Nonbacterial Etiology of Severe Pneumonia

고려의대 호흡기 내과
이 영 석

KOREA UNIVERSITY MEDICAL CENTER

Case

CASE REPORT Open Access

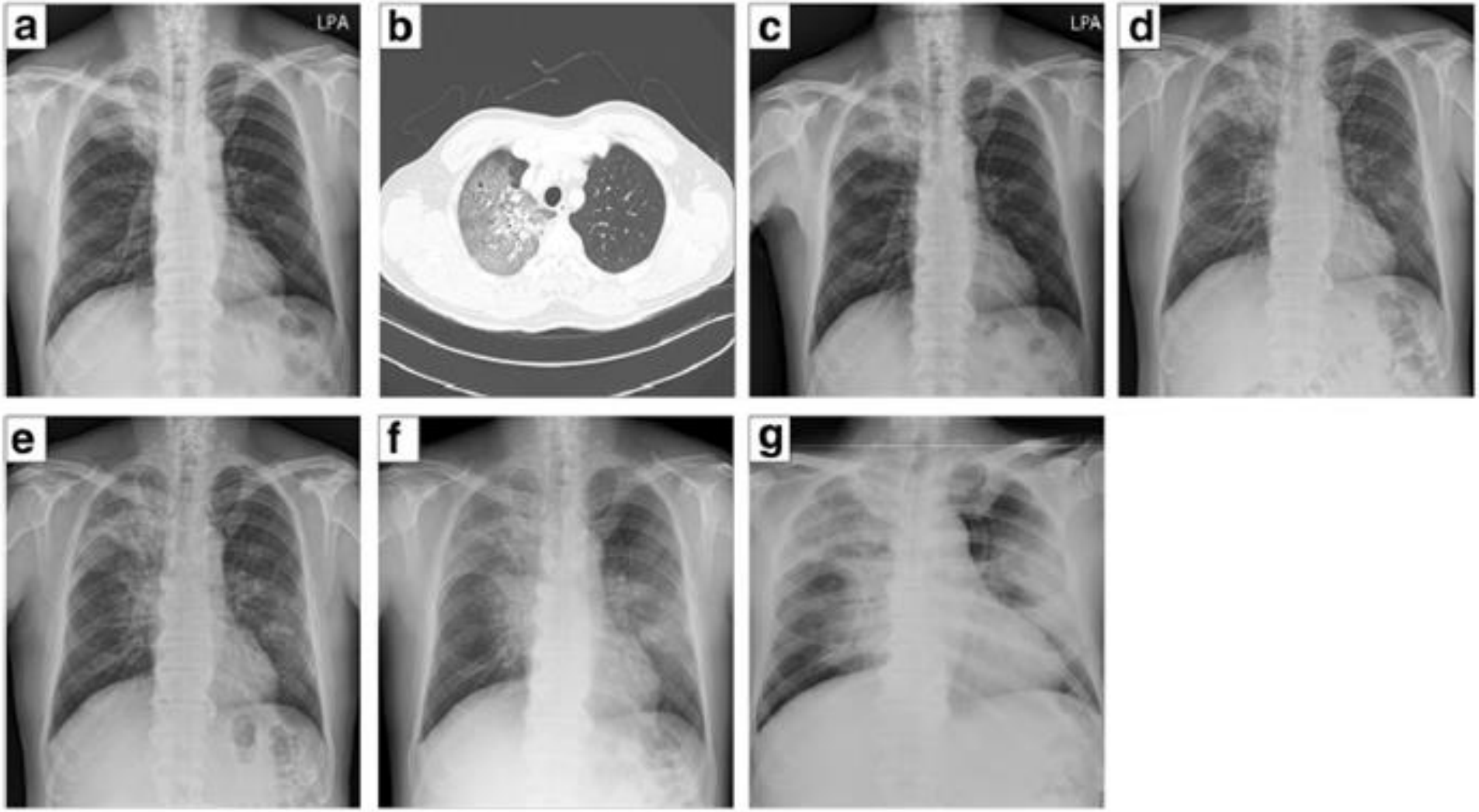
CrossMark

The clinical and virological features of the first imported case causing MERS-CoV outbreak in South Korea, 2015

KOREA UNIVERSITY MEDICAL CENTER

BMC Infect Dis 2017;17:498

Case



Case

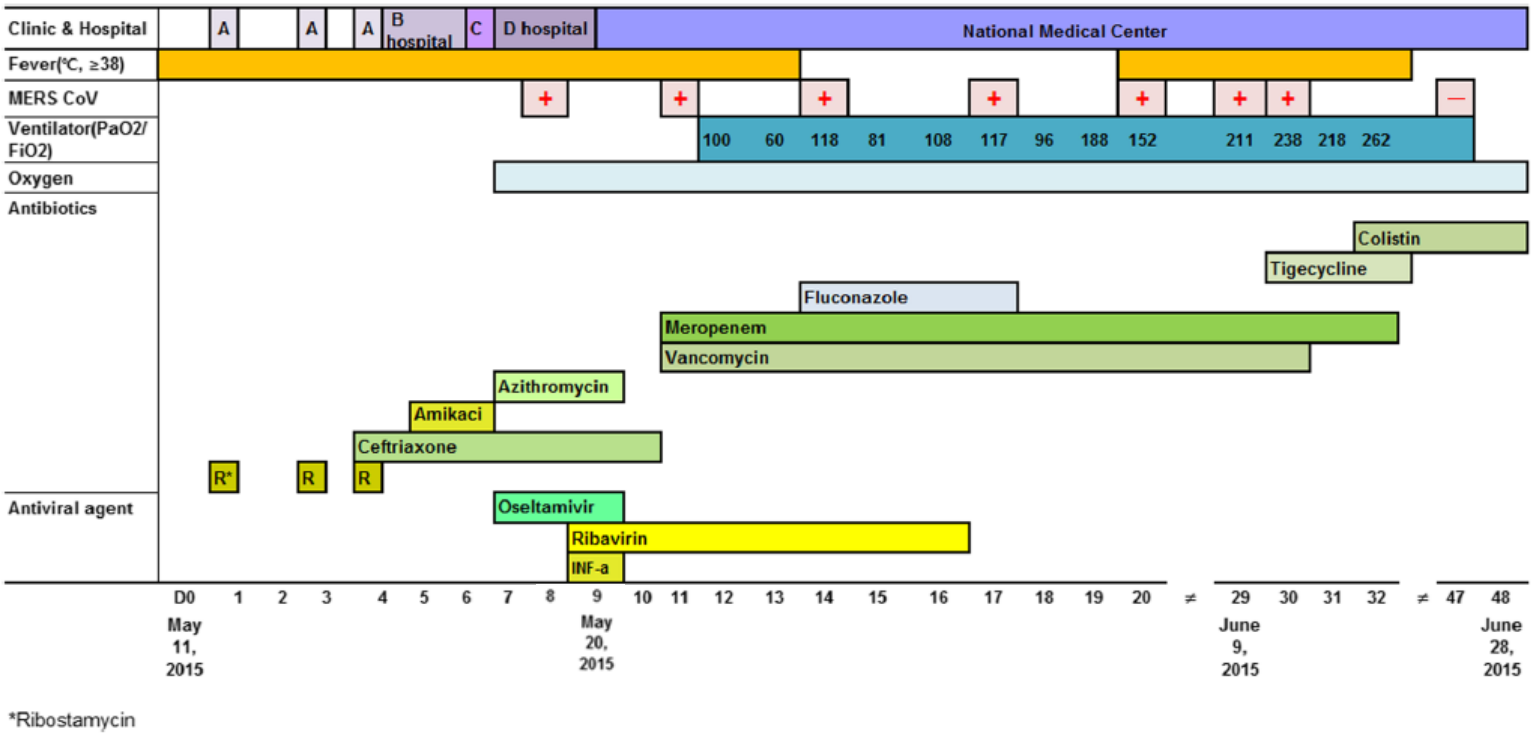


Fig. 3 Hospital course and treatment of the first case of the Korean MERS-CoV outbreak

KOREA UNIVERSITY MEDICAL CENTER

MERS results in Korea

숫자로 본 메르스 사태

1 1번 환자
국내 최초 메르스 환자인 1번(68) 환자.

14 14번 환자
14번(35) 환자는 자신도 모르는 새
80명이 넘는 사람에게 바이러스를 퍼뜨렸다.

국내 메르스 치명률 **19.35%**
전세계 메르스 치명률(38.65%)의 절반 수준.

23명 1일 최다
메르스 확진 환자 수

국내 메르스 사망자 수 **36명**

186명 국내 메르스 환자 수
39명은 병원 관련 종사자.

600km
132번 환자가
음압격리병실을 찾아 헤맨 거리

2,704곳
휴업한 유치원과 학교 수

6,729명 최대 격리자 수
방역 당국이 5월 하순 뒤늦게 '원점 재조사'를
천명하면서 격리자 수가 급격히 늘었다.

누적 격리자 수
16,693명

레벨D 보호구 지급량
993,826개
5월 20일 최초 환자 발생 이후 시·도, 보건소,
의료기관 등에 보건복지부가 지급한 총량.

1,510,280개
같은 기간
N95 마스크 지급량

연합뉴스

문가원 인턴기자 / 20150728
트위터 @yonhap_graphics 페이스북 tuney.kr/LeYN1

2015년 메르스 사태로 인한 경제적 피해비용 추산 (단위: 원)

직접피해액	개인·기업·국가 등 보상금	1927억
간접피해액	노동생산성 손실	140억
	관광산업 피해	2500억
	전산업 파급액	1조8443억
	합계	2조3010억

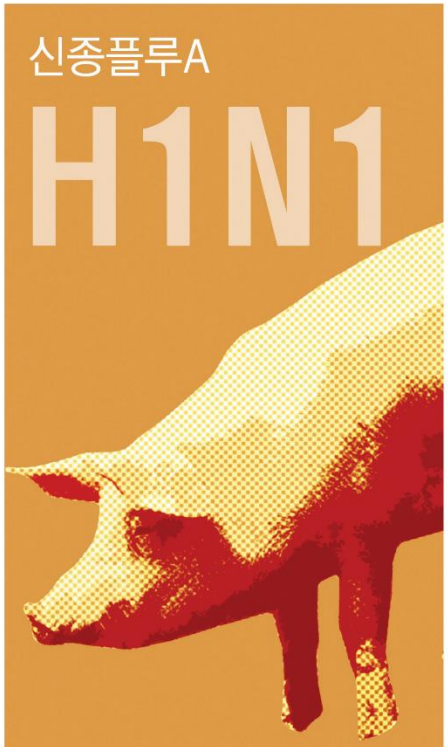
〈자료: 국립재난안전연구원〉

Viral Pneumonia

사스
중증급성호흡기 증후군

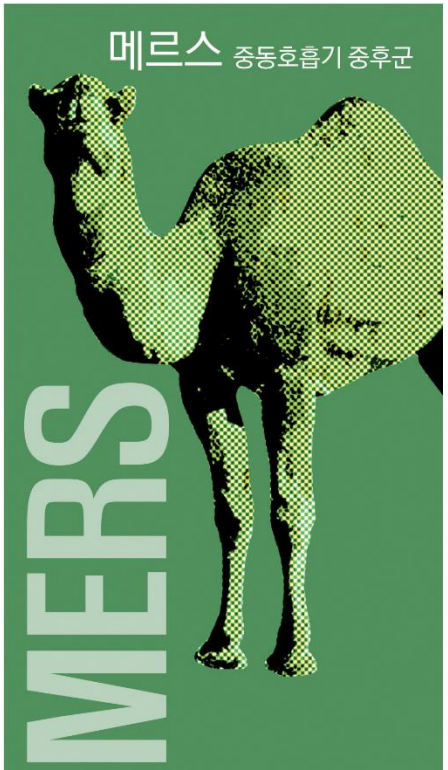
SARS

유행시기	2002년 11월~2003년 7월
증상	발열, 무력감, 두통, 근육통, 기침 및 호흡 곤란 증상과 함께 설사동반
잠복기	2~7일
감염경로	공기 중에 떠다니는 입자를 통해 전염
치사율	11%(국내: 0%)



신종플루A
H1N1

	2009년 4월 ~2010년 8월
	고열증상(38~40℃), 근육통, 두통, 오한 등의 전신증상, 마른기침, 인후통 등 호흡기
	7일 이내
	기침과 재채기를 통한 다른 사람의 호흡기로 침투해 전염
	0.07%(국내:0.008%)

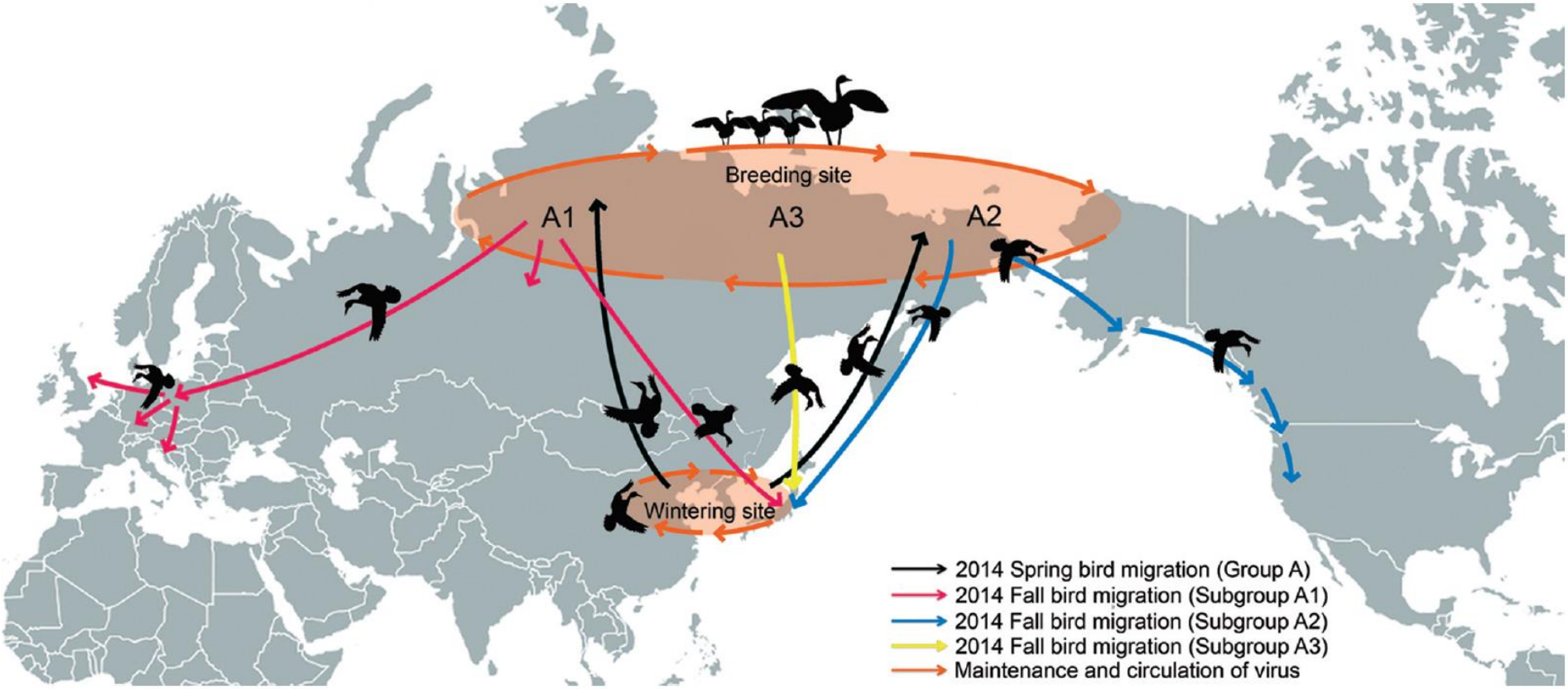


메르스 중동호흡기 증후군
MERS

	2015년 5월~ 진행중
	기침, 호흡곤란, 가래 등 호흡기 증상, 식욕부진, 매스꺼움 등 소화기 증상, 콧물, 오한
	14일 이내
	기침과 재채기를 통한 다른 사람의 호흡기로 침투해 전염
	37.5%(국내: 6.89%)

KOREA UNIVERSITY MEDICAL CENTER

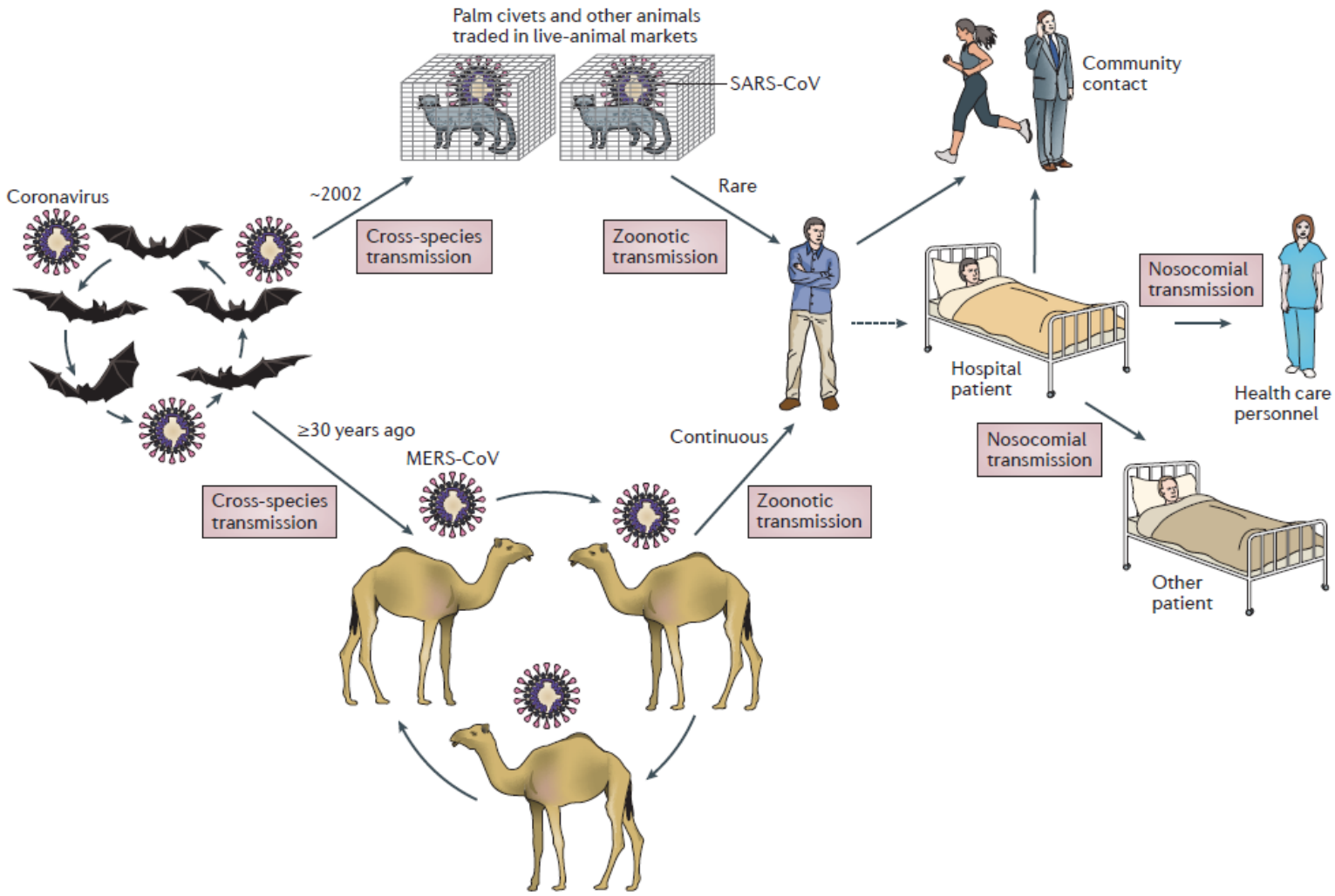
Viral Transmission



J Virol 2015;89:6521-4

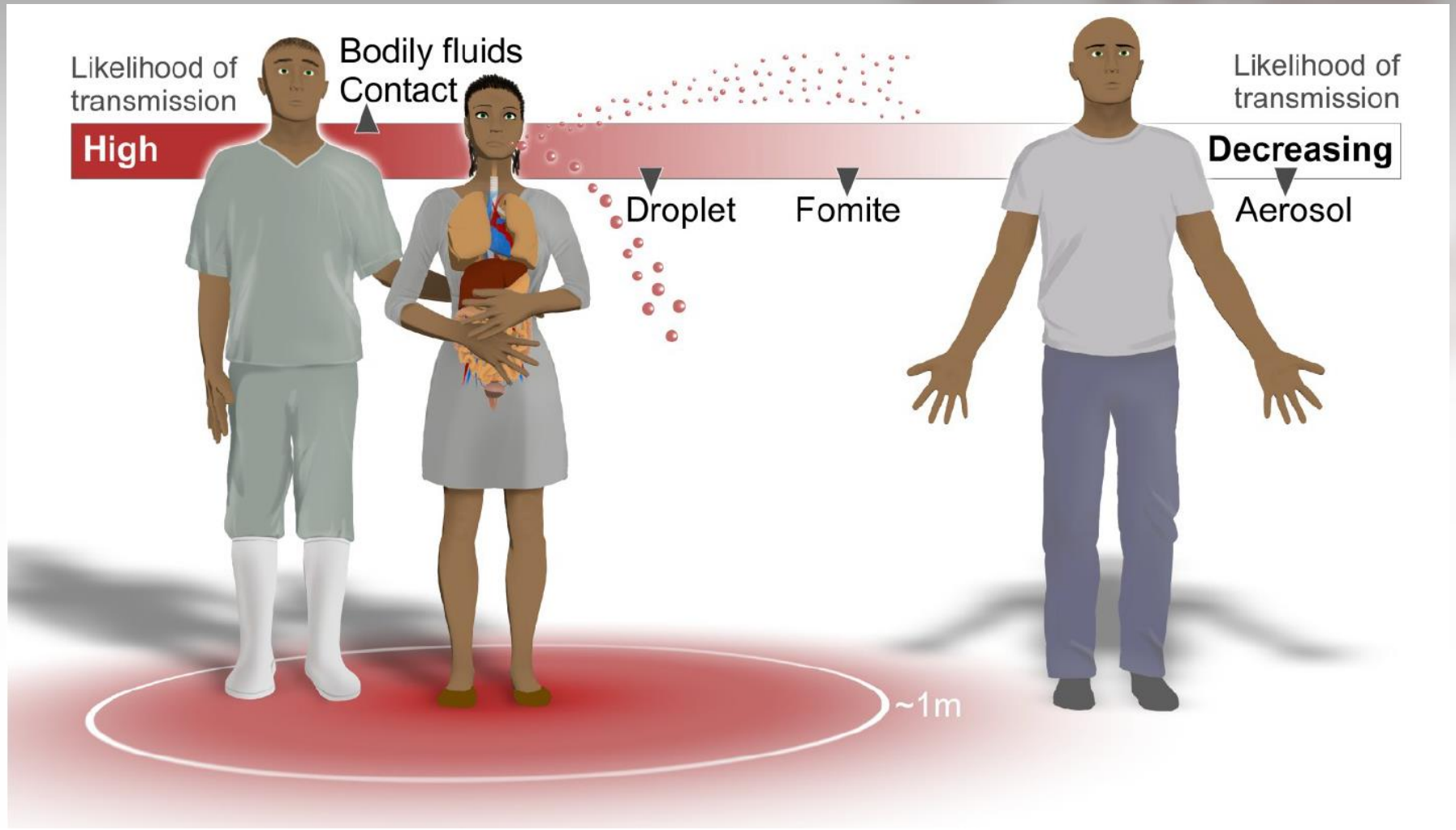
Viral Transmission

Viral Transmission



Nat Rev Microbiol 2016;14:523-34

Viral Transmission



Viruses 2015;7:511-21

Viral Transmission

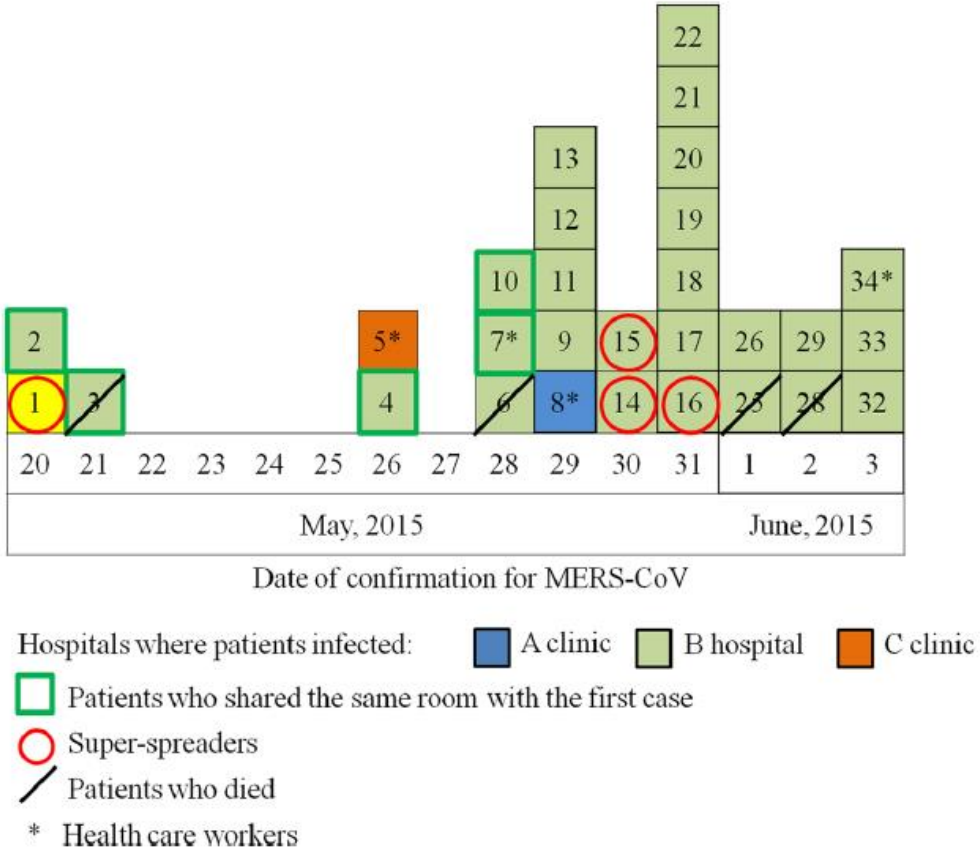


Fig. 2 Transmission of MERS-CoV associated with the first case of the Korean MERS-CoV infection outbreak [4, 8, 32]

Virus related disease

	Rhinovirus (n=580)	Respiratory syncytial virus (n=1655)	Adenovirus (n=902)	Parainfluenza virus 1 (n=94)	Parainfluenza virus 2 (n=49)	Parainfluenza virus 3 (n=315)	Influenza A virus (n=544)	Influenza B virus (n=139)
Pneumonia	18%	16%	8%	9%	6%	14%	9%	8%
Wheezy bronchitis	22%	12%	2%	2%	4%	8%	6%	6%
Otitis media	23%	59%	24%	27%	20%	30%	26%	19%
Non-specified acute respiratory infection	14%	32%	37%	27%	22%	50%	44%	53%
Bronchiolitis	3%	34%	1%	2%	10%	5%	1%	1%
Laryngitis	2%	2%	1%	37%	53%	10%	5%	4%
Tonsillitis	2%	0	30%	1%	0	2%	5%	4%
Fever without a focus	2%	1%	5%	10%	0	2%	1%	2%
Febrile convulsion	1%	2%	7%	4%	0	5%	12%	9%
Fever ≥38°C	44%	63%	81%	77%	76%	63%	94%	89%

Rhinovirus infections are from 1987 to 2006; other respiratory virus infections are from 1980 to 1999. Modified from reference 51, with permission of John Wiley and Sons.

Table 2: Occurrence of pneumonia and other findings in 4277 children with laboratory-confirmed viral respiratory infection at Turku University Hospital, Finland

Lancet 2011;377:1264-75

Antiviral agents

	Treatment	Prevention
Influenza A and B viruses	Oseltamivir (oral); zanamivir (inhalation, intravenous); peramivir (intravenous)	Vaccines (inactivated, live); oseltamivir; zanamivir
Influenza A virus	Amantadine (oral); rimantadine (oral)	..
Respiratory syncytial virus	Ribavirin (inhalation, intravenous)	Palivizumab (intramuscular)
Adenovirus	Cidofovir (intravenous)	Vaccine for types 4 and 7*
Rhinovirus	Pleconaril†	Alfa interferon (intranasal)
Enteroviruses	Pleconaril†	..
Human metapneumovirus	Ribavirin (intravenous)	..
Hantavirus	Ribavirin (intravenous)	..
Varicella-zoster virus	Aciclovir (intravenous)	Vaccine

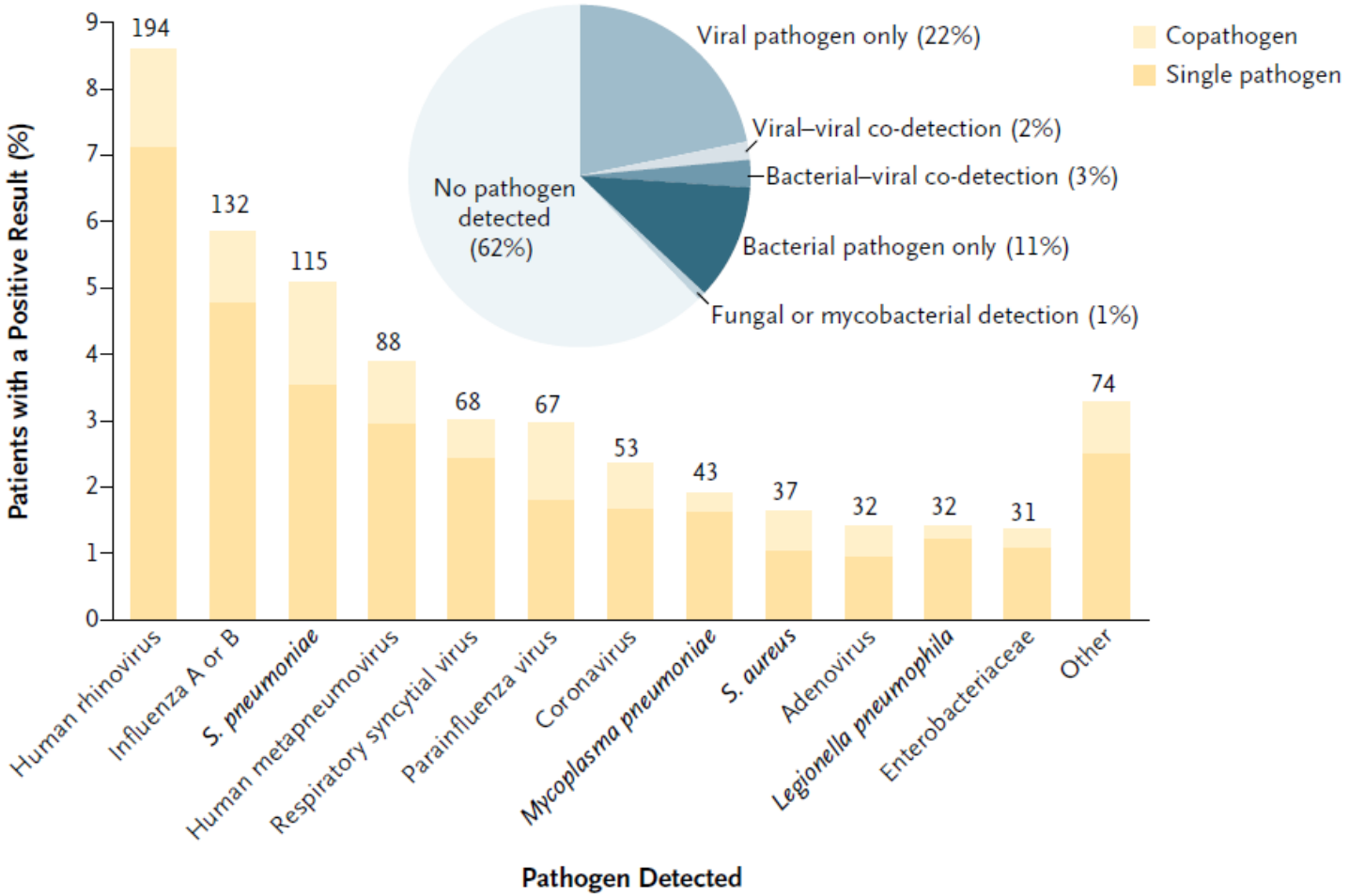
*Long successful use in US military conscripts, no production now. †Has been used for compassionate cases.

Table 3: Possibilities for antiviral treatment and prevention of severe viral pneumonia

Lancet 2011;377:1264-75

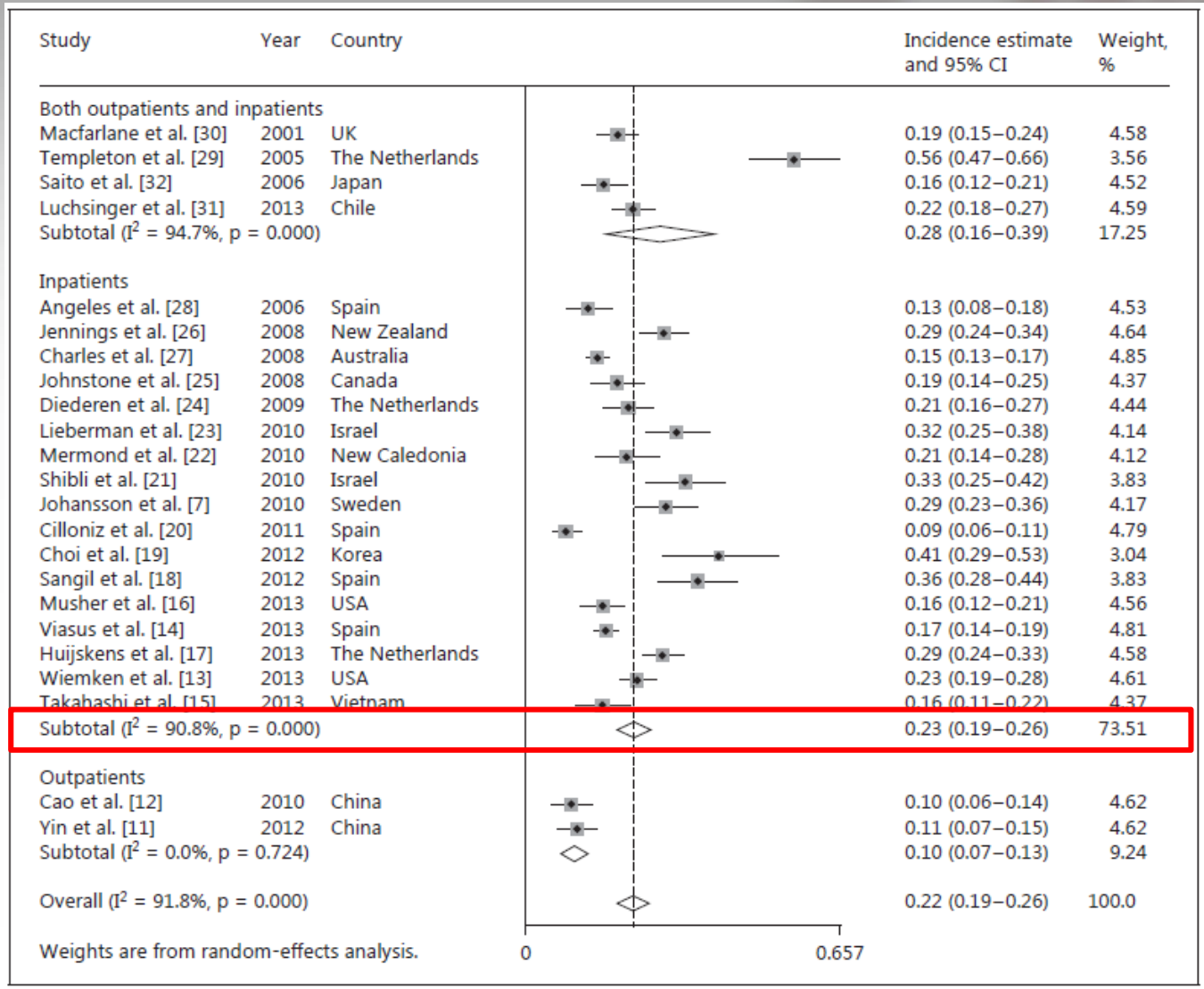
Epidemiology

The Etiology of Pneumonia in the Community (EPIC) study



N Engl J Med 2015;373:415-27

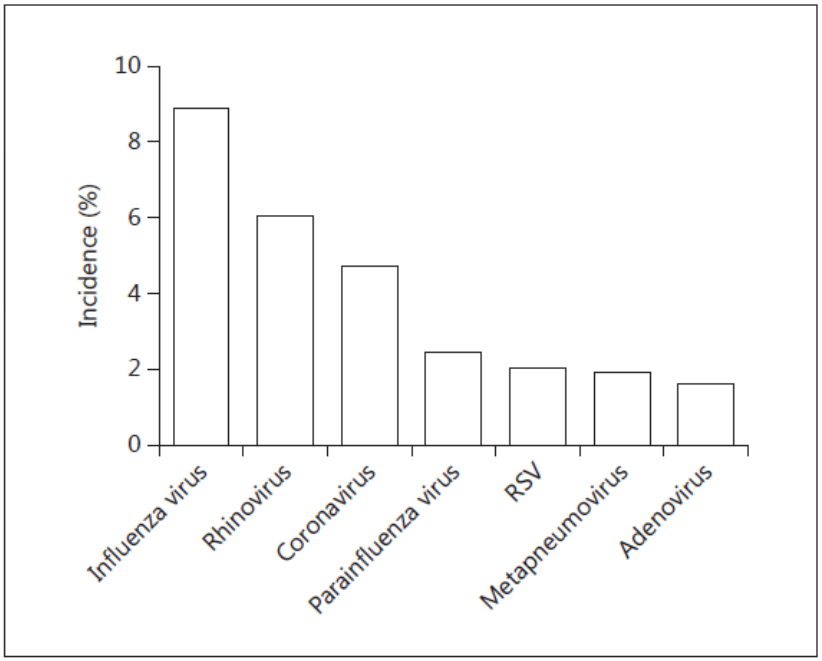
Epidemiology



Respiration 2015;89:343-52

Epidemiology

Region	Incidence of respiratory viral infections, %	95% CI	I^2, %	χ^2	p
Europe	24.7	18.0–31.5	95.1	162.6	0.000
Southeast Asia	16.6	10.5–22.8	85.1	26.9	0.000
Australia	21.5	12.2–30.8	91.9	24.6	0.000
America	20.4	17.1–23.8	52.9	6.4	0.095
Middle East	32.4	27.1–37.6	0.0	0.1	0.763



Viral species	Incidence, %
Influenza virus	8.9
Rhinovirus	6.0
Coronavirus	4.7
Parainfluenza virus	2.4
RSV	2.0
Metapneumovirus	1.9
Adenovirus	1.6

Respiration 2015;89:343-52

In Korea

Identified organism*	Total ($n = 198$)	CAP ($n = 64$)	HCAP ($n = 134$)	P Value
Virus	72 (36.4)	26 (40.6)	46 (34.3)	0.43
Rhinovirus	17 (8.6)	4 (6.3)	13 (9.7)	0.59
Parainfluenza virus	15 (7.6)	3 (4.7)	12 (9.0)	0.39
Type 3	8 (4.0)	0	8 (6.0)	0.06
Type 1	5 (2.5)	2 (3.1)	3 (2.2)	0.66
Type 2	1 (0.5)	1 (1.6)	0	0.32
Type 4	1 (0.5)	0	1 (0.7)	1.00
Human metapneumovirus	13 (6.6)	5 (7.8)	8 (6.0)	0.76
Influenza virus	12 (6.1)	6 (9.4)	6 (4.5)	0.21
Influenza A	11 (5.6)	6 (9.4)	5 (3.7)	0.18
Influenza B	1 (0.5)	0	1 (0.7)	1.00
Respiratory syncytial virus	10 (5.1)	7 (10.9)	3 (2.2)	0.01
Respiratory syncytial virus A	4 (2.0)	4 (6.3)	0	0.01
Respiratory syncytial virus B	6 (3.0)	3 (4.7)	3 (2.2)	0.39
Cytomegalovirus	8 (4.0)	0	8 (6.0)	0.056
Human coronavirus OC43	4 (2.0)	3 (4.7)	1 (0.7)	0.10

Am J Respir Crit Care Med 2012;186:325-32

Surveillance

www.cdc.go.kr

질병으로부터 자유로운 세상을 여는 질병관리본부

질병관리본부

감염병 표본감시 주간소식지

2019년도 15주차 (4.7.~4.13.)

Weekly Sentinel Surveillance Report

1. 인플루엔자

- 인플루엔자 의사환자 분율(ILI)은 외래환자 1,000명당 42.1명으로 '18년 52주(73.3명) 정점에 도달한 이후 지속적으로 감소하다 9주차부터 지속적인 증가 추세를 보임

  ※ 2018-2019절기 인플루엔자 유행기준 : 6.3명(/외래환자 1,000명 당)

- (병원체) 바이러스는 15주 143건[A(H3N2)형 22건, B형 121건], 이번절기 총 1,468건[A(H1N1)pdm09 757건, A(H3N2)형 349건, B형 362건] 검출됨

2. 급성호흡기감염증

- 바이러스성 급성호흡기감염증 환자는 1,436명(리노바이러스 631명(43.9%), 사람메타뉴모바이러스 283명(19.7%), 아데노바이러스 178명(12.4%), 파라인플루엔자바이러스 136명(9.5%), 코로나바이러스 73명(5.1%))으로 전주대비 감소
- 세균성 급성호흡기감염증 환자는 131명(마이코플라즈마균 127명, 클라미디아균 4명)으로 전주대비 증가
- 중증급성호흡기감염병(SARI) 신규 환자는 183명(인플루엔자 47명(25.7%), 폐렴 87명(47.5%))으로 전주대비 감소
- (병원체) 급성호흡기감염증 바이러스는 총 247건 검출(검출율 76.2%, 리노바이러스 44.1%, 인플루엔자바이러스 13.9%)

3. 장관감염증

- 바이러스성 장관감염증 환자는 299명(노로바이러스 184명, 로타바이러스 94명 등), 세균성 장관감염증 환자는 154명(클로스트리듐 퍼프린젠스 76명, 살모넬라균 35명 등) 발생
- (병원체) 14주차 바이러스는 총 14건 검출(검출률 48.3%, 노로바이러스 41.4%, 로타바이러스 3.4%), 세균은 총 8건 검출(검출률 8.0%, 황색포도알균 3.0%, 클로스트리듐 퍼프린젠스 2.0%)

4. 수족구병 및 엔테로바이러스

- (수족구병) 의사환자 분율은 1,000명당 2.3명(0~6세 3.1명, 7~18세 0.2명)으로 전주(2.4명) 대비 감소
- (엔테로바이러스감염증) 환자는 11명(수족구병 10명, 포진성구협염 1명)로 전주(12명) 대비 감소
  - (병원체) 14주 엔테로바이러스 3건 검출(검출률 18.8%)

5. 안과감염병

- (유행성각결막염) 의사환자 분율은 1,000명당 13.8명(0-6세 49.5명, 7~19세 23.3명, 20세 이상 11.3명)으로 전주(13.8) 대비 동일
- (급성출혈성결막염) 의사환자 분율은 1,000명당 0.5명(0-6세 1.5명, 20세 이상 0.5명, 7~19세 0.2명)으로 전주(0.6) 대비 감소함

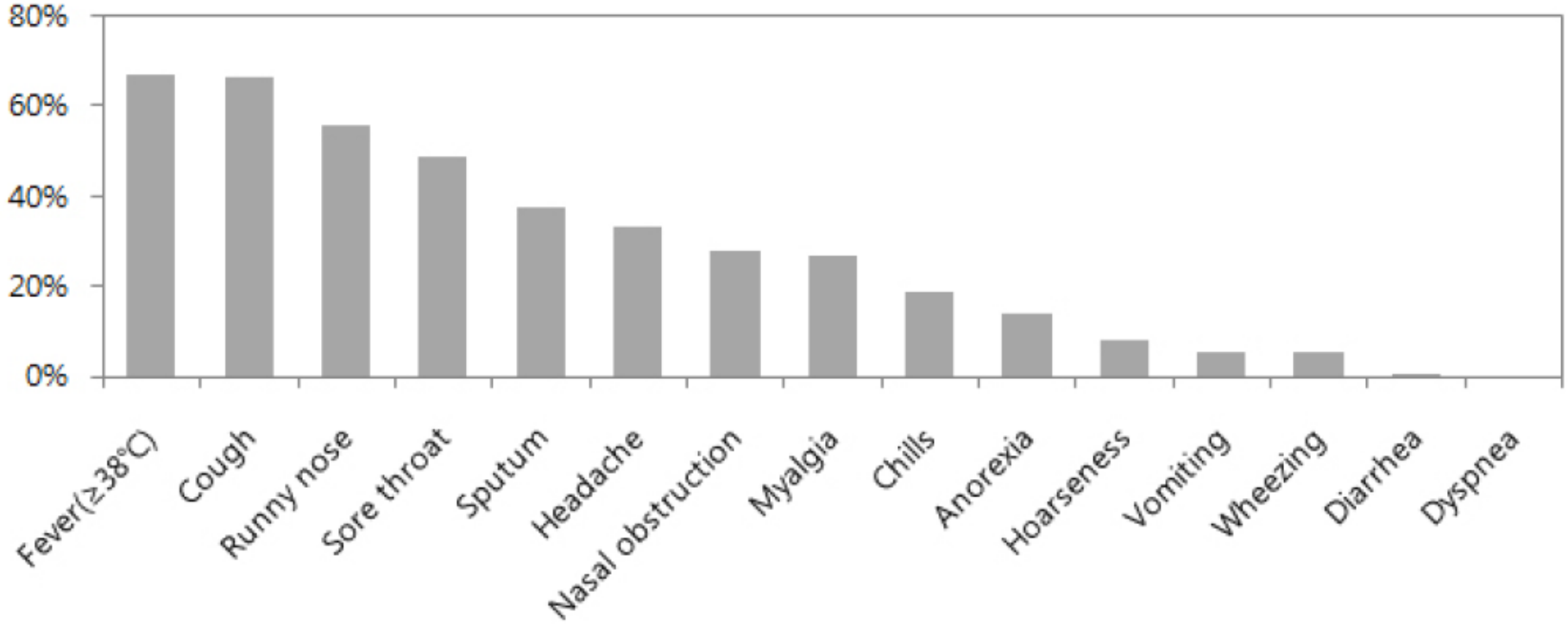
질병관리본부

2019년 제 14호

주간 해외 감염병 발생동향

■ 제14주('19.3.29~4.3) 주요 감염병 발생현황

Initial Symptoms



Public Health Weekly Report, KCDC

Chest CT

Family [subfamily]	Common Name	Transmission*	Pathogenesis	Typical CT Findings: Distribution	Consolidation	GGO	Nodule	Bronchial Wall Thickening	Pleural Effusion	Systemic Involvement
Adeno-	Adenovirus	Respiratory, fecal-oral, conjunctival	Bronchiolar and alveolar damage	Multifocal	+++	+++	Centrilobular+	UC	C	Not definite
Herpes- [Alphaherpes-]	HSV	Contact (oral or genital secretion)	Cytopathic effect with diffuse alveolar damage	Multifocal random, or segmental	++	+++	+	UC	F	Gingivostomatitis, pharyngitis and herpes labialis (HSV1)
	Varicella-zoster virus	Contact, airborne (aerosol, droplets)	Hematogenous spread to alveolus, cytopathic effect with mononuclear cell infiltration	Multifocal	Rare	Surrounding halo	1–10 mm (in late phase, calcification)	UC	Rare	Skin rash
Herpes- [Betaherpes-]	CMV	Contact, transplacental, blood transfusion	Cytopathic effect with diffuse alveolar damage	Diffuse	++	++++	++	UC	Rare	Not definite
Herpes- [Gammaherpes-]	Epstein-Barr virus	Oral, blood transfusion, organ transplantation	Mononuclear inflammatory cell infiltration along bronchovascular bundles and interlobular septa	Diffuse (pneumonia is rare)	Rare	++	Rare	UC	V	Infectious mononucleosis, mediastinal LAP, splenomegaly
Parvo-[Parvo-]	Bocavirus†	Aerosol and contact	Induced cytokine expression	Diffuse	++	++	Rare	UC	C	Not definite
Paramyxo-	HPIV	Contact, droplet	Bronchiolar and alveolar damage with mucus plugging	Airway, multifocal	+	+	Centrilobular++	C	UC	Not definite
	Measles	Airborne (aerosol, droplets), contact with secretion or skin rash	Bronchiolar and alveolar epithelial damage with multinucleated giant cell formation	Multifocal	Rare	+	+	UC	C	Hilar LAP, gastroenteritis, encephalins
	Mumps†	Droplets or aerosol, transplacental	Mononuclear cell infiltration of bronchiole and alveolar septa	Multifocal	Rare	++	Rare	UC	Rare	Parotid gland (95% of patients)

KOREA UNIVERSITY MEDICAL CENTER

Radiographics 2018;38:719-39

Chest CT

Family [subfamily]	Common Name	Transmission*	Pathogenesis	Typical CT Findings						Systemic Involvement
				Distribution	Consolidation	GGO	Nodule	Bronchial Wall Thick-ening	Pleural Effu-sion	
Pneumo-	RSV	Contact, aerosol	Destruction of bronchial and alveolar epithelium with small airway ob-struction	Airway, multi-focal	+	+	Centrilobu-lar+++	C	C	Not definite
	HMPV	Direct or close contact, droplet, aerosol	Upregulation of cytokines leads to perivascular and peribronchiolar infiltra-tion	Airway, multi-focal	+	+	Centrilobu-lar+++	C	UC	Not definite
Hanta-	HCPS, HFRS	Aerosol	Direct involvement of vascular endothelium resulting in increased endothelial permeability	Pulmonary edema	Rare	Rare	Rare	UC	F	ARF (HFRS), thrombocytopenia, hypotension, shock (HCPS)
Phenui-	SFTS	Tick-borne	Upregulation of cytokines resulting in increased endothelial permeability	Pulmonary edema	Rare	Rare	Rare	UC	F	Shock, multiorgan failure, thrombocy-topenia
Orthomyxo-	Influenza	Droplet, airborne	Destruction of airway epi-thelial barrier, resulting in necrotizing bronchitis and diffuse alveolar damage	Airway, multi-focal	+	+	++	C	UC	Not definite
Corona- [Corona-]	Human coronavi-rus	Droplet, airborne, contact	SARS: diffuse alveolar damage by involving angiotensin-converting enzyme; MERS: dys-regulation of the host cellular transcriptome resulting in apoptosis	Peripheral, multifocal	+++	+	Rare	UC	Rare	Not definite
Picorna-	Rhinovirus	Droplet, aerosol, or contact	Disruption of epithelial barrier function causing increase vascular leakage and mucus secretion; no cytopathic effect	Multifocal	+	++	Rare	UC	Rare	Not definite
	Enterovirus	Fecal-oral, contact, droplet	Attachment to decay-accelerating factor of the	Multifocal	+	++	Rare	UC	Rare	Not definite

Diagnosis (Multiplex Virus PCR)

TABLE 3. Sensitivity of direct fluorescent antibody (DFA), culture and four multiplex assays for detection and identification of respiratory viruses. Number of positives (within brackets)

Target	DFA	Culture	Resplex II Panel v2.0	Seeplex RV15	xTAG® RVP	xTAG® RVP Fast
INFA	76.7% (46)	60.3% (35)	96.9% (62)	96.9% (62)	98.4%[a] (63)	93.7%[b] (60)
INFB	78.4% (29)	75.0% (21)	100% (37)	100% (37)	100% (36)	64.9% (24)
PIV (1–4)	72.4% (21)	61.5% (16)	82.9% (34)	97.6% (40)	85.4% (35)	65.8% (26)
PIV1	76.9%	66.7%	86.7%	93.3%	71.4%	46.7%
PIV2	55.5%	44.4%	88.9%	100%	100%	77.8%
PIV3	100%	66.7%	100%	85.7%	71.4%	42.8%
PIV4	–	–	60.0%	100%	100%	100%
hMPV	68.6% (24)	43.3% (13)	82.0% (32)	97.4% (38)	97.4% (38)	92.3% (36)
RSV (A/B)	93.5% (130)	86.5% (96)	84.0% (121)	100% (144)	88.2% (127)	91.7% (132)
RSVA	–	–	90.4%	100%	85.5%	92.5%
RSVB	–	–	79.3%	100%	98.3%	94.8%
ADV	38.1% (8)	44.4% (8)	71.4% (15)	100% (21)	85.7% (18)	52.4% (11)
BoV	–	–	75.0% (18)	100% (24)	–	100% (24)
CoV OC43/HKU1	–	–	92.6% (25)	100% (27)	48.1% (13)	59.3% (16)
CoV 229E/NL63	–	–	100% (17)	100% (17)	88.2% (15)	88.2% (15)
Enterovirus/rhinovirus	–	–	96.7% (172)	71.7% (127)	93.8% (167)	97.7% (174)

TABLE 4. Specificity of direct fluorescent antibody (DFA), culture and four multiplex assays for detection and identification of respiratory viruses

Target	DFA (%)	Culture (%)	Resplex II Panel v2.0 (%)	Seeplex RV15 (%)	xTAG® RVP (%)	xTAG® RVP Fast (%)
INFA	99.7	100	100	98.8	100	100
INFB	99.8	100	100	100	100	100
PIV (1–4)	99.8	100	100	99.0	99.6	97.6
hMPV	99.4	100	100	99.7	99.7	100
RSV (A/B)	99.6	100	100	97.7	100	100
ADV	100	100	99.9	98.1	99.9	100
BoV	–	–	100	100	–	99.6
CoV OC43/HKU1	–	–	100	99.3	99.9	100
CoV 229E/NL63	–	–	100	98.8	99.9	100
Entero/rhinovirus			99.3	99.1	96.0	99.8

Viral pneumonia vs. Bacterial pneumonia

	Suggests viral cause	Suggests bacterial cause
Age	Younger than 5 years	Adults
Epidemic situation	Ongoing viral epidemic	..
History of illness	Slow onset	Rapid onset
Clinical profile	Rhinitis, wheezing	High fever, tachypnoea
Biomarkers		
Total white-blood cell count	$<10\times10^9$ cells per L	$>15\times10^9$ cells per L
C-reactive protein concentration in serum	<20 mg/L	>60 mg/L
Procalcitonin concentration in serum	<0·1 µg/L	>0·5 µg/L
Chest radiograph findings	Sole interstitial infiltrates, bilaterally	Lobar alveolar infiltrates
Response to antibiotic treatment	Slow or non-responsive	Rapid

Table 1: Variables used to distinguish viral from bacterial pneumonia

Lancet 2011;377:1264-75

Antibiotics

Table 4 Clinical outcomes of patients with viral pneumonia according to empiric antibacterial therapy

	Long course ($n = 67$)	Short course ($n = 28$)	Mixed infection ($n = 79$)
Instances of subsequent MDRO infection or colonization	25/47 (53.2)	4/19 (21.1)*	20/53 (37.7)
MRSA colonization	2/10 (20)	0/7 (0)	3/15 (20)
VRE colonization	3/6 (50)	1/4 (25)	9/20 (45)
MDRO infection	20/31 (64.5)	3/8 (37.5)	8/18 (44.4)
Patients with subsequent MDRO infection or colonization	16 (23.9)	3 (10.7)	16 (20.3)
MRSA colonization	2 (3.0)	0 (0)	3 (3.8)
VRE colonization	3 (4.5)	1 (3.6)	9 (11.4)
MDRO infection	13 (19.4)	3 (10.7)	7 (8.9)
Subsequent *Clostridium difficile* infection	1 (1.5)	0 (0)	2 (2.5)
In-hospital mortality	8 (11.9)	3 (10.7)	23 (29.1)**
Non-ICU	1/23 (4.3)	0/11 (0)	0/16 (0)
ICU (all)	7/44 (15.9)	3/17 (17.6)	23/63 (36.5)**
ICU – oncology	4/18 (22.2)	2/5 (40)	10/16 (62.5)**
ICU – nononcology	3/26 (11.5)	1/12 (8.3)	13/47 (27.7)
Hospital LOS (days)	11 (7–25)	8.5 (5–20)	17 (8.5-28) ***
ICU LOS (days)	8.1 (4.9-17.9)	4.2 (2.8-14.7)*	12 (5.1-19.1) ***
Readmit within			
30 days	14 (20.9)	4 (12.9)	19 (24.0)
90 days	22 (32.8)	8 (25.8)	27 (48.2)
180 days	30 (44.8)	11 (35.5)	29 (51.8)

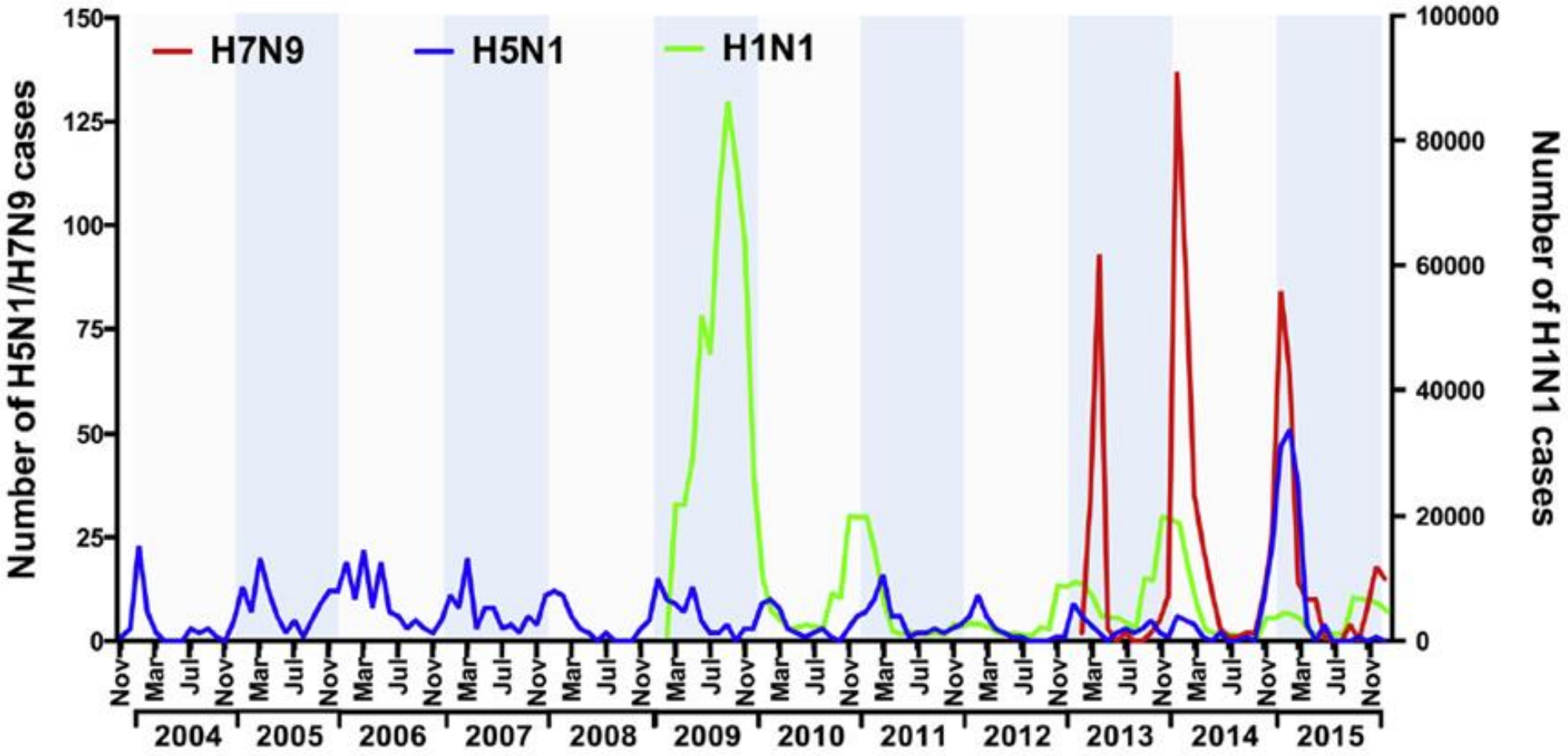
Data expressed as number (% of total) or median (interquartile range)
LOS length of stay, *MDRO* multidrug-resistant organism, *MRSA* methicillin-resistant *Staphylococcus aureus*, *VRE* vancomycin-resistant enterococci
*Statistically significant difference ($P < 0.05$) between short-course and long-course groups
**Statistically significant difference ($P < 0.05$) between long-course and mixed-infection groups
***Statistically significant difference ($P < 0.05$) between short-course and mixed-infection groups

Crit Care 2015;19:404

Seasonal Viruses

- ✓ Influenza
- ✓ Adenovirus
- ✓ Coronavirus
- ✓ Human metapneumovirus
- ✓ Respiratory syncytial virus
- ✓ Rhinovirus
- ✓ Parainfluenza virus

Influenza, Epidemiology



Clin Chest Med 2017;38:59-70

Influenza, Symptoms

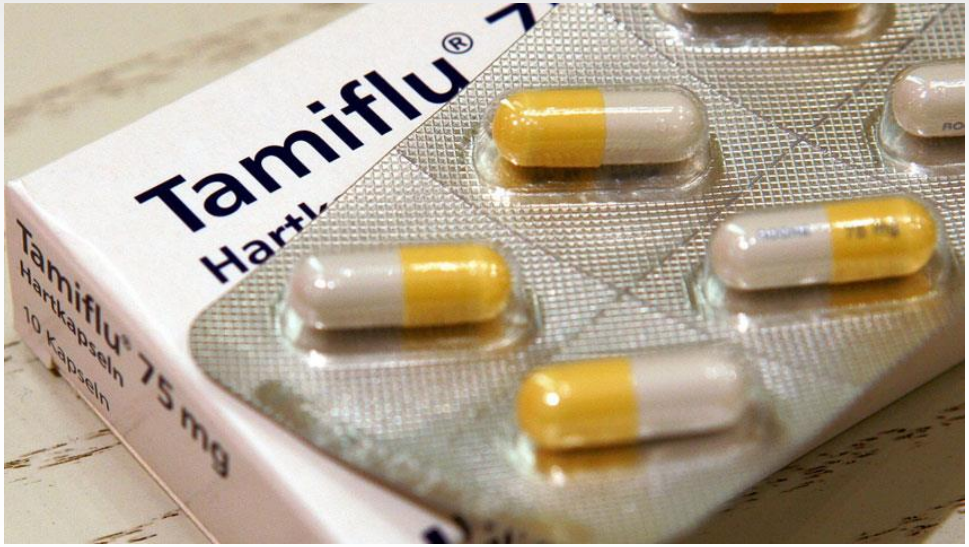
https://mypositiveparenting.org/2015/04/19/whats-up-influenza/

Influenza, complications

Category	Disease
Pulmonary complications	Primary Influenza pneumonia
	Secondary bacterial pneumonia
	Pulmonary superinfection (fungus, atypical)
	Exacerbations of chronic lung diseases
Extrapulmonary complications	Pericarditis, Myocarditis
	Myositis, Rhabdomyolysis
	Encephalopathy, Encephalitis
	Transverse myelitis, Aseptic meningitis
	Guillain-Barre syndrome
	Neuropsychiatric events (suicide attempts)

Crit Care Med 2010;38:e91-97

Influenza, Treatments



KOREA UNIVERSITY MEDICAL CENTER

Influenza, Antiviral resistance

REVIEW

CURRENT OPINION

Neu nfluenza: a
clini

KEY POINTS

- At present, NAI resistance remains uncommon among the circulating viruses (oseltamivir <3.5%, zanamivir <1%). Resistance risk is slightly higher in A(H1N1) than A(H3N2) and B viruses.
- NAI resistance may emerge during drug exposure, particularly among young children (<5 years), the immunocompromised, and individuals receiving prophylactic regimens.
- Outbreaks caused by H275Y A(H1N1) variant highlight the importance of continuous surveillance, and assessment of viral fitness and transmissibility of resistant virus strains.
- Detection can be challenging, especially in a mix of resistant and wild-type viruses. Recent advances in molecular techniques (e.g. ddPCR, pyrosequencing, NGS) have improved its detection and our understanding on viral dynamics.
- Treatments options for oseltamivir-resistant viruses are limited, and susceptibility testing of different NAIs may be required, but non-NAI antivirals (e.g. polymerase inhibitors) that are active against these resistant viruses are in late-stage clinical development.

ect Dis 2018;31:520-26

KOREA UNIVERSITY MEDICAL CENTER

Dose and Duration in Critically-ill Patients

Use of antivirals for treatment of influenza

Population	Pandemic influenza A (H1N1) 2009 and other seasonal influenza viruses	Influenza viruses known or suspected to be oseltamivir resistant
Uncomplicated clinical presentation		
Patients in higher risk groups	Treat with oseltamivir or zanamivir as soon as possible (05)	Treat with zanamivir as soon as possible (05)
Severe or progressive clinical presentation		
All patients (including children and adolescents)	Treat with oseltamivir as soon as possible (01) (zanamivir should be used if oseltamivir unavailable) (02)	Treat with zanamivir as soon as possible (03)
Patients with severe immunosuppression	Treat with oseltamivir as soon as possible. Consider higher doses and longer duration of treatment (03)	Treat with zanamivir as soon as possible (03)

2010 WHO recommendation

Dose and Duration in Critically-ill Patients

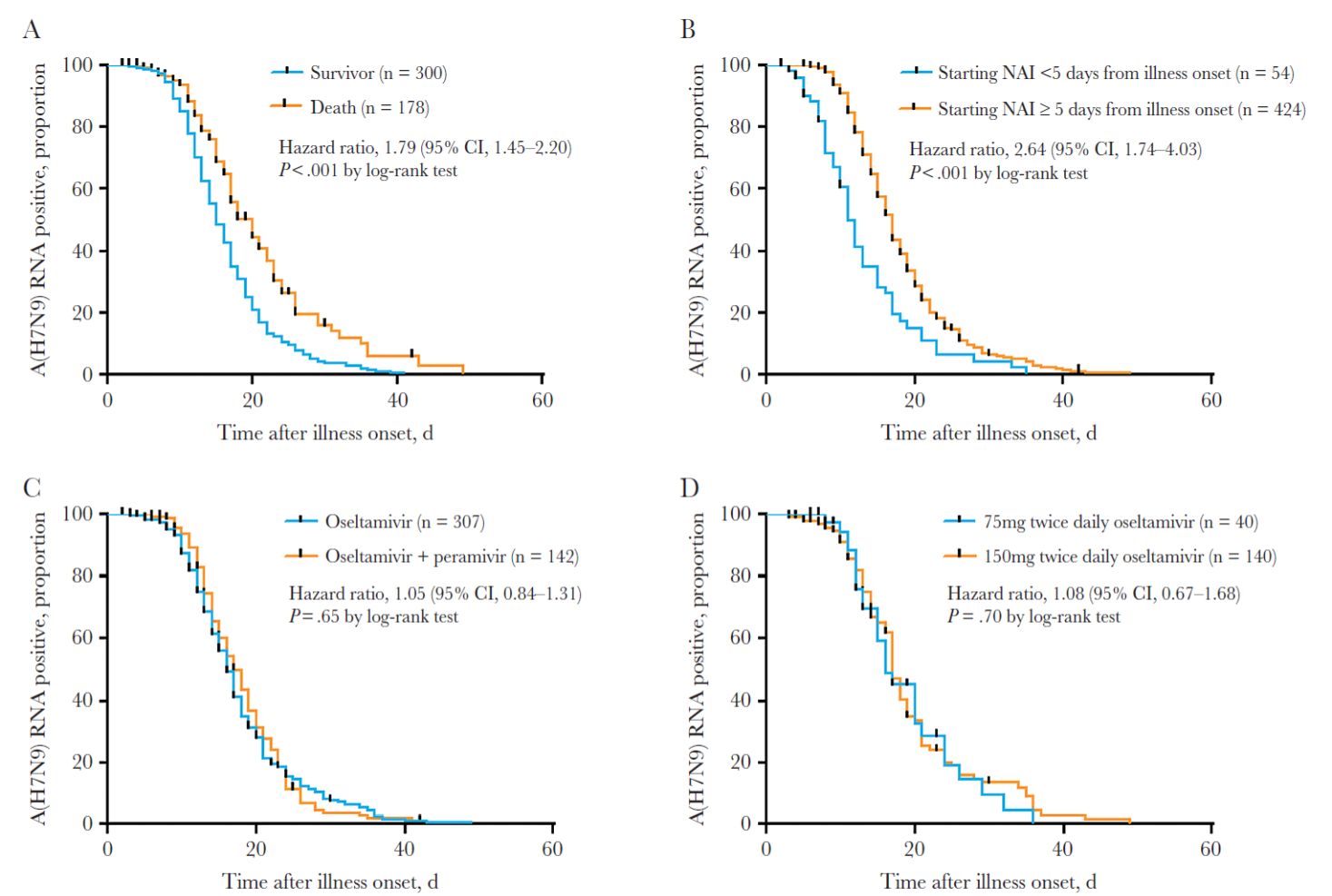


Figure 3. *A*, Cumulative proportion of patients between patients who survived and those who died with detectable avian influenza A(H7N9) virus RNA, by day after onset of illness. *B*, Cumulative proportion of patients who started neuraminidase inhibitor (NAI) therapy <5 days versus ≥5 days after illness onset who had detectable A(H7N9) RNA, by day after onset of illness. *C*, Cumulative proportion of patients treated with oseltamivir versus oseltamivir and peramivir who had detectable A(H7N9) RNA, by day after onset of illness. *D*, Cumulative proportion of patients treated with oseltamivir (75 mg twice daily) versus oseltamivir (150 mg twice daily) with detectable A(H7N9) RNA, by day after onset of illness. CI, confidence interval.

J Infect Dis 2018;217:1708-17

Dose and Duration in Critically-ill Patients

Table 3. Baseline Characteristics

Characteristic	Standard Dose (N= 46)	High-Dose (N= 77)	P Value
Influenza A H1N1	12 (26.1)	12 (15.6)	
Influenza B	9 (19.6)	5 (6.5)	
Concomitant bacterial pneumonia	2 (4.3)	12 (15.6)	0.06
Concomitant bacterial infection	11 (23.9)	15 (19.5)	0.56
Hospital transfer	29 (63.0)	55 (71.4)	0.42

Table 1 Outcomes of intensive care unit patients treated with high-dose of standard dose oseltamivir

Variable	Standard dose oseltamivir ($n = 46$)	High-dose oseltamivir ($n = 77$)	p value
Intensive care unit-free (days)	16.5 (1.5–25.0)	2 (0–21.5)	0.015
Ventilator-free (days)	22 (7.5–28.0)	10 (0–25.0)	<0.01
Delta $SOFA_{0–48h}$ [a]	1 (−1–2)	1 (−1–2)	0.43
28-Day mortality	7 (15.2)	30 (39.0)	<0.01
	Standard dose ($n = 39$)[b]	High-dose ($n = 47$)[b]	
Hospital length of stay (days)	20 ± 15	20 ± 18	0.88
Time back to pre-morbid O_2 requirements (days)	15 ± 14	18 ± 19	0.49

All data are reported as the mean ± standard deviaiton, or as the median with the interquartile range in parenthesis, as appropriate

[a] Sequential Organ Failure Assessment score between 0 and 48 h after initiation of oseltamivir therapy

[b] Assessment of these outcomes did not include patients who died before 28 days

KOREA UNIVERSITY MEDICAL CENTER

Intensive Care Med 2015;41:1365-66

Dose and Duration in Critically-ill Patients

Viral clearance and inflammatory response patterns in adults hospitalized for pandemic 2009 influenza A(H1N1) virus pneumonia

Figure 1. Viral RNA concentration in nasopharyngeal aspirates at presentation according to days from symptom onset

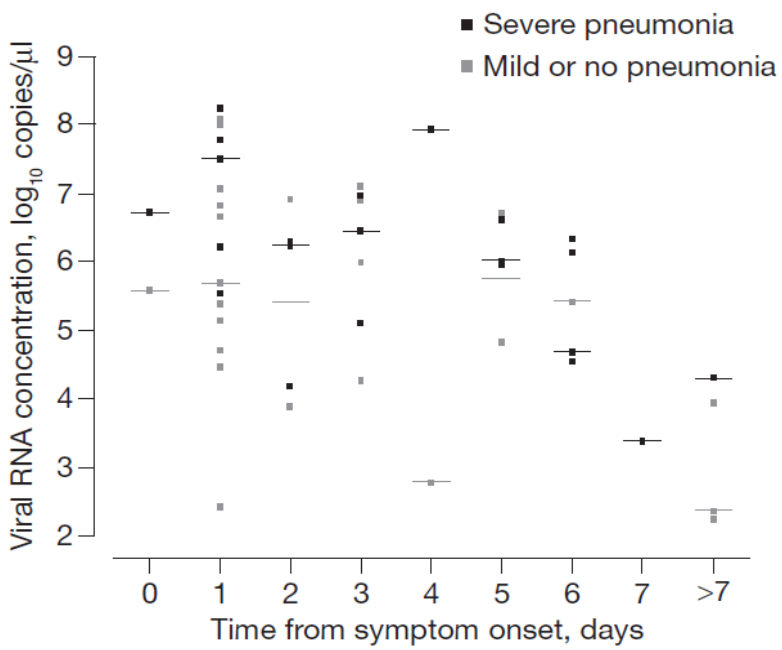
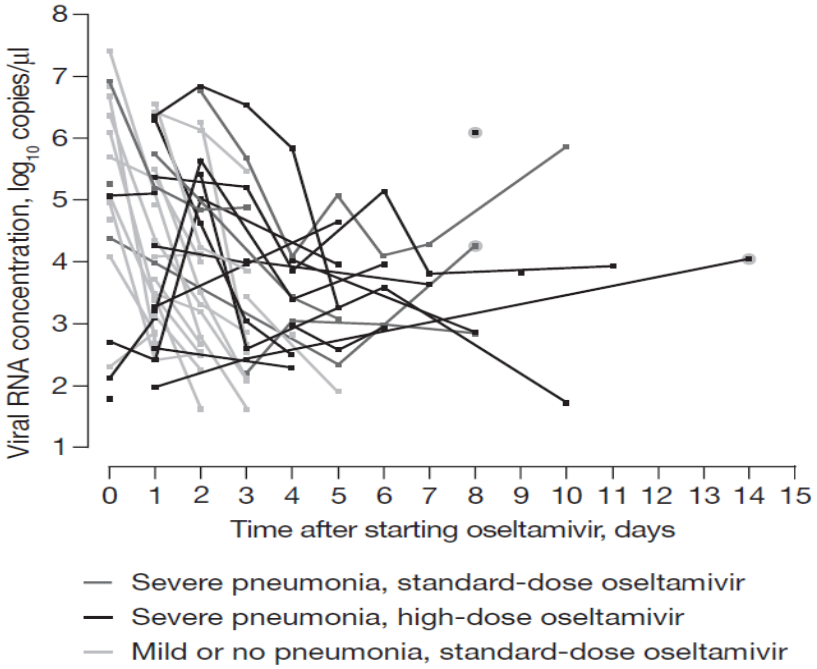


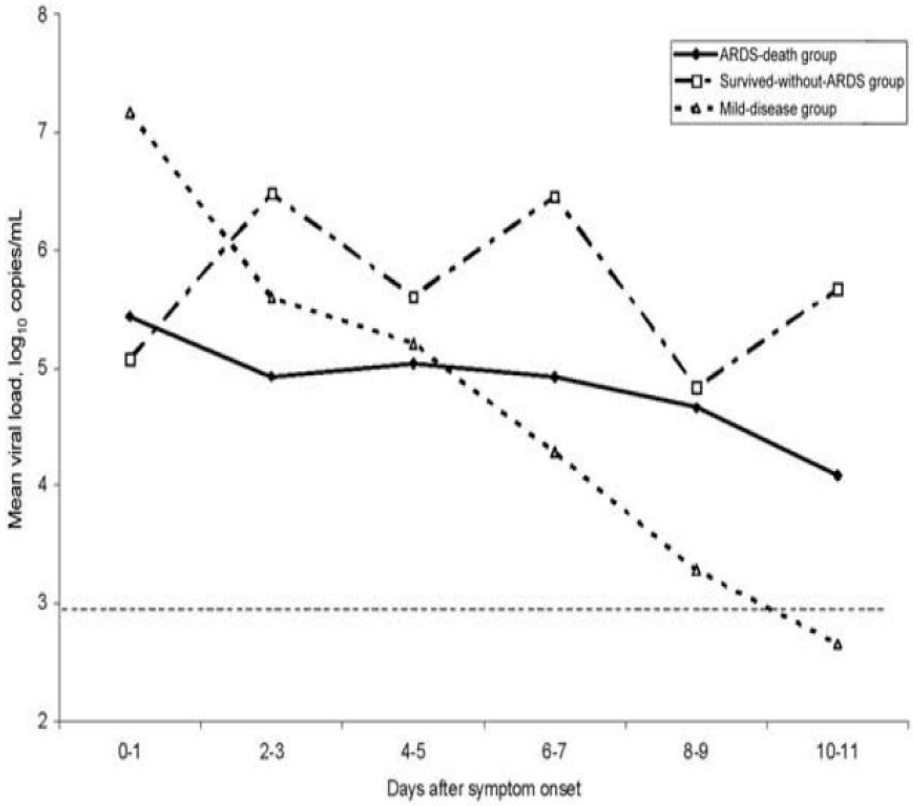
Figure 2. Quantitative viral RNA detection in serial nasopharyngeal flocked swabs after commencement of antiviral treatment

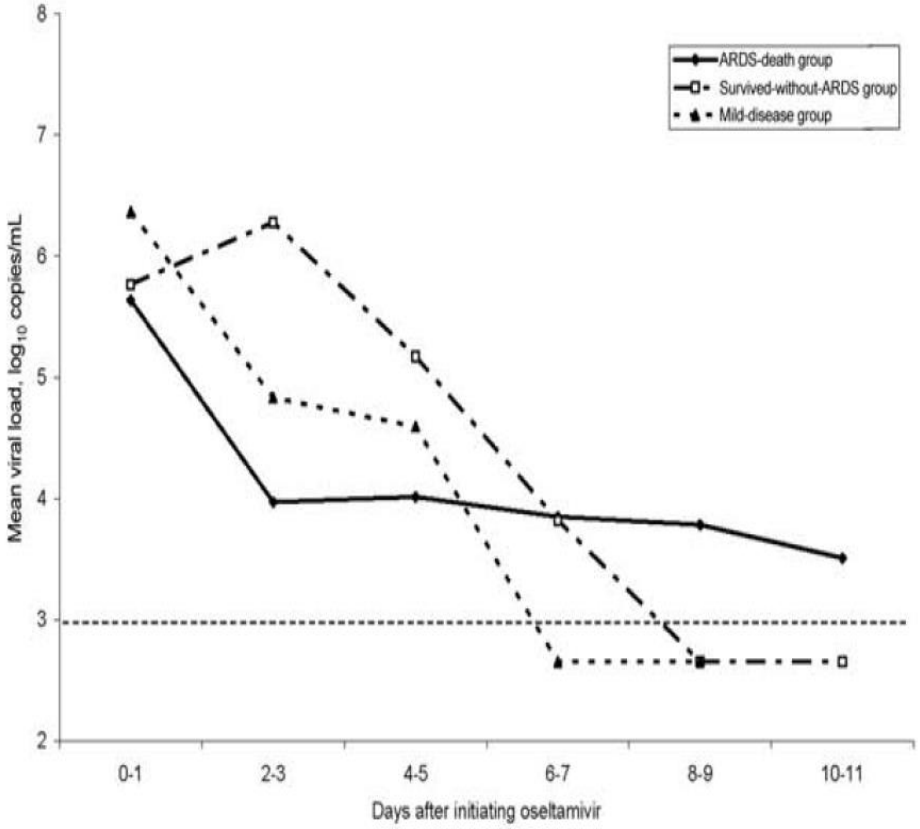


Antivir Ther 2011;16:237-47

Dose and Duration in Critically-ill Patients

Delayed Clearance of Viral Load and Marked Cytokine Activation in Severe Cases of Pandemic H1N1 2009 Influenza Virus Infection





Clin Infect Dis 2010;50:850-9

Dose and Duration in Critically-ill Patients

Usual Dose > Double Dose

Standard duration < Prolong duration

IDSA guideline 2018

Influenza, Steroid

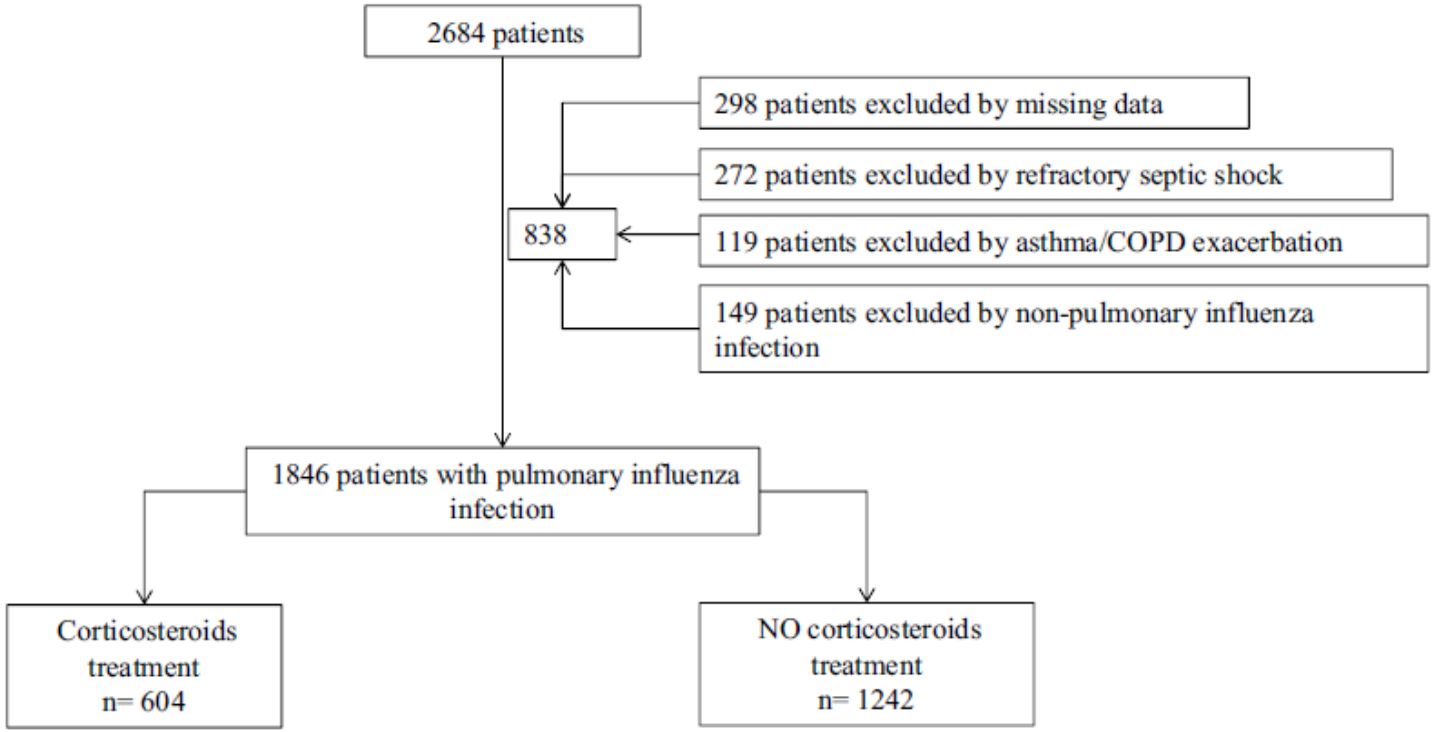


Fig. 1 Flowchart of all excluded and included patients

Prospective and observational cohorts in Spain between June 2009 and April 2014

Influenza, Steroid

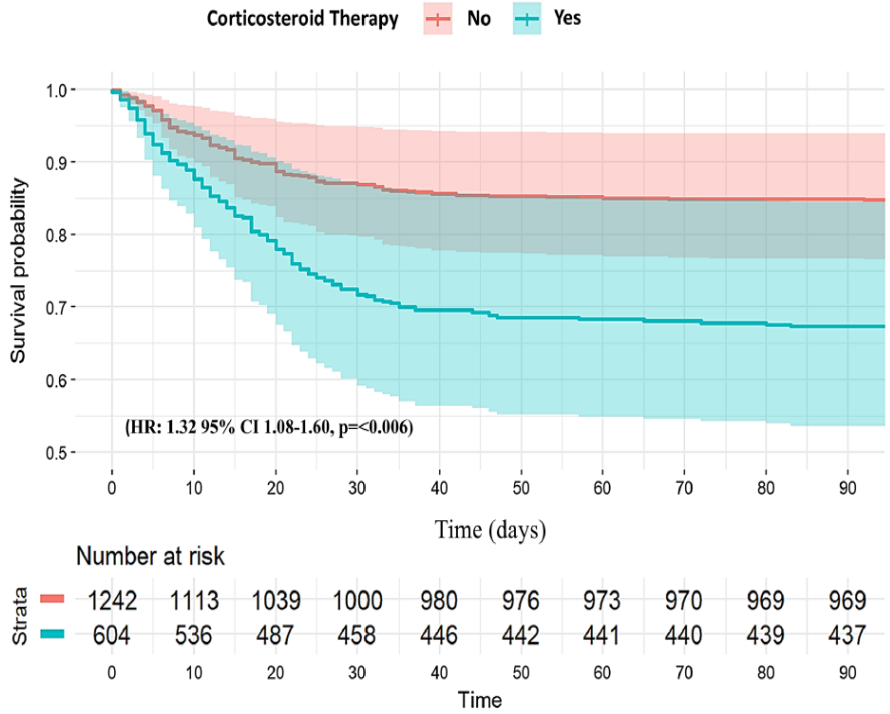


Fig. 3 Cox regression survival plot during ICU admission according to corticosteroid therapy

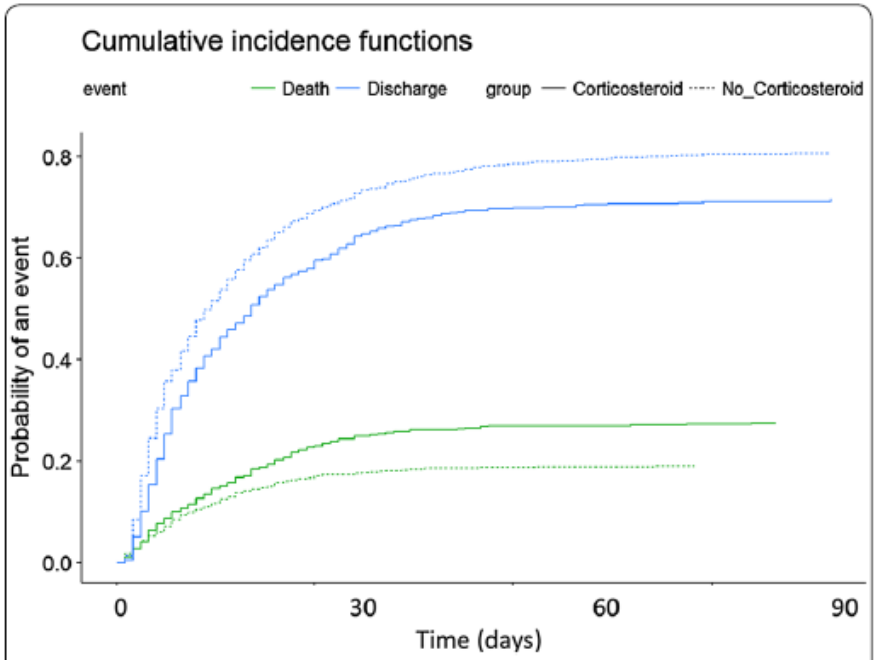


Fig. 4 Cumulative incidence function of ICU death and being discharged alive according to corticosteroid therapy

Intensive Care Med 2018;44:1470-82

KOREA UNIVERSITY MEDICAL CENTER

Influenza, Steroid

Subgroups	Corticosteroid Therapy YES	Corticosteroid Therapy NO	OR (95%CI)	P-value
	number of patients dead/total number of patients (%)			
APACHE II ≥ 15	120/319 (37.6)	169/562 (30.1)	1.4 (1.03-1.9)	0.022
APACHE II < 15	42/259 (16.2)	55/612 (9.0)	1.9 (1.2-3.0)	0.002
Shock YES	125/313 (39.9)	183/624 (29.3)	1.6 (1.2-2.1)	0.001
Shock No	41/287 (14.3)	49/606 (8.1)	1.9(1.2-3.0)	0.004
MV YES	161/506 (31.8)	220/921 (23.9)	1.5(1.1-1.9)	0.001
MV No	5/97 (5.2)	13/319 (4.1)	1.3(0.4-3.9)	0.64
SOFA ≥ 5	123/315 (39.0)	155/586 (26.5)	1.8(1.8-2.4)	0.001
SOFA < 5	28/207 (13.5)	45/466 (9.7)	1.4(0.8-2.5)	0.13
CRP ≥ 25	67/226 (29.5)	94/511 (18.4)	1.8 (1.3-2.7)	0.001
CRP < 25	47/211 (22.3)	68/389 (17.5)	1.3(0.8-2.1)	0.15
COPD	54/154 (29.2)	36/179 (20.1)	2.1(1.3-3.6)	0.002
No COPD	120/446 (26.9)	196/1052(18.6)	1.6(1.2-2.1)	0.000
Asthma	15/79 (19.0)	14/75 (18.7)	1.02(0.4-2.4)	0.95
No asthma	150/521 (28.8)	218/1156(18.9)	1.7(1.3-2.2)	0.000
Bact. Coinfection	47/139 (33.8)	64/248 (25.8)	1.5(0.9-2.3)	0.09
No bact. coinfection	119/465 (25.6)	170/994 (17.1)	1.6(1.3-2.1)	<0.001

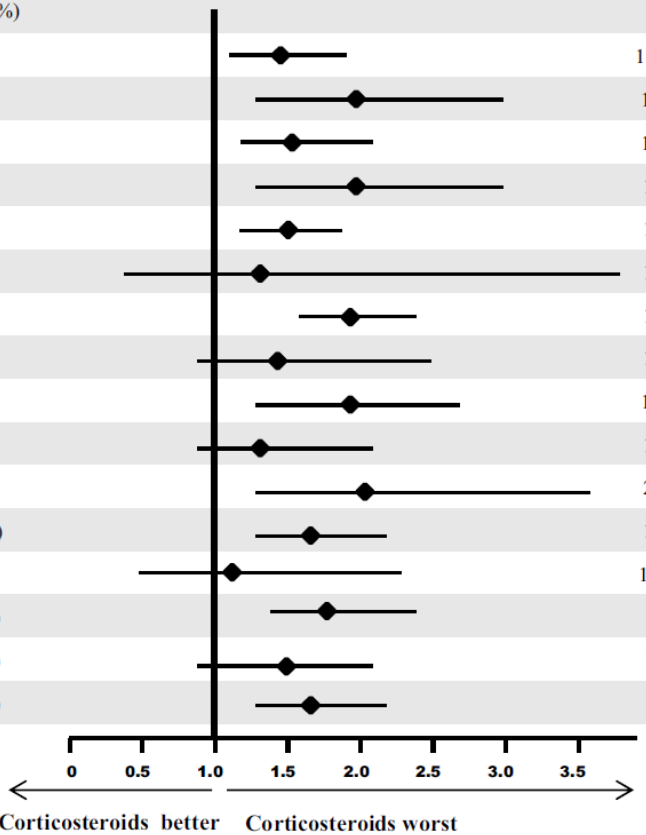


Fig. 2 Subgroup analysis of ICU mortality according to corticosteroid treatment. *APACHE II* Acute Physiology and Chronic Health Evaluation II score, *MV* mechanical ventilation, *SOFA* Sequential Organ Failure Assessment, *CRP* C-reactive protein, *COPD* chronic obstructive pulmonary disease

KOREA UNIVERSITY MEDICAL CENTER

Intensive Care Med 2018;44:1470-82

Peramivir

Evaluation of Intravenous Peramivir for Treatment of Influenza in Hospitalized Patients

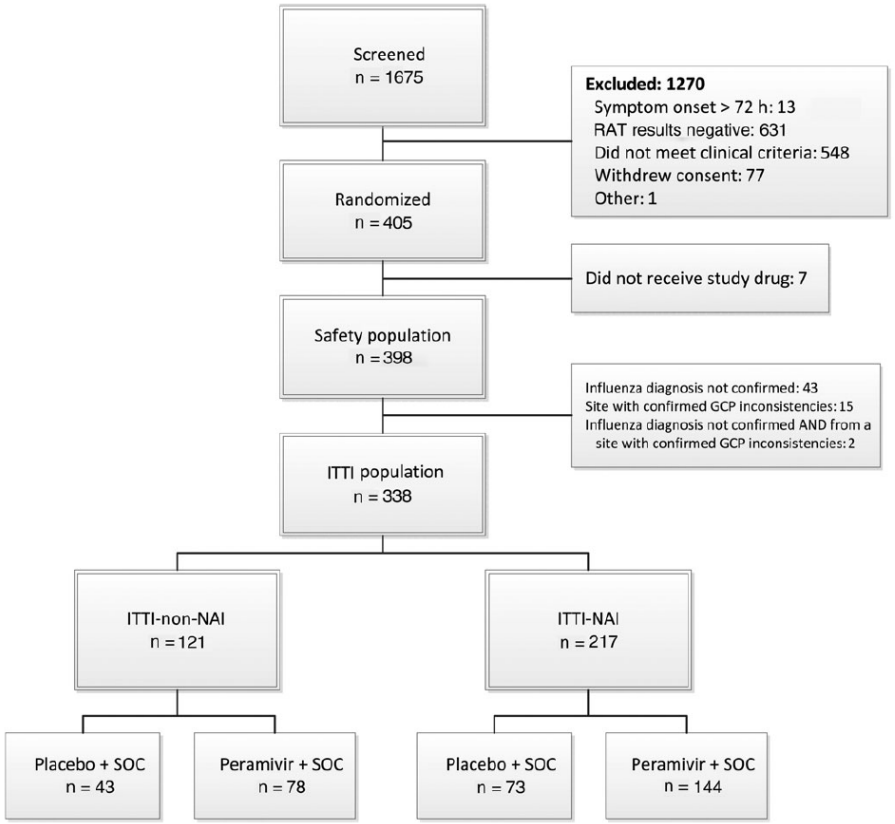


Figure 1. Overall disposition of subjects. Abbreviations: GCP, good clinical practice; ITTI, intent-to-treat infected; NAI, neuraminidase inhibitor; RAT, rapid antigen test; SOC, standard of care.

Clin Infect Dis 2014;59:e172-85

Peramivir

Table 8. Viral Shedding in Subjects With Positive Baseline and Postbaseline Viral Titer (ITTI Non-NAI SOC Population)

Titer Measurement	Placebo + SOC	Peramivir[a] + SOC	*P* Value
Measured by viral culture, $\log_{10}$ $TCID_{50}$/mL			
Baseline, median (range)	2.00 (0.75–4.50) (n = 15)	2.75 (0.75–4.50) (n = 23)	. . .
Change from baseline, median (95% CI)			
At 24 h	−1.13 (−1.75 to −.25) (n = 14)	−1.75 (−2.25 to −1.00) (n = 19)	.44
At 48 h	−1.38 (−1.75 to −.25) (n = 14)	−2.25 (−3.00 to −1.50) (n = 17)	.29
At 108 h	−1.75 (−2.75 to −.25) (n = 9)	−2.13 (3.50 to −.25) (n = 8)	.90
Measured by RT-PCR, $\log_{10}$ viral particles/mL			
Baseline, median (range)	5.84 (2.60–7.99) (n = 34)	5.43 (2.60–7.97) (n = 61)	. . .
Change from baseline, median (95% CI)			
At 24 h	−1.09 (−1.62 to −.80) (n = 34)	−1.49 (−1.84 to −1.22) (n = 57)	.56
At 48 h	−1.67 (−2.14 to −.87) (n = 33)	−2.02 (−2.49 to −1.46) (n = 55)	.17
At 108 h	−2.39 (−3.29 to −1.59) (n = 18)	−2.48 (−3.05 to −2.11) (n = 29)	.93

KOREA UNIVERSITY MEDICAL CENTER

Clin Infect Dis 2014;59:e172-85

Adenovirus

Table 1
Adenovirus species and serotypes, and associated clinical syndromes

Species	Serotypes	Clinical Syndromes
A	12, 18, 31, 61	Unknown; oncogenic in hamsters
B	3, 7, 11, 14, 16, 21, 34, 35, 50, 55	Respiratory infections (7, 14, 21 particularly in military recruits), conjunctivitis, hemorrhagic cystitis (7, 11, 21), myocarditis (7, 21), meningoencephalitis (7), disseminated disease (11, 34, 35)
C	1, 2, 5, 6, 57	Respiratory infections, intussusception, disseminated disease (1, 2, 5)
D	8–10, 13, 15, 17, 19, 20, 22–30, 32, 33, 36–39, 42–49, 51, 53, 54, 56, 58, 59, 60, 62–65	Respiratory infections, conjunctivitis
E	4	Respiratory infections (particularly in military recruits), conjunctivitis
F	40, 41	Gastroenteritis
G	52	Gastroenteritis

Clin Lab Med 2014;34:409-30

Adenovirus

- ✓ **Closed populations**
  - ➢ **Hospitals, Neonatal nurseries, Psychiatric, Long term care**
  - ➢ **Job training centers**
  - ➢ **Children's home, Orphangae**
  - ➢ **Public swimming pools**
  - ➢ **Military**
- ✓ **95% ethanol solution**

Adenovirus

- ✓ No antiviral drug has been approved to treat AdV

- ✓ Cidofovir
  - ➢ Preferred therapeutic agent
  - ➢ Only intravenously
  - ➢ Standard doses: 5mg/kg every 1-2 weeks
  - ➢ Duration of therapy: weeks to months (clinical response)
  - ➢ Adverse effects: nephrotoxicity, Myelosuppression, Uveitis
  - ➢ Minimize nephrotoxicity: Hydration+Probenecid

Mycoplasma pneumonia, peak age

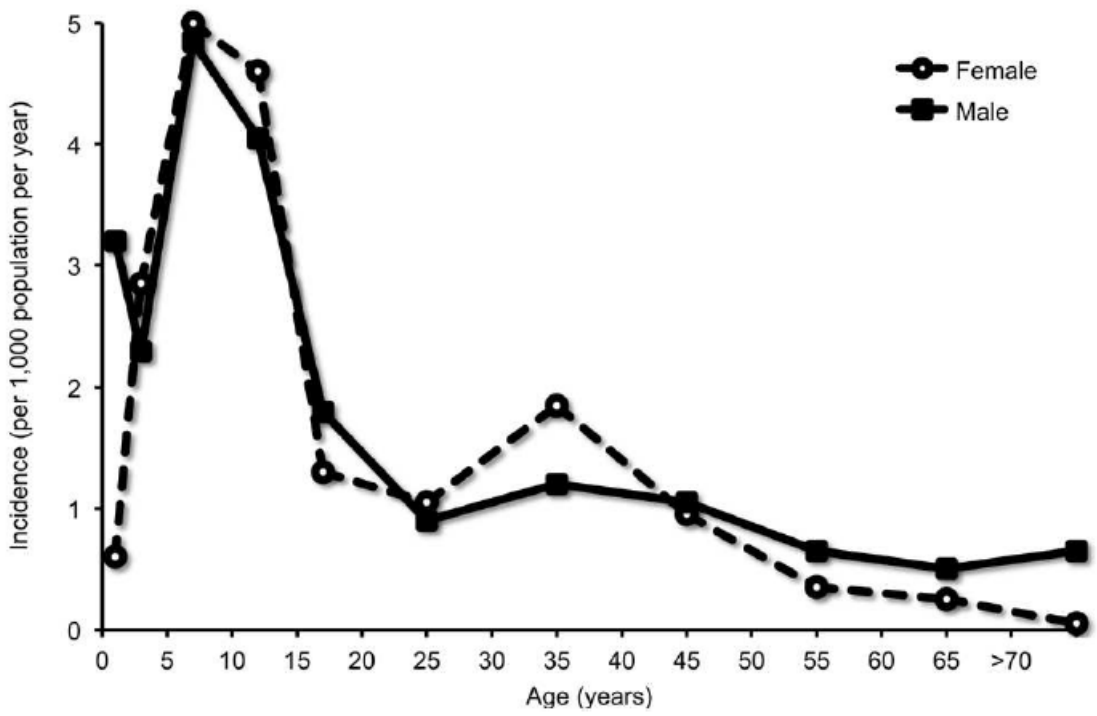


FIGURE 2 | Detection of *M. pneumoniae* in community-acquired pneumonia (CAP) according to age group. Infection was diagnosed by culture of respiratory specimens and/or a fourfold titer rise in complement fixation test (CFT). Adapted with permission from Foy et al. (1979).

KOREA UNIVERSITY MEDICAL CENTER

Front Microbiol 2016;7:329

Mycoplasma pneumonia

Table 1. Pulmonary and Extrapulmonary Manifestations of *Mycoplasma pneumoniae* Infection

Organ involvement	Manifestation
Pulmonary	Asthma/chronic obstructive pulmonary disease (COPD) exacerbation Tracheobronchitis Pneumonia: lobar and multi-lobar infiltrates Diffuse alveolar hemorrhage
Gastrointestinal	Nausea, vomiting, abdominal pain, anorexia Diarrhea Transaminitis
Cardiovascular	Myocarditis, pericarditis Cardiac arrhythmias Thrombotic events
Neurological	Meningitis, encephalitis, optic neuritis Guillain-Barre syndrome
Renal	Acute tubular necrosis, glomerulonephritis, interstitial nephritis
Musculoskeletal/skin	Erythema nodosum, cutaneous leukocytoclastic vasculitis Erythema multiforme, Stevens-Johnson syndrome MP-associated mucositis Myopathy, arthritis, and rhabdomyolysis
Thrombotic	Pulmonary embolism Splenic artery and left atrium and right ventricle thrombosis Aortic thrombosis/renal artery thrombosis
Other	Vasculitis (positive antineutrophil cytoplasmic antibodies) Cytopenias, cold agglutinin-induced autoimmune hemolytic anemia, sickle cell disease, idiopathic thrombocytopenic purpura-like syndrome Kawasaki disease

J Clin Med Res 2018;10:535-44

Mycoplasma pneumonia, lab

TABLE 1 | Overview of diagnostic tests for *M. pneumoniae*.

Method	Test	Target/antigen	Antibodies	Specimen(s)	Performance	Value	Comments
Direct identification of *M. pneumoniae*	Polymerase chain reaction (PCR)	Different target genes (e.g., P1 gene, 16S rDNA, 16S rRNA, RepMP elements etc.)	–	Respiratory specimen Cerebrospinal fluid (CSF) Other bodily fluids or tissues	High sensitivity, high specificity	RD	- Validation and standardization required for routine diagnostic (Loens et al., 2010); - Epidemiological differentiation of clinical strains on the basis of differences in the P1 gene by PCR (Spuesens et al., 2009) or in the number of repetitive sequences at a given genomic locus by multiple-locus variable-number tandem repeat analysis (MLVA) (Chalker et al., 2015).
	Culture	–	–	Respiratory specimen	Low sensitivity, high specificity	AD	- Special enriched broth or agar media; - Isolation takes up to 21 days.
Non-specific serological tests for *M. pneumoniae*	Cold agglutinin test ("bedside test")	Erythrocytes (I antigen)	Cold agglutinins (IgM)	Serum	Low sensitivity, low specificity	–[1]	- Cold agglutinins target the I antigen of erythrocytes; - Positive in only about 50% and in the first week of symptoms; - Less well studied in children; - Cross-reactivity with other pathogens and non-infectious diseases.
Specific serological tests for *M. pneumoniae*	Complement fixation test (CFT)	Crude antigen extract with glycolipids and/or proteins	Igs (no discrimination between isotypes)	Serum	Sensitivity and specificity comparable to EIA	–[1]	- Positive criteria: fourfold titer increase between acute and convalescent sera or single titer ≥1:32; - Cross-reactivity with other pathogens and non-infectious diseases.
	Particle agglutination assay (PA)		IgM and IgG simultaneously			–[1]	
	Enzyme immunoassay (EIA)	Proteins (e.g., adhesion protein P1) and/or glycolipids	IgM, IgG, IgA	Serum CSF[2]	Moderate-high sensitivity, Moderate-high specificity	RD	- The sensitivity depends on the time point of the first serum and on the availability of paired sera (for seroconversion and/or rise in titer); - "Gold standard": fourfold titer increase as measured in paired sera.
	Immunoblotting				High sensitivity, high specificity	AD	- Confirmatory assay (Dumke et al., 2012).
	Immunofluorescent assay (IFA)				Less sensitive and less specific than EIA	AD	- Subjective interpretation.

Adapted from Meyer Sauteur et al. (2014b). AD, advanced diagnostic test; CFT, complement fixation test; CSF, cerebrospinal fluid; EIA, enzyme immunoassay; IFA, immunofluorescent assay; Ig, immunoglobulin; PA, particle agglutination assay; PCR, polymerase chain reaction; RD, routine diagnostic test; RepMP, repeated M. pneumoniae DNA. [1]Largely replaced by EIA; [2]For the evaluation of an intrathecal antibody synthesis (Granerod et al., 2010), either by calculation of an antibody index (Reiber, 1994) or through parallel immunoblotting of simultaneously collected CSF and serum samples (Monteyne et al., 1997).

KOREA UNIVERSITY MEDICAL CENTER

Front Microbiol 2016;7:329

Macrolide resistance

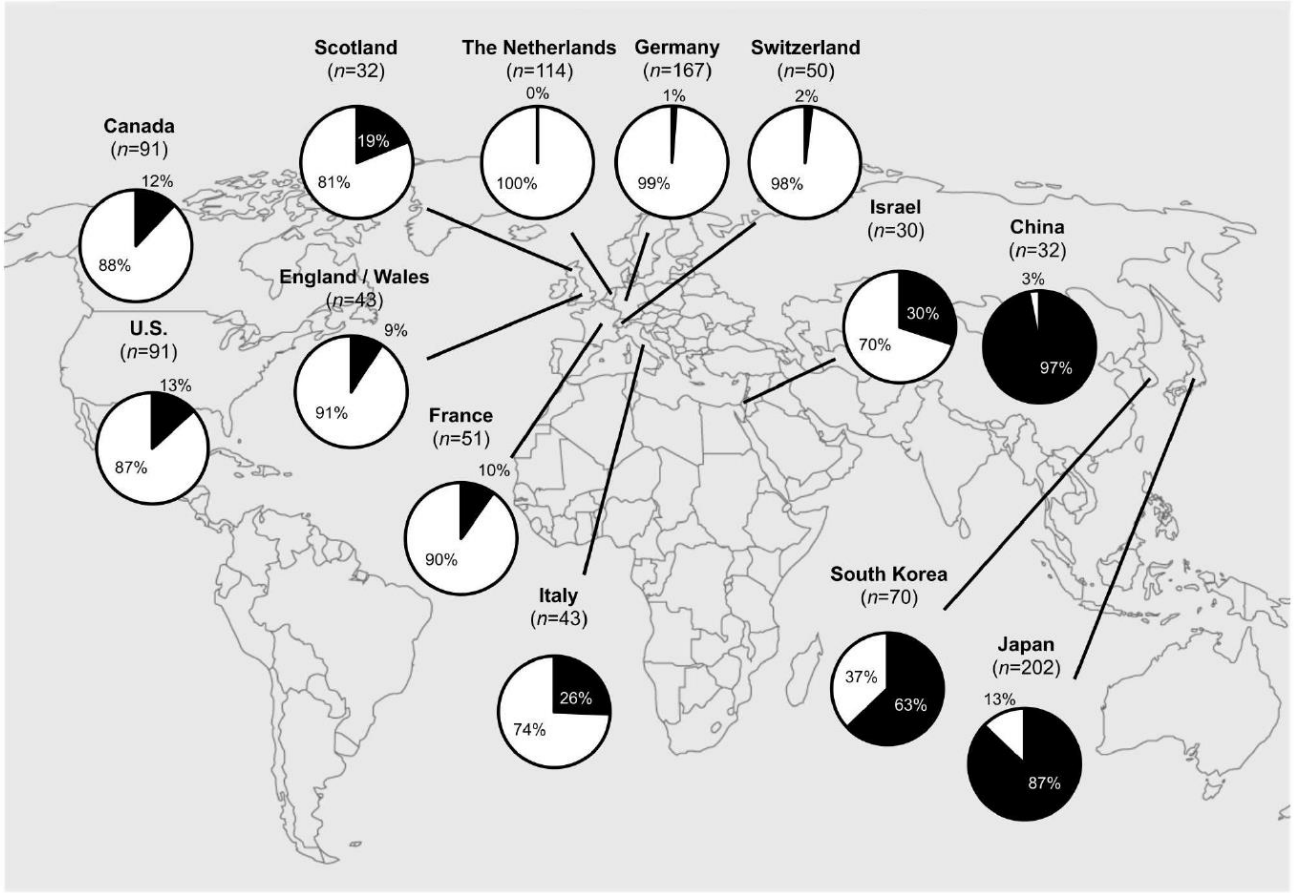


FIGURE 6 | Worldwide macrolide-resistant *M. pneumoniae* (MRMP) rates. Actual MRMP rates are punctually depicted in pie charts (in black) over the world map. **Asia:** Japan (2011): 87% (176/202) (Okada et al., 2012), South Korea (2011): 63% (44/70) (Hong et al., 2013), China (2012): 97% (31/32) (Zhao et al., 2013), Israel (2010): 30% (9/30) (Averbuch et al., 2011); **North America:** U.S. (2012–2014): 13% (12/91) (Zheng et al., 2015), Canada (2010–2012): 12% (11/91) (Eshaghi et al., 2013); **Europe:** The Netherlands (1997–2008): 0% (0/114) (Spuesens et al., 2012), Germany (2003–2008): 1% (2/167) (Dumke et al., 2010), France (2005–2007): 10% (5/51) (Peuchant et al., 2009), Italy (2010): 26% (11/43) (Chironna et al., 2011), Scotland (2010–2011): 19% (6/32) (Ferguson et al., 2013), Switzerland (2011–2013): 2% (1/50) (Meyer Sauteur et al., 2014a), England and Wales (2014–2015): 9% (4/43) (Brown et al., 2015).

Front Microbiol 2016;7:329

Macrolide resistance in Korea

70

Table 1. MICs of macrolide antimicrobial drugs for 123 *Mycoplasma pneumoniae* strains in a study of macrolide resistance, South Korea, 2000–2011*

	Strains with 23S rRNA mutation, n = 69			Strains without 23S rRNA mutation, n = 54		
Macrolides	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}
Erythromycin	2 to >128	16	128	0.001 to 0.004	0.001	0.002
Clarithromycin	8 to >128	64	128	0.001 to 0.002	0.001	0.002
Roxithromycin	0.008 to 128	8	32	0.001 to 0.008	0.001	0.004
Azithromycin	1 to 64	8	16	0.001 to 0.001	0.001	0.001
Josamycin	1 to 8	4	8	0.001 to 0.016	0.001	0.008

*MIC_{50} and MIC_{90} are minimum inhibitory concentrations at which 50% and 90% of the isolates, respectively, were inhibited by the drug. In each instance, $p<0.0001$.

Table 2. MICs of tetracyclines and fluoroquinolones for *Mycoplasma pneumoniae* strains in a study of macrolide resistance, South Korea, 2000–2011*

	Strains with 23S rRNA mutation, n = 69			Strains without 23S rRNA mutation, n = 54		
Antimicrobial drug	Range	MIC_{50}	MIC_{90}	Range	MIC_{50}	MIC_{90}
Tetracyclines						
Tetracycline	0.016 to 0.5	0.06	0.25	0.016 to 0.5	0.06	0.25
Doxycycline	0.002 to 0.125	0.06	0.06	0.004 to 0.125	0.03	0.06
Fluoroquinolones						
Levofloxacin	0.016 to 0.5	0.25	0.25	0.016 to 0.5	0.25	0.5
Ciprofloxacin	0.125 to 1.0	0.5	1.0	0.06 to 1.0	0.5	1.0
Moxifloxacin	0.008 to 0.06	0.016	0.06	0.004 to 0.06	0.016	0.06

*MIC_{50} and MIC_{90} are minimum inhibitory concentrations at which 50% and 90% of the isolates, respectively, were inhibited by the drug.

25 of 53 (2010) and 44 of 70 (2011) strains were resistant. Numbers on the bars are the percentages of resistant strains for each year.

KOREA UNIVERSITY MEDICAL CENTER

Emerg Infect Dis 2013;19:1281-4

Fluoroquinolone side effect

Musculoskeletal Complications of Fluoroquinolones: Guidelines and Precautions for Usage in the Athletic Population

Table 3. *Potential risk factors*

Increasing age
Systemic corticosteroid use
Participation in a sport

Table 4. *Management*

Identify higher-risk individuals
Avoid concomitant corticosteroid administration
Limit high-intensity physical activity during antibiotic course
Discontinue use of the fluoroquinolone if symptoms develop
Protect the symptomatic area to limit further injury
Initiate a graduated return to physical activities based on symptoms
Initiate further diagnostic evaluation and treatment as clinically indicated

Crohn disease
Diabetes mellitus
Hyperparathyroidism
Hypothyroidism

2011;3:132-42

Steroid therapy in mycoplasma pneumonia

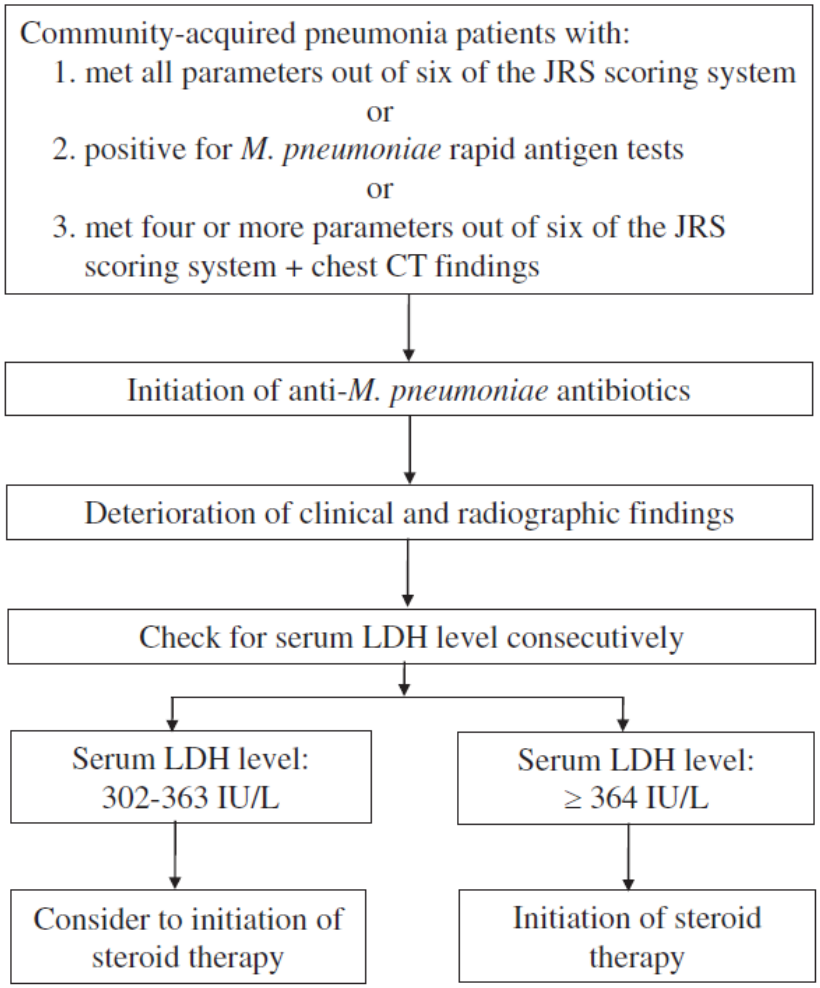


Fig. 7. A stepwise algorithm to correlate diagnosis, serum markers, and initiation of steroid therapy in *M. pneumoniae* pneumonia.

KOREA UNIVERSITY MEDICAL CENTER

J infect chemother 2015;21:153-60


Thank you