Navigating Through Current and Emerging Issues in Outbreaks

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Purpose

1. Review the approach to investigating outbreaks in healthcare facilities.

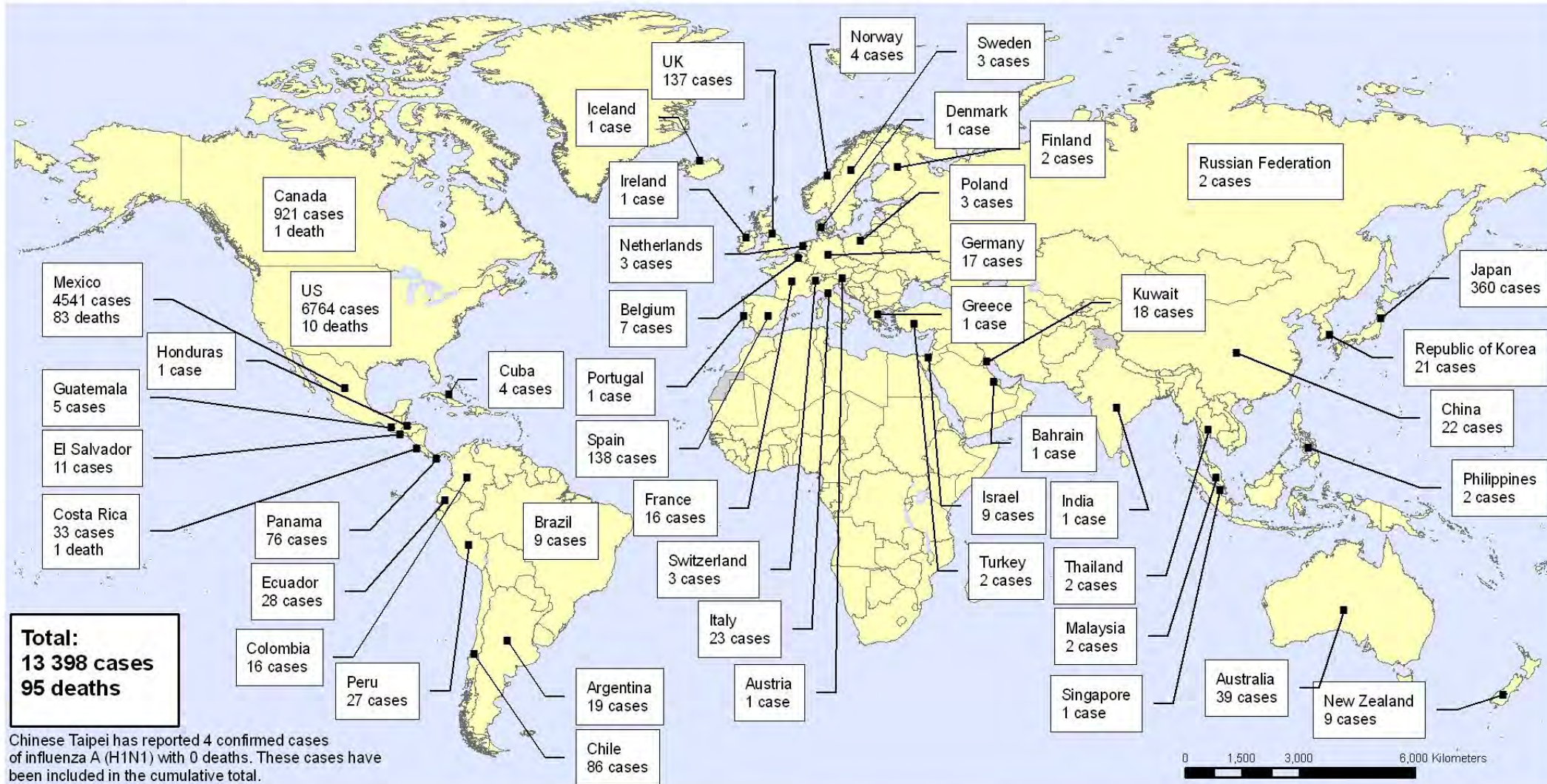2. Illustrate the epidemiologic and laboratory aspects of outbreak investigations.

Recent Emerging Diseases
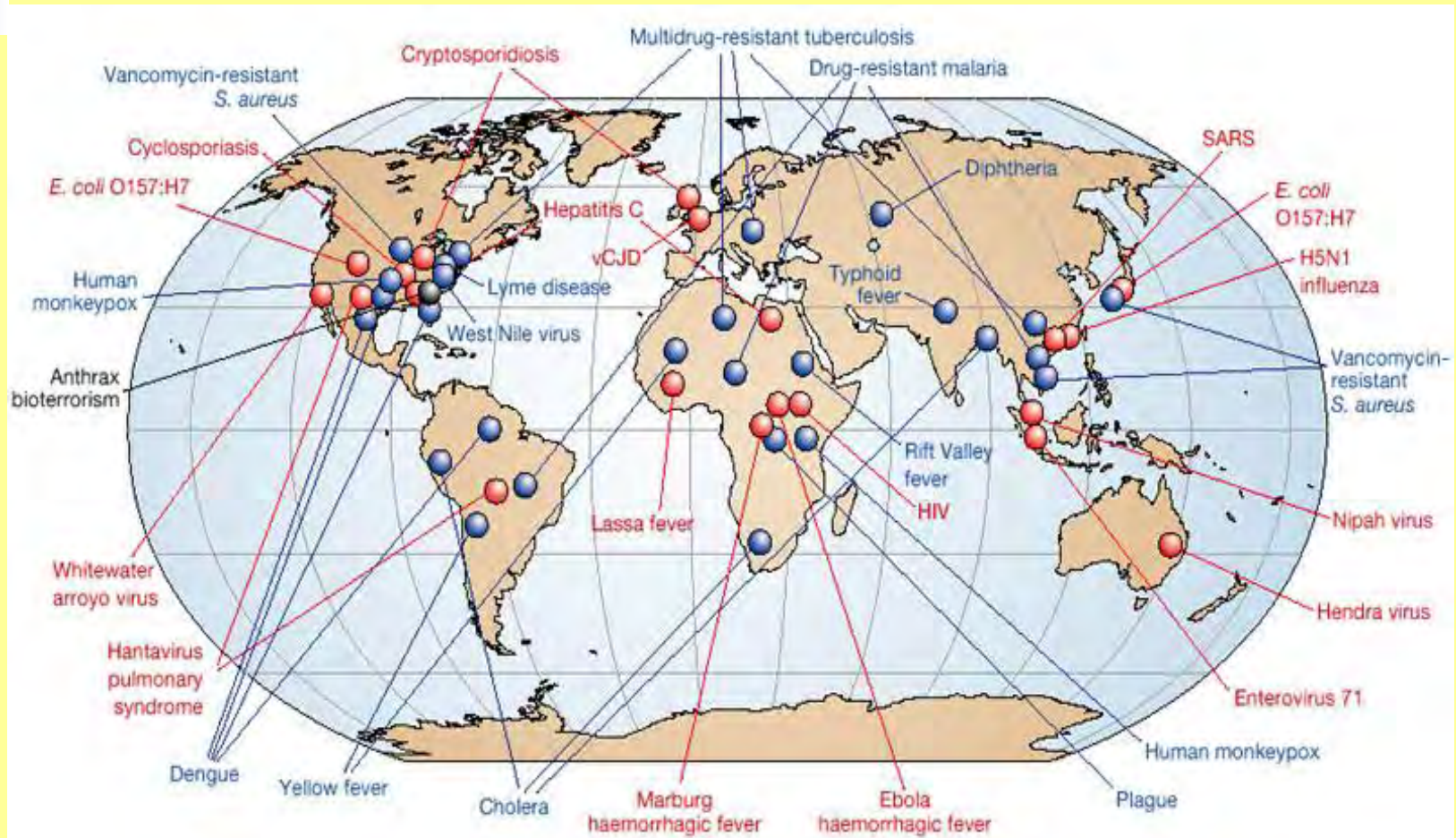
Source: NATURE 2004; 430. www.nature.com/nature

New Influenza A (H1N1),
Number of laboratory confirmed cases and deaths as reported to WHO

Norway
4 cases

Sweden
3 cases

UK
137 cases

Iceland
1 case

Denmark
1 case

Finland
2 cases

Russian Federation
2 cases

Ireland
1 case

Poland
3 cases

Canada
921 cases
1 death

Netherlands
3 cases

Germany
17 cases

Japan
360 cases

Mexico
4541 cases
83 deaths

Belgium
7 cases

US
6764 cases
10 deaths

Kuwait
18 cases

Greece
1 case

Republic of Korea
21 cases

Honduras
1 case

Cuba
4 cases

Portugal
1 case

China
22 cases

Guatemala
5 cases

Bahrain
1 case

Spain
138 cases

Philippines
2 cases

El Salvador
11 cases

Panama
76 cases

Brazil
9 cases

France
16 cases

Israel
9 cases

India
1 case

Costa Rica
33 cases
1 death

Ecuador
28 cases

Switzerland
3 cases

Turkey
2 cases

Thailand
2 cases

Peru
27 cases

Italy
23 cases

Malaysia
2 cases

Colombia
16 cases

Argentina
19 cases

Austria
1 case

Singapore
1 case

Australia
39 cases

New Zealand
9 cases

Chile
86 cases

**Total:
13 398 cases
95 deaths**

Chinese Taipei has reported 4 confirmed cases
of influenza A (H1N1) with 0 deaths. These cases have
been included in the cumulative total.

0   1,500   3,000   6,000 Kilometers

The boundaries and names shown and the designations used on this map do not imply the expression of any opinion whatsoever
on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities,
or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which
there may not yet be full agreement.

Data Source: World Health Organization
Map Production: Public Health Information
and Geographic Information Systems (GIS)
World Health Organization

**World Health
Organization**

Map produced: 27 May 2009 06:30 GMT

No infectious disease has spread so fast and far as SARS did in 2003

SARS: The First Emerging Infectious Disease Of The 21st Century

Lesson Learned from SARS

- An infectious disease in one country is a threat to all.
- Important role of air travel in international spread.
- Tremendous negative economic of impact of outbreaks on trade, travel and tourism, estimated loss from SARS of $30 to $150 billion.
- High level National and International commitment is crucial for rapid containment.
- Global partnerships & rapid sharing of data/information enhances preparedness and response.
- Critical importance of infection control in controlling spread.
- Healthcare epidemiologists play a critical role in understanding how such pathogens are transmitted and how to control them.
- A systematic approach to investigating outbreaks is essential.

Epidemic

- Increase in incidence beyond the expected in a defined geographic area, within a defined period of time.

- A significant increase ($p < 0.05$) in the rate of adverse events above that noted in the past.

Rule to Live By

- Do not believe anything anyone tells you, <u>see it for yourself</u>.

Nosocomial Infections

- Endemic infections
  - Sporadic
  - Many/most are preventable
  - Account for majority of infections
- Outbreaks/Epidemics
  - Significant increase from endemic rate
  - Minority of infections
  - 100% preventable

● Epidemic   ● Endemic
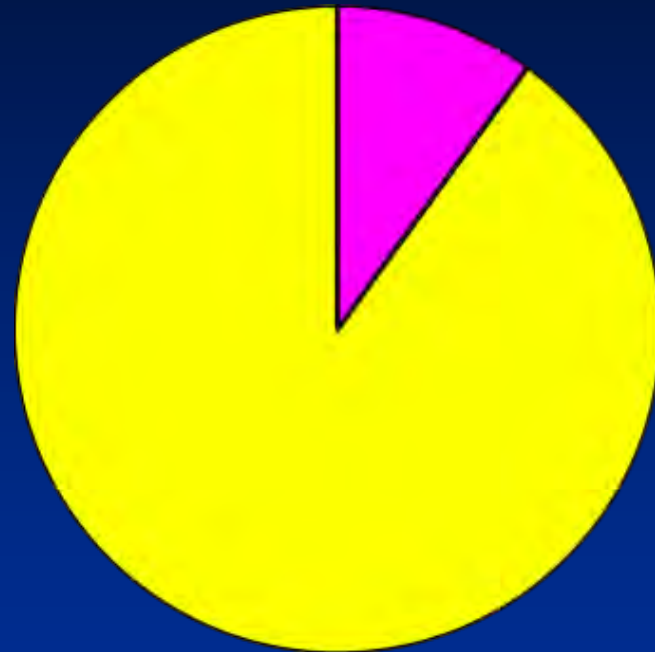
Implicit Assumptions

- Case definition has not changed.
- Methods for diagnosing the disease or identifying the organism have not changed.
- Case finding methods have not changed.

★These changes can lead to "pseudo-outbreaks".

Goals of an Outbreak Investigation

- Identify the etiologic agents
- Identify the reservoir(s)
- Identify the mode of transmission
- Eliminate the reservoir(s) and transmission
- Prevent future outbreaks

Microbiology Laboratory

- Important source for case-finding, if you know the etiologic agent.
- Identify the organisms as completely as possible
  - Genus and species
  - Epidemiologic typing
- Save all isolates!!!

Case Definition

- A description of the cases that changes as new data are accumulated, include time, place and person.

- Example (who, what, when and where):

- SSI outbreak. Pus at the operative site in a patient in the SICU at Hospital A from November 1-10, 2013 with wound or blood cultures positive for methicillin-resistant Staphylococcus aureus (MRSA) that has a particular PFGE pattern.

Literature Review

- What is the usual reservoir?

- What is the usual mode of transmission?

- Has it been reported to cause outbreaks?

- What factors were important in those outbreaks? (intravenous catheters, contaminated products, respiratory therapy, breaks in sterile technique, etc.)?

Define the Extent of the Problem

- Surveillance system
- Microbiology laboratory
- Employee health
- Other healthcare facilities
- Local, regional, international
- Reference laboratories

Calculate the Attack Rate

- Number of patients affected divided by number of patients at risk.

- Number of infections divided by number of patients at risk.

- Number of adverse outcomes divided by number of patients at risk.

Epidemic Period

- The time from the onset of the first case to the cases currently under investigation.

Pre-Epidemic Period

- Arbitrarily defined period of time that is long enough to provide sufficient cases of a low frequency event.

- Usually at least 6 months of surveillance data should be examined.

- 12 months will avoid seasonal bias.

Epidemic Curve

- Graphic display of outbreak with time (minutes, hours, days, weeks, months, years) on the X-axis and the number of persons meeting the case definition on the Y-axis.

- Both pre-epidemic and epidemic periods should be plotted.

Search for Risk Factors: The Line Listing

- Admission date
- Infection data
- Demographic data
- Underlying diseases
- Pre-infection exposures to
  - service
  - Ward, unit, bed or room (e.g., operating room)
  - Diagnostic tests
  - Therapeutic interventions
  - Personnel

Form a Hypothesis

- Using data from the epidemic curve, line-listing, literature, etc. form a hypothesis regarding:
  - the reservoir
  - the mode of spread

Test the Hypothesis Using a Comparative Study

- Case-control study
- Cohort study
- What factors determine the choice?
  - Number of cases
  - Duration of the outbreak
  - Rarity of the adverse event
  - How much time you have
  - Personnel resources

Test the Hypothesis Using a Case-Control Study

- Cases are compared to controls.
- The proportion in each group exposed to various risk factors are compared.
- Were case-patients exposed to a risk factor that controls were not exposed to?
- Is the association statistically strong (Chi-square or Fisher's exact test
  $p < 0.05$)?

Selecting Controls

- Choose patients from appropriate subpopulation.
- 2 to 4 controls per case, if fewer than 10 cases.
- Initially don't match
  - Stringent matching obscures risk factor
  - Can't analyze matched variables

Important Clues in Investigating an Outbreak

- <u>Multiple organisms</u> causing infection at a single site or associated with invasive procedures may suggest problems with aseptic technique.

- <u>A single pathogen</u>, particularly clonal, suggests a common source.

- The epidemic curve may suggest the mode of transmission.

- An unusual organism may be a clue to a problem (Enterobacter cloacae, Enterobacter agglomerans, Salmonella muenchen).

Epidemiologic Typing

- Epidemiologically related isolates:
  - Are derived from a single clone
  - Share characteristics that differ from those of epidemiologically unrelated isolates
- Are isolates from >2 patients or from patients & environment the same or different?
- Doesn't replace epidemiological analyses!!!

Evaluating Typing Systems

- <u>Typeability</u>:
  Ability to obtain an unambiguous positive result for each isolate analyzed.

- <u>Reproducibility</u>:
  Ability to give the same result each time a strain is tested.

- <u>Discriminatory power</u>:
  Ability to differentiate among unrelated strains.

Hierarchical Approach to Typing

- Start with simple, inexpensive, readily available tests.

- Do more expensive, more difficult, less readily available tests only if the clinical, epidemiologic, and microbiologic data indicate that they are necessary.

Phenotypic Techniques

- Colony morphology
- Biotyping
- Serotyping
- Phage typing
- Immunoblotting
- Antimicrobial susceptibility
- Multilocus enzyme electrophoresis

Characteristics of Phenotypic Typing Systems

Typing System	Proportion of Strains Typeable	Reproducibility	Discriminatory Power
Biotyping	All	Poor	Poor
Antibiogram	All	Good	Poor
Serotyping	Most	Good	Variable
Phage typing	Most	Fair	Variable
Immunoblotting	All	Good	Good
MLEE	All	Excellent	Good

Maslow & Mulligan ICHE 17:595-604;1996

Molecular Techniques

- Cellular fatty acids
- Pyrolysis mass spectrometry
- Whole cell polypeptide analysis
- Plasmid pattern analysis (PPA)
- Ribotyping
- Pulsed Field Gel Electrophoresis (PFGE)
- Polymerase chain reaction (PCR)

Characteristics of Genotypic Typing Systems

Typing System	Proportion of Strains Typeable	Reproducibility	Discriminatory Power
PPA	Most	Fair	Variable
REA	All	Variable	Variable
Ribotyping	All	Excellent	Good
PFGE	All	Excellent	Excellent
PCR	All	Excellent	Unknown

Maslow & Mulligan ICHE 17:595-604;1996

Non-useful Approaches to Outbreak Investigations

- Do not conduct widespread environmental cultures.
- Do not perform widespread healthcare worker cultures.
- Do not start with organism typing.
- Do not let laboratory results over-ride epidemiologic data.

Middle East Respiratory Syndrome Coronavirus (MERS CoV) Background

- Viral respiratory disease first identified in Saudi Arabia during 2012.
- Caused by a novel coronavirus
  - Distinct from coronavirus associated with Severe Acute Respiratory Syndrome (SARS).
- Source(s) not clearly understood yet.

MERS CoV: Symptoms and Transmission

- <u>Symptoms and care</u>
  - Fever, cough, shortness of breath.
  - Most develop severe respiratory disease.
  - Supportive care only.

- <u>Transmission</u>
  - Person-to-person, close contacts.
  - Eight clusters identified in six countries among close, person contacts.
  - One cluster involving healthcare personnel caring for a MERS CoV-infected patient.

MERS CoV Case Count

- Case count as of September 20, 2013:
    - 130 case-patients, 58 (45%) deaths.
    - Countries With Lab-Confirmed MERS Cases (April 2012 - September 20, 2013): France, Italy, Jordan, Kuwait, Oman, Qatar, Saudi Arabia, Tunisia, United Kingdom (UK), and the United Arab Emirates (UAE).
    - All case-patients have a direct or indirect link to one of four countries: Saudi Arabia, Qatar, Jordan, or United Arab Emirates.
    - Dates of onset: April 2012 – May 2013.
    - Median age of case-patients: 56 years

Characteristics and Symptoms of Patients with Laboratory-Confirmed Middle East Respiratory Syndrome Coronavirus Infection, April–May 2013.

Table 1. Characteristics and Symptoms of Patients with Laboratory-Confirmed Middle East Respiratory Syndrome Coronavirus Infection, April–May 2013.

Characteristic	Patients with Confirmed Cases (N=23)
Male sex — no. (%)	17 (74)
Age — yr	
Median	56
Range	24–94
Age ≥50 yr — no. (%)	17 (74)
Age ≥65 yr — no. (%)	6 (26)
Obesity — no./total no. (%)*	5/21 (24)
Underlying Illness — no. (%)	
End-stage renal disease	12 (52)
Diabetes mellitus	17 (74)
Cardiac disease	9 (39)
Lung disease, including asthma	10 (43)
Immunosuppressive condition other than renal disease	0
Symptoms before presentation — no. (%)	
Fever	20 (87)
Cough	20 (87)
Shortness of breath	11 (48)
Gastrointestinal symptoms	
Any	8 (35)
Vomiting	4 (17)
Diarrhea	5 (22)
Laboratory testing at presentation — no/total no. (%)	
Abnormal white-cell count†	5/23 (22)
Abnormal platelet count‡	5/23 (22)
Elevated aspartate aminotransferase	3/13 (23)
Oxygen saturation <95% while breathing ambient air	7/23 (30)
Chest radiographic findings at presentation — no. (%)	
Normal	3 (13)
Increased bronchovascular markings	4 (17)
Unilateral infiltrate	10 (43)
Bilateral infiltrates	5 (22)
Diffuse reticulonodular pattern	1 (4)
Clinical course — no. (%)	
Admitted to hospital	22 (96)
Admitted to intensive care unit	18 (78)
Received mechanical ventilation	18 (78)
Outcome as of June 12, 2013 — no. (%)	
Recovered	6 (26)
Remained in hospital§	2 (9)
Died	15 (65)

* Obesity was defined as a body-mass index (the weight in kilograms divided by the square of the height in meters) of 30 or more.
† Two patients had an abnormally low white-cell count (2.2×10⁹ per liter and 3.1×10⁹ per liter), and three had abnormally high counts (12.1×10⁹, 17.9×10⁹, and 22×10⁹ per liter).
‡ Four patients had abnormally low platelet counts (ranging from 110×10⁹ to 122×10⁹ per liter) and one had an abnormally high count (468×10⁹ per liter)
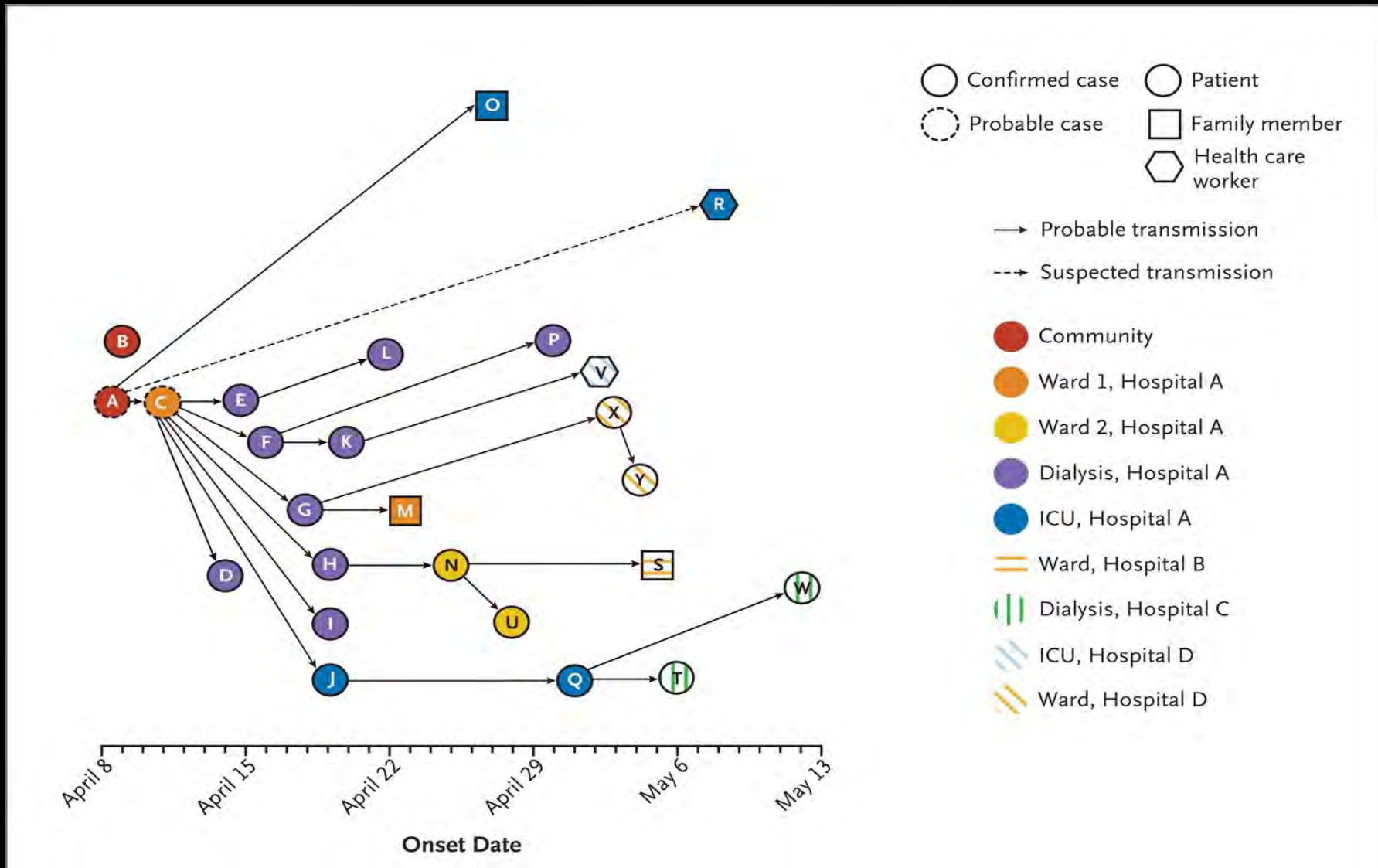§ Both of these patients remain in the intensive care unit and continue to receive mechanical ventilation.

Assiri A et al. N Engl J Med 2013;19:19.

Epidemiologic Curve of Confirmed and Probable Cases of MERS-CoV Infection in Saudi Arabia, April 1–May 23, 2013.
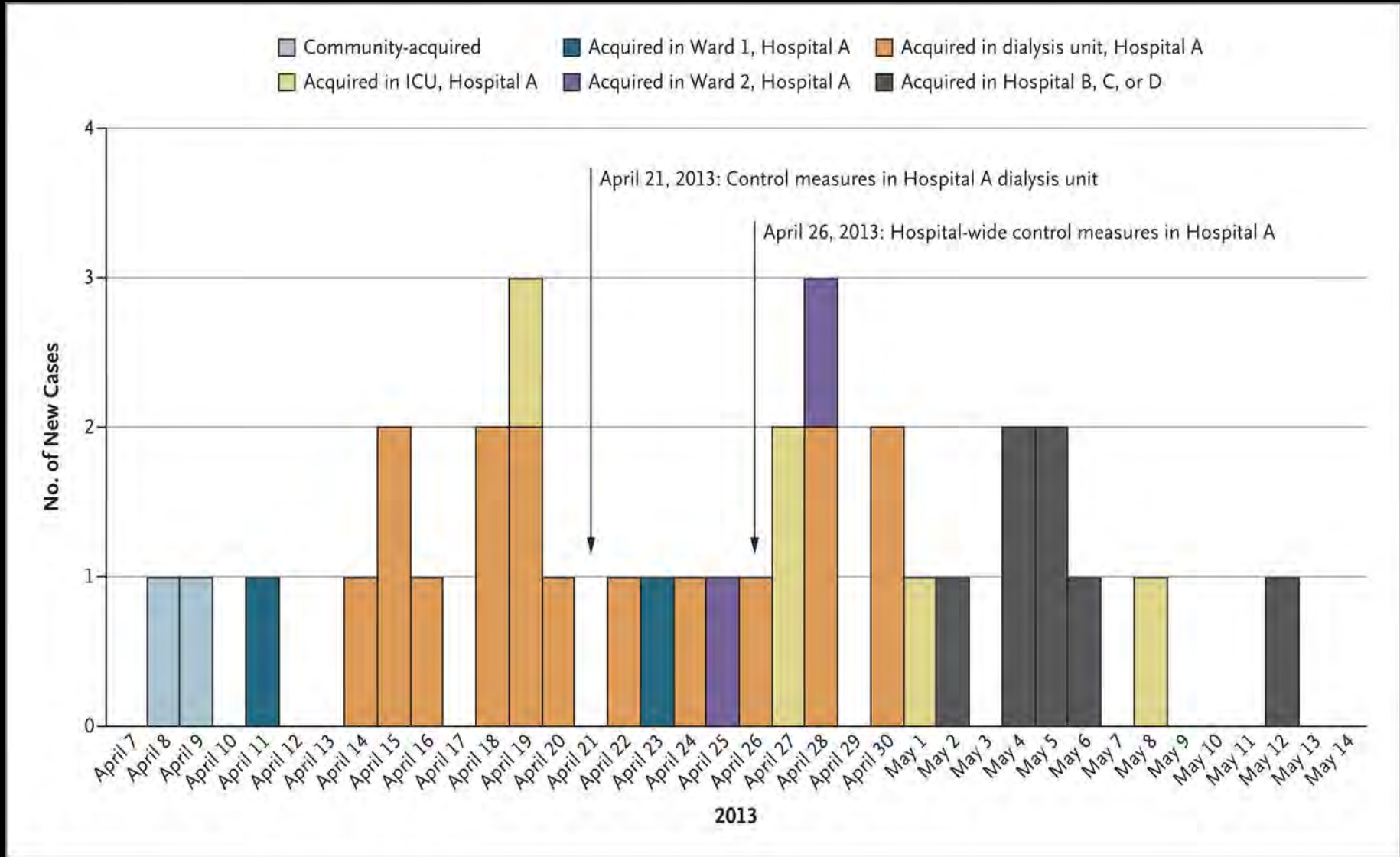
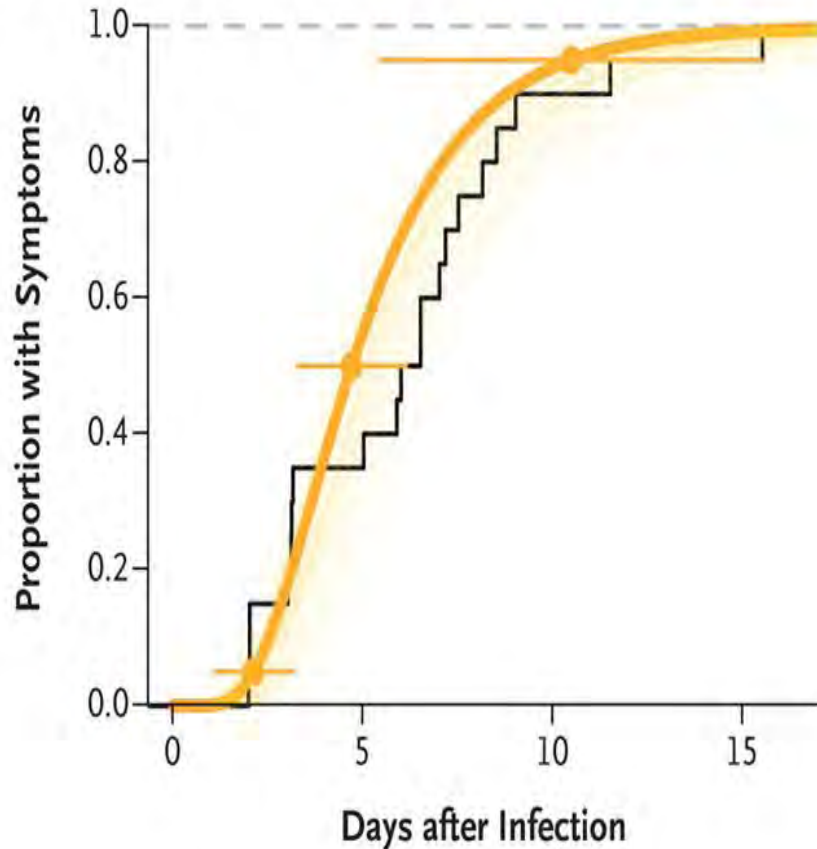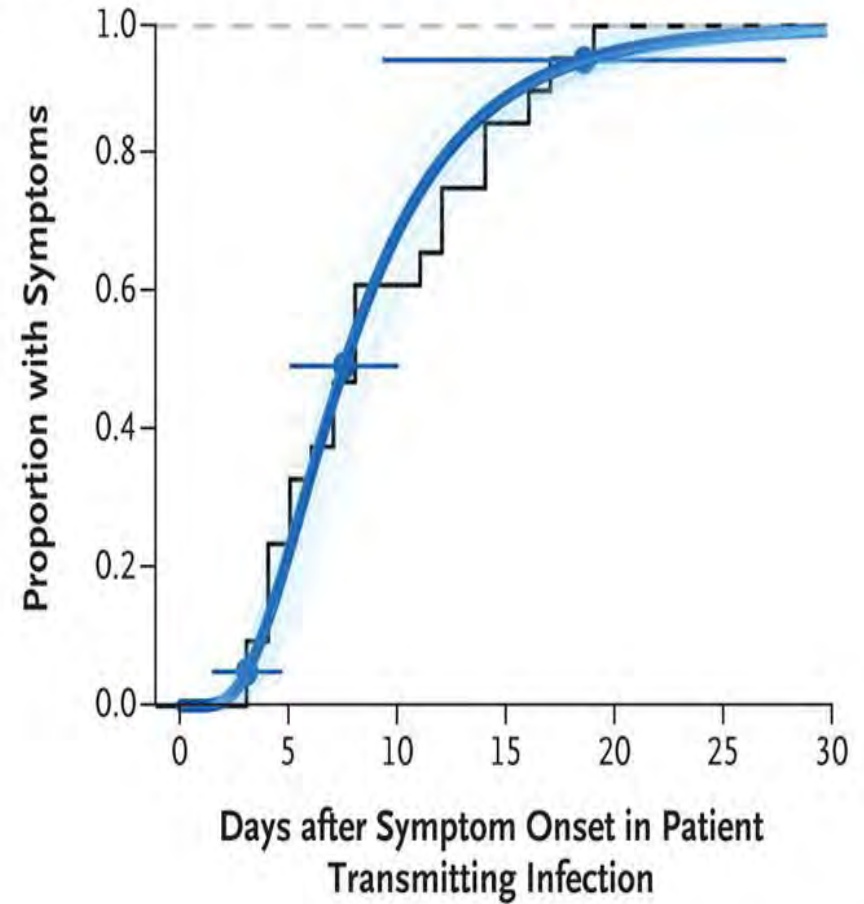# Transmission Map of Outbreak of MERS-CoV Infection.

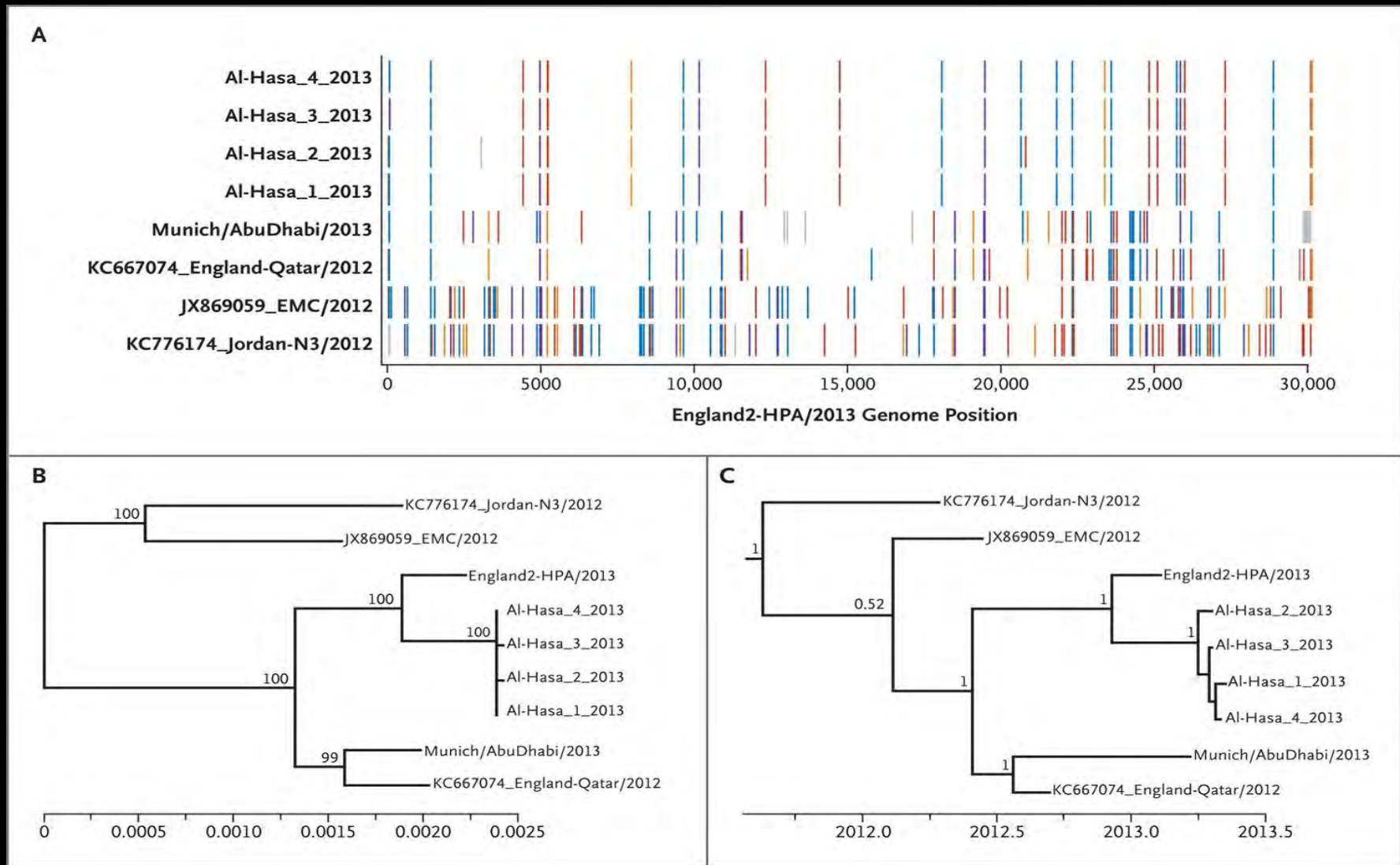# Estimates of the Incubation Period and Serial Interval of MERS-CoV Infection.

Phylogenetic Analysis of the Sequences of All Genes Identified in Four Patients Infected with MERS-CoV.

Emerging Carbapenem Resistance in Gram-Negative Bacilli

- Significantly limits treatment options for life-threatening infections.

- No new drugs for gram-negative bacilli.

- Emerging resistance mechanisms, carbapenemases are mobile.

- Detection of carbapenemases and implementation of infection control practices are necessary to limit spread.

Carbapenem Resistance: Mechanisms

Enterobacteriaceae	Cephalosporinase + porin loss
	Carbapenemase
P. aeruginosa	Porin loss
	Up-regulated efflux
	Carbapenemase
Acinetobacter spp.	Cephalosporinase + porin loss
	Carbapenemase

Carbapenemases

Classification	Enzyme	Most Common Bacteria
Class A	KPC, SME, IMI, NMC, GES	Enterobacteriaceae (rare reports in P. aeruginosa)
Class B (metallo-®-lactamse)	IMP, VIM, GIM, SPM	P. aeruginosa Enterobacteriacea Acinetobacter spp.
Class D	OXA	Acinetobacter spp.

Klebsiella Pneumoniae Carbapenemase

- KPC is a class A ®-lactamase
  - Confers resistance to all ®-lactams including extended-spectrum cephalosporins and carbapenems

- Occurs in Enterobacteriaceae
  - Most commonly in Klebsiella pneumoniae
  - Also reported in: K. oxytoca, Citrobacter freundii, Enterobacter spp., Escherichia coli, Salmonella spp., Serratia spp.,

- Also reported in Pseudomonas aeruginosa (Columbia)

KPC Outside of United States

- France (Nass et al. 2005. AAC 49:4423-4424)

- Singapore (report from survey)

- Puerto Rico (ICAAC 2007)

- Columbia (Villegas et al. 2006. AAC 50:2880-2882 & ICAAC 07)

- Brazil (ICAAC 2007)

- Israel (Navon-Venezia et al. 2006. AAC 50:3098-3101)

- China (Wei Z, et al. 2007. AAC 51: 763-765)

Epidemiology of CRE

- Enterobacteriaceae are normal flora of the respiratory and gastrointenstinal tract.

  – Also the nasopharynx, respiratory tract, and urinary tract.

- Transmission from person-to-person occurs via the hands of healthcare personnel.

- Colonization rates vary

  – May persist up to several months.

- Some strains may be transmitted more readily.

- Environment thought to play a lesser role

CRE: Who's at risk?

- Patients with long hospitalizations.
- Long-term acute care (LTAC) residents.
- Immunocompromised patients.
- Patients with invasive devices.
- Patients with open wounds.
- Colonized patients can be a source for transmission.

Recent CRE Outbreaks

- KPC outbreak at U.S. National Institutes of Health (NIH) for 6 months, starting in June 2011.

  – Total of 18 patients: transmission to 17 patients, 8 developed bloodstream infections (BSIs), and 6 attributable deaths.

  www.sciencetranslationalmedicine.org, 22 Aug. 2012, Vol 4., Issue 148

- KPC (CRKP) outbreak in an acute-care hospital in Denver, starting in May 2012.

  – Total of 8 patients: three were infected, five were colonized. No deaths

  MMWR, Feb. 15, 2013, Vol. 62, No. 6, p 108

Recent CRE Outbreaks (cont)

- KPC (CRKP) outbreak in an acute care hospital in West Virginia, from April 2009 – February 2011.
  - 40 total cases
  - Spread among 14 acute care hospitals, 2 LTACs, and 10 nursing homes.

Clinical Infectious Diseases, Volume 53, Issue 6, p. 532-540
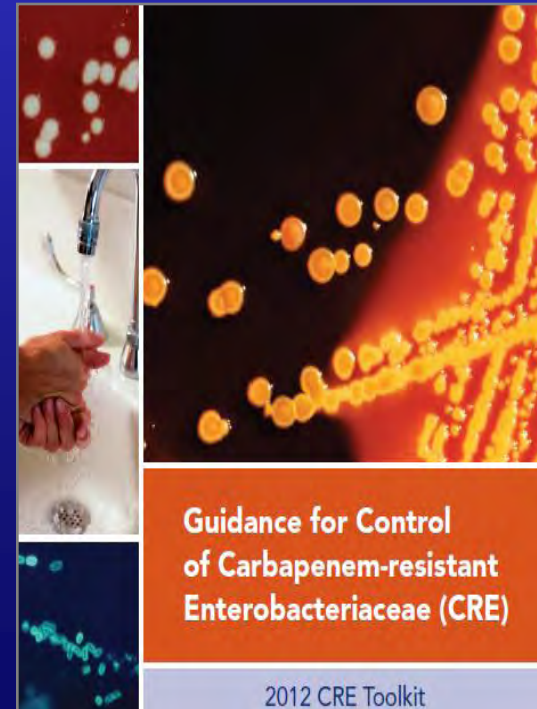
CRE Prevention Strategies

- **Core measures:**
  1. Hand hygiene
  2. Contact Precautions
  3. Healthcare personnel education
  4. Minimizing device use
  5. Patient and staff cohorting
  6. Lab notification
  7. Promote antimicrobial stewardship
  8. CRE screening

- **If transmission occurs in the facility:**
  1. Active surveillance
  2. Chlorhexidine bathing

Guidance for Control of Carbapenem-resistant Enterobacteriaceae (CRE)

2012 CRE Toolkit

www.cdc.gov/hai/organisms/cre/cre-toolkit/index.html

Conclusion

- A systematic approach to investigating outbreaks using both epidemiologic and laboratory methods can identify the source of the outbreak and terminate transmission-- regardless of whether it is an "old" pathogen (i.e., MRSA, VRE, etc.) or a new or emerging pathogen.

Thank You!