

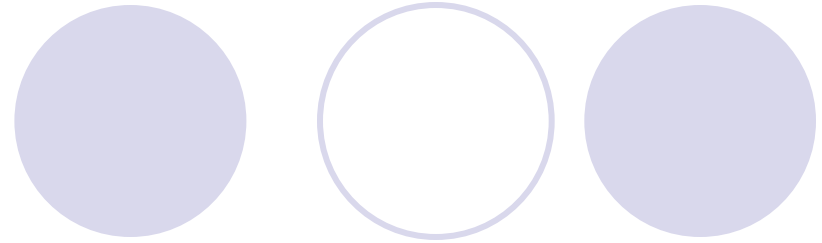
Emerging Pulmonary Infections

**Tsunami lung, Bird flu,
SARS**

Dr. Zia Hashim

Avian Influenza

- Established as an epizootic
- *Will it be a long feared human pandemic*



Pandemics: Occur every 11-39 years

- When new virus is introduced

- H1N1 1918 Spanish flu: 20-40 million deaths

- H2N2 1957 Asian flu

- H3N2 1968 Hong Kong flu (H3N2: still circulates)

All 3 pandemics spread world wide within 1 year

Outbreak



- 1983: U.S. (H5N2)
- 1999-2000: Italy (H7N1)
- 1997: Hong Kong (H5N1)
- 2001: Hong Kong (H5N1)
- 2003: European (H7N7)
- 2003-2004: SE Asia 8 countries (H5N1)
- 2004-2005: SE Asia and Eurasia

Indian scenario



- Feb 18: India first case of H5N1 strain
- 30,000 chickens died in Navapur
- Jalgaon: 26 samples sent in February end to the High Security Animal Disease Laboratory (HSADL) in Bhopal
- Tested positive: 4
- Poultry within 10 km from the affected villages culled: 73,000

Influenza Viruses: Types



Family: Orthomyxoviridae

- Type A
- Type B
- Type C



- Multiple species
 - Humans
 - Avian Influenza
- Most virulent group
- Varying degrees of virulence, can infect humans, birds, pigs, horses

Influenza A viruses



Further divided into subtypes based on

➤ **Hemagglutinin (H):** 15 (H1 to H15)

Function: Sites for attachment to infect host cells

➤ **Neuraminidase (N):** 9 (N1 to N9)

Remove neuraminic acid from mucin and release from cell

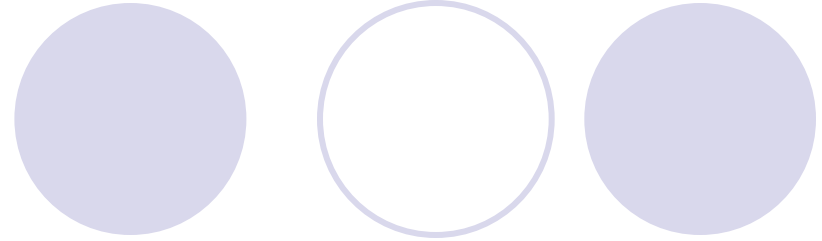
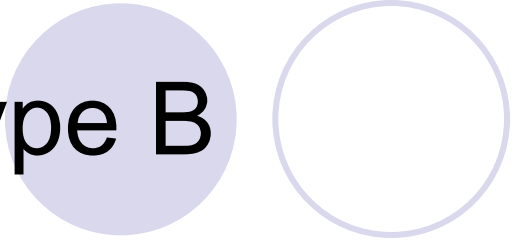
Possibility of unique 135 combinations

Contents



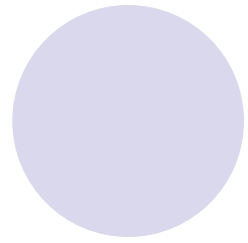
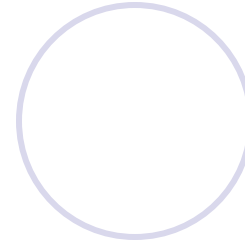
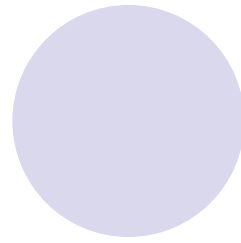
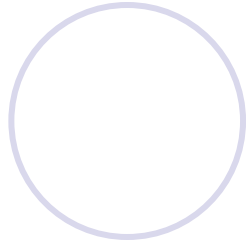
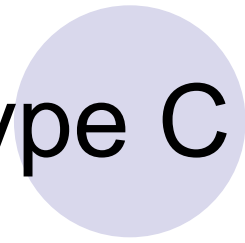
- Host-cell-derived envelope
- Envelope glycoproteins: important for entry and egress from cells
- Genome: RNA
 - Segmented
 - Negative-sense
 - Single-stranded

Type B



- Mostly humans
- Common
- Less severe than A
- Epidemics occur less often than A

Type C



- Humans and swine
- Different pattern of surface proteins
- Rare
 - Mild to no symptoms
- By 15 years: most have antibodies

“Antigenic Drift”

- Type A: genetically labile
- Don't have good mechanisms for proofreading and repairing of errors that occur during replication
- Genetic composition changes with replication in humans and animals
- Minor changes called antigenetic drift

“Antigenic Drift”

Lack of effective proofreading by RNA polymerase



High rate of transcription errors



AA substitutions in surface glycoproteins



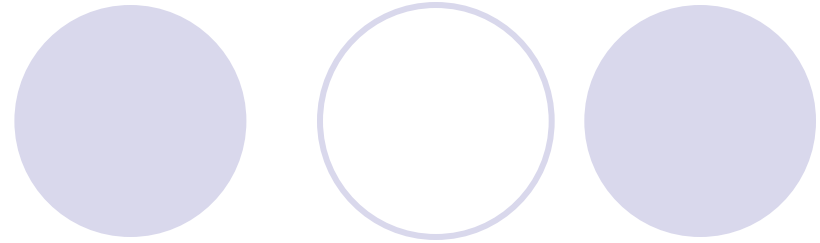
Substitutions in Ag-Ab binding sites



Evade humoral immunity



Reinfection

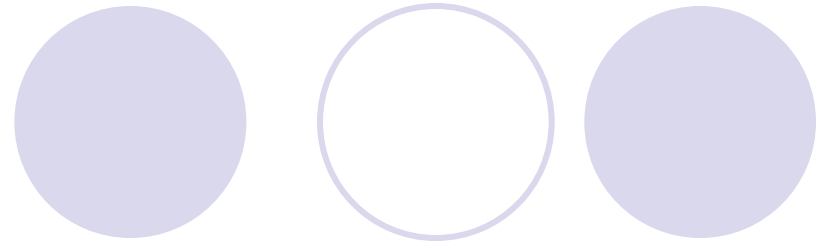




“Antigenic Shift”: new subtype

- Swap genetic materials with other subtypes of influenza A including those of different species
- **“Mixing vessel”**
 - **Humans**
 - **Pigs** *because both species can be infected with human influenza and avian influenza simultaneously*

“Antigenic Shift”



If 2 influenza viruses simultaneously infect



novel virus with new surface/internal proteins



with new haemagglutinin subtype
spreads efficiently in a naive human population



Pandemic influenza viruses

Antigenic Shift: Asia



- Favorable conditions for antigenic shift are common in Asia
- Humans: close proximity to
 - Domestic poultry
 - Pigs



Why is H5N1 a concern?

- Mutates rapidly
- Acquire genes from viruses infecting other animal species
- Birds that survive infection excrete virus for at least 10 days, orally and in feces
- Human-to-human transmission: mark the start of an influenza pandemic; no current evidence that this has occurred



H5N1: Characteristics

- Poor human transmission
- All the genes in H5N1 are still of bird origin
- Every human infection with avian influenza allows an opportunity for co-infection with both avian and human influenza
- Acquiring genes from human influenza viruses → Human transmission easier

H5N1



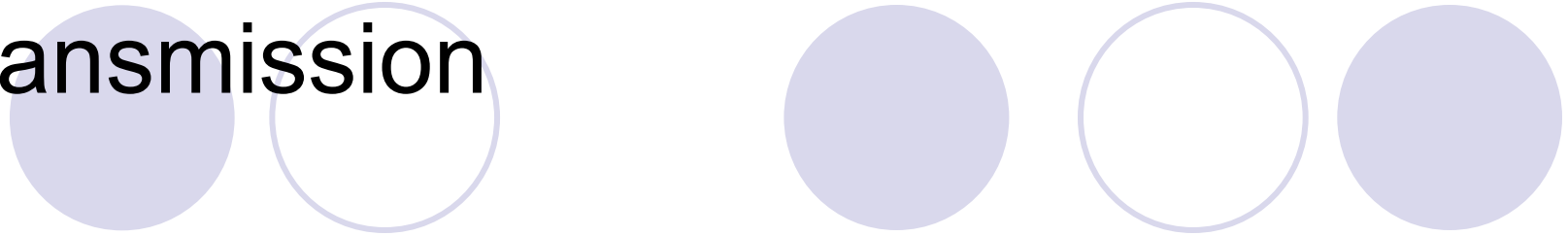
- Maximum human cases of severe disease
- Characteristics to start pandemic
- 3 occasions in recent years:
 - Hong Kong in 1997 (18 cases with 6 deaths)
 - Hong Kong in 2003 (2 cases with 1 death)
 - Current outbreaks began in December 2003 first recognized in January 2004

H5N1: A tough virus



- Multiplies in the intestines of birds & shed in saliva, nasal secretions and feces
- Can survive in bird faeces for
 - 4°C: > 35 days
 - 37°C: 6 days
- **Destroyed by**
 - 1% Na Hypochlorite
 - 70% Alcohol

Transmission



- Inhalation of infectious droplets
 - By direct contact
 - ? indirect (fomite) contact
- Bird-to-human
- Possibly environment-to-human
- Limited, non-sustained human-to-human transmission

Contact with poultry



- Slaughtering, defeathering, butchering and preparation for consumption of infected birds
- Exposure to chicken faeces
- Virus present in eggs but eggs unlikely to survive and hatch
- Consumption of undercooked poultry



Not a risk factor

- ✓ **Poultry consumption** in an affected country is not a risk factor:
 - *If thoroughly cooked*
 - *Person not involved in food preparation*
- ✓ **Simply traveling to country with ongoing outbreaks in poultry or sporadic human cases**

Incubation Period



- Longer than for other known human influenzas
- 2 to 4 days up to 8 days
- Working field: 7 d
- Upper limit: 8 to 17 days
- *Some time margin for public health authorities to intervene in the face of an epidemic*

Avian Influenza: 2 forms



- Pathogenicity based on genetic features or severity of disease in poultry

Low pathogenic AI (LPAI)

- H1 to H15 subtypes

Highly pathogenic AI (HPAI)

- Some H5 or H7 subtypes
- LPAI H5 or H7 subtypes can mutate into HPAI

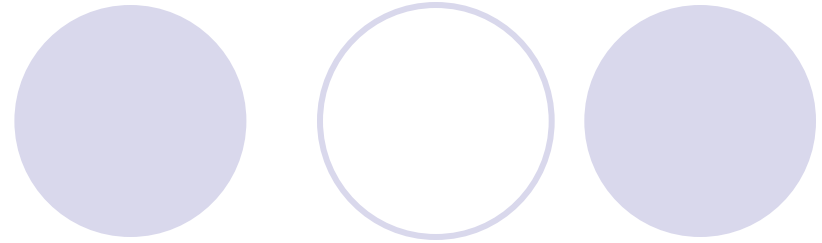
Signs in Birds



- Incubation period: 3-14 days
- Birds found dead
- Drop in egg production
- Neurological signs
- Depression, anorexia, ruffled feathers
- Combs swollen, cyanotic
- Conjunctivitis and respiratory signs

Birds Affected

- Chicken
- Turkey
- Guinea fowl
- Quail
- Pheasants
- Partridge
- Psittacines
- Ostriches
- Some Sea Birds





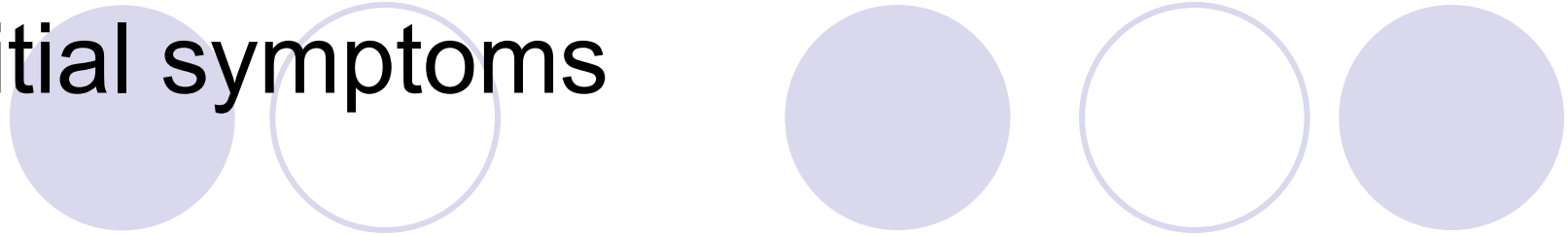
Differential diagnosis in Birds

- Virulent Newcastle disease
- Avian pneumovirus
- Infectious laryngotracheitis
- Infectious bronchitis
- Chlamydia
- Mycoplasma
- Acute bacterial diseases: Fowl cholera, *E. coli* infection

The image features six light purple circles arranged in two rows. The top row contains three circles, and the bottom row contains three circles. The text 'Human Influenza' is centered over the top row of circles.

Human Influenza

Initial symptoms



- High fever ($> 38^{\circ}\text{C}$)
- LRT Symptoms early
- Upper respiratory tract symptoms: uncommon
- Conjunctivitis rare: unlike H7
- Diarrhea, vomiting, abdominal pain, pleuritic pain, bleeding from the nose and gums: may be early

Clinical course

A decorative graphic consisting of two rows of circles. The top row has a solid light purple circle on the left and an outlined light purple circle on the right. The bottom row has a solid light purple circle on the left, an outlined light purple circle in the middle, and a solid light purple circle on the right.

- Dyspnea: median 5 days (range: 1 to 16)
- Respiratory distress, tachypnea, and inspiratory crackles: common
- Sputum production: variable; sometimes bloody

Suspicion



- Severe acute respiratory illness in countries or territories particularly in patients who have been exposed to poultry
- Serious unexplained illness: encephalopathy or diarrhea in areas with known H5N1 activity in humans or animals

Radiology



- Radiographic abnormalities: median 7 days (range: 3 to 17)
- Diffuse/Multifocal/interstitial patchy infiltrates
- Segmental or lobular consolidation with air bronchograms
- Pleural effusion: uncommon

Complications

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- ARDS
- MODS
- Cardiac: cardiac dilatation SVT
- VAP
- Pulmonary hemorrhage
- Pneumothorax
- Pancytopenia
- Reye's syndrome
- ✘ **Secondary bacterial infection has not been a factor**

Mortality: How do people die?

- Replicates in wide range of cell types
- Severe disseminated disease affecting multiple organs
- Recent avian influenza A : high rates of death among infants and young children
- CFR: 89 %
- Death: average 9 or 10 days after the onset of illness (range: 6-30)

Laboratory findings: Nonspecific



- Leukopenia: lymphopenia
- Thrombocytopenia: Mild-to-moderate
- Transaminitis
- Hyperglycemia
- Elevated creatinine levels

Virologic diagnosis



- Viral isolation:
 - Detection of H5-specific RNA
-
- Throat-swab
 - Pharyngeal swabs
 - Fecal samples
 - Urine

Laboratory confirmation of influenza A (H5N1)

One or more of the following:

- ✓ Positive viral culture
- ✓ Positive PCR assay for influenza A H5N1 RNA
- ✓ Positive IF test for Ag with use of monoclonal antibody against H5
- ✓ At least 4 x ↑ in H5-specific antibody titer in paired serum samples



Management

- Empirical treatment with broad-spectrum antibiotics
- Neuraminidase inhibitor pending the results of diagnostic laboratory testing
- Corticosteroids \pm
- Nebulizers and high-air flow oxygen masks: with strict airborne precautions
nosocomial spread

Antiviral agents



- **Amantadine/Rimantadine**

- Interfere with influenza A virus M2 protein (membrane ion channel protein) → inhibit replication
- **Not active against H5N1**

- **Zanamivir/Osetamivir: Neuraminidase inhibitors**

- → viral aggregation at host cell surface → reduces number of viruses released from the infected cell

Antiviral agents



❖ **Early mild cases**

➤ Oseltamivir

- 75 mg BD x 5d in adults
- Children >1 yr 30 mg BD; <15 kg/ 45 mg
15-23 kg/ 60 mg BD 23-40 kg

❖ **Severe infections:** Higher dose 150 mg BD in adults x 7 to 10 days



Resistance

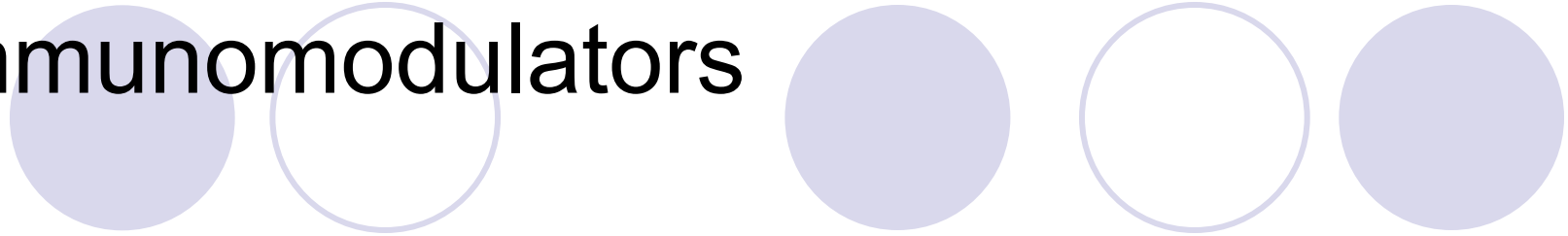
- Oseltamivir: substitution of a single amino acid in N1 neuraminidase (his274tyr)
- Incidence: 16%
- Full susceptibility to zanamivir and partial susceptibility to the peramivir in vitro
investigational neuraminidase inhibitor



Other possible agents

- Zanamivir
- Peramivir
- Long-acting topical neuraminidase inhibitors
- Ribavirin
- Interferon alfa ??

Immunomodulators



➤ **Steroids in H5N1:**

- Uncertain effects
- Fibroproliferative phase of ARDS
- Vietnam: all 4 patients given dexamethasone died

➤ **Interferon alfa:** antiviral and immunomodulatory activities: No RCTs, No recommendations



Vaccine

- Drawbacks to vaccination
 - Expensive
 - No cross protection between 15 H subtypes
 - Possible creation of reassortant virus
- Inactivated H5 and recombinant vaccine licensed in the U.S. for emergency in HPAI outbreaks

Prevention: Immunization



- **Reverse genetics**: rapid generation of nonvirulent vaccine viruses from recent influenza A (H5) isolates
- Inactivated vaccine: from human H5N1 isolate from 2004: immunogenic at high hemagglutinin doses
- Live attenuated, cold-adapted intranasal vaccines: under development

Hospital-Infection Control



- Surgical masks: multiple ones
- N-95 masks
- Chemoprophylaxis with 75 mg of oseltamivir OD x 7 to 10 days for possible unprotected exposure
- Preexposure prophylaxis: likelihood of a high-risk exposure (e.g., an aerosol-generating procedure)

Infection control precaution: Time

After onset of symptoms

□ **Adult** (>12 years) :

- 7 days or
- until discharge

□ **Child** (>12 years) :

- 21 days or
- until discharge

Confirmed cases of influenza A (H5N1):
postexposure prophylaxis



Prevention of a pandemic

- Prompt culling of infected poultry populations
- Vaccinate persons at high risk of exposure to infected poultry, reducing the likelihood of co-infection
- Workers involved in culling of poultry: prophylactic antivirals

Tsunami Lung



- Tsunami struck the Asian subcontinent and Africa on December 26, 2004:
>200,000 deaths
- Onslaught of waterborne illnesses including malaria and cholera
- Pulmonary complications

Immediate Pulmonary Complications

- Over hours
 - Massive hemorrhage
 - Hemo-pneumothorax
 - Pulmonary embolism



Later Pulmonary Complications

- Saltwater aspiration
- Hemopneumothorax
- PTE
- Aspiration pneumonia
- Pneumothorax, pneumomediastinum
- ARDS
- *Burkholderia pseudomallei*: endemic

Tsunami Lung

A decorative graphic consisting of six circles arranged in two rows. The top row has three circles: a solid light purple circle, an outlined light purple circle, and a solid light purple circle. The bottom row has three circles: a solid light purple circle, an outlined light purple circle, and a solid light purple circle.

- Type of aspiration pneumonia
- People swept by Tsunami waves inhaled contaminated salt-water
- Hydropneumothorax
- Bacteremia
- Brain abscess: FND

Other Mechanism

Soft tissue injuries



Bacteremia



Secondary Lung Involvement



Course of events

- Subacute presentation weeks after immersion in Tsunami
- No response to broad spectrum antibiotic
- Development of radiological and clinical manifestations of necrosis with pleural involvement

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Presentation

- Fever
- Cough sputum production
- Dyspnea
- Respiratory failure
- Focal neurological deficits

Natural disasters produce odd combinations of pathogens

- ***B. Pseudomallei***
- *Pseudomonas aeruginosa*
- *Stenotrophomonas maltophilia*
- *Acinetobacter baumannii*
- *Escherichia coli*
- *Klebsiella*
- *Enterobacter*
- *Neisseria*
- *Citrobacter*
- *Corynebacteria* (in 2)
- Viridans streptococcus (in 2)
- *Nocardia*
- Fungus

A decorative graphic at the top of the slide consists of two groups of three circles. The first group on the left has a solid light purple circle on the left, a white circle with a light purple outline in the middle, and a solid light purple circle on the right. The second group on the right has a solid light purple circle on the left, a white circle with a light purple outline in the middle, and a solid light purple circle on the right.

Treatment

- Imipenem + Cotrimoxazole: active against *Pseudomonas* and *B. Pseudomallei* & Anaerobes
- Debridement
- Respiratory care

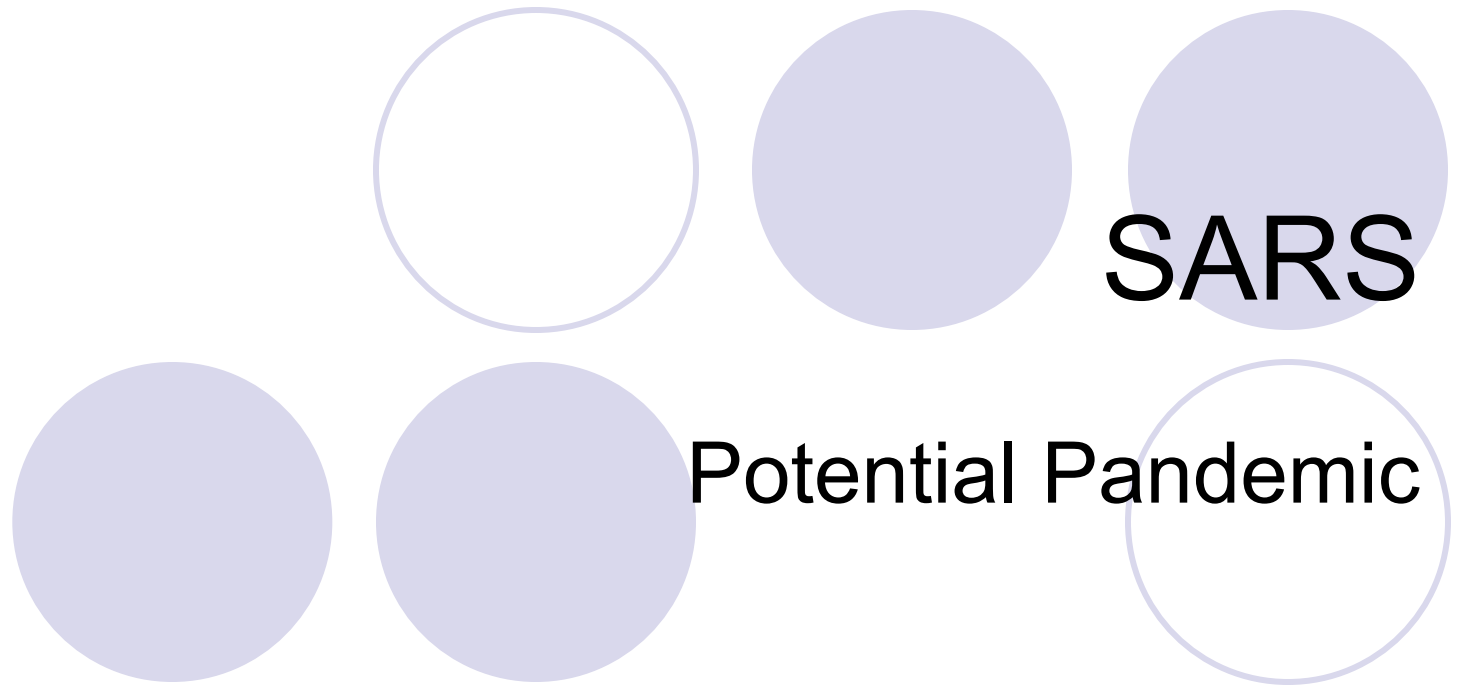
Hurricane Katrina: Why not
Katrina Lung



Could an infection like Tsunami Lung
emerge in victims of Hurricane Katrina?

No

Water not forced to lungs by high-speed
waves





Introduction

- First described 26 February 2003 in Hanoi
- Total: 8098 cases reported
- Deaths: 774
- Reported in 26 countries

Causative Organism

Coronavirus

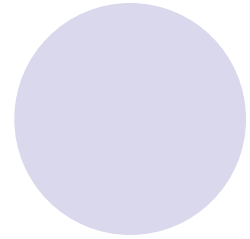
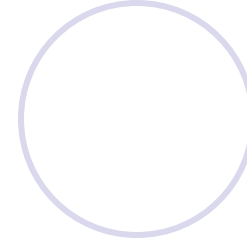
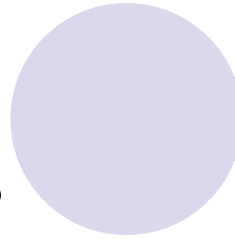
Lancet 22nd July 2003

Natural Reservoir



- Himalayan masked palm civet (*Paguma larvata*): Most commonly associated with animal to human transmission
- Chinese ferret badger (*Melogale moschata*)
- Raccoon dog (*Nyctereutes procyonoides*)

Consider all Possible Transmission Routes



- Most likely

- Droplet

- Contact

- Direct (Contamination of skin, clothing)

- Indirect (Contaminated fomites)

- Possible

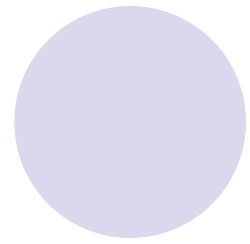
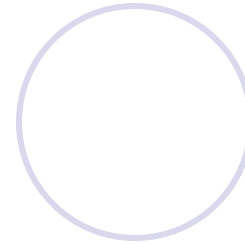
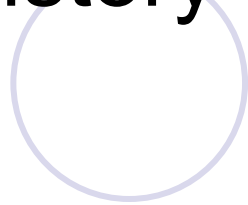
- Airborne

Incubation period

- Mean: 5 days range 2–10 days
- Respiratory symptoms: 3-7 days
- No transmission: before onset of symptoms
- Secondary transmission ↓↓ if cases are **isolated within 3 days** of onset of symptoms
- Global Interruption: **28 days** after the last reported case has been placed in isolation or died

Natural history of the disease

Ist Week



- Influenza-like prodromal symptoms
- Fever, malaise, myalgia, headache, and rigors
- No individual symptom or cluster of symptoms has proven specific
- Fever: most frequently symptom *may be absent on initial measurement*

Natural history of the disease

IInd Week

- Cough (initially dry)
- Dyspnea
- **Diarrhea** large volume and watery 70% without blood or mucus more commonly 2nd week of illness
- Rapidly progressing respiratory distress: 20% requiring ICU
- **TRANSMISSION OCCURS MAINLY DURING THE 2nd WEEK OF ILLNESS**

Elderly Children & Pregnancy



- **Elderly**

- Atypical presentations
- Afebrile illness
- Concurrent bacterial sepsis/pneumonia
- Underlying chronic conditions

- **Children: Mild**

- **Pregnancy**

- fetal loss: early pregnancy
- maternal mortality: later pregnancy



Radiology

Infiltrates on CXR > 80%

Infiltrates

- Initially focal in 50-75%
- Interstitial
- Most progress to involve multiple lobes, bilateral involvement



Laboratory Confirmation

RT-PCR positive for SARS-CoV from:

At least 2 different clinical specimens

OR

Same clinical specimen collected on ≥ 2 occasions
(e.g. sequential NPA)

OR

Two different assays or repeat RT-PCR using
RNA extract from original clinical sample on
each occasion of testing

Seroconversion by ELISA or IFA



- Negative Ab test on acute state serum followed by positive Ab test on convalescent phase serum

OR

- 4X or greater rise in antibody titre between acute and convalescent phase sera tested in parallel

Yield of different samples

Days after symptom onset	10	16	21
NPA	95%	90%	47%
Stool	100%	95%	66%
Urine	50%	35%	23%

Confirmed Case



At least 1 case in the 1st chain of transmission identified in country verified by WHO Lab

OR

Clinical & epidemiological evidence

- e/o SARS-CoV infection based on tests performed at national lab

A single +ve Ab test for SARS-CoV

OR

+ve PCR for SARS-CoV on single clinical specimen

Treatment Protocol

Fever & Chills
Suspected SARS



IV Cefotaxime
IV Levofloxacin

De-saturation



Oral Ribavirin 3.6g per day
Oral Prednisolone 1mg/kg/day

IV Ribavirin 1.2g per day
IV hydrocortisone 100mg q6h



IV Methyl-prednisolone 0.5 g/day
For 2 consecutive days

A diagram consisting of six circles arranged in a horizontal line. The first circle is solid light purple. The second circle is a light purple outline. The third circle is solid light purple. The fourth circle is a light purple outline. The fifth circle is solid light purple. The sixth circle is a light purple outline. The text 'Present situation' is positioned to the left of the first two circles.

Present situation

Inter-epidemic period

➤ Laboratories

➤ Animal reservoir

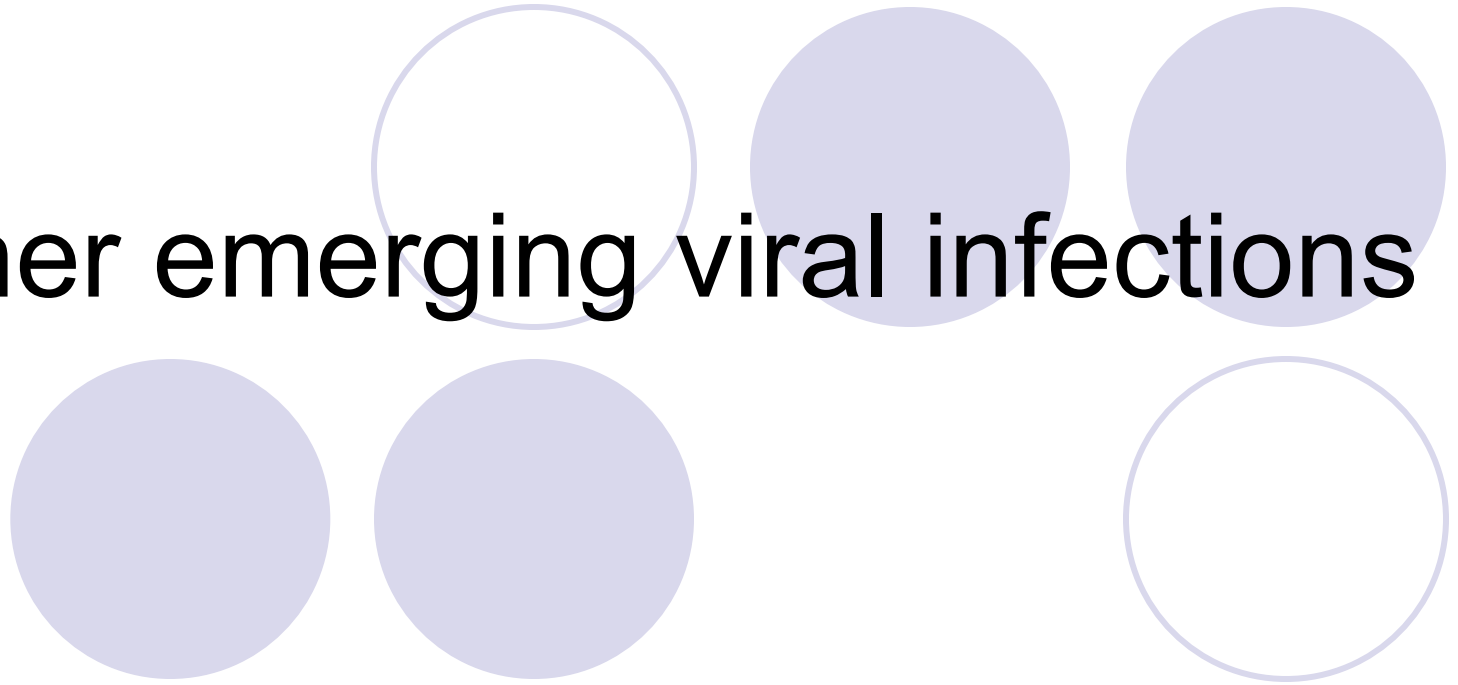
- 4 occasions when SARS reappeared
- 3 of these incidents: breaches in laboratory biosafety resulted in one or more cases
- The most recent incident: cluster of 9 cases 1 death affecting family and hospital contacts of a laboratory worker

Infection Control



- Respiratory protection
 - N95 mask preferred
 - Surgical mask if not available
- Contact protection of skin and clothing
- Avoid use of nebulizers when possible
 - If needed, perform nebulization in protected, negative pressure environment

Other emerging viral infections





Other emerging viral infections

□ **Filovirus:** Marburg & Ebola virus
Haemorrhagic fever

□ **Hantavirus:**

- Hemorrhagic fever with renal syndrome (HFRS) in Eastern hemisphere
- Hantavirus pulmonary syndrome: USA

Hemorrhagic fever with renal syndrome (HFRS)

- Incubation period: 2-3 weeks
- Hypotensive phase
- Oliguric phase
- Diuretic phase
- Convalescence
- ✓ I/V Ribavirin within 4 days
- **HPS**: No coagulopathy



Other emerging viral infections

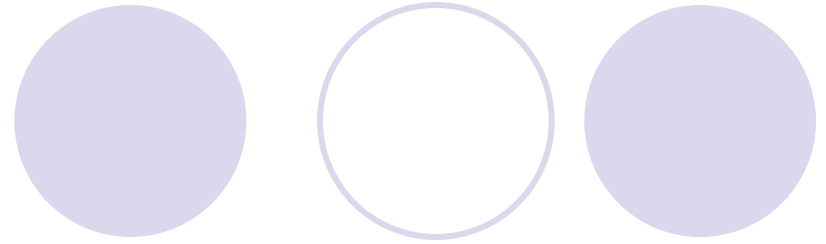
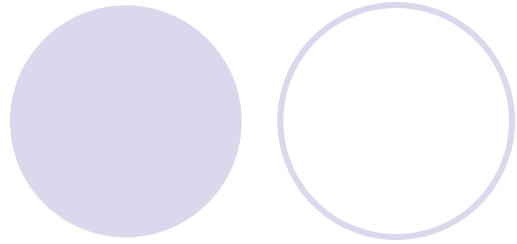
❑ **Henipavirus:**

- **Hendra virus:** in 1994 Horses
- **Nipah virus:** Encephalitis 105 deaths
culling of millions of pigs

❑ **Human metapneumovirus (hMPV)**

❑ **Poxviruses**

- ❑ **West Nile Virus (Flavivirus):** member of the Japanese encephalitis virus antigenic complex



Thank

You