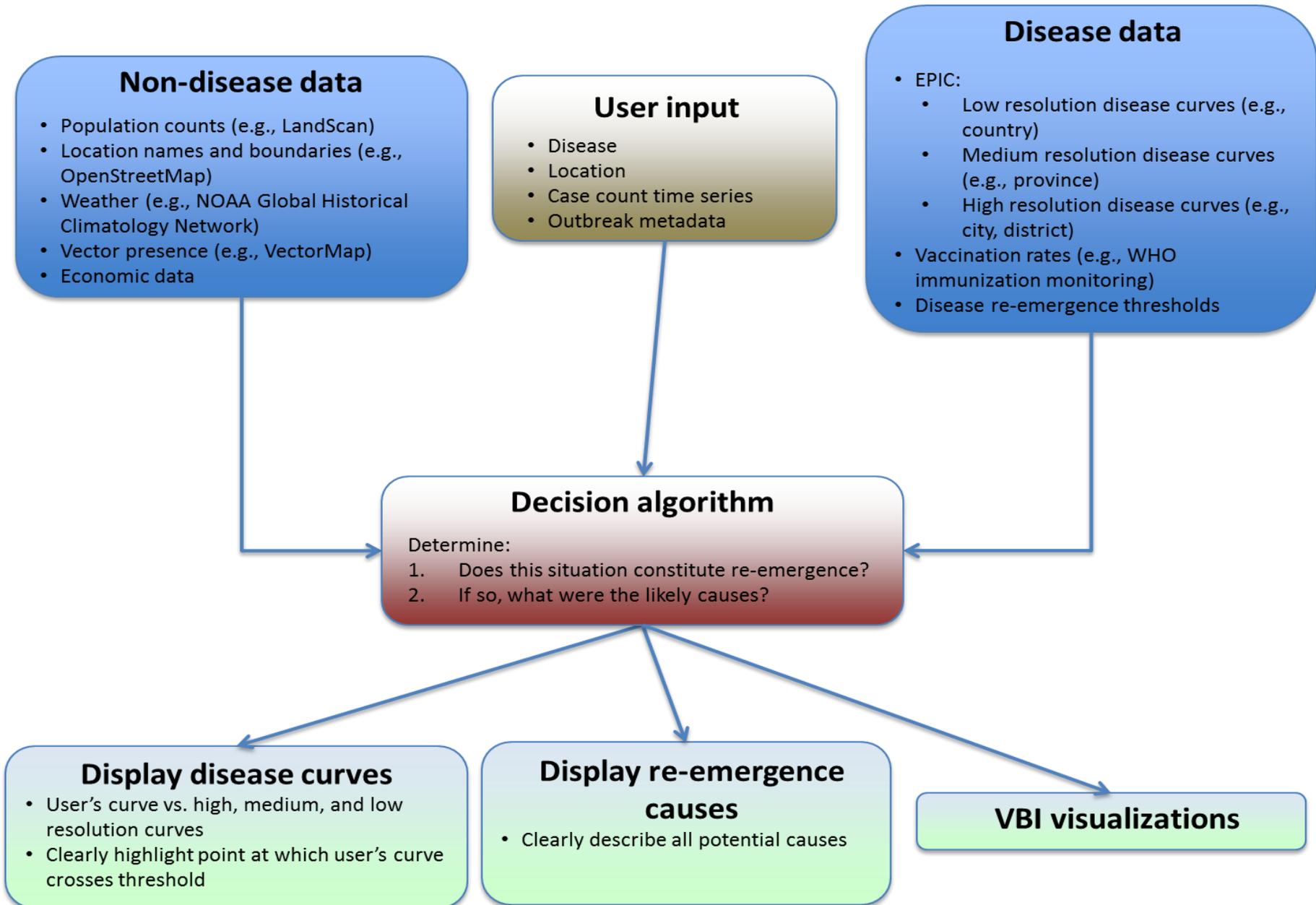
# Algorithm work flow

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- For a given disease, collect and analyze data on historical outbreaks that indicated re-mergence and develop sufficient component causal pies
- Compare pies to identify component causes that are;
  - Necessary, strong and weak causes to build probabilities or weights
- Use some form of multiple regression approach to develop algorithm that identifies most probable cause for a given occurrence of re-emergence
- Bin component causes into host, environment and pathogen categories to facilitate generalizing probabilities across diseases (e.g. pathogen presence, new serotype presence)



# RED Alert Schema



# Data Sources

## World population

- **LandScan**
- WorldPop
- GPWv(3|4)

## Location names/boundaries

- **OpenStreetMap**

## Weather

- NOAA Global Summary of the Day (GSOD)
- **NOAA Global Historical Climatology Network (GHCN)**

## Vector Density

- **VectorMap**
- Discover Life

## Vaccination rates

- **WHO immunization surveillance**

## Economic factors

- TBD

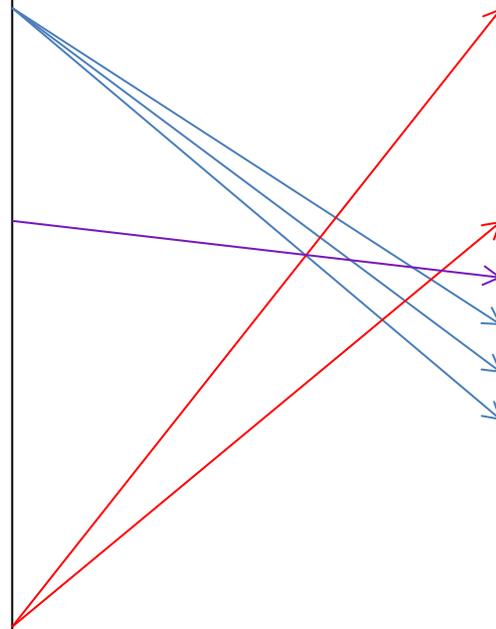
# Case study matrix

## List of diseases

EVD and Marburg (Filovirus diseases)  
Crimean Congo Hemorrhagic fever  
Yellow Fever  
Dengue/DHF  
Highly pathogenic Coronaviruses (e.g. SARS, MERS, PEDV)  
Vaccine preventable diseases (Measles, Diphtheria, Yellow fever)  
Influenza (Avian, Swine)  
Lassa Fever  
Rift Valley Fever  
Nipah  
Plague

## List of countries

USA  
Peru/Brazil  
Georgia  
Vietnam  
India  
Egypt  
Liberia  
Sierra Leone  
Guinea  
Uganda



## Criteria for selection of disease location pairs

- WHO regions, COCOMS, Species, Mode of transmission, Type of data availability

## Case studies will be used to;

- Build RED Alert and demonstrate proof of principle
- Demonstrate the functionality of RED Alert

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# Demo of prototype visualization component for global context of re-emergence

## Virginia Bioinformatics Institute

# What do we need from the SME panel?

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- Your expert opinion and feedback on the proposed approach for RED Alert
- Your guidance on algorithms that we are developing
- Recommendations for data sources and points of contacts for them
- Recommendations for diseases and locations for case studies
- We will send you a questionnaire for written feedback **requested by the end of July**
  - Feedback will be analyzed and a report generated that will be made available to you at a later date in 2016.

# What do you get from this effort?

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- Co-authorship in peer reviewed publication(s)
- Recognition on reports to DTRA
- New contacts in the infectious disease surveillance field outside of your area of focus

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**Thank you for your time today!**

Questions?

# Task 1 and 2: Dengue in Brazil

- Background:
  - 1982: DENV-4 in Roraima
  - 2010: <30 cases DENV-4 identified in Roraima
  - 2012-2013 Minas Gerais, Brazil, ~ 500,000 dengue fever cases; many thought to be DENV-4
- Task 1: When to alert? What ‘counts’ as re-emergence?
  - Incidence changes
- Task 2: What caused the re-emergence
  - Sequence of events (serotypes, vector control, climate etc)
  - Literature



# Denv-4 Re-emergence

All changes saved in Drive

Add layer Share

Dengue-4 Locations 2005-2013

Sequence of color and letters

- A Boa Vista
- B State of Minas Gerais
- C Manaus
- D State of Piauí
- E State of Pernambuco
- F State of Bahia
- G Rio de Janeiro
- H State of Ceará
- I São Paulo

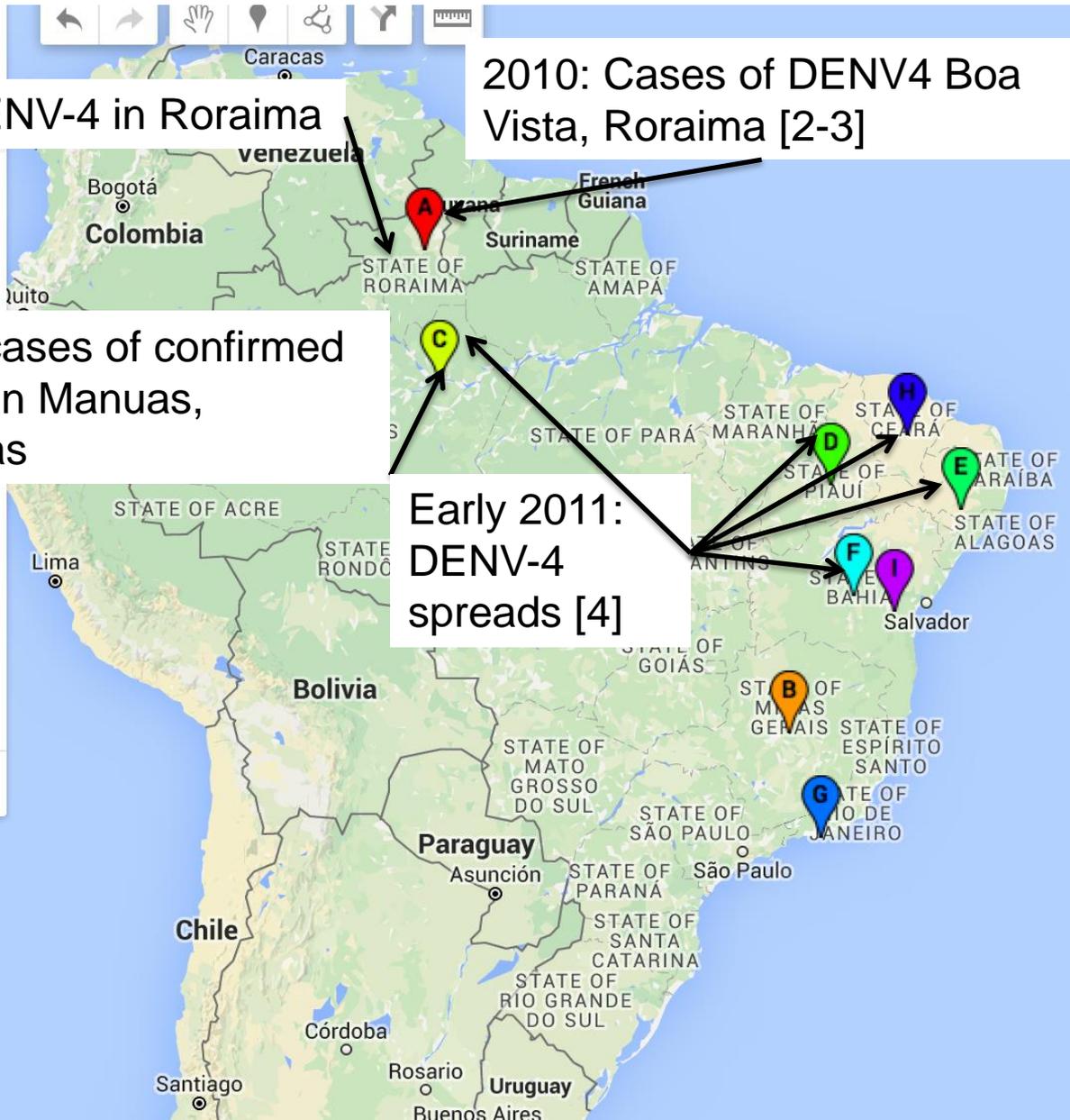
Base map

1982: DENV-4 in Roraima

2010: Cases of DENV4 Boa Vista, Roraima [2-3]

2005: 3 cases of confirmed DENV-4 in Manuas, Amazonas

Early 2011: DENV-4 spreads [4]



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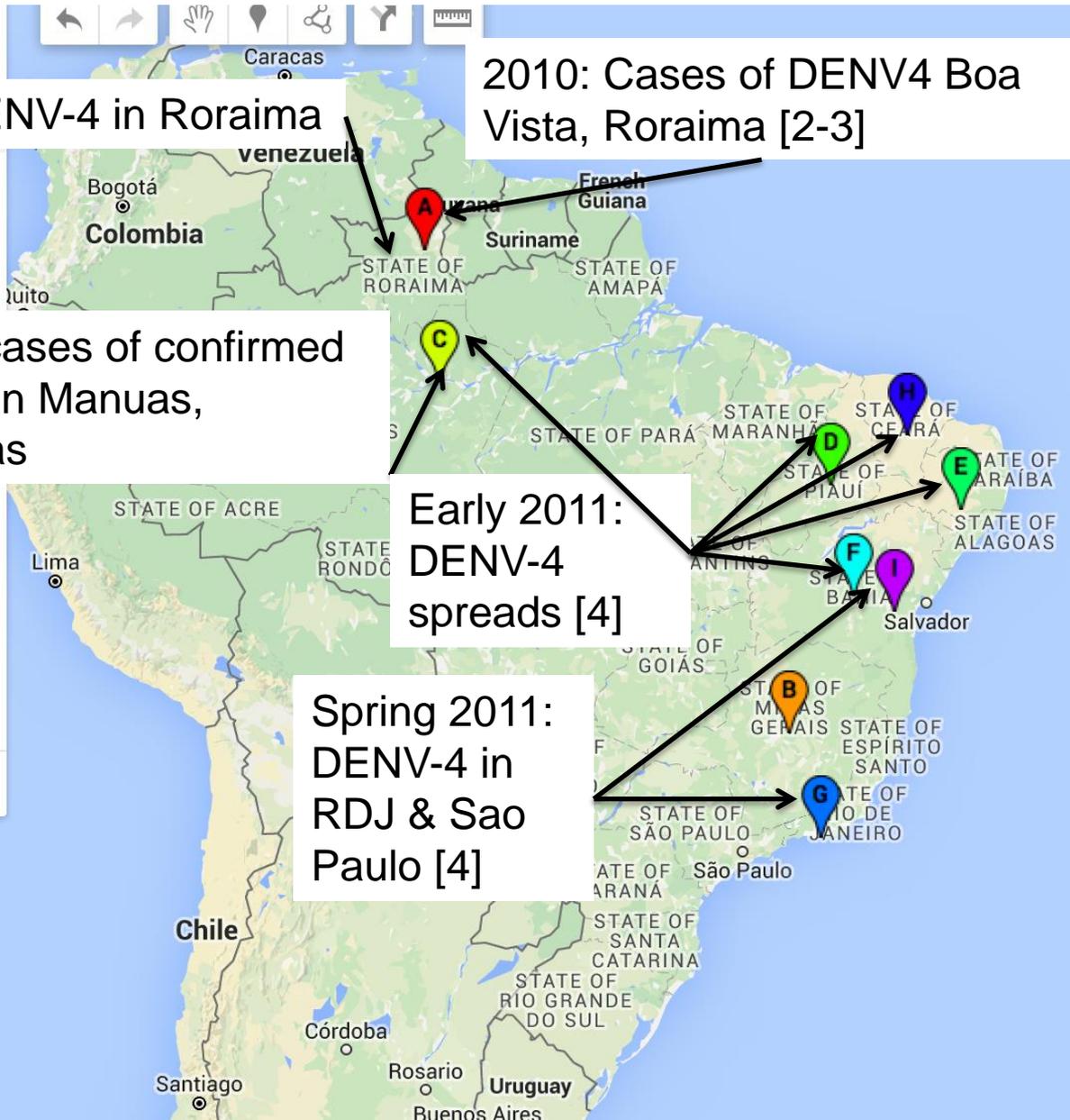
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2005: 3 cases of confirmed DENV-4 in Manuas, Amazonas

Early 2011: DENV-4 spreads [4]

Spring 2011: DENV-4 in RDJ & Sao Paulo [4]



# Denv-4 Re-emergence

All changes saved in Drive

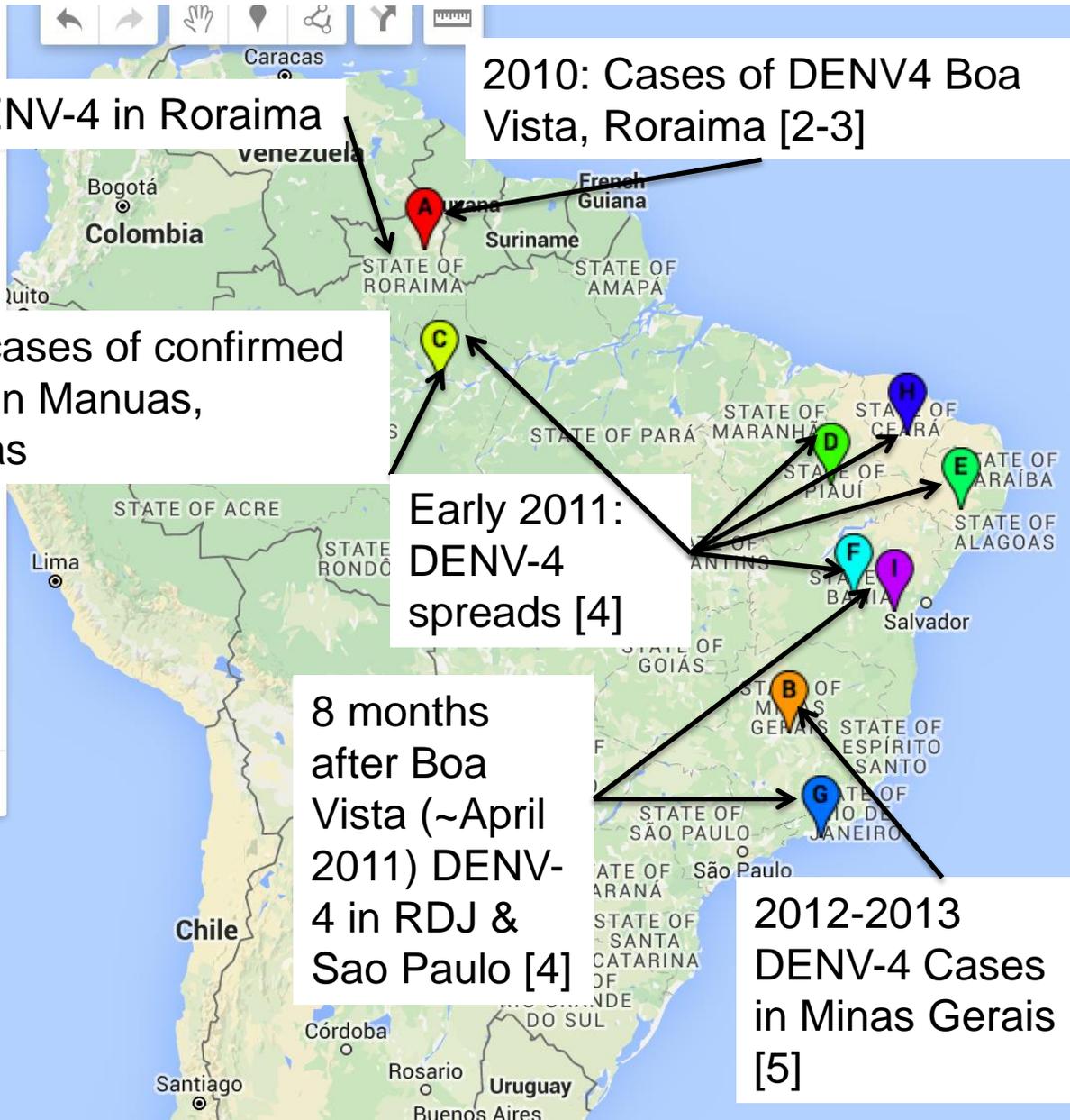
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Base map



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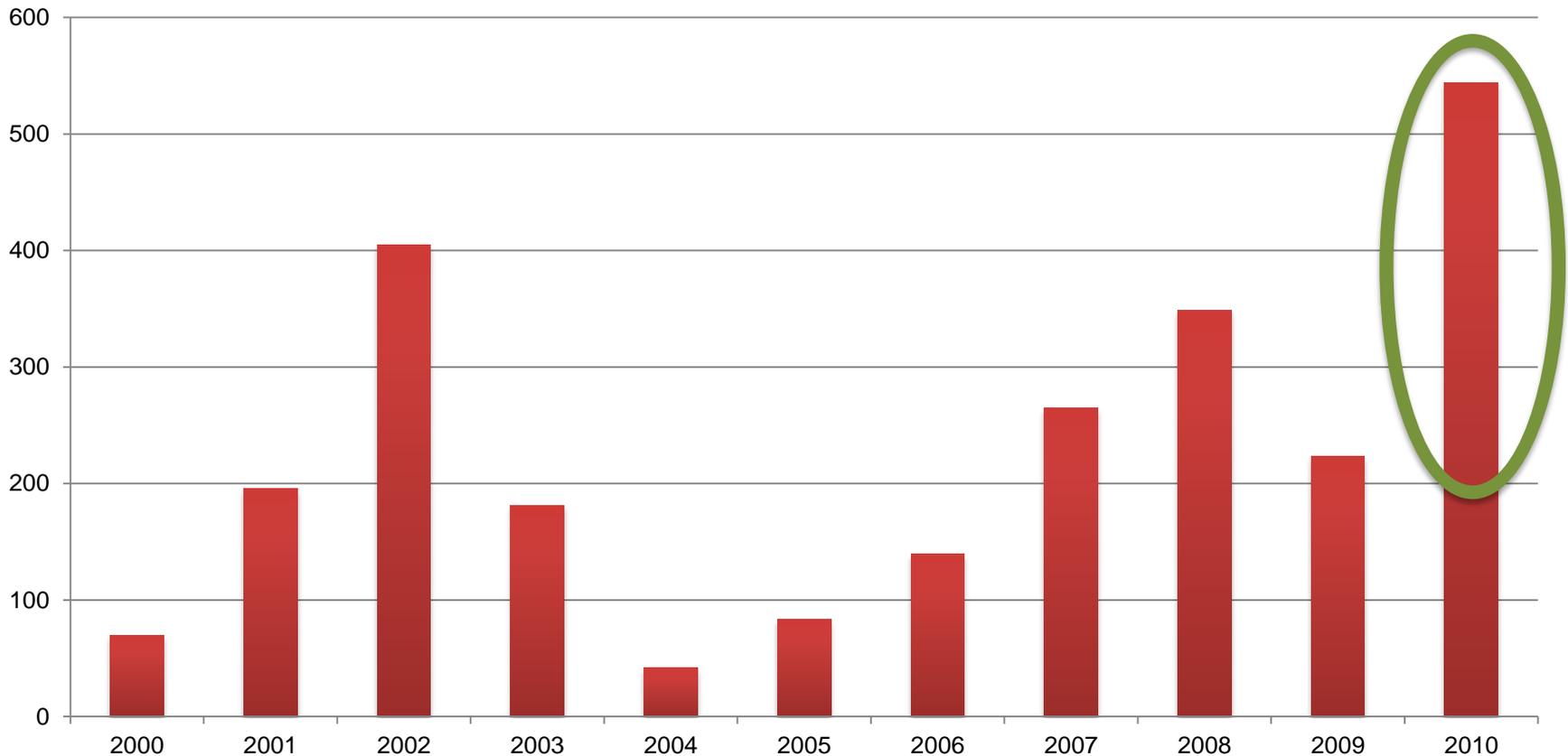
8 months after Boa Vista (~April 2011) DENV-4 in RDJ & Sao Paulo [4]

2012-2013 DENV-4 Cases in Minas Gerais [5]

# Algorithm 1: Calculating disease incidence

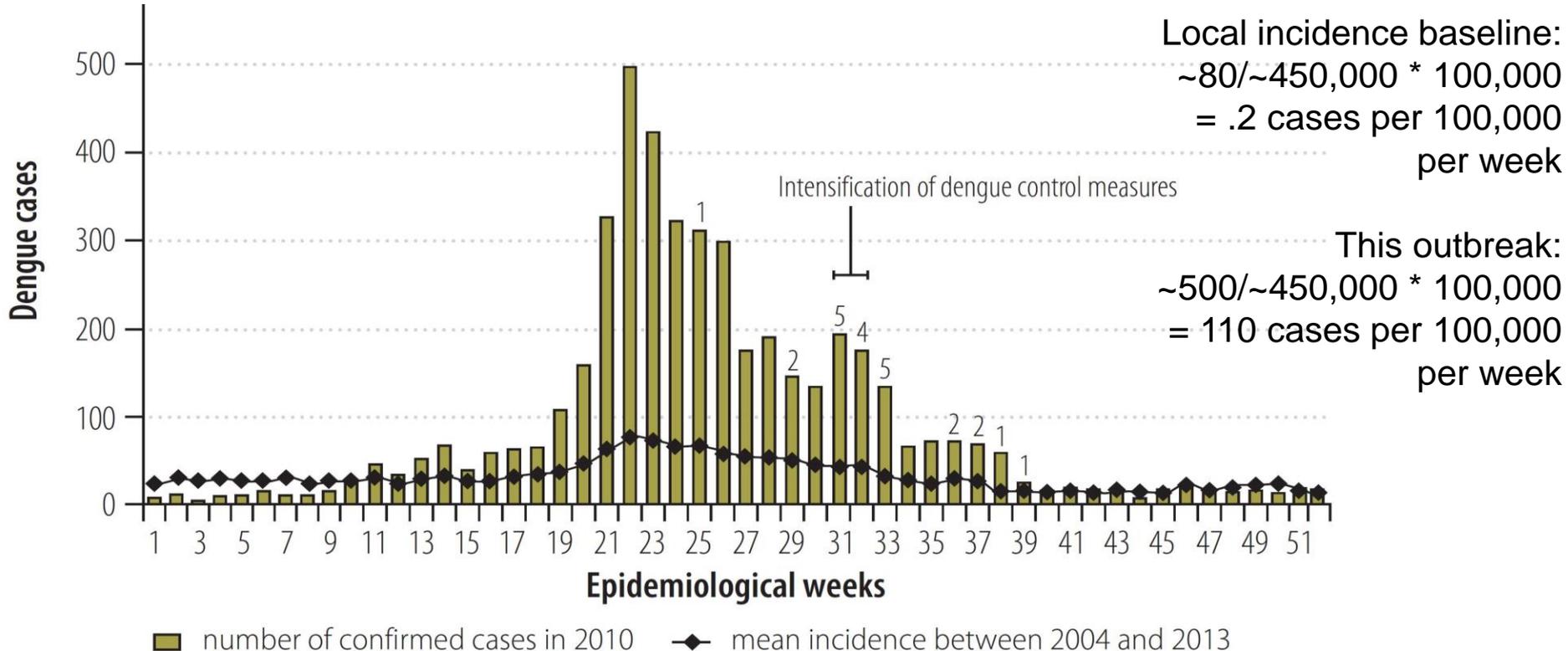
- All strains; all Brazil

Dengue Incidence per 100,000 Brazil



# Local dengue incidence – 2010 Roraima

- Roraima Population:
  - least populated area of Brazil
  - ~350,000 to ~380,000 2003-2005
  - <500,000 in 2010 [1]



“endemic channel plus two standard deviations method ... [and] requiring two successive weeks above the threshold before response activity is triggered” [2]

However... there are a lot of outbreak definition options (see Brady et al. [3]) It's not always clear which to use. For our purposes go to SMEs

# Example: Dengue

- Background:
  - 1982: DENV-4 in Roraima
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  - **Sequence of events (serotypes, vector control, climate etc)**



# Component Cause Model for Dengue Re-Emergence in Roraima

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	Necessary component cause	Other component causes
Microbial Agent	New serotype [1]	NA
Human/Animal/Plant Host	Susceptible population [1]	Age (more cases among children) [3]
Host Environment	Vector present [1]	Increased vector (via weather patterns, poorer vector control etc.)  Social factors (, urbanization) [2]  Increased exposure to vectors