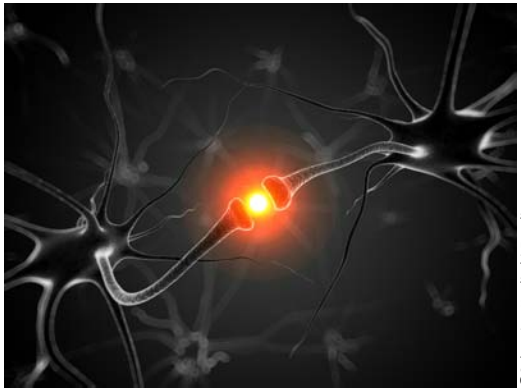
National Emerging Respiratory Virus Surveillance Strategy (NERVSS):

H7N9 and MERS-CoV Examples

Danuta M Skowronski MD, FRCPC
BC Centre for Disease Control
Zoonosis Meeting, Paris
June 10, 2013

NERVSS: PRINCIPLES

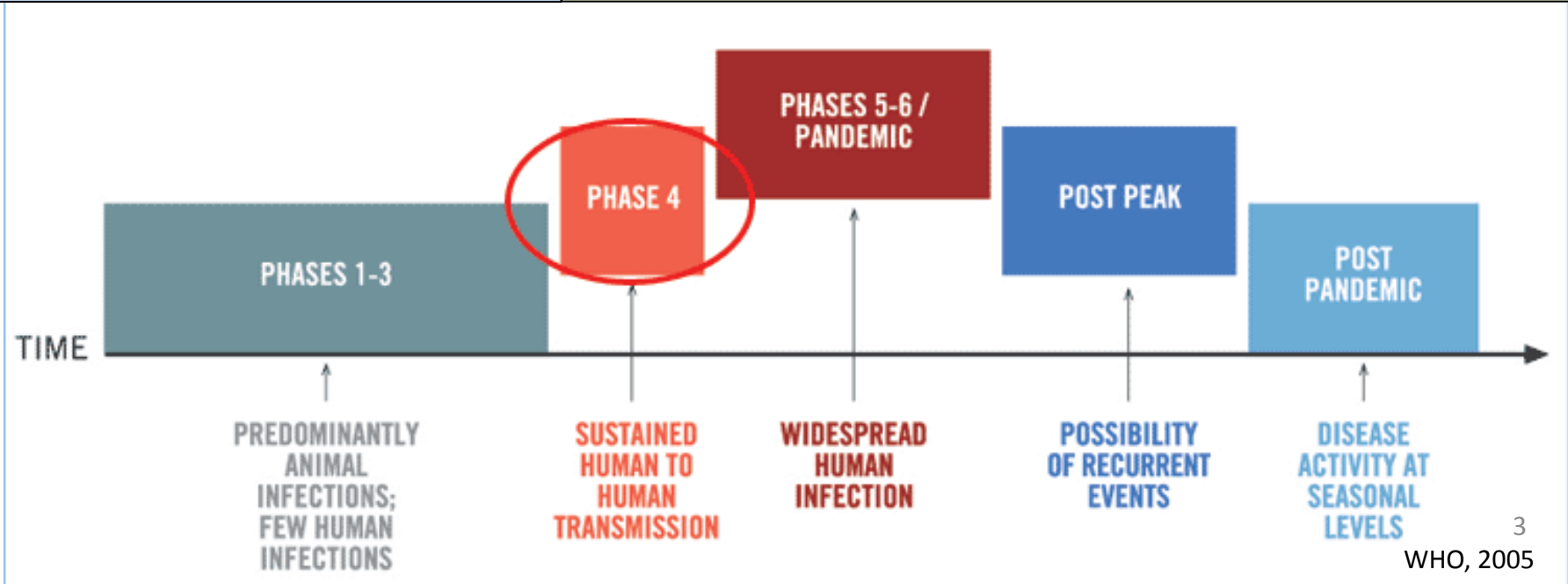


- **Over-arching considerations:**
  - Illness severity
  - Stage of adaptation for human-to-human (H2H) spread
  - Likelihood of containment
- **Horizontal (strategic) and vertical (subject matter) perspectives**
- **Goal-, objective- and feasibility- oriented**
- **NERVSS and public health measures are closely linked**
  - Early intense surveillance efforts to detect and contain
    - **Can spare downstream amplification of public health activities/costs**
  - Public health response depends on timely knowledge & learning
    - **Virologic and epidemiologic characteristics by stage of adaptation**

NERVSS: Goals, Objectives, Actions

Goal: To minimize disease burden and disruption

Containment	Mitigation
Individual-level focus Containment focus Isolation and quarantine Risk characterization & control Active case/contact follow-up Special investigations (research)	Population-level focus Impact mitigation focus Vaccine and other intervention readiness Risk group characterization for targeted deployment Special investigations (research)



WHO, 2005

Containment is not always practical or possible

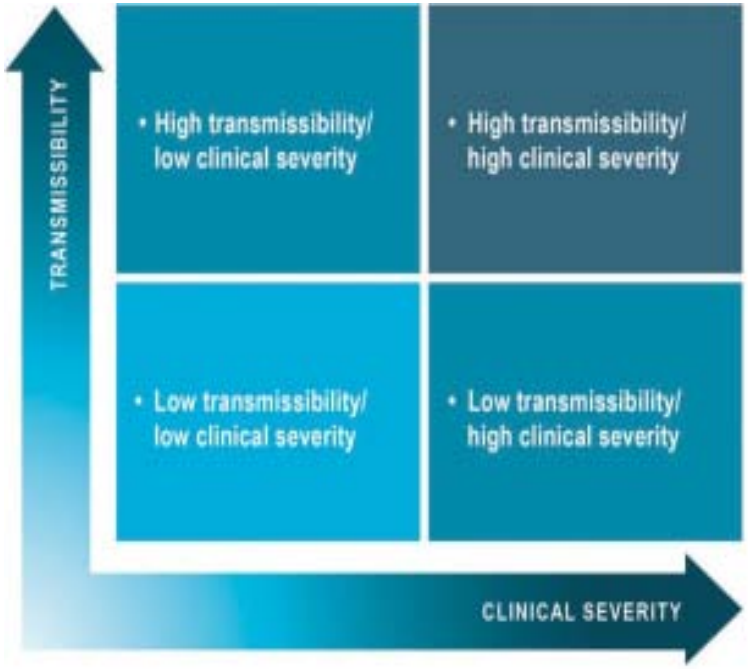


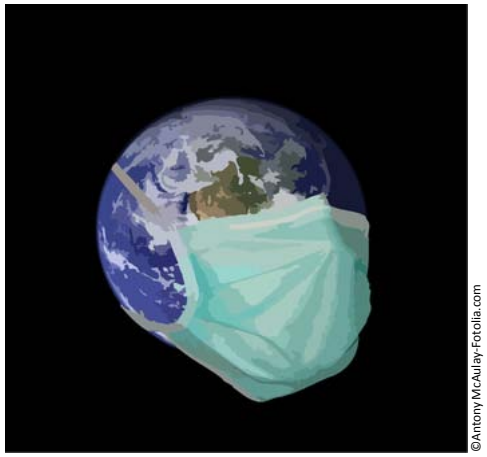
FIGURE 1. FOUR SEVERITY SCENARIOS USED IN THE OHPIP

Figure from: Ontario Pandemic Influenza Preparedness Plan

- Pathogens capable of severe illness are the main concern
- A pathogen already highly adapted or with a large proportion of mild or asymptomatic illness cannot be contained
  - Would require enormous effort and resources to detect and intervene upon the first cases
    - Cannot test, isolate and/or quarantine everyone
  - Focus of NERVSS is severe acute respiratory illness (SARI)

Successful containment: The unique example of SARS

- Despite ~8000 cases and ~800 deaths globally in 26 countries, SARS was contained within 5 months of first report
- SARS had very unique features that enabled containment:
  - **Severe presentation with few mild/asymptomatic cases**
    - Could detect it
  - **No pre-symptomatic shedding**
    - Further minimized surreptitious (silent) spread
  - **Delay to peak infectious period (day 10)**
    - Gave time to identify and isolate cases
  - **Long incubation (median 4-5; range 2- 10 d)**
    - Gave time to identify and quarantine contacts
  - **Not very transmissible**
    - Except under certain conditions of facilitated spread (aerosol-generating)
    - Nosocomial (20-40% HCWs) and limited close contact transmission
    - Importance of Patient Zero connectedness



Should not assume all emerging pathogens can be halted & successfully contained like SARS.

The goals and objectives of NERVSS will depend upon severity, stage of adaptation for H2H spread, containment feasibility and other characteristics.

NERVSS: EXAMPLES

H7N9 [133 cases; 38 deaths] (First report: Mar 31, 2013)

- Novel **influenza A virus**
- Avian origin, China
- Current reservoir unknown
  - Believed to be poultry but no clear outbreaks owing to low path
- Severe acute respiratory illness
  - Mild & asymptomatic pediatric infections uncommonly identified
- Sporadic community cases: limited instances possible H2H transmission in family settings
  - No evidence sustained H2H
- No vaccine; NAIs available as tx

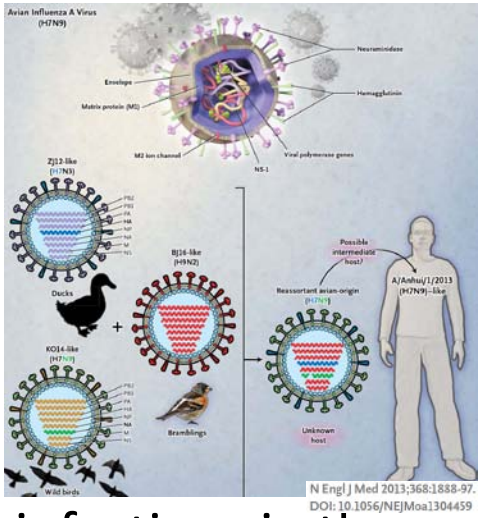
MERS-CoV [55 cases; 30+ deaths] (First report: Sept 20, 2012)

- Novel **coronavirus**
- Bat origin, Saudi Arabia
- Current reservoir unknown
  - No obvious animal outbreaks
  - Role of intermediary species UNK
- Severe acute respiratory illness
  - Atypical presentations observed with comorbidity/immunecomprom
- Documented clusters in family & health care settings
  - No evidence sustained H2H
- No vaccine; no specific tx

Genotypic & Phenotypic Diversity

H7N9
(Enveloped 8-segmented RNA)

- Other H7Nx infections (N2, N7, N3)
  - Poultry outbreaks: mild human URTI mostly conjunctivitis (1 prior death)
- H7N9 a complex reassortment
- Further genetic markers of human adaptation and virulence

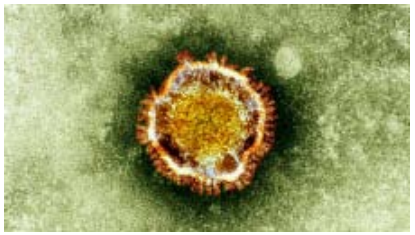


N Engl J Med 2013;368:1888-97.
DOI: 10.1056/NEJMoa1304459

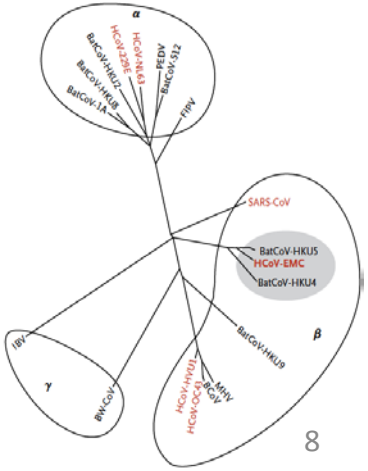
- More human infections in the shortest period than any other AI
  - More in four weeks than H5N1 in ten years in China

MERS-CoV
(Enveloped single-stranded RNA)

- Other CoVs mild URTI in humans
  - Except with comorbidity
- Nearest CoV to MERS is of bat origin, but nearest human virus is SARS-CoV
  - Different viral receptors
- Severity & nosocomial pattern of seeding and spread reminiscent of SARS-CoV



N Engl J Med 2012;367:1814-20.
DOI: 10.1056/NEJMoa1211721

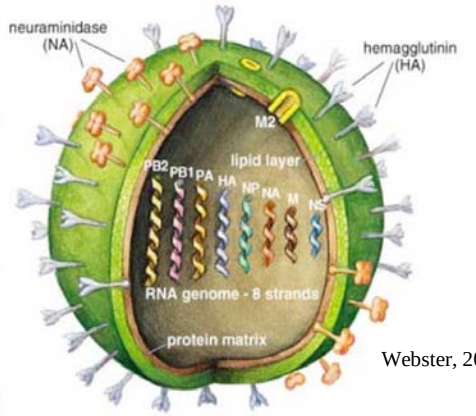


H7N9 Adaptation & Virulence Gene Mutation Markers

Table 2. Molecular Analysis of Three of the 2013 H7N9 Viruses.*

Gene	Sites†	Position	A/Shanghai/1/2013	A/Shanghai/2/2013	A/Anhui/1/2013
HA	Cleavage site		PEIPKGR*G	PEIPKGR*G	PEIPKGR*G
	RBS positions (H3 numbering), altered receptor specificity				
	Q226L	226	Q	L	L
	G228S	228	G	G	G
	Glycosylation motifs		30NGTK, 46NATE, 249NDTV, 421NWTR, 493NNTY (conserved in H7 HA viruses)	30NGTK, 46NATE, 249NDTV, 421NWTR, 493NNTY (conserved in H7 HA viruses)	30NGTK, 46NATE, 249NDTV, 421NWTR, 493NNTY (conserved in H7 HA viruses)
NA	Stalk		69–73 deletion	69–73 deletion	69–73 deletion
	Antiviral resistance R294K (oseltamivir)	294	K	R	R
PB2	Enhanced polymerase activity and increased virulence in mice				
	L89V	89	V	V	V
	E627K	627	K	K	K
PB1	H5 virus transmissible among ferrets				
	H99Y	99	H	H	H
	I368V	368	I	V	V
PB1-F2	Full length		90 aa	90 aa	90 aa
M1	Increased virulence in mice				
	N30D	30	D	D	D
	T215A	215	A	A	A
M2	Antiviral resistance S31N (amantadine)	31	N	N	N
NS1	Increased virulence in mice P42S	42	S	S	S

* Single letters refer to the amino acid (aa) found in the noted gene at a specific site.
† Sites are numbered from M, the start codon.



Webster, 2003

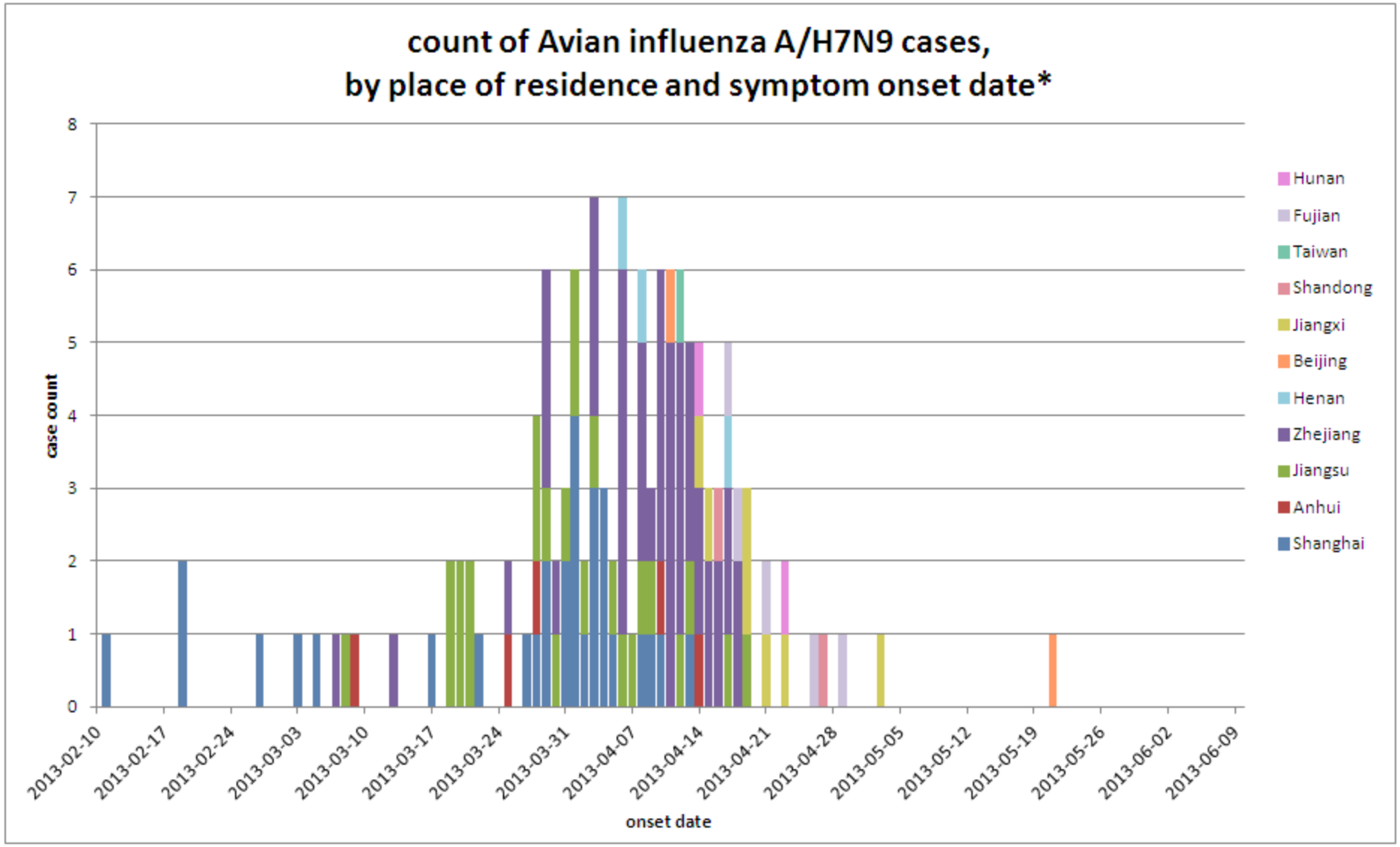
N Engl J Med 2013;368:1888-97.
DOI: 10.1056/NEJMoa1304459

H7N9 influenza activity in China/Taiwan by case residence, as of June 4th, 2013

Province	Deaths / Cases
Anhui	4 / 5
Beijing	0 / 3
Fujian	0 / 5
Henan	1 / 4
Hunan	1 / 2
Jiangsu	10 / 29
Jiangxi	1 / 7
Shandong	0 / 2
Shanghai	12 / 30
Zhejiang	7 / 45
Taiwan	0 / 1
Total	38+ / 133

Notes: +Two deaths could not be attributed to a province of residence due to insufficient data.
*City of residence for some cases/deaths not available. Taiwan case resides in Taiwan but works in Suzhou. Fatal Jiande case resided in Jiande but worked in Taicang. Data compiled from ProMed, GPHIN alerts and other public reports. Map created June 4th, 2013 by BCCDC.

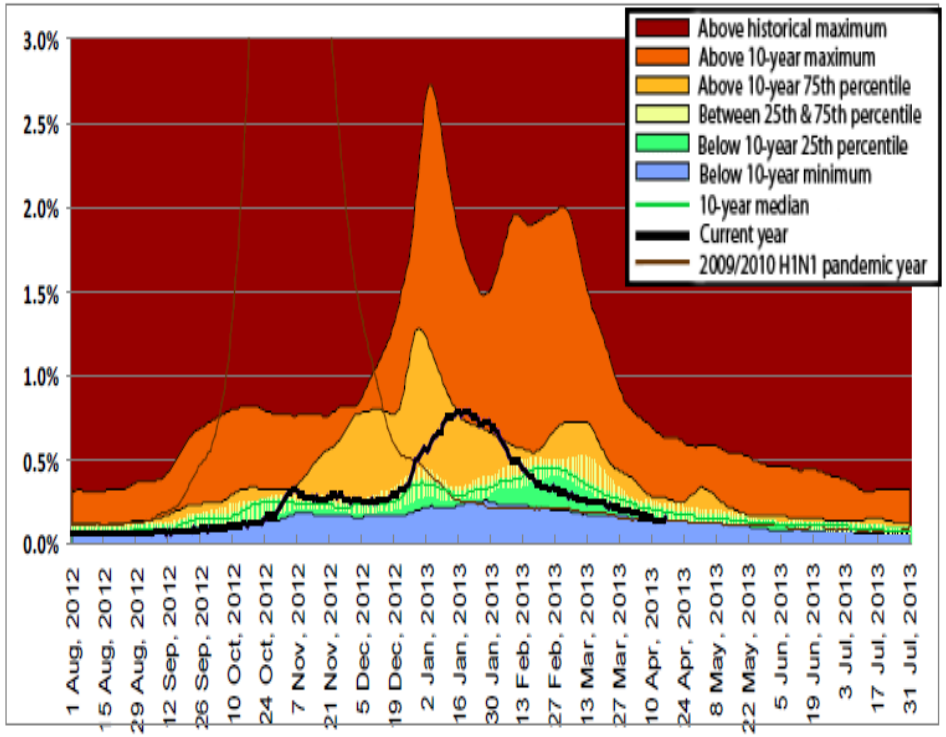
June 5, 2013 H7N9 Epidemic Curve



*Does not include: 1 Henan, 4 Jiangsu cases with unknown onset date; one asymptomatic case in Beijing.

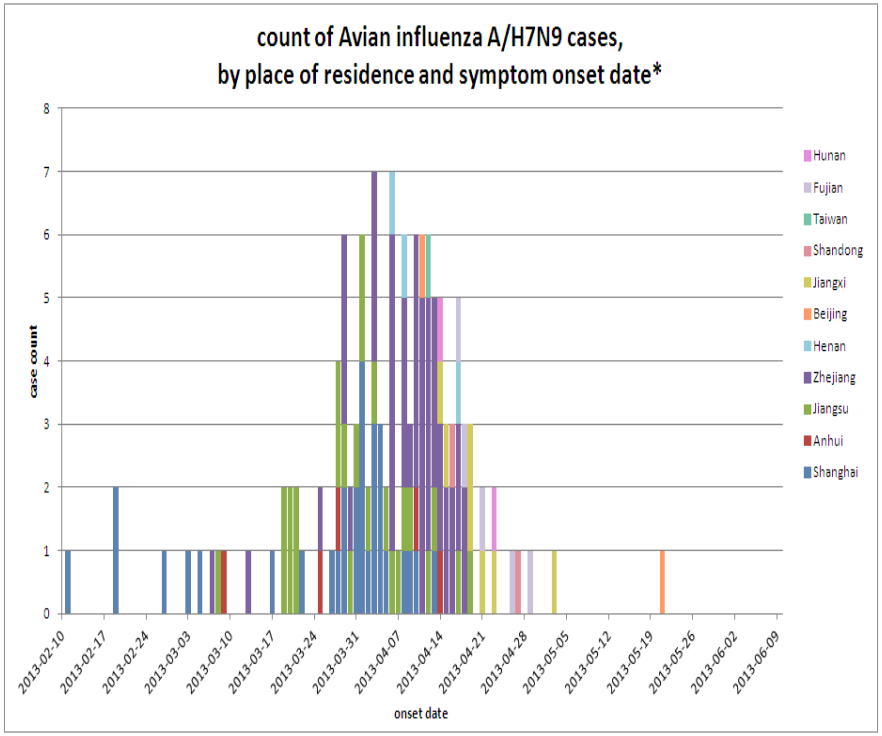
Influenza Epidemic Curve

Typical Seasonal/Pandemic Influenza – Outpatient ILI



H2H transmission

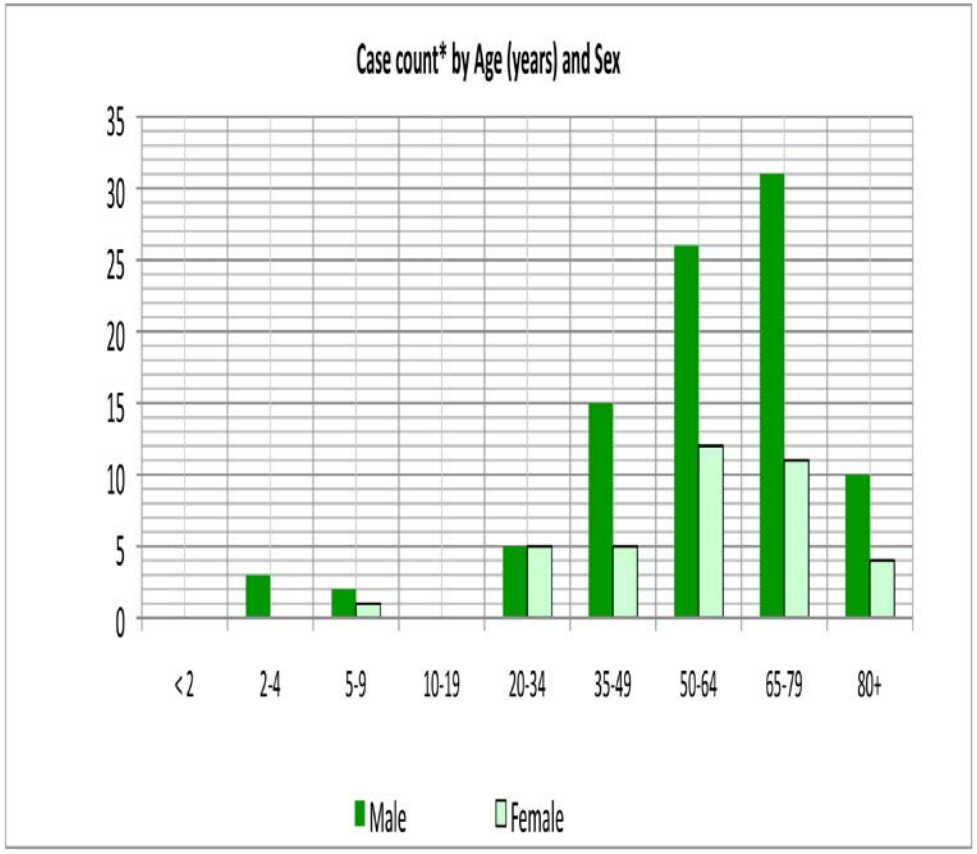
H7N9 Enhanced SARI

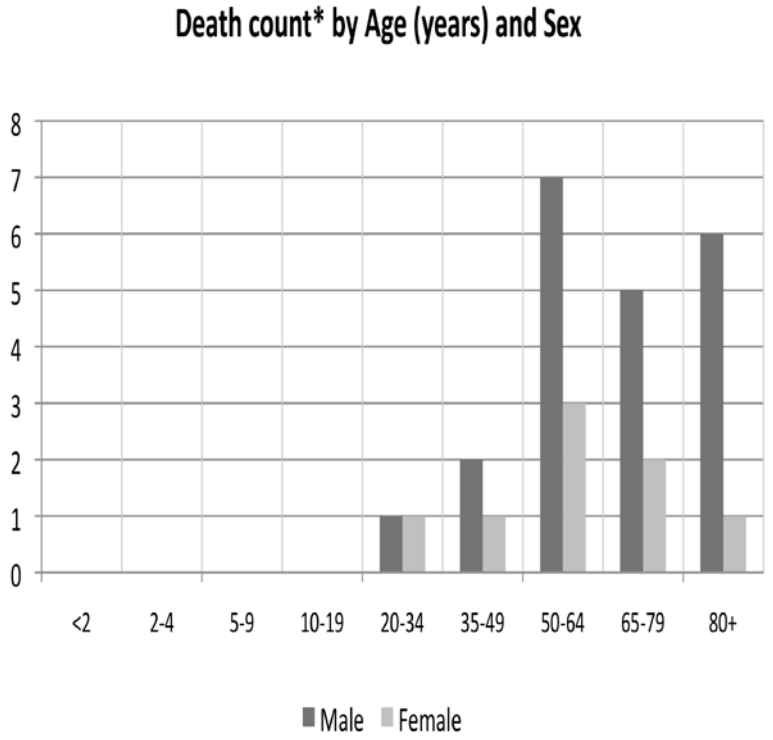


Broad epidemic in birds that SARI in humans mirrors <u>OR</u> H2H transmission?

H7N9 Epidemiology: Person

Unusual age and sex distribution – why older males?



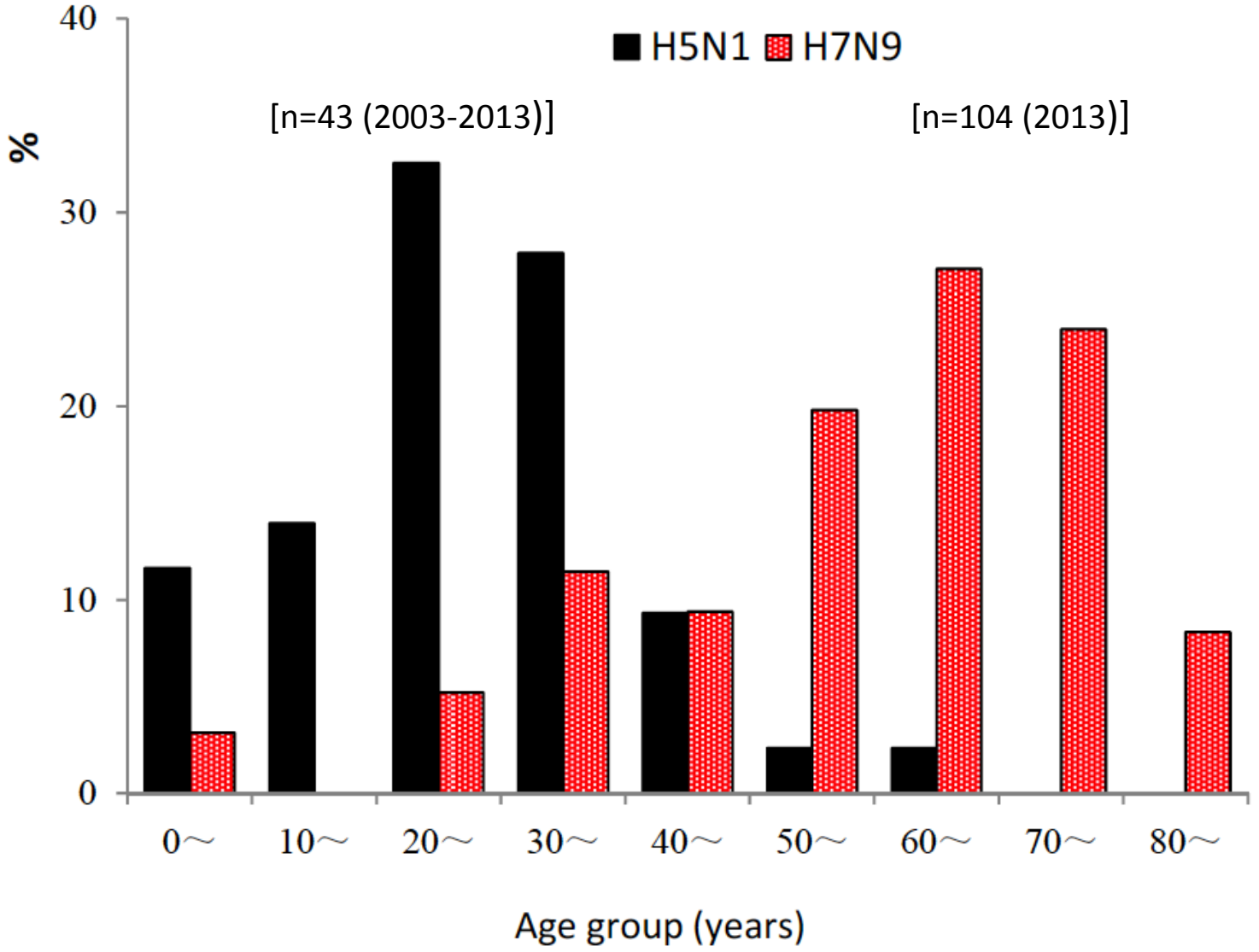


Age range: 2-91 years; median 60 years

*3 missing information not shown

*9 missing information not shown

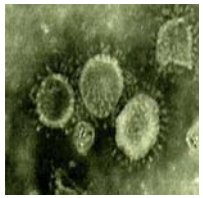
H7N9 vs H5N1 age distribution, China

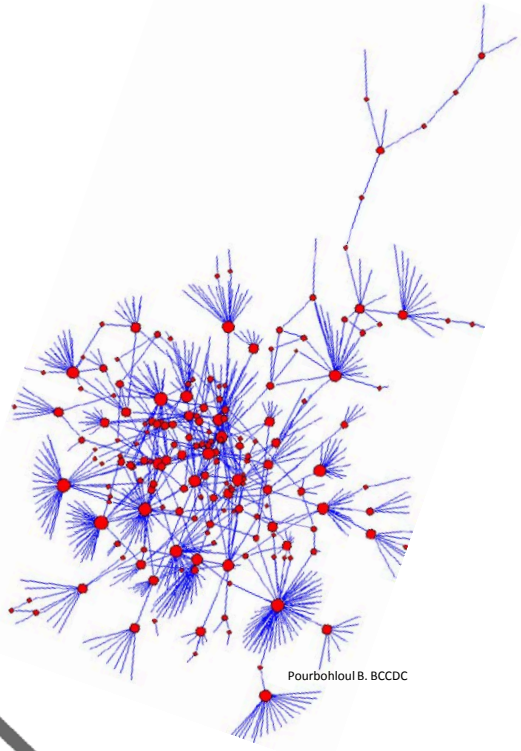


China-WHO Joint Mission on Human Infection with Avian Influenza A (H7N9) Virus
18-24 April Mission Report

Epidemiologic Triad: Disease Occurrence

Agent





Host

Environ

Virus-host interactions and the unusual age and sex distribution of human cases of influenza A(H7N9) in China, April 2013

D M Skowronski (danuta.skowronski@bccdc.ca)[1,2], N Z Janjua[1,2], T L Kwindt[1,2], G De Serres[3,4,5]

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2. University of British Columbia, Vancouver, Canada
3. Institut National de Santé Publique du Québec (National Institute of Health of Quebec), Québec, Canada
4. Laval University, Quebec, Canada
5. Centre Hospitalier Universitaire de Québec (University Hospital Centre of Quebec), Québec, Canada

Citation style for this article:
Skowronski DM, Janjua NZ, Kwindt TL, De Serres G. Virus-host interactions and the unusual age and sex distribution of human cases of influenza A(H7N9) in China, April 2013 . Euro Surveill. 2013;18(17):pii=20465. Available online: http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20465

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The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Serologic Study for Influenza A (H7N9) among High-Risk Groups in China

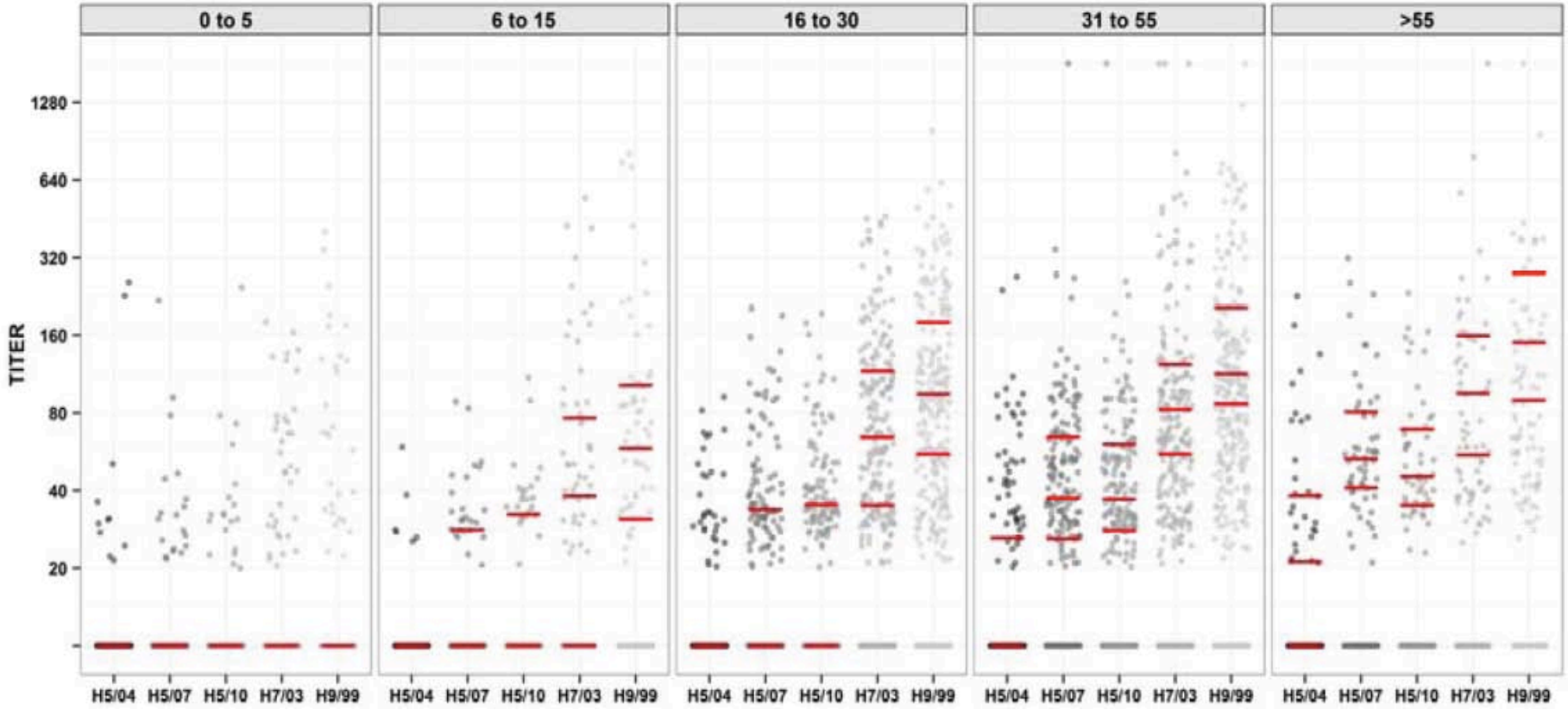
Tian Bai, M.D.
Jianfang Zhou, M.D.
Yuelong Shu, Ph.D.
National Institute for Viral Disease Control
China CDC

DOI: 10.1056/NEJMc1305865

2013 (H7N9) virus was used for the HAI and MN assays. HAI titers of 20 or more were detected in 7 of 1544 serum samples (5 with an HAI titer of 20 and 2 with an HAI titer of 40), but none of the 1544 samples were positive by the MN assay (MN titer <10). This retrospective serologic study does not find any evidence for human infection with the novel avian-origin influenza A (H7N9) virus in poultry workers before November 2012 in eastern China. It is possible that transmission from poultry to humans was occurring in other populations.

Increase in A/H7N7 antibody with age, Vietnam 2010-2012

Boni et al, JID [in press]



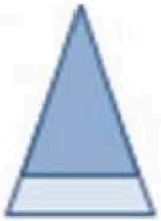
Hospital-based sampling two cities (n=1723), antibody measured by protein micro-array.

H9>H7>H5

H7=A/Chicken/Netherlands/1/2003 (H7N7); 96% HA1 homology A/H7N9 (10 aa Δ; 8 antigenic site)

H7N9: Possible Interpretations

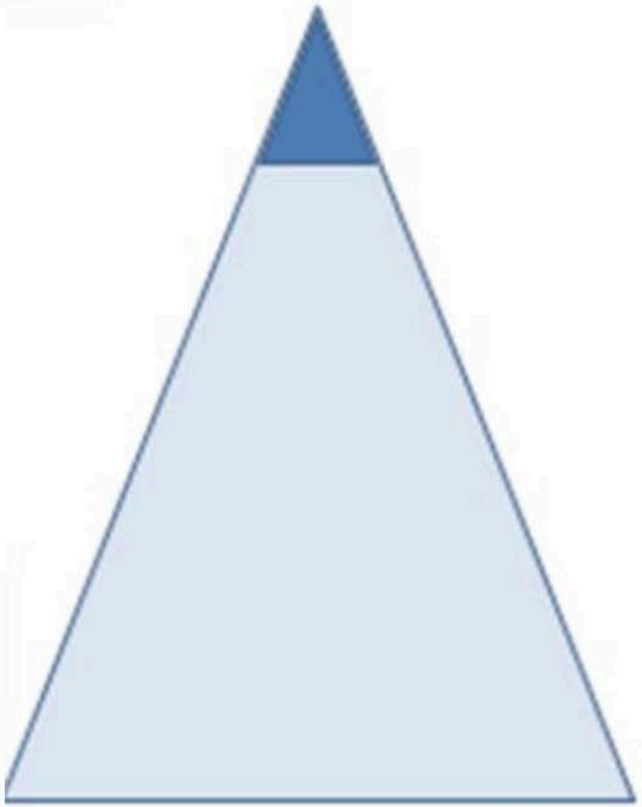
A The observed A(H7N9) cases are a high proportion of all cases and there are few mild or asymptomatic cases



Severe cases including deaths

Mild and asymptomatic cases

B The observed severe A(H7N9) cases are only a proportion of all the cases and there are many mild or asymptomatic cases



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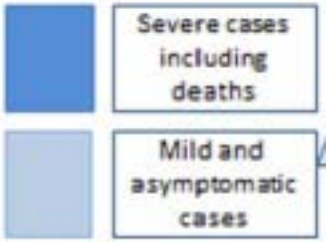

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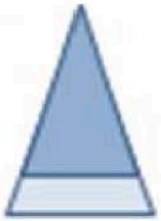
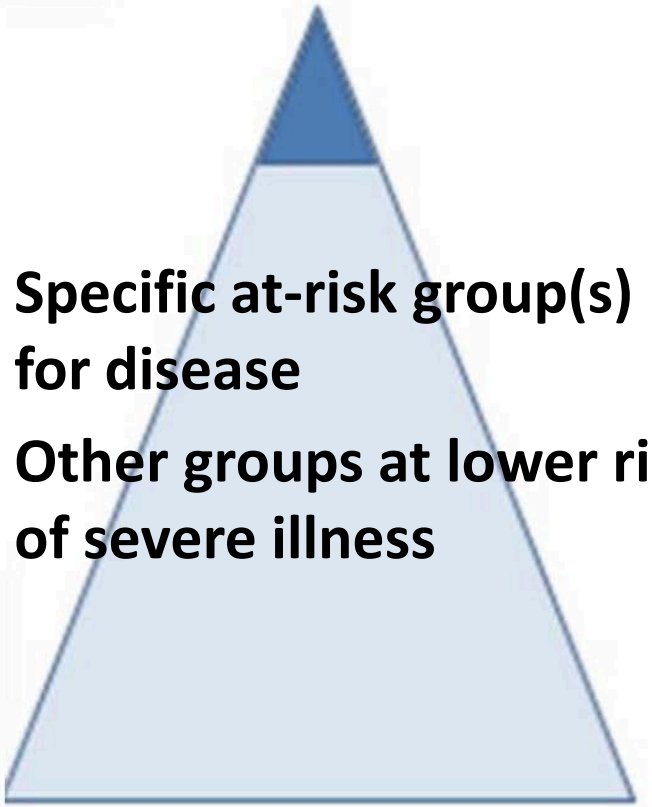


- Specific at-risk group(s) for exposure
- Other groups at lower risk of exposure



- Specific at-risk group(s) for disease
- Other groups at lower risk of severe illness

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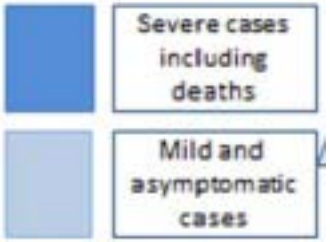
H7N9: Possible Interventions

A The observed A(H7N9) cases are a high proportion of all cases and there are few mild or asymptomatic cases



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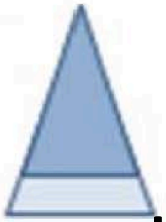
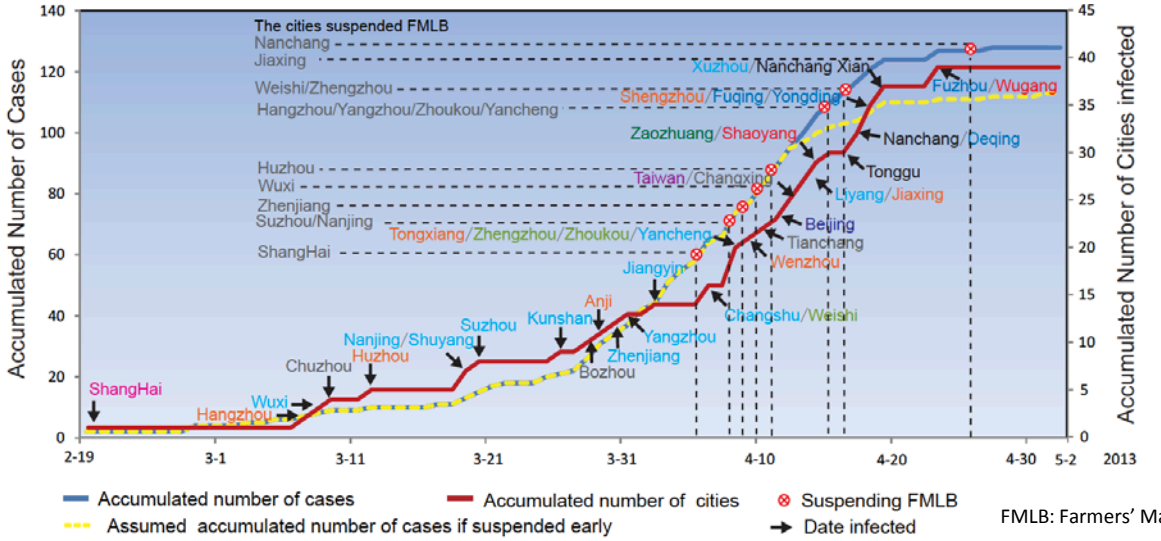


- **Containment possible**
- **Individual-level isolation**
- **Surveillance for early detection**
- **Active investigations to learn about virus characteristics**

- **Containment impossible**
- **Population-level mitigation**
- **Surveillance to guide interventions and impact**
- **Active investigations to learn about human risk factors**

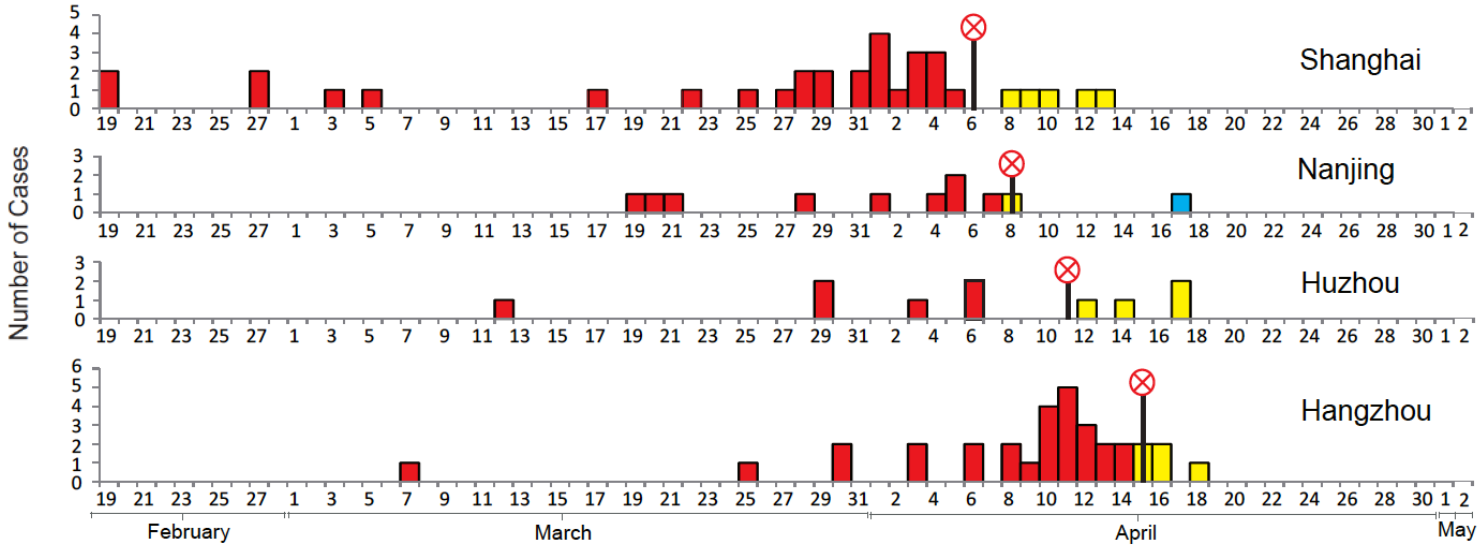
China-WHO Joint Mission on Human Infection with Avian Influenza A (H7N9) Virus
18-24 April Mission Report

H7N9: Impact of Poultry Suspensions



Supplement to: Xu J, Lu S, Wang H, Chen C. Reducing exposure to avian influenza H7N9. *Lancet* 2013; published online May 10. http://dx.doi.org/10.1016/S0140-6736(13)60950-2.

FMLB: Farmers' Market Live Birds



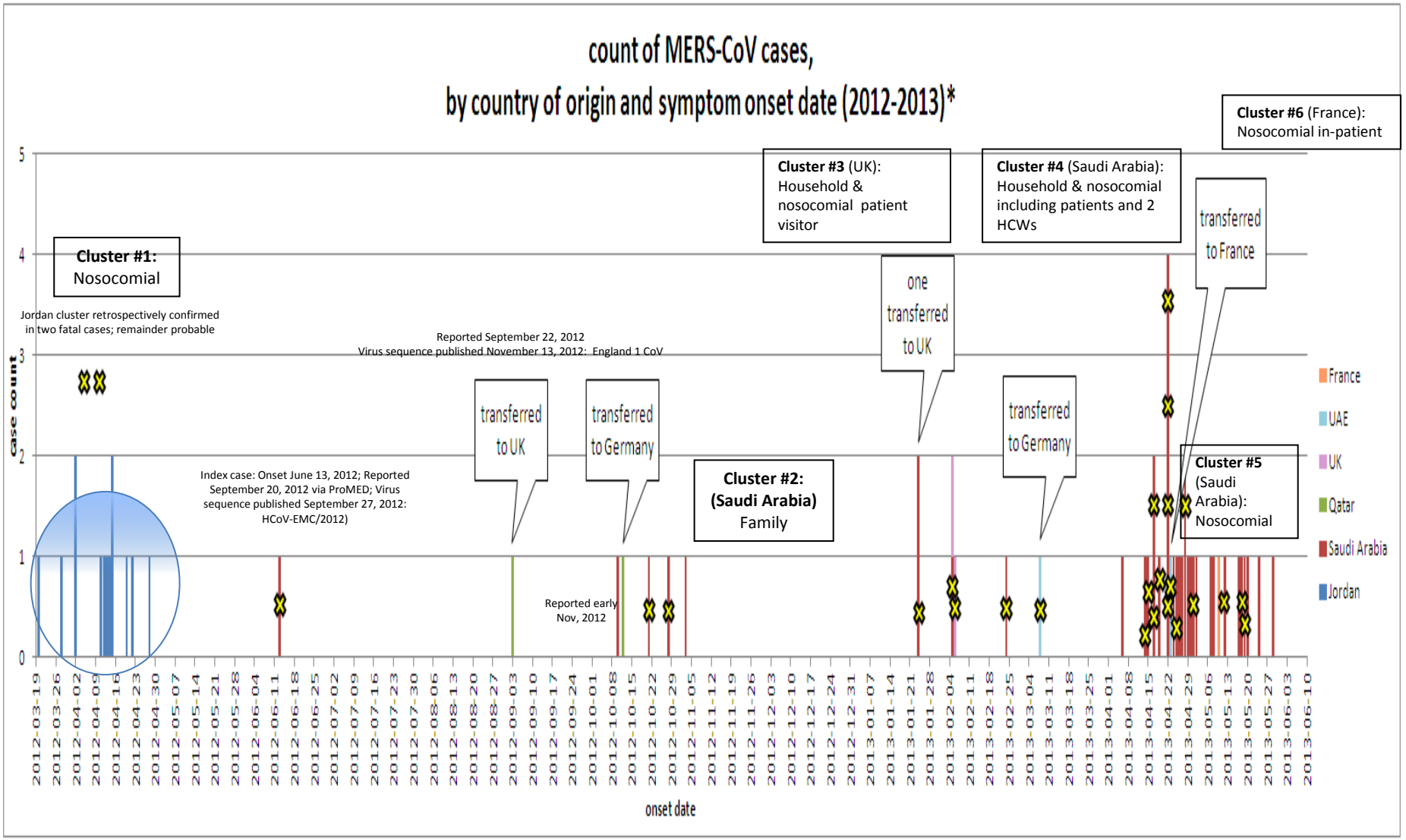
Human Illness from Avian Influenza H7N3, British Columbia

S. Aleina Tweed,* Danuta M. Skowronski,* et al

Emerging Infectious Diseases
Vol. 10, No. 12, December 2004

To date, illness in humans from H7 subtypes differs markedly in severity from that of avian influenza H5N1 (12). Their lower virulence should not be inferred to indicate lower pandemic potential since subclinical or mild infections may have greater opportunity through surreptitious spread to reassort and through mutation to become more virulent.

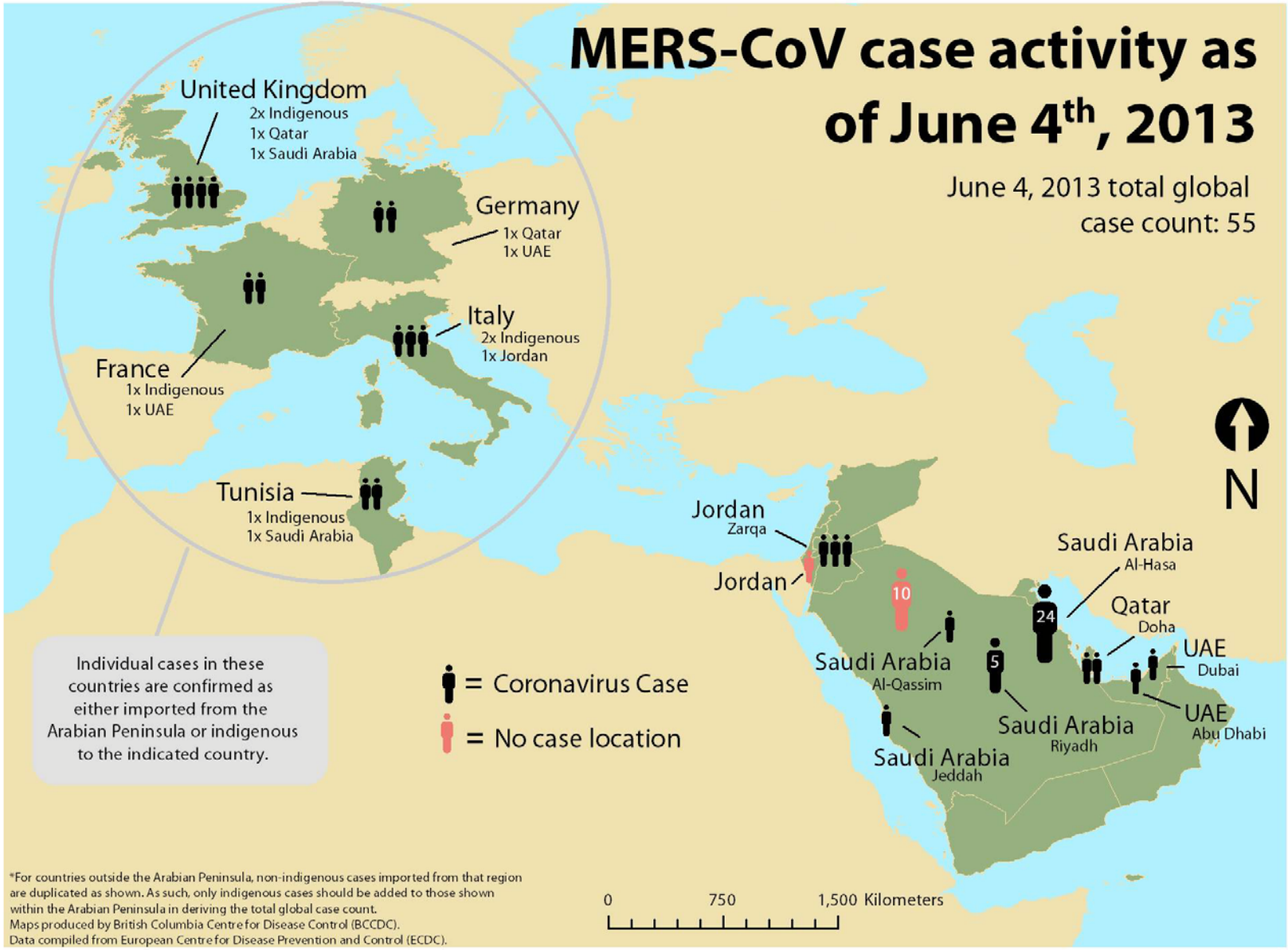
June 5, 2013 MERS-CoV Epidemic Curve



*Not shown: one fatality lacking details, seven others lacking onset date (3 KSA, 2 Tunisia, 3 Italy of which 1 x Jordan)

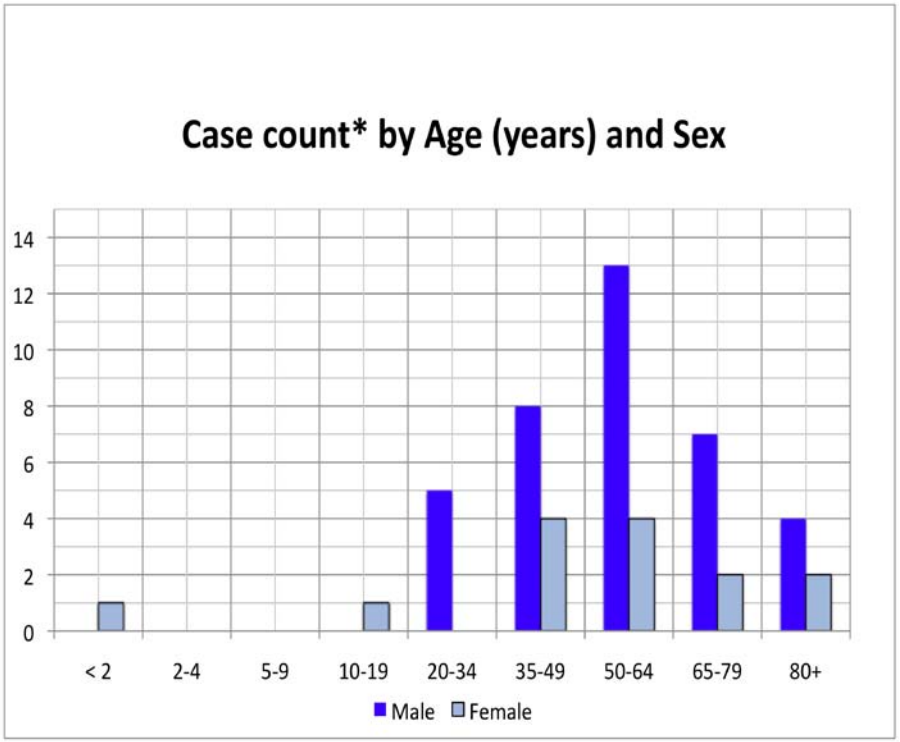
Cluster #7 (Tunisia): Family

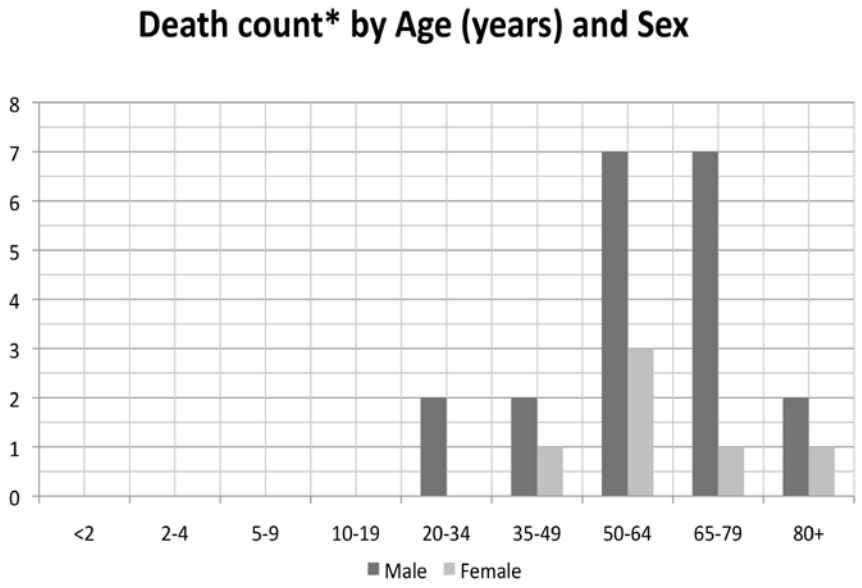
Cluster #8 (Italy): Family & Co-worker


MERS-CoV case activity as of June 4th, 2013
June 4, 2013 total global case count: 55
United Kingdom
2x Indigenous
1x Qatar
1x Saudi Arabia
Germany
1x Qatar
1x UAE
Italy
2x Indigenous
1x Jordan
France
1x Indigenous
1x UAE
Tunisia
1x Indigenous
1x Saudi Arabia
Individual cases in these countries are confirmed as either imported from the Arabian Peninsula or indigenous to the indicated country.
= Coronavirus Case
= No case location
Jordan
Zarqa
Jordan
10
Saudi Arabia
Al-Hasa
24
Qatar
Doha
UAE
Dubai
Saudi Arabia
Al-Qassim
5
Saudi Arabia
Riyadh
UAE
Abu Dhabi
Saudi Arabia
Jeddah
N
0
750
1,500 Kilometers
*For countries outside the Arabian Peninsula, non-indigenous cases imported from that region are duplicated as shown. As such, only indigenous cases should be added to those shown within the Arabian Peninsula in deriving the total global case count.
Maps produced by British Columbia Centre for Disease Control (BCCDC).
Data compiled from European Centre for Disease Prevention and Control (ECDC).

MERS-CoV Epidemiology: Person

Unusual age and sex distribution – why older males?





Age range 2-94 years; median 56 years

*4 missing information not shown

*4 missing information not shown

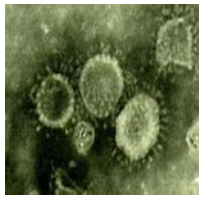
H7N9 and MERS-CoV: Questions

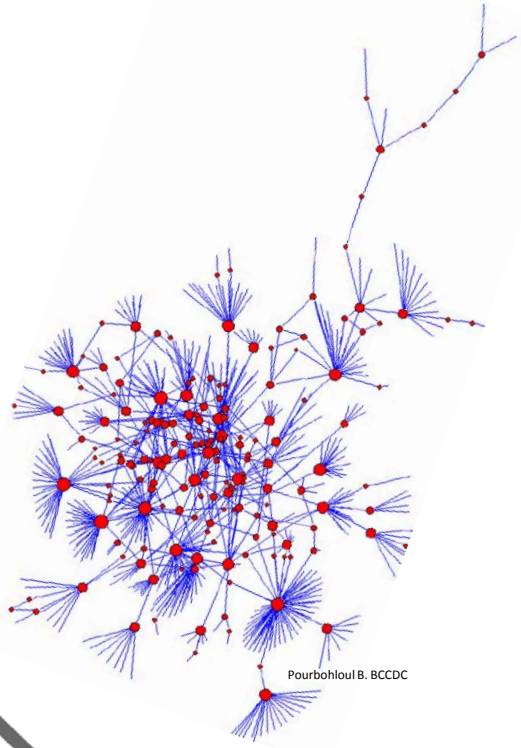
- **Virologic / epidemiologic characteristics**
  - Spectrum of illness and true infection rate
  - Risk factors for severe disease
  - Incubation period
    - Prolonged?
      - H7N9: median: 5-7 days; range: 1-15 days (WHO Mission Report)
      - MERS-CoV: nosocomial cluster 9-12 days
  - Shedding period
  - Infectious and Peak infectious periods
  - Transmissibility
  - Laboratory positivity
    - Timelines
    - Specimens
    - Serologic – needed to assess population prevalence

UNKNOWN

Epidemiologic Triad: Disease Occurrence

Agent





Host

Environ

Public Health Triad: Disease Mitigation

Surveillance

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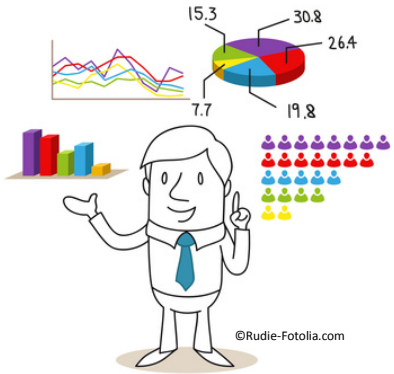

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Response


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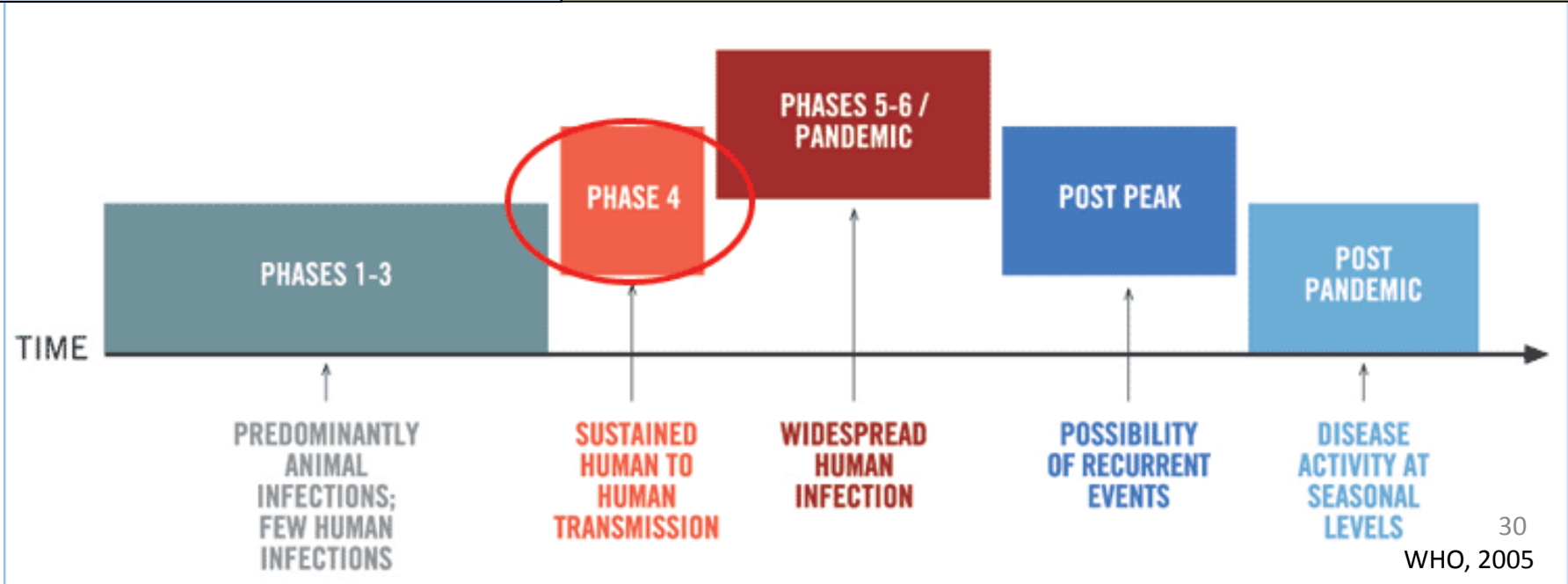
Investigation (Research)

NERVSS: Goals, Objectives, Actions

Goal: To minimize disease burden and disruption

Containment	Mitigation
Individual-level focus Containment focus Isolation and quarantine Risk characterization & control Active case/contact follow-up Special investigations (research)	Population-level focus Impact mitigation focus Vaccine and other intervention readiness Risk group characterization for targeted deployment Special investigations (research)



WHO, 2005

H7N9 and MERS-CoV: Questions

- Is containment possible?
- **H7N9 ?**
- **MERS-CoV ?**

- What should we be anticipating and doing?

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- **Lisan Kwindt, BC Centre for Disease Control**
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  - Literature assembly

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