

Emerging Viral Diseases



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LEADING CAUSES OF DEATH, 2004 AND 2030 COMPARED

2004			2030		
Disease or injury	Deaths (%)	Rank	Rank	Deaths (%)	Disease or injury
Ischaemic heart disease	12.2	1	1	14.2	Ischaemic heart disease
Cerebrovascular disease	9.7	2	2	12.1	Cerebrovascular disease
Lower respiratory infections	7.0	3	3	8.6	Chronic obstructive pulmonary disease
Chronic obstructive pulmonary disease	5.1	4	4	3.8	Lower respiratory infections
<u>Diarrhoeal diseases</u>	3.6	5	5	3.6	Road traffic accidents
HIV/AIDS	3.5	6	6	3.4	Trachea, bronchus, lung cancers
<u>Tuberculosis</u>	2.5	7	7	3.3	Diabetes mellitus
Trachea, bronchus, lung cancers	2.3	8	8	2.1	Hypertensive heart disease
Road traffic accidents	2.2	9	9	1.9	Stomach cancer
Prematurity and low birth weight	2.0	10	10	1.8	HIV/AIDS
Neonatal infections and other*	1.9	11	11	1.6	Nephritis and nephrosis
Diabetes mellitus	1.9	12	12	1.5	Self-inflicted injuries
<u>Malaria</u>	1.7	13	13	1.4	Liver cancer
Hypertensive heart disease	1.7	14	14	1.4	Colon and rectum cancers
Birth asphyxia and birth trauma	1.5	15	15	1.3	Oesophagus cancer
Self-inflicted injuries	1.4	16	16	1.2	Violence
Stomach cancer	1.4	17	17	1.2	Alzheimer and other dementias
Cirrhosis of the liver	1.3	18	18	1.2	Cirrhosis of the liver
Nephritis and nephrosis	1.3	19	19	1.1	Breast cancer
Colon and rectum cancers	1.1	20	20	1.0	<u>Tuberculosis</u>
Violence	1.0	22	21	1.0	Neonatal infections and other*
Breast cancer	0.9	23	22	0.9	Prematurity and low birth weight
Oesophagus cancer	0.9	24	23	0.9	<u>Diarrhoeal diseases</u>
Alzheimer and other dementias	0.8	25	29	0.7	Birth asphyxia and birth trauma
			41	0.4	<u>Malaria</u>

* Comprises severe neonatal infections and other, noninfectious causes arising in the perinatal period.

EMERGING AND REEMERGING INFECTIONS

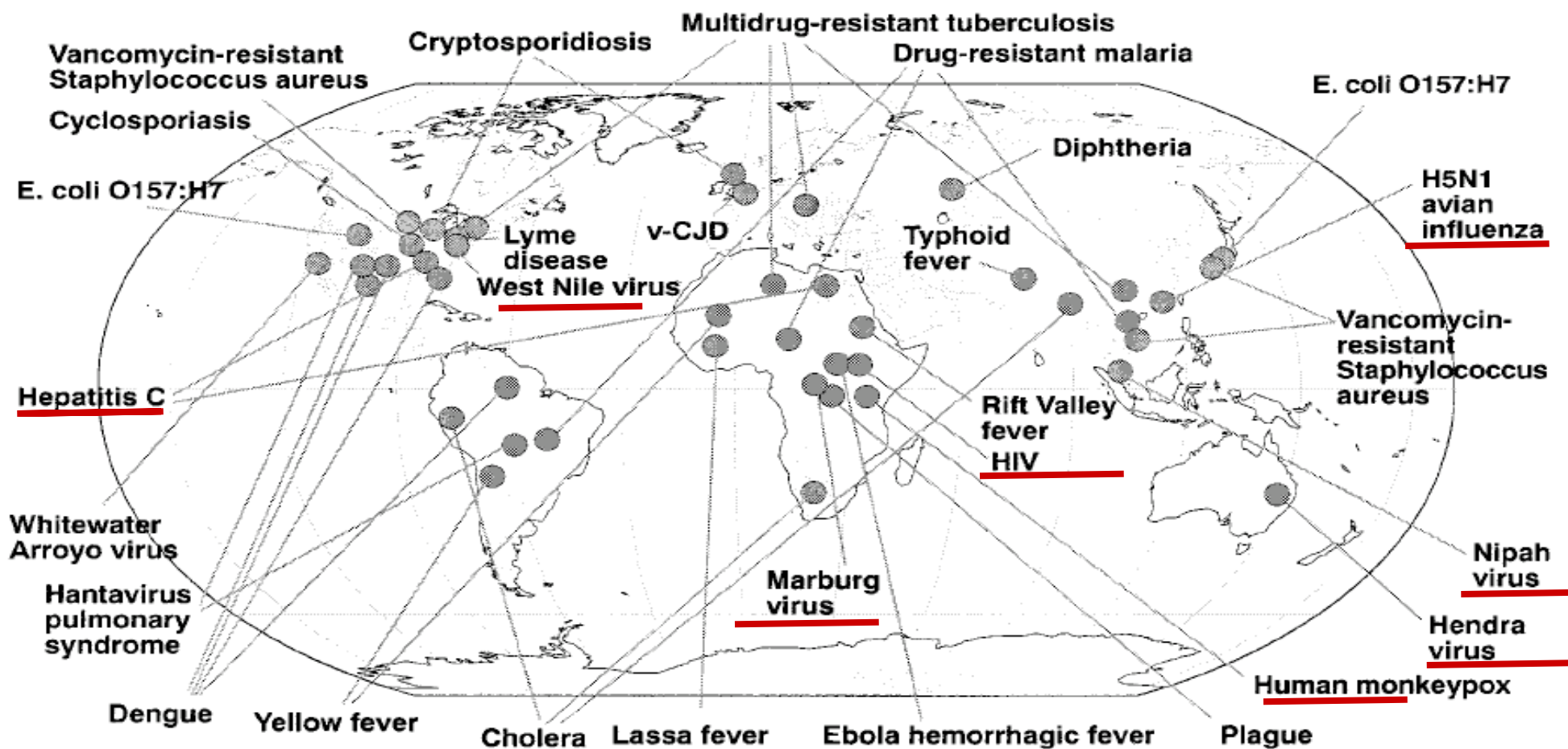


Figure 1. Range and recognized site(s) of origin of variety of emerging and reemerging infections. v-CJD, variant Creutzfeldt-Jakob disease; *E. coli*, *Escherichia coli*.

Global climate changes, travel of vectors and humans, immunological vacuum created by disappearance of certain viruses and other factors have open the door to new viruses and re-emergence of old viruses

- ◆ Influenza (H5N1)
 - ◆ SARS
 - ◆ Human metapneumovirus
 - ◆ Human bocavirus
 - ◆ Human parechoviruses
 - ◆ West Nile Virus
 - ◆ Chandipura encephalitis
 - ◆ Arena viruses
 - ◆ Hepatitis E
-

New viruses and re-emergence of old viruses with significant cutaneous involvement

- ◆ Chikungunya virus
 - ◆ Ross river virus
 - ◆ Monkeypox virus
 - ◆ Human herpes virus 6 (HHV-6)
 - ◆ Human herpes virus (HHV-7)
 - ◆ Measles
 - ◆ Rubella
-

Human bocavirus (HBoV) has been classified in the family *Parvoviridae*, subfamily *Parvovirinae*, genus *Bocavirus*

- ◆ Human bocavirus (HBoV) was first described in 2005 in nasopharyngeal aspirates of patients with respiratory tract infections in Sweden
- ◆ HBoV has been mainly detected in children at a frequency ranging from about 2% to 18%
- ◆ despite the high rate of coinfection with other respiratory pathogens and the few studies including asymptomatic controls, there is increasing evidence for a causal role of HBoV in respiratory illness.
- ◆ viral respiratory tract infections in children: RSV, HMPV, influenza viruses, parainfluenza viruses, picornaviruses (rhinoviruses or enteroviruses), adenoviruses, and coronaviruses

Human Bocavirus Infection in hospitalized Children < 5 yo With Respiratory Tract Disease and positive for HBoV by RT-PCR

- ◆ University Hospital of Montpellier (France) between November 1, 2006 and October 31, 2007
- ◆ 550 nasopharyngeal aspirates were obtained from 507 children with RTD
- ◆ 279 (55%) males and 228 (45%) females
- ◆ median age of 5.2 months (range, 10 days-60 months)
- ◆ asymptomatic controls were 68 children without any respiratory sign or fever; most of these control children attended the pediatric emergency unit for traumatic injuries, or were seen either for elective surgery or for routine well child visits

Human bocavirus was detected in 55 (10.8%) of the 507 children tested and in none of the 68 asymptomatic control children (P 0.01)

TABLE 1. Clinical Characteristics of Children Infected With Human Bocavirus (HBoV)

Characteristics	HBoV Positive Children			
	All N = 55	HBoV Mono Infection N = 33 Viral Load (Log HBoV DNA Copies/ng of DNA)		
		>5 N = 11	<5 N = 22	P^*
Median age, mos (range)	7.6 (0.7–57.2)	8.5 (2.4–25.3)	11.3 (0.7–57.2)	0.16
Abnormal x-ray findings, no. (%)	43 (78.2)	10 (90.9)	15 (68.2)	0.22
Median duration of hospitalization, days (range)	3 (0–8)	2.5 (0–7)	3 (2–8)	0.46
Admission to intensive care unit, no. (%)	2 (3.6)	2 (18.2)	0	—
Oxygen requirement, no. (%)	24 (43.6)	4 (36.4)	8 (36.4)	1
Median duration of oxygen requirement, days (range)	2 (1–6)	2 (1–2)	2.5 (1–6)	0.71
Diagnostic, no. (%)				
Bronchitis	3 (5.5)	1 (9.1)	2 (9.1)	1
Bronchiolitis	29 (52.7)	7 (70)	8 (44.4)	0.16
Atypical pneumonia	3 (5.5)	1 (9.1)	2 (9.1)	1
Pneumonia	1 (1.8)	0	1 (4.5)	—
Asthma	15 (27.3)	1 (9.1)	8 (36.3)	0.21
Upper respiratory tract infection	4 (7.2)	1 (9.1)	1 (4.5)	1
Clinical findings, no. (%)				
Cough	30 (54.5)	3 (27.3)	10 (45.4)	0.45
Rhinorrhea	18 (32.7)	3 (27.3)	6 (27.3)	1
Dyspnea	22 (40)	9 (81.9)	10 (45.5)	0.07
Wheezing	19 (34.5)	4 (36.3)	6 (27.3)	0.69
Respiratory distress	5 (9)	2 (18.2)	2 (10)	0.59
Pharyngitis, laryngitis	3 (5.4)	1 (9.1)	0	—
Conjunctivitis	1 (1.8)	0	0	—
Otitis	2 (3.6)	0	2 (9.1)	—
Diarrhea, vomiting	7 (12.7)	0	3 (13.6)	—

* P value for comparison of the 2 groups defined by a HBoV DNA level above or below 5 log HBoV DNA copies/ng of DNA.

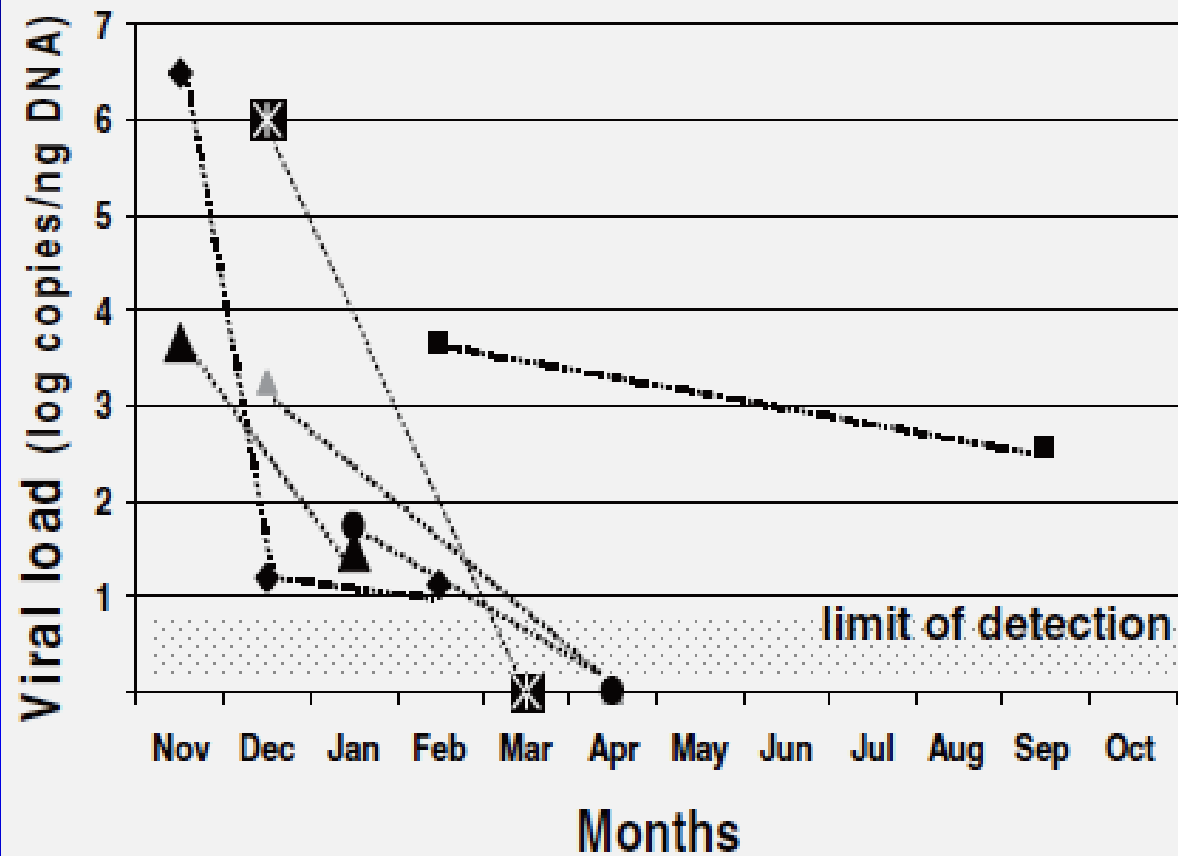


FIGURE 1. HBsV viral load changes over time in nasopharyngeal secretions from 6 children.

TABLE 2. Comparison of Features Associated With HBoV, HMPV, and RSV, Excluding Co-Infections

Characteristics	HBoV N = 33	HMPV N = 46	RSV N = 139	<i>P</i>
<u>Median age, mos (range)</u>	<u>9.8 (0.7–57.2)</u>	6.0 (0.7–35.9)	<u>4.1 (0.5–43)</u>	<0.001
Male/female ratio	1.27	1.31	1.41	0.92
Median temperature, °C (range)	37.6 (36.6–40.0)	37.8 (36.2–40)	37.2 (36.3–39)	0.32
Median oxygen saturation, % (range)	98 (88–100)	97 (85–100)	97 (85–100)	0.29
<u>Abnormal roentgenogram findings, no. (%)</u>	<u>25 (77)</u>	35 (76)	<u>124 (89)</u>	0.035
Median duration of hospitalization, days (range)	3.0 (0–8)	3.5 (0–10)	4.0 (0–10)	0.14 (0.047)*
Admission to intensive care unit, no.(%)	2 (6.0)	2 (4.3)	8 (5.7)	0.93
<u>Oxygen requirement, no. (%)</u>	12 (36.3)	23 (50.0)	<u>90 (64.7)</u>	0.006 (0.004)*
Median duration of oxygen requirement, days (range)	2.0 (1–6)	2.5 (1–8)	3.0 (0.5–6)	0.061 (0.011)*
Underlying conditions (including preterm birth), no. (%)	12 (21.8)	15 (32)	35 (25.2)	0.52
Previous bronchiolitis or asthma episode, no. (%)	18 (54.4)	7 (15.2)	18 (12.9)	0.001
Diagnostic, no. (%)				
Bronchiolitis	19 (57.5)	21 (45.6)	89 (64.1)	0.08
Atypical pneumonia	3 (9.0)	8 (17.4)	21 (15.1)	0.57
Pneumonia	1 (3.0)	2 (4.3)	7 (5.0)	0.88
Asthma	7 (21.2)	5 (11.6)	19 (13.6)	0.41
<u>Upper respiratory tract infection</u>	3 (9.0)	<u>10 (21.8)</u>	3 (2.1)	0.001

**P* value for comparison of children positive for HBoV and children positive for RSV; only significant values are shown.

Human metapneumovirus (HMPV) HMPV is an enveloped RNA virus classified in the Paramyxoviridae family (Pneumovirinae subfamily) and closely related to RSV and parainfluenza viruses

- ◆ HMPV was first identified in 2001 in the Netherlands from archived respiratory cultures collected from infants and young children in whom other pathogens could not be isolated (wheezing and bronchiolitis)
 - ◆ it accounts for 5% to 15% of respiratory diseases among hospitalized infants with a clinical syndrome similar to RSV
 - ◆ Viral respiratory tract infections in adults: influenza A, RSV, parainfluenza viruses, coronaviruses, rhinoviruses, adenovirus
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HMPV Infections in 2825 Adults

Prospective study: four consecutive winters from 1999 through 2003
in Rochester, NY

Table 1. Demographic and Clinical Characteristics of Cohorts

Characteristic	Healthy Elderly (n=611)	High Risk (n=537)	Young (n=291)	Hospitalized (n=1386)
Age, mean (SD), y	75 (6)	70 (11)	33 (5)	75 (12)
Female, %	57.6	45.6 ^a	83.8	55.3
Race, %				
White	97.7	93.7	82.1	84.9 ^a
Black	2.1	5.4	11.0	9.6
Hispanic	0.2	0.9	5.2	5.5
Living situation, %				
Alone	25.9	27.4	1.7	28.2
With adults only	72.0	66.7	10.7	64.4
With children	2.2	6.0	87.6	7.4
Chronic illnesses, %				
Any cardiac disease	16.5	47.9	0.0	54.6
Lung disease	2.1	64.6	10.0	58.6
Diabetes mellitus	9.8	16.4	1.4	28.7
Smoking (current or past), %	55.3	81.9	33.3	73.6
Influenza vaccine, %	89.6	89.9	38.1	78.1 ^a
IADL score, mean (SD) ^b	0.31 (1.1)	1.2 (2.2)	0.03 (0.4)	3.8 (4.1)
No. of illnesses	525	519	314	1471

Abbreviation: IADL, instrumental activities of daily living.

^aSignificantly different compared with the other groups of older patients ($P < .001$).

^bInstrumental activities of daily living are functional assessments based on a 12-point scale, with 0 representing total independence and 12, total dependence.

healthy adults: ≥65 years old; high-risk adults:

young adults: 19-40 years old;

acute cardiopulmonary syndrome

Walsh, E. E. et al. Arch Intern Med 2008;168:2489-2496

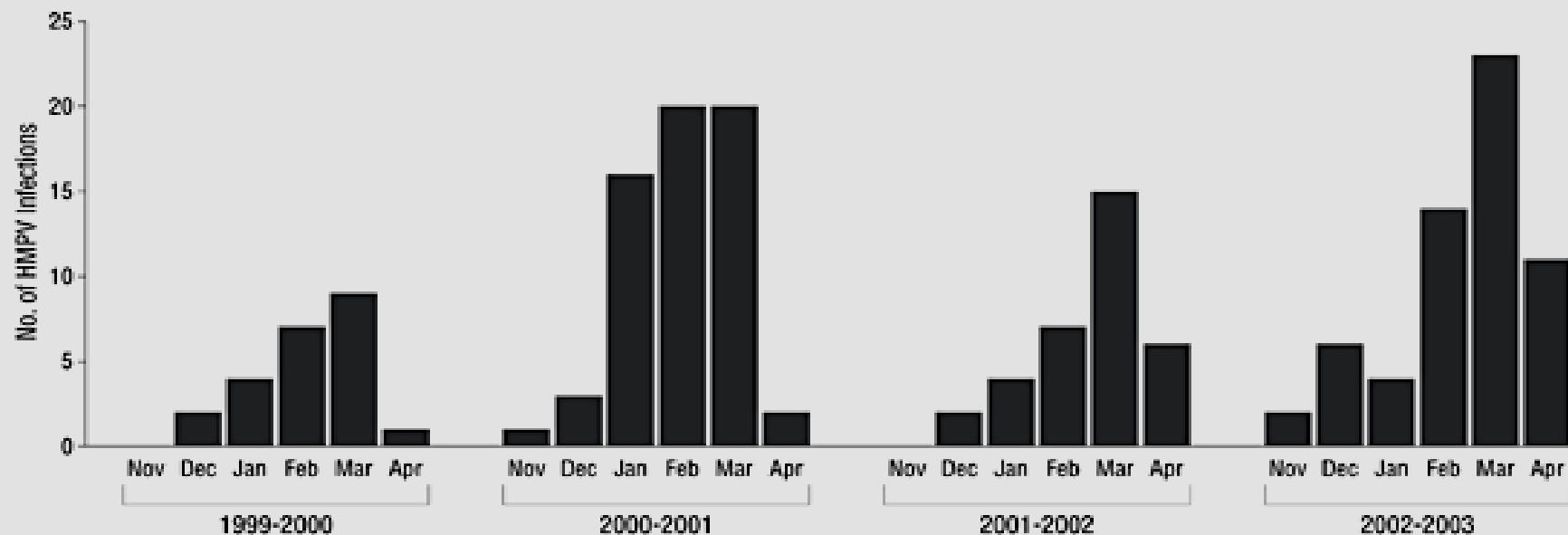
Table 2. Incidence of HMPV Infection by Year

Year	Healthy Elderly	High Risk	Young	Hospitalized
1999-2000				
No. in cohort	212	206	103	274
No. of illnesses	123	146	78	289
No. of HMPV infections (% of cohort)	5 (2.4)	6 (2.9)	6 (5.8)	12 (4.4)
No. of asymptomatic HMPV infections	1	2	3	NA
2000-2001				
No. in cohort	280	271	180	296
No. of illnesses	159	160	113	307
No. of HMPV infections (% of cohort)	8 (2.9)	17 (6.3)	<u>19 (10.6)</u>	<u>39 (13.2)</u>
No. of asymptomatic HMPV infections	3	5	13	NA
2001-2002				
No. in cohort	180	195	164	434
No. of illnesses	102	115	101	465
No. of HMPV infections (% of cohort)	4 (2.2)	8 (4.1)	7 (4.3)	30 (6.9)
No. of asymptomatic HMPV infections	2	6	7	NA
2002-2003				
No. in cohort	295	210	90	384
No. of illnesses	135	103	37	410
No. of HMPV infections (% of cohort)	<u>19 (6.4)</u>	<u>18 (8.6)</u>	6 (6.7)	37 (9.6)
No. of asymptomatic HMPV infections	10	6	4	NA
All years combined				
No. in cohort ^a	611	537	291	1386
No. of illnesses	519	524	329	1471
No. of HMPV infections (% of cohort)	36 (5.9)	49 (9.1)	38 (13.1)	118 (8.5)
No. of asymptomatic HMPV infections	16	19	27	NA

Abbreviations: HMPV, human metapneumovirus; NA, not applicable.

^a Most subjects were in the study for more than 1 year; therefore, the number in the cohort for all years does not sum to the total of the numbers from the individual years.

Epidemic pattern of symptomatic human metapneumovirus (HMPV) infections in combined prospective and hospitalized cohorts during four consecutive winters (23, 62, 34, and 60)



Clinical Characteristics of Symptomatic HMPV Infections in Patients, Exclusive of Mixed Viral Infections

Table 3. Clinical Characteristics of Symptomatic HMPV Infections in Patients, Exclusive of Mixed Viral Infections

Characteristic	Healthy Elderly (n=13)	High Risk (n=17)	Young (n=11)	Hospitalized (n=91)
Symptoms, No. (%) ^a				
<u>Congestion</u>	12 (92)	12 (71)	<u>11 (100)</u>	42 (49) ^b
Sore throat	7 (58)	7 (41)	7 (64)	23 (27)
<u>Hoarseness</u>	5 (38)	5 (29)	<u>10 (91)^a</u>	25 (29)
Cough	13 (100)	17 (100)	10 (91)	84 (94)
Sputum	6 (62)	11 (65)	5 (45)	65 (74)
<u>Dyspnea</u>	4 (31)	13 (76)	2 (18)	<u>88 (98)^b</u>
<u>Wheeze</u>	4 (31)	7 (41)	1 (9)	<u>68 (79)^b</u>
<u>Constitutional</u>	12 (92)	12 (72)	7 (64)	<u>29 (33)^b</u>
Feverish	4 (31)	6 (35)	6 (55)	48 (53)
Signs, No. (%) ^a				
Rhinorrhea	11 (85)	11 (65)	8 (73)	8 (9) ^b
<u>Wheezing</u>	2 (15)	2 (12)	0	<u>75 (82)^b</u>
Rales	3 (23)	4 (24)	0	49 (54)
Temperature, mean (SD), °C	36.4 (0.9)	36.8 (1.1)	36.7 (0.8)	37.8 (1.0) ^b
<u>SaO₂ on room air, mean (SD)</u>	96.2 (2.9)	95.4 (2.3)	97.8 (1.2)	<u>88.4 (9.6)^b</u>

Abbreviations: HMPV, human metapneumovirus; SaO₂, arterial oxygen saturation.

^a Denominators vary because of missing data.

^b $P < .01$ compared with other groups.

Outcomes in HMPV-Infected Patients in Prospective Cohorts

Table 4. Outcomes in HMPV-Infected Patients in Prospective Cohorts

Outcome	Healthy Elderly (n=13)	High Risk (n=17)	Young (n=11)
Outcome of illness, No. (%) ^a			
Days of illness, mean (range)	12 (5-30)	16 (5-34)	10 (3-21)
Days house bound, mean (SD)	1.8 (3.1)	3.9 (6.6)	0.6 (1.1)
Telephone call to physician	3 (23)	8 (53)	4 (36)
Office visit	5 (38)	<u>10 (67)^b</u>	1 (9)
Emergency department visit	0	1 (7)	0
Hospitalization	0	3 (18)	0
Medications, No. (%) ^a			
Antipyretics	9 (69)	4 (27)	8 (73)
Cough suppressants	9 (69)	9 (60)	4 (36)
Decongestants	5 (38)	0 ^c	6 (55)
Bronchodilators	0	6 (35) ^c	0
Systemic glucocorticosteroids	0	6 (35) ^c	0
Antibiotics	3 (23)	14 (82) ^c	2 (18)

^a Denominators vary because of missing data.

^b $P < .05$ compared with young group.

^c $P < .05$ compared with other 2 groups.

Comparison of clinical presentation for human metapneumovirus (HMPV) (n = 91), respiratory syncytial virus (RSV) (n = 109), and influenza A (n = 138) in hospitalized patients, exclusive of mixed viral infections

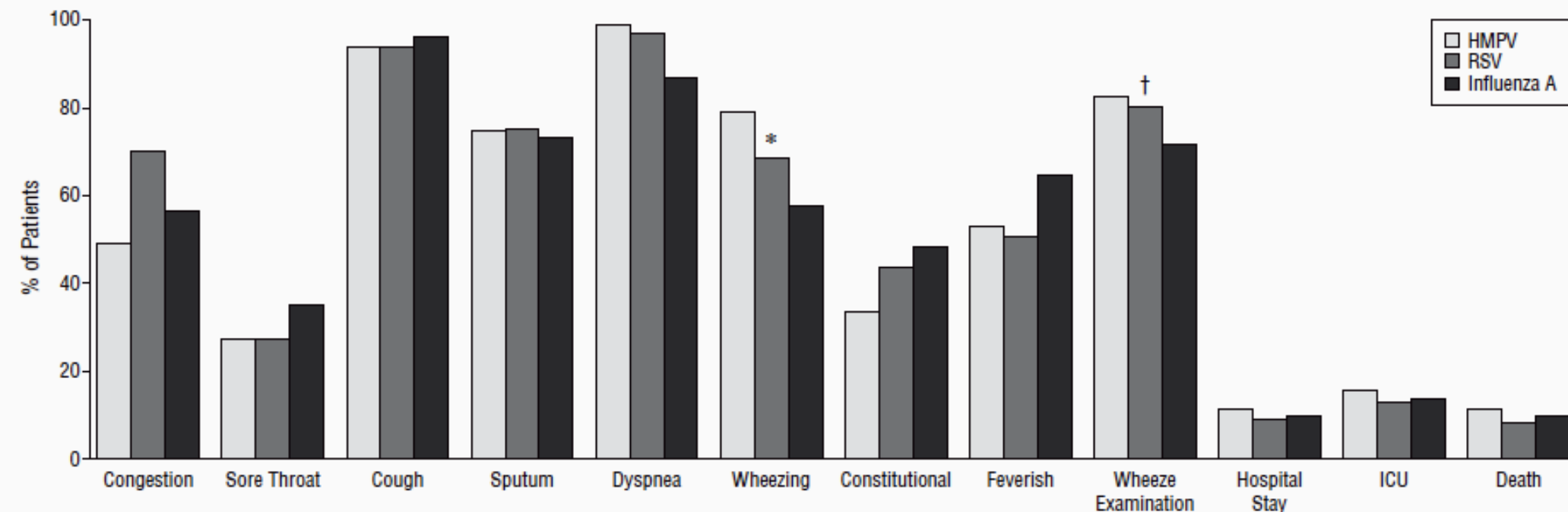


Figure 2. Comparison of clinical presentation for human metapneumovirus (HMPV) (n=91), respiratory syncytial virus (RSV) (n=109), and influenza A (n=138) hospitalized patients, exclusive of mixed viral infections. RSV and influenza data are from Falsey et al.² * $P=.006$ for HMPV compared with influenza A; † $P=.06$ for HMPV compared with influenza A. ICU indicates intensive care unit.

HMPV is a relatively frequent infection in adults of all ages with a wide disease spectrum spectrum, ranging from asymptomatic to severe respiratory failure.

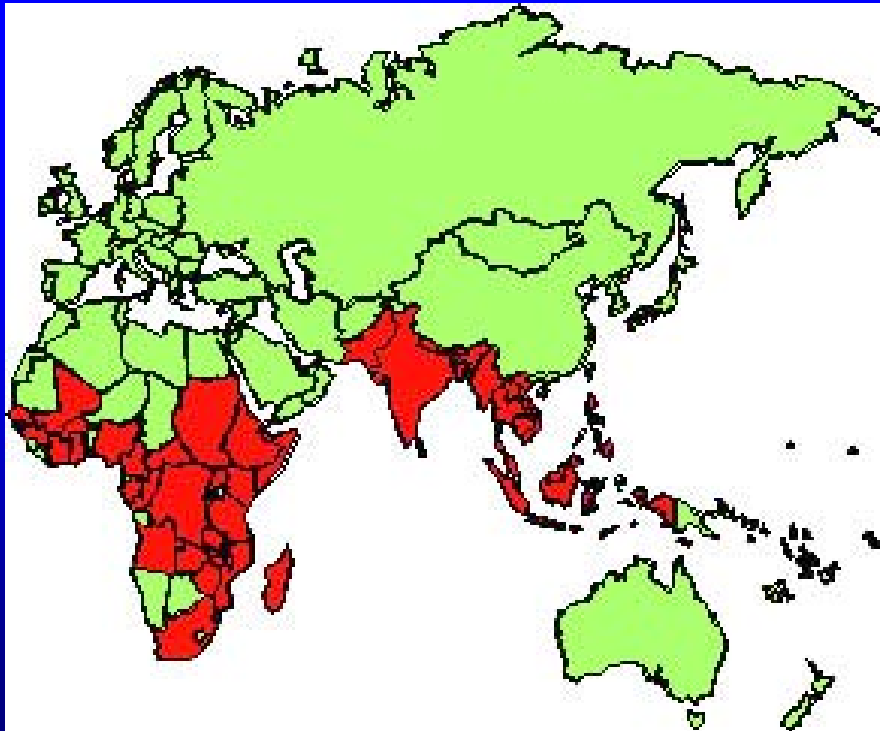
- ◆ Overall, HMPV has a substantial impact, although less than that of influenza A and RSV infection, especially in frail older persons with heart or lung disease.
 - ◆ Collectively, these 3 viruses were associated with nearly 30% of hospitalizations for acute respiratory illness during the winter
 - ◆ Immunocompromised hosts
 - ◆ Monoclonal antibodies and vaccine
-

New viruses and re-emergence of old viruses with significant cutaneous involvement

- ◆ Chikungunya virus
 - ◆ Ross river virus
 - ◆ Monkeypox virus
 - ◆ Human herpes virus 6 (HHV-6)
 - ◆ Human herpes virus (HHV-7)
 - ◆ Measles
 - ◆ Rubella
-

Chikungunya virus

- ◆ Alphaviruses are enveloped, plus-strand RNA viruses with icosahedral symmetry
- ◆ Swahili name of *chikungunya* meaning "that which bends up"
- ◆ causes epidemics in most of sub-Saharan Africa, India, Southeast Asia, Indonesia, the Philippines
- ◆ *Aedes* spp.



Chikungunya virus

- ◆ increasingly recognized as a cause of fever in travelers
 - ◆ sudden onset, with an incubation period estimated at 3 to 12 days
 - ◆ fever rises rapidly to 103°F to 104°F and may be accompanied by a rigor
 - ◆ joint pain appears suddenly and is often incapacitating in its severity
 - ◆ headache is typically present
 - ◆ in 80% of cases, a maculopapular rash appears 4 to 8 days after the initial illness
 - ◆ the rash may be associated with a second rise in fever, lasts approximately 2 days, and is described as *irritating* or *itchy*
-

Chikungunya virus maculopapular rash



Chikungunya virus

- ◆ leukopenia is typical; fatalities are rare and, when they occur, are associated either with young age or with a thrombocytopenic, hemorrhagic version of the illness that can lead to shock
 - ◆ primary differential diagnosis for CHIK is between dengue and o'nyong-nyong (ONN) fevers.
 - ◆ dengue overlaps the CHIK geographic distribution extensively, but is characterized more by myalgia than by arthralgia
 - ◆ ONN is clinically similar, but has geographic overlap only in east Africa
 - ◆ Laboratory diagnosis: isolation, PCR, IgM
-

Mosquito-borne Chikungunya virus 'in Europe'

Sambri V et al. "The 2007 epidemic outbreak of Chikungunya virus infection in the Romagna region of Italy: a new perspective for the possible diffusion of tropical diseases in temperate areas?" *New Microbiol.* 2008 Jul;31(3):303-4.

this outbreak of Chikungunya fever is evidence of an active endogenous circulation of the virus and could represent a possible introduction of this disease in Italy

Monkeypox virus

- ◆ orthopoxviruses are perhaps best known for their most notorious member, variola virus, the causative agent of human smallpox
 - ◆ can be classified as systemic or localized
 - ◆ Monkeypox virus main target is nonhuman primates
 - ◆ the virus needs to be introduced to the dermis if systemic infection is to eventually result. Virus replicates in the Malphigian layer of the epidermis, and dermal infection consists of fibroblasts and histiocytes (from here to lymphatics)
-

Monkeypox virus was introduced to USA in 2003 via a consignment of pet prairie dogs from Ghana

Monkeypox was first identified to cause disease in humans in the 1970s in the Democratic Republic of the Congo (formerly the Republic of Zaire) and is endemic in the rain forests of central and western Africa



The febrile illness with later appearance of a pustular rash developed in patients with close contact with recently purchased pet prairie dogs



prairie dogs appeared to have acquired the virus from Gambian giant rats at a distribution center in Illinois

rash starts on the trunk, spreads peripherally to involve the palms and soles of the feet. Lesions can also involve the mucous membranes and usually range from 0.5 to 1 centimeters in size.

some patients develop only a localized rash on their hands associated with direct contact with the infected animal.

during the first week of the rash, the patient is infectious and should be isolated until all scabs separate and results of throat swab PCR are negative

Typical Clinical Response to Smallpox Vaccination

macula



papule



vesicle



pustule



ulcer



eschars



scab separation



Day 7



Day 8



Day 10

Vaccinia Timecourse - Lesion Progression

Day 2



Day 3



Day 4



Day 5



Day 6



Day 7



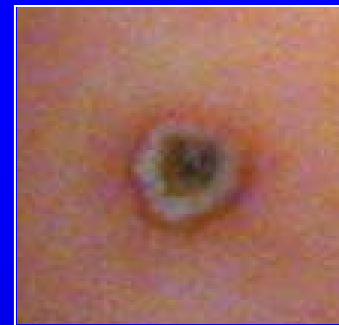
Day 8



Day 9



Day 10



Day 11



Day 12



Day 14



Day 17



Day 21



Day 23



Day 33



Day 39



Day 51



If the diagnosis of monkeypox is being considered, local and state public health officials, along with the CDC, should be notified

laboratory Diagnosis: virus isolation, electron microscopy, PCR, IgG and IgM detection

cidofovir has in vitro activity against monkeypox

vaccination with vaccinia virus against monkeypox infection

contact and airborne precautions are recommended for any generalized vesicular rash of unknown etiology in which monkeypox and smallpox are included in the differential diagnosis

1st US case of Marburg fever confirmed in Colorado. Press released Feb 7, 2009

Patient traveled to Uganda

visited a python cave in Maramagambo Forest in Queen Elizabeth Park and encountered fruit bats, which can carry the Marburg virus. The Ugandan government closed the cave after a tourist from the Netherlands died from Marburg in July

The patient was treated at Lutheran Medical Center in January 2008 and sought follow-up care in July, after learning of the tourist's death. The patient recovered and his or her identity wasn't disclosed.

Marburg and Ebola viruses can cause large hemorrhagic fever (HF) outbreaks with high case fatality (80–90%) in human and great apes

The CDC's Web site counts fewer than 500 confirmed cases since the virus was first recognized in 1967.
