Imperial College London

ESWI Webinar: Immunisation & Treatment, 30th Nov 2023

Influenza in the time of COVID

What do they share, and how to treat them

Peter Openshaw

National Heart and Lung Institute, Imperial College London

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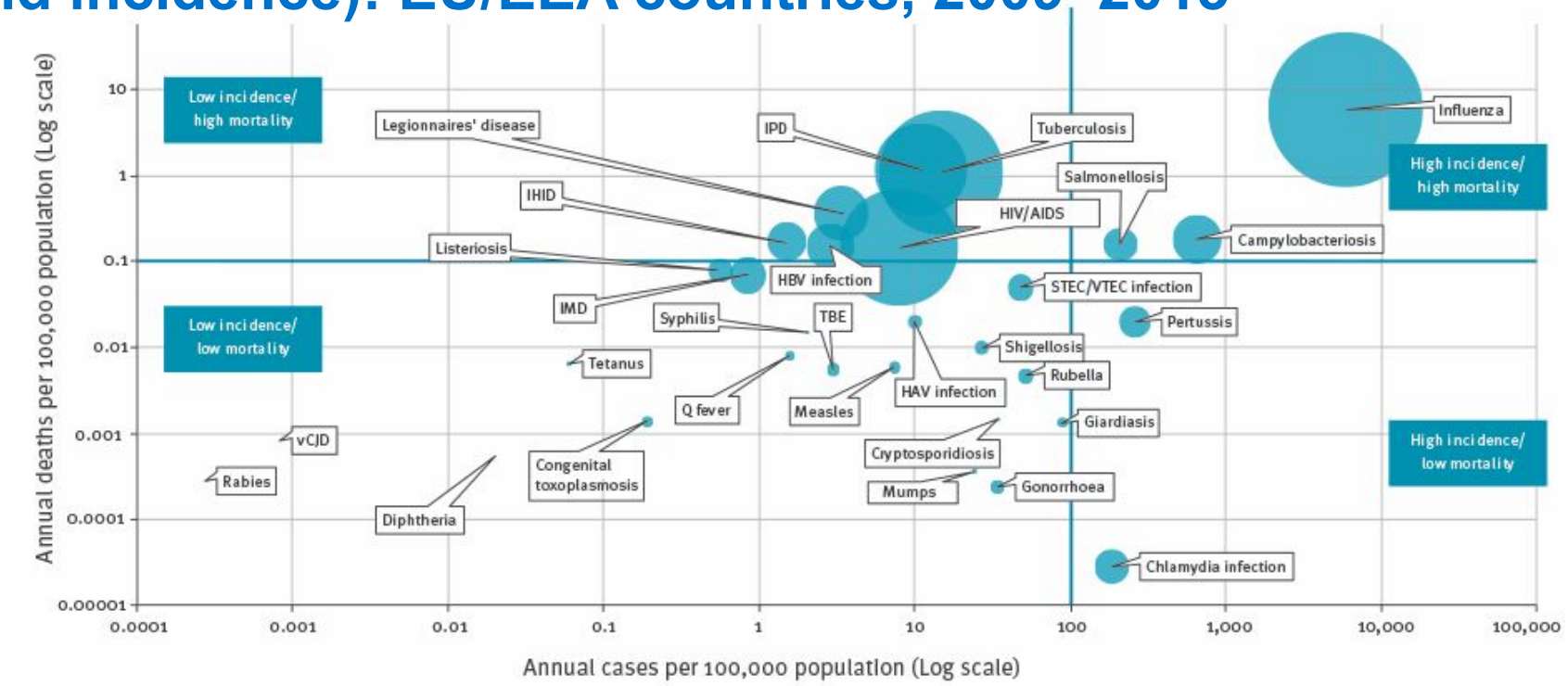
Burden of selected infectious diseases (mortality and incidence): EU/EEA countries, 2009–2013



The diameter of the bubble reflects the number of DALYs per 100,000 population per year

DALY, disability-adjusted life year; EEA, European Economic Area; EU, European Union; HAV, hepatitis A virus; HBV, hepatitis B virus; IHID, invasive Haemophilus influenzae disease; IMD, invasive meningococcal disease; IPD, invasive pneumococcal disease; STEC, Shiga toxin-producing *Escherichia* coli; TBE, tick-borne encephalitis; vCJD, variant Creutzfeldt-Jakob disease; VTEC, verocytotoxin-producing *Escherichia* coli

Cassini A, et al. Euro Surveill 2018;23:17-00454

nature immunology

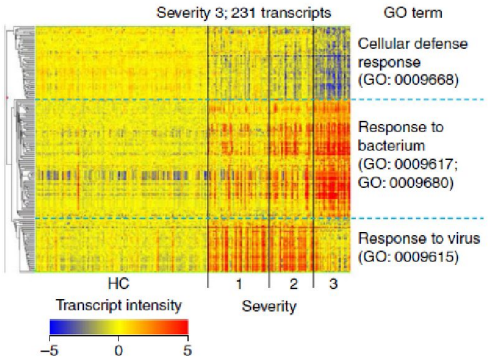
RESOURCE

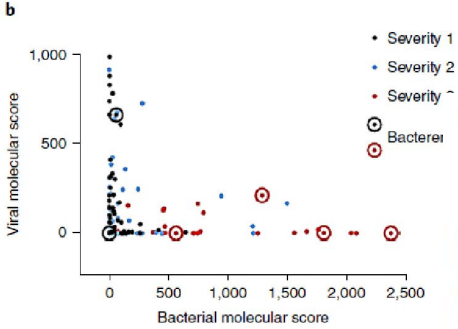
https://doi.org/10.1038/s41590-018-0111-5

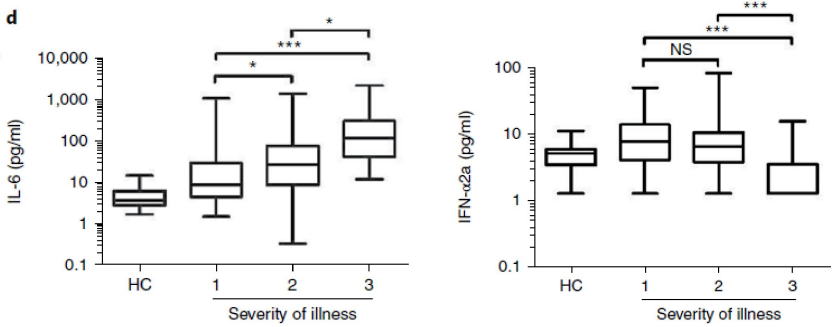
Nature Immunology 16, 625-35 PMC5985949

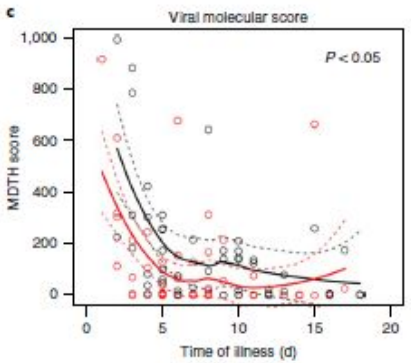
Progression of whole-blood transcriptional signatures from interferon-induced to neutrophil-associated patterns in severe influenza

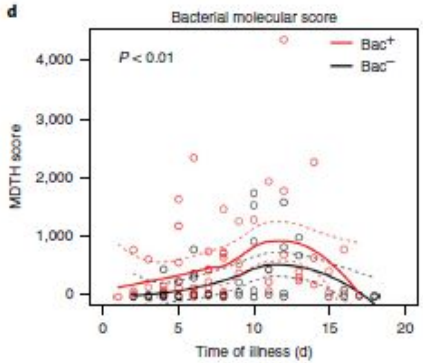
Jake Dunning[1,8], Simon Blankley[2], Long T. Hoang[1], Mike Cox[3], Christine M. Graham[2], Philip L. James[3], Chloe I. Bloom[2], Damien Chaussabel[4], Jacques Banchereau[5], Stephen J. Brett[6], MOSAIC Investigators[7], Miriam F. Moffatt[3], Anne O'Garra[2*] and Peter J. M. Openshaw[1*]











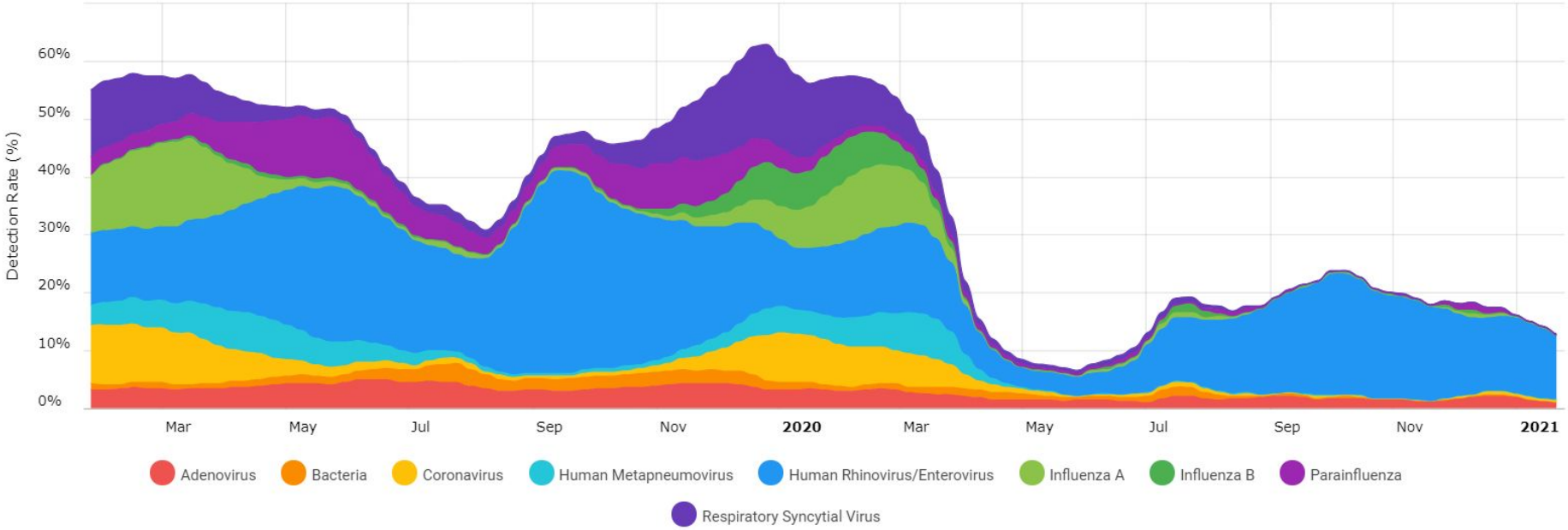
https://doi.org/10.1038/s41590-018-0111-5 (2018).

BIOFIRE® Syndromic Trends

Respiratory Pathogen Trends

SyndromicTrends.com is a website displaying trends in the U.S. for various infectious pathogens related to syndromic diseases such as respiratory and gastrointestinal illnesses. SyndromicTrends.com's data comes from laboratories using BioFire's clinical diagnostic systems for detecting infectious disease pathogens and that have joined BioFire's data aggregating program, BioFire® Syndromic Trends (Trend). BioFire® FilmArray® Systems detect the presence of pathogen-specific nucleic acid in patient samples.

CHART



Respiratory pathogen trends. Available from: https://syndromictrends.com/. Accessed March 2022.

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Pathogen interactions in pathogenesis

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When we sneeze, does the immune system catch a cold?

BMJ LONDON, SATURDAY 19 OCTOBER 1991

Viral infections may have important effects on the body's response to bacteria and other viruses

The presence of pathogens is often insufficient alone to produce illness. Many healthy people carry pathogenic bacteria (such as *Neisseria meningitidis* or *Streptococcus pneumoniae*) in the upper respiratory tract yet only a few develop invasive disease. Among the factors that convert carriage to disease is coinfection with common cold viruses. This interaction was recently studied in Chad, where about one in three children were carriers of *N meningitidis*, probably imported from Mecca by returning pilgrims. An epidemic of meningococcal meningitis occurred the year after the pilgrimage, and at its peak 141 patients were admitted to one hospital in a single day. Some 4500 cases of meningococcal disease occurred in the city of N'Djamena—an attack rate of 0·9%. Careful attempts were made to isolate respiratory pathogens from 62 patients with meningococcal meningitis and from 62 matched controls. Positive isolations of *Mycoplasma* spp, adenovirus, respiratory syncytial virus, or parainfluenza viruses were made in 47% of the patients with meningitis and 11% of the control group, giving a matched odds ratio of 23 (95% confidence interval 3·1 to 170).[1]

"infections do not occur in isolation and need to be viewed in the context of the previous and concurrent experience of the immune system"

P J M OPENSHAW

Wellcome Trust Senior Research Fellow in Clinical Sciences,
Respiratory Unit,
St Mary's Hospital Medical School,
London W2 1PG

Openshaw PJ. *BMJ*. 1991;19;303(6808):935–6.

Interactions between influenza and bacterial respiratory pathogens: implications for pandemic preparedness

Lancet Infect Dis 2006; 6: 303–12

John F Brundage

In 1919, Abrahams and colleagues[32] reviewed their extensive experience during the 1918–19 influenza pandemic. They reported that *Streptococcus pyogenes longus* (36%), pneumococcus (29%), and *B influenzae* (25%) were recovered relatively frequently from cultures (n=28) of lung tissue of fatal "influenzal pneumonia"

Expeditionary Forces in Europe documented a sharp rise in reports of cerebrospinal meningitis approximately 1 week after sharp increases in reports of influenza and pneumonia. The bulletin noted that "it has been a usual observation that when infections of the upper respiratory tract prevail, the incidence of meningitis in the community increases soon after and this rule prevails at present".[67]

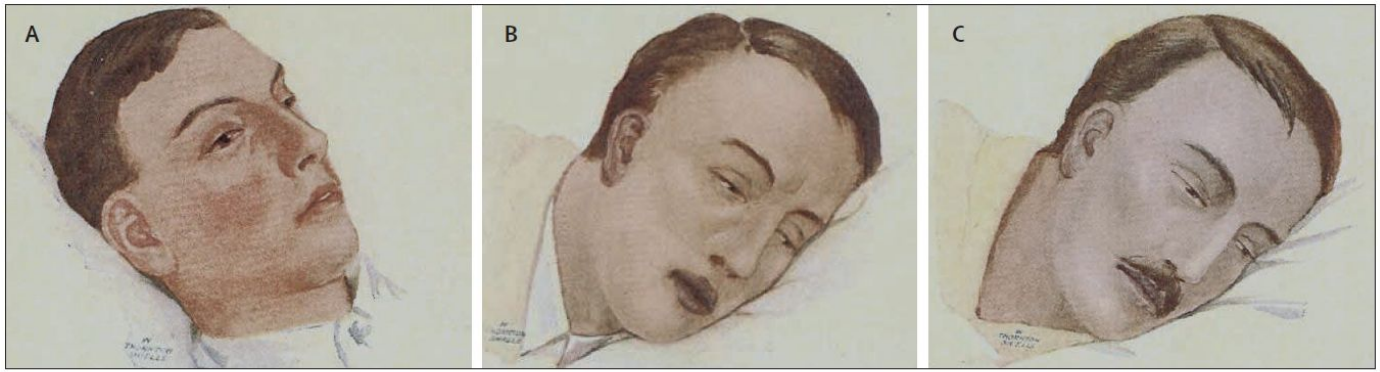


Figure 2: **Faces of "influenzo-pneumonic septicaemia"**
(A) "An early case in which the facial colour is frankly red, and the patient might not appear ill were it not for the drooping of the upper eye-lids and a half-closed appearance to the eyes." (B) "Cyanosis in which the colour of the lips and ears arrests attention in contrast to the relative pallor of the face. The patient may yet live for twelve hours or more." (C) "The heliotrope cyanosis. The patient is not in physical distress, but the prognosis is almost hopeless." Reproduced from reference 32.

Coinfection with influenza is associated with worse outcomes in severe Covid-19

Maaike C Swets MD, Clark D Russell MBChB, Prof Ewen M Harrison PhD, Annemarie B Docherty PhD, Nazir Lone PhD, Michelle Girvan BSc, Hayley E Hardwick, ISARIC4C Investigators, Prof Leonardus G. Visser PhD, Prof Peter JM Openshaw PhD, Geert H Groeneveld PhD*, Prof Malcolm G Semple PhD*, Prof J Kenneth Baillie PhD*.

Published Online
March 25, 2022
https://doi.org/10.1016/
S0140-6736(22)00383-X

- Studied co-infection in 212,466 people with COVID-19 in isaric4c.net/; 583 (8.4%) had viral co-infections (influenza: 227; RSV: 220; adenovirus:136)
- After inverse probability weighting, multivariable regression showed that **flu co-infection increased the odds of receiving IMV (OR 4.14; 95% CI 2.00-8.49) or death (OR 2.35; CI 1.07-5.12).**

Important to test for influenza and to prevent and treat co-infections appropriately

The Lancet, March 25, 2022
https://doi.org/10.1016/S0140-6736(22)00383-X

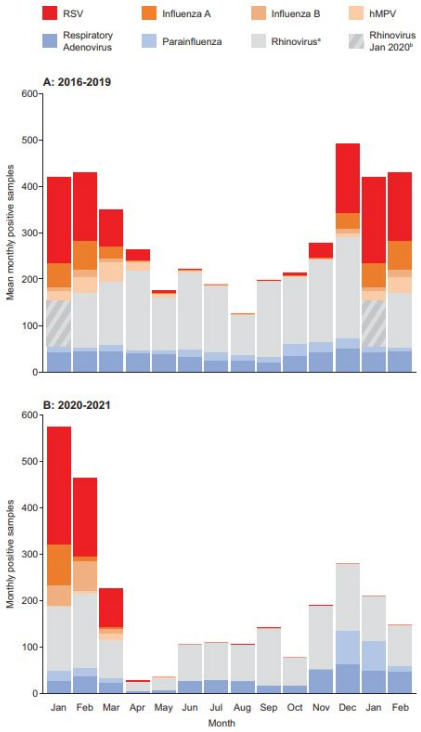
	Unweighted		Weighted	
	OR (95% CI)	p value	OR (95% CI)	p value
Invasive mechanical ventilation				
Adenovirus	1·22 (0·72–1·99)	0·44	0·64 (0·18–1·68)	0·42
Influenza virus	1·68 (1·14–2·45)	0·0073	4·14 (2·00–8·49)	0·0001
Respiratory syncytial virus	1·05 (0·68–1·59)	0·82	0·78 (0·15–2·70)	0·73
In-hospital mortality				
Adenovirus	1·60 (1·03–2·44)	0·033	1·53 (0·67–3·33)	0·29
Influenza virus	1·49 (1·04–2·12)	0·027	2·35 (1·07–5·12)	0·031
Respiratory syncytial virus	1·20 (0·84–1·72)	0·31	0·60 (0·69–2·10)	0·47

Model is adjusted for the following confounders: age, sex, number of comorbidities, treatment with corticosteroids, days since the start of the pandemic, co-infection, and 4C Mortality Score. OR=odds ratio.

Table: Multivariable model of the effect of co-infection compared with SARS-CoV-2 monoinfection

Lockdown caused a major reduction in pneumococcal disease without affecting carriage rates

Study from Israel: https://pubmed.ncbi.nlm.nih.gov/34904635/



Report from France https://pubmed.ncbi.nlm.nih.gov/35763298/

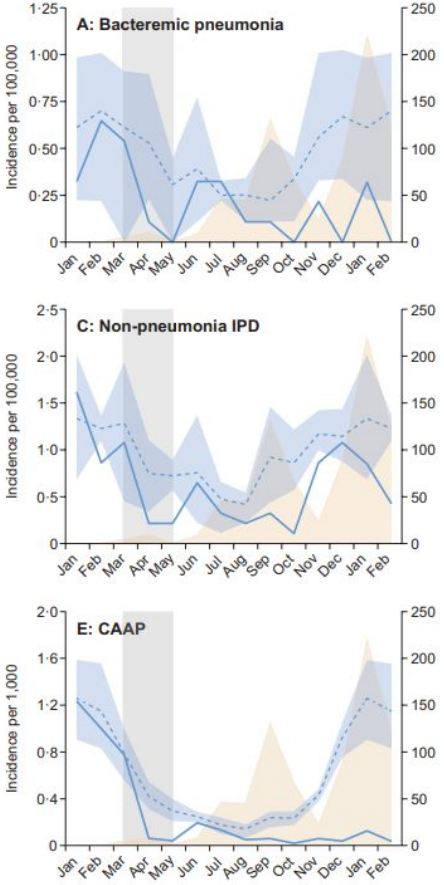
'The association between pneumococcal carriage and IPD was potentially modified by changes in the number of RSV and influenza cases, suggesting that interventions targeting respiratory viruses, such as ***immunoprophylaxis or vaccines for RSV and influenza, may be able to prevent a large proportion of pediatric IPD cases****.'*

JAMA Network Open

Original Investigation | Pediatrics

Association of Nonpharmaceutical Interventions During the COVID-19 Pandemic With Invasive Pneumococcal Disease, Pneumococcal Carriage, and Respiratory Viral Infections Among Children in France

Alexis Rybak, MD; Corinne Levy, MD; François Angoulvant, PhD; Anne Auvrignon, MD; Piotr Gembara, MD; Kostas Danis, PhD; Sophie Vaux, PharmaD; Daniel Levy-Bruhl, MD; Sylvie van der Werf, PhD; Stéphane Béchet, MSc; Stéphane Bonacorsi, PhD; Zein Assad, MD; Andréa Lazzati, PhD; Morgane Michel, PhD; Florentia Kaguelidou, PhD; Albert Faye, PhD; Robert Cohen, MD; Emmanuelle Varon, MD; Naïm Ouldali, PhD



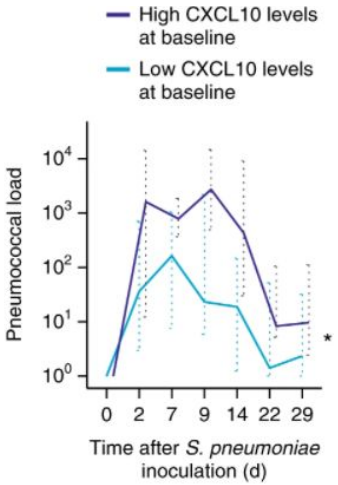
nature immunology ARTICLES
https://doi.org/10.1038/s41590-018-0231-y

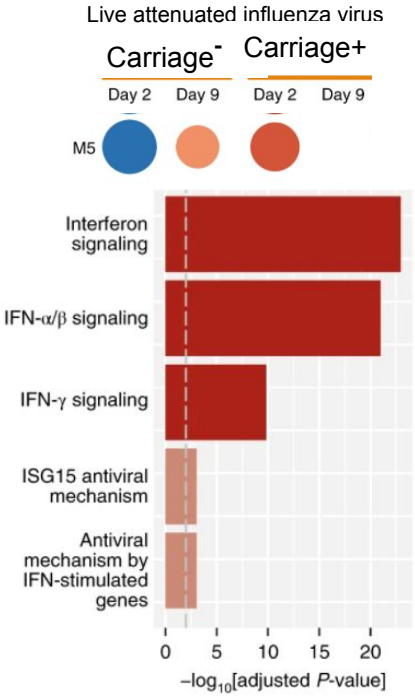
Inflammation induced by influenza virus impairs human innate immune control of pneumococcus

Simon P. Jochems[1,8*], Fernando Marcon[2,8], Beatriz F. Carniel[1], Mark Holloway[1], Elena Mitsi[1], Emma Smith[1], Jenna F. Gritzfeld[1], Carla Solórzano[1], Jesús Reiné[1], Sherin Pojar[1], Elissavet Nikolaou[1], Esther L. German[1], Angie Hyder-Wright[1,3], Helen Hill[1,3], Caz Hales[1,3], Wouter A. A. de Steenhuijsen Piters[4,5,6], Debby Bogaert[4,5,6], Hugh Adler[1], Seher Zaidi[1], Victoria Connor[1,3], Stephen B. Gordon[1,7], Jamie Rylance[1], Helder I. Nakaya[2*] and Daniela M. Ferreira[1*]

Jochems SP, et al. *Nature Immunology* .2018;19:1299–1308.

- In human challenge with 6B pneumococcus, early degranulation of resident neutrophils and recruitment of monocytes to the nose was observed
- Nasal infection with live attenuated influenza virus induced inflammation, impaired innate immune function and altered nasal gene transcription to the carriage of pneumococcus
- Levels of CXCL10, promoted by viral infection, positively associated with increased bacterial load
- **Disinhibition of resident pneumococci leads to bacterial pneumonia during influenza**





Over-representation analysis of module M5 of the live attenuated influenza virus group using gene sets from the Reactome Pathway database

"Carriage [of pneumococci] in the absence of live attenuated influenza virus was associated with only limited inflammation, corroborating the view of S. pneumoniae as a commensal bacterium"

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What does human challenge with respiratory viruses tell us about pathogenesis?

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Influenza challenge team

- **Suzanna Paterson**
- Satwik Kar
- Veda Avadhan
- Agnieszka Jozwik
- Aleks Guvenel
- Zoe Gardener
- Emma Bergstrom
- Anakin Ung
- Mohini Kalyan
- Peter Openshaw
- **Chris Chiu**

Experimental Medicine Initiative to Explore New Therapies (EMINENT)

EMINENT represents a unique collaborative network, funded up to £8M by the MRC matched in-kind by GSK.

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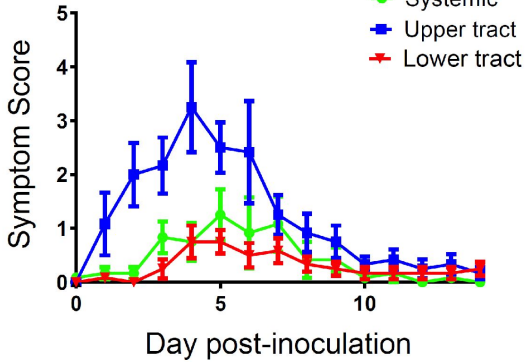
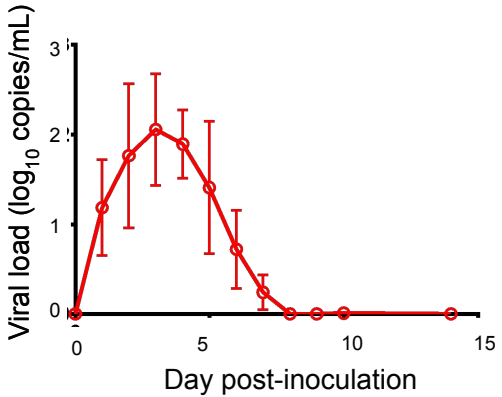
Symptoms & viral load: comparing RSV and flu

Pre-selected for seronegativity

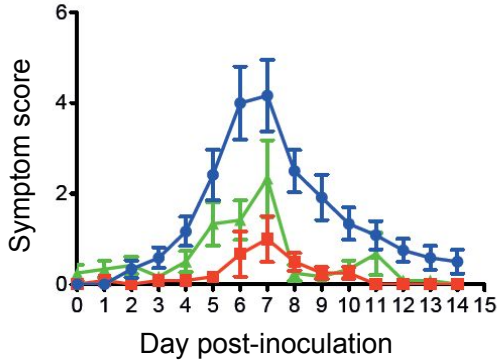
Influenza

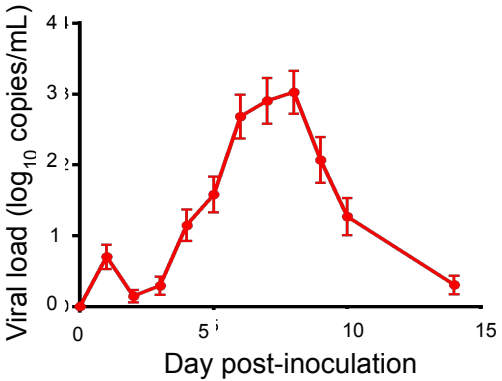




Not pre-selected for seronegativity

RSV





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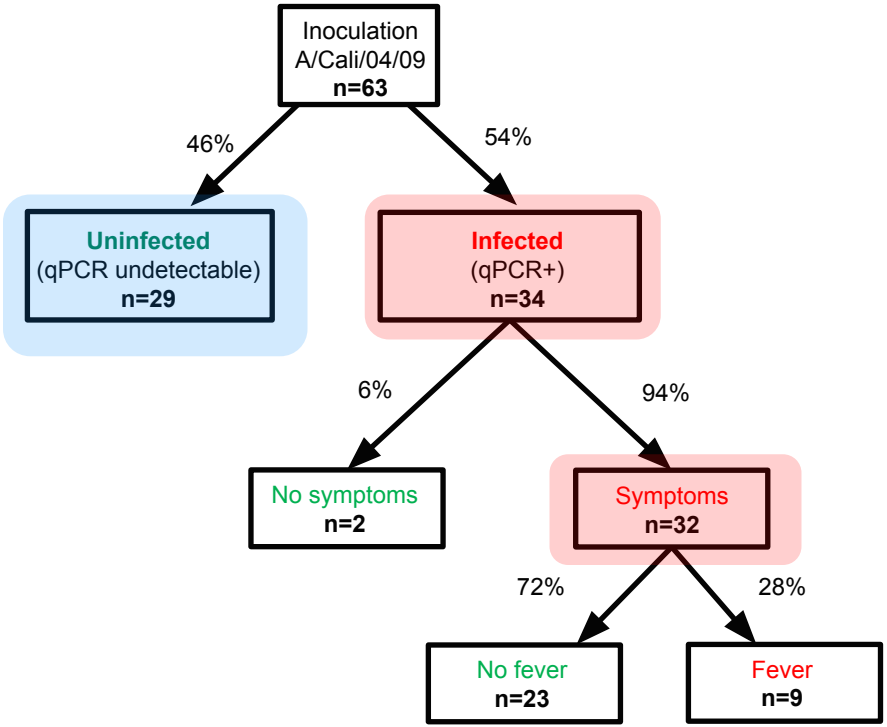
Heterogeneity of outcome



Modular analysis of time-course transcriptional response to Influenza H1N1 in human volunteers

Fatih Bogaards[1], Cosimo Cristella[1], Karen de Haan[1], Sarah van Leeuwen[1], Christopher Chiu[2], Zoe Gardener[2], Peter Openshaw[2], Menno de Jong[1]

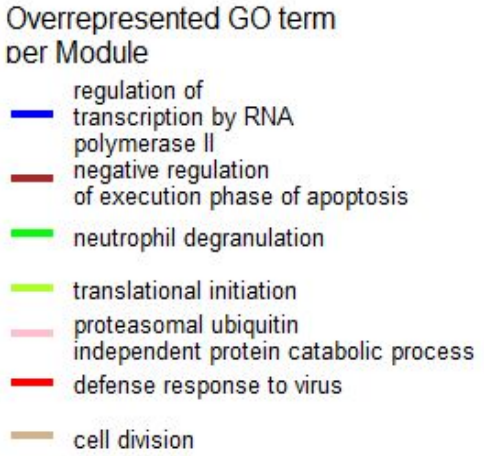
[1]Medical Microbiology, Medical Integromics, Amsterdam UMC

[2]Faculty of Medicine, National Heart & Lung Institute, Imperial College London

Whole blood RNA

GO Terms and modules

First 10 days



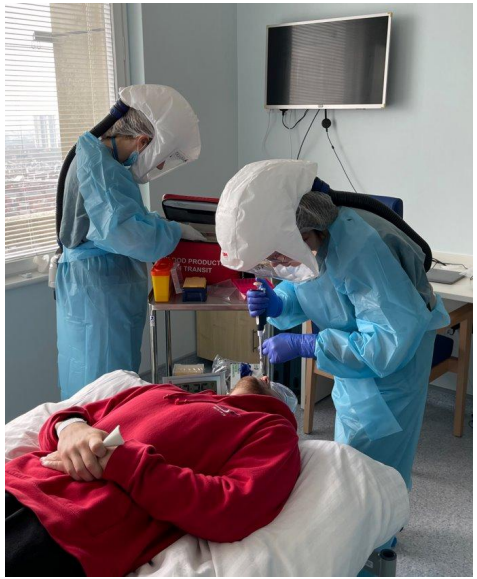
Cosimo Cristella & Menno de Jong

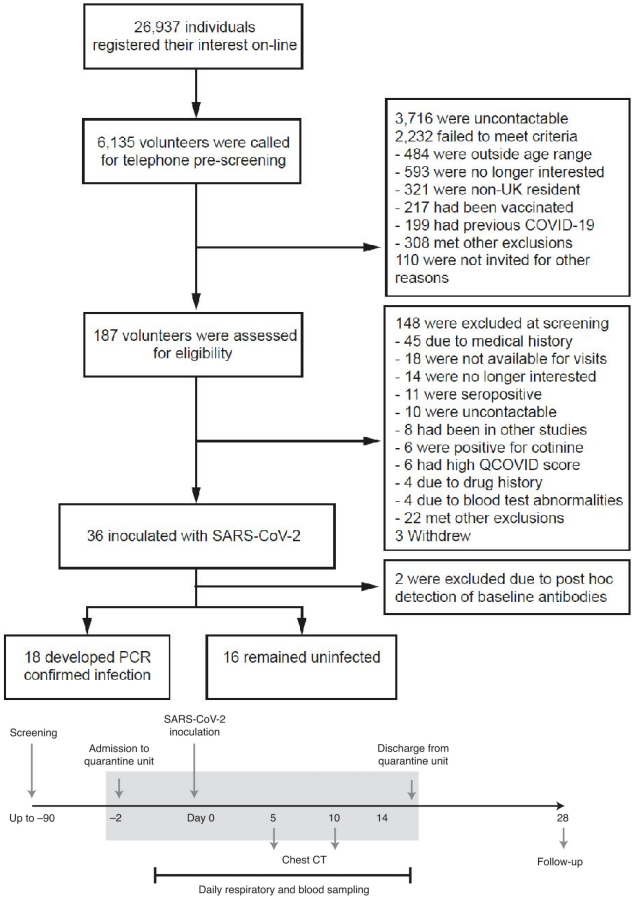
Imperial College London

First SARS-CoV-2 challenge study

Clinical design and recruitment

- Extensive public support & interest: ~27,000 on-line registrations
- Seronegative volunteers
- 53% infection rate using **10 TCID50** inoculum dose





Killingley, Mann *et al.* Nat Med 2022

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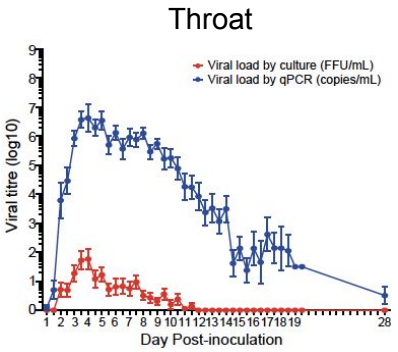
First SARS-CoV-2 challenge study

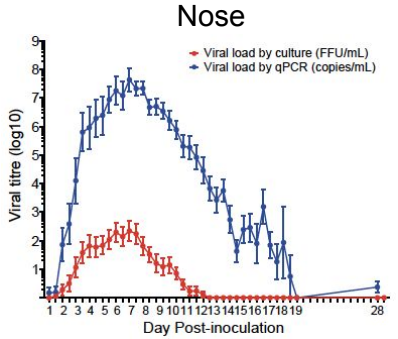
Viral & clinical headlines

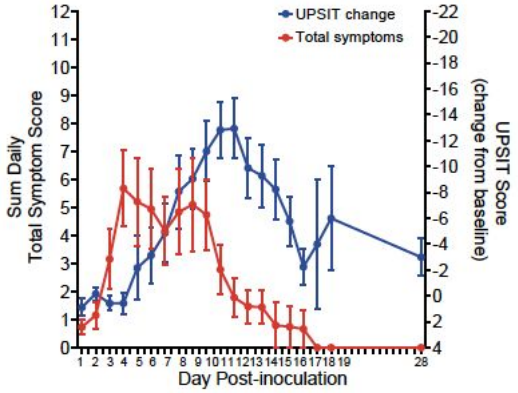
- Short incubation (40h, variable)
- Rapid onset VL in throat
- Peak VL higher in nose

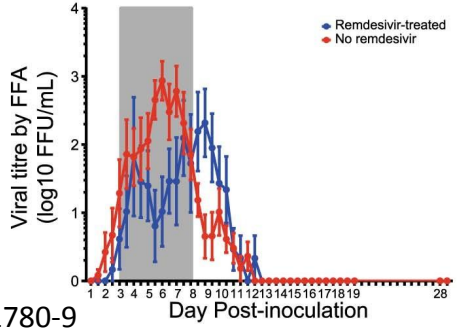
Highly abundant viral shedding

- Mild symptoms
- Remdesivir had little benefit
- Frequent smell disturbance
- Full recovery in all cases









Nature Medicine **28:**1031–1041 **(2022)** https://www.nature.com/articles/s41591-022-01780-9

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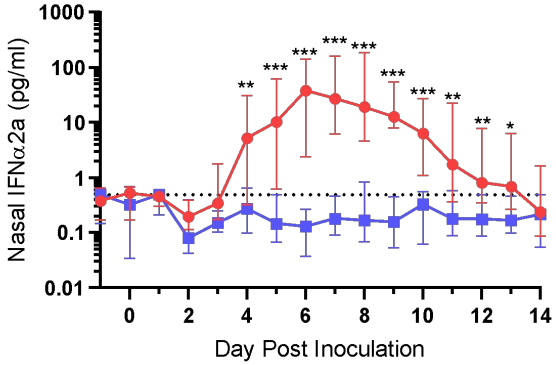
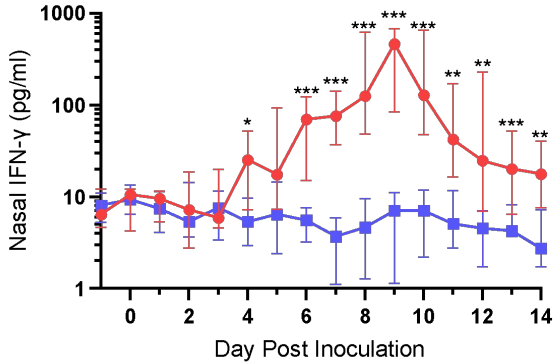
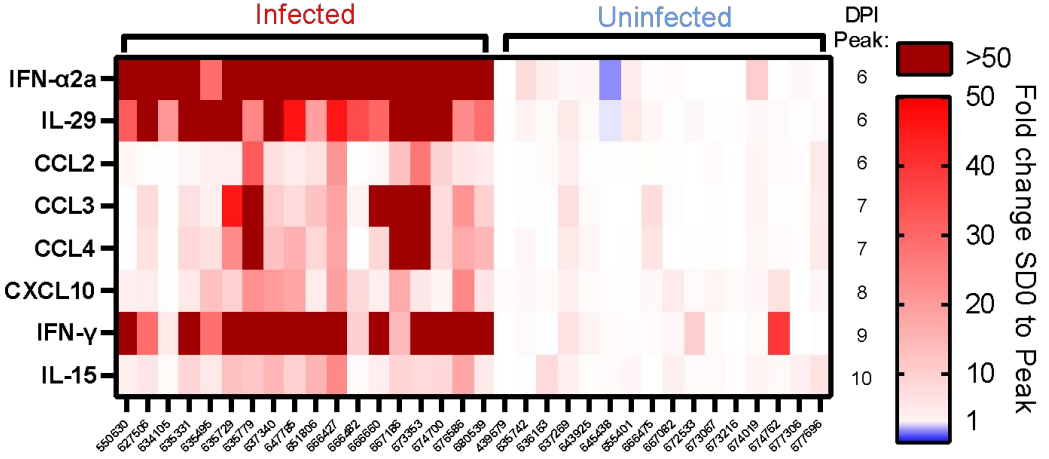
Mucosal Mediators







- Strong mucosal response in Infected group
- Mediators peak at different times and at different levels in different individuals

Nasosorption samples (morning sample)

Matt Siggins

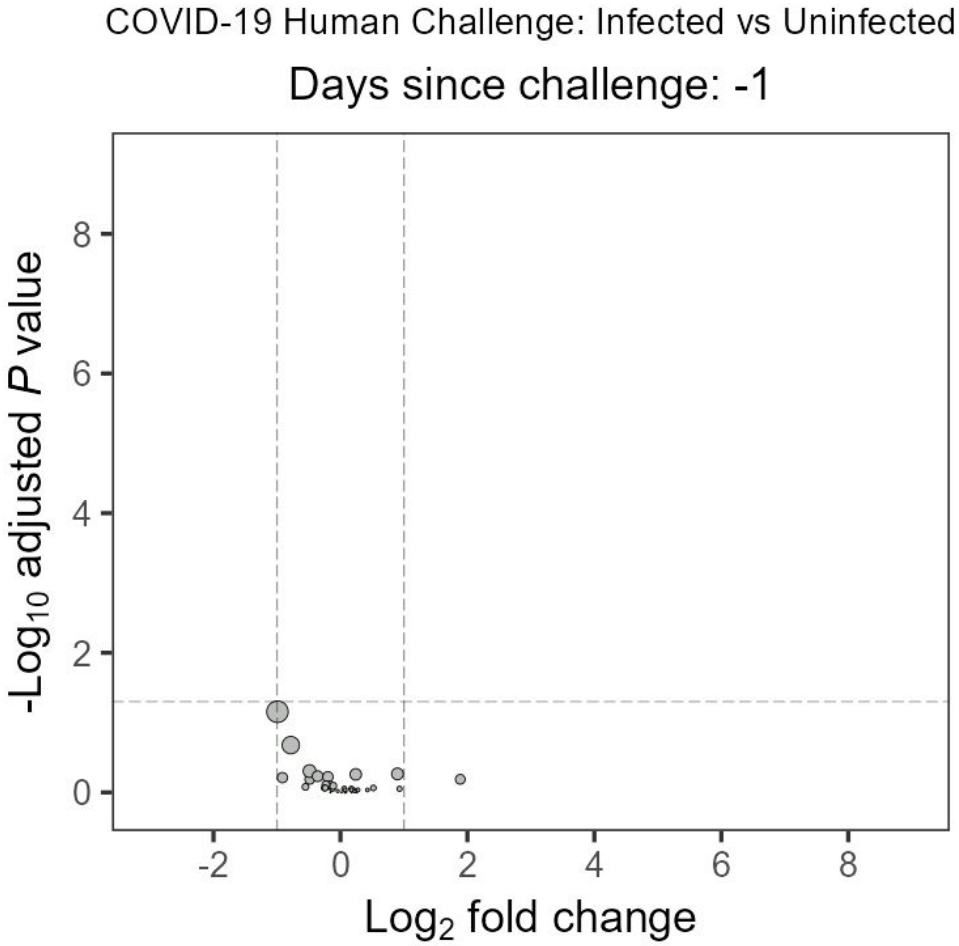
Ryan Thwaites

Cytokines: Infected Vs Uninfected

Log2 fold change of geometric mean

P values = Mann Whitney with Benjamini & Hochberg multiple comparison adjustment

Size of point = relative to effect size



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What have we learnt about treating COVID and does that help in treating flu?

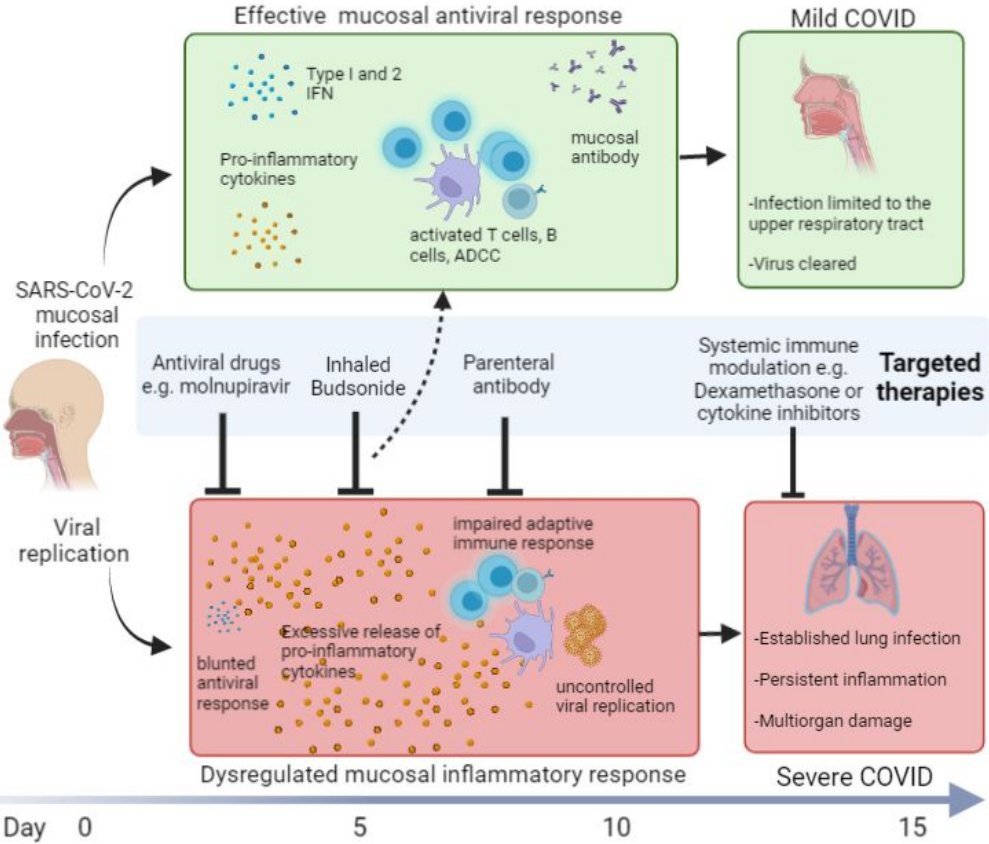
THE LANCET
Respiratory Medicine

Inhaled corticosteroids: not just for asthma, but for COVID-19?

Felicity Liew MRCP and Peter JM Openshaw FMedSci

Early mucosal events and disease outcome in COVID-19.

Different aspects of the dysregulated inflammatory response (red box) can be targeted through early intervention to prevent severe disease (blue box).



See also https://www.bmj.com/content/370/bmj.m3379

April 07, 2022
DOI:https://doi.org/10.1016/S2213-2600(22)00053-4

nature medicine
ARTICLES
https://doi.org/10.1038/s41591-021-01488-2
Check for updates

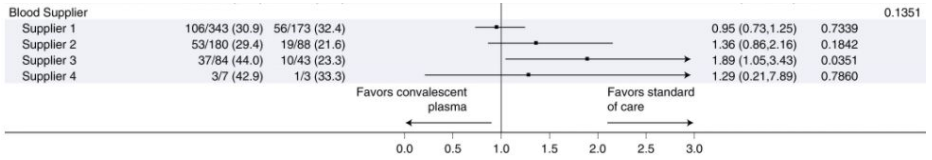
OPEN

Convalescent plasma for hospitalized patients with COVID-19: an open-label, randomized controlled trial

Philippe Bégin[1,2,87], Jeannie Callum[3,4,5,6,87], Erin Jamula[7], Richard Cook[8], Nancy M. Heddle[6,7,9],

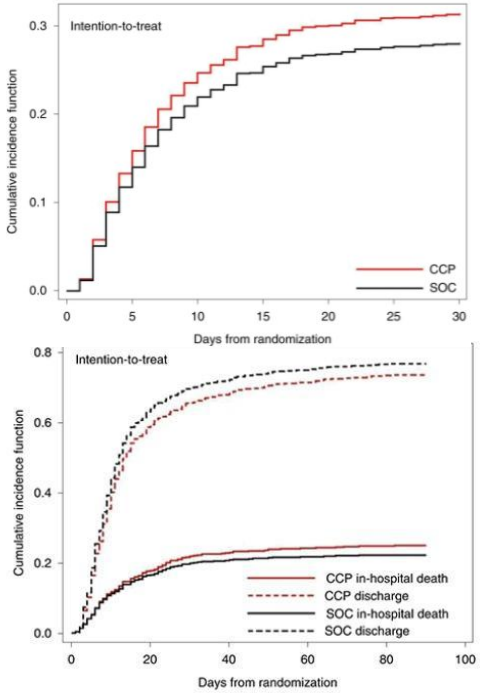
https://www.nature.com/articles/s41591-021-01488-2.pdf

https://doi.org/10.1038/s41591-021-01488-2



- Open-label, randomized trial of convalescent plasma for adults with COVID-19 receiving oxygen within 12 d of respiratory symptoms
- Allocated 940 patients 2:1 to 500 ml convalescent plasma
- Trial terminated after meeting stopping criteria for futility
- Intubation/death occurred in 199/614 (32.4%) patients in the convalescent plasma arm and 86/307 (28.0%) control patients
- **Patients given plasma had more serious adverse events**

  (33.4% versus 26.4%; RR = 1.27, 95% CI 1.02–1.57, *P* = 0.034).
- Increases in neutralization or antibody-dependent cellular cytotoxicity reduced the potential harmful effect of plasma, whereas IgG against the full TM spike protein increased it (OR = 1.53, 95% CI 1.14–2.05).



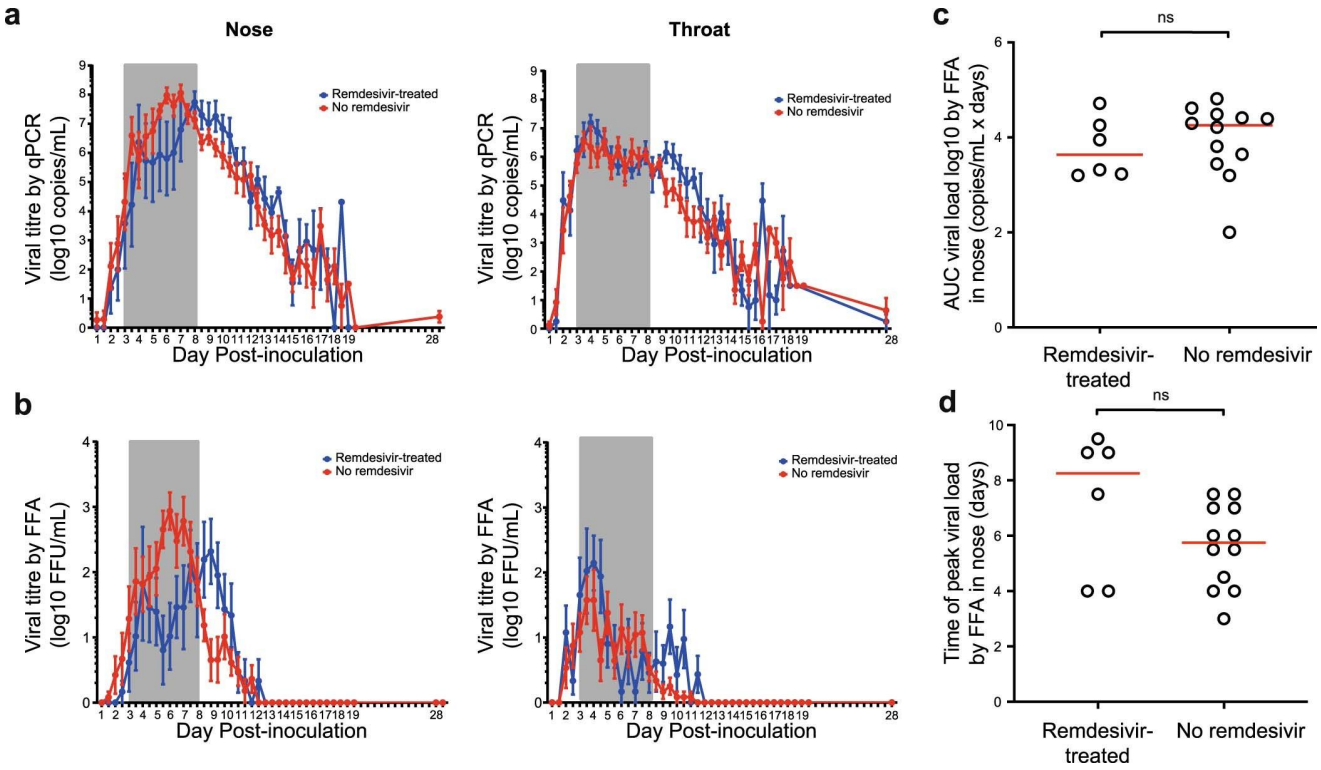
Transfusion of convalescent plasma with unfavorable antibody profiles could be associated with worse clinical outcomes compared to standard care

Randomized trial of plasma in COVID-19 showed no benefit, and potentially increased harm associated with IgG against full transmembrane spike protein

Imperial College London

Remdesivir transiently reduces nasal VL following human SARS-CoV-2 challenge.

From: Safety, tolerability and viral kinetics during SARS-CoV-2 human challenge in young adults



Wang et al *Lancet* 2020; 395: 1569–78 Published Online April 29, 2020 https://doi.org/10.1016/

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang*

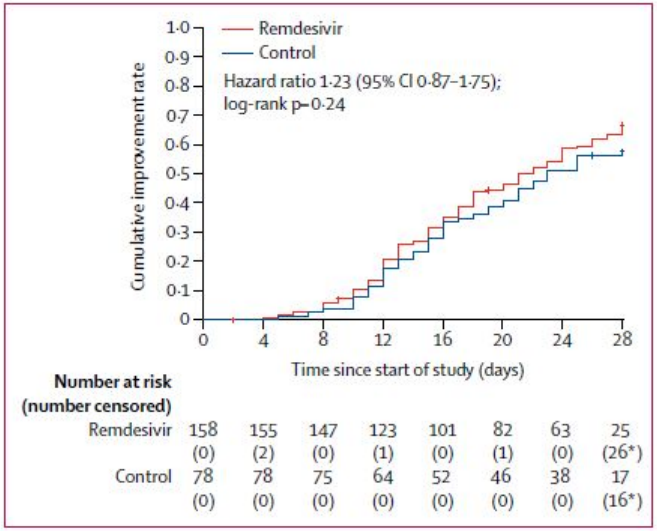


Figure 2: **Time to clinical improvement in the intention-to-treat population**
Adjusted hazard ratio for randomisation stratification was 1·25 (95% CI 0·88–1·78). *Including deaths before day 28 as right censored at day 28, the number of patients without clinical improvement was still included in the number at risk.

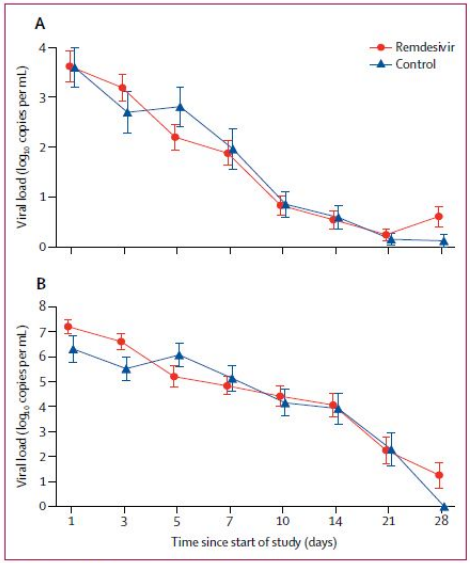


Figure 3: **Viral load by quantitative PCR on the upper respiratory tract specimens (A) and lower respiratory tract specimens (B)**
Data are mean (SE). Results less than the lower limit of quantification of the PCR assay and greater than the limit of qualitative detection are imputed with half of actual value; results of patients with viral-negative RNA are imputed with 0 $\log_{10}$ copies per mL.

No statistically significant benefits but did not attain the predetermined sample size because the outbreak of COVID-19 was brought under control in China.

"Earlier treatment and higher-dose regimens alone or in combination with other antivirals or SARS-CoV-2 neutralising antibodies in those with severe COVID-19 are needed to better understand its potential effectiveness."

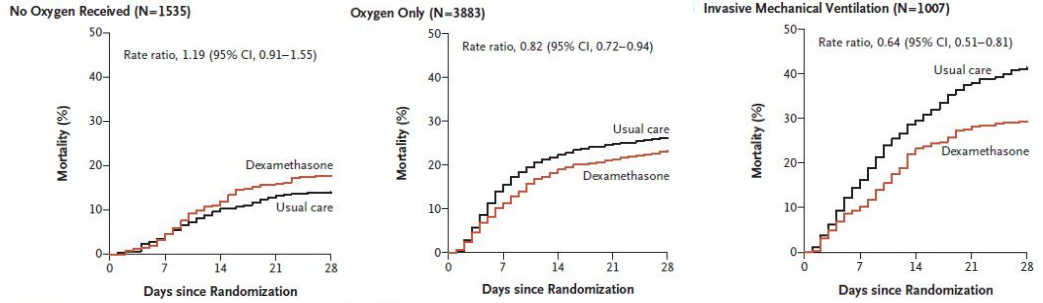
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report

The RECOVERY Collaborative Group*

- **RECOVERY:** Adaptive randomised trial
- Over 11,500 COVID-19 patients, 175 NHS UK hospitals
- 8 June 2020: recruitment to dexamethasone halted. 2,104 patients given **dexamethasone 6 mg** (= 40mg of Prednisolone) **once per day** either by mouth or i.v. for **ten days;** cf. 4,321 patients on usual care
- Among the patients who received usual care, 28-day mortality:
  - 41% in those on ventilators
  - 25% in those on O2
  - 13% in those with normal O2 levels



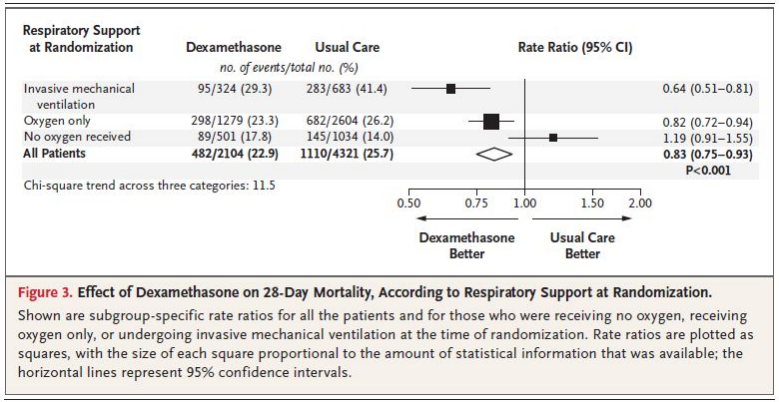


Figure 3. **Effect of Dexamethasone on 28-Day Mortality, According to Respiratory Support at Randomization.**
Shown are subgroup-specific rate ratios for all the patients and for those who were receiving no oxygen, receiving oxygen only, or undergoing invasive mechanical ventilation at the time of randomization. Rate ratios are plotted as squares, with the size of each square proportional to the amount of statistical information that was available; the horizontal lines represent 95% confidence intervals.

Dexamethasone:

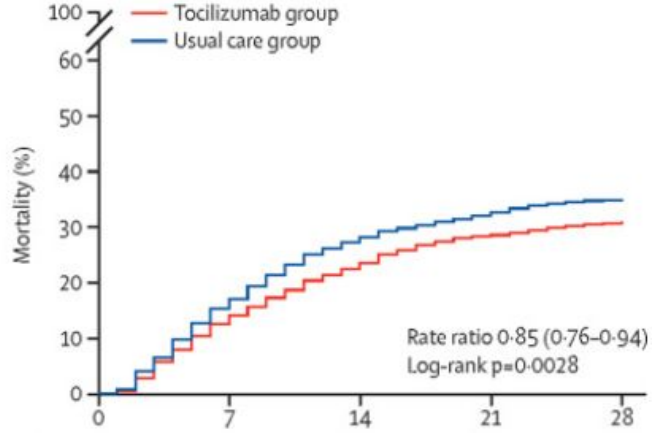
- **reduced deaths by one-third** in ventilated patients (0.65, CI 0.48 to 0.88; p=0.0003)
- **reduced deaths by on fifth** in other patients on oxygen (0.80 [0.67 to 0.96]; p=0.0021)

UK policy was immediately changed

Lancet 2021; 397: 1637–45

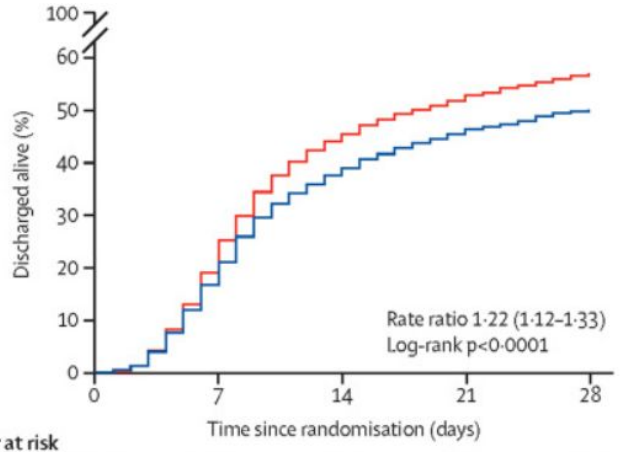
Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial

RECOVERY Collaborative Group*



Number at risk

Tocilizumab	2022	1736	1547	1445	1398
Usual care	2094	1735	1503	1410	1361



Number at risk

Tocilizumab	2022	1509	1101	956	869
Usual care	2094	1653	1278	1124	1046

- Hypoxic, CRP>75mg/L
- Decreased mortality and progression to invasive ventilation
- 3x larger than all other studies combined
- 1-2x 400-800mg doses

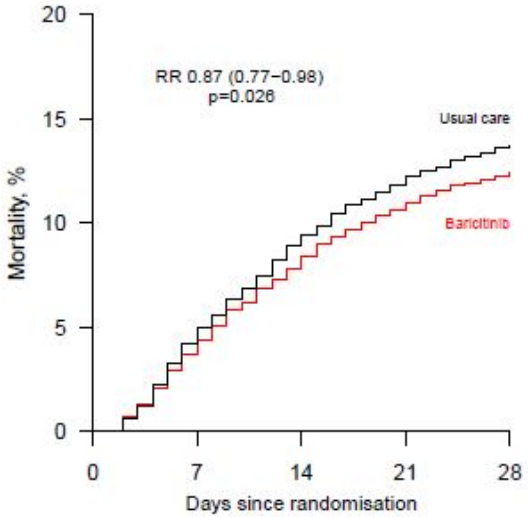
Interpretation In hospitalised COVID-19 patients with hypoxia and systemic inflammation, tocilizumab improved survival and other clinical outcomes. These benefits were seen regardless of the amount of respiratory support and were additional to the benefits of systemic corticosteroids

https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(21)00676-0/fulltext

Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis

Peter W Horby and Prof Martin J Landray for the RECOVERY Collaborative Group

- **Janus kinase (JAK) 1/2 inhibitors** may be used for COVID-19, but trials have varied.
- **Tested its use in hospitalised COVID-19**, baricitinib 4 mg daily by mouth for 10 days or until discharge
- **Findings:** Between 2.02.2021 and 29.12.2021, 8156 patients were randomly allocated (95% receiving corticosteroids, 23% initially receiving tocilizumab).
- 12% of those given baricitinib died vs. 14% those allocated to usual care (p=0·026).
- This 13% proportional reduction in mortality was smaller than that seen in a meta-analysis of 8 previous trials involving 3732 patients and 425 deaths, which suggested a 43% proportional reduction in mortality.
- **Conclusion:** The total randomised evidence suggests that JAK inhibitors reduce mortality in hospitalised COVID-19 patients by about one-fifth.



	Deaths / Patients randomised (%)		Observed–Expected		Ratio of death rates, RR (95% CI)
	JAK inhibitor	Control	(O–E)*	Var(O–E)	
Murugesan***	0/50 (0%)	0/50 (0%)	0.0	0.0	
Cao et al.***	0/20 (0%)	3/21 (14%)	−1.5	0.7	0.13 (0.01–1.31)
RUXCOVID***	9/287 (3%)	(3/145) x2** (2%)	1.0	2.6	1.48 (0.44–4.99)
Guimarães et al.***	4/144 (3%)	8/145 (6%)	−2.0	2.9	0.50 (0.16–1.60)
COV–BARRIER (critically ill)	20/51 (39%)	29/50 (58%)	−4.7	6.4	0.47 (0.22–1.03)
RUXCOVID–DEVENT***	90/164 (55%)	(36/47) x4** (77%)	−7.9	8.8	0.41 (0.21–0.79)
ACTT2	24/515 (5%)	37/518 (7%)	−6.4	14.4	0.64 (0.38–1.07)
COV–BARRIER	62/764 (8%)	100/761 (13%)	−19.2	36.2	0.59 (0.43–0.82)
Subtotal: 8 trials	**209/1995 (10%)**	**327/2023 (16%)**	**−40.7**	**72.0**	**0.57 (0.45–0.72)**
RECOVERY	513/4148 (12%)	546/4008 (14%)	−36.2	264.0	0.87 (0.77–0.98)
All trials	**722/6143 (12%)**	**873/6031 (14%)**	**−76.9**	**336.0**	**0.80 (0.71–0.89) p<0.001**

Heterogeneity between RECOVERY and previous trials: χ^2_1=10.3 (p=0.001)

0.25 0.5 1 2 4
JAK inhibitor better
Control better

Baricitinib is the fourth treatment that the RECOVERY trial has shown to save lives, following the steroid dexamethasone (June 2020), the arthritis treatment tocilizumab (February 2021), and a combination of monoclonal antibodies (casirivimab plus imdevimab) targeting the viral spike protein, known as Ronapreve (June 2021).

https://doi.org/10.1101/2022.03.02.22271623

Implementation of corticosteroids in treatment of COVID-19 in the ISARIC WHO Clinical Characterisation Protocol UK: prospective, cohort study

Fiina Närhi, S Ramani Moonesinghe, Susan D Shenkin, Thomas M Drake, Rachel H Mulholland, Cara Donegan, Jake Dunning, Cameron J Fairfield, Michelle Girvan, Hayley E Hardwick, Antonia Ho, Gary Leeming, Jonathan S Nguyen-Van-Tam, Riinu Pius, Clark D Russell, Catherine A Shaw, Rebecca G Spencer, Lance Turtle, Peter J M Openshaw, J Kenneth Baillie, Ewen M Harrison, Malcolm G Semple*, Annemarie B Docherty,* on behalf of the ISARIC4C investigators†

- Dexamethasone was the first intervention proven to reduce mortality in patients with COVID-19 being treated in hospital.
- Evaluated the adoption of corticosteroids in the treatment of COVID-19 in the UK after the RECOVERY trial publication on June 16, 2020
- Prospective, observational, cohort study in 237 UK acute care hospitals between March 16, 2020, and April 14, 2021, in patients aged 18 years or older with proven or high likelihood of COVID-19 who received supplementary oxygen.
- Those 50 years or older were significantly less likely to receive corticosteroids than those younger than 50 years (OR 0·79).
- Rates of steroid administration increased from 27·5% in the week before June 16, 2020, to 75–80% in January, 2021.
- Implementation practice change for UK for patients was successful, but not universal.

***Lancet Digit Health* 2022; 4: e220–34**

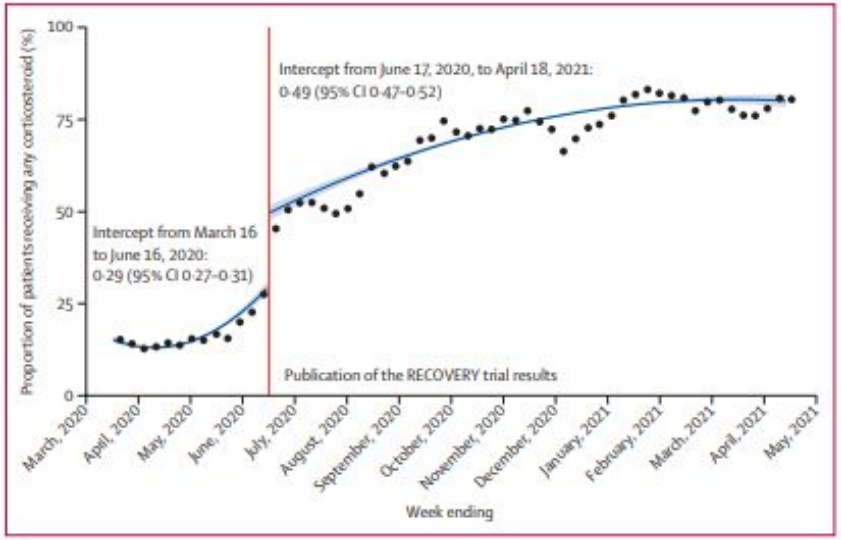
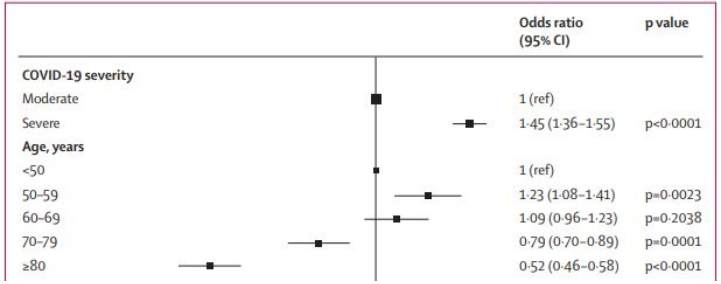


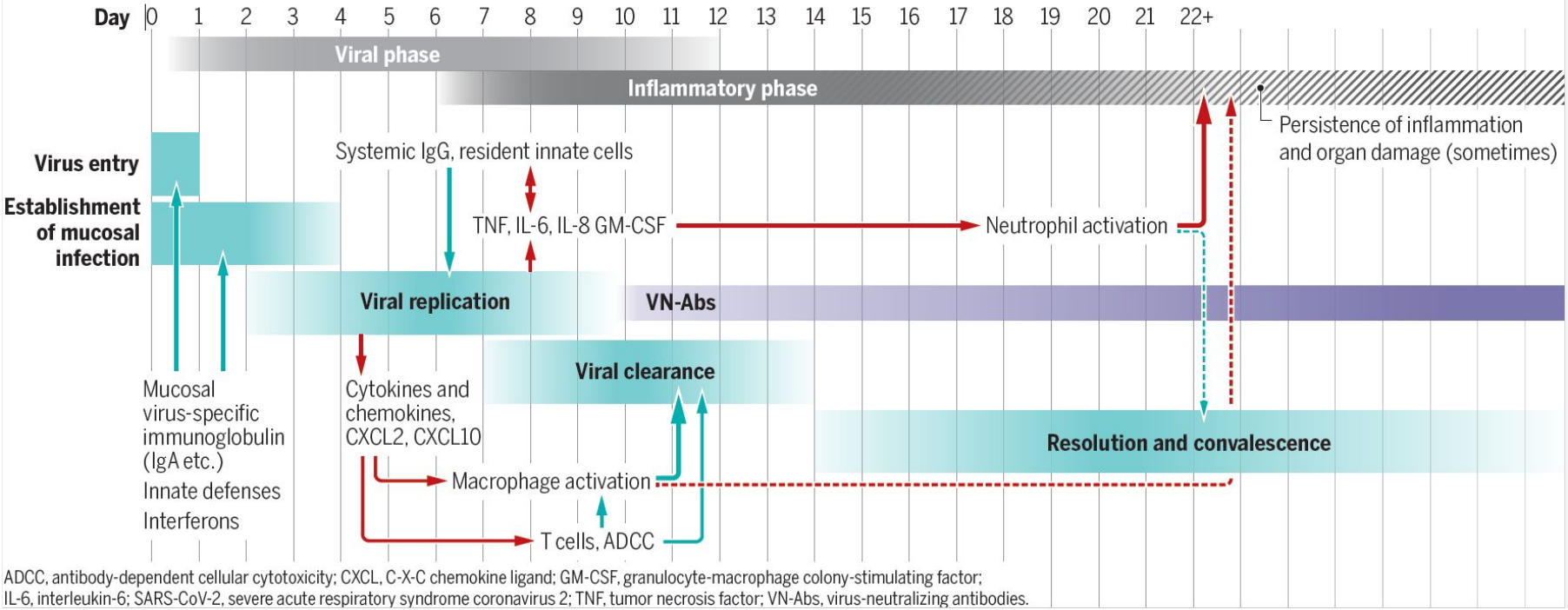
Figure 3: Fitted lines of the linear regression model for corticosteroid administration to patients who required oxygen, admitted to hospital between March 16, 2020, and April 18, 2021
Points represent weekly percentage of patients receiving any corticosteroid (dexamethasone, hydrocortisone, prednisolone, or methylprednisolone). The red vertical line represents the publication of the RECOVERY trial results and initial guidelines for steroid administration on June 16, 2020. Shaded areas around the fitted lines represent 95% CIs.



https://www.thelancet.com/pdfs/journals/landig/PIIS2589-7500(22)00018-8.pdf

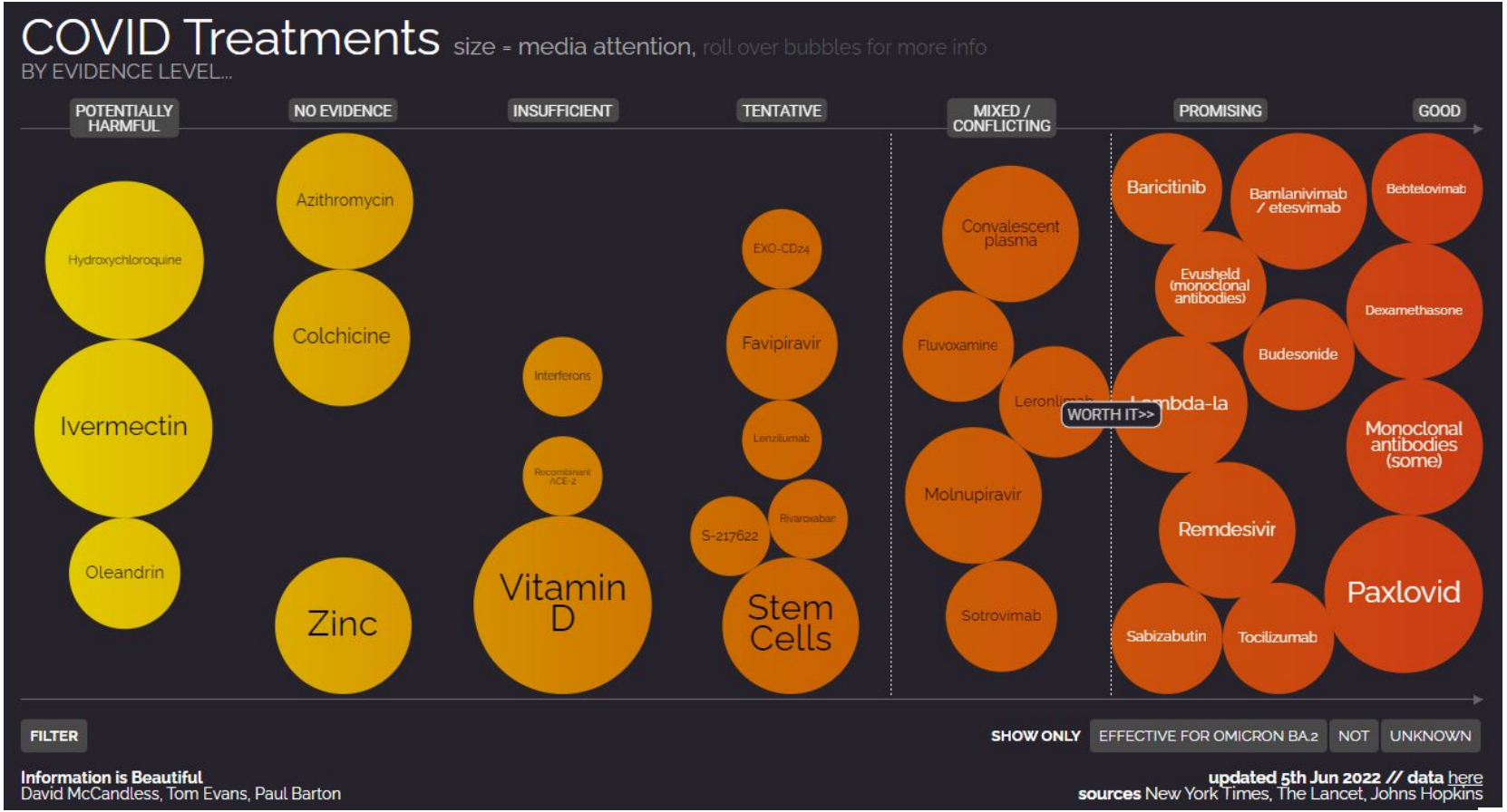
Sequential events during SARS-CoV-2 infection

The immunopathogenesis of COVID-19 can be depicted as an early viral phase followed by an inflammatory phase, which may be restricted or spread outside the respiratory tract. Immune control occurs at various stages (blue arrows), while inflammation is important in disease pathogenesis (red arrows). Local and systemic immunoglobulin (Ig) operates at multiple levels, direct and indirect; VN-Abs are detectable from day ~10 for at least 3 months.



ADCC, antibody-dependent cellular cytotoxicity; CXCL, C-X-C chemokine ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-6, interleukin-6; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; TNF, tumor necrosis factor; VN-Abs, virus-neutralizing antibodies.

‘**Using correlates to accelerate vaccinology’** Openshaw, PJM. *Science* **2022**



https://informationisbeautiful.net/visualizations/covid-19-coronavirus-infographic-datapack/ accessed 14th June 2022

What did we learn during COVID that also applies to influenza?

Thank you!

X: P_Openshaw
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