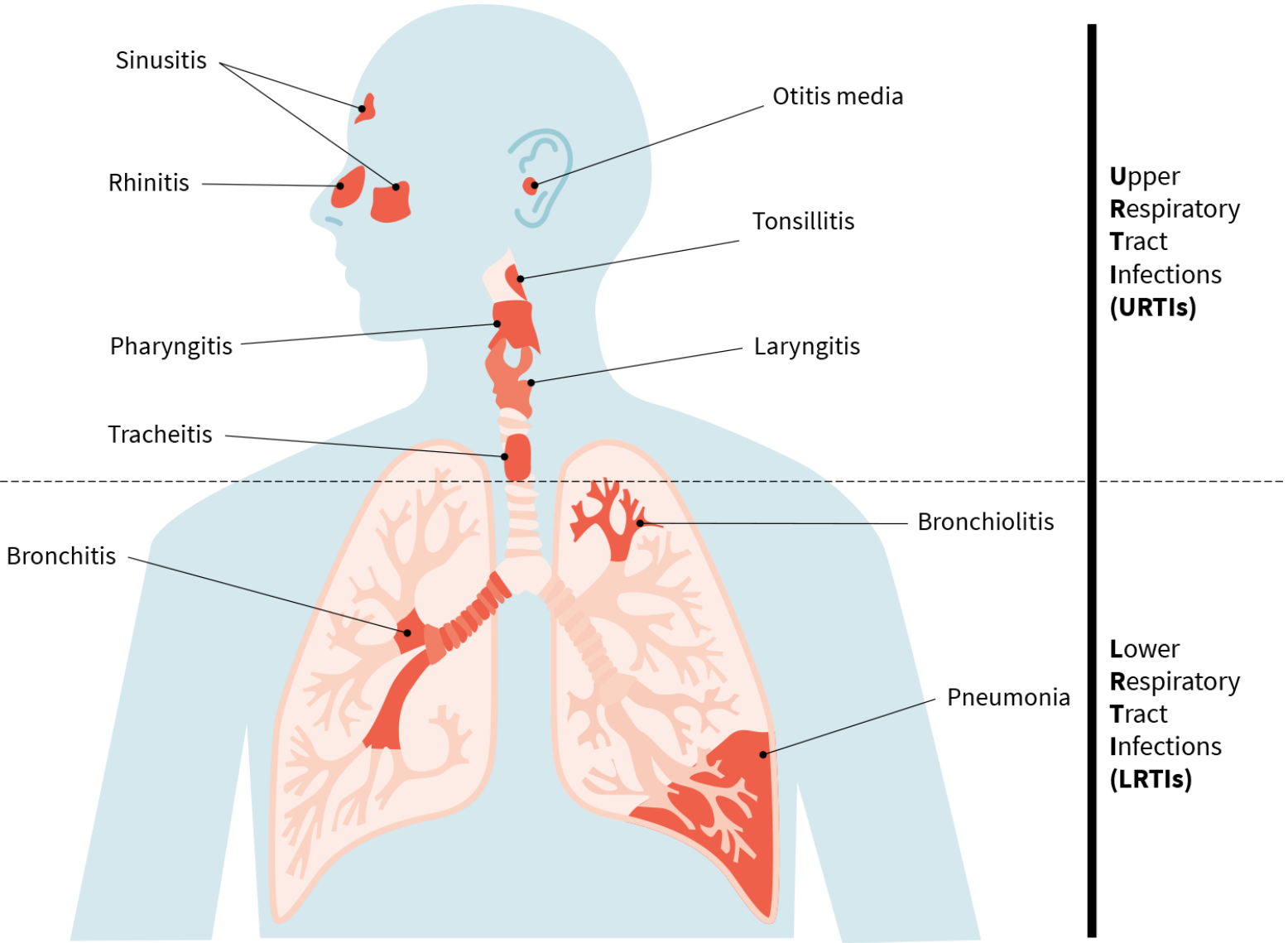
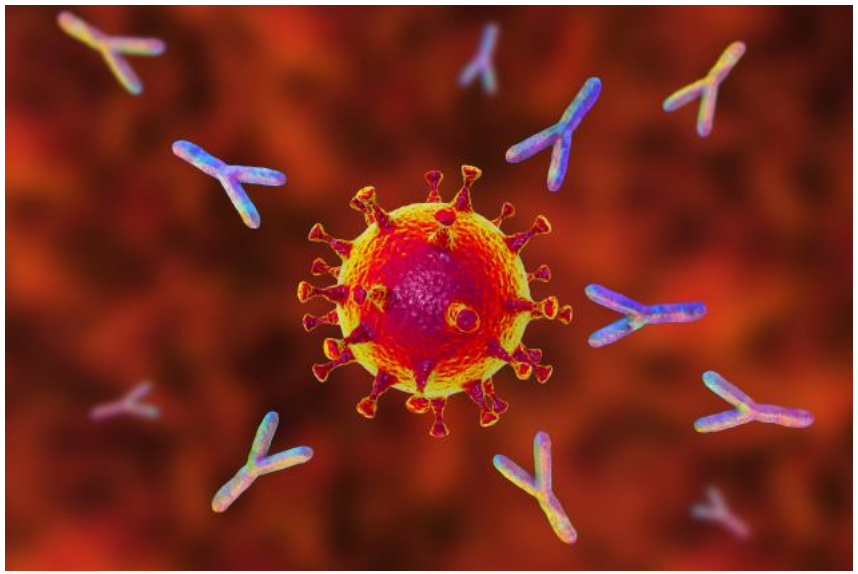
Wat dieper in de virale pneumonie

Marco Goeijenbier M.D. PhD. EDIC

Internist intensivist Spaarne Gasthuis
Research aanstelling Erasmus MC

Spaarne Gasthuis





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SARI? Nieuwe term

World Health Organization (WHO) case definition of severe acute respiratory infections (SARI) is anyone with an acute respiratory infection with symptoms within 10 days of presentation, cough, fever, and hospitalization. This is used to standardize global influenza surveillance with the caveat not all cases will be captured[1]

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[1] https://www.who.int/teams/global-influenza-programme/surveillance-and-monitoring/case-definitions-for-ili-and-sari

Human Metapneumovirus (HMPV)

- Geen vaccin
- Ontdekt in Erasmus MC
- Geen antiviralen
- Onder diagnostiek

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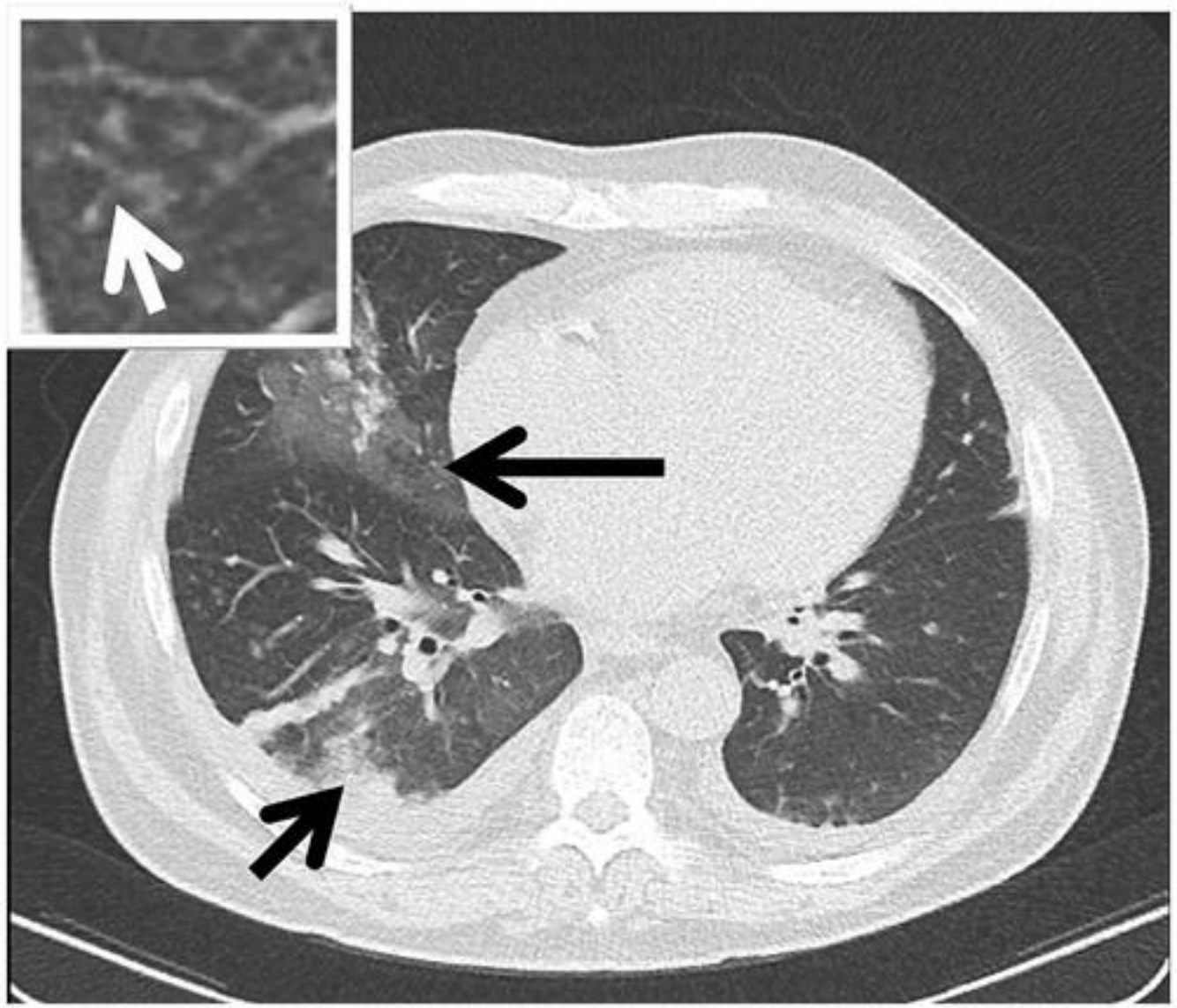

Mortaliteit bij opgenomen patiënten serieus (6%)
ICU opname tot 15%
Co circulatie gedurende covid
Risico: stamcel, COPD, laag BMI, astma en COPD

Negatief RNA pneumoviridae

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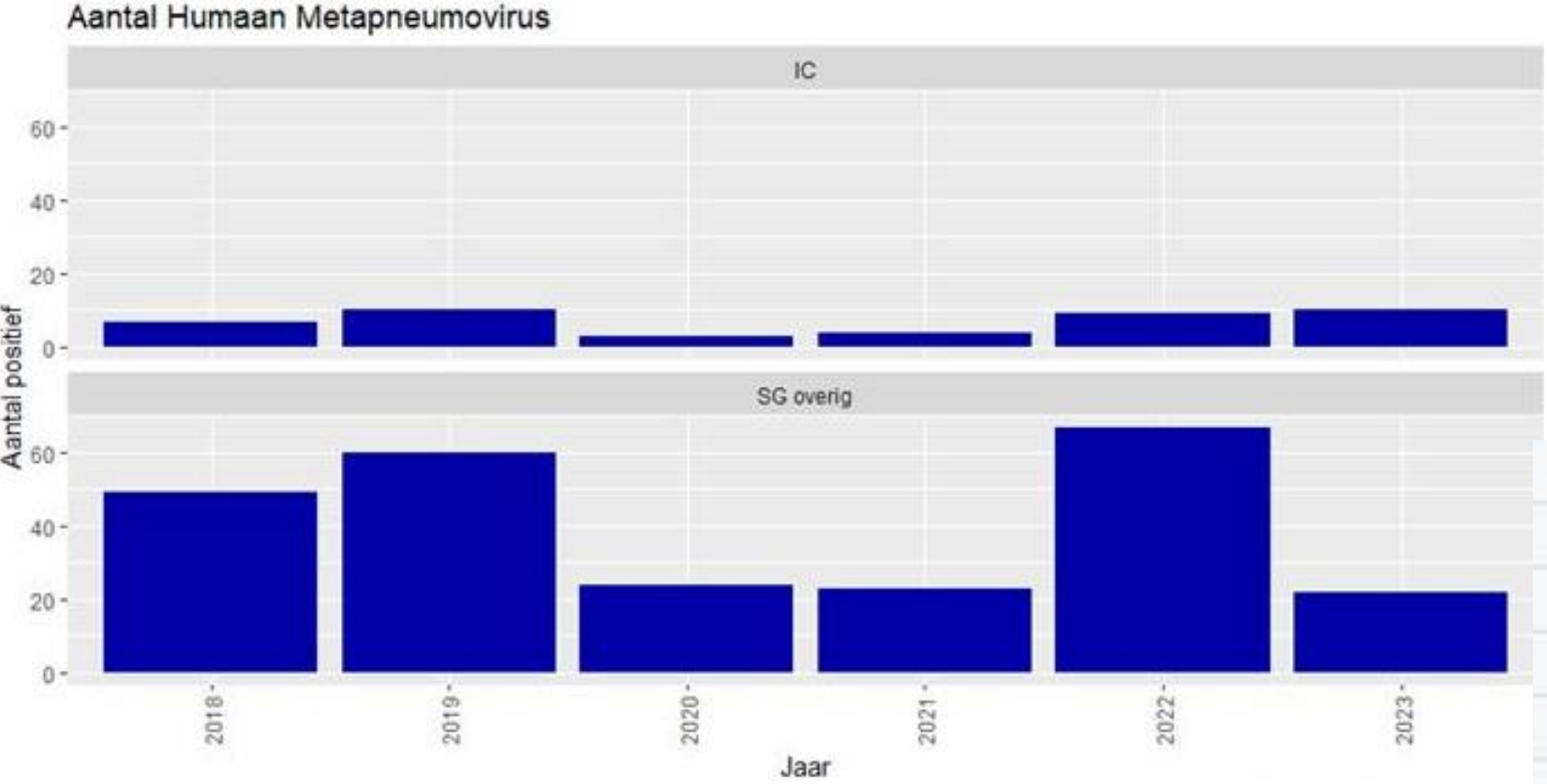

	jaar	groep_IC	Negatief	Positief
1	2018	IC	390	7
2	2018	SG overig	1516	49
3	2019	IC	298	10
4	2019	SG overig	1484	60
5	2020	IC	316	3
6	2020	SG overig	1703	24
7	2021	IC	147	4
8	2021	SG overig	848	23
9	2022	IC	227	9
10	2022	SG overig	1203	67
11	2023	IC	225	10
12	2023	SG overig	1190	22

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New Immunizations to Protect Against Severe RSV

Who Does It Protect?	Type of Product	Is It for Everyone in Group?
 Adults 60 and over	RSV vaccine	Talk to your doctor first
 Babies	RSV antibody given to baby	All infants entering or born during RSV season. Small group of older babies for second season.
	OR	
 Babies	RSV vaccine given during pregnancy	Can get if you are 32–36 weeks pregnant during September–January

www.cdc.gov/rsv

Vaccinaties

- Pfizer: ABRYSVO bivalent subunit vaccin
- GSK: RSV F glycoprotein antigen (RSVPreF3) combined with GSK’s proprietary AS01E adjuvants
- Passieve immunisatie

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respiratoire ondersteuning, IC opname, ziekenhuis mortaliteit gesplitst naar leeftijd.

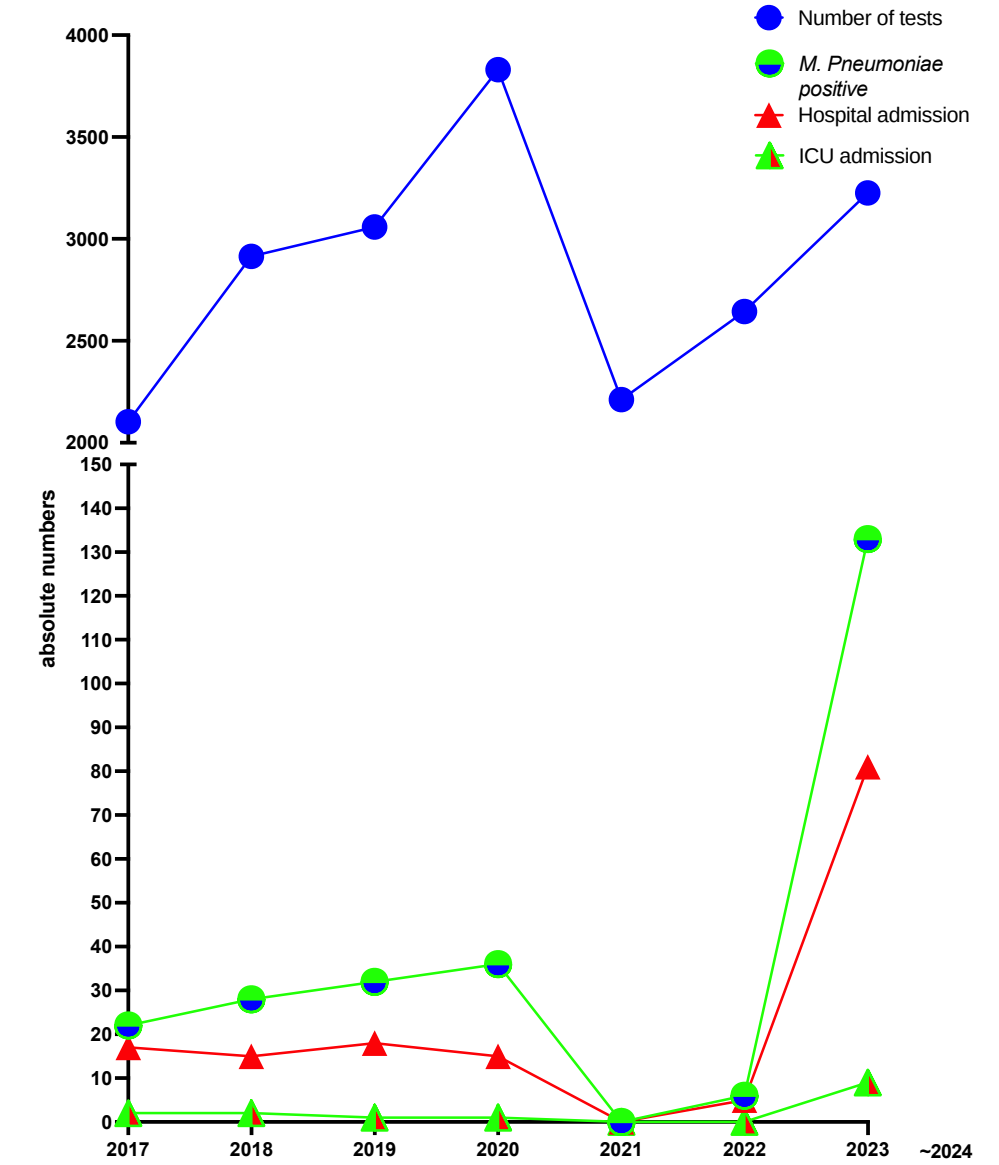
	Totaal (N=1035)	Influenza (N = 813)	RSV (N=222)	OR [95% CI]	P-waarde
Opnameduur, mediaan [IQR]	5.0 [3.0-9.0]	5.0 [3.0-9.0]	5.0 [3.0-10.0]	0.999 [0.979-1.02]	0.909
Opnameduur, mean (SD) (dagen)	7.42 (8.1)	7.44 (8.2)	7.37 (7.5)		
Respiratoire ondersteuning – no. (%)	666 (64.3%)	507 (62.4%)	159 (71.6%)	1.52 [1.11-2.12]	0.011
IC opname – no. (%)	139 (13.4%)	105 (12.9%)	34 (15.3%)	1.22 [0.793-1.84]	0.353
Mortaliteit in ziekenhuis – no. (%)	84 (8.1%)	65 (8.0%)	19 (8.6%)	1.08 [0.616-1.80]	0.785
- **Leeftijd 18-49**	1 (0.1%)	0 (0%)	1 (0.5%)		
- **Leeftijd 50-64**	9 (0.9%)	8 (1.0%)	1 (0.5%)		
- **Leeftijd 65-74**	13 (1.3%)	11 (1.4%)	2 (0.9%)		
- **Leeftijd 75+**	61 (5.9%)	46 (5.7%)	15(6.8%)		

Influenza ongeveer 2-3x zoveel in SG
RSV oudere patiëntengroep dan influenza

COPD en maligniteit brengen een significant grotere odds op RSV met zich mee vergeleken met influenza.

Vaker bijvangst bij bacteriële pneumonie
(Lelyveld en Dore 2023)

M. Pneumoniae



% positive	1%	1%	1%	0.9%	0%	0.2%	4.1%	8.1%
% admitted	77.3%	53.6%	56.2%	41,7%	0%	83,3%	60.9%	66%
% ICU	11.8%	13,3%	5.6%	6.7%	0%	0%	11.1%	6.5%

Table 2 in depth case description and radiology findings

> Euro Surveill. 2024 Jan;29(4). doi: 10.2807/1560-7917.ES.2024.29.4.2300724.

Increased incidence of *Mycoplasma pneumoniae* infections and hospital admissions in the Netherlands, November to December 2023

Dita C Bolluyt [1], Sjoerd M Euser [2 3], Dennis Souverein [2 3], Annemarie Mc van Rossum [4], Jayant Kalpoe [3], Mireille van Westreenen [5], Marco Goeijenbier [6 7], Dominic Snijders [8], Dirk Eggink [9], Femke Jongenotter [9], Steven Fl van Lelyveld [1 2], Marlies A van Houten [2 10]

Affiliations + expand

PMID: 38275014 DOI: 10.2807/1560-7917.ES.2024.29.4.2300724

Free article

				lobe			
77/M	Organizing pneumonia	none	Hypoxia	Right lower middle and upper lobe new consolidations, pleural effusion right	2/79/24	6 days	IMV: no NIMV: 5 days of high flow nasal canula ROX at admission: 5.17
27/F	none	none	Hypoxia	consolidation left lower lobe	2/25/9	5 days	IMV: no NIMV: 4 days of high flow nasal canula ROX at admission: 8.61
26/M	none	none	Hypoxia	Reticonodular consolidiations right lower lobe	4/37/22	7 days	IMV: yes, duration 4 days NIMV: yes
36/M	none	none	Hypoxia	Consolidation righ lower lobe and peribronchial cuffing	4/41/17	11 days	IMV: no NIMV: High flow nasal canula ROX at admission: -
44/M	Coeliac disease	none	Hypoxia	Bilateral consolidations	3/45/20	19 days	IMV: yes, duration 9 days Proning: yes NIMV: yes
36/M	none	none	Hypoxia	Reticonodular consolidations in the lower lobes	4/46/21	5 days	IMV: no NIMV: high flow nasal canula
29/F	Colitis Ulcerosa	none	Hypoxia	Bilateral patchy consolidations	3/51/21	2 days	IMV: no NIMV: high flow nasal canula
65/M	Heart failure, OSAS, chronic renal insufficiency, diabetes mellitus type 2	SARS-CoV-2 (PCR NP/OP swab), Streptococcus pneumonia (pleural fluid and blood culture)	Hemodynamic instability	Consolidation left lower lobe with pleural effusion	5/79/37	1 day	IMV: no NIMV: no

ration ICU stay	Summary
days	IMV: yes, duration 13 days Proning: yes
ay	IMV: no NIMV: no Hemodynamic instability (new onset arrhythmia)
ays	IMV: no NIMV: High flow nasal canula ROX at admission 3.61
ays	IMV: yes, duration 6 days Proning: yes (non-responder) NIMV: High flow nasal canula ROX at admission: 2.8
ay	IMV: no NIMV: no Hemodynamic instability (new onset arrhythmia)
ays	IMV: no NIMV: yes, 48 hours of high flow nasal canula ROX at admission: 5.47
ays	IMV: no NIMV: yes, 108 hours of high flow nasal canula ROX at admission: 3.26
ays	IMV: yes, Upper airway obstruction. Duration 48 hours
ays	IMV: no NIMV: 5 days of high flow nasal canula ROX at admission: 7.46

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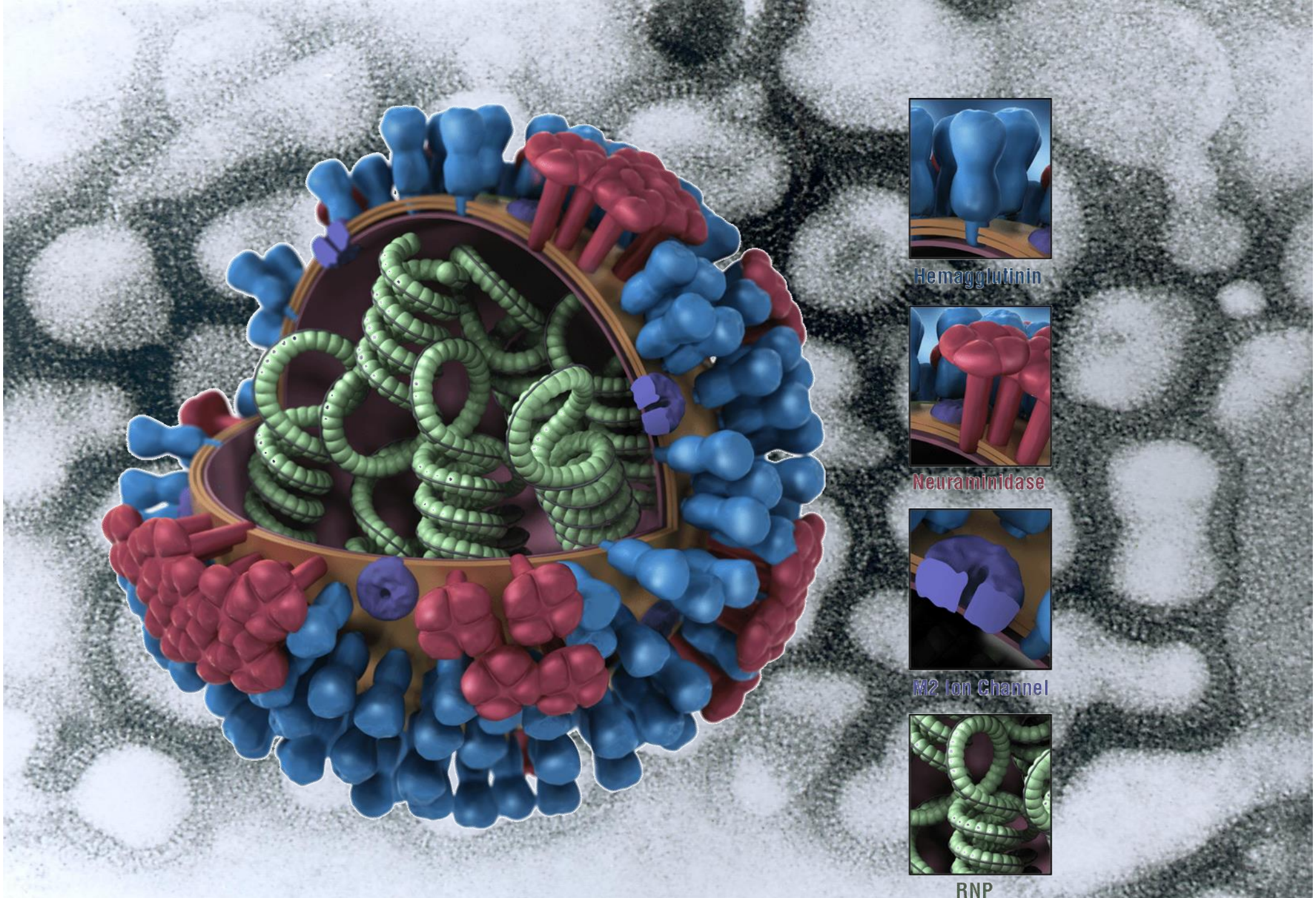
Hemagglutinin
Neuraminidase
M2 Ion Channel
RNP

The ‘usual’ three suspects

Seizoen-

Pandemische-

Vogel-

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Flu cijfers

- 10% symptomatisch 750 miljoen infecties
- Daarvan 5 miljoen gecompliceerde gevallen (+/- 0.75%)
- Half miljoen doden (0.1%)

Bron: CDC

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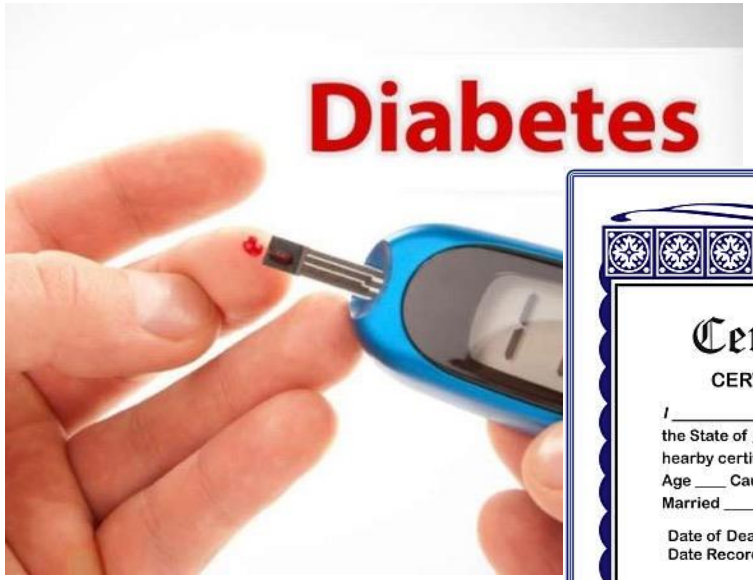
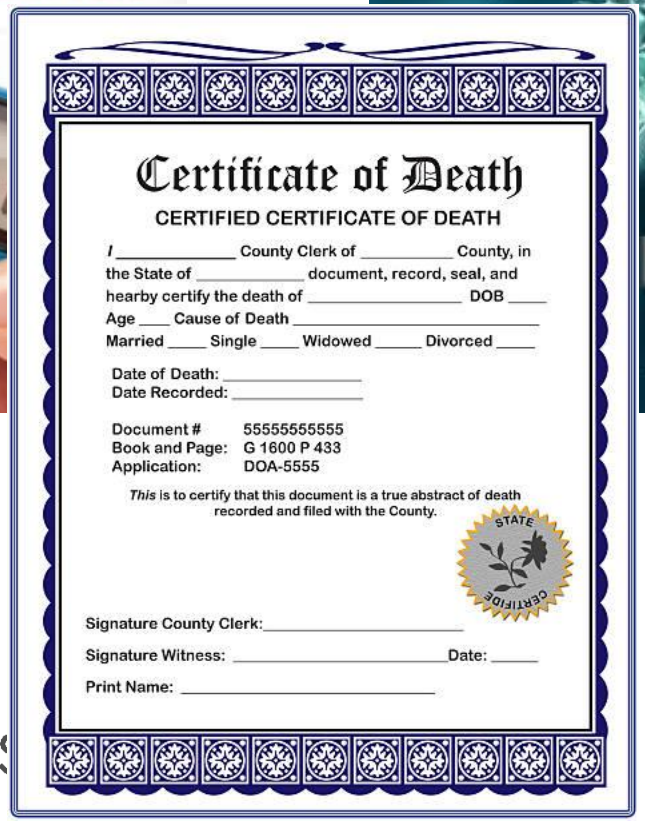
Flu snapshot

- Anti-virals (oseltamivir, baloxavir)
- Vaccinaties (trivalent, quadrivalent, mrna?)
- Diagnostiek: PCR of direct antigen; serologie uitdagend
- Risicogroepen: 65+, diabetes, immuungecompromitteerd

American Journal of Public Health in 1999 Valdez et al.





3x

Orzeck et al 2007
Muller et al 2005
Goeijenbier et al 2010

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4x

Allard et al 2010
Gomez et al 2021

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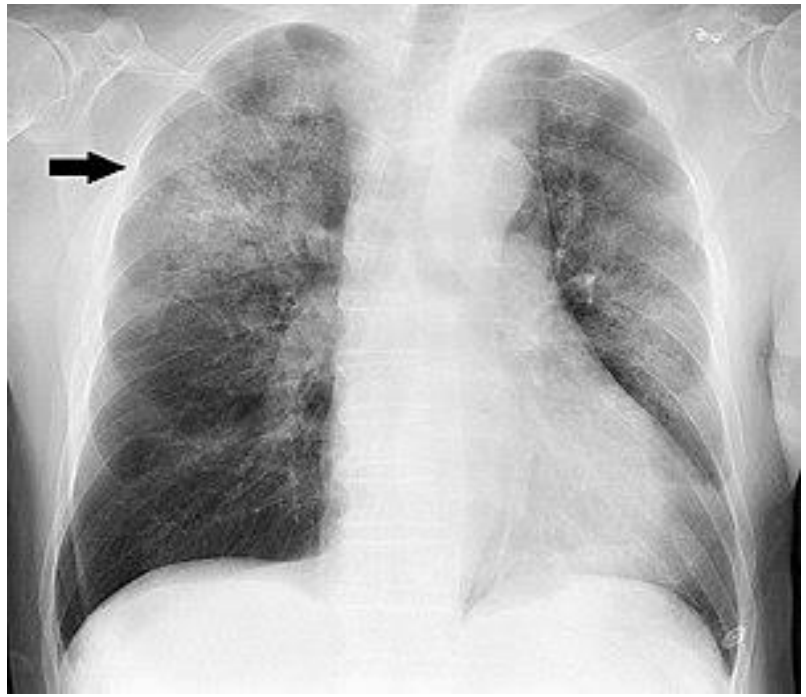

2x

Koziel et al 1995
Joshie et al 1999
Gupta et al 2007

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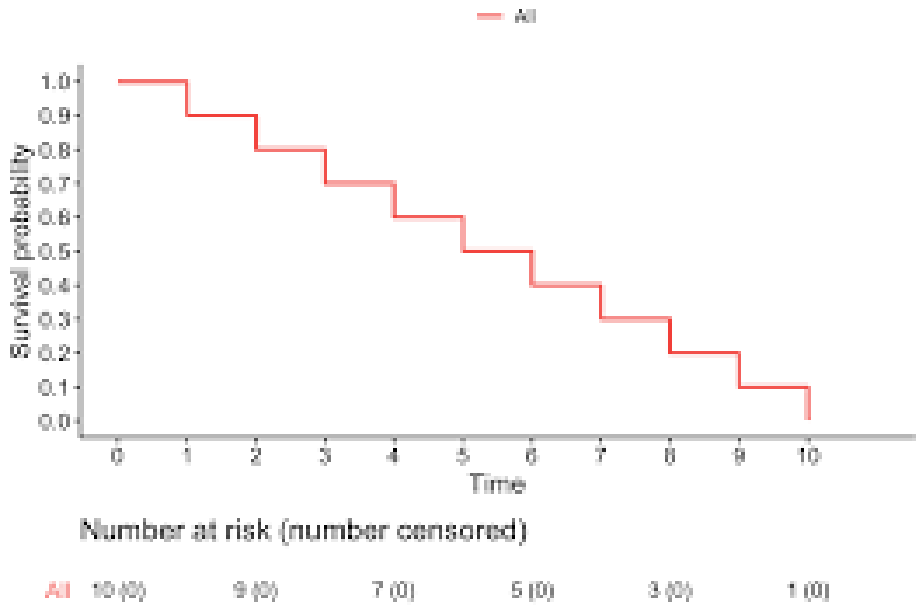
2x



Valdez et al 2009
Gomez et al 2021
Mertz et al 2013

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- Hazard ratios for death reached 1.9
- Tuberculosis tends to be more seve mellitus and especially in those wit
- The risk of developing tuberculosis complications or a higher Diabetes
- Although less strongly documented bacteremia, especially upon *Strepto* pneumonia caused by gram- negati
- Many studies did not distinguish be
- Biggest potential bias often are oth

Infections in Diabetes Mellitus and Hyperglycemia

Smita Gupta, MD[a,*], Janak Koirala, MD, MPH[b], Romesh Khardori, MD, PhD[a], Nancy Khardori, MD, PhD[b]

[a]*Division of Endocrinology, Metabolism and Molecular Medicine, Southern Illinois University School of Medicine, 701 North First Street, D-405B, PO Box 19636, Springfield, IL 62794–9636, USA*

[b]*Division of Infectious Diseases, Department of Internal Medicine, Southern Illinois University School of Medicine, 701 North First Street, D-405B, PO Box 19636, Springfield, IL 62794–9636, USA*

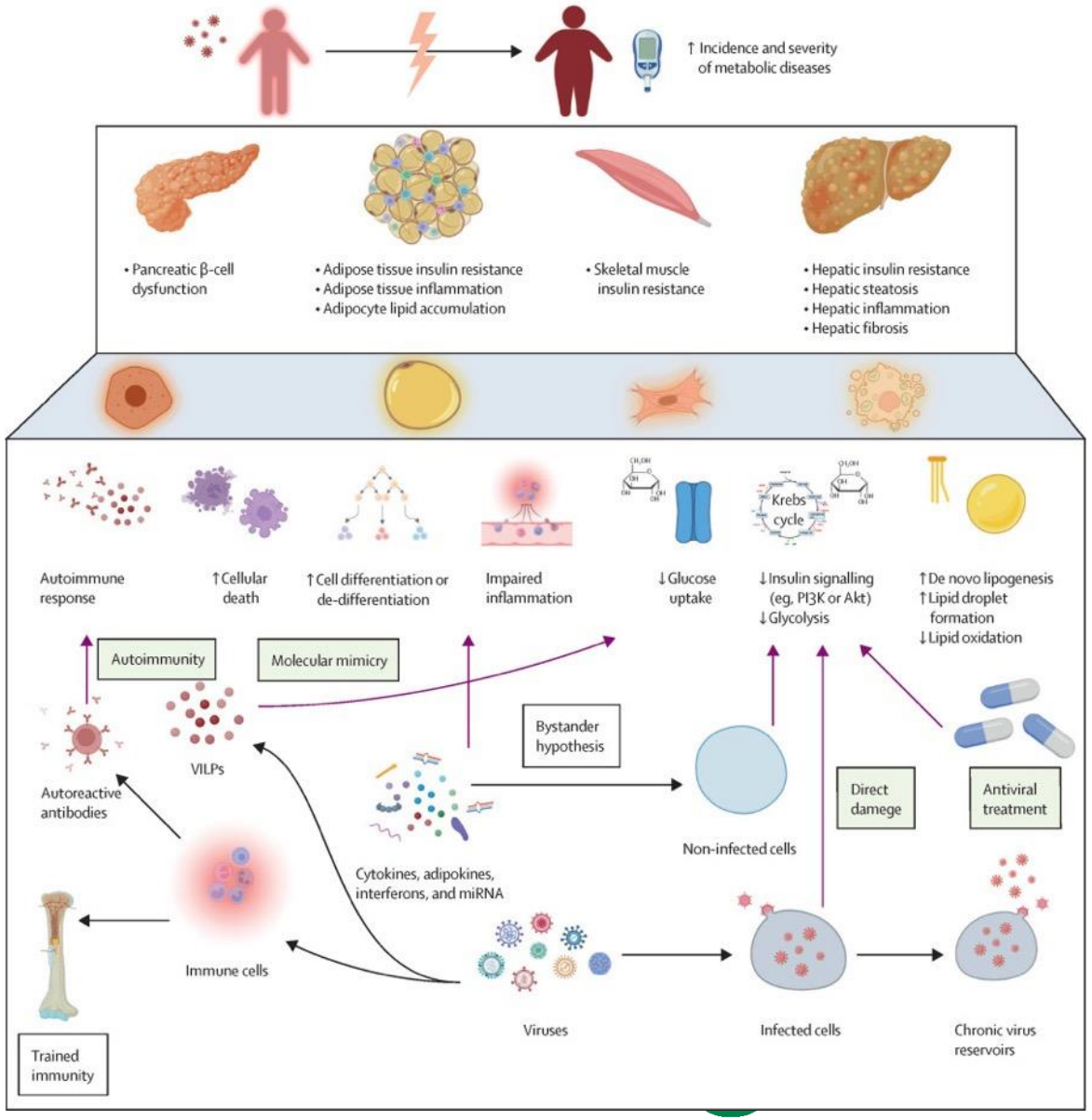
Tropical Medicine and International Health doi:10.1111/tmi.12206

VOLUME 18 NO 12 PP 1510–1519 DECEMBER 2013

Obesity, diabetes and pneumonia: the menacing interface of non-communicable and infectious diseases

Susan P. Fisher-Hoch, Christine E. Mathews and Joseph B. McCormick

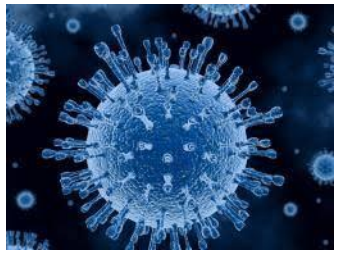
Division of Epidemiology, Human Genetics and Environmental Sciences, University of Texas School of Public Health, Brownsville, TX, USA



A MUST READ

Perakakis et al 2023
Mechanisms and clinical relevance of the bidirectional relationship of viral infections with metabolic diseases

Lancet Diabetes & Endocrinology



Infection

Obesity

IFNγ →  → **↑↑↑Glucose** ← 

Muscle IR **Liver IR**

Pancreas

Insufficient Hyperinsulinemia

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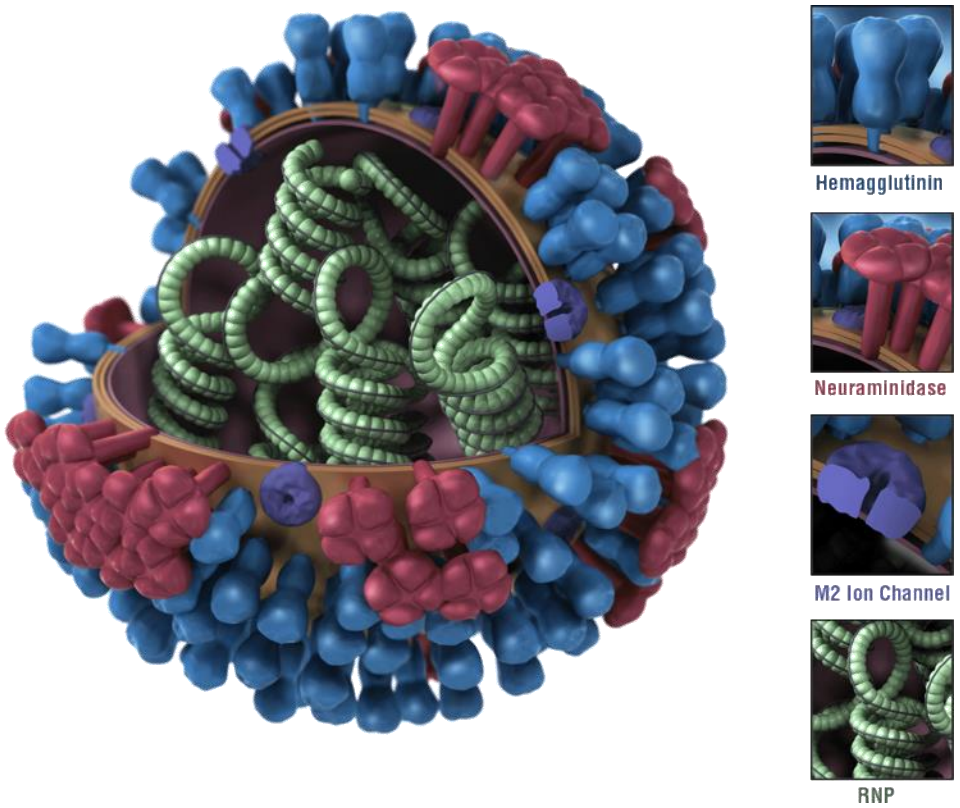
Euglycemia

Loss of glycemic control (DM2)

Šestan *Immunity* 2018

Wensveen lab 2023



Glycemic Variability in Diabetes Increases the Severity of Ifluenza in vitro and in vivo (Marshall et al Mbio 2020 and Hulme et al. 2022 and 2024)

Hba1C directly correlated to influenza severity and hampers the CD8 T cell response (Hulme et al 2024)

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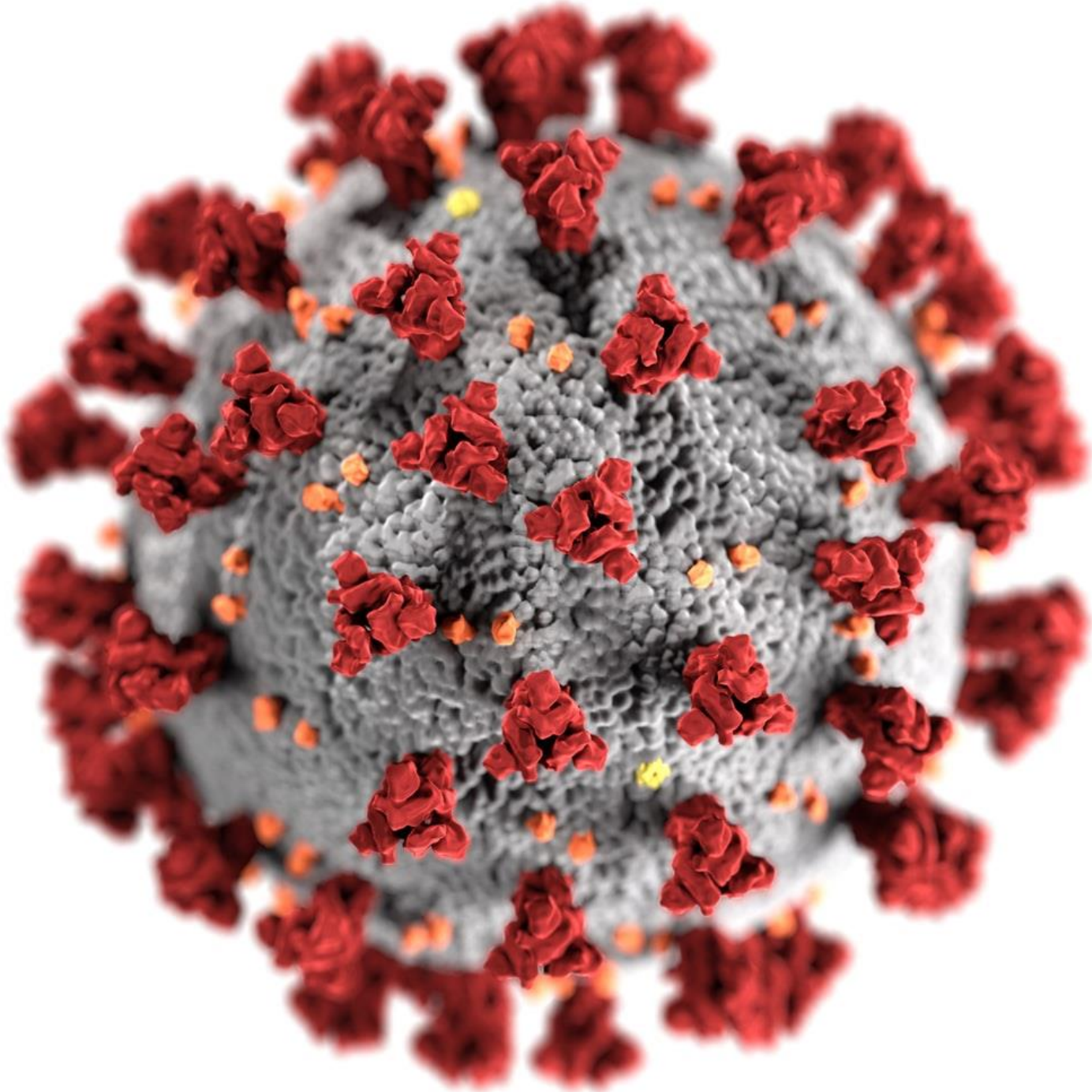
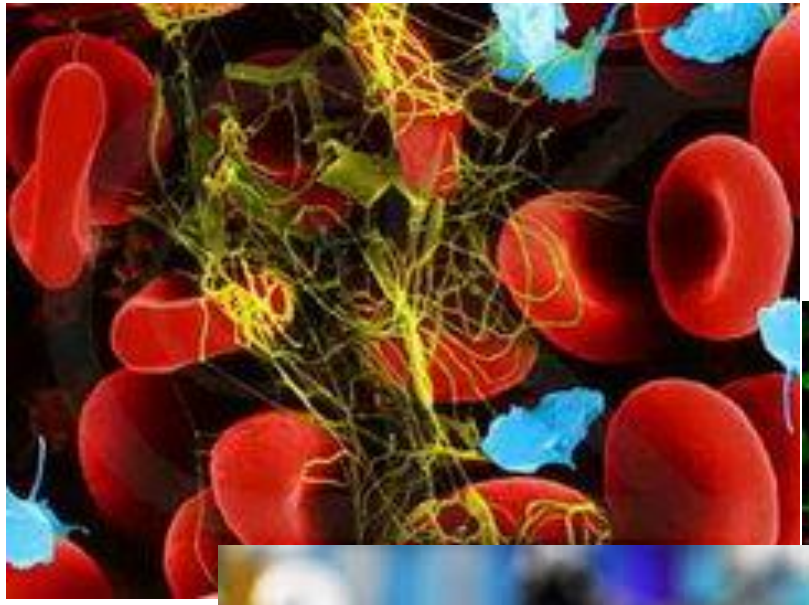
- Flu vaccination given during STEMI presenation results in better survival *(Frobert et al 2021 Circulation)*
- Known up to 3 fold increased risk of MI in weeks following respiratory infection. Strongest during flu season.
  (Warren-Gash et al. 2012 JID)
- Consistent association between MI & flu and MI and RSV
  (Kwong et al 2018 NEJM; Foster et al.2013 Epid. Infect; Barnes BMJ 2015)
- In patients with diabetes, influenza vaccination was associated with a reduced risk of all-cause death, cardiovascular death, and death from AMI or stroke. *(Modin et al Diabetes Care 2020)*

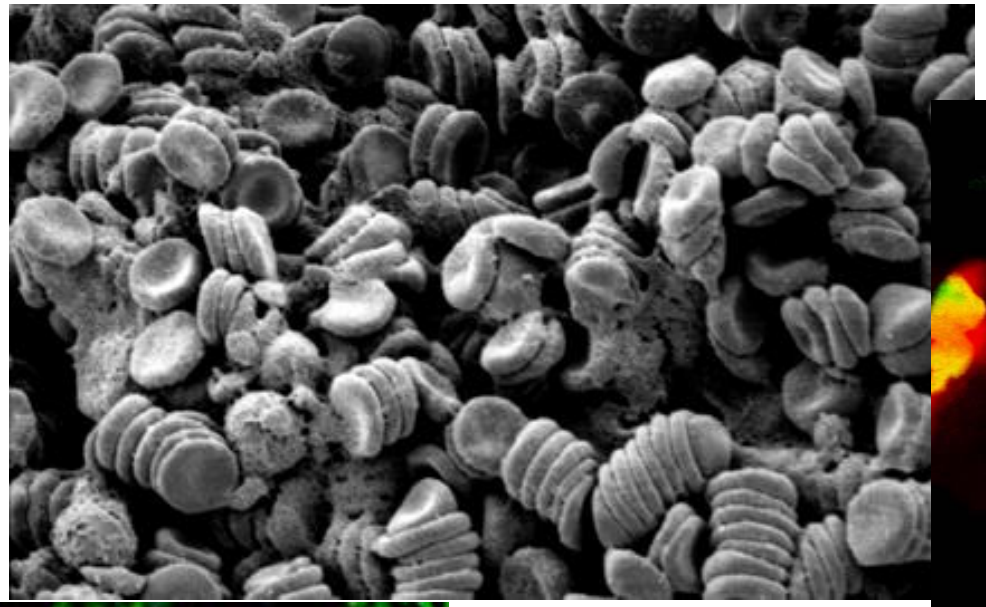
Influenza vaccination			
FLUVACS	2004	300 vaccination	0.59 (0.34-0.86)
FLUCAD	2008	650 vaccinations	0.55 (0.29-0.99)

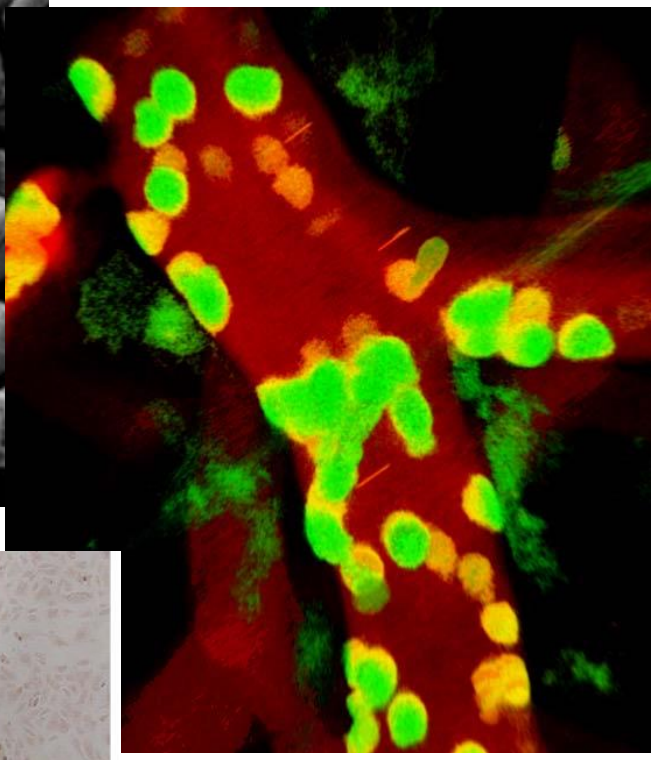
Meta-analysis of 5 trials (n = 292 383 OR 0.574-0.931 vaccin/ no vaccin
(Loomba et al. 2012 JCPT)

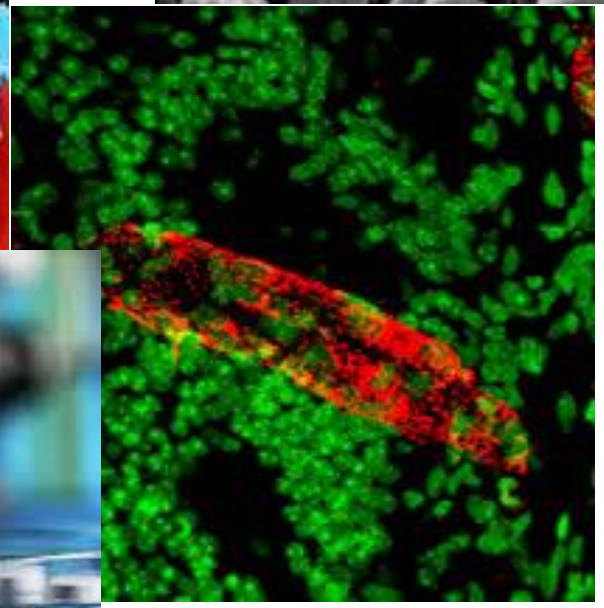


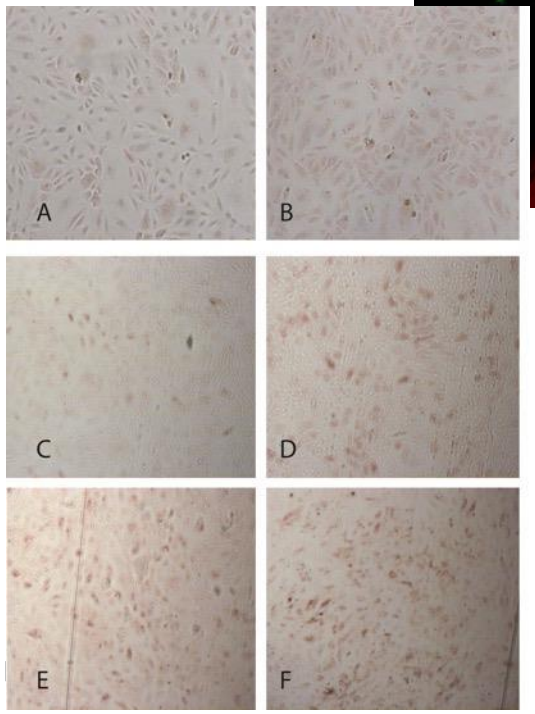
Waarom?











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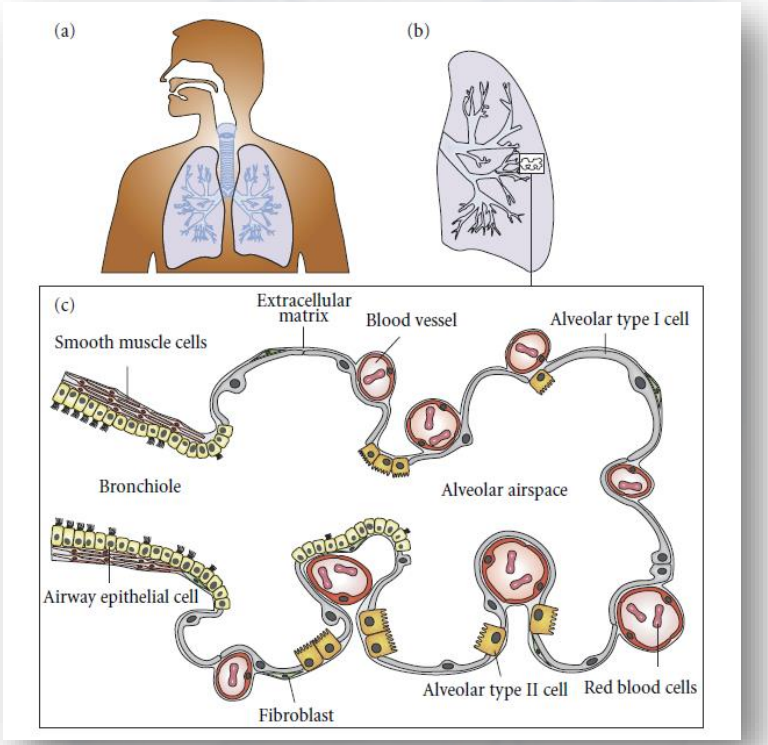
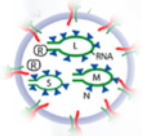
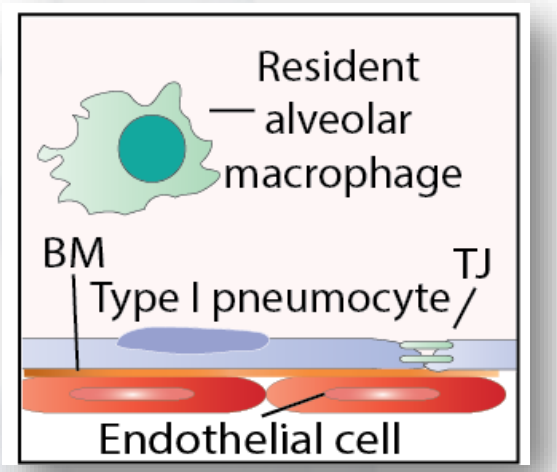
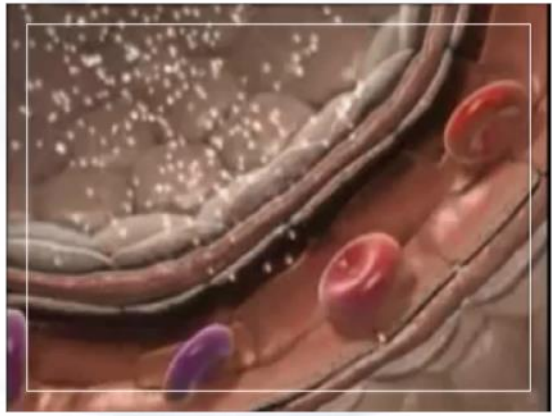
- **Tropisme**
- **Receptor**
- **Immuunrespons & virale load**

PULMONARY EPITHELIAL-ENDOTHELIAL BARRIER









Erasmus MC
Universitair Medisch Centrum Rotterdam

Short & Goeijenbier 2016

104 ♂

4 ferrets/time point

Prothrombin time

Activated partial thromboplastin time

vWf activity

D-dimer

Thrombin-Antithrombin complexes

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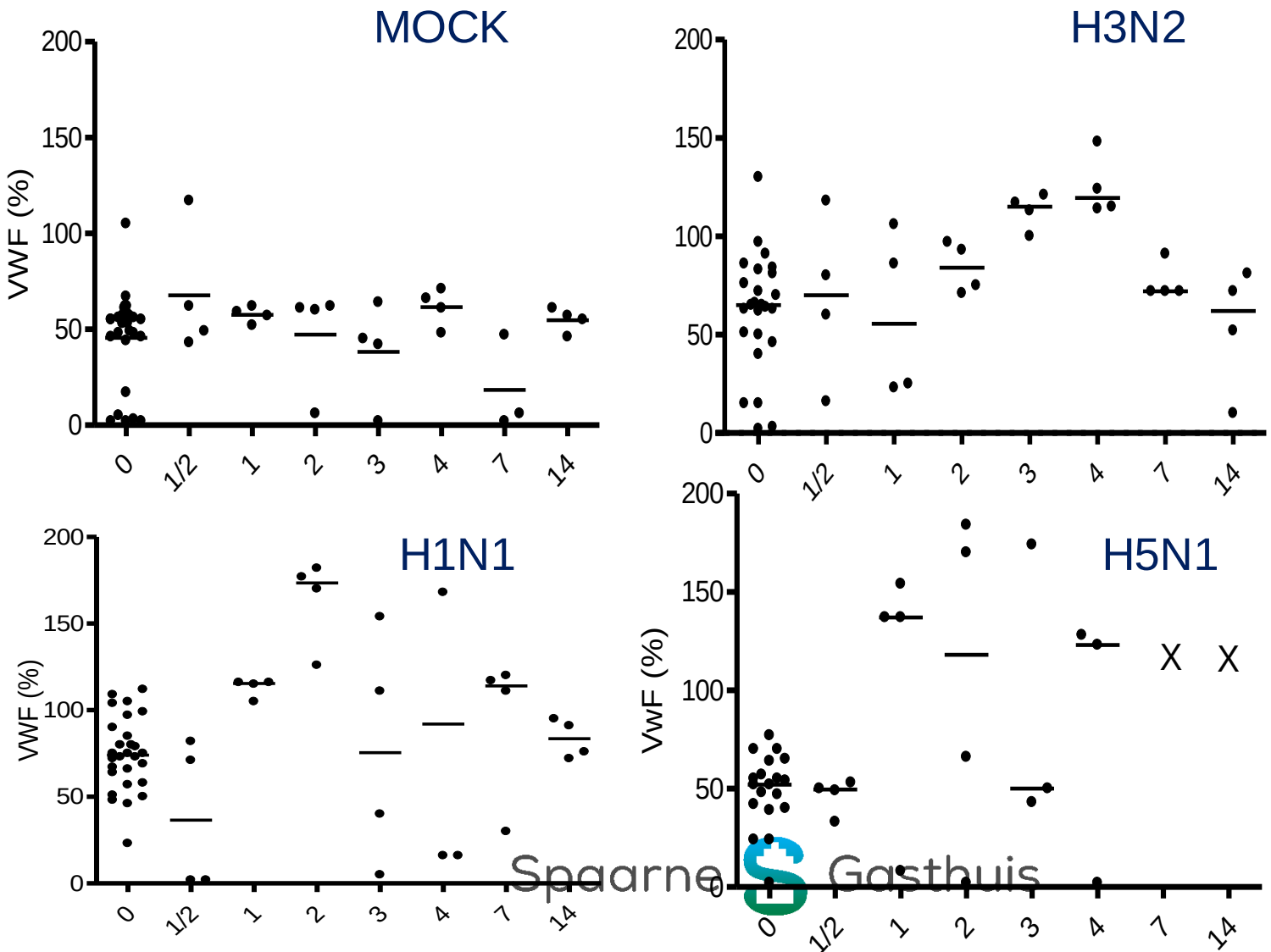
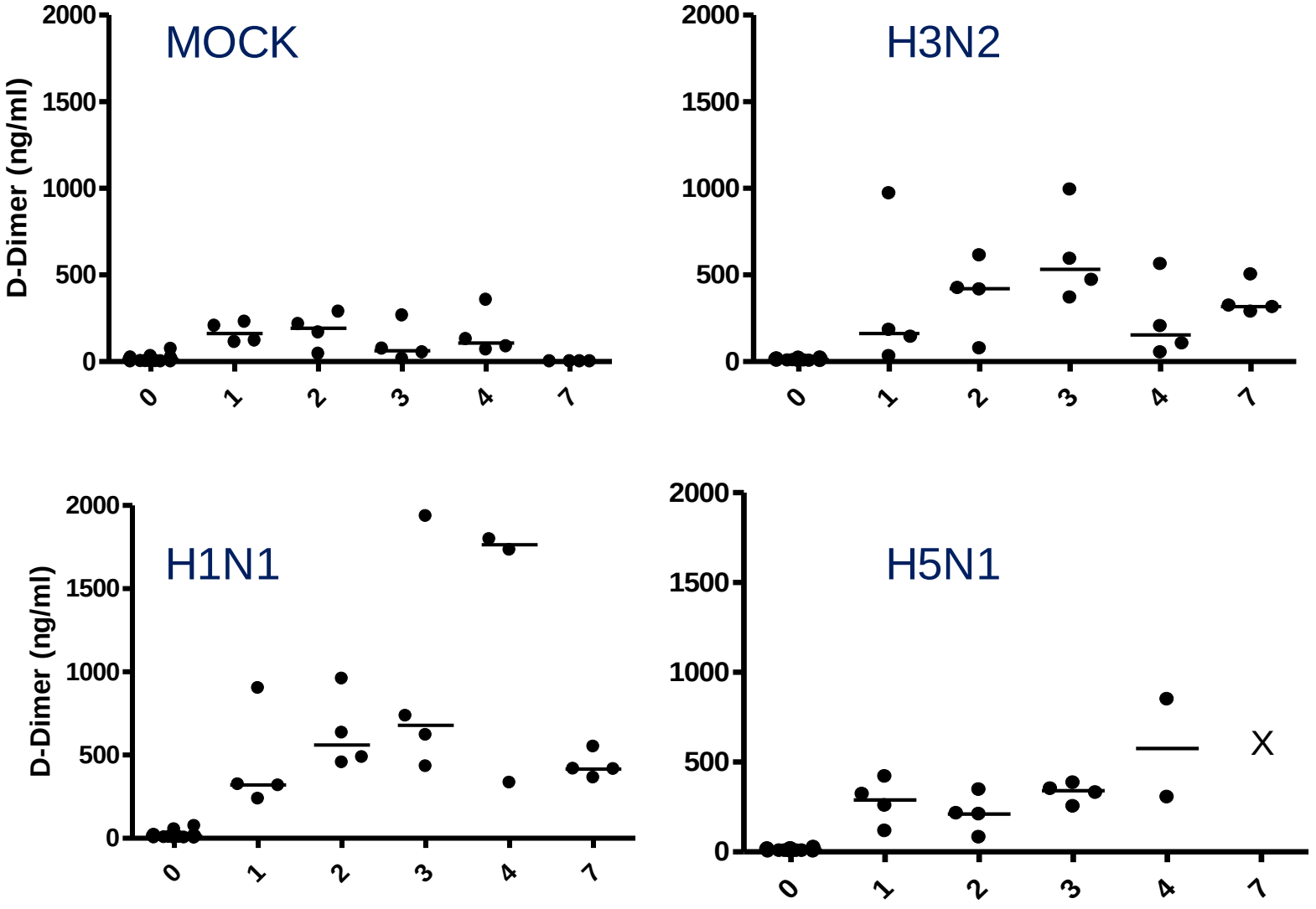
Von Willebrand factor activity



D-Dimer



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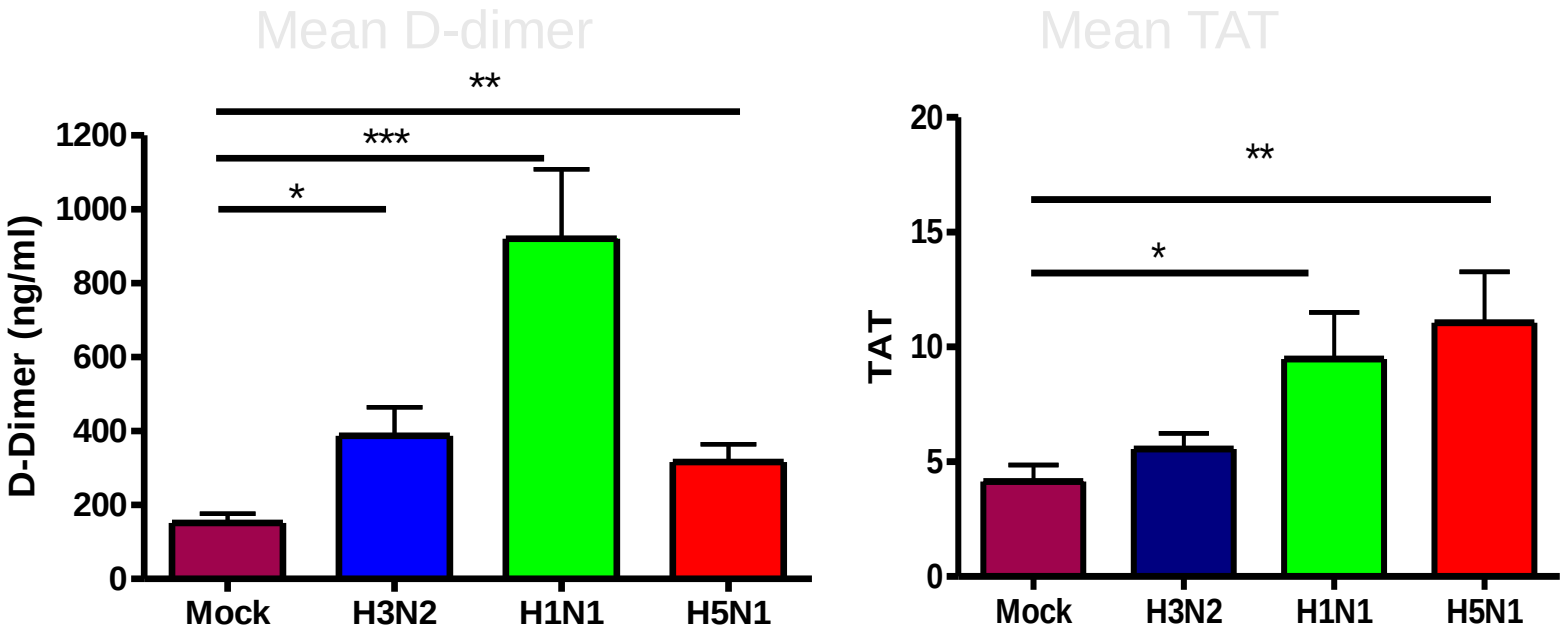
D-dimer & Thrombin-antithrombin complexes



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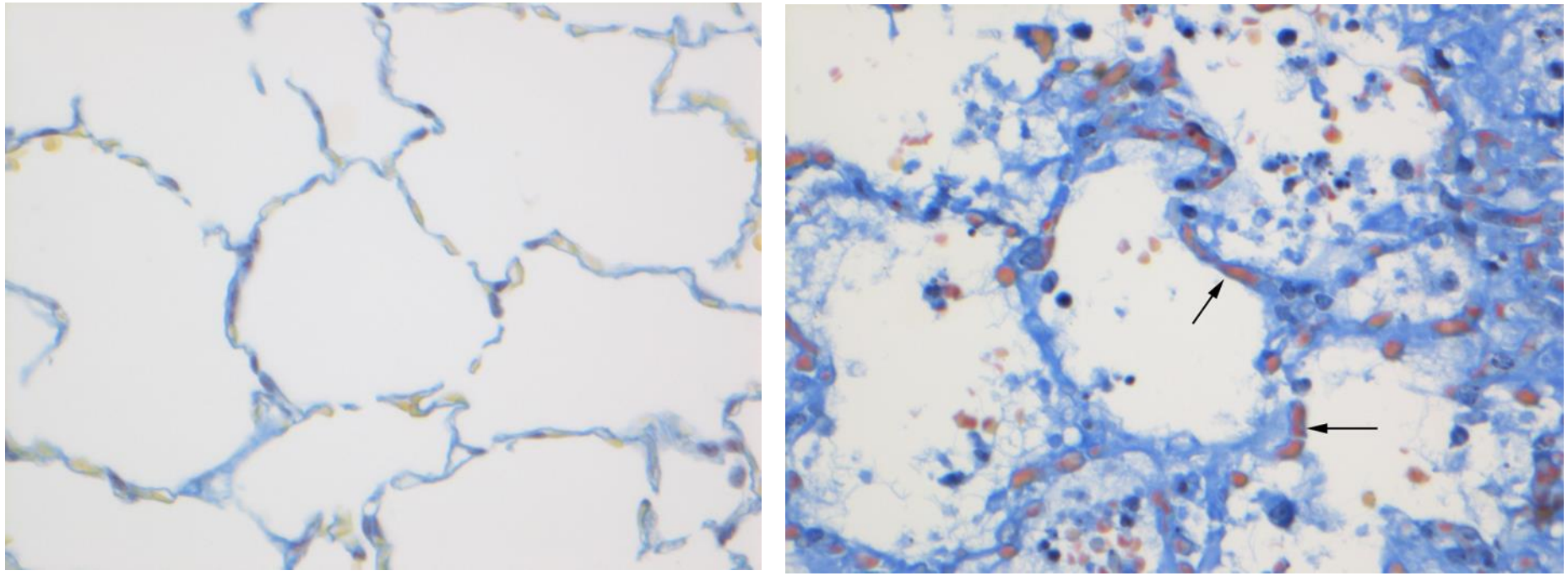

Lendrum staining for fibrin depsosits

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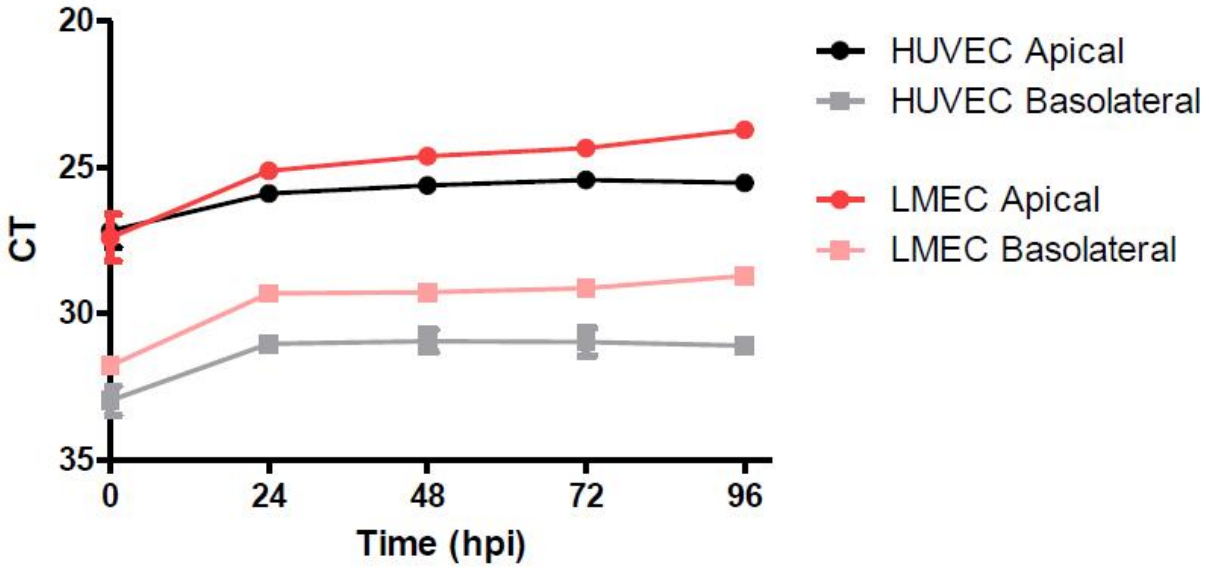
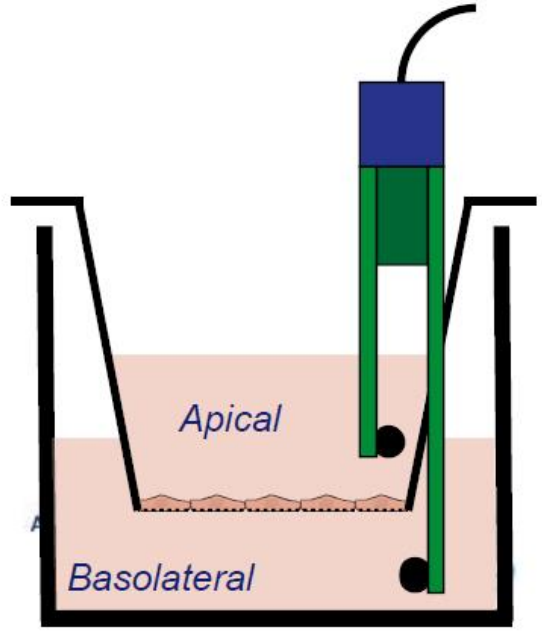
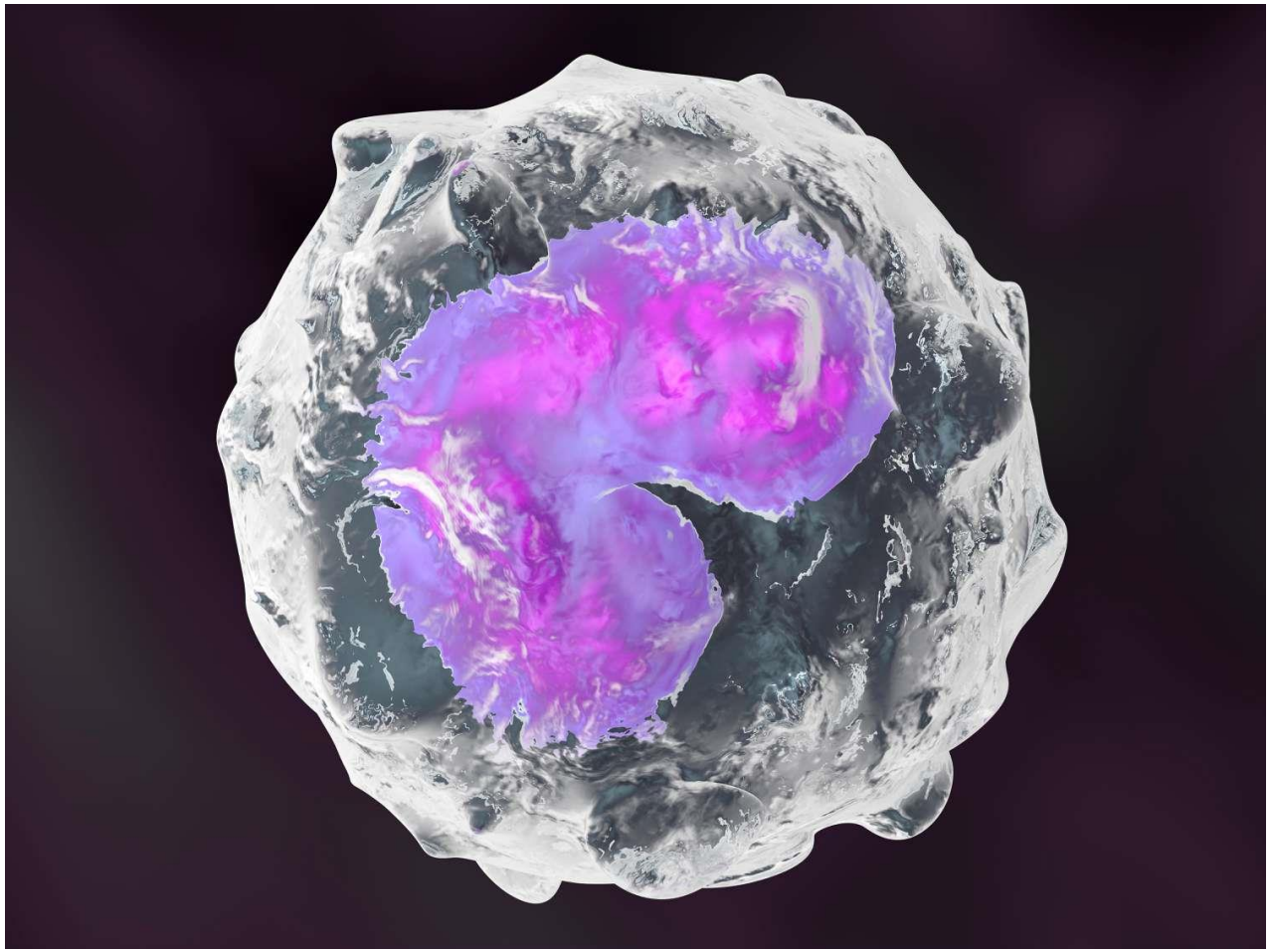
To identify the molecular mechanisms of SARS-CoV-2 induced thrombosis: *in vitro*

- Can SARS-CoV-2 infect endothelial cells and thereby have a direct effect on function?

SARS-CoV-2 infection in endothelial cells







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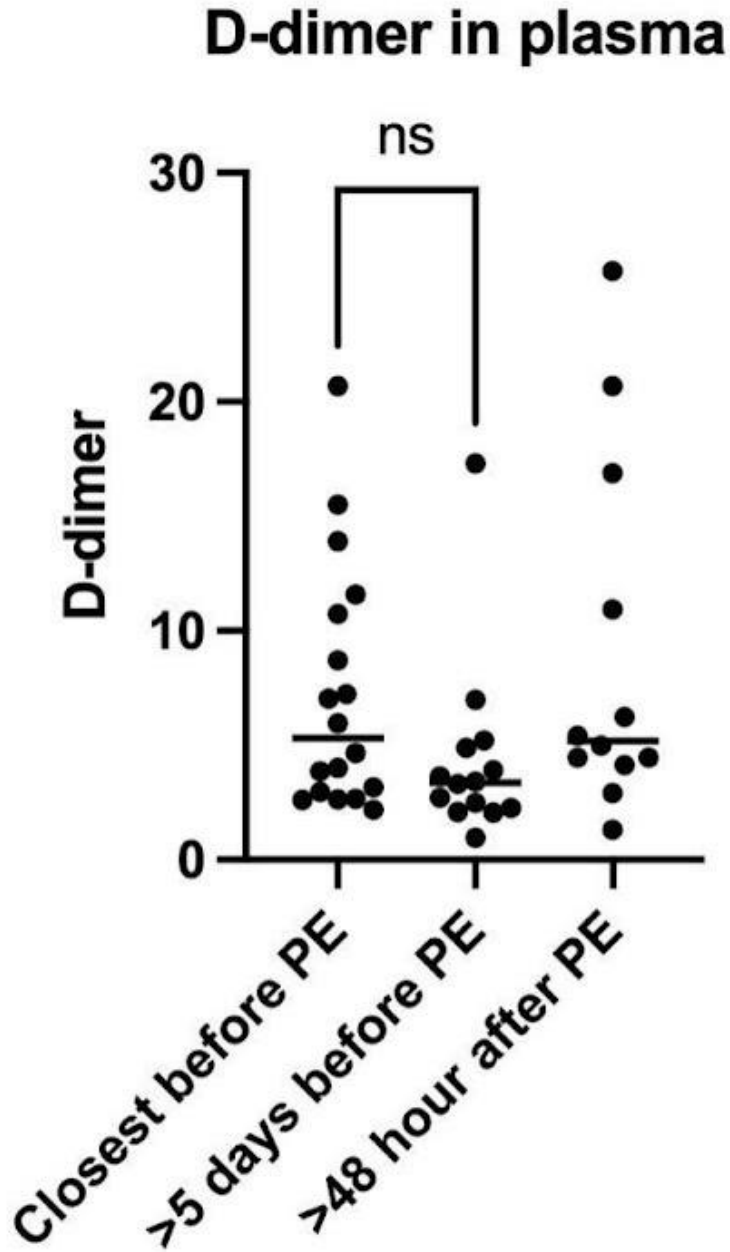
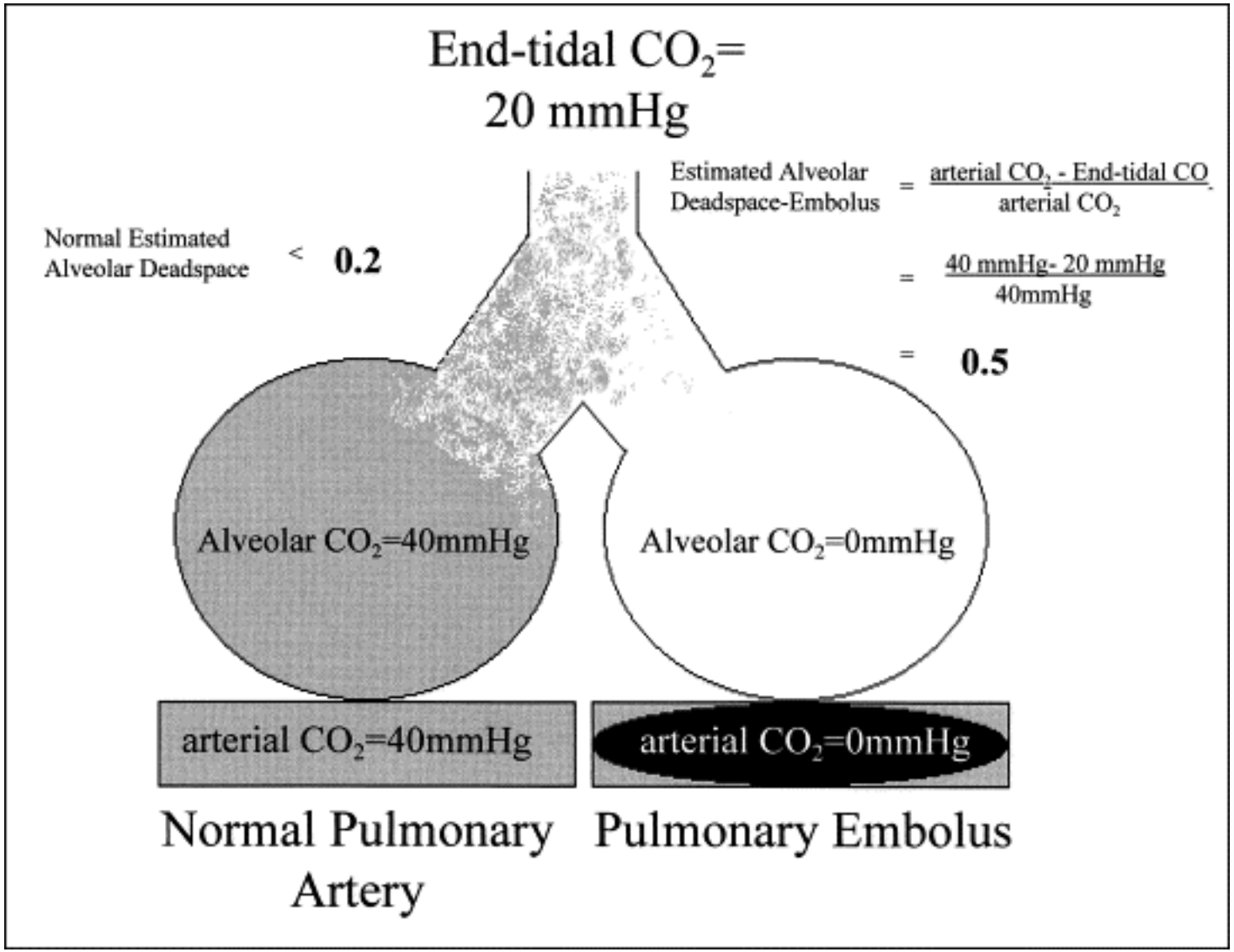
- 20 patiënten met CTa bewezen longembolie
- 15 patiënten zonder Cta bewezen longembolie
- Geselecteerde gezonde controles
- IC cohort eerste en tweede COVID “ golf”
- D-dimeer beschikbaar en beademingsinstellingen
- TGT op PBMC’s met name geïnteresseerd in monocyten


D-dimer in plasma
ns
30
20
10
0
D-dimer
Closest before PE
>5 days before PE
>48 hour after PE



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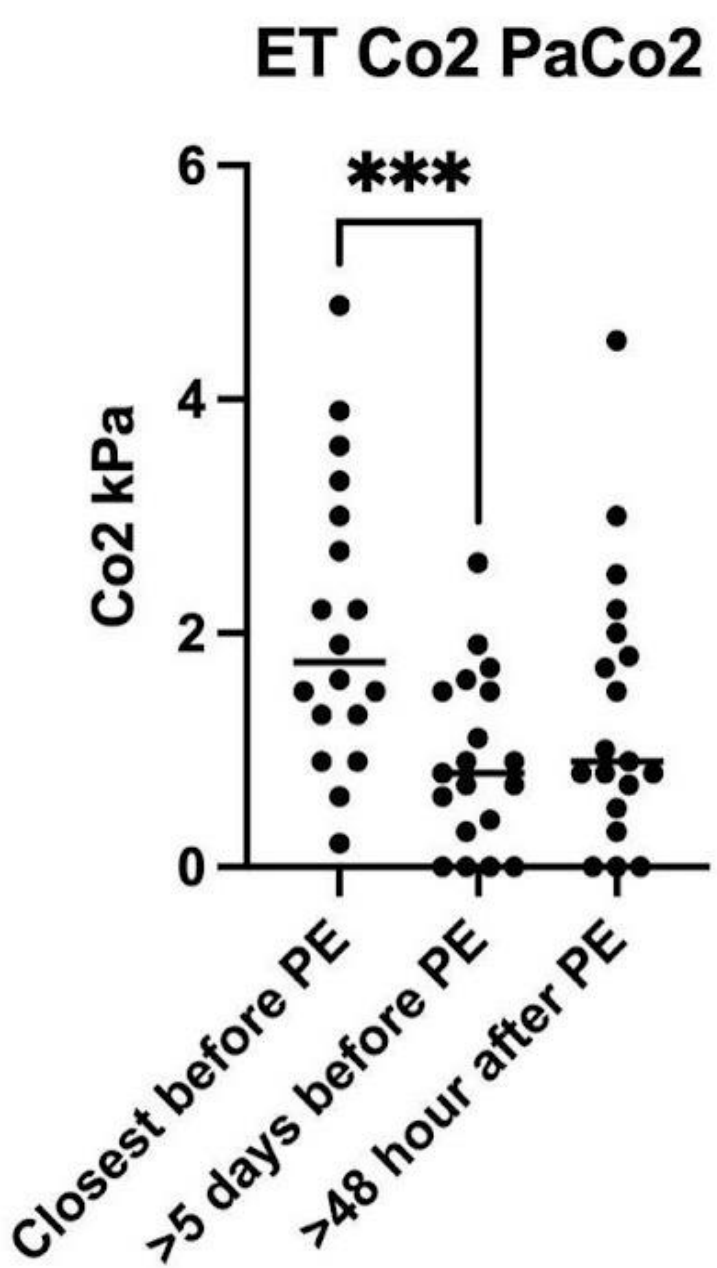

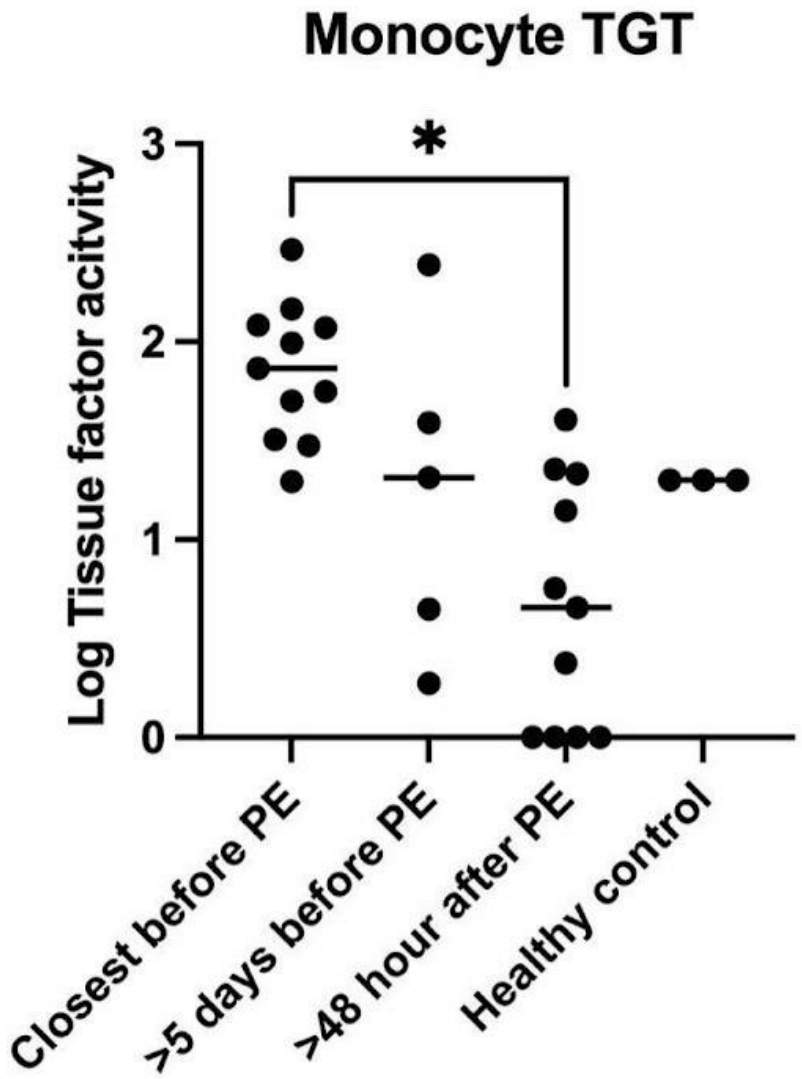

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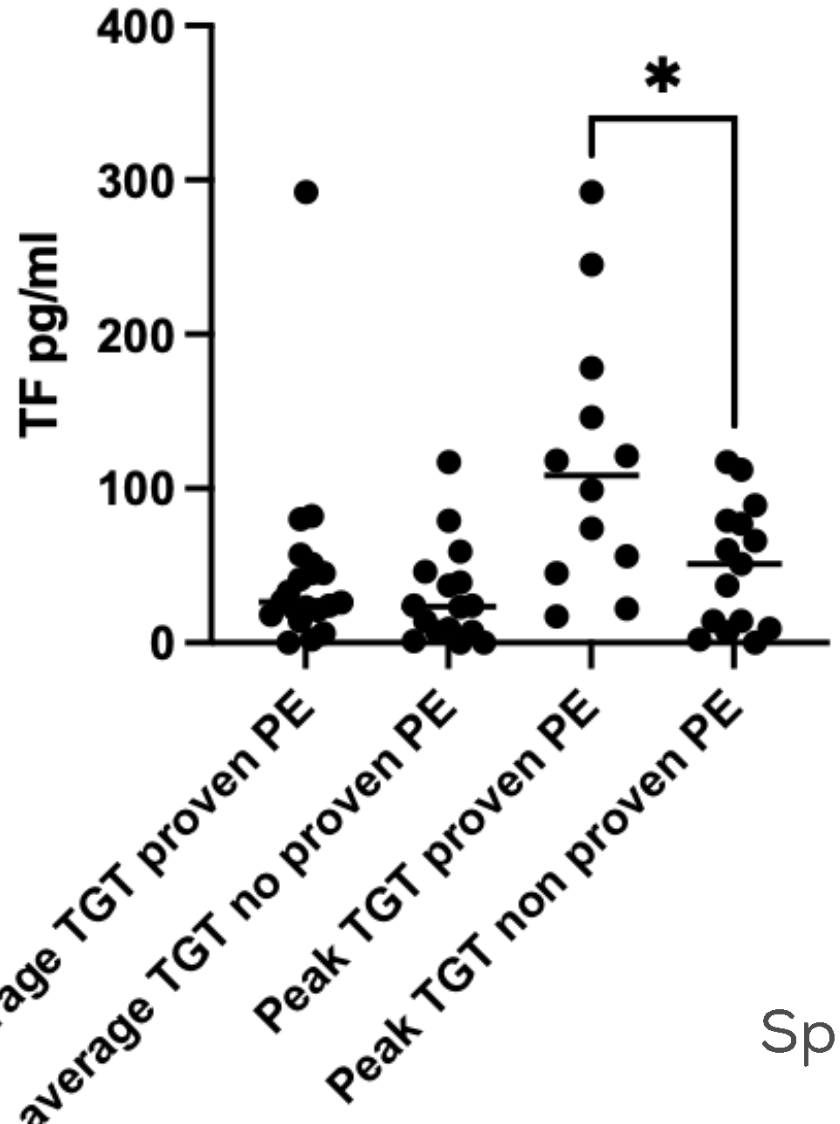
Groep van 15 patiënten zonder positieve CTa



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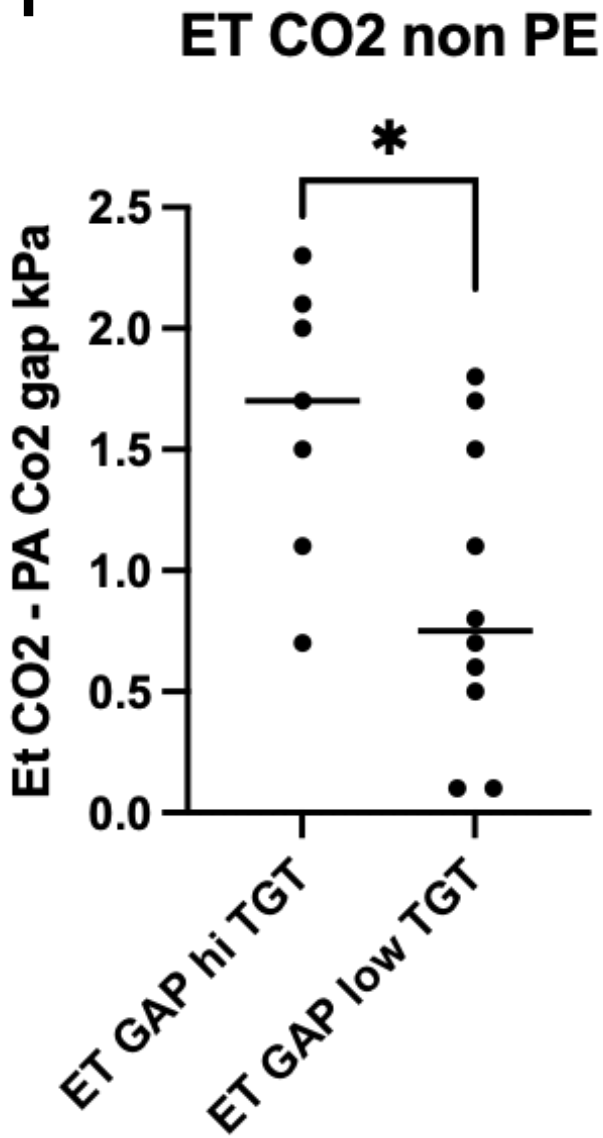
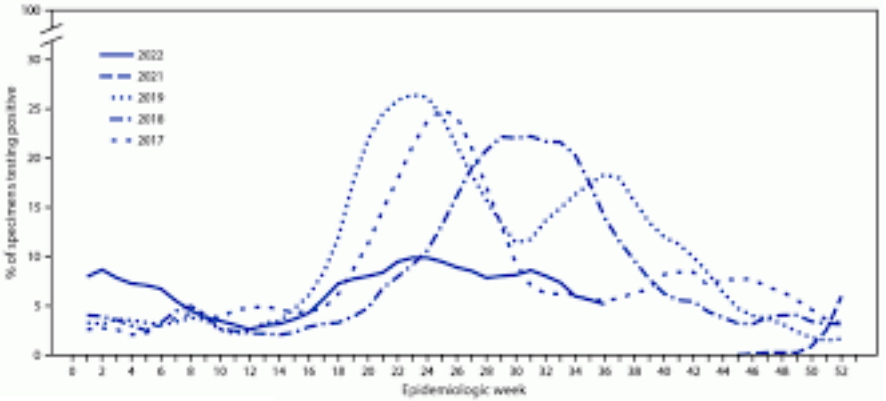
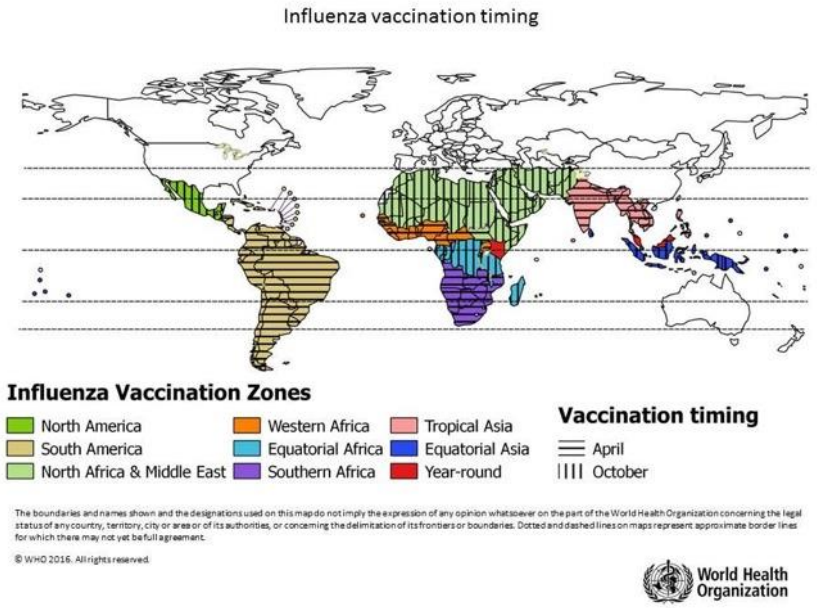


Toch meer thrombine dan HC maar geen LE?

- Niet meer gescand
- 1 scan negatief = negatief?
- Thromboflebitis
- Bekende maligniteit
- Behandeling met DOAC obv AF
- Hoe goed is een CTa in het aantonen van locale longtrombose itt embolie?

Uitdagingen in preventie





- inactivated influenza vaccine [IIV], recombinant influenza vaccine [RIV], or live attenuated influenza vaccine (LAIV)
- No preference is expressed for any influenza vaccine over another
- Both trivalent (three-component) and quadrivalent (four-component)

Antivirals

- Oseltamivir, Zanamivir and Peramivir
- Pre- and post-exposure prophylaxis

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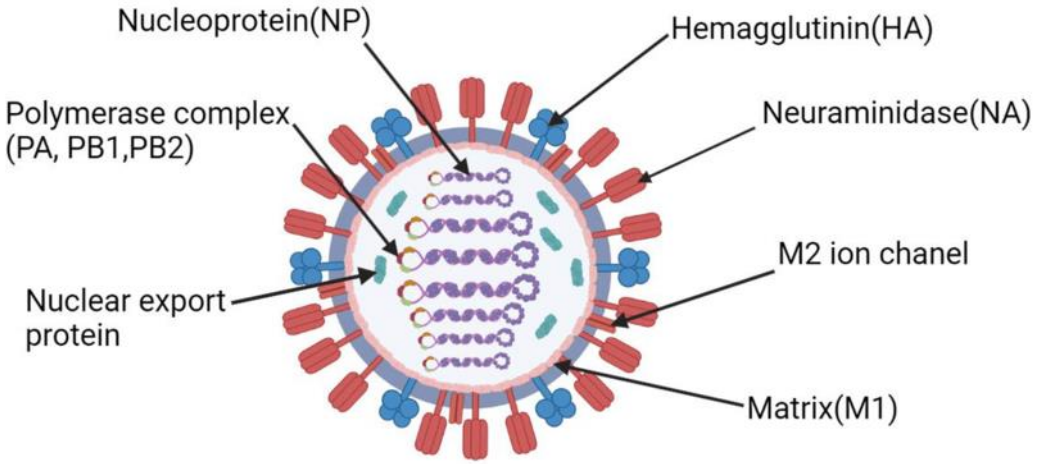
- Accelerates clinical symptom alleviation, reduces risk of lower respiratory tract complications, and admission to hospital

- Especially indicated for severe cases or those **with co morbidities**

Future

- MRNA platform
- Co-administration (COVID-FLU-RSV) or combined vaccine
- Role in prevention of DM complications or DM itself



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