

# Scientifically Relevant Issues for Large Outbreaks/Epidemics

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# Objectives

- **Review key scientific elements of epidemic responses**
- **Approaches to H1N1 and Ebola**
- **Role of modeling**
- **Need for and challenges of scientific decision-making in the midst of uncertainty**

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# ***Steps in Investigating an Outbreak***

- 1. Confirm there is an outbreak (vs pseudo-outbreak)**
- 2. Gather descriptive information**
  - a. determine etiology (cause)
  - b. describe the outbreak by person, place, and time  
including magnitude (# cases, how widespread)
  - c. write a case definition
  - d. conduct surveillance for more cases, including a line listing
- 3. Take immediate control measures as able**
- 4. Generate hypotheses for risk of spreading (e.g., interviews)**
- 5. Test hypotheses for risk factors**
  - a. gather data relevant to the hypothesis
  - b. design and analyze a study
- 6. Determine control measures**
- 7. Prevent more illnesses, deaths**
- 8. Communicate**

# Implementing control measures

- Ultimately, primary goal is to stop transmission
- Likely will need to implement a variety of control measures targeting various possibilities based on initial observations and incomplete information
- Be flexible to adapt as information available
- Communication is critical



# Information Needed

- **Varies by disease, modes of transmission (if known); in part depends who is affected, on control measures needed**
  - For influenza, don't need to identify every case
  - For Ebola, need to identify all cases AND their contacts: follow all contacts for 21 days
- **Some available through surveillance**
- **Some assessed via investigation**
  - hypothesis generation
  - outbreak studies
- **Some assessed via modeling**
- **May change over time**

# Need to Monitor over Time for Changes

- Track appearance, rise and fall, and movement of virus
- Changes in:
  - rates of morbidity (illness) or mortality (death)
  - age distribution of morbidity or mortality
  - transmissibility
  - clinical pattern of disease
    - New or unusual presentations
    - Clinical course – e.g. bacterial co infections, viral pneumonias, pulmonary emboli
    - Risk groups: e.g. obesity, pregnant, age, others?
  - severity
  - virus
    - Antigenicity, mutations related to virulence, and antiviral sensitivity
- Strain dominance

# Some Primary Challenges

- **Time pressure**
- **Need to produce information quickly to meet demand**
  - Health infrastructure in country very busy with response
- **Communication of preliminary / incomplete information**
  - Need to develop different messages for different audiences
    - May need to conduct studies to understand how to effect behavior change
  - Challenges of misinformation
- **Public demand for information that was not useful; media biases**
- **Legal, political, and financial pressures**
  - Numbers of cases
- **Completeness and reliability of data;**
  - statistical power
  - Delays in obtaining human or environmental samples
- **Countries are different**
  - Ability of countries to collect and report data is different
- **Need to reorganize public health quickly to meet the demand**



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**Epidemic: H1N1**

## Swine Influenza A (H1N1) Infection in Two Children – Southern California, March–April 2009

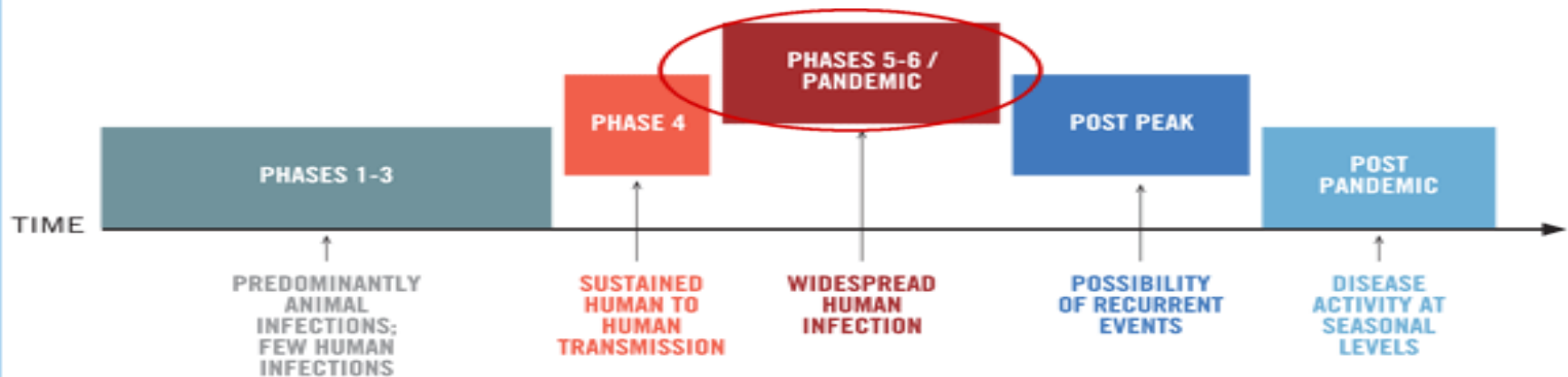
*On April 21, this report was posted as an MMWR Early Release  
on the MMWR website (<http://www.cdc.gov/mmwr>).*

# Novel Influenza A (H1N1) Detected



- March 2009
  - 2 cases of febrile respiratory illness in children
  - No common exposures, no pig contact
  - Uneventful recovery
  - Residents of adjacent counties in southern California
- Reported to CDC as possible Novel influenza A virus infections
- Swine influenza A (H1N1) virus detected on April 15<sup>th</sup>, 17<sup>th</sup> at CDC
- Both viruses genetically identical
  - Unique combination of gene segments previously not recognized among swine or human influenza viruses in the US

## PANDEMIC INFLUENZA PHASES



**June 11, 2009**

“On the basis of available evidence, and these expert assessments of the evidence, the scientific criteria for an influenza pandemic have been met. I have therefore decided to raise the level of influenza pandemic alert from phase 5 to phase 6. The world is now at the start of the 2009 influenza pandemic.”

- Dr Margaret Chan, Director-General of the World Health Organization

# 2009 H1N1 Influenza Disease Burden Estimates for April 2009 – March 13, 2010

▪

2009 H1N1	Mid-Level	Estimated Range
Cases	~60 million persons	~43 M to ~88 million persons
Hospitalizations	~270,000 persons	~192,000 to ~398,000 persons
Deaths	~12,270 persons	~8,720 to ~18,050 persons

# H1N1 Pandemic

- **First pandemic since 1968**
- **Initially, unknown if greater severity**
  - Reports from Mexico of severe hospitalizations/deaths
  - Lack of information regarding community illness
- **Initial concerns whether different transmission patterns from seasonal flu**
- **Initially no available vaccine**
  - Rapid manufacture of vaccine candidate but estimated a minimum of 4-6 months to start developing supply
  - Would there be safety concerns with a 'new' vaccine
- **Inadequate global supplies of antiviral medications**

# Seasonal vs Pandemic Influenza

## □ Seasonal Influenza – Generally known:

- Incubation period
  - 1-7 days (mainly 2-3 days)
- Modes of transmission
  - Can be contagious starting about a day before illness – greatest during fever
  - May be contagious for about 5-7 days. Longer in some people
  - Mainly through large droplets (within about 6 feet) and aerosol; some contact (fomite) possible
- Known high risk groups (e.g., extremes of age, co-morbid conditions)
- Mortality rates (which can be strain-dependent)
- Prevention/control mainly through vaccination. Also e.g., through antiviral agents, good hygiene, infection control, social distancing
- Antiviral therapy available for high risk groups and those severely ill

## □ Are these all true for a new pandemic strain???

- Always a question when a new strain starts to circulate
- No prior immunity

# Key Indicators

Influenza activity is monitored by various approaches, primarily with key indicators:

- Virus characteristics
- Geographic spread
- Outpatient illness reports (clinics and emergency rooms)
- Hospitalizations, including ICU
- Deaths



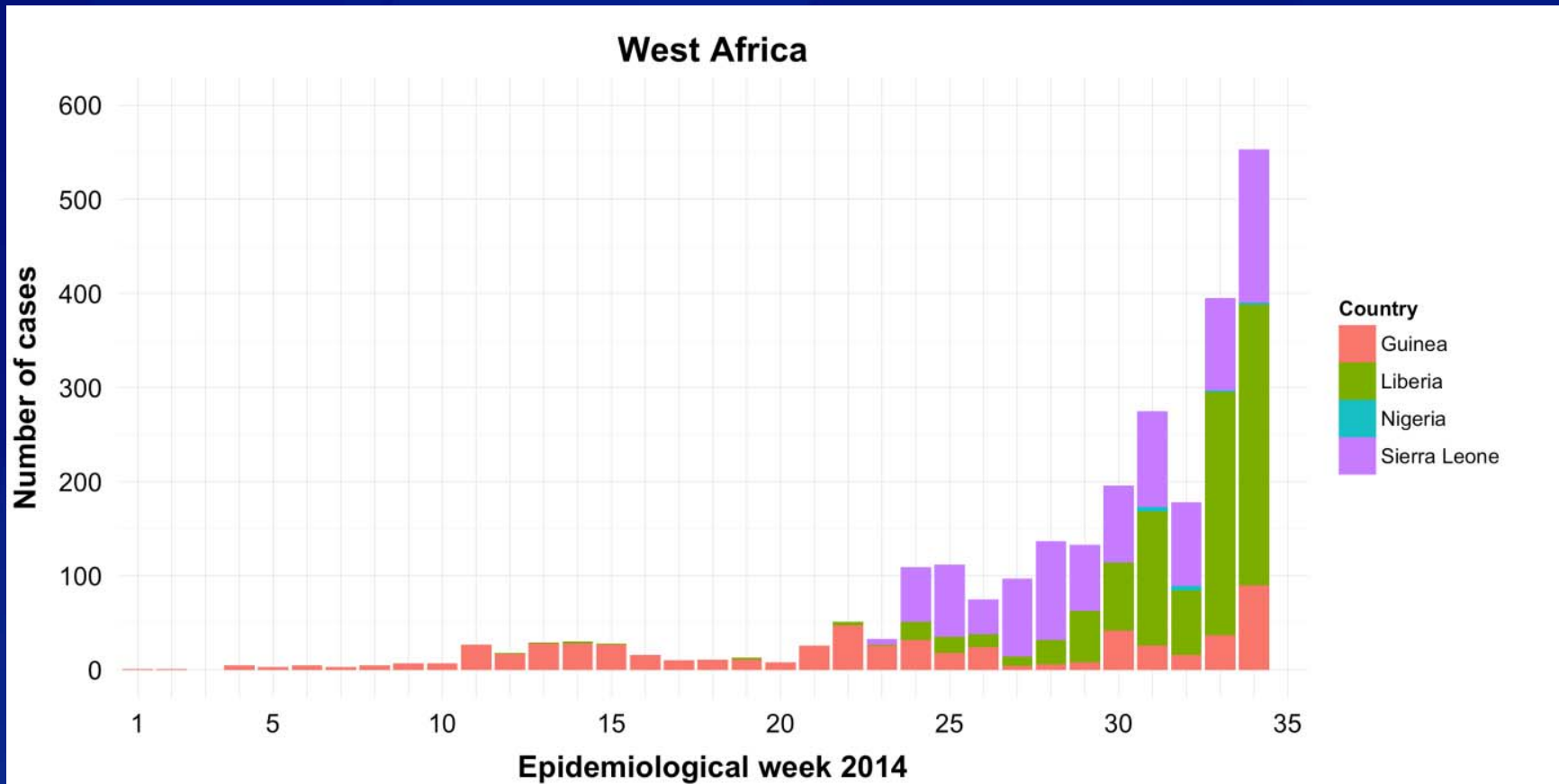
# Assessment of Influenza Pandemic Severity

- **Severity is not an intrinsic characteristic**
  - Varies with population vulnerability and capacity of health care system
  - Important to evaluate all data in context
- **Composite picture of severity**
  - Crude influenza-related mortality rates
  - Age specific mortality
  - ICU/Hospitalization, Death/Hospitalization
  - Proportion with co-morbid (underlying) conditions
  - Clinical pattern of disease
  - Impact on health care infrastructure
  - Absenteeism
- **Based on both formal and informal information sources**

# Epidemic: Ebola

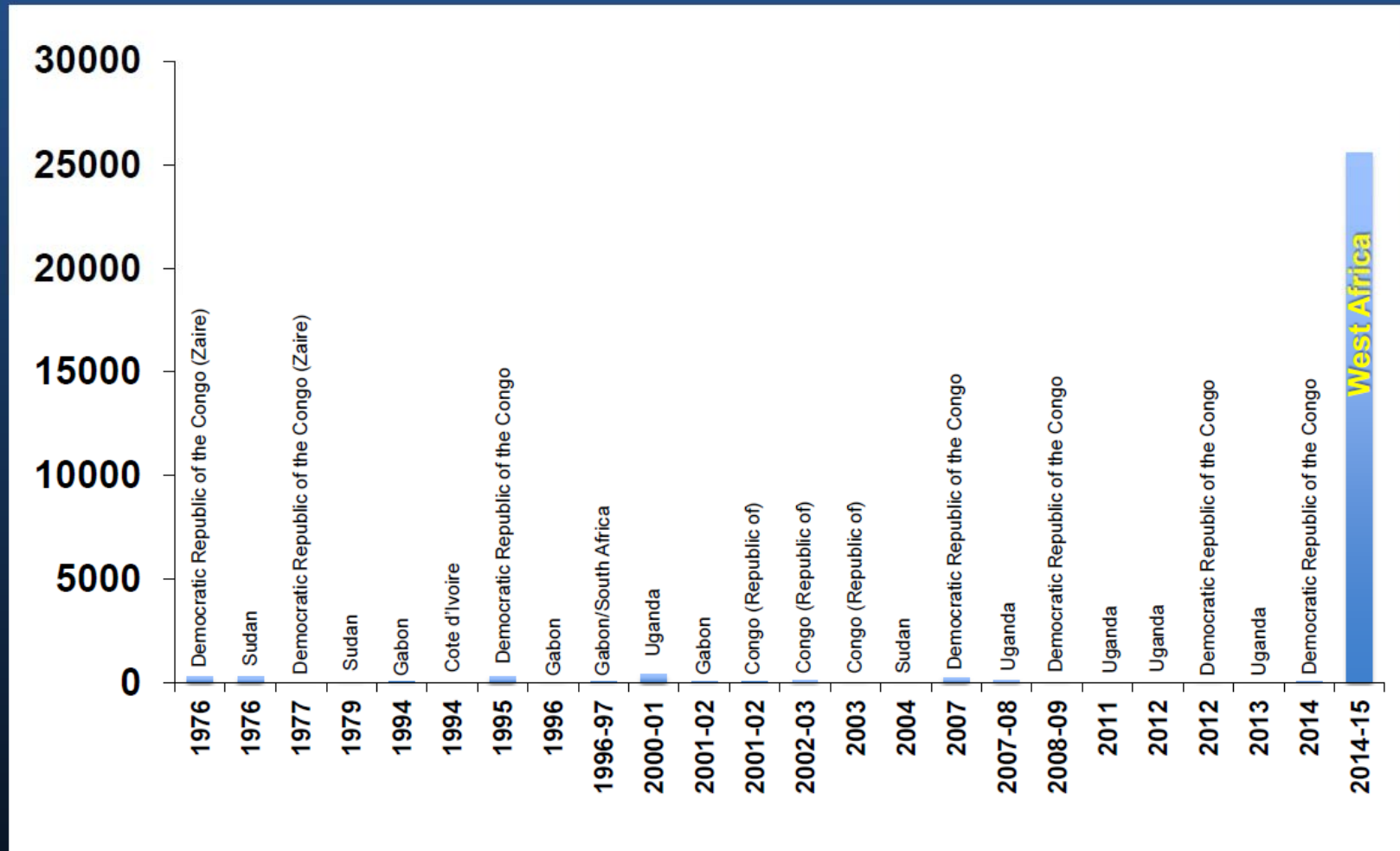


## Cases by Week, January 2014 through August 25, 2014

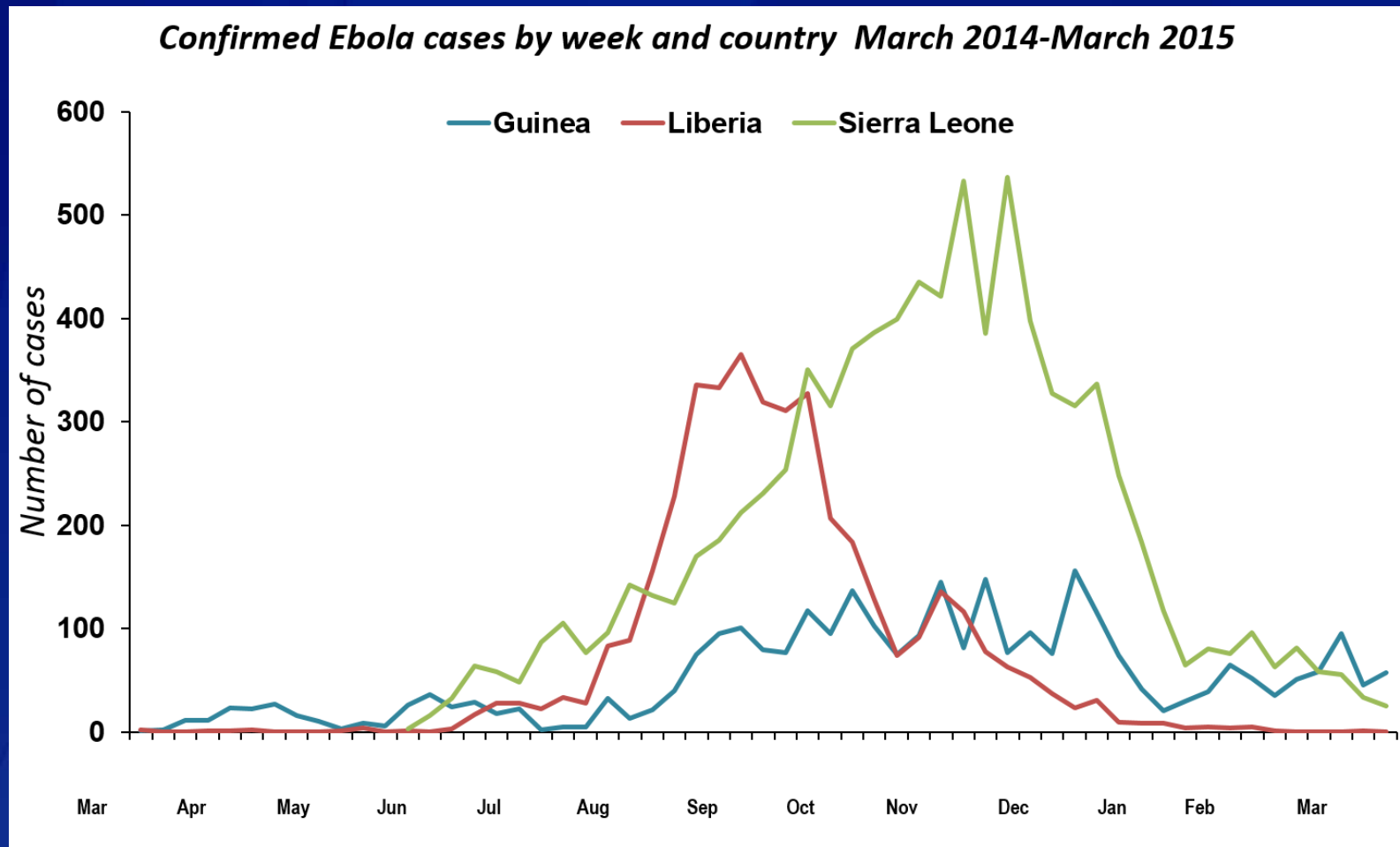


Source, WHO Website

There have been  $>10x$  more cases during the current Ebola epidemic than in all other outbreaks combined



# Ebola response resulted in exponential decreases in Liberia then Sierra Leone



As of May 3, 26,536 reported (suspected, probable, and confirmed) cases, 10,980, reported deaths.

# Information Generally Known About Ebola

- **Scientific Information for Ebola (used for control):**
  - Incubation period: 2-21 days (median 8-10 days)
  - Modes of transmission
    - Contagious only after sick
    - Through direct contact (through broken skin or unprotected mucus membranes) with a sick person's blood/body fluids
    - Through contaminated objects (e.g., needles, syringes)
    - Through infected bats/primates
    - Possibly through semen from survivors
  - Known high risk groups (e.g., healthcare workers, household contacts, burials)
  - Mortality rates (typically 50-90%)
  - Clinical picture (fever, headache, fatigue, diarrhea, vomiting, stomach pain, bleeding, muscle pain)
  - Prevention/control through isolation/contact tracing, infection control, safe burials, communication
  - Has something changed in any of this during this outbreak?

# Overall Goals in Outbreak Response

- ❑ **Stop human-to-human transmission**
  - Case identification
    - Isolation/care
    - Limitations-> ETU/CCC needs
  - Contact tracing
  - Infection control
  - Safe burials
  - Health communication
- **Prevent spread to other countries**
- ❑ **Improve patient care**
  - Triage
  - Experienced staff
  - Strict use of personal protective equipment



# Examples of Basic Information Collections Needed for Ebola Response

- ❑ **Identify all cases**
- ❑ **Laboratory confirmation**
- ❑ **Identify all contacts**
  - Usually entails detailed information of cases' activities and movement, possible mode of transmission – healthcare, burial, household, etc.
- ❑ **Up-to-date information on availability and location of treatment beds, holding/assessment centers**
  - Availability of personal protective equipment (PPE)
    - Gowns, gloves, masks, boots, etc.
  - Availability of laboratory testing
- ❑ **Movement patterns**
- ❑ **Cultural practices (e.g., burials)**
- ❑ **Key audiences for dissemination of information**



# Additional Information to Help Determine Priority Control Measures

- ❑ Can help to target interventions, especially when overwhelmed systems
- ❑ High risk groups, morbidity/mortality rates
- ❑ **Transmission**
  - Relative contribution of different transmission patterns?
    - Healthcare, burials, households? May vary by geographic area and culture patterns
    - Role of sexual transmission?
  - Role of persistence in the environment?
  - Role of movement (need for travel restrictions?)
  - Potential changes in transmission patterns?
  - When persons are infectious – degrees of infectivity over time
  - Possible role of asymptomatic infections?

# Additional Information to Help Determine Priority Control Measures - 2

## □ Possible determinants of severity of illness

- Changes in virus?
- Characteristics of patients?
  - Age
  - Other underlying conditions
  - Time to seeking healthcare (early treatment → better survival)
  - Medical interventions

## □ Effectiveness of control strategies

- Safe burials – culturally sensitive ways
- Adequate contact tracing? If not, is there a need for active case finding?
  - Possible markers for adequacy contact tracing include:
    - Are there unexplained chains of transmission?
    - Are there adequate numbers of contacts identified?

## □ Scan of information/misinformation circulating

- Information needed to educate regarding behavioral change(s)

# Unanswered Questions and Innovations

- May be only opportunity to answer scientific questions important to control current and/or future responses and understand the agent better – e.g., for Ebola...
  - Duration of shedding of Ebola virus in semen
  - Household transmission studies
  - Virus mutation rates
  - Diagnostics
    - E.g., rapid diagnostics that can be done close to patient
  - Therapeutics
  - Vaccines

## Some General Challenges to Studies

- ❑ Need to ensure do not interfere with outbreak response
- ❑ Time for development, clinical trials, and approvals
- ❑ Infrastructure needs, especially in low resource settings
- ❑ Ethical issues and cultural challenges
- ❑ Legal, policy, and financial challenges of public-private partnerships
- ❑ Compliance with federal regulations
- ❑ Costs associated with development
- ❑ Appropriate treatment continues



# Outbreak Challenges in West Africa

- ❑ Porous borders
- ❑ High population mobility
- ❑ Geographic breadth



# Outbreak Challenges in West Africa

## Overburdened Public Health and Healthcare Systems

- ❑ Unpaid healthcare workers
- ❑ Insufficient treatment centers, beds, medical supplies, and personal protective equipment (PPE)



# Outbreak Challenges in West Africa

Lack of Knowledge and Acceptance of Ebola

- ❑ Not overcome by education
- ❑ Fear and superstition
- ❑ Stigma
- ❑ Distrust of outsiders
- ❑ Role of war exposure
- ❑ Traditional beliefs

**THERE IS STRENGTH IN UNITY!  
LET US HELP ONE ANOTHER FIGHT AGAINST EBOLA!**

Help your family

Help your neighbors

Help your community

When we help each other we can save lives! Let's help one another fight Ebola!

**There is Strength in Unity!**

U.S. Centers for Disease Control and Prevention (CDC) CS251127-C

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# The Role of Modeling

(with special thanks to Martin  
Meltzer)



# Role of Modeling in a Response

- Valuable tool to aid projections and help focus response
- Modeling's major contribution is estimation before large amounts of data are available
- Catch 22 (from me):
  - Only as good as the data inputs
  - If you have all of the data inputs, you may not need a model

# Examples of Modeling During the H1N1 Response

- **Impact of interventions**
  - School and community event closures
  - Vaccine use
  - Antiviral use
- **Winter wave likelihood**
- **Vaccine priority group recommendations**
- **Transmission dynamics**
- **Burden of illness**
- **Hospital bed needs; ventilator needs etc**

# Examples of Modeling Informing the Ebola Outbreak

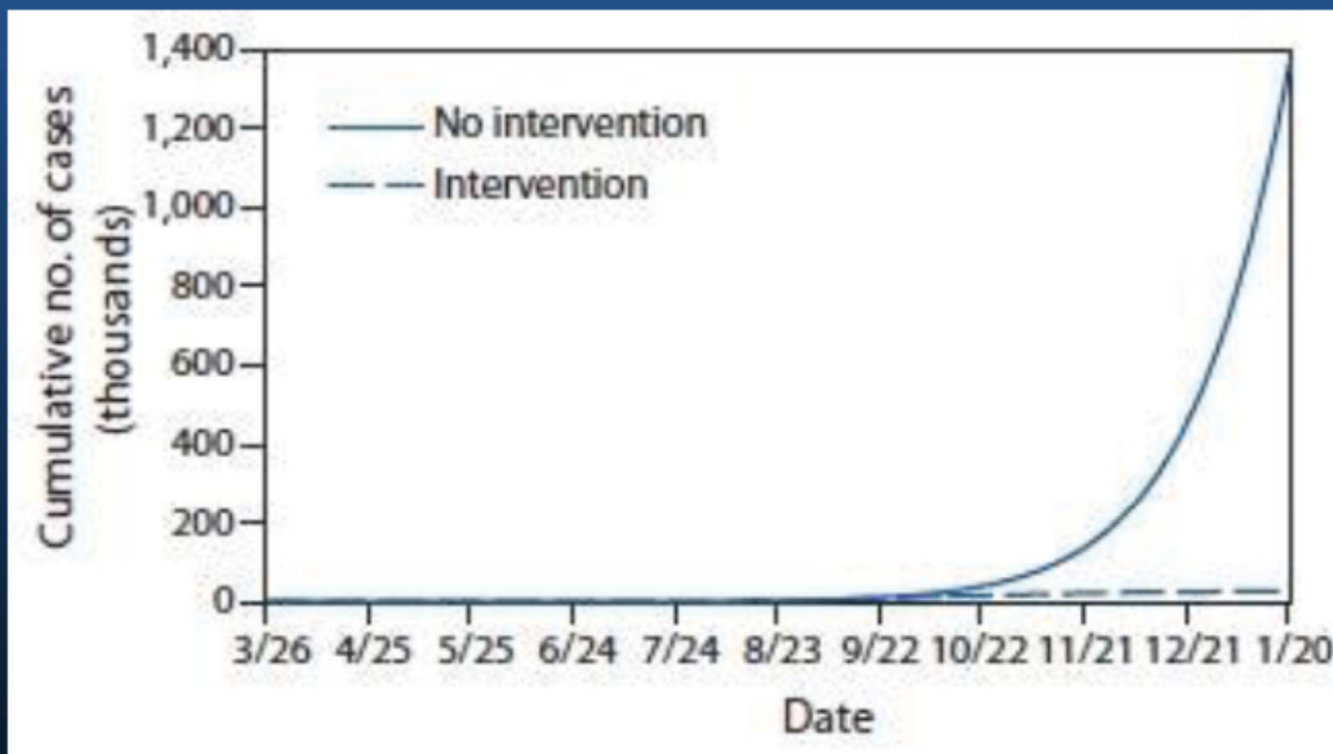
- **Forecasting: How many cases will there be at any point and in total (serial estimates) ?**
  - What would be the impact of interventions?
  - When will the epidemic end?
    - With and without intervention
- **Spread- Which neighboring areas/countries are at the highest risk of an outbreak?**
- **Ebola Treatment Units:**
  - How many ETU beds will be needed (resources- people and money)?
  - What ETU construction schedule will suffice to 'bend the curve'?
  - What ETU expansion schedule is possible including construction and staffing?
- **Impact of presumptive malaria treatment (contact tracing)**

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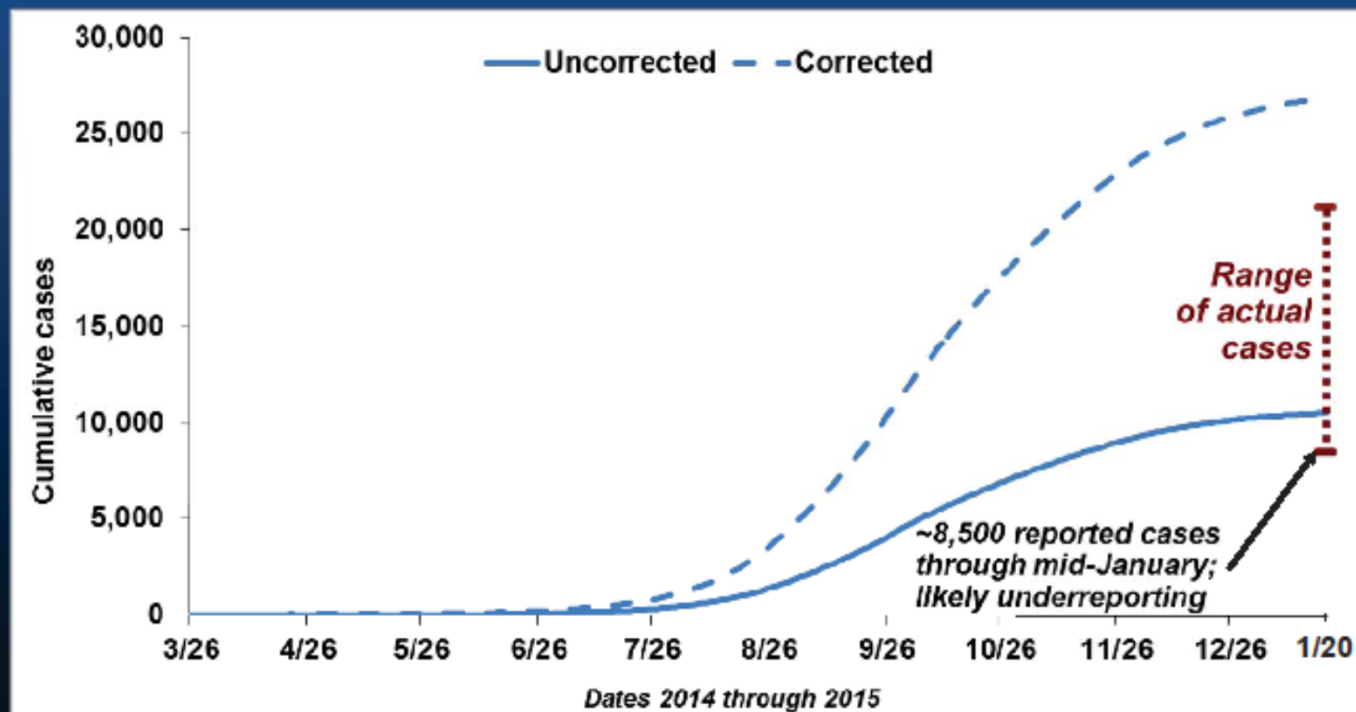
# Modeling projected an exponential increase in cases without intervention

*Modeling conducted September 2014*



*MMWR Surveill Summ 2014;63 Suppl 3:1-14. Corrected for potential underreporting by multiplying reported cases by a factor of 2.5.*

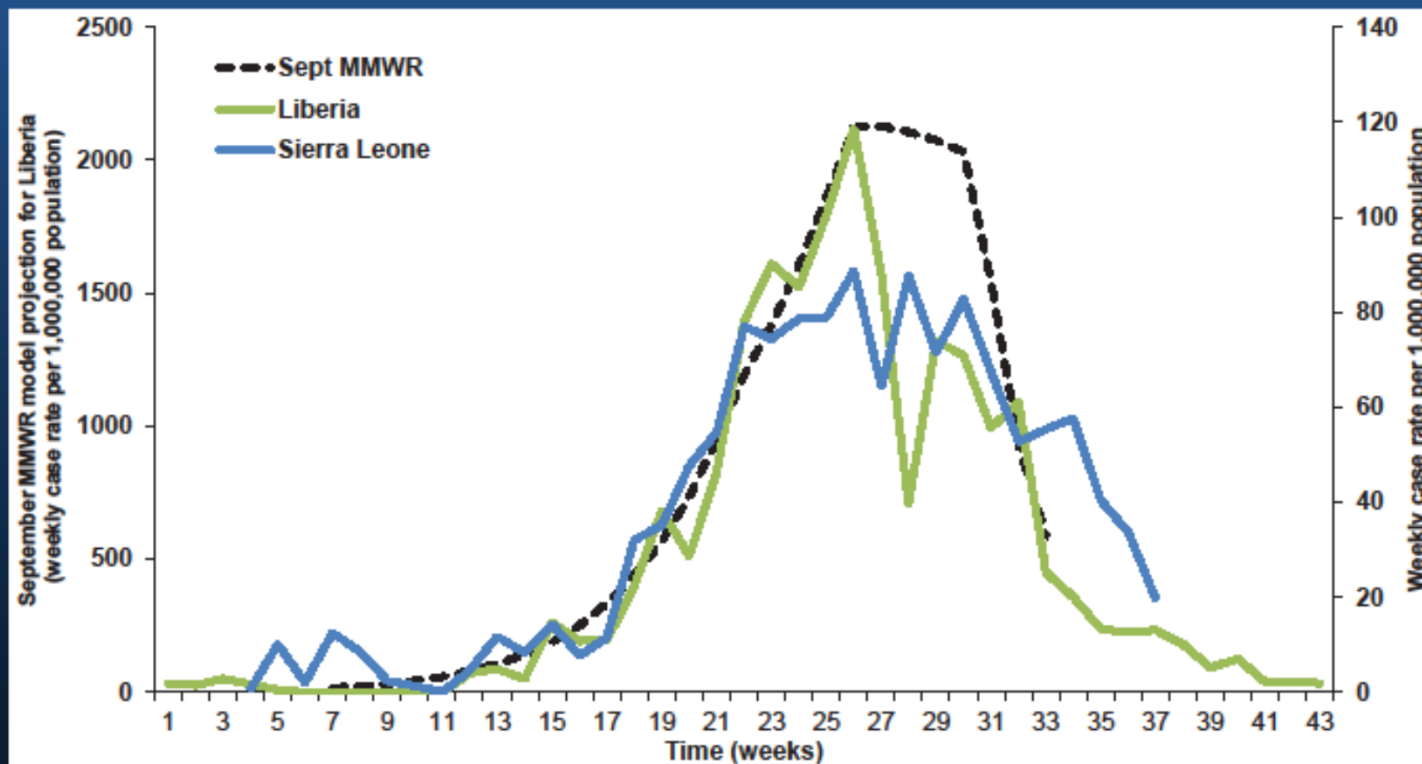
## With intervention modeling projected **10,000-27,000 cases by early 2015** *Liberia; modeling conducted September 2014*



*MMWR Surveill Summ 2014;63 Suppl 3:1-14. Corrected curve of projected cases is adjusted for potential underreporting by multiplying reported cases by a factor of 2.5. Range of actual cases is corrected for underreporting up to a factor of 2.5.*

*WHO Situation Report 21 January 2015.*

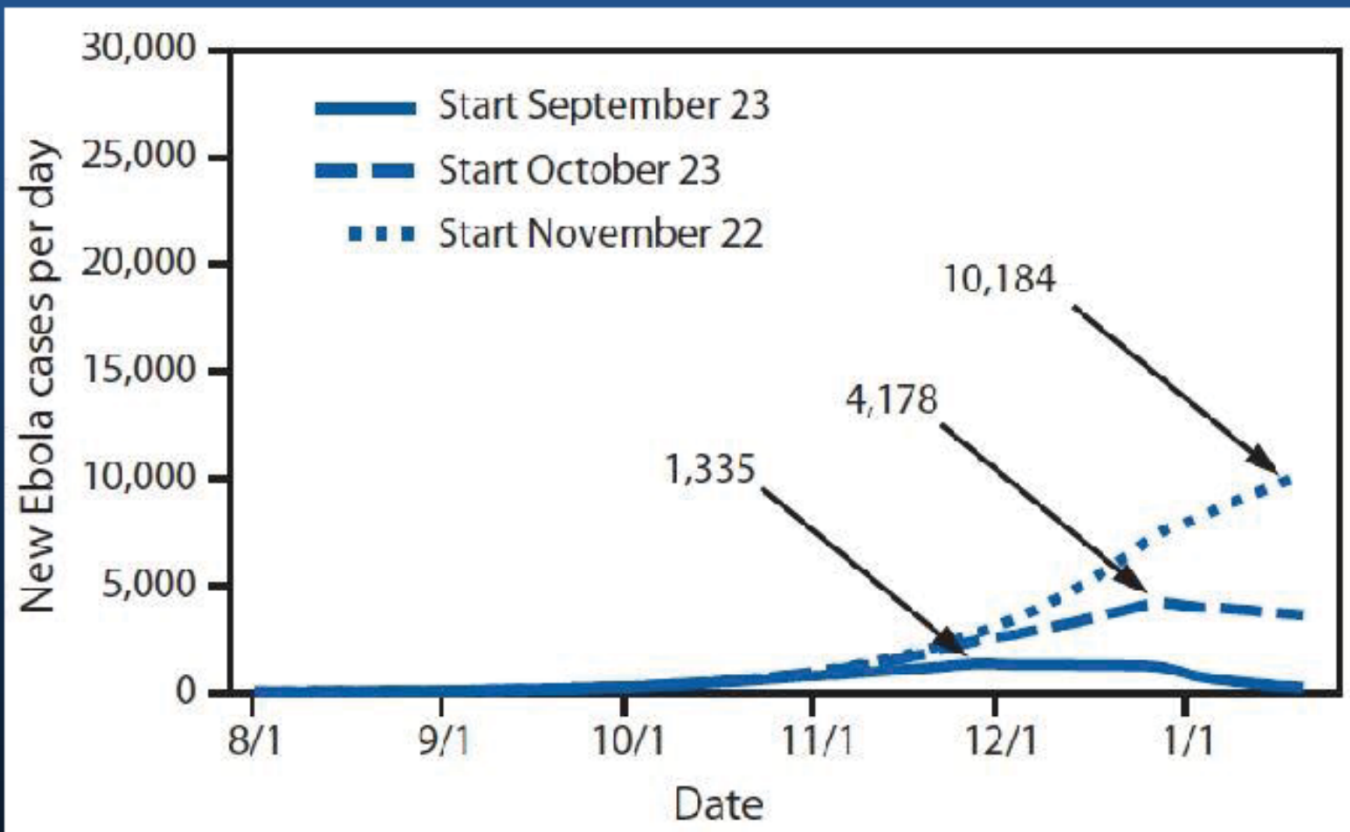
## Modeling predicted rapid rise in cases – and rapid decline if interventions implemented rapidly



*Weekly case rates for Liberia and Sierra Leone time-shifted so that curves align compared with September MMWR projection for Liberia.*



## Response time matters – cases could triple for every month of inaction



*MMWR Surveill Summ 2014;63 Suppl 3:1-14. Not corrected for potential underreporting.*

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# Key Related Decisions - 1

- **Target groups for intervention with vaccine or antivirals/therapeutics, especially when insufficient availability**
  - Risk groups in need protection (e.g., young children, elderly).
  - Workers to maintain infrastructure (e.g., public health responders, healthcare workers, law enforcement, emergency workers)
  - Target groups that might have greatest impact on transmission.
- **Should a vaccine be developed? What strain?**
  - Should it be developed?
  - What data needed prior to use?
    - Safety data
    - Immunogenicity data
  - Rigorousness of studies
    - Likely depends on combination of factors
      - Severity of disease
      - Brand new vaccine vs previous formulation with different strain
  - Consequences of adverse events/impact on response

*Each of the above require repeated re-evaluation  
Often need to make decisions in absent of information*

## Key Related Decisions - 2

- **Appropriate clinical management**
- **Which antivirals/therapeutics to use.**
  - When data available on effectiveness
    - E.g. oseltamivir and influenza
    - Allocation of resources
  - When only in vitro or animal data available
    - What kind of data needed to use?
      - Randomized trials?
      - Observational studies?
      - Prospective vs retrospective

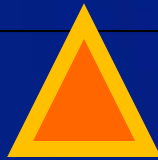
*Each of the above require repeated re-evaluation  
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# Key Related Decisions - 3

- **Role of non-pharmaceutical interventions**
  - isolation, quarantine – of note, needs of individuals must be met
  - school closures
  - cancel large public gatherings (concerts, theatres)
  - Minimize other exposures (markets, churches, public transit)
  - telework, non-essential personnel sent home
  - Consider additional measures
    - Distribution of surgical masks?
    - Temperature screening at public venues?
    - Scaling back transportation services?

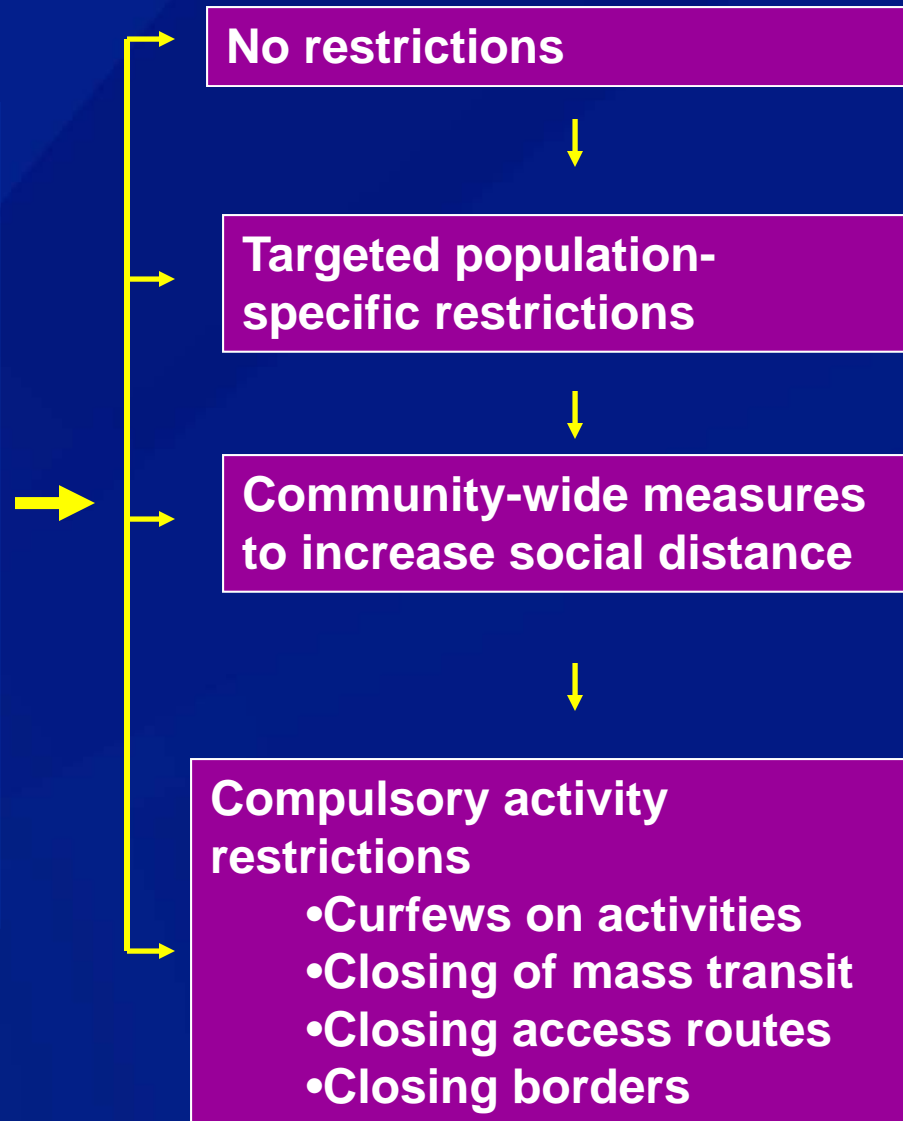
**Public good**

**Civil liberties**



# Community Responses to SARS

- Number of cases/exposed
- Exposure category
  - Known
  - Unknown (unlinked)
- Generations of transmission
- Morbidity and mortality
- Ease/ rapidity of spread
- Movement in /out of community
- Resources for response
- Risk of public panic



# ***Conclusions***

## Conclusions

- **Responses to epidemics have the same goal regardless of the agent**
  - Reduce morbidity/mortality
  - Control the outbreak
  - Prevent future outbreaks
- **Same general approach to outbreaks and core scientific information needed, but details vary by epidemic agent and situation**
- **Control measures**
  - May have to make decisions in absence of data
  - Modeling can assist
  - Complex ethical issues
  - Communication to different audiences critical
- **Repeated reassessment needed as situation evolves**



**There is no substitute for being prepared**



**There is no substitute for being prepared**

**Flexibility critical!**



**Be prepared to make significant changes to your plans based upon circumstances**

# THANK YOU

# QUESTIONS?

**For more information please contact Centers for Disease Control and Prevention**

1600 Clifton Road NE, Atlanta, GA 30333

Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348

Visit: [www.cdc.gov](http://www.cdc.gov) | Contact CDC at: 1-800-CDC-INFO or [www.cdc.gov/info](http://www.cdc.gov/info)

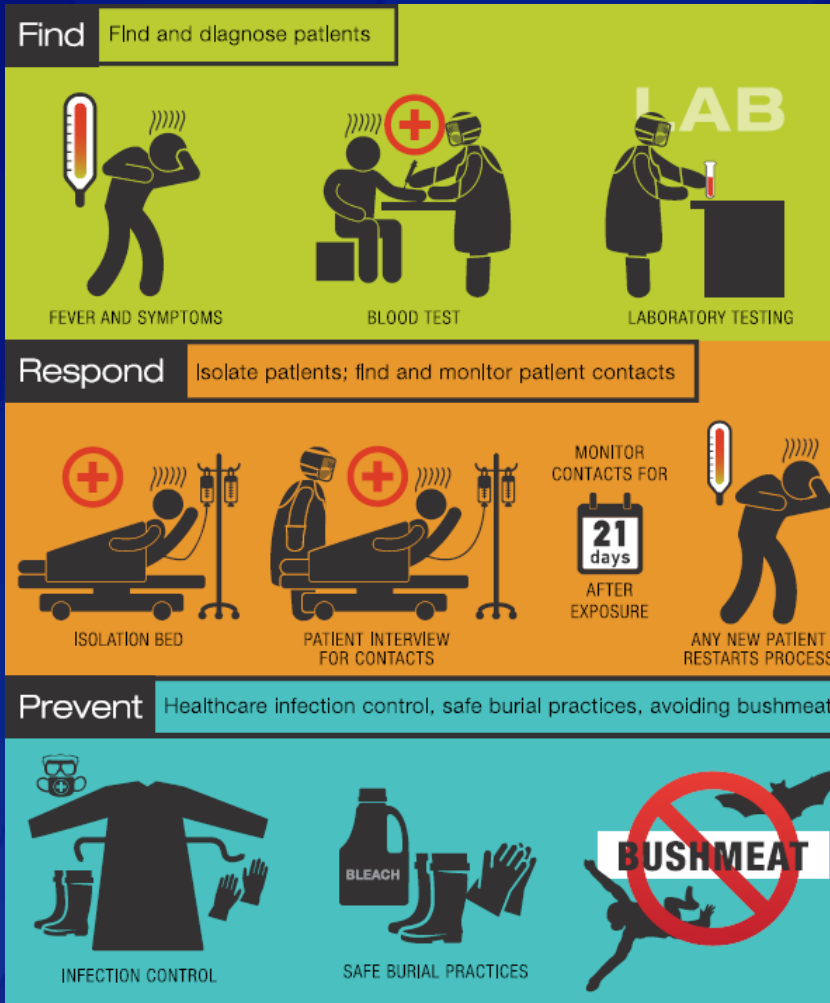
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.



Department of Health and Human Services  
Centers for Disease Control and Prevention

# Responding to International Challenges

## Immediate



## Long Term

### Global Health Security

☐ Detect Threats Early

☐ Respond Effectively

☐ Prevent Avoidable Catastrophes