



World Health
Organization

Update on H7N9 epidemiologic situation and vaccine development

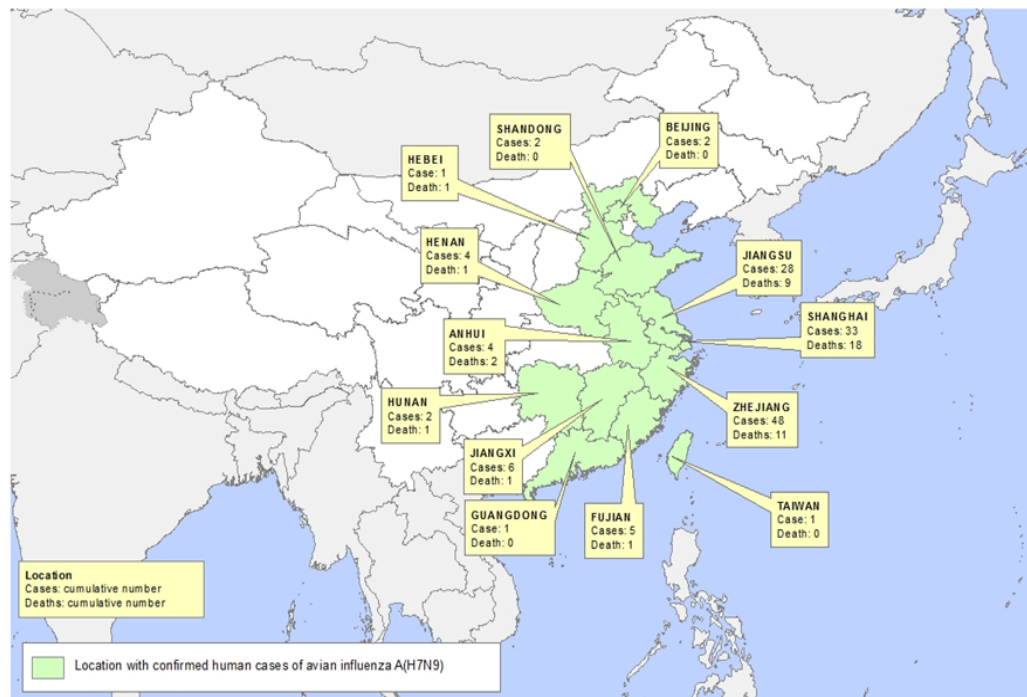
Wenqing Zhang

Meeting of SAGE
5-7 November 2013 • CICG Geneva

Epidemiologic situation

(as of 5 November 2013)

- 137 confirmed cases have been reported from China with 45 deaths
 - Currently 4 cases hospitalized; 88 cases discharged,



Data as of 25 October 2013, 8:00 GMT+1
Source: WHO/GIP

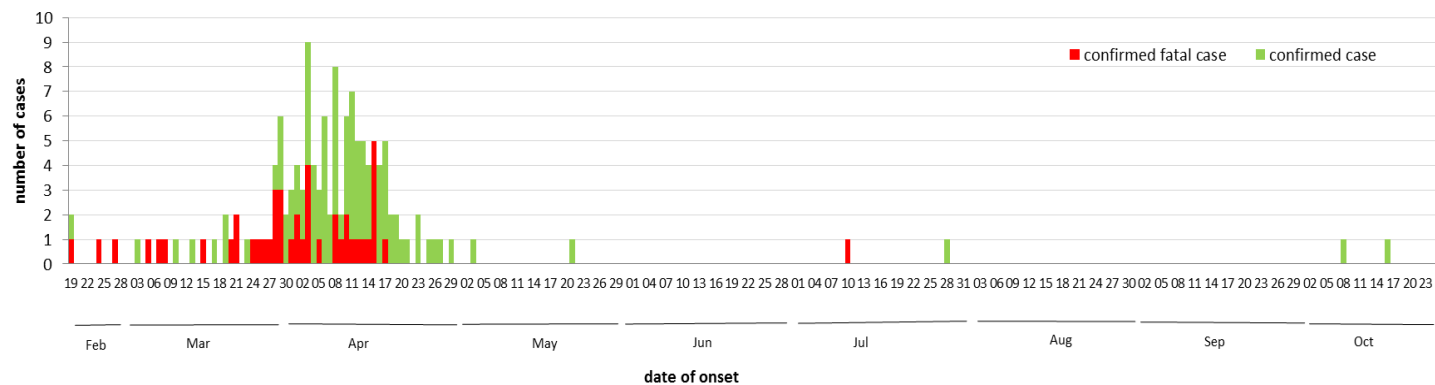
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Epidemiologic situation

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Epidemiologic situation

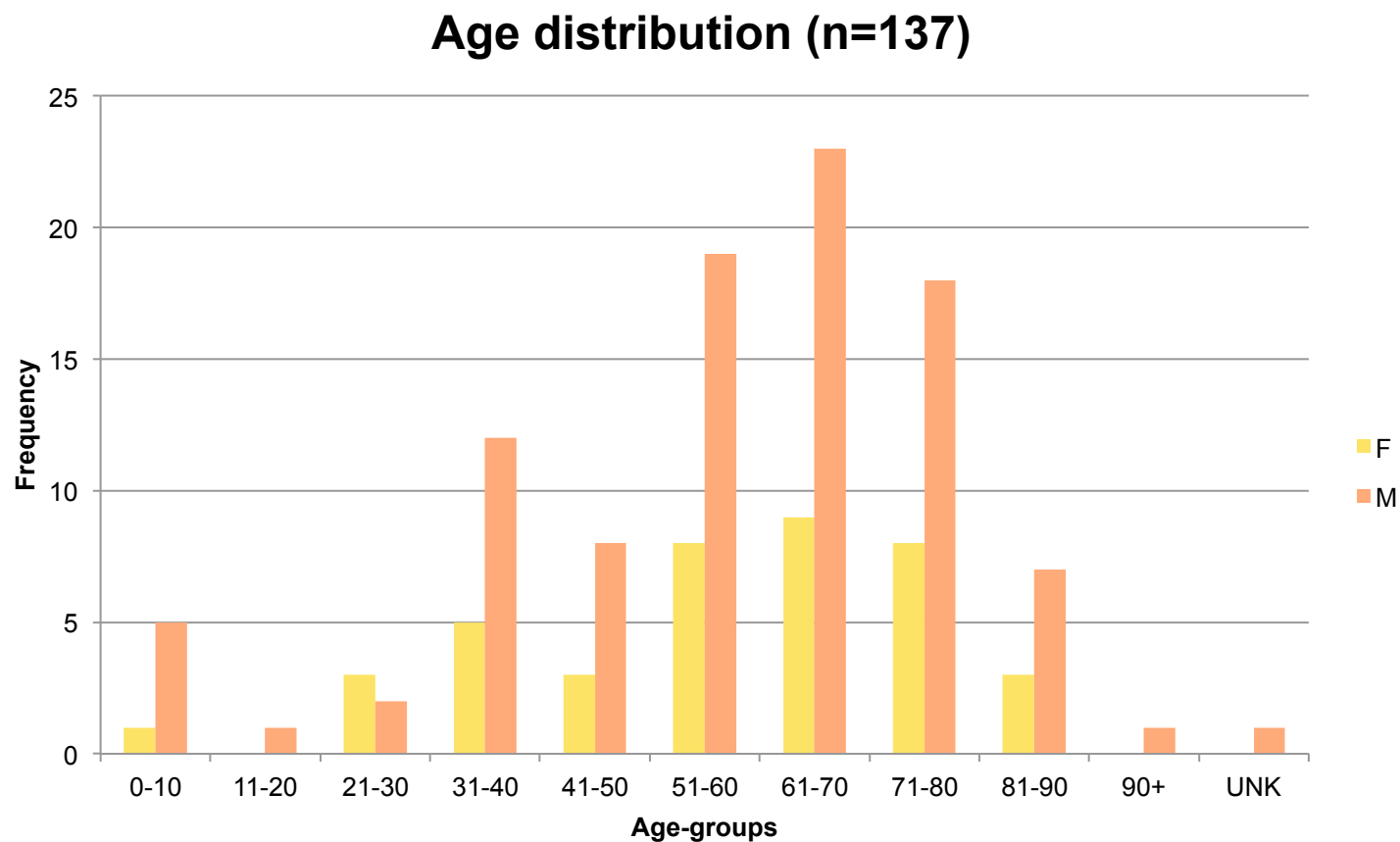
(as of 5 November 2013)

- 137 confirmed cases have been reported from China with 45 deaths
 - Currently 4 cases hospitalized; 88 cases discharged,
- Confirmed cases:
 - Median age 61 years old (range 2 to 91)
 - 71% male (40F/97M)
- 4 family clusters, one potential cluster between neighbors
- Clinical picture:
 - Most cases presented with severe pneumonia
 - CFR: 33%



Age distribution

(as of 5 November 2013)



Risk factors of infection

- Of 133¹ cases, 69% exposed to poultry or LBMs, 6% only exposed to other mammals and 6% were poultry workers
- Independent Risk Factors (case-control study)²
 - Direct contact with poultry OR 9.1 (1.6-50.9) p= 0.012
 - Chronic medical conditions (hypertension excluded) OR 6.0 (1.3-27.3) p=0.021
 - Environment-related exposures OR 4.2 (0.9-19.6) p=0.064

¹ Unpublished data, presented in the FAO – USAID Meeting on H7N9, Rome 12-13 Sept 2013

² Ai J, Huang Y, Xu K, Ren D, Qi X, Ji H, Ge A, Dai Q, Li J, Bao C, Tang F, Shi G, Shen T, Zhu Y, Zhou M, Wang H. Case-control study of risk factors for human infection with influenza A(H7N9) virus in Jiangsu Province, China, 2013. *Euro Surveill.* 2013;18(26):pii=20510. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20510>



Surveillance sensitivity

- ILI surveillance¹

- 6/46 807 swabs from 554 sentinel hospitals tested positive for H7N9
 - one pneumonia, five uncomplicated illness; age: 2-26 years
- No un-subtypeable influenza viruses detected from provinces/municipalities

- Sero-surveys: no evidence of asymptomatic infections

- 126 serum samples from healthy healthcare workers in Zhejiang province in April and controls²
- Poultry workers before Nov 2012 in eastern China³
- 14 close contacts (family unprotected, friends unprotected, HCW with standard precaution contact) none developed respiratory symptoms within 28 days follow-up⁴

¹ Cuiling et al, Monitoring avian influenza A(H7N9) virus through national influenza-like illness surveillance, China

² CID, Xu et al, Serological investigation of subclinical influenza A(H7N9) infection among HCW and non-HCW in Zhejiang Province, China

³ NEJM Bai et al, Serologic study for influenza A(H7N9) among high-risk groups in China.

⁴ Serological survey in close contacts with a confirmed case of H7N9 influenza in Taiwan, letter to editor, *Journal of infection* (2013) <http://dx.doi.org/10.1016/j.jinf.2013.08.003>



The A(H7N9) virus

(genetic analysis)

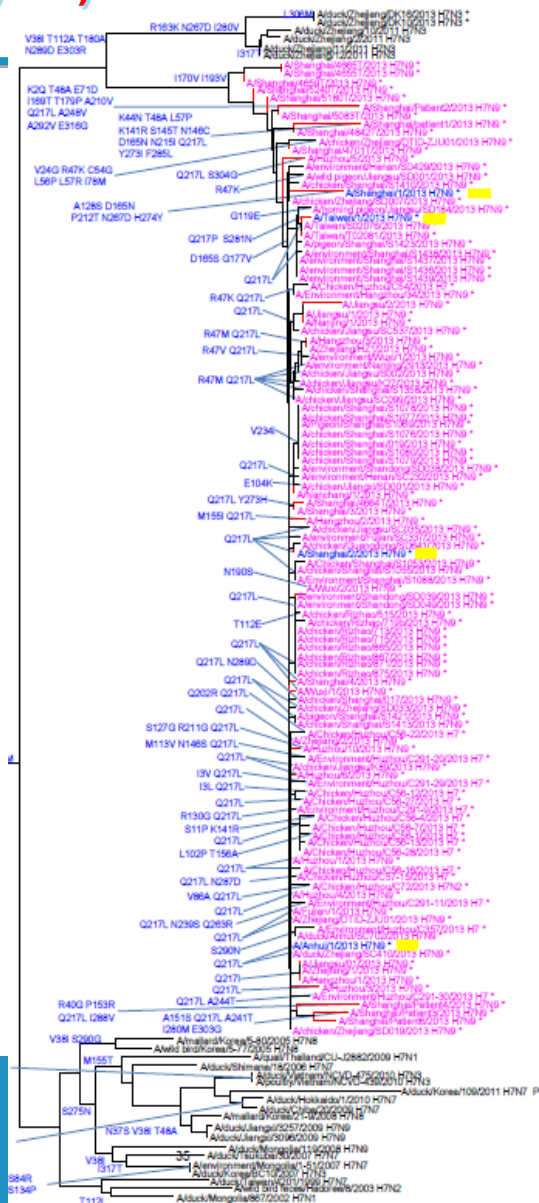
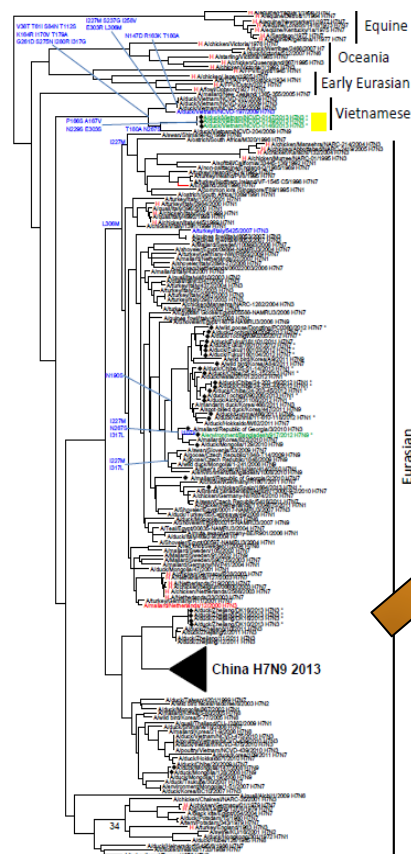
| GISAID/GenBank | # of viruses | # of viruses with full genome sequences |
|----------------|--------------|---|
| Human | 60 | 33 |
| Animal | 33 | 31 |
| Environment | 16 | 16 |
| Total | 109 | 80 |



The A(H7N9) virus

(genetic analysis)

- Contains genes of multiple avian origin
- All viruses are clustered together



The A(H7N9) virus

(genetic analysis)

- Contains genes of multiple avian origin
- All viruses are clustered together
- The receptor binding site of the HA shows conservation of AA typical of avian H7
 - Exceptions: L, I replacing Q at position 217 (equivalent to 226 in H3 numbering) in most viruses (birds/humans)
- Full genome analysis indicates some molecular signatures associated with mammalian adaptation
- Appears:
 - Increased transmissibility in ferret models
 - Enhanced replication at the temperature of upper airway of mammalian hosts and possibly humans



The A(H7N9) virus

(antigenic and other characteristics)

- Antigenically all tested viruses similar to each other

Haemagglutination inhibition reactions of influenza A(H7N9) viruses.

| REFERENCE ANTIGENS | Subtype | AH1 | SH2 | PC360 | NL12 |
|--------------------------------|---------|------------|------------|------------|------------|
| A/Anhui/1/2013 | H7N9 | <u>320</u> | 640 | 80 | 320 |
| A/Shanghai/2/2013 | H7N9 | 320 | <u>640</u> | 80 | 1280 |
| A/wild gs/Dongting/PC0360/2012 | H7N7 | 40 | 160 | <u>160</u> | 640 |
| A/mallard/Netherlands/12/2000 | H7N3 | 160 | 320 | 80 | <u>640</u> |
| TEST ANTIGENS | | | | | |
| A/Shanghai/1/2013 | H7N9 | 160 | 320 | 80 | 640 |
| A/Jiangsu/01/2013 | H7N9 | 320 | 640 | 80 | 640 |
| A/Zhejiang/01/2013 | H7N9 | 320 | 640 | 80 | 640 |
| A/Beijing/01-A/2013 | H7N9 | 320 | 640 | 80 | 640 |
| A/Henan/01/2013 | H7N9 | 160 | 320 | 80 | 320 |
| A/Shandong/01/2013 | H7N9 | 320 | 640 | 80 | 320 |
| A/Fujian/01/2013 | H7N9 | 320 | 640 | 80 | 640 |
| A/Jiangxi/01/2013 | H7N9 | 320 | 640 | 80 | 640 |
| A/Hunan/01/2013 | H7N9 | 160 | 640 | 80 | 640 |
| A/Anhui/02/2013 | H7N9 | 320 | 1280 | 80 | 640 |
| A/Shandong/0068A/2013 | H7N9 | 320 | 640 | 160 | 640 |
| A/chicken/Shanghai/S1053/2013 | H7N9 | 160 | 320 | 80 | 640 |
| A/pigeon/Shanghai/S1069/2013 | H7N9 | 320 | 640 | 80 | 640 |
| A/environment/Shandong/1/2013 | H7N9 | 320 | 640 | 160 | 1280 |

The A(H7N9) virus

(antigenic and other characteristics)

- Antigenically all tested viruses similar to each other
- Antivirals susceptibility
 - All viruses so far are resistant to M2 Inhibitors
 - In general susceptible to NAIs
 - In the course of treatment with NAIs, resistant mutations emerged in 3 patients
- LP – confirmed by IVPI testing
- In animals
 - Very few detections among huge number of specimens (< 0.01%)¹
 - Higher proportion in live markets (chickens, environment, pigeons) (20%-40%)^{2,3}
 - No positive detection in poultry farms, swine, wild birds or wild bird environments

¹ http://www.oie.int/fileadmin/Home/eng/Media_Center/docs/pdf/China_H7N9_final.pdf

² Chen Y et al, Human infections with the emerging avian influenza A H7N9 virus from wet market poultry: clinical analysis and characterization of viral genome. *The Lancet*, Published online April 25, 2013 [http://dx.doi.org/10.1016/S0140-6736\(13\)60903-4](http://dx.doi.org/10.1016/S0140-6736(13)60903-4)

³ J Han et al, Epidemiological link between exposure to poultry and all influenza A(H7N9) confirmed cases in Huzhou city, China, March to May 2013, *Euro Surveill.* 2013;18(20):pii=20481. Available online: <http://www.eurosurveillance.org/ViewArticle.aspx?ArticleId=20481>



WHO risk assessment on A(H7N9)

- Knowledge about the main virus reservoirs and the extent and distribution of the virus in animals remains limited
- Evidence does not support sustained human-to-human transmission
 - The A(H7N9) virus may have greater ability infecting mammals
 - Most cases reported contact with poultry or live animal markets
 - Human infections decreased sharply after live animal market closure
- Not unexpected: sporadic human cases and small clusters
 - Seasonality might have impact on the outbreak
- Likelihood of community level spread of this virus is considered low currently
- Not advise special screening at points of entry, nor any travel or trade restrictions



A(H7N9) vaccine development (1)

- WHO recommendation on A(H7N9) vaccine virus

- Update the provisional recommendation of 31 May 2013
- Recommend A/Anhui/1/2013-like



WHO recommendation on influenza A(H7N9) vaccine virus

26 September 2013

Since 31 March 2013, the public health authorities of China have reported a total of 135 human cases of novel avian influenza A(H7N9) infection including 44 deaths¹. To date, there has been no evidence of sustained human-to-human transmission.

Since the A(H7N9) virus seems to transmit from animals to humans more readily than the highly pathogenic avian influenza A(H5N1) viruses, and little or no immunity against the novel virus A(H7N9) exists in the human population, WHO is actively working with its Member States and partners on effective responses and preparedness. As part of these efforts,

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Based on genetic and antigenic analysis, it is recommended that:

- An **A/Anhui/1/2013-like*** virus is used for the development of influenza A(H7N9) vaccines for pandemic preparedness purposes.

* A/Shanghai/2/2013 is an A/Anhui/1/2013-like virus.

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A(H7N9) vaccine development (1)

- WHO recommendation on A(H7N9) vaccine virus
 - Update the provisional recommendation of 31 May 2013
 - Recommend A/Anhui/1/2013-like
- A(H7N9) candidate vaccine viruses
 - 6 RG vaccine viruses available
 - Classical reassortment in efforts, no success so far

| Parent virus | Candidate vaccine virus | Type of virus or reassortant | Developing institute | Available from |
|--------------------------------------|-------------------------|------------------------------|----------------------|----------------|
| A/Shanghai/2/2013 Synthetic HA&NA | IDCDC-RG32A * | Reverse genetics | CDC, USA | CDC, USA |
| | NIBRG-267 * | Reverse genetics | NIBSC, UK | NIBSC, UK |
| | CBER-RG4A * | Reverse genetics | CBER, USA | CBER, USA |
| A/Anhui/1/2013 | Wild type virus | | | WHO CCs |
| | NIBRG-268 * | Reverse genetics | NIBSC, UK | NIBSC, UK |
| | NIIDRG-10.1 * | Reverse genetics | NIID, Japan | NIID, Japan |
| | IDCDC-RG33A ** | Reverse genetics | CDC, USA | CDC, USA |

* These viruses are candidate vaccine viruses which have passed relevant safety testing and two-way haemagglutination inhibition (HI) tests. They can be handled under BSL-2 enhanced containment¹.

** This is a potential candidate vaccine virus which has passed two-way haemagglutination inhibition (HI) tests but the safety testing is still being finalized. It must be handled under BSL-3 containment.



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 - 6 RG vaccine viruses available
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- Distribution from WHO GISRS of high-growth reassortants (as of 5 Nov)

| From CCs/ERLs to | # of viruses | | | | | |
|---------------------|--------------|-------------|-----------|-----------|-----------|-------|
| | # of labs | NIIDRG-10.1 | CDC-RG32A | NIBRG-267 | NIBRG-268 | Total |
| GISRS labs | 48 | 0 | 6 | 6 | 6 | 18 |
| Non-GISRS labs | 92 | 3 | 22 | 17 | 22 | 64 |

- Yield evaluation – early stage
 - Lower than seasonal candidates in general
 - Except ion Medimmune LAIV and NVD – RG1603 – similar to seasonal
 - Comparable to H5 candidate vaccine viruses



A(H7N9) vaccine development (2)

- A(H7N9) vaccine reagents
 - Antisera to HA7, anti NA9 available in NIBSC
 - Ongoing development/calibration in CBER, NIBSC and TGA
- Clinical trials
 - Public database: not much details

| Type of vaccine | Producer | Adjuvant | Substrate | Dose /ug | Clinical phase | Timing |
|---------------------|----------------|------------------|-----------|-------------------|----------------|---------|
| Inactivated subunit | NVD | w/o MF59 | Cells | | I | 2013-14 |
| Inactivated split | Sanofi Pasteur | w/o MF59 or AS03 | Eggs | 3.75, 7.5, 15, 45 | II | 2013-14 |
| Inactivated split | Sanofi Pasteur | w/o MF59 | Eggs | 3.75, 7.5, 15, 45 | II | 2013-14 |
| Recombinant | Novavax | | | | I | |
| Live attenuated | MedImmune | | | | I | |



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 - Ongoing development/calibration in CBER, NIBSC and TGA
- Clinical trials
 - Public database: not much details
 - NIAID trials: Sanofi pasteur's inactivated H7N9 vaccine (egg-based)
 - Protocol 1: +/- MF59 (Novartis)
 - Enroll up to 700 adults; 2 doses, 21 days apart
 - 700 healthy adults enrolled-as of 21 October
 - Blood draws: day 0, 8, 21, 29, 42
 - Protocol 2: +/- AS03 (GSK)
 - Enroll up to 1,000 adults; 2 doses, 21 days apart
 - 643 healthy adults enrolled- as of 28 October
 - Blood draws: day 0, 8, 21, 29, 42

