Influenza 2019 – Licht am Ende des Tunnels?

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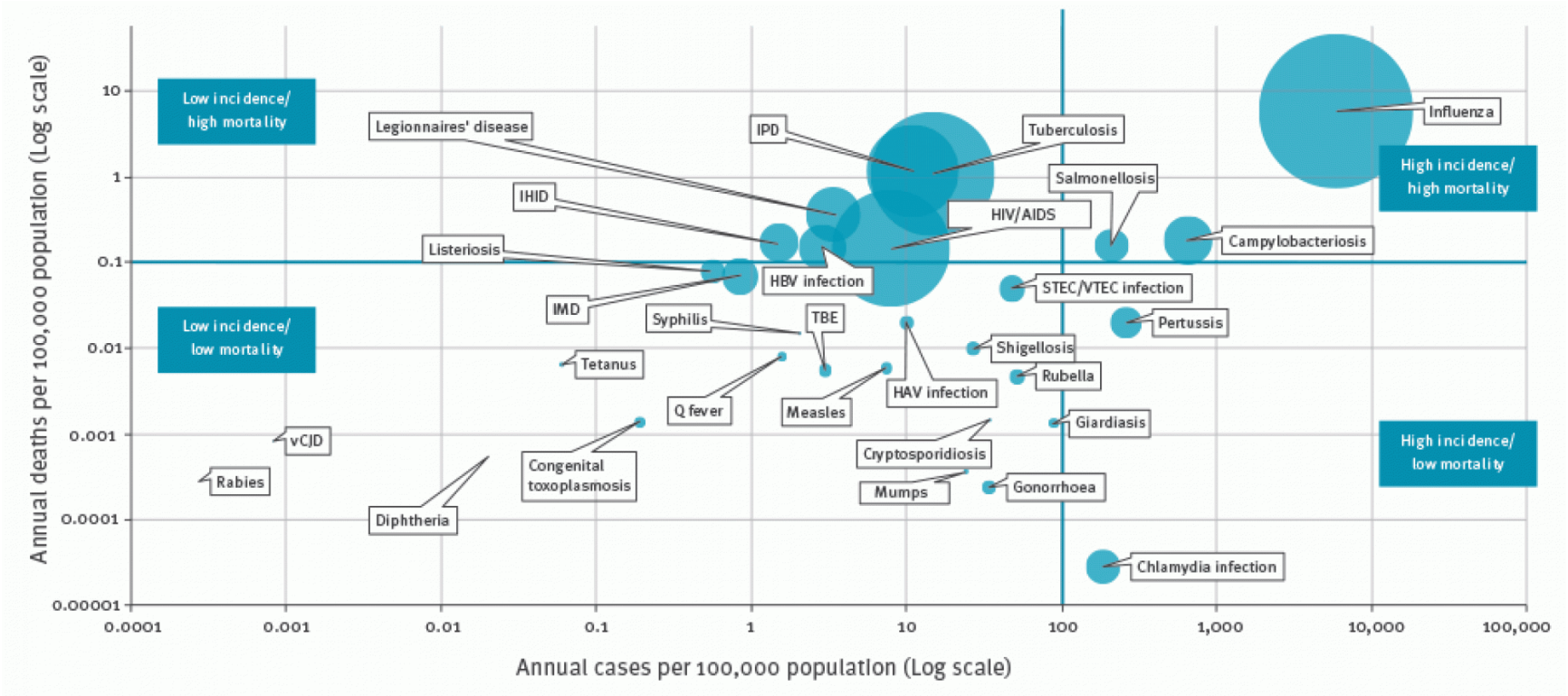
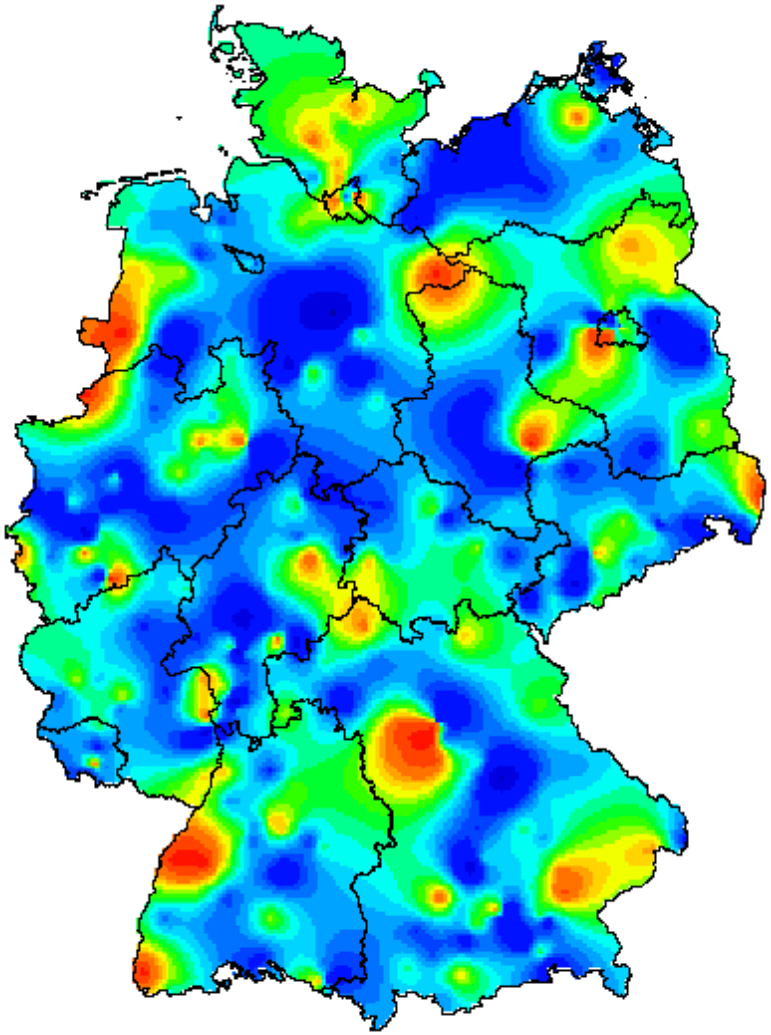
Burden of Influenza



https://ecdc.europa.eu/en/news-events/influenza-ranked-highest-burden-disease-measured-dalys

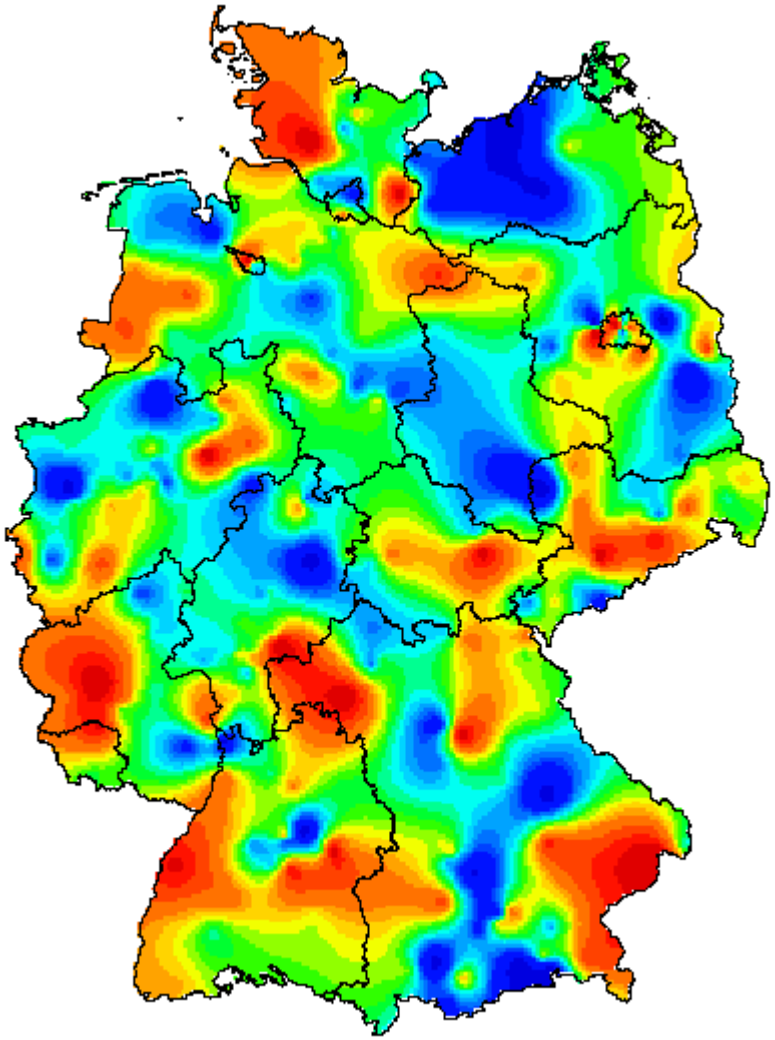
Influenza in Germany 2018



https://influenza.rki.de/MapArchive.aspx

4th week in 2018

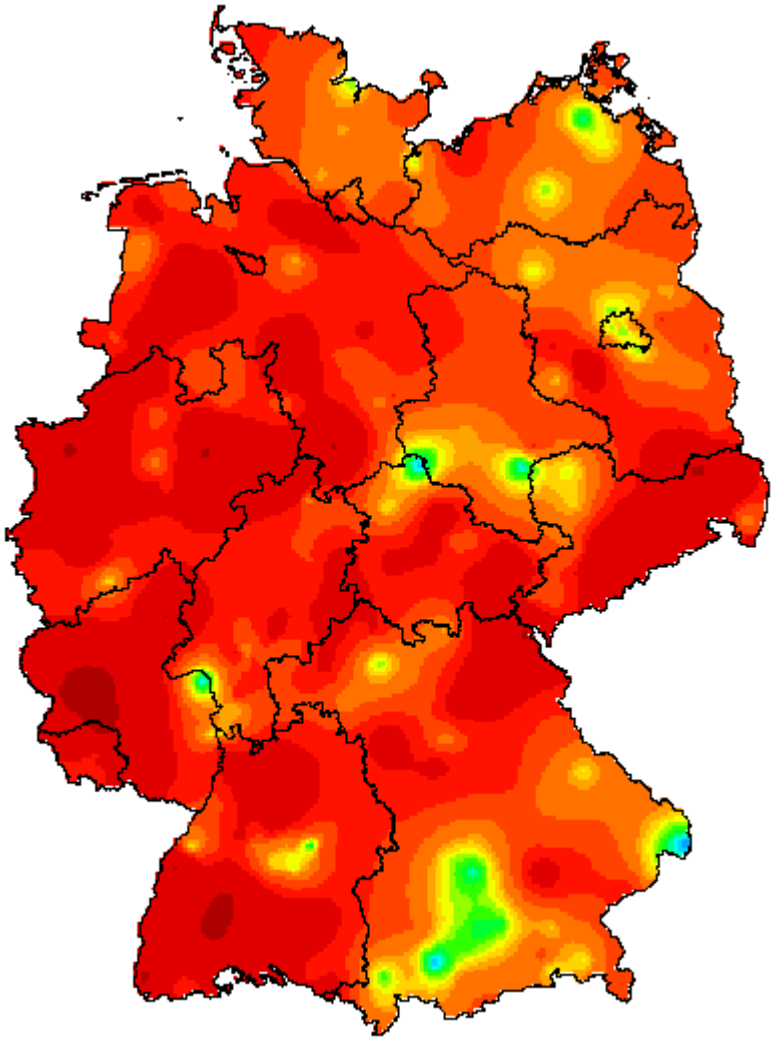
Influenza in Germany 2018



https://influenza.rki.de/MapArchive.aspx

6th week in 2018

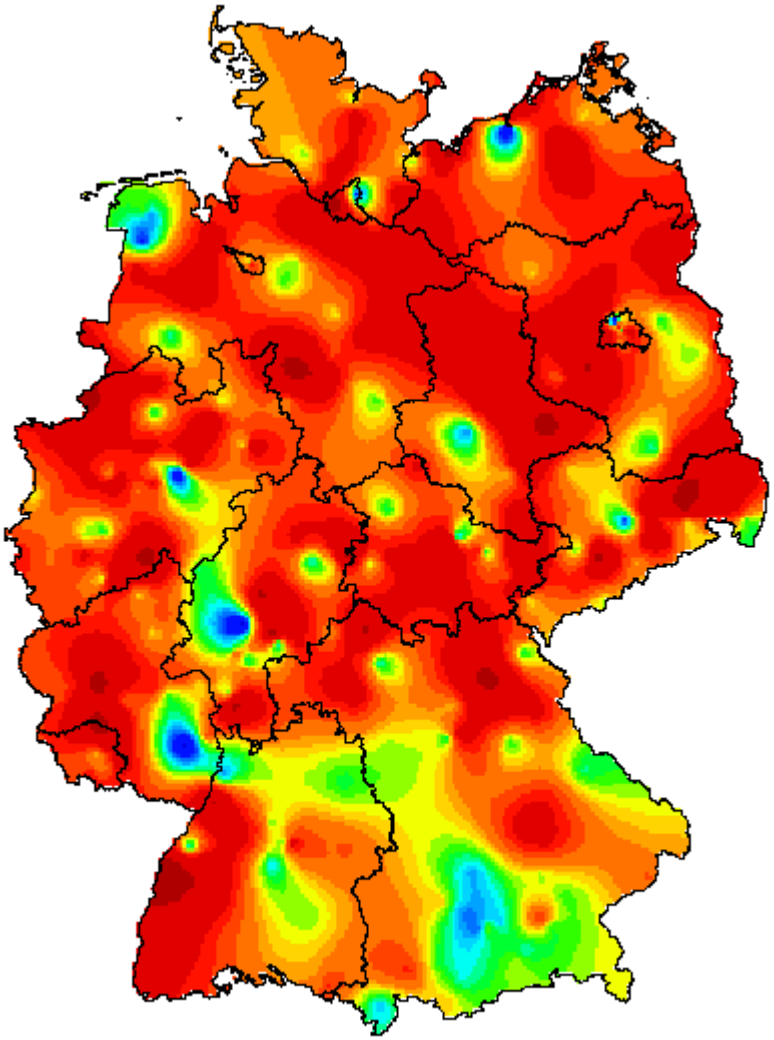
Influenza in Germany 2018



https://influenza.rki.de/MapArchive.aspx

8th week in 2018

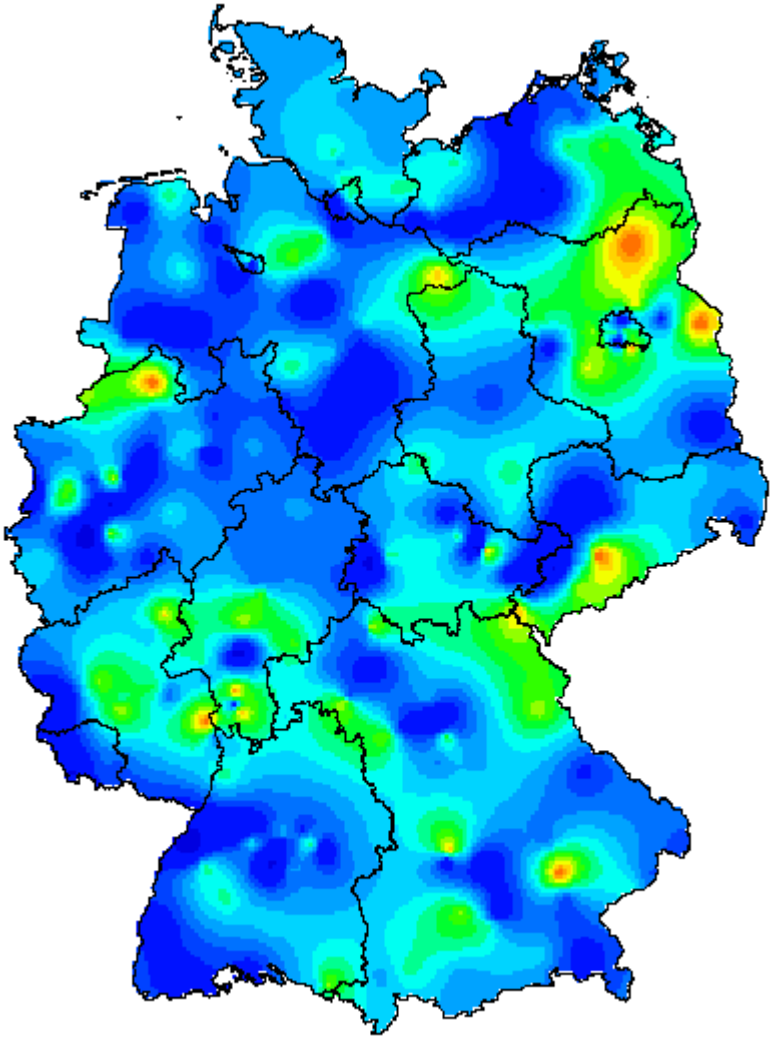
Influenza in Germany 2018



https://influenza.rki.de/MapArchive.aspx

10th week in 2018

Influenza in Germany 2018



https://influenza.rki.de/MapArchive.aspx

14th week in 2018

Influenza in Germany 2018

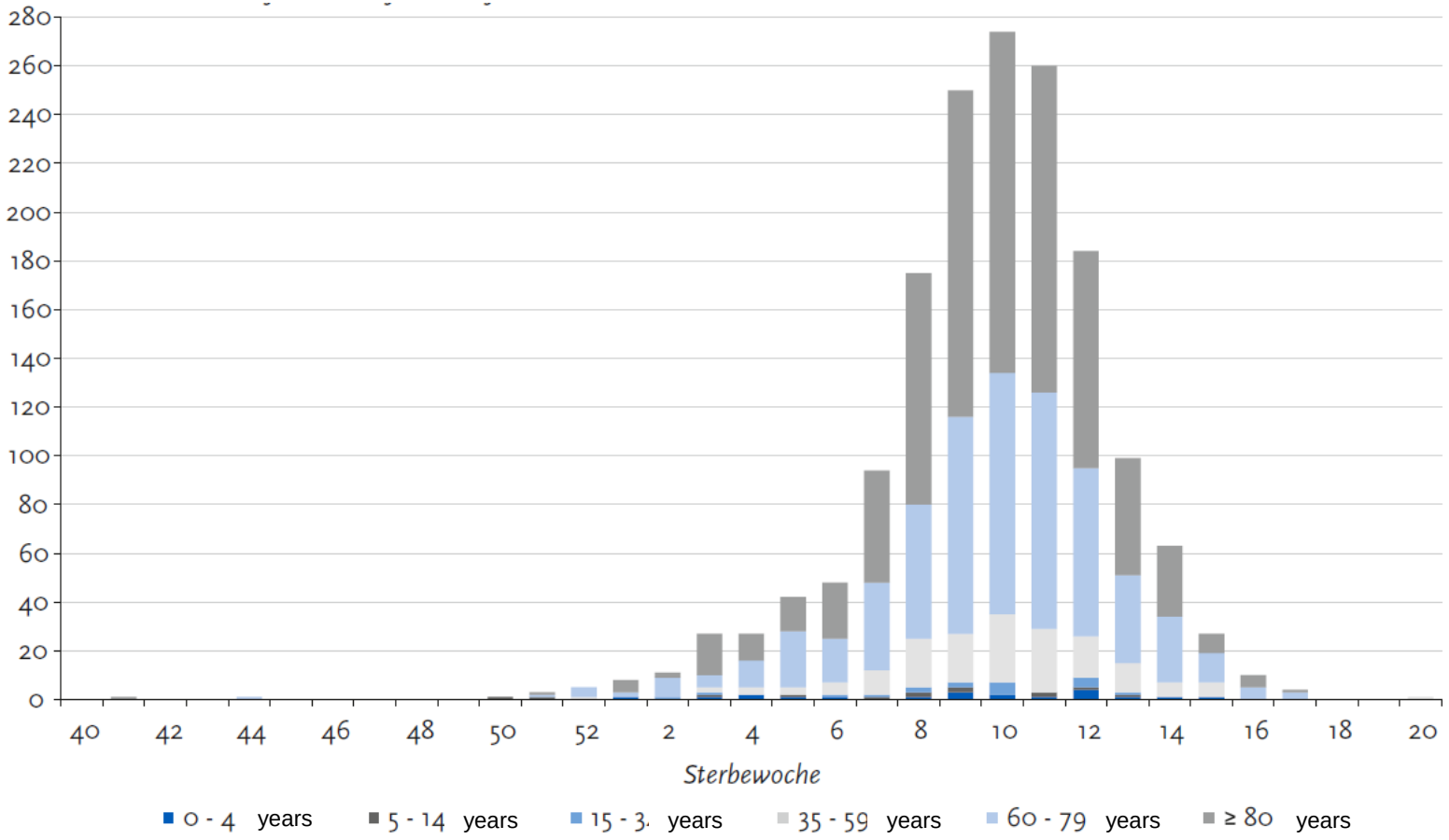
https://influenza.rki.de/Wochenberichte.aspx

		9. MW	10. MW	11. MW	12. MW	13. MW	14. MW	Gesamt ab 40. MW 2017
Influenza	A(nicht subtypisiert)	9.605	13.633	13.071	8.938	5.993	3.005	76.420
	A(H1N1)pdm09	1.084	1.811	1.750	1.250	811	439	9.901
	A(H3N2)	51	81	82	124	80	31	584
	nicht nach A / B differenziert	2.218	2.264	1.605	741	342	115	13.099
	B	33.778	38.772	32.003	16.637	7.118	3.104	224.412
Gesamt		46.736	56.561	48.511	27.690	14.344	6.694	324.416

100% of Influenza B strains are: B/Yam 3 Phuket/3073/2013-like

Death due to Influenza 2018 Germany

n=1615



Acute Myocardial Infarction after Laboratory-Confirmed Influenza Infection

N Engl J Med 2018;378:345-53.

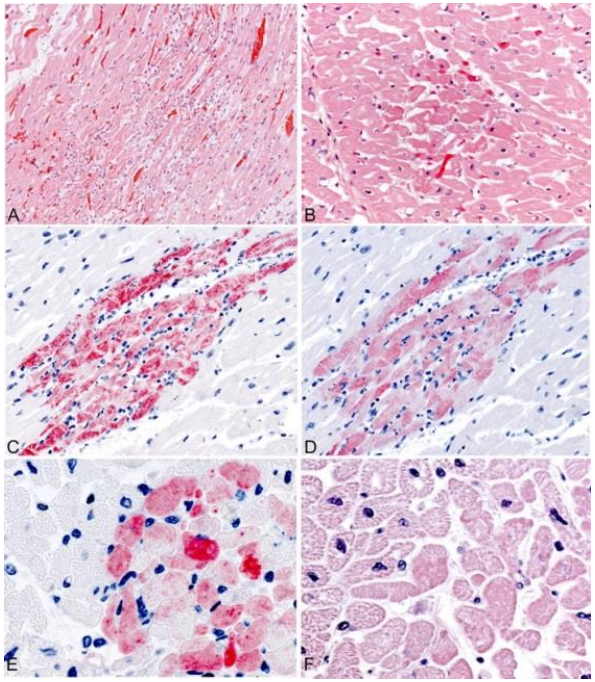
Jeffrey C. Kwong, M.D., Kevin L. Schwartz, M.D., Michael A. Campitelli, M.P.H., Hannah Chung, M.P.H., Natasha S. Crowcroft, M.D., Timothy Karnauchow, Ph.D., Kevin Katz, M.D., Dennis T. Ko, M.D., Allison J. McGeer, M.D., Dayre McNally, M.D., Ph.D., David C. Richardson, M.D., Laura C. Rosella, Ph.D., M.H.Sc., Andrew Simor, M.D., Marek Smieja, M.D., Ph.D., George Zahariadis, M.D., and Jonathan B. Gubbay, M.B., B.S., M.Med.Sc.

Variable	Incidence Ratio (95% CI)
Primary analysis: risk interval, days 1–7	6.05 (3.86–9.50)
Days 1–3	6.30 (3.25–12.22)
Days 4–7	5.78 (3.17–10.53)
Days 8–14	0.60 (0.15–2.41)
Days 15–28	0.75 (0.31–1.81)
Alternative exposure	
RSV	3.51 (1.11–11.12)
Respiratory virus other than influenza or RSV	2.77 (1.23–6.24)
Illness with no respiratory virus identified‡	3.30 (1.90–5.73)
Hospitalization for diabetes and associated complications§	1.35 (0.50–3.62)

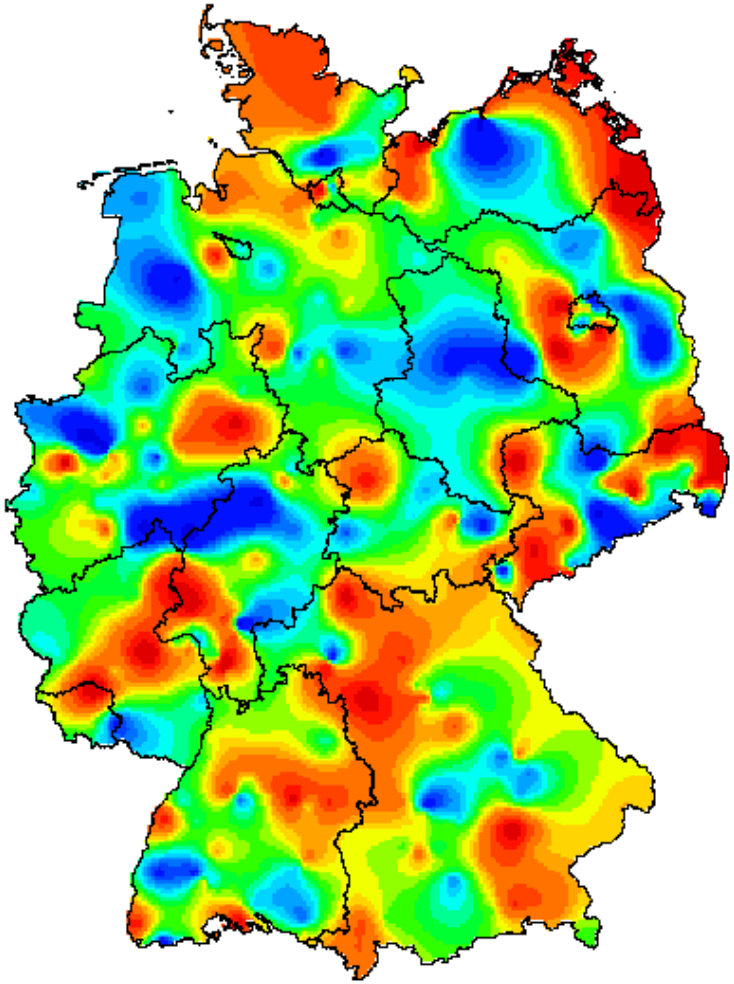
Pathophysiology of fatal influenza B

Paddock C *et al J Infect Dis*. 2012;205:895–905. McCullers J & Hayden M, *J Infect Dis*. 2012;205:870–872.

- Inflammation of the trachea and bronchi (similar to IAV) is the most common feature
- Just over 1/3 had bacterial superinfections, most frequently *Staphylococcus aureus*
- Myocardial injury was identified by histology and immunohistochemistry in 20 (69%) of 29 case-patients with samples
- Histological evidence of myocyte damage for 17 case-patients, including 10 with unequivocal myocarditis



Influenza in Germany 2019

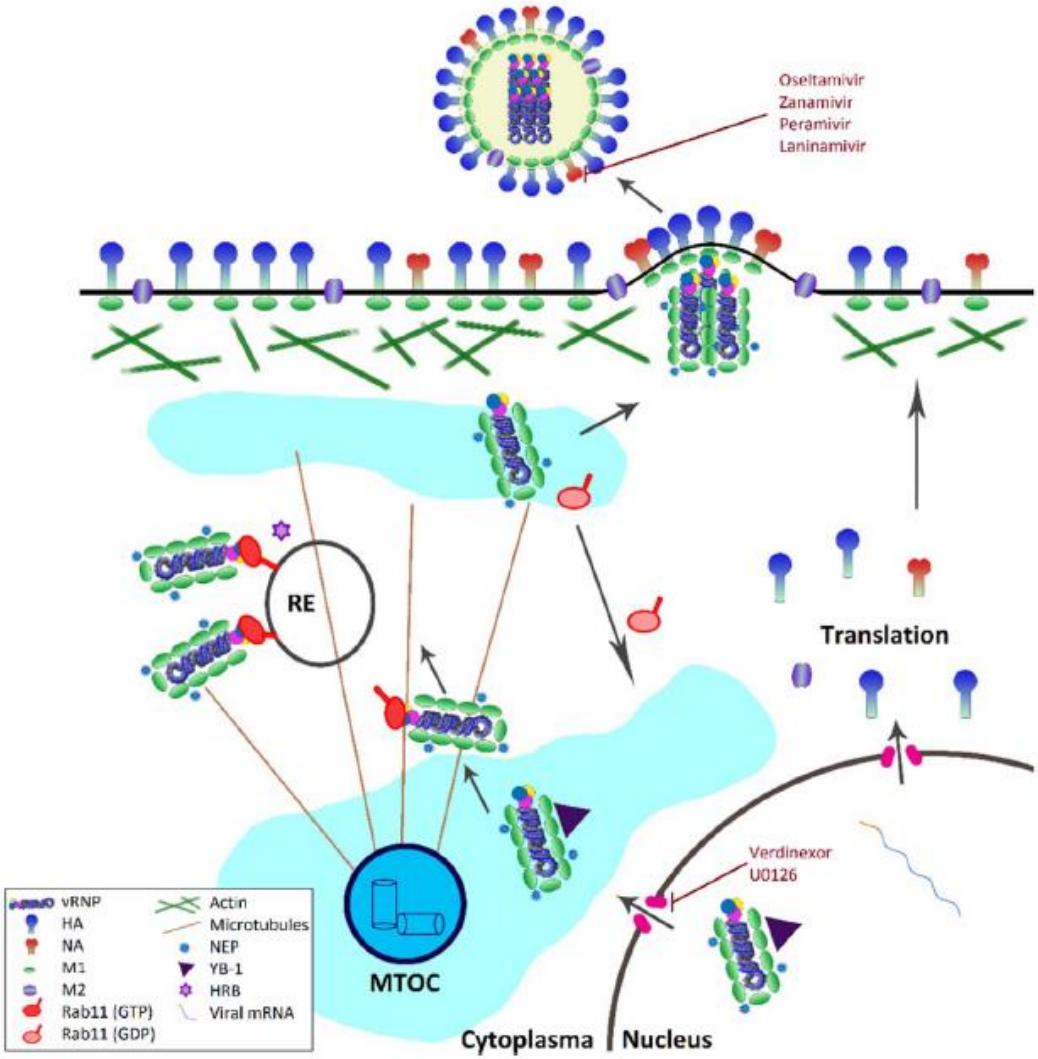


https://influenza.rki.de/MapArchive.aspx

Week 8 in 2019

Until 29 MAR 2019
600 deaths reported
Dominat: A(H1N1)pdm09 6B.1 Michigan

Export of viral RNPs and proteins into the host cell



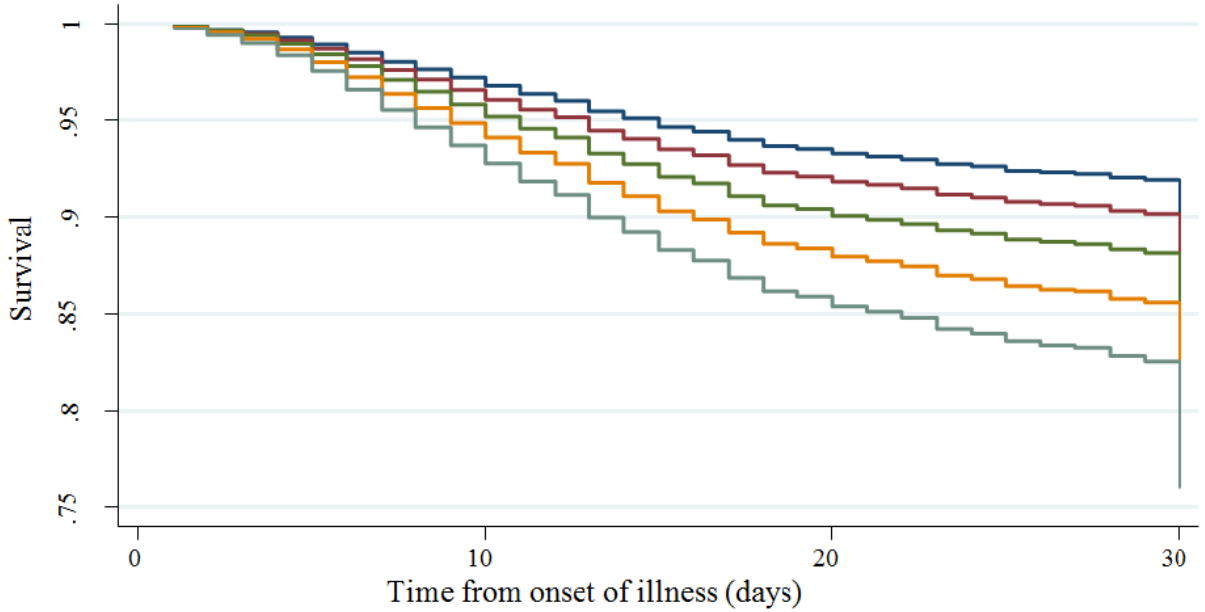
Mortality in hospitalized Influenza patients
Oseltamivir vs. None therapy

Subgroups	Crude analysis		Adjusted† analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
Laboratory confirmed or clinically diagnosed (all ages); n=29,234	0·92 (0·81 to 1·05)	0·21	0·81 (0·70 to 0·93)	0·0024
Laboratory confirmed cases (all ages) ; n=25,001	0·94 (0·81 to 1·09)	0·42	0·82 (0·70 to 0·95)	0·0104
Adults (16 years and above) ; n=19,816	0·82 (0·70 to 0·95)	0·0071	0·75 (0·64 to 0·87)	0·0002
Children (below 16 years); n=9,218	1·02 (0·73 to 1·42)	0·90	0·82 (0·58 to 1·17)	0·28
Pregnant women; n=2,166	0·47 (0·24 to 0·90)	0·0228	0·46 (0·23 to 0·89)	0·0215
ICU patients				
Adults (≥16 years); n=5,103	0·74 (0·57 to 0·95)	0·0187	0·72 (0·56 to 0·94)	0·0155
Children (<16 years); n=1,725	0·84 (0·52 to 1·37)	0·49	0·70 (0·42 to 1·16)	0·17

Muthuri SG et al. Lancet Respir Med. 2014 May;2(5):395-404.

Muthuri SG et al. Lancet Respir Med. 2014 May;2(5):395-404.

Mortality with regard to start of NAI treatment



Number at risk (days)	0-10	10-20	20-30	>30
Early NAI treatment (within 2 days)	5192	2414	1939	1843
Treated with NAI Day 3	1477	689	492	460
Treated with NAI Day 4	1012	567	322	282
Treated with NAI Day 5	812	541	272	241
Treated with NAI after Day 5	2298	1981	1009	735

Early NAI treatment (within 2 days): reference group

Treated day 3: adj. HR 1.78 (95% CI; 1.41 – 2.24)

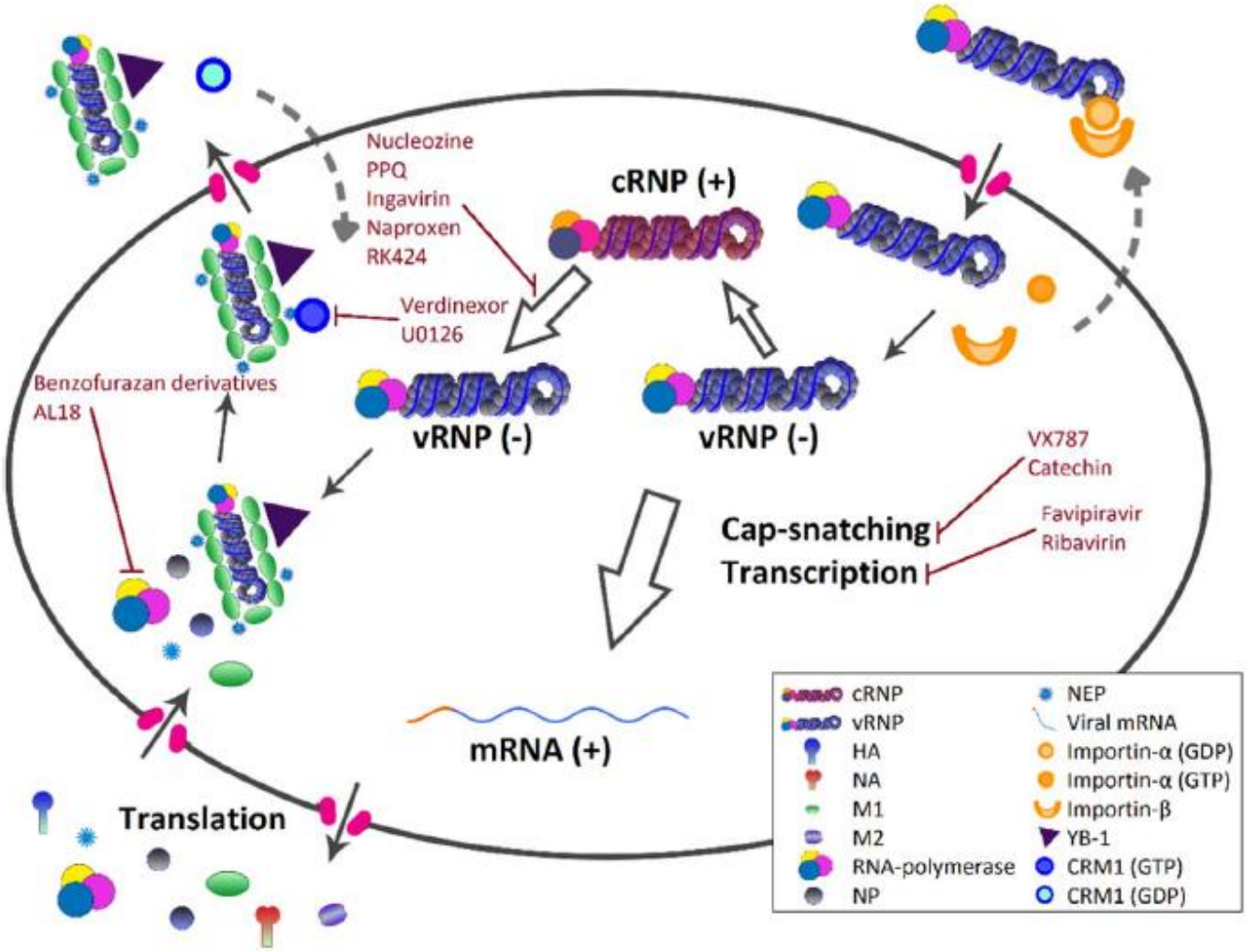
Treated day 4: adj. HR 1.80 (95% CI; 1.36 – 2.37)

Treated day 5: adj. HR 2.30 (95% CI; 1.79 – 2.97)

Treated day 5: adj. HR 1.95 (95% CI; 1.61 – 2.36)

van de Wakker SI et al. European Journal of Pharmacology 809 (2017) 178–190

The viral transcription-replication cycle



The NEW ENGLAND JOURNAL of MEDICINE

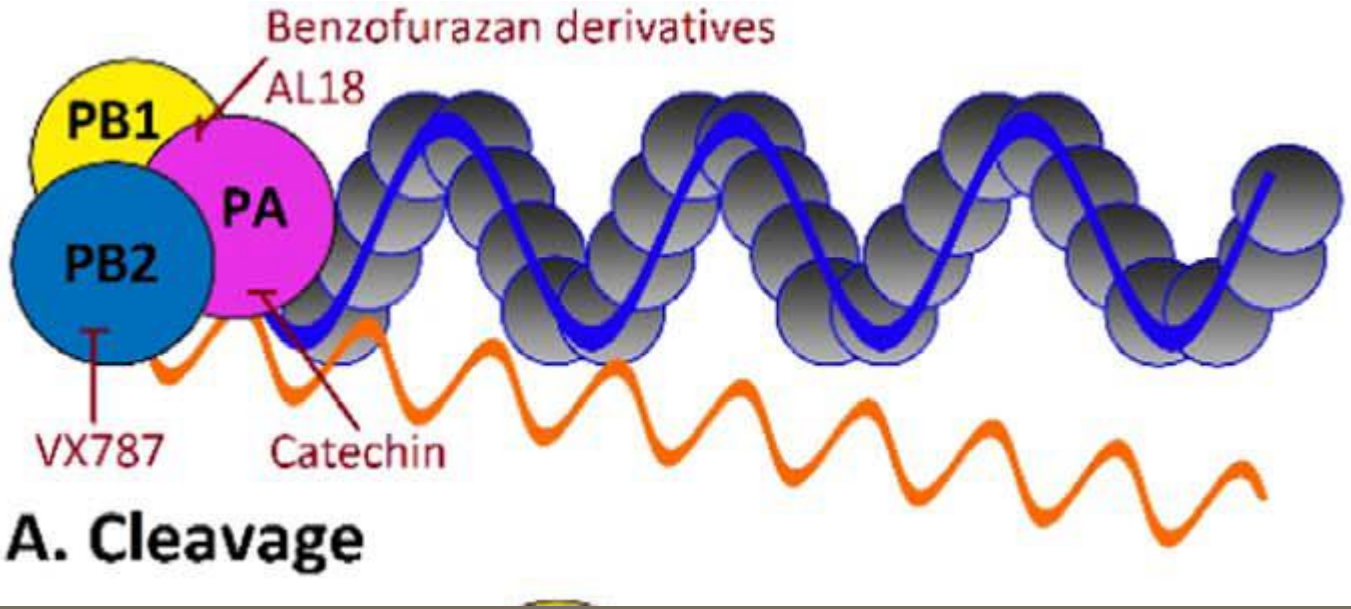
ESTABLISHED IN 1812 SEPTEMBER 6, 2018 VOL. 379 NO. 10

Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents

Frederick G. Hayden, M.D., Norio Sugaya, M.D., Nobuo Hirotsu, M.D., Ph.D., Nelson Lee, M.D., Menno D. de Jong, M.D., Ph.D., Aeron C. Hurt, Ph.D., Tadashi Ishida, M.D., Ph.D., Hisakuni Sekino, M.D., Ph.D., Kota Yamada, M.D., Simon Portsmouth, M.D., Keiko Kawaguchi, M.Sc., Takao Shishido, Ph.D., Masatsugu Arai, M.Sc., Kenji Tsuchiya, M.Sc., Takeki Uehara, Ph.D., and Akira Watanabe, M.D., Ph.D., for the Baloxavir Marboxil Investigators Group*

N Engl J Med. 2018 Sep 6;379(10):913-923.

van de Wakker SI et al. European Journal of Pharmacology 809 (2017) 178–190



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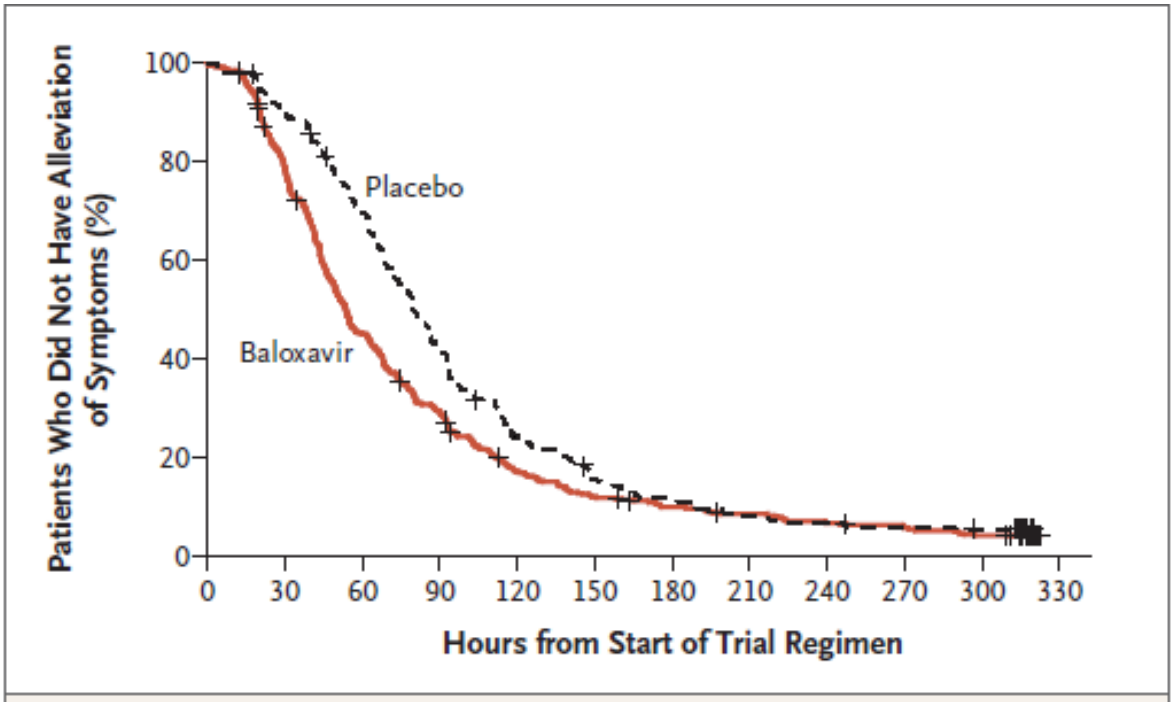
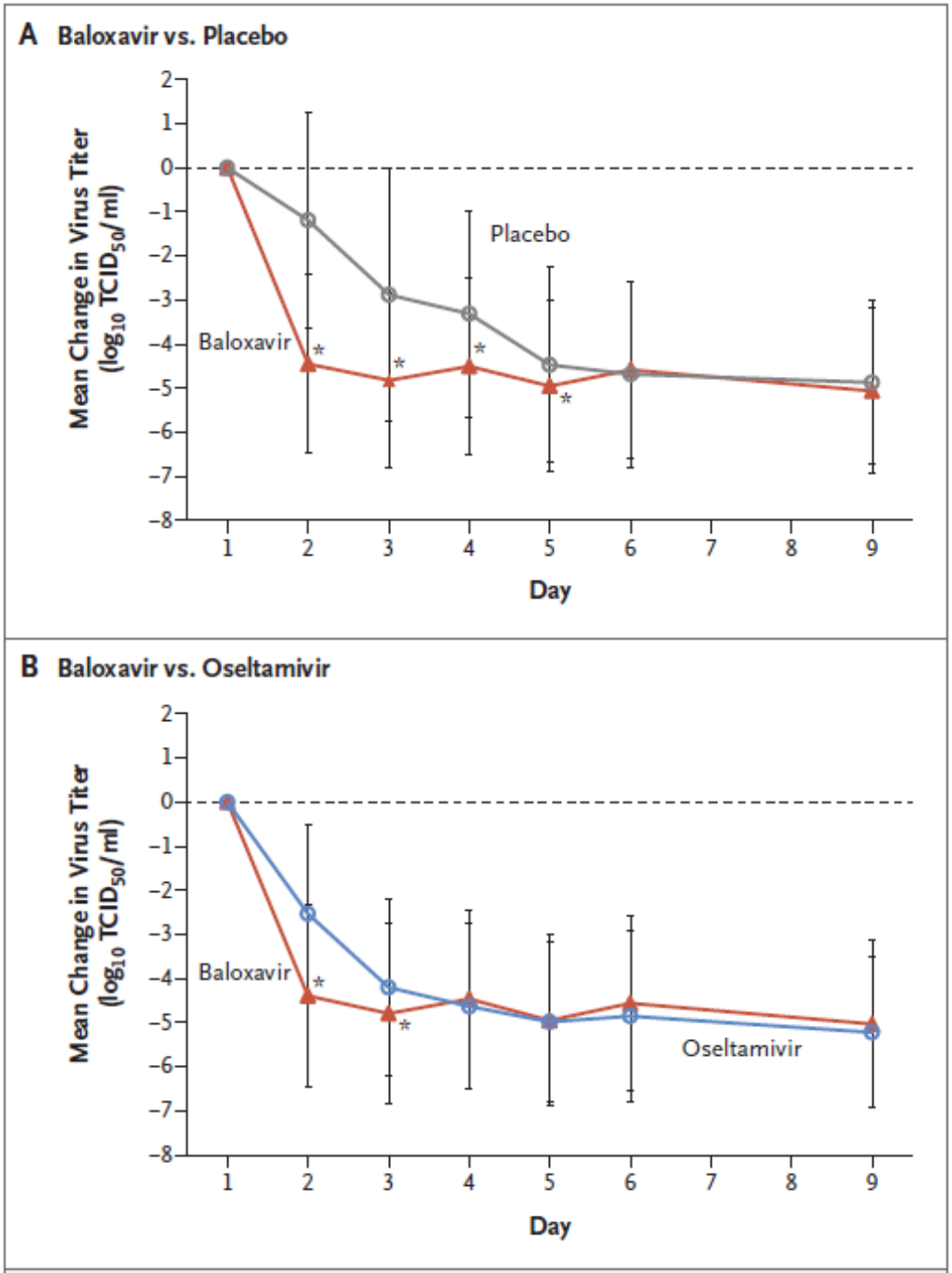


Viral Load over Time

Hayden FG et al. N Engl J Med. 2018 Sep 6;379(10):913-923.



Host factors and their inhibitors

van de Wakker SI et al. European Journal of Pharmacology 809 (2017) 178–190

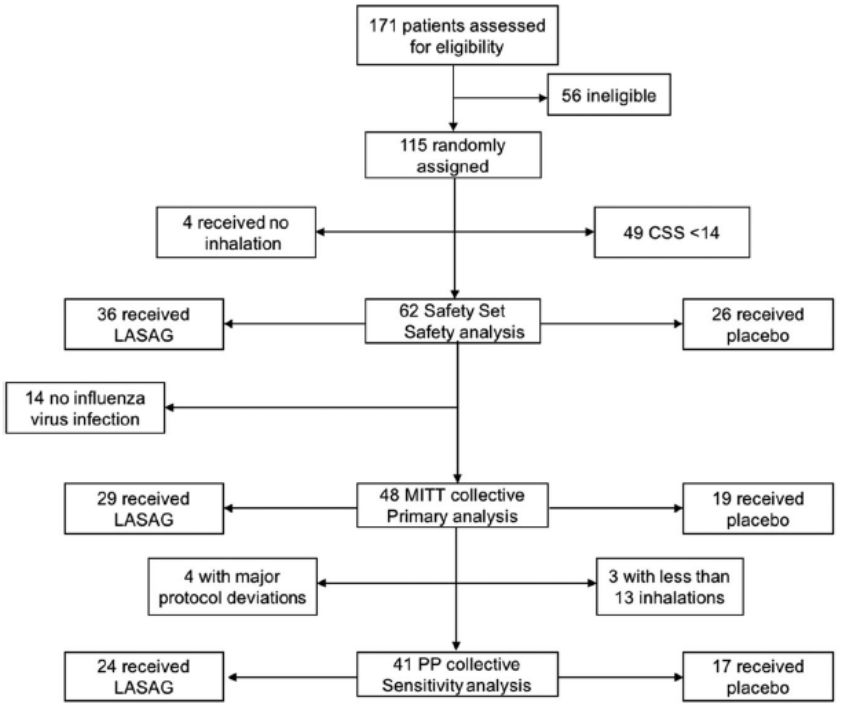
Targeted host factor	Infection process	Inhibitors	Research phase	Potential	Reference
Sialic acid	Attachment	DAS181	Phase II	+/-	Moss et al. (2012)
Dynamin	Internalization	Dynasore	Preclinical	–	de Vries et al. (2011)
Na^+/H^+-transporter	Internalization	EIPA	Preclinical	–	de Vries et al. (2011)
Membrane fluidity	Internalization,	Fattiviracin	Preclinical	+/-	Harada et al. (2007)
	Immune dystegulation	Glycyrrhizin	Preclinical	+	Harada et al. (2007), Michaelis et al. (2011)
		LJ001	Preclinical	+/-	Wolf et al. (2010)
PKC	Internalization	Bisindolymaleimide I	Preclinical	–	Root et al. (2000)
vATPase	Fusion	Bafilomycin A1	Preclinical	+/-	Yeganeh et al. (2015)
		Concanamycin	Preclinical	+/-	Müller et al. (2011)
		Diphyllin	Preclinical	+/-	Chen et al. (2013)
		Saliphenylhalamide	Preclinical	+/-	Bimbo et al. (2013)
Inosine-5′-monophosphate dehydrogenase	Transcription, replication	Ribavirin	Approved[a]	+	Marcellin et al. (2010)
		Viramidine	Phase III	+	Marcellin et al. (2010)
Exportin	Nuclear export	Verdinexor	Preclinical	+/-	Perwitasari et al. (2014)
COX-2	Immune dysregulation	Celecoxib	Approved[a]	+/-	Zheng et al. (2008)
Lipoxygenase and COX pathways	Immune dysregulation	Mesalazine	Approved[a]	+/-	Zheng et al. (2008)
HMG-CoA	Immune dysregulation	Statins	Approved[a]	+/-	Mehrbod et al. (2014), Frost et al. (2007)
Multiple targets	Immune dysregulation	Corticosteroids	Approved[a]	–	Rodrigo et al. (2016)
S1PRs	Immune dysregulation	AAL-R	Preclinical	+/-	Marsolais et al. (2009), Walsh et al. (2011)
		CYM-5442	Preclinical	+/-	Teijaro et al. (2011)
C-Jun-N-terminal kinase	Immune dysregulation	SP600125	Preclinical	+/-	Zhang et al. (2016)
IKK2	Immune dysregulation	Acetylsalicylic acid	Approved[a]	+/-	Mazur et al. (2007)
NFκB pathway	Immune dysregulation	Pyrrolidine dithiocarbamate	Preclinical	+	Wiesener et al. (2011)
NFκB	Immune dysregulation	SC75741	Preclinical	+	Ehrhardt et al. (2013), Haasbach et al. (2013b)
MEK	Nuclear export	U0126	Preclinical	+	Pleschka et al. (2001), Droebner et al. (2011)
p38 MAPK	Immune dysregulation	NJK14047	Preclinical	+/-	Choi et al. (2016)

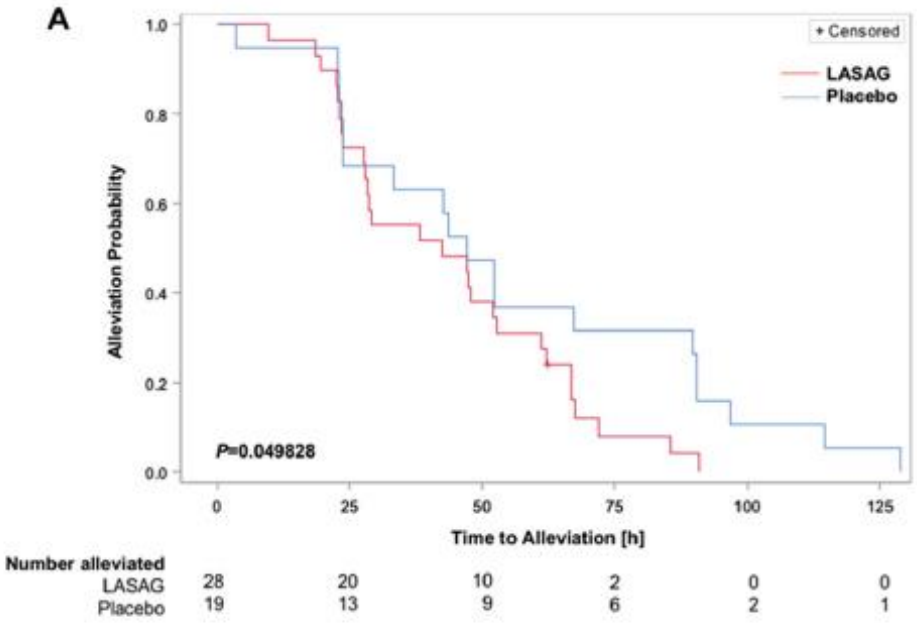
ARTICLE Open Access

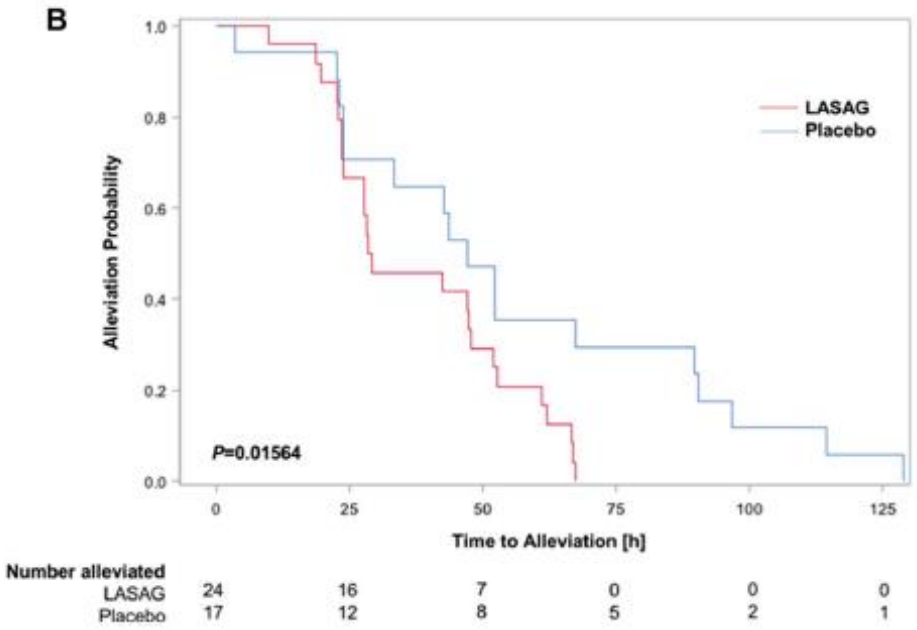
Scheuch et al. Emerging Microbes & Infections (2018) 7:21

Targeting intracellular signaling as an antiviral strategy: aerosolized LASAG for the treatment of influenza in hospitalized patients

Gerhard Scheuch[1], Sebastian Canisius[2], Karlheinz Nocker[2], Thomas Hofmann[3], Rolf Naumann[2], Stephan Pleschka[4], Stephan Ludwig[5], Tobias Welte[6] and Oliver Planz[7]



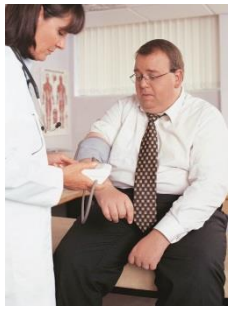

A
+ Censored
LASAG
Placebo
Alleviation Probability
1.0
0.8
0.6
0.4
0.2
0.0
P=0.049828
0
25
50
75
100
125
Time to Alleviation [h]
Number alleviated
LASAG 28 20 10 2 0 0
Placebo 19 13 9 6 2 1


B
LASAG
Placebo
Alleviation Probability
1.0
0.8
0.6
0.4
0.2
0.0
P=0.01564
0
25
50
75
100
125
Time to Alleviation [h]
Number alleviated
LASAG 24 16 7 0 0 0
Placebo 17 12 8 5 2 1

Influenza: risk groups

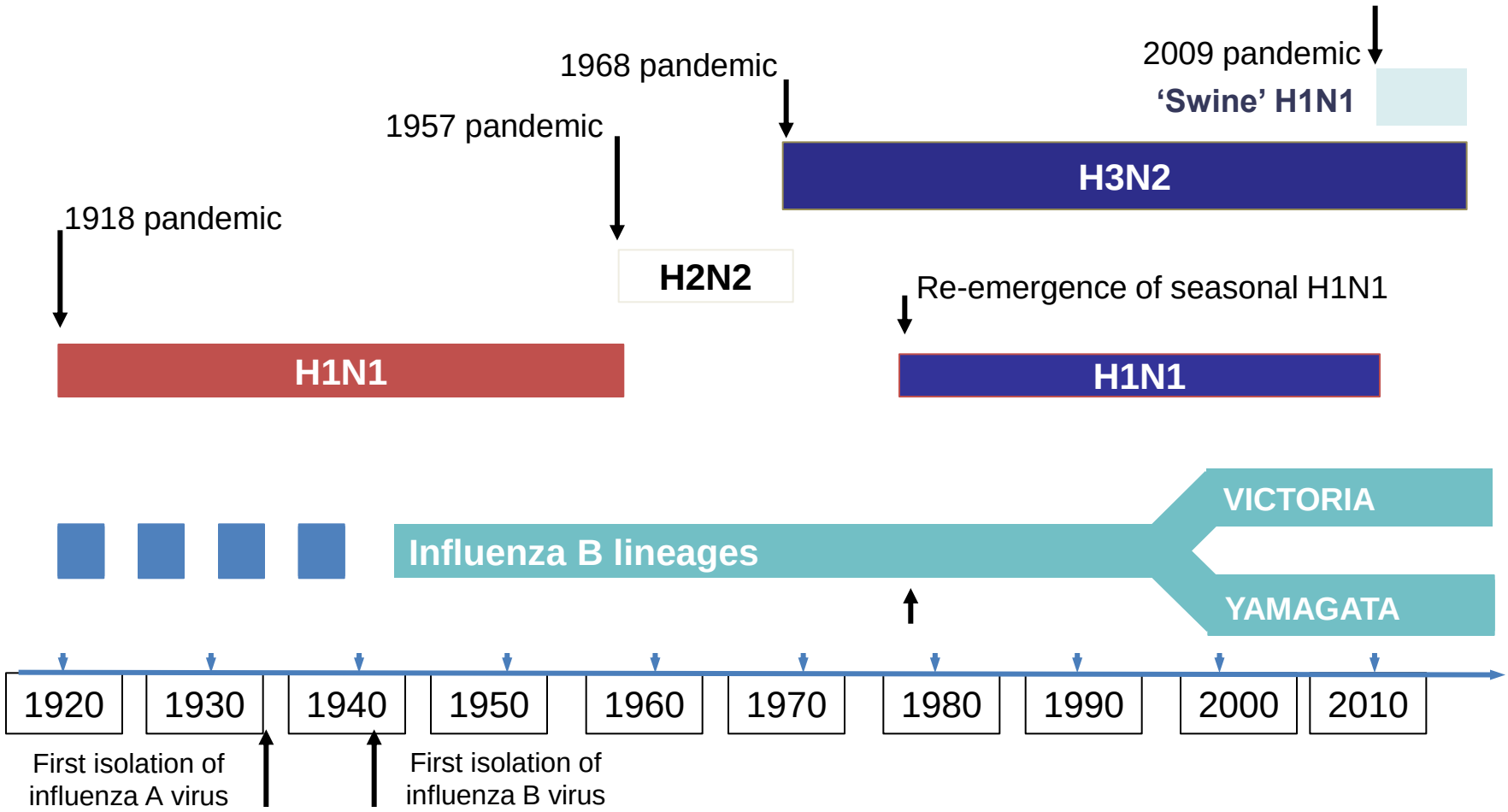
- **Compared with otherwise healthy adults, influenza can cause more serious illness and greater mortality in:[1–3]**
  - **Children aged <2 years**
  - **Adults aged ≥65 years**
  - **Pregnant women**
  - **Those with weakened immune systems**
  - **Those with certain medical conditions, e.g. chronic heart, lung, kidney, liver, blood or metabolic diseases**
- **Particularly high case-fatality rates can be seen among residents of long-term care facilities and in children <6 months of age[3]**





1 US CDC. Pink Book 2012. 2 WHO. Influenza (Seasonal) Fact sheet N°211. 2009. 4. WHO. *Wkly Epidemiol Rec* 2005;80:279–288.

CHANGES IN INFLUENZA STRAINS



1. McCullers & Huber. *Hum Vaccin Immunother* 2012;8:34-44 (adapted).

Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies

Edward A Belongia, Melissa D Simpson, Jennifer P King, Maria E Sundaram, Nicholas S Kelley, Michael T Osterholm, Huong Q McLean

Lancet Infect Dis 2016;
16: 942–51

Interpretation Influenza vaccines provided substantial protection against H1N1pdm09, H1N1 (pre-2009), and type B, and reduced protection against H3N2. Vaccine improvements are needed to generate greater protection against H3N2 than with current vaccines.

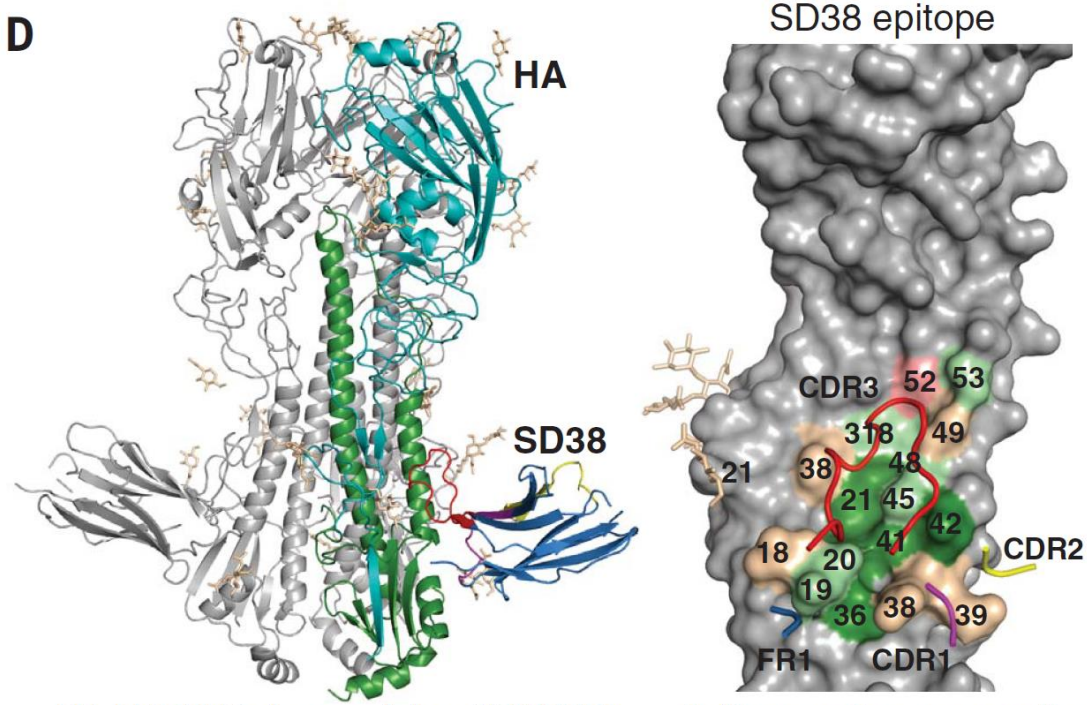
	Vaccine type	Pooled VE (%)	Pooled standard error	VE estimates (n)	p value for heterogeneity	I^2
Type B	Seasonal	54% (46–61)	0·083	36	<0·0001	61·3
H3N2	Seasonal	33% (26–39)	0·050	34	0·005	44·4
H1N1pdm09	Seasonal	61% (57–65)	0·048	29	0·783	0·0
H1N1pdm09	Monovalent	73% (61–81)	0·188	10	0·217	31·4
H1N1 (pre-2009)	Seasonal	67% (29–85)	0·397	5	0·093	57·6

Data in parentheses are 95% CIs. VE=vaccine effectiveness.

Laursen et al., Science 362, 598–602 (2018)

Universal protection against influenza infection by a multidomain antibody to influenza hemagglutinin

Nick S. Laursen[1*], Robert H. E. Friesen[2†], Xueyong Zhu[1], Mandy Jongeneelen[3], Sven Blokland[3], Jan Vermond[4], Alida van Eijgen[4], Chan Tang[3], Harry van Diepen[4], Galina Obmolova[2], Marijn van der Neut Kolfschoten[3], David Zuijdgeest[3], Roel Straetemans[5], Ryan M. B. Hoffman[1], Travis Nieusma[1], Jesper Pallesen[1], Hannah L. Turner[1], Steffen M. Bernard[1], Andrew B. Ward[1], Jinquan Luo[2], Leo L. M. Poon[6], Anna P. Tretiakova[7‡], James M. Wilson[7], Maria P. Limberis[7], Ronald Vogels[3], Boerries Brandenburg[3], Joost A. Kolkman[8§], Ian A. Wilson[1,9§]



H1 HA (A/Solomon Island/3/2006)

Influenza A conservation

Multidomain Antibody MD 3606

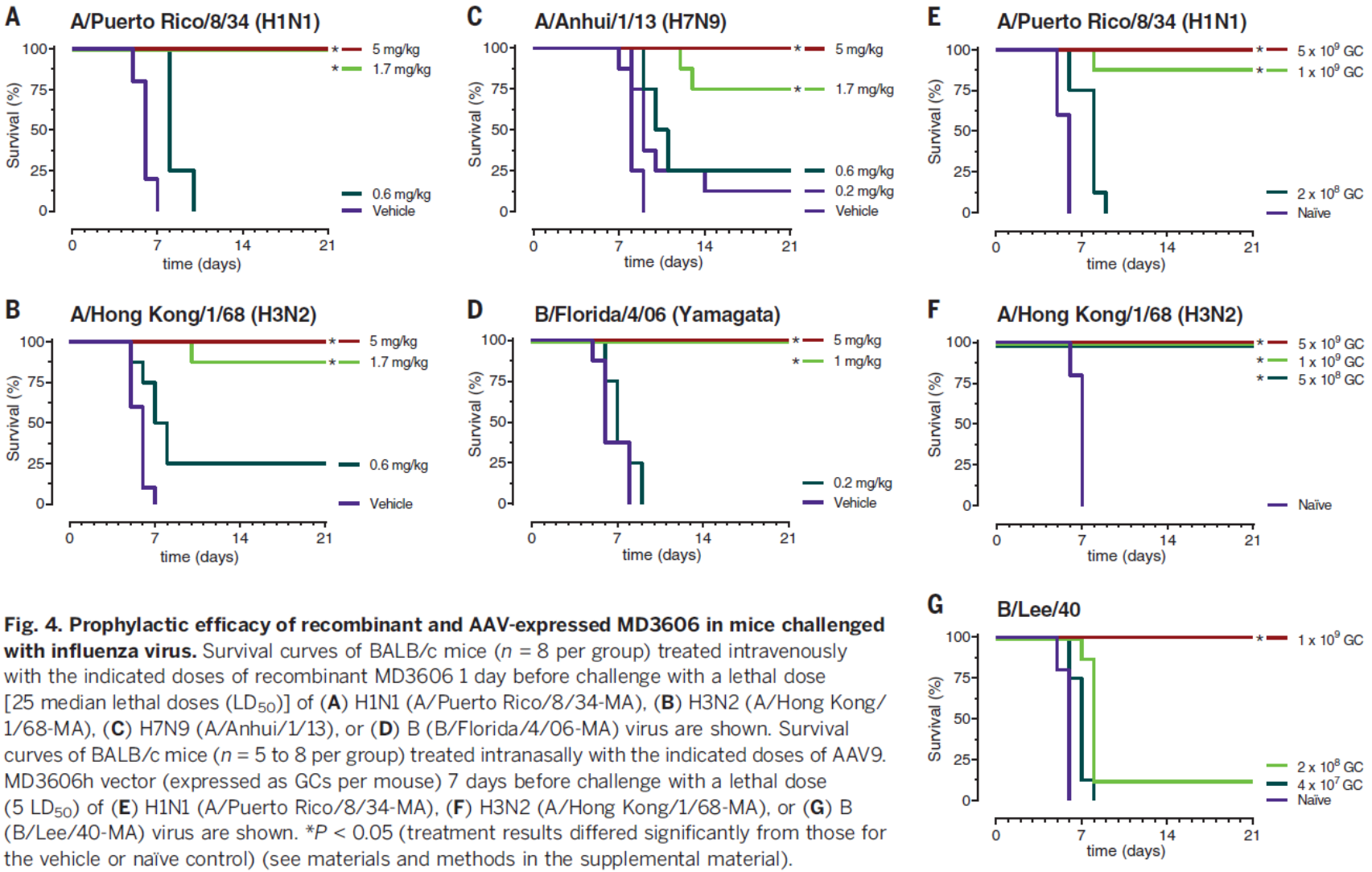


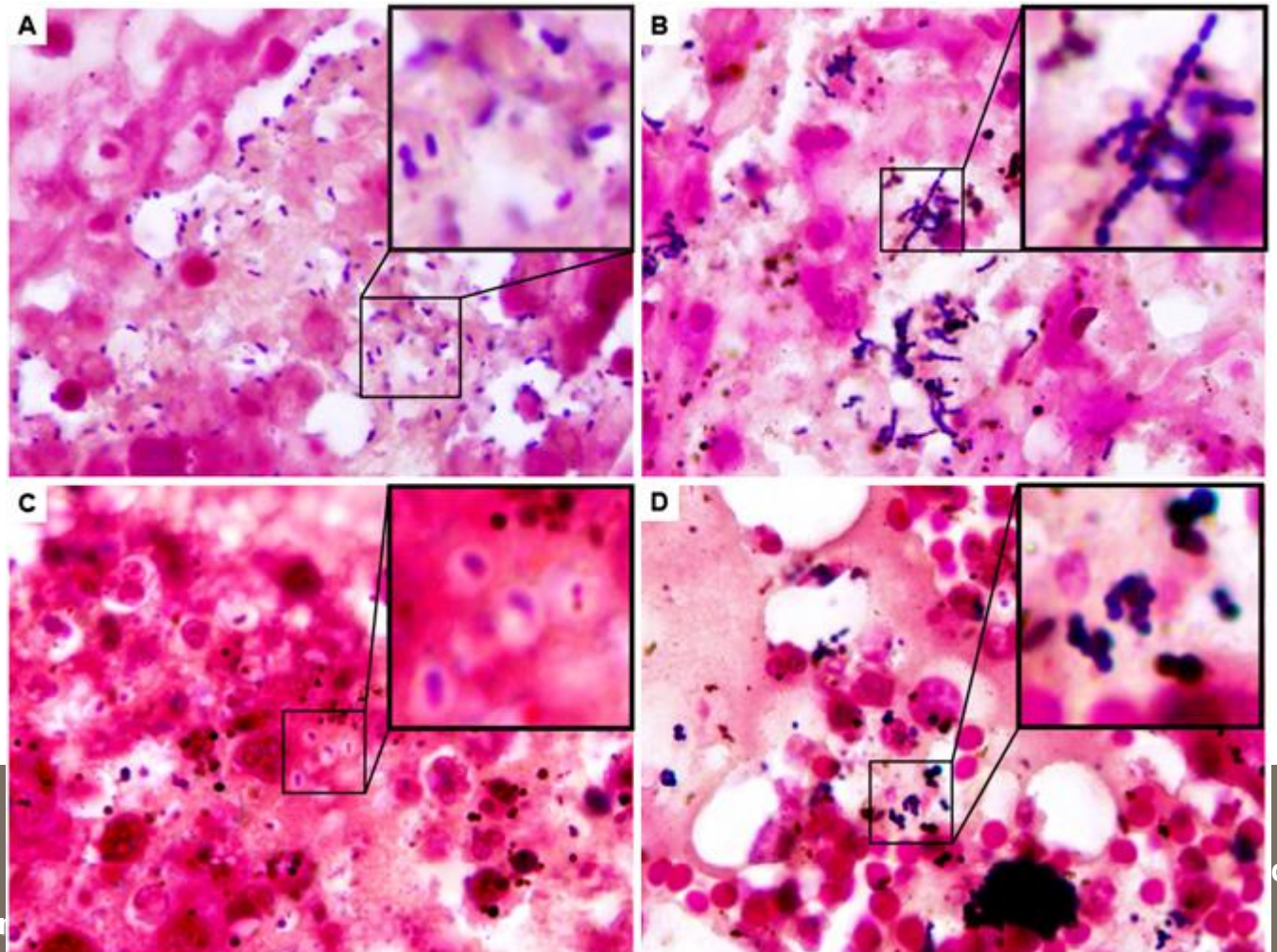
Fig. 4. Prophylactic efficacy of recombinant and AAV-expressed MD3606 in mice challenged with influenza virus. Survival curves of BALB/c mice (n = 8 per group) treated intravenously with the indicated doses of recombinant MD3606 1 day before challenge with a lethal dose [25 median lethal doses (LD_{50})] of (**A**) H1N1 (A/Puerto Rico/8/34-MA), (**B**) H3N2 (A/Hong Kong/1/68-MA), (**C**) H7N9 (A/Anhui/1/13), or (**D**) B (B/Florida/4/06-MA) virus are shown. Survival curves of BALB/c mice (n = 5 to 8 per group) treated intranasally with the indicated doses of AAV9.MD3606h vector (expressed as GCs per mouse) 7 days before challenge with a lethal dose (5 LD_{50}) of (**E**) H1N1 (A/Puerto Rico/8/34-MA), (**F**) H3N2 (A/Hong Kong/1/68-MA), or (**G**) B (B/Lee/40-MA) virus are shown. *P < 0.05 (treatment results differed significantly from those for the vehicle or naïve control) (see materials and methods in the supplemental material).

Sheng ZM et al. Proc Natl Acad Sci U S A. 2011 Sep 27;108(39):16416-21

Autopsy series of 68 cases dying before and during the 1918 influenza pandemic peak

Zong-Mei Sheng[a], Daniel S. Chertow[a], Xavier Ambroggio[b], Sherman McCall[c], Ronald M. Przygodzki[d], Robert E. Cunningham[e], Olga A. Maximova[f], John C. Kash[a], David M. Morens[g], and Jeffery K. Taubenberger[a,1]

[a]Viral Pathogenesis and Evolution Section, Laboratory of Infectious Diseases, [b]Bioinformatics and Computational Biosciences Branch, [f]Office of the Chief, Laboratory of Infectious Diseases, and [g]Office of the Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, MD 20892; [c]Clinical Pathology Laboratory, US Army Medical Research Institute of Infectious Diseases, Fort Detrick, MD 21702; [d]Department of Veterans Affairs, Washington, DC 20420; and [e]Department of Biophysics, Armed Forces Institute of Pathology, Rockville, MD 20850



1918 culture result (current preferred nomenclature)	No./total (%)
Pneumococcus (*Streptococcus pneumonia*)	22/42 (52.4)
Pneumococcus, Serotype I	2/42 (4.8)
Pneumococcus, Serotype II	5/42 (11.9)
Pneumococcus, Serotype III	7/42 (16.7)
Pneumococcus, Serotype IV*	5/42 (11.9)
Pneumococcus, not serotyped	3/42 (7.1)
Streptococcus, hemolytic (*Streptococcus pyogenes*)	4/42 (9.5)
Streptococcus, nonhemolytic	1/42 (2.4)
Staphylococcus	4/42 (9.5)
Friedländler's bacillus (*Klebsiella pneumonia*)	1/42 (2.4)
Bacillus coli (*Escherichia coli*)	1/42 (2.4)
Diplococci observed in sections	1/42 (2.4)
Mixed cultures	6/42 (14.3)
Pneumococcus + *Streptococcus*	2/42 (4.8)
Pneumococcus + *Staphylococcus*	1/42 (2.4)
Streptococcus + *Staphylococcus*	2/42 (4.8)
Pneumococcus + *Staphylococcus* + Friedländler's bacillus	1/42 (2.4)
Negative	2/42 (4.8)

Bacterial Superinfection following Viral Infection

Sex	Age	Bacteria	Trachea	Blood Culture	U-Stpnag	*Mycoplasma*	Virus	NP	Trachea	BAL
Bacterial–viral group (n = 19)										
M	55	*S. pneumoniae*	+	+	–	–	Rhinovirus	+	–	+
M	51	*S. pneumoniae*	+	–	+	–	Parainfluenza virus 3	–	+	NA
M	81	*P. aeruginosa*	+	+	–	–	Rhinovirus	–	+	NA
F	73	*H. influenzae* *M. catarrhalis*	+	–	–	–	Rhinovirus	–	–	+
F	69	*S. pneumoniae*	+	–	+	–	Coronavirus	–	+	NA
F	59	–	–	–	–	+[a]	Rhinovirus	+	–	NA
M	43	*S. pneumoniae*	+	–	+	–	Adenovirus	–	+	NA
F	54	*S. pneumoniae*	+	+	+	–	Rhinovirus	–	+	NA
F	59	*S. pneumoniae*	+	+	+	–	Respiratory syncytial virus	+	+	+
M	39	*S. pneumoniae*	+	+	+	+[a]	Enterovirus	+	+	NA
F	44	*S. pneumoniae*	+	–	–	–	Rhinovirus	+	+	+
F	75	*S. pneumoniae*	–	+	+	–	Rhinovirus	+	+	+
F	73	*S. pneumoniae*	–	–	+	–	Rhinovirus	+	+	–
F	60	*S. pneumoniae*	–	–	+	–	Adenovirus Enterovirus	– –	– +	+ +
F	29	*S. pneumoniae*	+	+	+	+[b]	Rhinovirus	+	–	–
M	37	*S. aureus*	+	–	–	–	Rhinovirus	+	–	NA
M	60	*H. influenzae*	+	+	–	–	Rhinovirus	+	–	+
M	47	*S. pneumoniae*	–	+	+	–	Rhinovirus	–	–	+
F	39	–	–	–	–	+[a]	Rhinovirus Adenovirus	– –	– –	+ +

Pneumonia and cardiovascular events

Clinical Infectious Diseases

MAJOR ARTICLE

Cardiovascular Complications and Short-term Mortality Risk in Community-Acquired Pneumonia

Francesco Violi,[1] Roberto Cangemi,[1] Marco Falcone,[2] Gloria Taliani,[3] Filippo Pieralli,[4] Vieri Vannucchi,[4] Carlo Nozzoli,[4] Mario Venditti,[2] Julio A. Chirinos,[5] and Vicente F. Corrales-Medina[6,7]; for the SIXTUS (Thrombosis-Related Extrapulmonary Outcomes in Pneumonia) Study Group

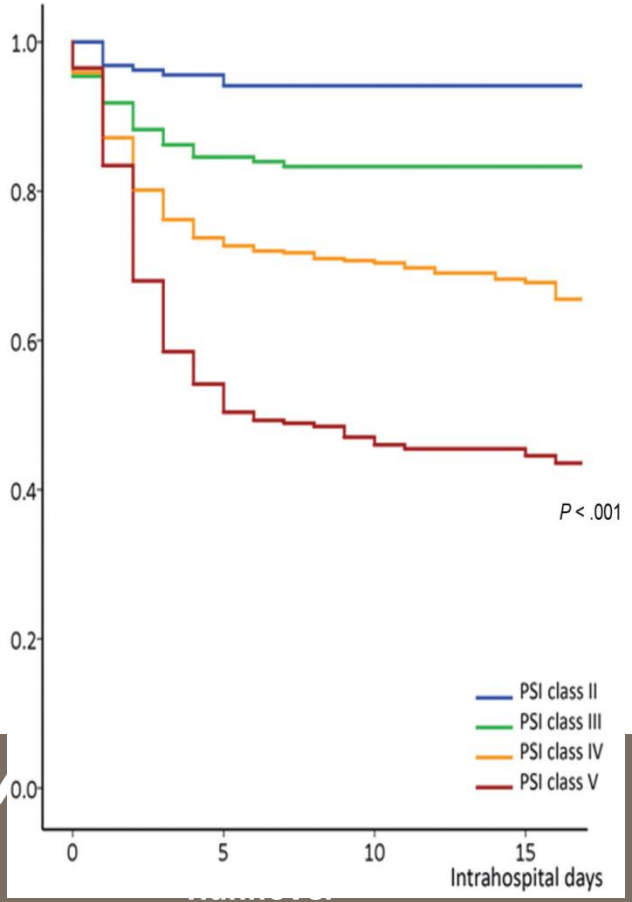
[1]Department of Internal Medicine and Medical Specialties, [2]Department of Public Health and Infectious Diseases, and [3]Infectious and Tropical Diseases Unit, Department of Clinical Medicine, Sapienza University of Rome, and [4]Internal and Emergency Medicine Unit, Careggi University Hospital, Florence, Italy; [5]Division of Cardiology, University of Pennsylvania, Philadelphia; [6]Department of Medicine, University of Ottawa, and [7]Clinical Epidemiology Program, Ottawa Hospital Research Institute, Ontario, Canada

Violi F et al. Clinical Infectious Diseases 2017;64(11):1486–93

Pneumonia and cardiovascular events

- **Prospective observational study for 30 days in 1182 patients hospitalisied for CAP**
- **Study endpoints**
  - **Myocardial infarction**
  - **Newly diagnosed or decompensated left heart failure**
  - **Atrial fibrillation**
  - **Stroke**
  - **Deep venous thrombosis**
  - **Sudden heart death**
  - **All cause mortality**

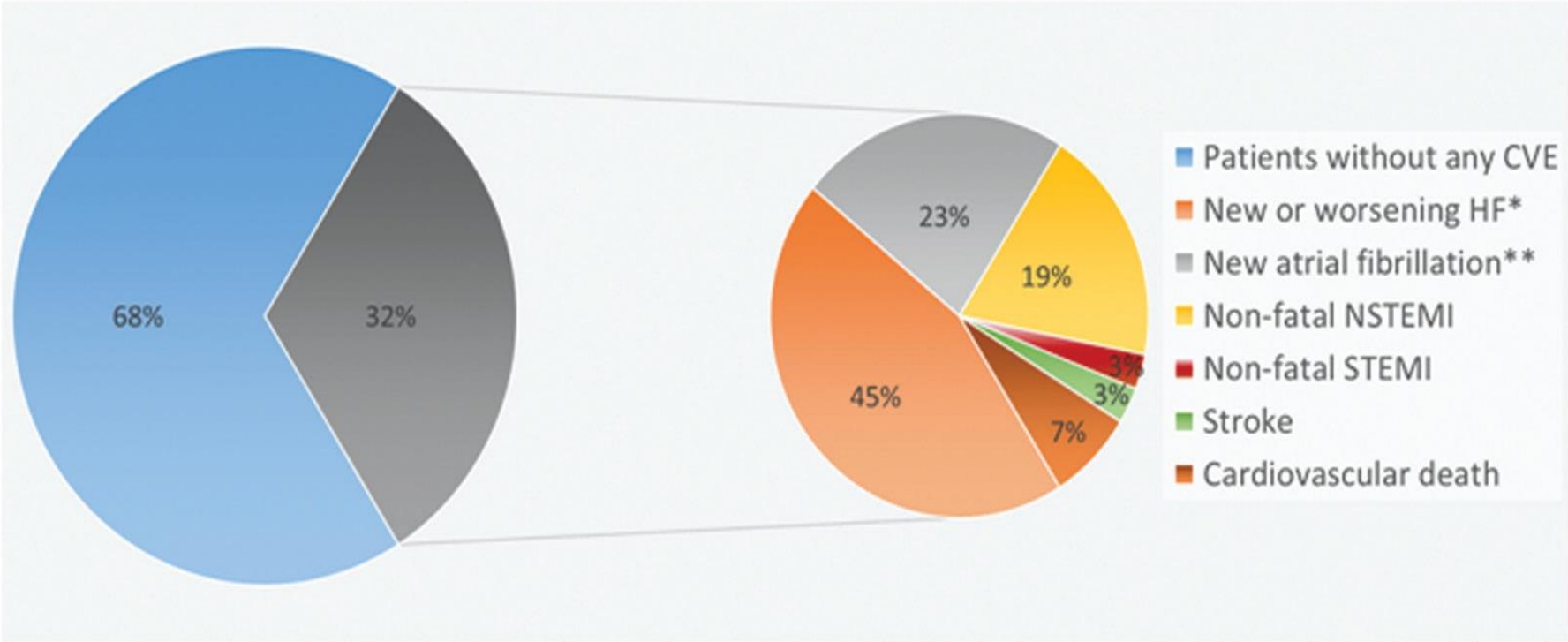
Cardiovascular events associated with pneumonia severity



Violi F et al. Clinical Infectious Diseases 2017;64(11):1486–93

Pneumonia and cardiovascular events

Violi F et al. Clinical Infectious Diseases 2017;64(11):1486–93



Corrales-Medina VF et al. JAMA. 2015;313(3):264-274.

CAP – Long term mortality

- **2 community-based cohorts:**
  - **CHS, n = 5888; age>65 y; enrollment period 1989–1994**
  - **ARIC, n = 15 792; age 45-64 years; enrollment period 1987–1989).**
- **Follow up through 31.12. 2010**
- **Matching of each participant hospitalized with CAP to 2 controls.**
- **Of 591 pneumonia cases in CHS, 206 had CVD events over 10 years after pneumonia hospitalization**
- **CVD risk among pneumonia cases was highest during the first year after hospitalization and remained significantly higher than among controls through 10 years.**

	Pneumonia Cases	Controls	HR (95% CI)
CHS			
No. of participants	591	1182	
CVD events			
0-30 d	54	6	4.07 (2.86-5.27)
31-90 d	11	9	2.94 (2.18-3.70)
91 d-1 y	22	55	2.10 (1.59-2.60)
9-10 y	4	12	1.86 (1.18-2.55)
ARIC			
No. of participants	680	1360	
CVD events			
0-30 d	4	3	2.38 (1.12-3.63)
31-90 d	4	0	2.40 (1.23-3.47)
91 d-1 y	11	8	2.19 (1.20-3.19)
1-2 y	8	7	1.88 (1.10-2.66)

Pneumonia and cardiovascular events

Reyes LF et al. Am J Respir Crit Care Med. 2017 Sep 1;196(5):609-620.

ORIGINAL ARTICLE

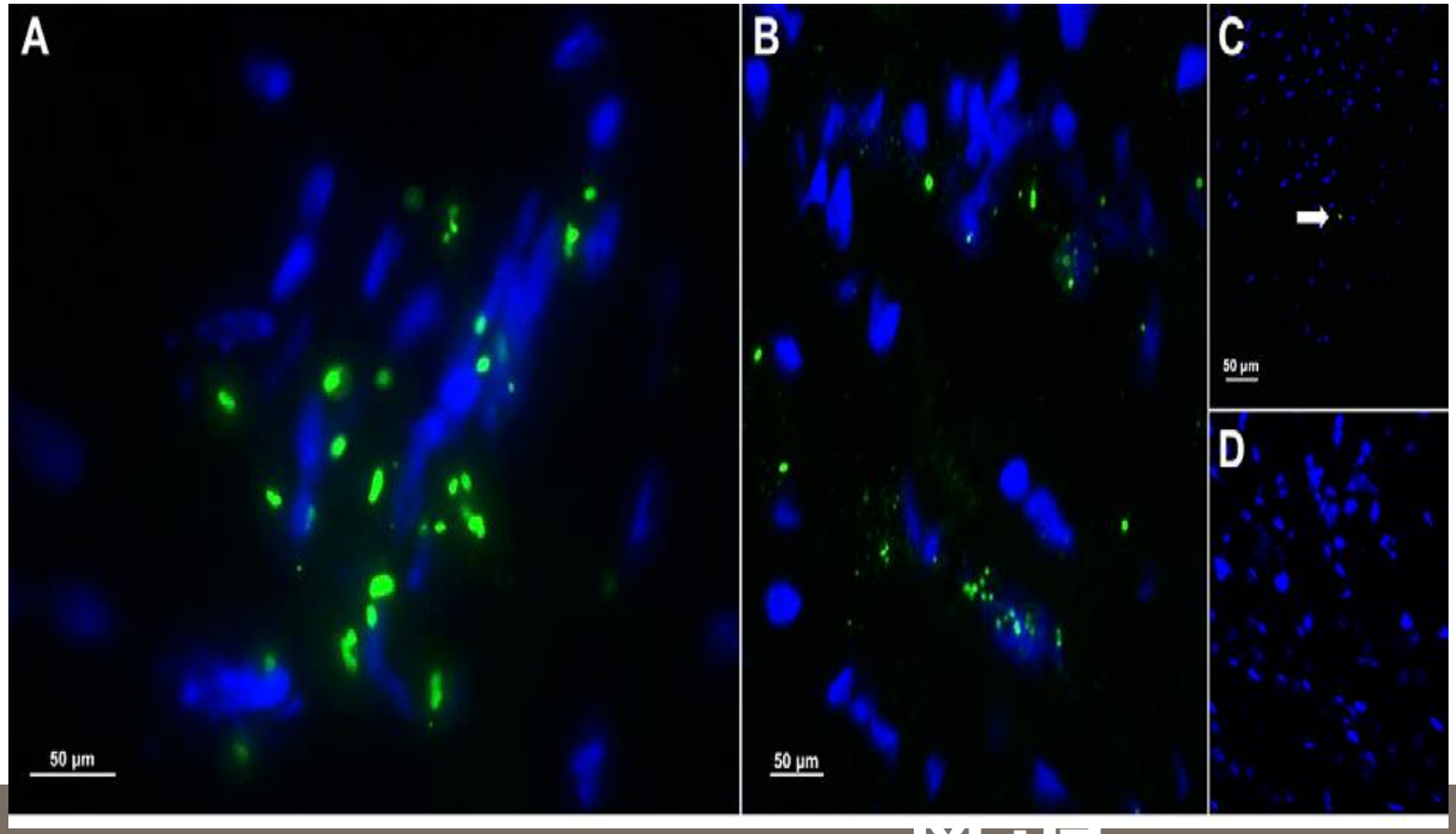
Severe Pneumococcal Pneumonia Causes Acute Cardiac Toxicity and Subsequent Cardiac Remodeling

Luis F. Reyes[1,2*], Marcos I. Restrepo[1,2*], Cecilia A. Hinojosa[1,2], Nilam J. Soni[1,2], Antonio Anzueto[1,2], Bettina L. Babu[1,2], Norberto Gonzalez-Juarbe[3], Alejandro H. Rodriguez[4,5], Alejandro Jimenez[6], James D. Chalmers[7], Stefano Aliberti[8,9,10], Oriol Sibila[11], Vicki T. Winter[12], Jacqueline J. Coalson[12], Luis D. Giavedoni[13], Charles S. Dela Cruz[14], Grant W. Waterer[15], Martin Witzenrath[16,17], Norbert Suttorp[16,17], Peter H. Dube[18], and Carlos J. Orihuela[3]

[1]Division of Pulmonary Diseases and Critical Care Medicine, [12]Department of Pathology, and [18]Department of Immunology and Microbiology, The University of Texas Health Science Center at San Antonio, San Antonio, Texas; [2]Division of Pulmonary Diseases and Critical Care Medicine, South Texas Veterans Health Care System, San Antonio, Texas; [3]Department of Microbiology, The University of Alabama at Birmingham School of Medicine, Birmingham, Alabama; [4]Critical Care Medicine, Hospital Universitari de Tarragona Joan XXIII, Rovira i Virgili University, Tarragona, Spain; [5]Biomedical Research Networking Center on Respiratory Diseases (CIBERES), Tarragona, Spain; [6]Cardiovascular Medicine, Heart & Vascular Institute, Cleveland Clinic, Abu Dhabi, United Arab Emirates; [7]School of Medicine, University of Dundee, Dundee, United Kingdom, [8]Department of Pathophysiology and Transplantation, University of Milan, Milan, Italy; [9]Cardio-thoracic Unit and Adult Cystic Fibrosis Centre, Milan, Italy; [10]Istituti di Ricovero e Cura a Carattere Scientifico, Granada Ospedale Maggiore Policlinico, Milan, Italy; [11]Division of Pulmonary Diseases, Department of Medicine, Hospital de la Santa Creu i Sant Pau, Autonomous University of Barcelona, Barcelona, Spain; [13]Texas Biomedical Research Institute, San Antonio, Texas; [14]Division of Pulmonary and Critical Care Medicine, Yale University, New Haven, Connecticut; [15]Royal Perth Hospital Unit, University of Western Australia, Perth, Australia; and [16]Department of Infectious Diseases and Pulmonary Medicine and [17]SFB-TR84 "Innate Immunity of the Lung," Charité-Universitätsmedizin Berlin, Berlin, Germany

Pneumonia and cardiovascular events

Reyes LF et al. Am J Respir Crit Care Med. 2017 Sep 1;196(5):609-620.



Serotype-specific effectiveness of 23-valent pneumococcal polysaccharide vaccine against pneumococcal pneumonia in adults aged 65 years or older: a multicentre, prospective, test-negative design study

*Motoi Suzuki, Bhim Gopal Dhoubhadel, Tomoko Ishifuji, Michio Yasunami, Makito Yaegashi, Norichika Asoh, Masayuki Ishida, Sugihiro Hamaguchi, Masahiro Aoshima, Koya Ariyoshi, Konosuke Morimoto, on behalf of the Adult Pneumonia Study Group-Japan (APSG-J)**

Methods For this multicentre, prospective study, we enrolled all individuals aged 65 years or older with community-onset pneumonia who visited four study hospitals in Japan between Sept 28, 2011, and Aug 23, 2014. *Streptococcus pneumoniae* was isolated from sputum and blood samples, and serotyped by the capsular Quellung method. Sputum samples were further tested by PCR assay to identify pneumococcal DNA, and positive samples were examined for 50 serotypes by a nanofluidic real-time PCR assay. Urine samples were tested by a urinary antigen test. Serotype-specific vaccine effectiveness was estimated using the test-negative design.

Serotype-specific effectiveness of PSV23 against pneumococcal pneumonia in adults ≥ 65 years : a multicentre, prospective, test-negative design study

- Effectiveness of PPV23 was 27·4% (95% CI 3·2 to 45·6) against all pneumococcal pneumonia, 33·5% (5·6 to 53·1) against PPV23 serotypes, and 2·0% (-78·9 to 46·3) against non-PPV23 serotypes.
- Although no significant differences between subgroups were seen, higher protection was noted in people younger than 75 years, women, and individuals with lobar pneumonia or health-care-associated pneumonia.

Suzuki M et al. Lancet Infect Dis. 2017 Mar;17(3):313-321..

A further interesting finding of the study is that the effectiveness of PPV23 is time dependent: vaccine effectiveness against PPV23-type pneumococcal pneumonia was 37·7% (95% CI 4·8–59·2) within the first 2 years after vaccination, and declined to no significant effectiveness (34·7% [–7·4 to 60·3]) after the second year. Within the first month after vaccination, the effectiveness was 58·8% (–226·7 to 94·8); however, the number of cases was too small for a meaningful calculation.

Clin Infect Dis. 2018 67(10):1498-1506.

Effectiveness of 13-Valent Pneumococcal Conjugate Vaccine Against Hospitalization for Community-Acquired Pneumonia in Older US Adults: A Test-Negative Design

John M. McLaughlin,[1] Qin Jiang,[1] Raul E. Isturiz,[1] Heather L. Sings,[1] David L. Swerdlow,[1] Bradford D. Gessner,[1] Ruth M. Carrico,[2] Paula Peyrani,[2] Timothy L. Wiemken,[3] William A. Mattingly,[2] Julio A. Ramirez,[2] and Luis Jodar[1]

[1]Pfizer Vaccines, Collegeville, Pennsylvania; and [2]Department of Medicine, Division of Infectious Diseases, School of Medicine and [3]Department of Epidemiology and Population Health, School of Public Health and Information Sciences, University of Louisville, Kentucky

Logistic Regression Model[a]	All VT-CAP (n = 2034)	Nonbacteremic VT-CAP (n = 2014)
Cases, No.	68	62
Controls, No.	1966	1952
	VE, % (95% CI)	
Crude model[b]	72.8 (12.8–91.5)	70.1 (4.1–90.7)
Univariate adjustment		
Seasonality/time period	72.4 (11.4–91.4)	69.2 (.8–90.4)
Age group	72.8 (13.0–91.5)	70.2 (4.4–90.7)
Gender	72.3 (11.3–91.4)	69.8 (2.9–90.7)
Race	72.9 (13.3–91.6)	70.4 (4.9–90.8)
Ethnicity	72.8 (12.9–91.5)	70.2 (4.1–90.7)
Place of residence	73.3 (14.4–91.7)	70.5 (5.3–90.8)
Risk level	73.3 (14.2–91.7)	70.7 (5.9–90.9)
BMI category	72.1 (10.4–91.3)	69.3 (1.3–90.5)
PSI	72.3 (11.3–91.4)	69.8 (2.9–90.6)
Healthcare facility exposure in last 3 mo	72.6 (12.1–91.4)	69.9 (3.3–90.6)
Weekly exposure to children aged <5 y	72.8 (12.7–91.5)	70.4 (4.8–90.8)
Influenza vaccination within previous y	71.1 (6.9–91.0)	67.5 (–5.2 to 90.0)
History of PPSV23 in last 5 y	72.8 (12.7–91.5)	70.1 (4.1–90.7)
Fully adjusted[c]	71.2 (6.1–91.2)	67.6 (–6.2 to 90.1)

Thorrington D et al. PLoS One. 2018 Feb 9;13(2):e0192640.

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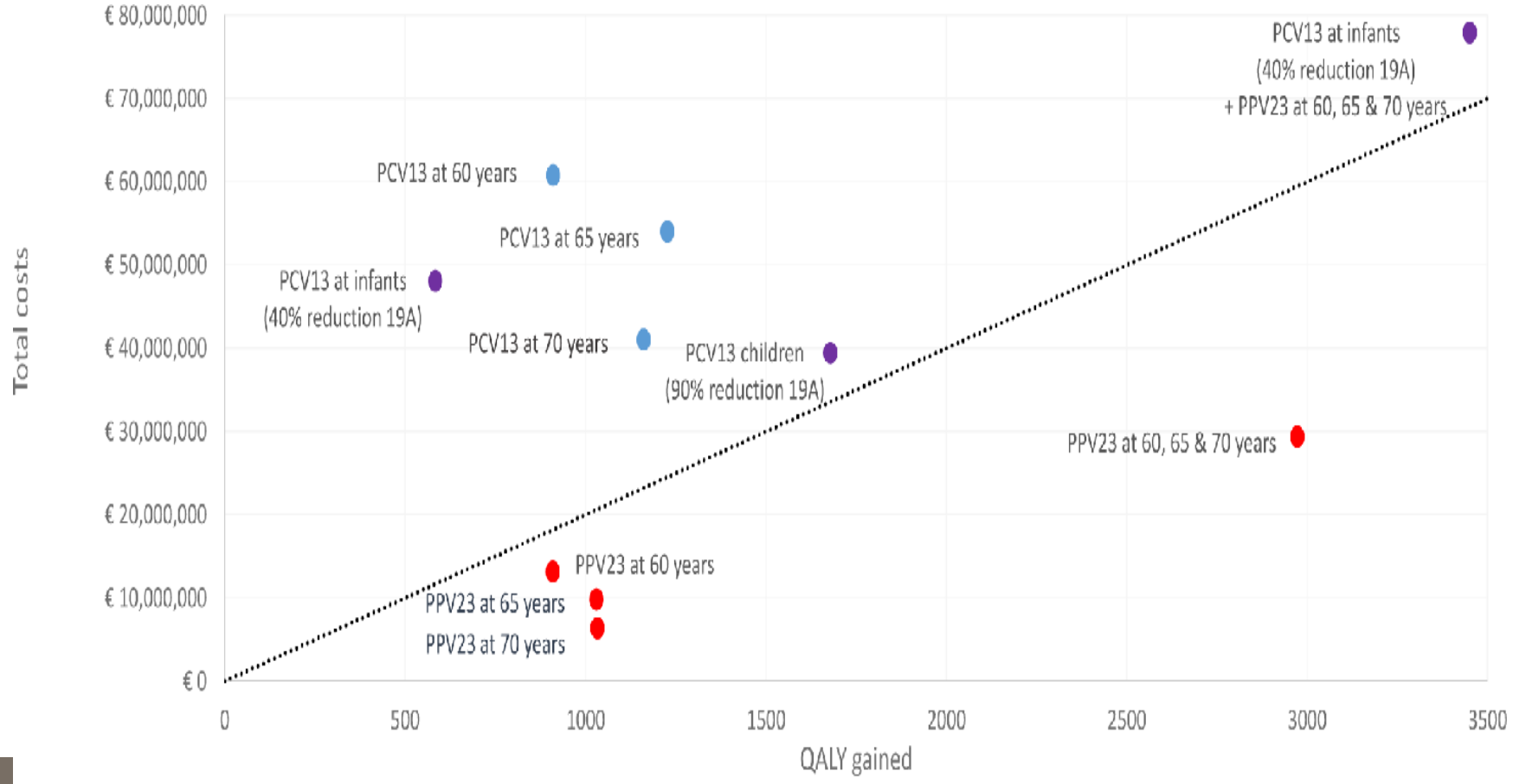
Money, money, money …



Just Wait and See

Vaccine 36 (2018) 6875–6882

Contents lists available at ScienceDirect

Vaccine

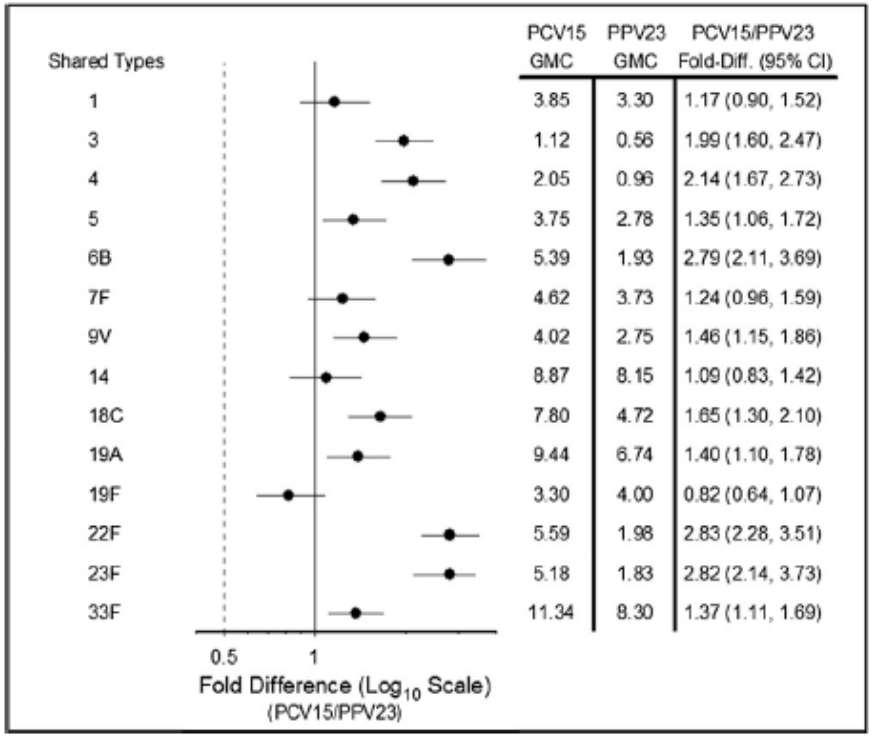
journal homepage: www.elsevier.com/locate/vaccine

Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine in pneumococcal vaccine-naïve adults ≥50 years of age

Susan J. Ermlich [a], Charles P. Andrews [b], Steven Folkerth [c], Richard Rupp [d], David Greenberg [e], Richard D. McFetridge [a], Jonathan Hartzel [a], Rocio D. Marchese [a], Jon E. Stek [a], Chitrananda Abeygunawardana [a], Luwy K. Musey [a,*]

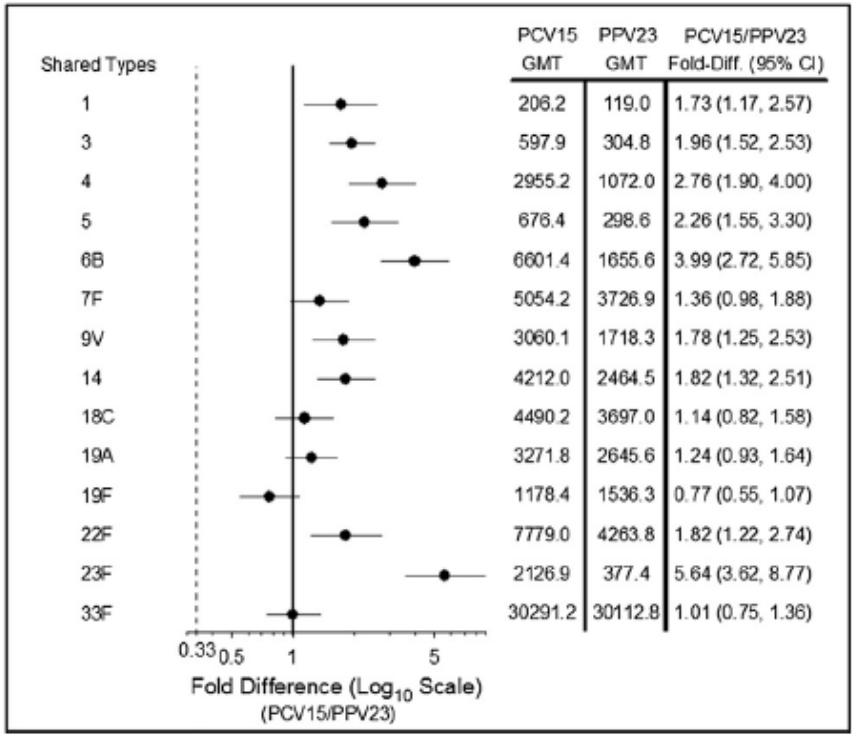
[a] Merck & Co., Inc., Kenilworth, NJ, USA

Panel A: Serotype-specific IgG Responses



Shared Types	PCV15 GMC	PPV23 GMC	PCV15/PPV23 Fold-Diff. (95% CI)
1	3.85	3.30	1.17 (0.90, 1.52)
3	1.12	0.56	1.99 (1.60, 2.47)
4	2.05	0.96	2.14 (1.67, 2.73)
5	3.75	2.78	1.35 (1.06, 1.72)
6B	5.39	1.93	2.79 (2.11, 3.69)
7F	4.62	3.73	1.24 (0.96, 1.59)
9V	4.02	2.75	1.46 (1.15, 1.86)
14	8.87	8.15	1.09 (0.83, 1.42)
18C	7.80	4.72	1.65 (1.30, 2.10)
19A	9.44	6.74	1.40 (1.10, 1.78)
19F	3.30	4.00	0.82 (0.64, 1.07)
22F	5.59	1.98	2.83 (2.28, 3.51)
23F	5.18	1.83	2.82 (2.14, 3.73)
33F	11.34	8.30	1.37 (1.11, 1.69)

Panel B: Serotype-specific OPA Responses

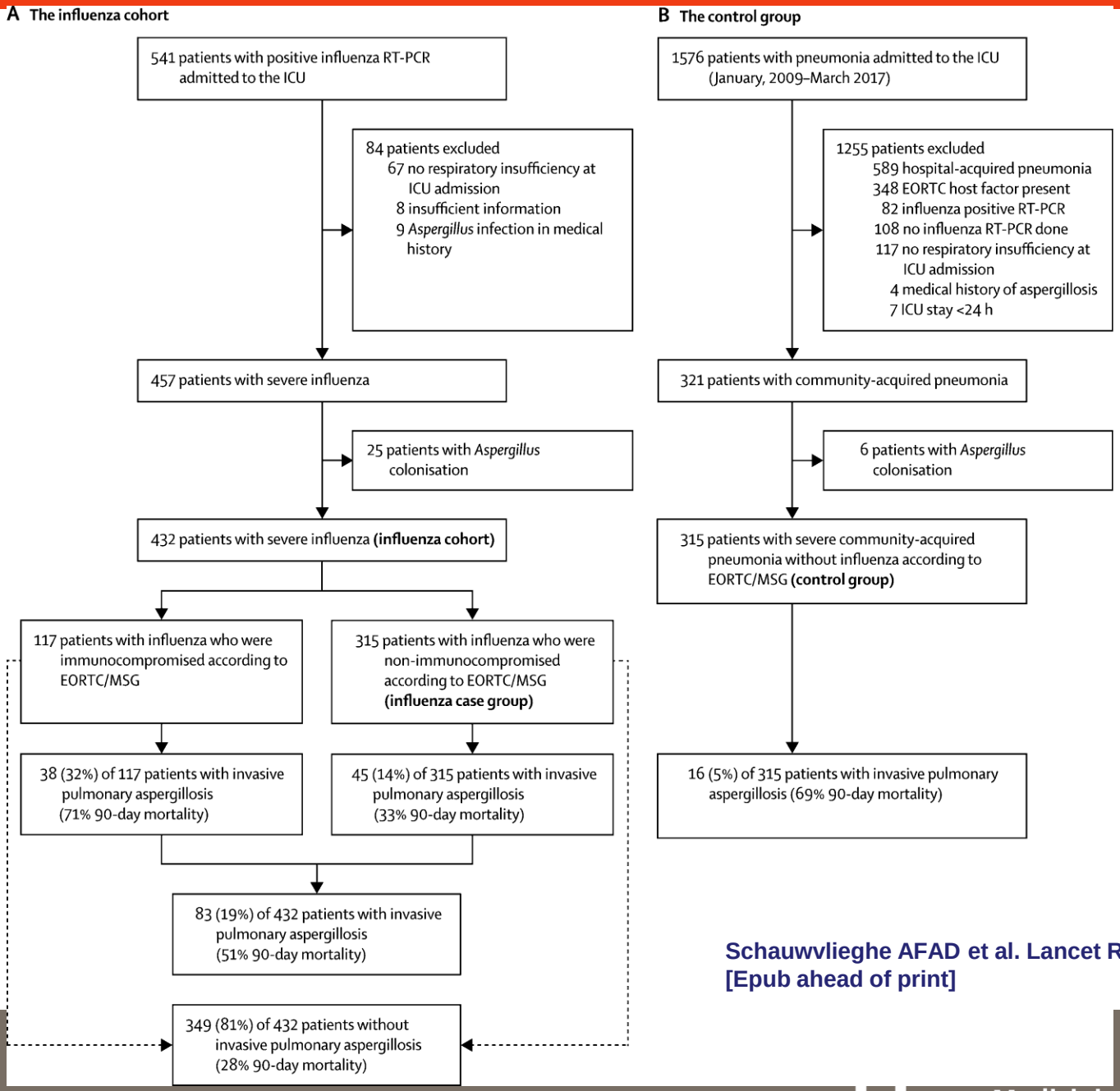


Shared Types	PCV15 GMT	PPV23 GMT	PCV15/PPV23 Fold-Diff. (95% CI)
1	206.2	119.0	1.73 (1.17, 2.57)
3	597.9	304.8	1.96 (1.52, 2.53)
4	2955.2	1072.0	2.76 (1.90, 4.00)
5	676.4	298.6	2.26 (1.55, 3.30)
6B	6601.4	1655.6	3.99 (2.72, 5.85)
7F	5054.2	3726.9	1.36 (0.98, 1.88)
9V	3060.1	1718.3	1.78 (1.25, 2.53)
14	4212.0	2464.5	1.82 (1.32, 2.51)
18C	4490.2	3697.0	1.14 (0.82, 1.58)
19A	3271.8	2645.6	1.24 (0.93, 1.64)
19F	1178.4	1536.3	0.77 (0.55, 1.07)
22F	7779.0	4263.8	1.82 (1.22, 2.74)
23F	2126.9	377.4	5.64 (3.62, 8.77)
33F	30291.2	30112.8	1.01 (0.75, 1.36)

Invasive aspergillosis in patients admitted to the intensive care unit with severe influenza: a retrospective cohort study

Alexander F A D Schauwvlieghe*, Bart J A Rijnders*, Niele Philips, Rosanne Verwijs, Lore Vanderbeke, Carla Van Tienen, Katrien Lagrou, Paul E Verweij, Frank L Van de Veerdonk, Diederik Gommers, Peter Spronk, Dennis C J J Bergmans, Astrid Hoedemaekers, Eleni-Rosalina Andrinopoulou, Charlotte H S B van den Berg, Nicole P Juffermans, Casper J Hodiamont, Alieke G Vonk, Pieter Depuydt, Jenina Boelens, Joost Wauters, on behalf of the Dutch-Belgian Mycosis study group

Lancet Respir Med. 2018 Jul 31. [Epub ahead of print]



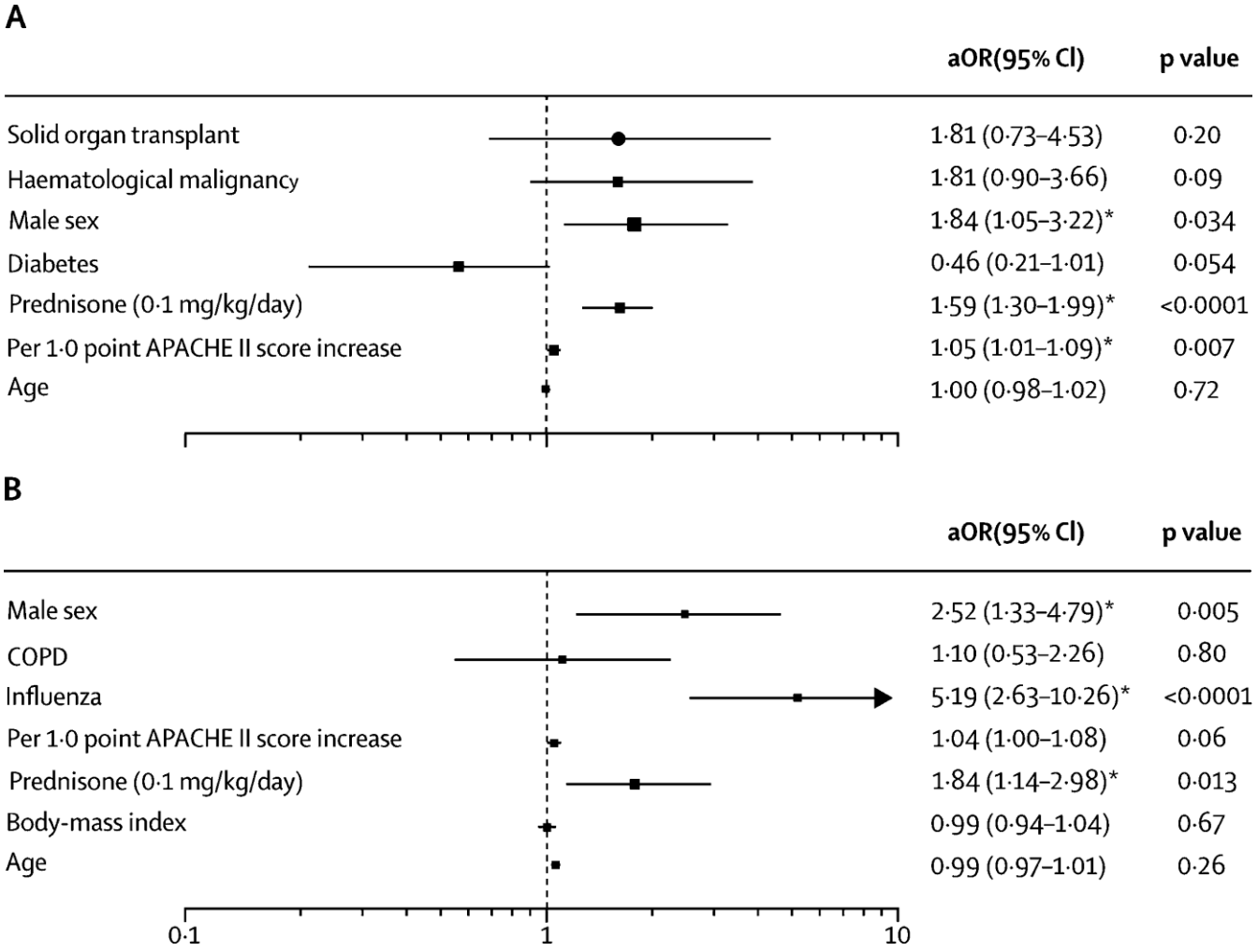
Schauwvlieghe AFAD et al. Lancet Respir Med. 2018 Jul 31. [Epub ahead of print]

Influenza Mortality

Schauwvlieghe AFAD et al. Lancet Respir Med. 2018 Jul 31.
[Epub ahead of print]

	Influenza cohort (n=432)	With invasive pulmonary aspergillosis (n=83)	Without invasive pulmonary aspergillosis (n=349)	p value
Outcome data				
Median days of ICU stay (IQR)	11 (6–23)	19 (12–38)	9 (5–20)	<0·0001
ICU mortality	107 (25%)	37 (45%)	70 (20%)	<0·0001
Hospital mortality	133 (31%)	41 (49%)	92 (26%)	<0·0001
90-days mortality after ICU admission	141 (33%)	42 (51%)	99 (28%)	0·0001
Influenza				
Influenza A	355 (82%)	71 (86%)	284 (81%)	0·37
Influenza B	77 (18%)	12 (14%)	65 (19%)	0·37
Influenza treatment with a neuraminidase inhibitor	338/428 (79%)	70/83 (84%)	268/345 (78%)	0·25
Diagnostics				
BAL sampling performed	233 (54%)	81 (98%)	152 (44%)	<0·0001
BAL galactomannan test performed	137 (32%)	76 (92%)	61 (17%)	<0·0001
Serum galactomannan test performed	47 (11%)	31/83 (37%)	16 (5%)	<0·0001

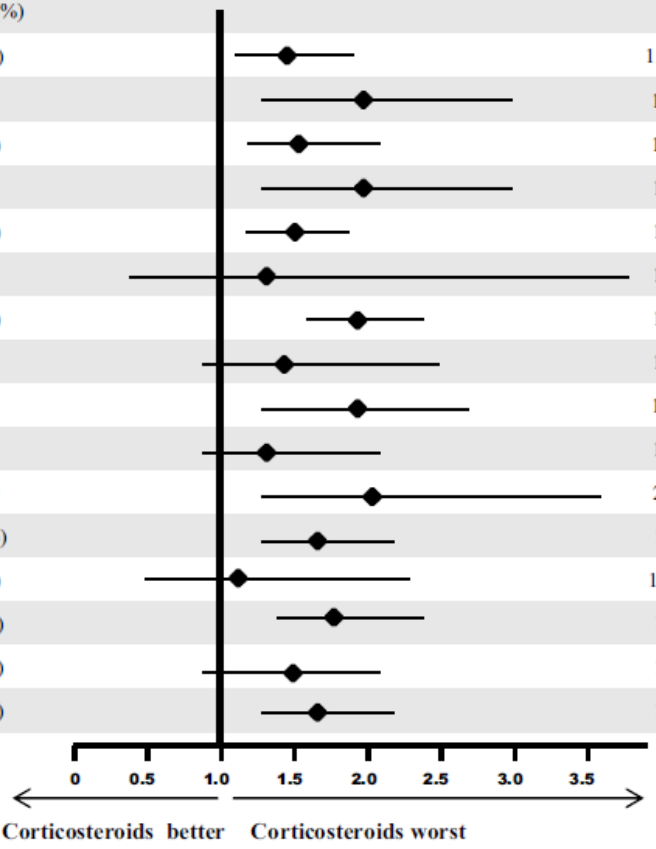
Risk factors for invasive aspergillosis



Moreno G et al. Intensive Care Med. 2018 Sep;44(9):1470-1482.

Influenza Treatment Corticosteroids

Subgroups	Corticosteroid Therapy YES number of patients dead/total number of patients (%)	Corticosteroid Therapy NO number of patients dead/total number of patients (%)	OR (95%CI)	P-value
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



ROEMER- UND PELIZAEUS-MUSEUM HILDESHEIM

„Seuchen“

die Bedrohung bleibt

06. November 2020

Medizinische Hochschule Hannover