RECENT, CURRENT & POTENTIAL PANDEMICS OF RESPIRATORY INFECTIONS

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H1N1 INFLUENZA VIRUS

INTRODUCTION

- Orthomyxoviridae family
- Three genera -A, B & C
- Subtypes – Based on H & N
- Nomenclature: eg- influenza A/Hiroshima/52/2005 (H3N2)
- No subtypes in B & C
- Influenza A(H1N1), A(H3N2) and Influenza B-presently circulating species

STRUCTURE OF INFLUENZA VIRUS

- Irregular, spherical shaped
- Lipid envelope
- H & N proteins
- Nucleo- capsid

- Genetic variation: surface proteins, viral genome containing eight RNA segements
- Antigenic shift: Major antigenic changes – causes pandemics
- Antigenic drift: Minor antigenic variations – causes epidemics
- Can occur in either HA or NA or both
- H1N1 2009 is significantly novel, 27.2% and 18.2% aminoacid sequence changes from H1N1 isolates of 2008

William R G,*Virology Journal 2009*, ***6:51***

TABLE 180-1 EMERGENCE OF ANTIGENIC SUBTYPES OF INFLUENZA A VIRUS ASSOCIATED WITH PANDEMIC OR EPIDEMIC DISEASE

Years	Subtype	Extent of Outbreak
1889–90	H2N8[a]	Severe pandemic
1900–03	H3N8[a]	?Moderate epidemic
1918–19	H1N1[b] (formerly HswN1)	Severe pandemic
1933–35	H1N1[b] (formerly H0N1)	Mild epidemic
1946–47	H1N1	Mild epidemic
1957–58	H2N2	Severe pandemic
1968–69	H3N2	Moderate pandemic
1977–78[c]	H1N1	Mild pandemic

Harrison's principles of internal medicine-17th edition

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Emergence of a Novel Swine-Origin Influenza A (H1N1) Virus in Humans

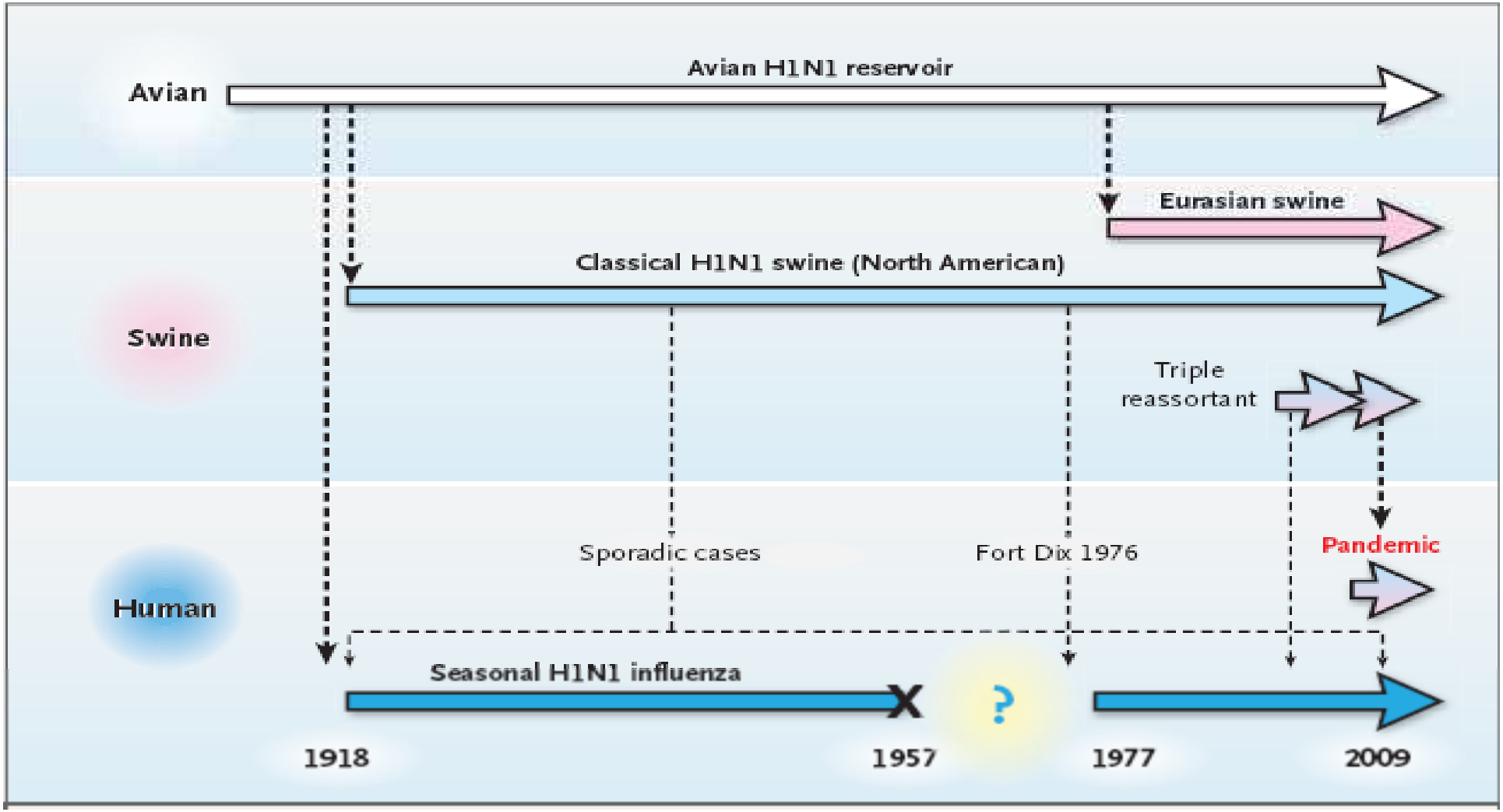
Novel Swine-Origin Influenza A (H1N1) Virus Investigation Team*

- On April 15&17, 2009 novel swine –origin influenza A(H1N1) virus (S-OIV) – identified in 2 epidemiologically unlinked patients in united states, following that 642 confirmed cases identified
- CDC recommendations- To consider the diagnosis of S-OIV in patients with acute febrile respiratory illness
- WHO raises pandemic alert from phase 4 to 5
- 60% of patients were 18 years of age or younger
- S-OIV is sensitive to Oseltamivir and Zanamavir - recommended for hospitalised patients & patients with high risk of complications

Historical Perspective — Emergence of Influenza A (H1N1) Viruses

Shanta M. Zimmer, M.D., and Donald S. Burke, M.D.

N Engl J Med 2009;361:279-85.



Important aspects of infection

- Risk population: chronic cardiovascular or pulmonary diseases,chronic metabolic diseases, immunodeficiency, second and third trimesters of pregnancy & young children
- Droplet and aerosol spread, fomites
- Incubation period: 2 to 7 days
- Viral shedding –starts 1 day before the onset of illness & lasts upto 5-7 days
- Course of clinical illness

CLINICAL FEATURES

- Systemic symptoms-fever, prostration, myalgias and malaise
- Respiratory symptoms
- Diarrhea and vomiting
- Reslove in 3 to 5 days
- Complications-primary viral pneumonia

  Secondary bacterial pneumonia
- Chest radiograph

DIAGNOSIS

- Specimen: Timing

  Nasopharyngeal(nasal) swab, throat swab, sputum

  ET aspirate for intubated patients
- Isolation of virus in culture- sensitive and specific, time taking
- Detection of antigen- Real time RT-PCR for novel H1N1- will test positive for influenza A and negative for H1 & H3
- Specific antigen- can detect novel H1N1
- Four fold rise in virus specific antibody titres (paired samples 14 days apart)
- Other tests: Rapid influenza antigen test, IFA(DFA or IFA)

CATEGORIES OF PATIENTS

- CATEGORY A- mild symptoms, mildfever, sore throat, myalgias, headache, diarrhea and vomiting, no need of testing for H1N1, symptomatic treatment, no oseltamivir
- CATEGORY B- CAT A + high grade fever, severe sore throat

  CAT A+ high risk conditions

  Home isolation & oseltamivir

  No need of testing for H1N1
- CATEGORY C- CAT A+ CAT B+ shortness of breath, chestpain, drowsiness, sputum mixed with blood, cyanosis, fall in blood pressure, refusal to accept feed- IMMEDIATE HOSPITILIZATION AND TREATMENT

Prescription of anti-influenza drugs for healthy adults: a systematic review and meta-analysis

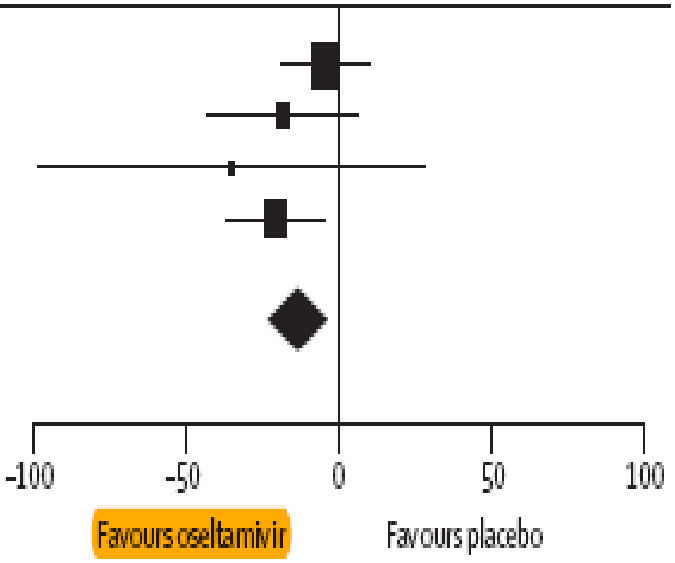
Jane Burch, Mark Corbett, Christian Stock, Karl Nicholson, Alex J Elliot, Steven Duffy, Marie Westwood, Stephen Palmer, Lesley Stewart

Lancet Infect Dis 2009; 9: 537–45

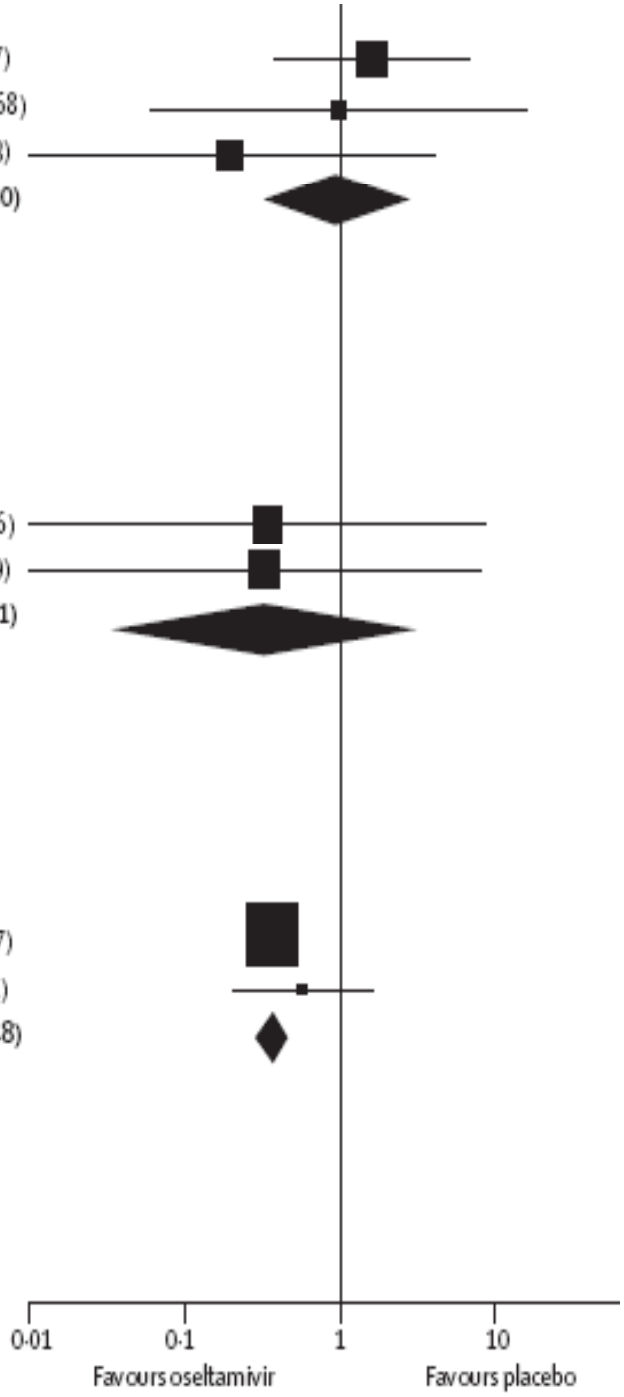
Study or subgroup	Oseltamivir Median	Oseltamivir SD	Total	Placebo Median	Placebo SD	Total	Median difference (95% CI)
Li 2003[26]	83·5	80·39	216	87·7	78·79	235	−4·20 (−18·91 to 10·51)
Nicholson 2000[27]	97·6	154·95	243	116·1	117·46	239	−18·50 (−43·02 to 6·02)
RocheWV15730[5]	74·5	45·66	31	109·8	162·12	27	−35·30 (−98·53 to 27·93)
Treanor 2000[28]	76·3	93·15	210	97	76·52	209	−20·70 (−37·02 to −4·38)
Total (95% CI)			700			710	−13·29 (−23·15 to −3·43)

Heterogeneity: χ^2=2·90, df=3 (p=0·41); I^2=0%

Test for overall effect: Z=2·64 (p=0·008)



Complications requiring hospitalisation						
Deng 2004[33]	5	599	3	577	46·3	1·61 (0·38 to 6·77)
Nicholson 2000[27]	1	241	1	235	15·4	0·97 (0·06 to 15·68)
Treanor 2000[29]	0	210	2	209	38·2	0·20 (0·01 to 4·13)
Subtotal (95% CI)		1050		1021	100·0	0·97 (0·33 to 2·90)
Total events	6		6			
Heterogeneity: χ^2=1·53, df=2 (p=0·47); I^2=0%						
Test for overall effect: Z=0·05 (p=0·96)						
Pneumonia						
Kashiwagi 2000[32]	0	154	1	159	49·3	0·34 (0·01 to 8·46)
Nicholson 2000[27]	0	241	1	235	50·7	0·32 (0·01 to 7·99)
Subtotal (95% CI)		395		394	100·0	0·33 (0·03 to 3·21)
Total events	0		2			
Heterogeneity: χ^2=0·00, df=1 (p=0·98); I^2=0%						
Test for overall effect: Z=0·95 (p=0·34)						
Antibiotic use						
Deng 2004[33]	129	599	248	577	95·3	0·36 (0·28 to 0·47)
Nicholson 2000[27]	6	241	10	235	4·7	0·57 (0·21 to 1·61)
Subtotal (95% CI)		840		812	100·0	0·37 (0·29 to 0·48)
Total events	135		258			
Heterogeneity: χ^2=0·71, df=1 (p=0·40); I^2=0%						
Test for overall effect: Z=7·78 (p<0·00001)						



SUPPORTIVE CARE

- IV fluids
- Parenteral nutrition
- Oxygen therapy/ventilatory support
- IV Antibiotics
- Angalgesics- avoid aspirin
- Vasopressors

GUIDELINES – USE OF FACE MASK

- Type of mask- depends on risk profile of the personnel & risk categorisation
- 2 types of masks: Triple layered surgical masks & N95 Respirators
- Triple layered surgical masks – screening area personnel, ambulance & mortuary staff. suspected/probable/confirmed cases and the close family contacts
- N95 Respirators – personnel involved in aerosol generation procedures (suctioning, intubation, nebulization etc), collecting clinical samples, critical care and laboratories

http://mohfw-h1n1.nic.in/

vaccines

- Two types of vaccine: Inactivated vaccine and live vaccine
- Inactivated vaccine: production of ab’s to H &N, trivalent(H1N1, H3N2 and B virus)
- Live vaccine: production of mucosal immunity
- At risk population: individuals at risk of developing complications or to contacts of high risk individuals

- seasonal vaccines – will not confer protection against new pandemic strains
- Should continue to take seasonal influenza vaccines as before
- Inactivated influenza vaccines -can be given simultaneously but at different sites
- Any new influenza vaccine takes 6 months for development

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Response after One Dose of a Monovalent Influenza A (H1N1) 2009 Vaccine — Preliminary Report

Michael E. Greenberg, M.D., M.P.H., Michael H. Lai, B.Med.Sc., M.B., B.S., M.Med.Sc., Gunter F. Hartel, M.S., Ph.D., Christine H. Wichems, Ph.D., Charmaine Gittleson, B.Sc., M.B., B.Ch., Jillian Bennet, M.Sc., M.P.H., Gail Dawson, B.Pharm., Wilson Hu, M.D., M.B.A., Connie Leggio, B.Sc., Diane Washington, M.D., and Russell L. Basser, M.B., B.S., M.D., F.R.A.C.P.

N Engl J Med 2009;361.

- Inactivated split virus 2009 H1N1 vaccine – 2 different doses 15µg or 30µg dose of hemagglutinin – intramuscular route
- Immunogenicity and safety after 21 days- hemagglutinin inhibition titres
- At 21 days 116 of 120(96.7%) & 112 0f 120(93.3%) who have received 15µg and 30µg respectively developed 1:40 titres of protective antibody
- No deaths/serious adverse effects, local discomfort(46.3%), systemic symptoms (eg: headache)

chemoprophylaxis

- All close contacts of suspected, probable and confirmed cases. Close contacts include household /social contacts, family members, workplace or school contacts, fellow travelers etc.
- All health care personnel coming in contact with suspected, probable or confirmed cases
- Oseltamivir is the drug of choice.
- Prophylaxis should be provided till 10 days after last exposure (maximum period of 6 weeks)
- >40 kgs – oseltamivir 75mg OD

- Definitions: suspected case
  Probable case
  Confirmed case
- Infection control measures: Pre-hospital
  In-hospital

CURRENT CONCEPTS

Avian Influenza A (H5N1) Infection in Humans

The Writing Committee of the World Health Organization (WHO) Consultation on Human Influenza A/H5

N Engl J Med 2005;353:1374-85.

- Occurence of human H5N1 influenza has paralled the occurence of avian H5N1 influenza in south-east asia-2005
- Spread-Inhalation, direct contact and inoculation
- Bird-Human transmission, No human-human transmission
- Presentation similar to other flu-like illness
- Atypical symptoms- nausea, vomiting, encephalopathy, bleeding gums, diarrhea common
- Case fatality rate- very high(upto 85% of children < 15 years) secondary to progressive respiratory failure

- All most all patients have pneumonia, radiology –diffuse and multifocal or patchy consolidation, pleural effusions-rare
- Viral isolation or detection of H5 specific RNA by PCR(highly sensitive and early detection possible)
- High viral RNA load in pharyngeal secretions
- Neuraminidase inhibitors- Oseltamivir, Zanamavir(no studies in human H5N1 infection)
- Resistant to M2 inhibitors(Amantidine & Rimantidine)

SEVERE ACUTE RESPIRATORY SYNDROME (SARS)

- Nov 2002, unusual epidemic of severe pneumonia of unknown etiology occurred in Guangdong province in southern china
- Spread to multiple locations in Asia in early 2003
- Human SARS Corona virus(Hu CoV-SARS) was identified
- 8096 cases and 774 deaths(9.6% cases) reported in 29 countries
- Introduced into the humans through animal species, palm civet or related animal

Transmission of virus

- Droplet or fomite transmission, requires close contact
- Viral shedding- peak at the time when the illness is most severe
- Preponderance of transmission in hospital setting
- Reproductive number- 3(in the absence of infection control measures)
- Super-spreaders- unknown phenomenon

Clinical features

- Mean incubation period- 4.6 days, mean time from onset to death- 23.7 days
- Non-specific complaints, cough and dyspnea- predominant respiratory complaints, sorethroat and rhinorrhea- infrequent
- Watery diarrhea(30-40% cases)
- Atypical symptoms in older individuals
- 2 phases: Phase 1(viral replication)

  Phase 2(immunopathological injury)

  (fever recurrence, hypoxemia, rad. Progression)

Monaldi Arch Chest Dis 2005;63:3

- 50% patients require respiratory supplemental oxygen
- 20% patients develop ARDS
- Case fatality rate-10%, higher in older adults

DIAGNOSIS

- Lymphopenia (both CD4 and CD8)- worse prognosis
- Thrombocytopenia
- DIC
- Elevated LDH, transaminases, creatine kinase
- Radiology: peripheral involvement, lower lung zones

  cavitation, hilar adenopathy, pleural effusion absent
- HRCT Chest: GGO, interlobular and intralobular septal thickening
- Nasopharyngeal aspirate & Blood- 80% sensitivity with real time quantitative PCR during first 3-7 days

- Poor prognostic features- Older age, presence of co-morbid conditions like diabetes, bilateral disease, very high LDH, lymphopenia, liver dysfunction

Treatment options

- Ribavarin- not beneficial
- Protease inhibitors- Lopinavir400mg/ritonavir100mg(LPV/r)

  Beneficial, reduction of death rate & intubation rate, reduction in steroid use, decrease in viral load

  increase in peripheral lymphocyte count
- Interferon
- Monoclonal antibody(against SARS-CoV S1 protein)
- Vaccines
- Systemic corticosteroids- given during phase 2 of SARS

HANTAVIRUS PULMONARY SYNDROME

- HPS rare rodent borne viral disease
- Four corners are of south western united states in 1993
- Sin Nombre virus, infects deer mouse. Other viruses-Andes virus, choclo virus
- Prodrome of 3-4 days, gastrointestinal symptoms, dizziness
- Cardio-pulmonary phase- hypoxaemic respiratory failure, shock, low cardiac index, high SVR but PACWP is N or low
- Perihilar distribution on CXR, both interstitial and alveolar opacities, pleural effusions
- Thrombocytopenia, left shift with circulating band forms, circulating immunoblasts, mildly deranged LFT's, DIC, raised hematocrit, mild renal dysfunction

- Conjunctival&cutaneous signs of vascular involvement absent
- Specific diagnosis- IgM testing of acute-phase serum, positive results even in prodrome
- RT-PCR- usually positive – in blood clots in 1st 7-9 days
- Retrospective analysis of cases from 1993-2006(28 cases)- Middle-aged adults
- Incubation period-9-33days
- Recover phase begins after 3 days
- Treatment- supportive, Ribavarin no role in HPS

Southern Medical journal Jan 2009;102

A pilot study for serological evidence of hantavirus infection in human population in south India

S. Chandy, S. Mitra*, N. Sathish, T.S. Vijayakumar, O.C. Abraham*, M.V. Jesudason**, P. Abraham
K. Yoshimatsu†, J. Arikawa† & G. Sridharan

Indian J Med Res 122, September 2005, pp 211-215

- 152 individuals with pyrexic illness were screened with Hanta virus IgM by EIA, positive samples tested by IFA
- 23(14.7%) were positive by EIA, as compared to 5.7% of normal individuals
- 18 of 22(82%) were positive by IFA, as compared to 2 of 5(40%) in normal individuals
- Evidence exists for SEOV-like infection in 12% and a PUUV-like infection in 5% of Indians presenting with a leptospirosis-like clinical picture from Cochin and Chennai area of India (Clement *et al 2006)*

CONCLUSIONS

- H1N1 2009 is antigenically different, sensitive to Oseltamivir
- Monovalent vaccines are under development
- At risk individuals should receive seasonal influenza vaccines as usual and chemoprophylaxis with Oseltamivir
- Avian influenza(H5N1) potential threat to humans in India & case fatality is very high
- HCPS should be suspected in middle aged adults with gastrointestinal symptoms, rodent exposure
- SARS CoV – High attack rate, high case fatality rate, supportive care, protease inhibitors