RIIP

RENCONTRES EN IMMUNOLOGIE & IMMUNOTHERAPIE PRATIQUES

29 et 30 SEPTEMBRE 2022

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L'auto-immunité contre l'immunité innée : un facteur de sévérité de la COVID-19

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September 29th 2022

Rencontres et Immunologie et Immunothérapie pratiques

Aucun conflit d’intérêt

Outline

Why do people die of COVID-19?

Type I IFN deficiencies in severe COVID-19

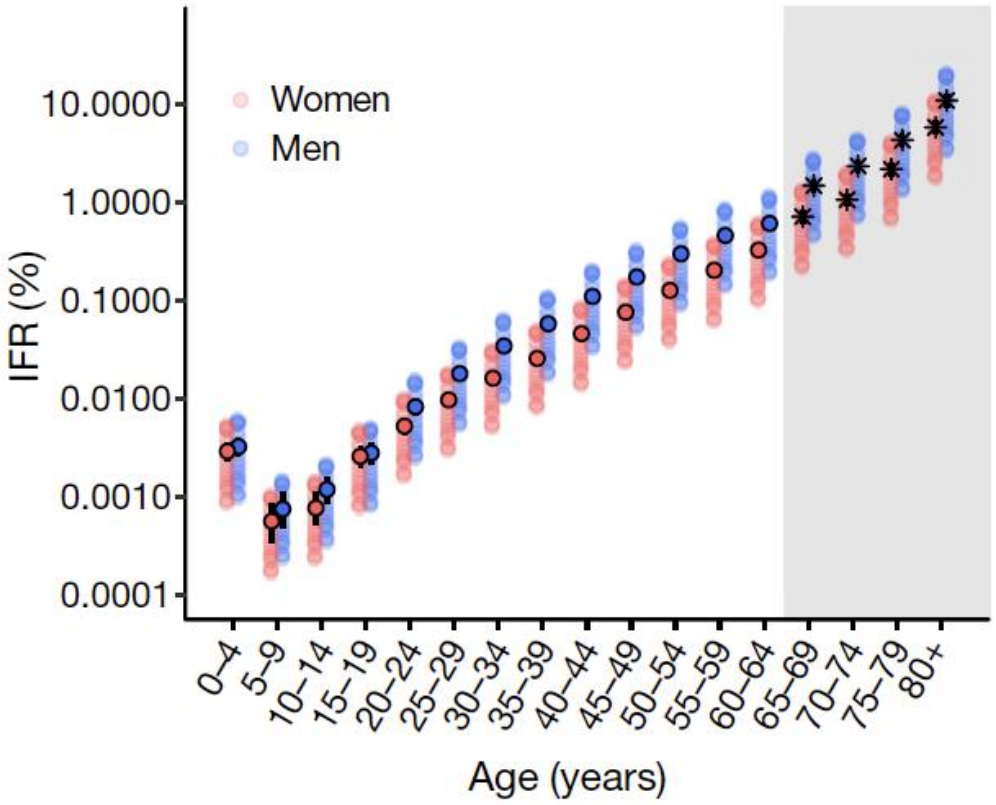
- Genetics
- Auto-immunity

Other viral infections

Conclusion & perspectives

Epidemiological factors associated with fatal COVID-19

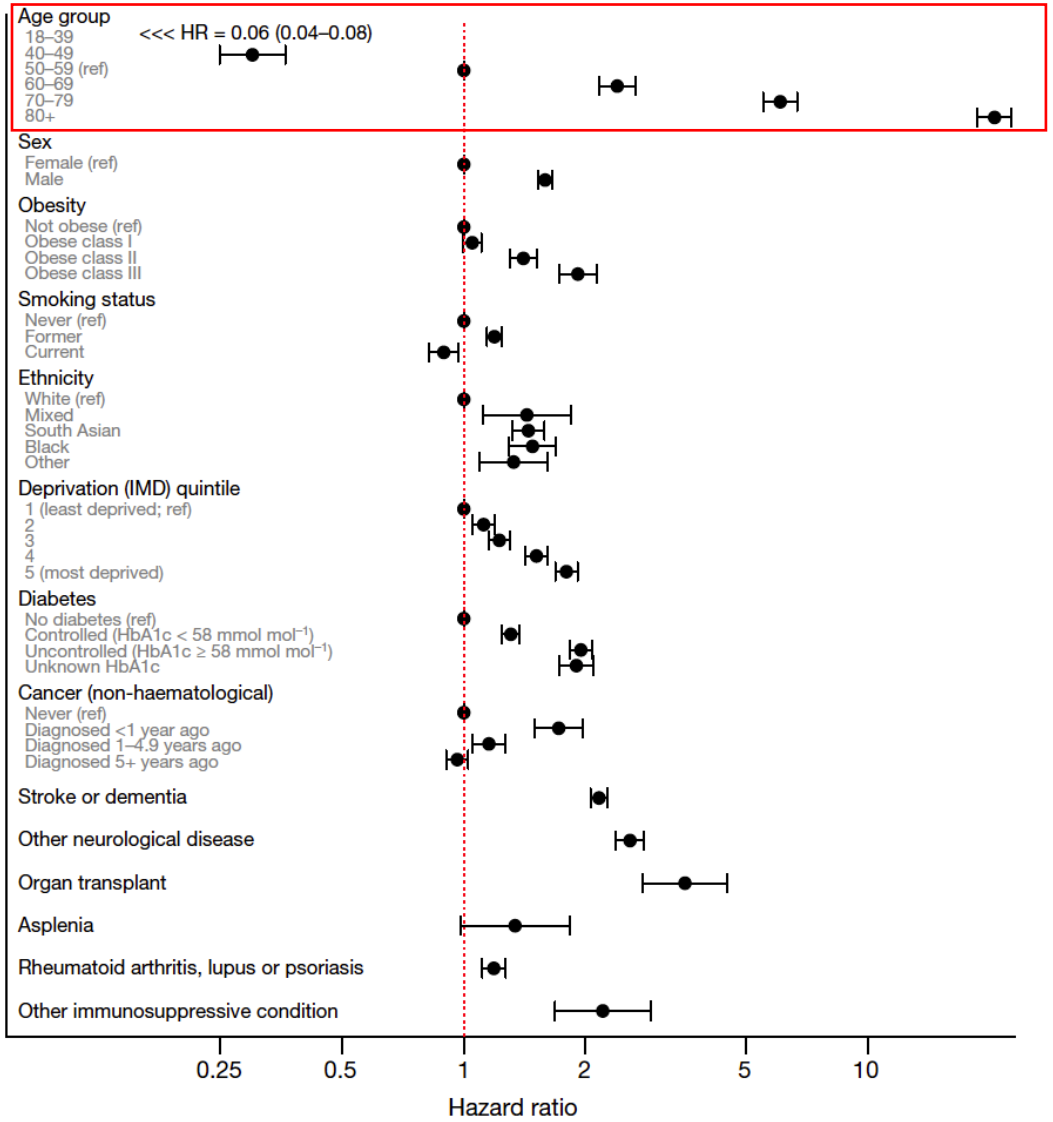
COVID-19 median of the infection fatality rate by age and sex (log-linear scale)



Total deaths > 6 million

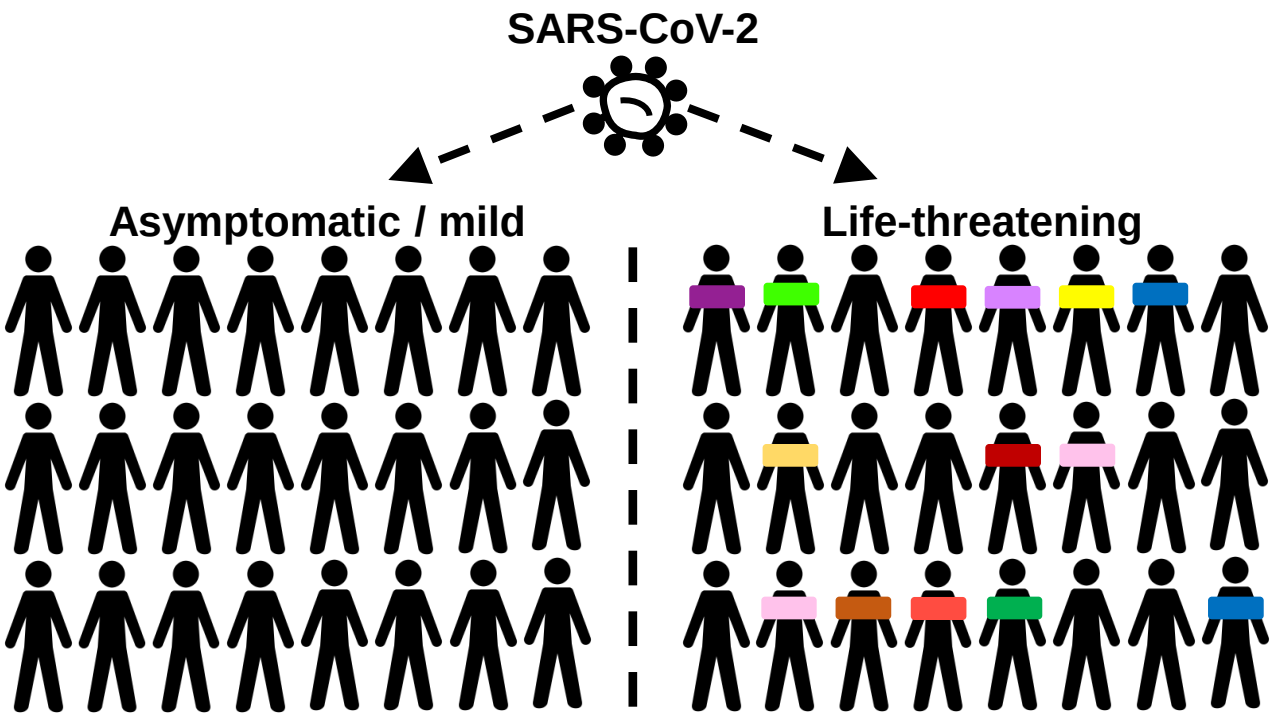
O'Driscoll et al., *Nature*, 2020

COVID-19 death hazard ratios (study on 17 million individuals)



Williamson et al., *Nature*, 2020

COVID HUMAN GENETIC EFFORT



>400 participating centers worldwide
>40 sequencing hubs

>13,000 patients recruited

Could some inborn errors of immunity underlie life-threatening COVID-19?

Type I IFNs

1957

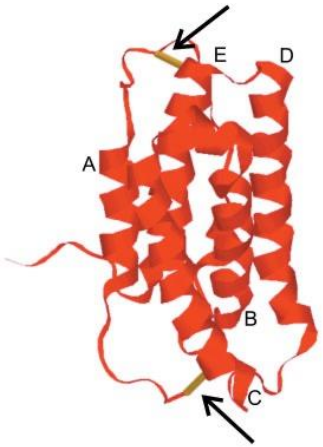
Virus interference. I. The interferon

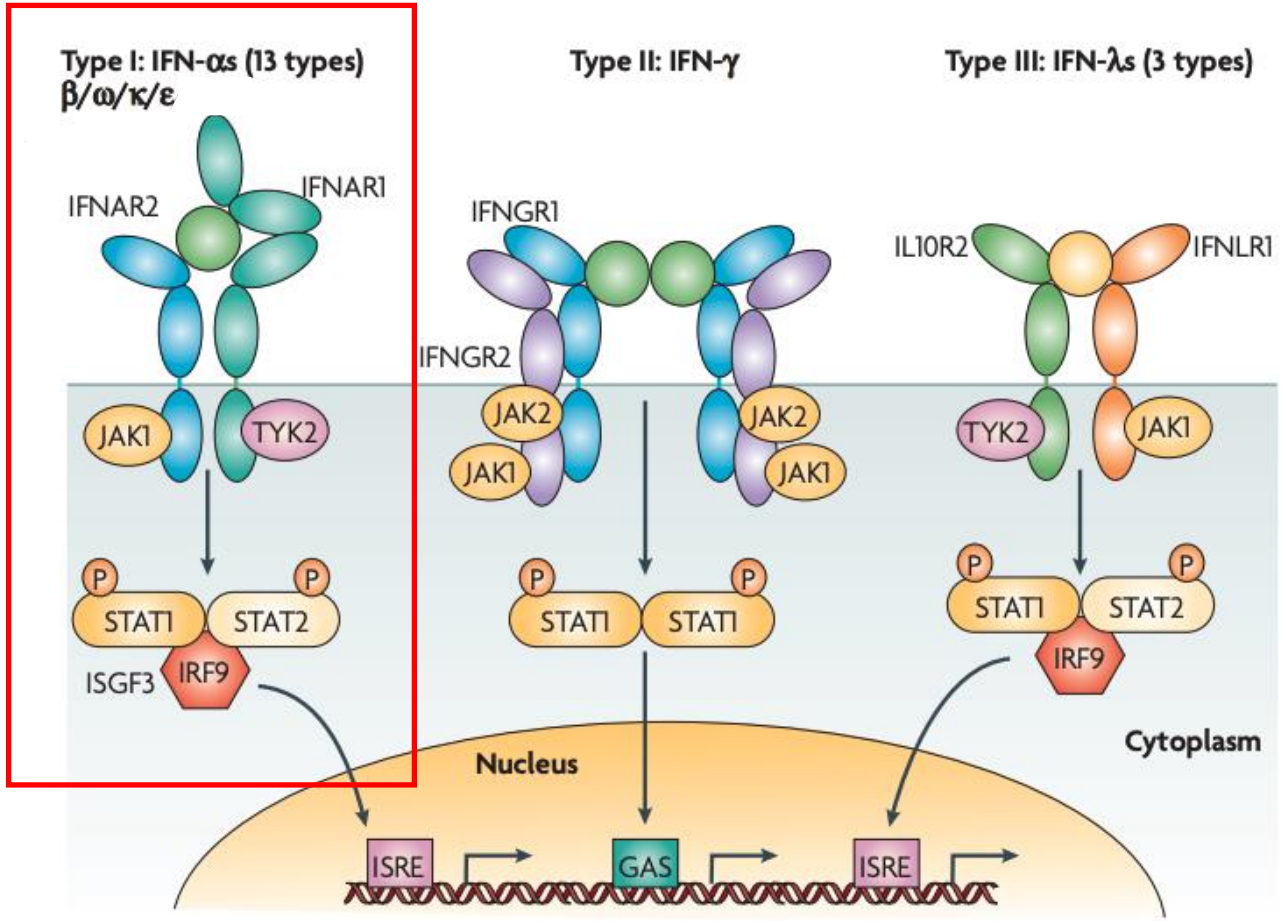
By A. Isaacs and J. Lindenmann*

National Institute for Medical Research, London

The 17 type 1 IFNs (13 IFN-α , IFN-ω, IFN-β, IFN-ε, IFN-κ) all bind to the IFNAR1/2 receptors

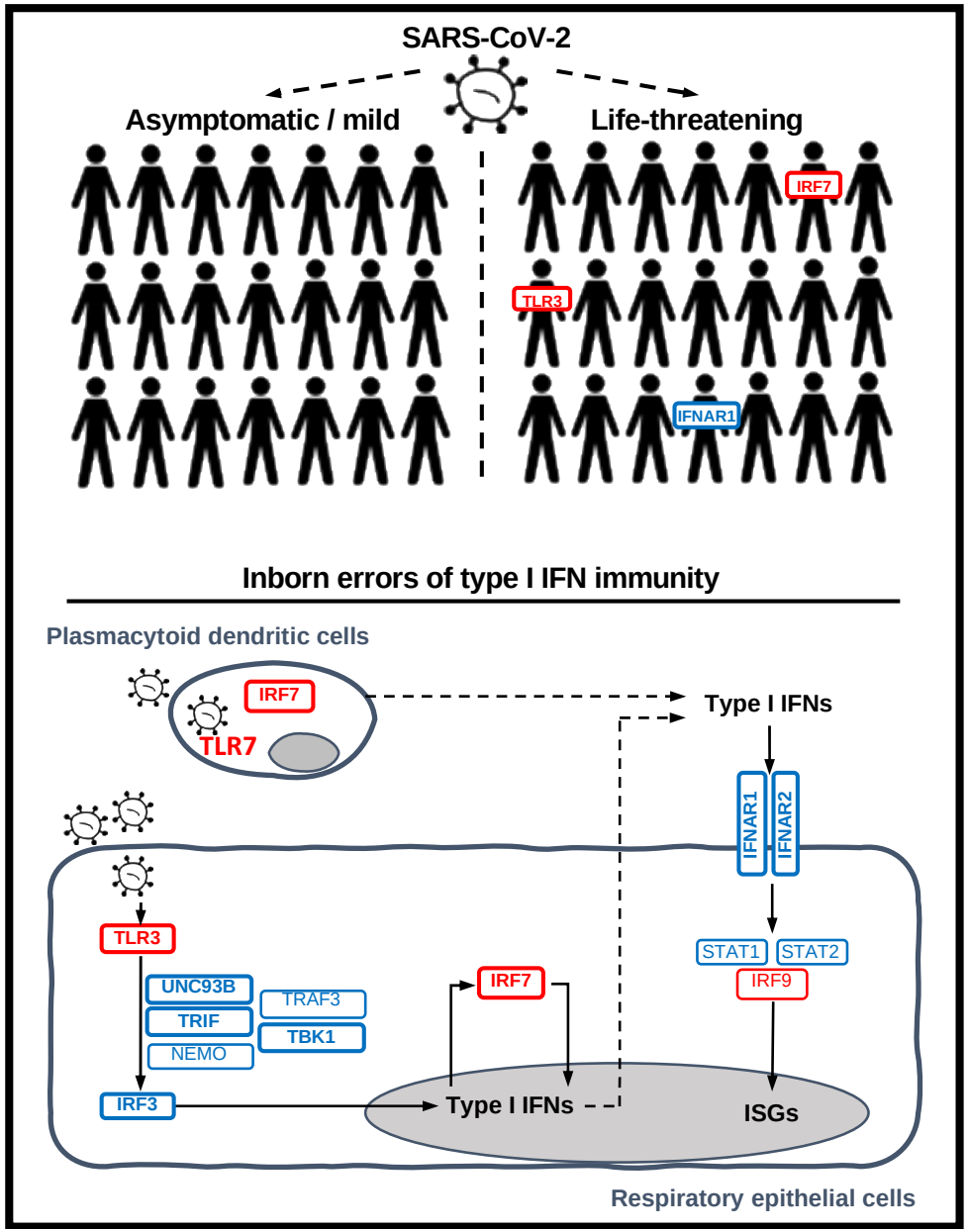
Genetic defects in the pathway cause severe viral infections



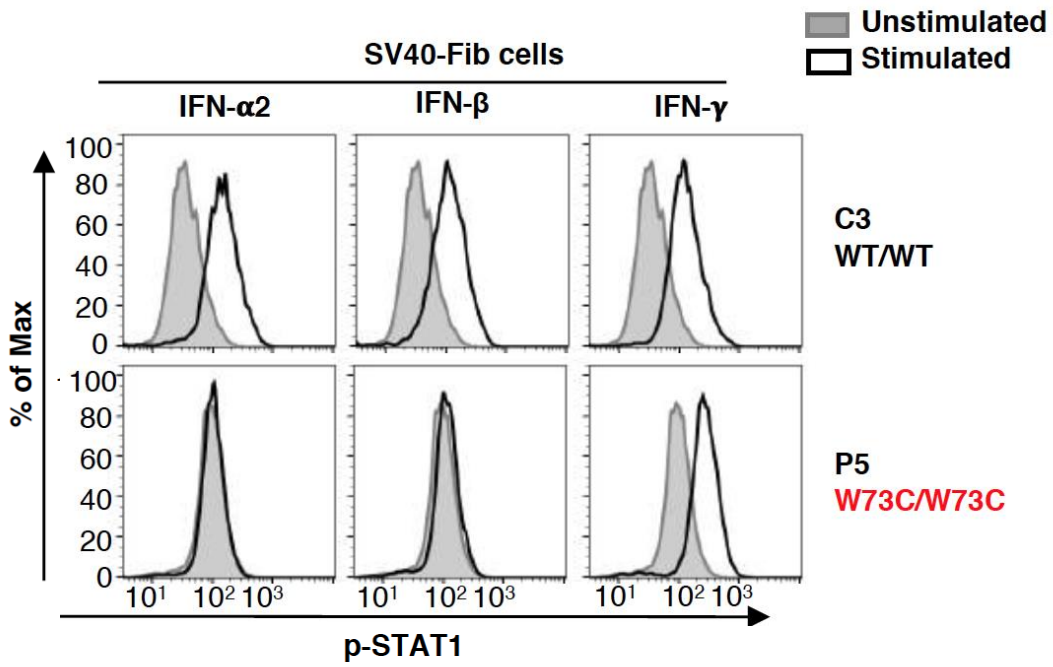


Branca and Baglioni, *Nature*, 1981
Novick & Cohen, *Cell*, 1994
Meager et al., *The interferons*, 2006
Borden et al., *Nat Drug Discov,* 2007
Hoffmann et al., *Trends Immonol*, 2015
Lazear et al., *Immunity*, 2019

Impaired type I IFN immunity in patients with life-threatening COVID-19 pneumonia



COVID HUMAN GENETIC EFFORT



AR IFNAR1 deficiency in adults with critical COVID-19,

TLR7 $^{y/-}$ **in >1% of men < 60 yrs with critical C-19**

>10% of children with COVID-19 pneumonia have AR IEIs

Zhang et al., *Science*, 2020
Asano et al., *Science Immunol*, 2021
Zhang et al., *JEM*, *2022*

Could other type I IFN deficiencies also underlie life-threatening COVID-19?

Auto-immune phenocopies of inborn errors of cytokine immunity

Mycobacterial disease

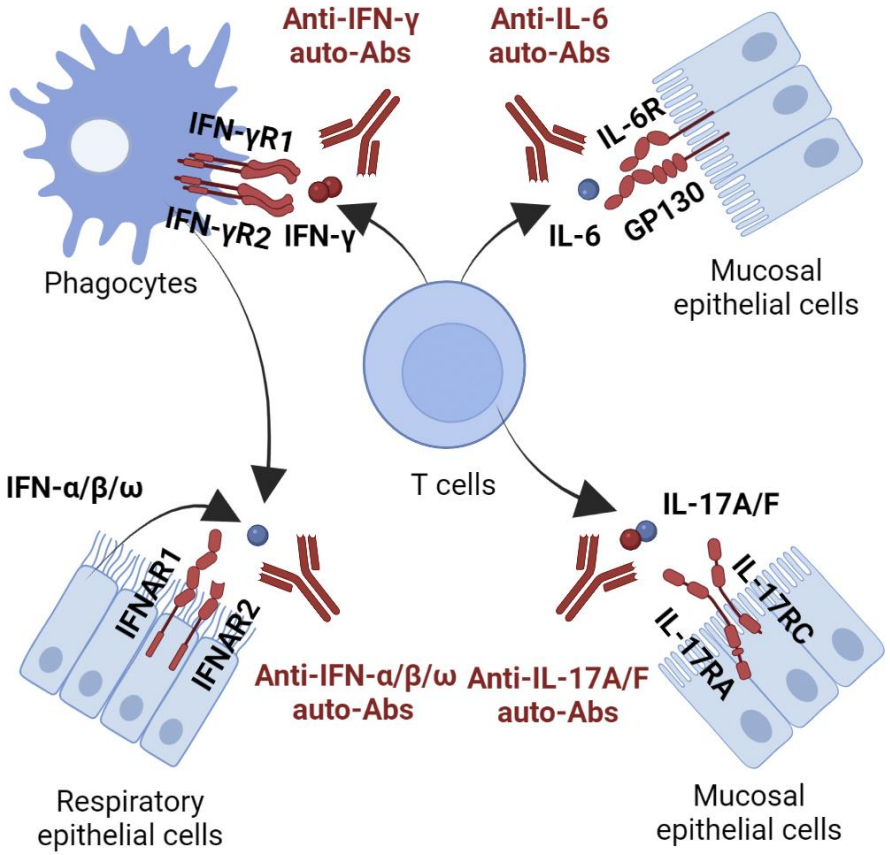
Auto-Antibodies (Abs) to IFN-γ	(2003-)
Inborn errors of IFN-γ (*IFNG*, *IFNGR1*, *IFNGR2*)	(1996-)

Mucocutaneous candidiasis

Auto-Abs to IL-17A and IL-17F	(2010-)
Inborn errors of IL-17 (*IL17F*, *IL17RA*, *IL17RC*)	(2011-)

Staphylococcal disease

Auto-Abs to IL-6	(2008-)
Inborn errors of IL-6 (*IL6R*)	(2019-)



JEM | Journal of Experimental Medicine

Anti-cytokine auto-Abs are usually genetically driven:

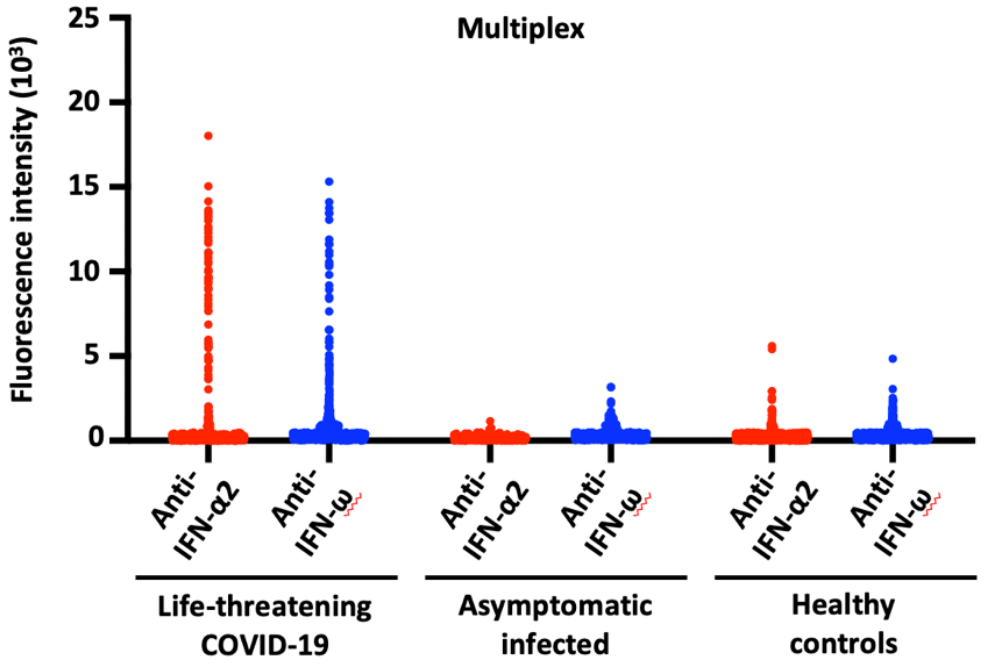
⇒ ***AIRE*** **deficiency (APS-1): auto-Abs to IL-17A/F**

⇒ **HLA-DRB1*16:02 and DRB1*15:02: auto-Abs to IFN-γ**

Could auto-Abs to type I IFNs underlie life-threatening COVID-19?

Reviewed in Puel & al., *JEM*, 2022

Auto-antibodies neutralizing type I IFNs in >10% of patients with life-threatening COVID-19



	N total	Anti-type I IFN auto-Abs positive		p-value
		N	%	
Life-threatening COVID-19	987	101	10.2	
Asymptomatic infection	663	0	0	$p < 10^{-16}$
Healthy controls	1224	4	0.3	$p < 10^{-16}$

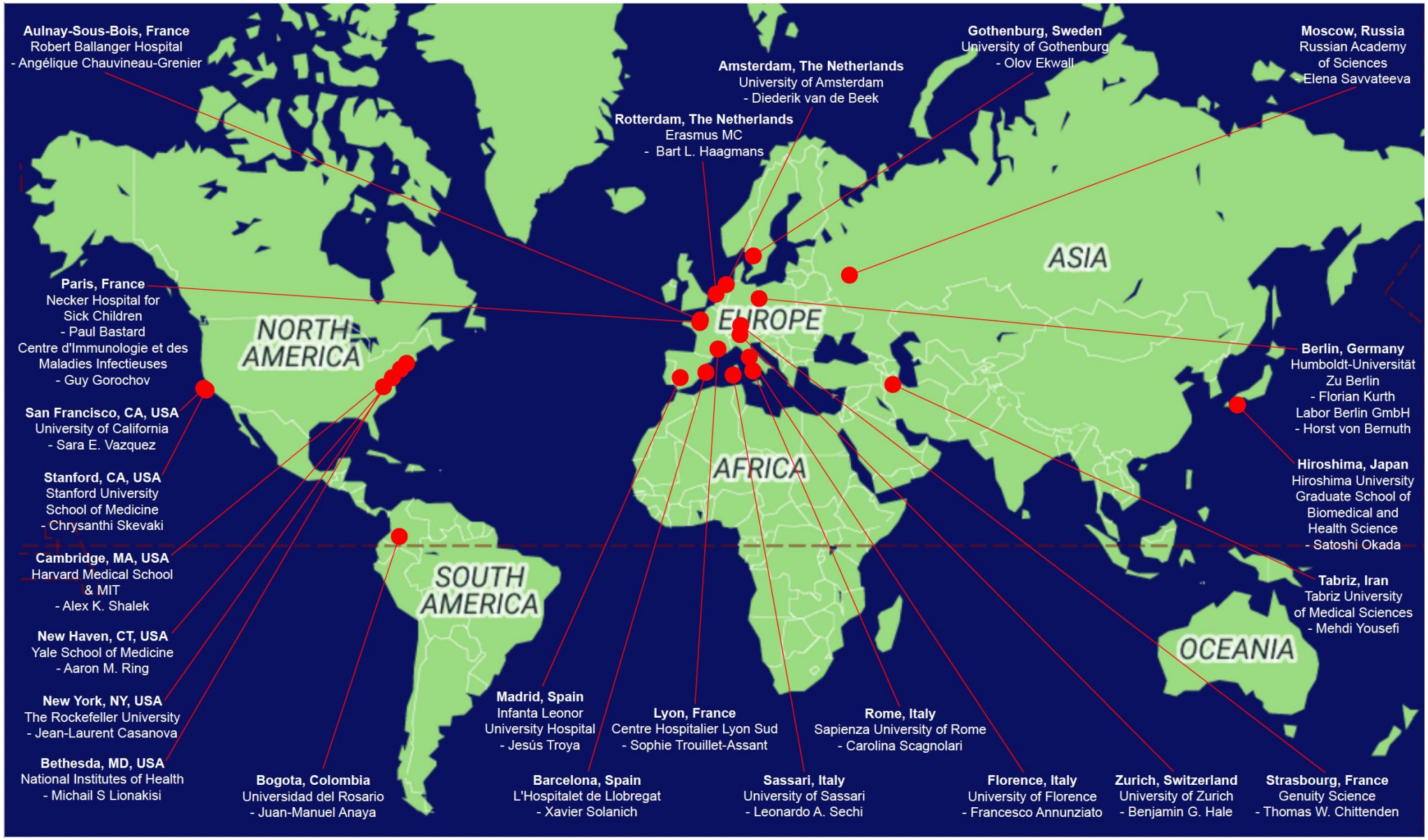
- Auto-Abs can block the protective effect of type I IFNs

- Auto-Abs found before infection in all cases tested
- Most patients with auto-Abs are men
- Most are > 65 years of age

Replicated world-wide

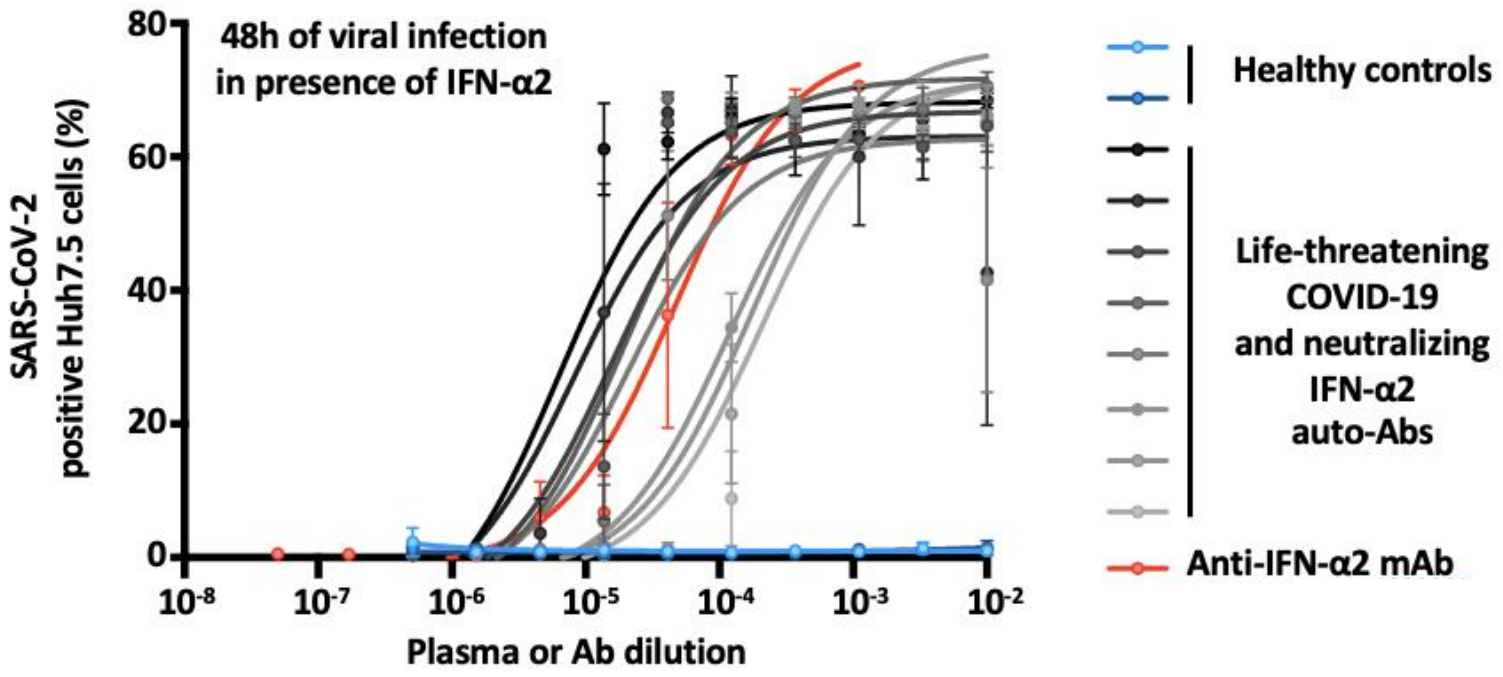
Bastard et al., *Science*, 2020

Auto-antibodies to type I IFNs: replications



Design by Dana Liu

The auto-Abs block the protective effect of IFN-α treatment against SARS-CoV-2



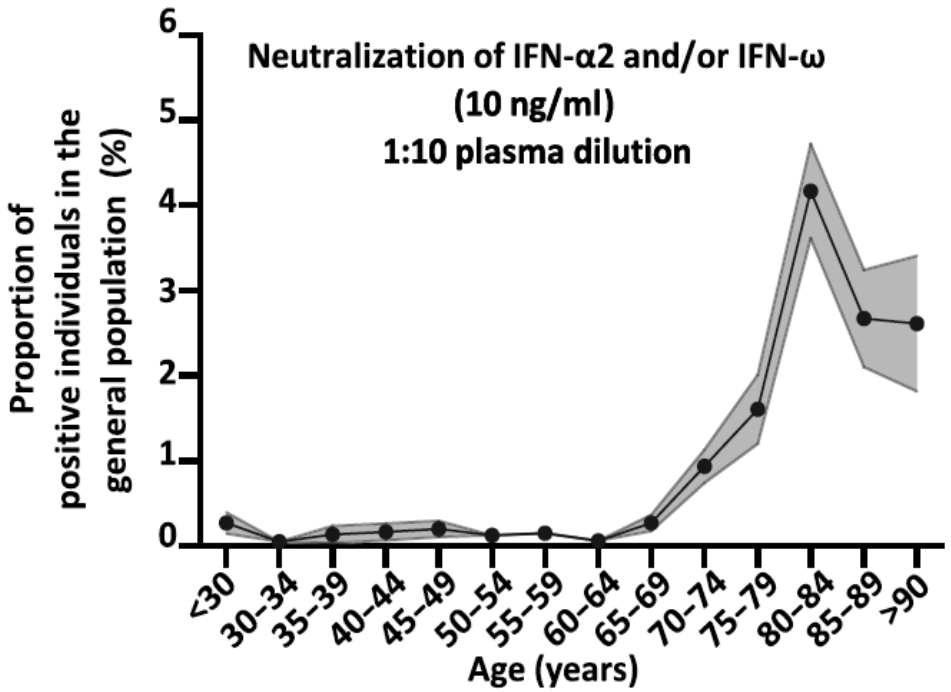
Rice lab

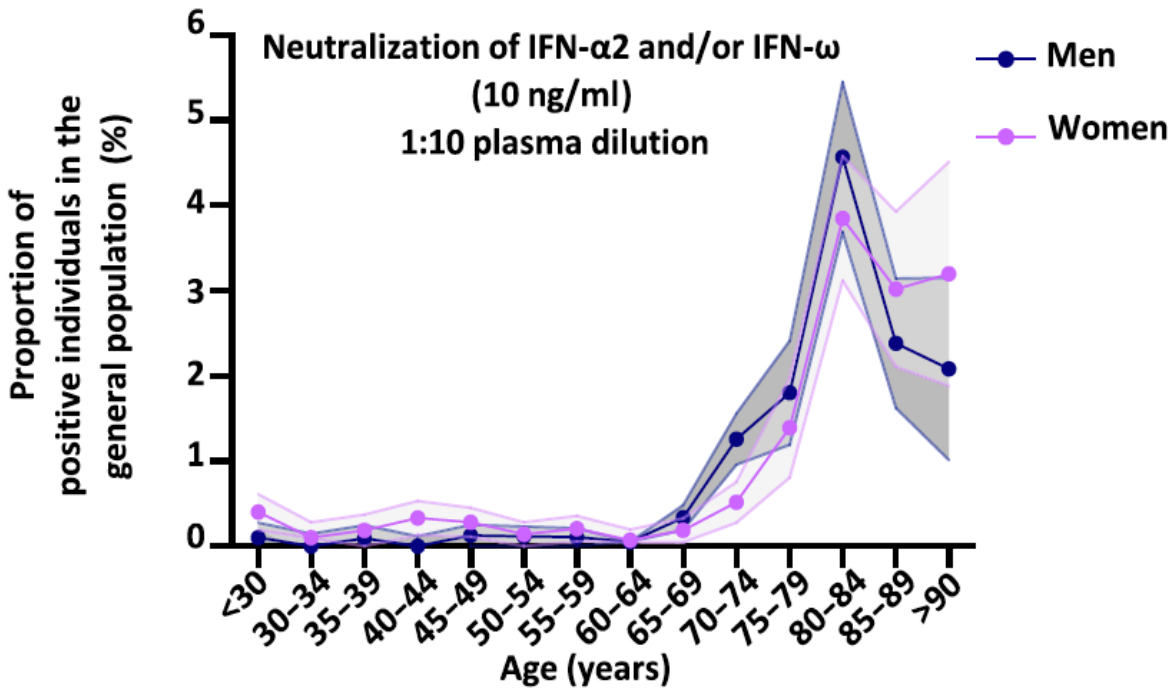
Auto-Abs to type I IFNs, even diluted 1:1,000 times, block the protective effect of IFN-α2 against SARS-CoV-2

What is the epidemiology of auto-Abs to type I IFNs in the general population ?

Increased prevalence of auto Abs neutralizing 10 ng/ml of IFN-α2 and/or IFN-ω in subjects older than 65 years

> 34,000 individuals

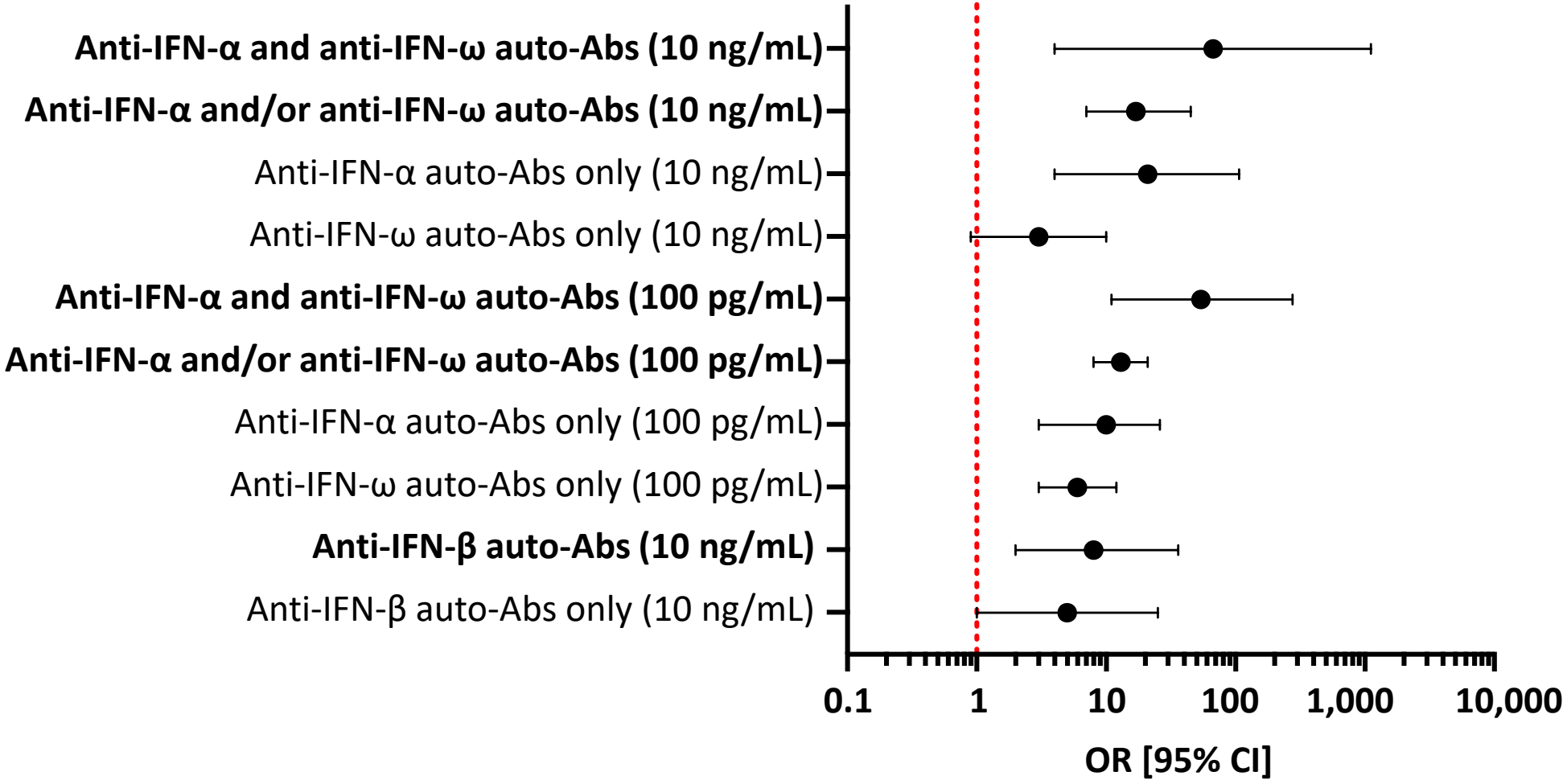




Risk of critical COVID-19 conferred by these auto-Abs is extremely high

Bastard et al., *Science Immunology*, 2021

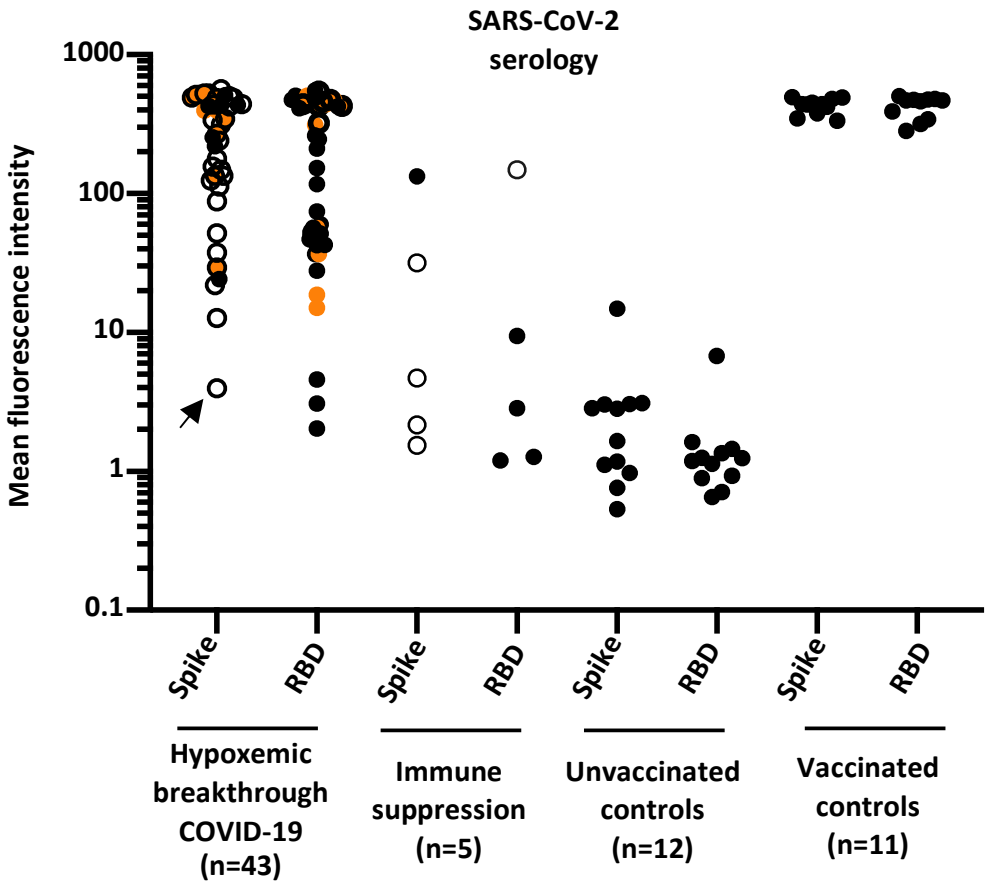
Risk of critical COVID-19 pneumonia in patients with neutralizing auto-Abs when compared with that of asymptomatic/mild infection

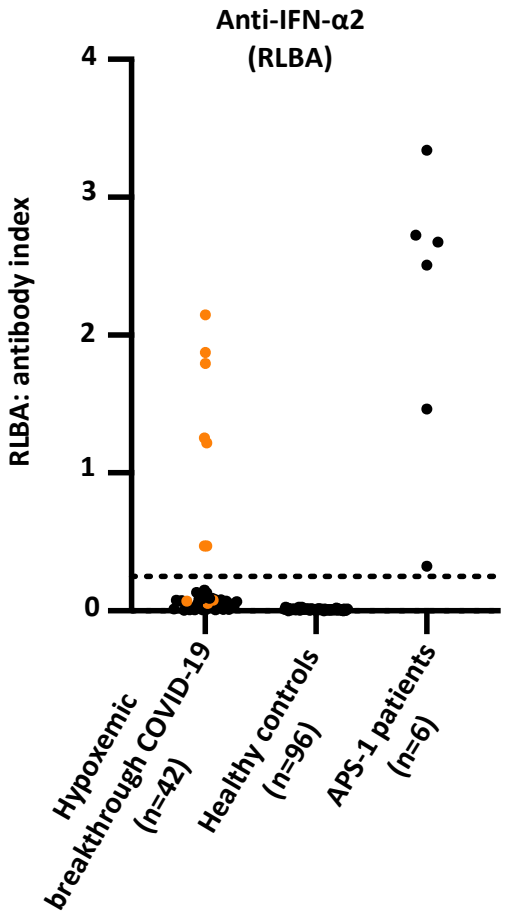


	Proportion of critical patients with auto-Abs	*P*-value
Anti-IFN-α and anti-IFN-ω auto-Abs (10 ng/mL)	5.6%	7.8×10^{-13}
Anti-IFN-α and/or anti-IFN-ω auto-Abs (10 ng/mL)	9.8%	$< 10^{-13}$
Anti-IFN-α auto-Abs only (10 ng/mL)	3.4%	$1.8.x\ 10^{-9}$
Anti-IFN-ω auto-Abs only (10 ng/mL)	0.8%	0.057
Anti-IFN-α and anti-IFN-ω auto-Abs (100 pg/mL)	7.1%	$< 10^{-13}$
Anti-IFN-α and/or anti-IFN-ω auto-Abs (100 pg/mL)	13.6%	$< 10^{-13}$
Anti-IFN-α auto-Abs only (100 pg/mL)	2.9%	2.8×10^{-9}
Anti-IFN-ω auto-Abs only (100 pg/mL)	3.6%	3.9×10^{-10}
Anti-IFN-β auto-Abs (10 ng/mL)	1.3%	1.7×10^{-3}
Anti-IFN-β auto-Abs only (10 ng/mL)	0.96%	0.043

Can these auto-Abs lead to severe disease despite vaccination ?

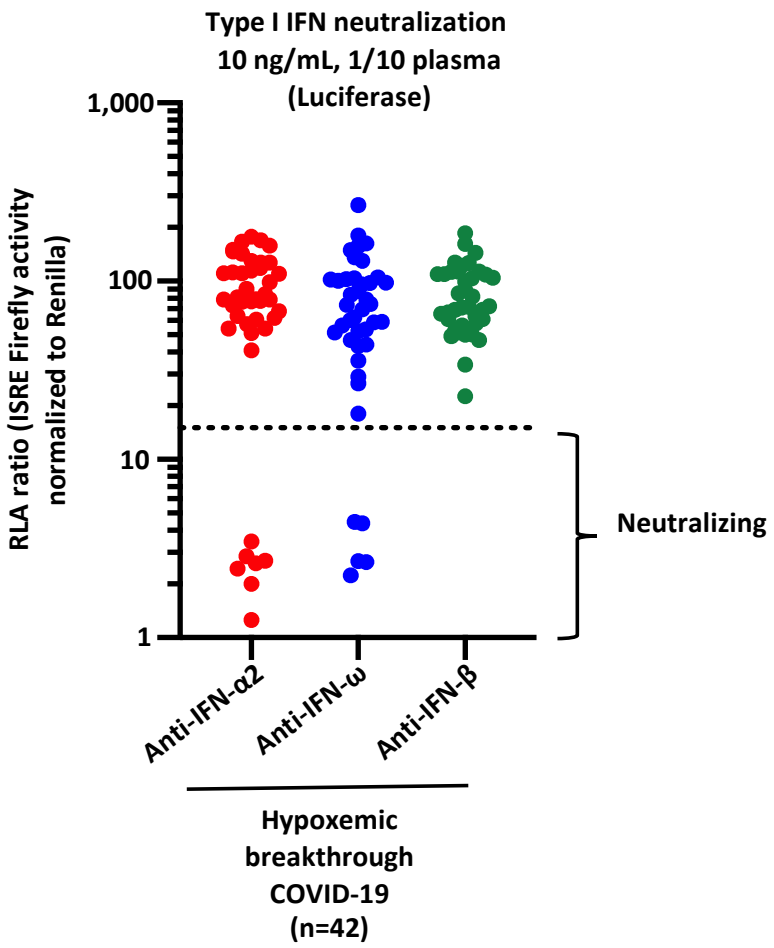
Hypoxemic breakthrough COVID-19 pneumonia in patients with good serological response but auto-Abs to type I IFNs

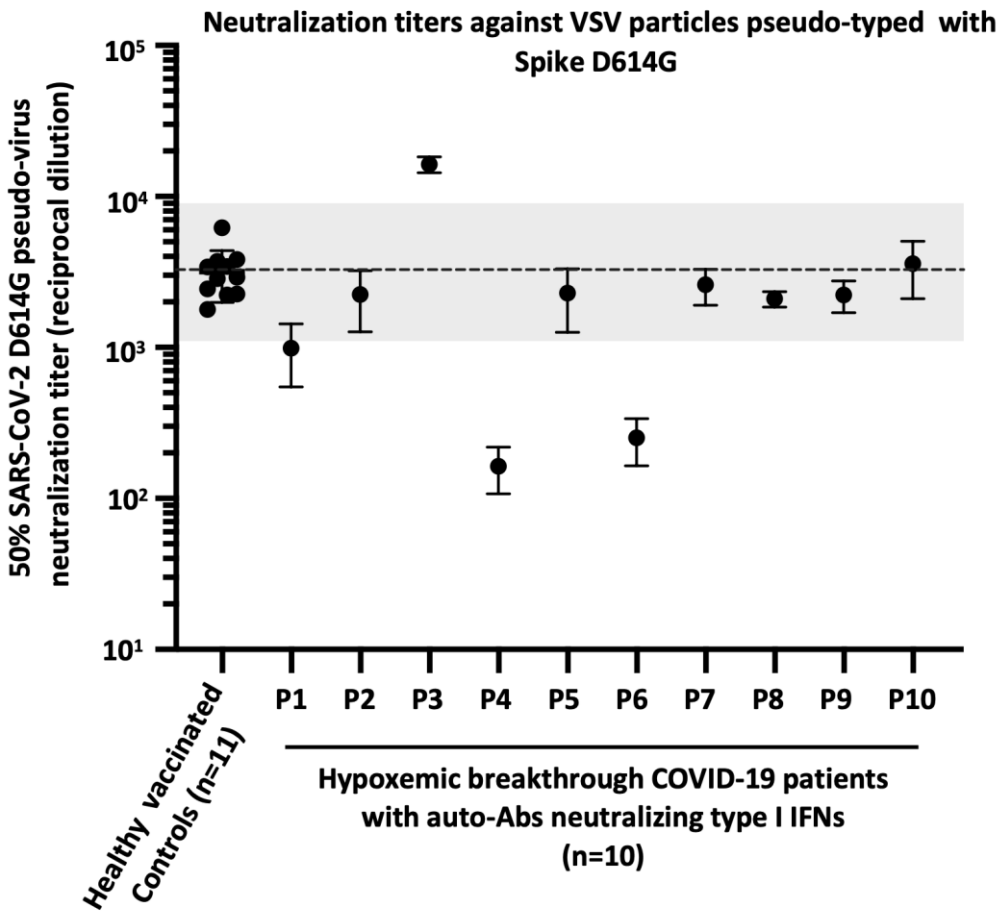




Bastard et al., *Science Immunology*, 2022

Hypoxemic breakthrough COVID-19 pneumonia in patients with auto-Abs neutralizing type I IFNs





Auto-Abs to type I IFNs underlie about 20% of hypoxemic breakthrough COVID-19 infections

Bastard et al., *Science Immunology*, *2022*

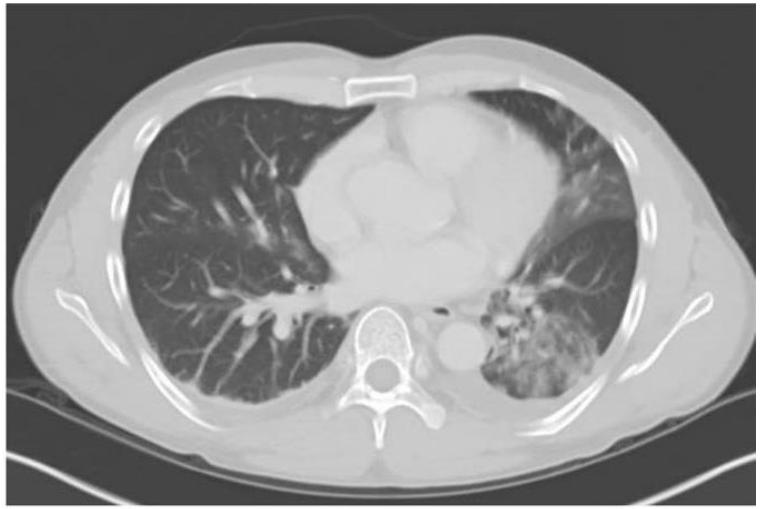
"Among the 4.4 million COVID-19 deaths reported in the MPIDR COVerAGE database, 0.4 per cent (over 17,200) occured in children and adolescents under 20 years of age"

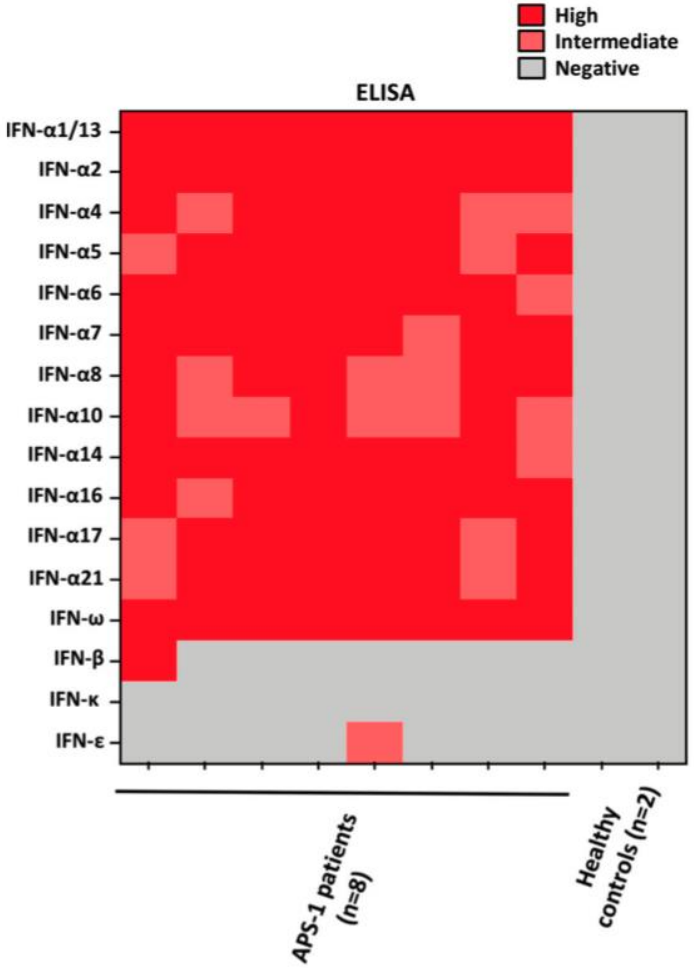
(Unicef)

Can children also suffer from severe COVID-19 pneumonia because of auto-Abs to type I IFNs ?

APS-1 patients have pre-existing auto-Abs to type I IFNs and are at high risk of severe COVID-19

Critical COVID-19 pneumonia
APS-1 (*AIRE*$^{-/-}$), 16-year-old
ICU for respiratory distress





22 APS-1 patients infected with SARS-CoV-2:
- From 7 countries
- 8 to 48 years old

- All have auto-Abs to type I IFNs since early childhood

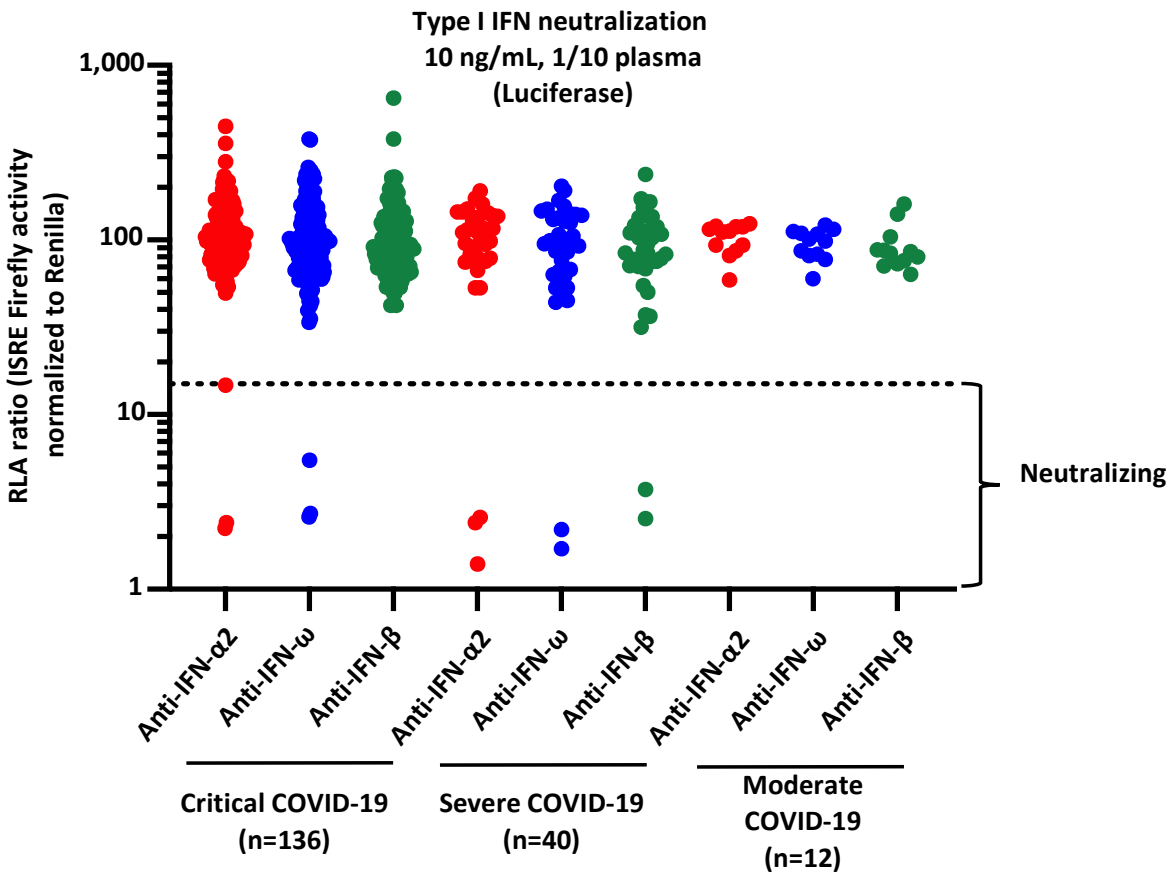
Out of 22 international patients
- 86% severe pneumonia
- 68% in ICU
- 4 deaths
- 2 asymptomatic

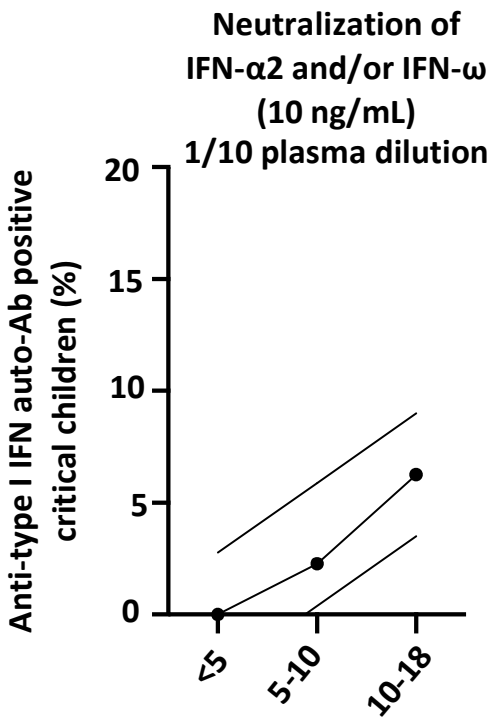
4 others without severe disease in Germany
2 Brazilian patients diagnosed with APS-1 after severe COVID-19

What about children without APS-1 ?

Meisel et al., *JCI*, 2021
Bastard et al., *JEM-b*, 2021

Auto-Abs against type I IFNs in children with hypoxemic COVID-19 pneumonia





7 (3.7%) children neutralize 10ng/mL of type I IFNs

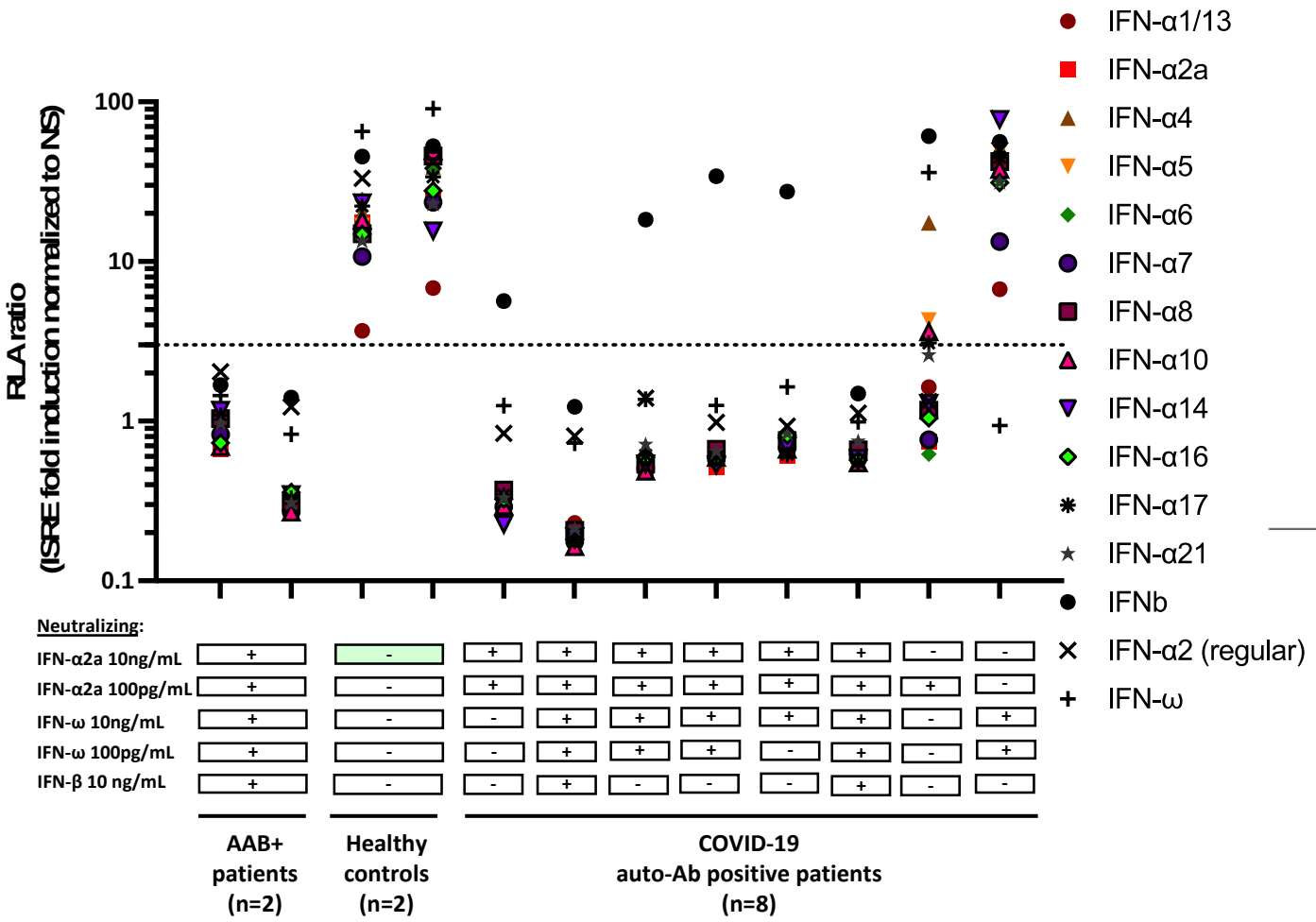
12 (6.4%) children neutralize only 100pg/mL of type I IFNs

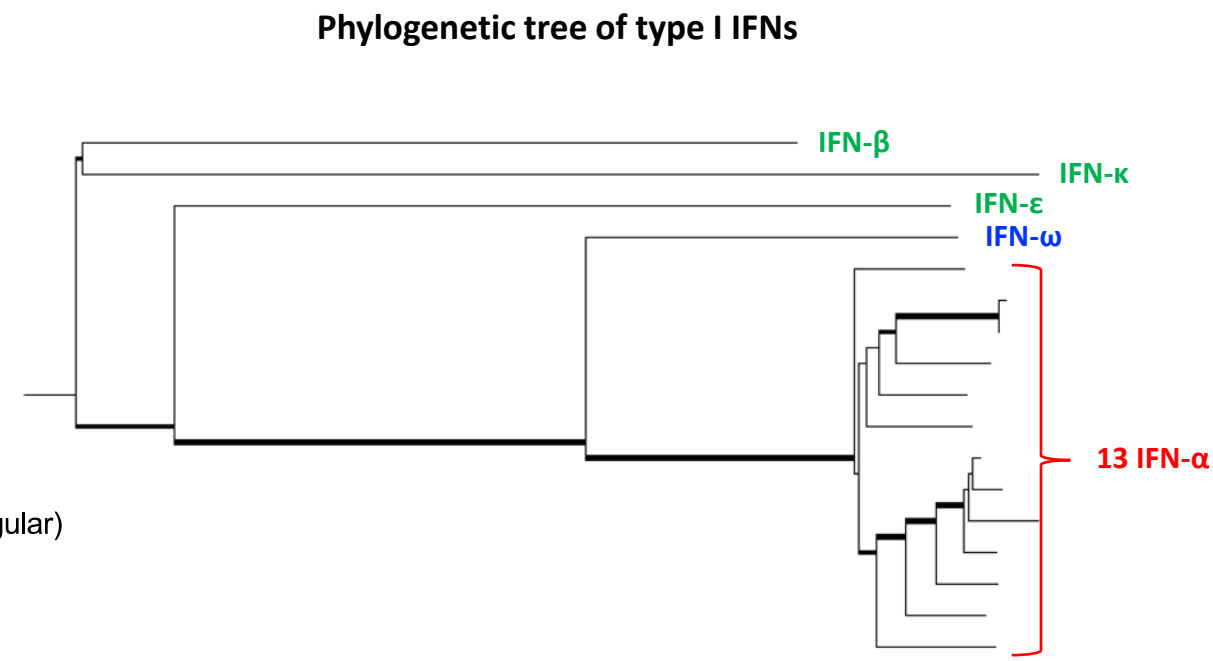
10% of children with COVID-19 pneumonia have auto-Abs neutralizing type I IFNs

What are the characteristics of auto-Abs to type I IFNs in children ?

Bastard et al., *In preparation*

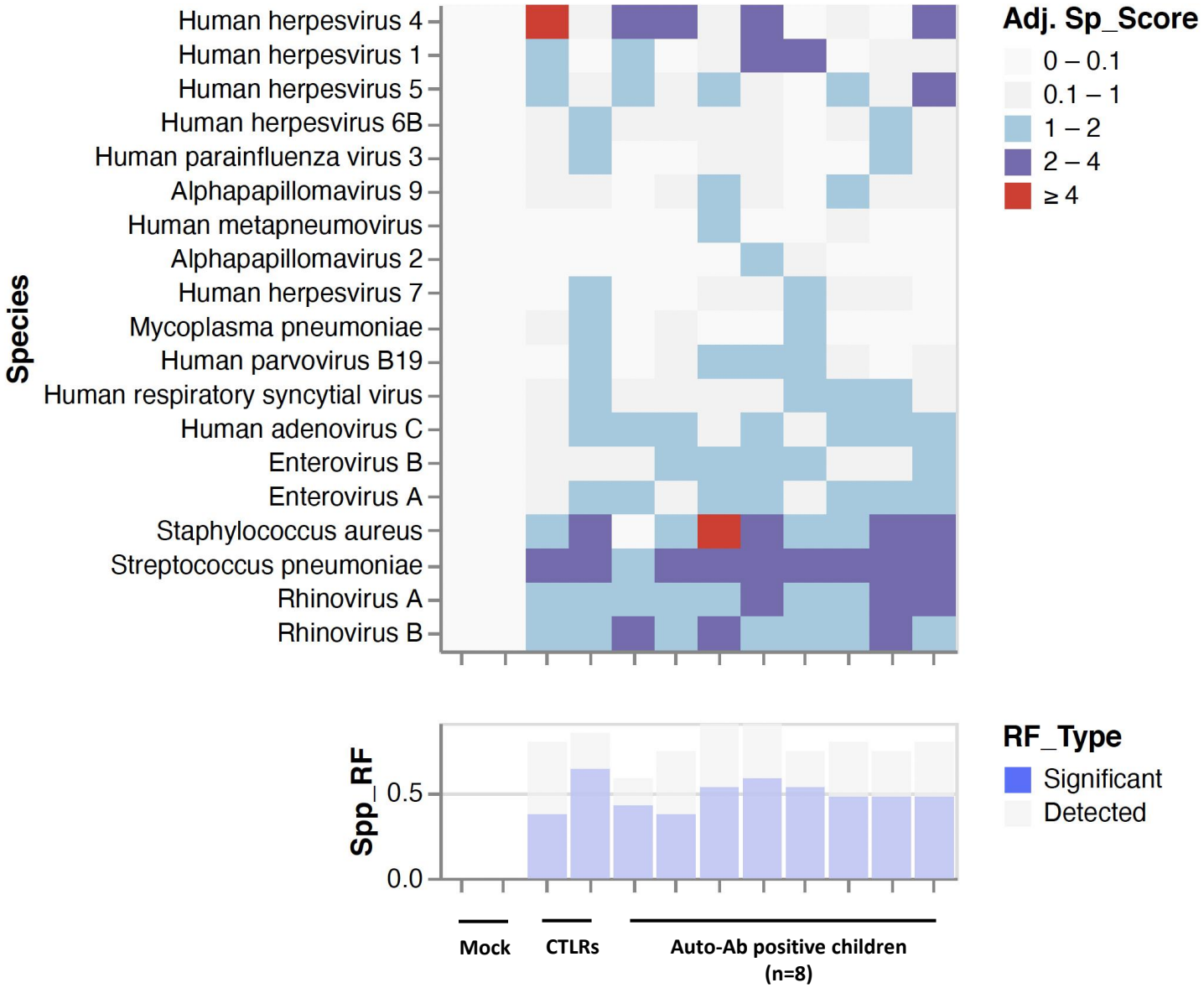
Auto-Abs to IFN-α2 neutralize the 13 IFN-α





Auto-Abs to IFN-α2 neutralize the 13 closely related IFN-α's, while auto-Abs to IFN-ω do not, at the concentrations tested

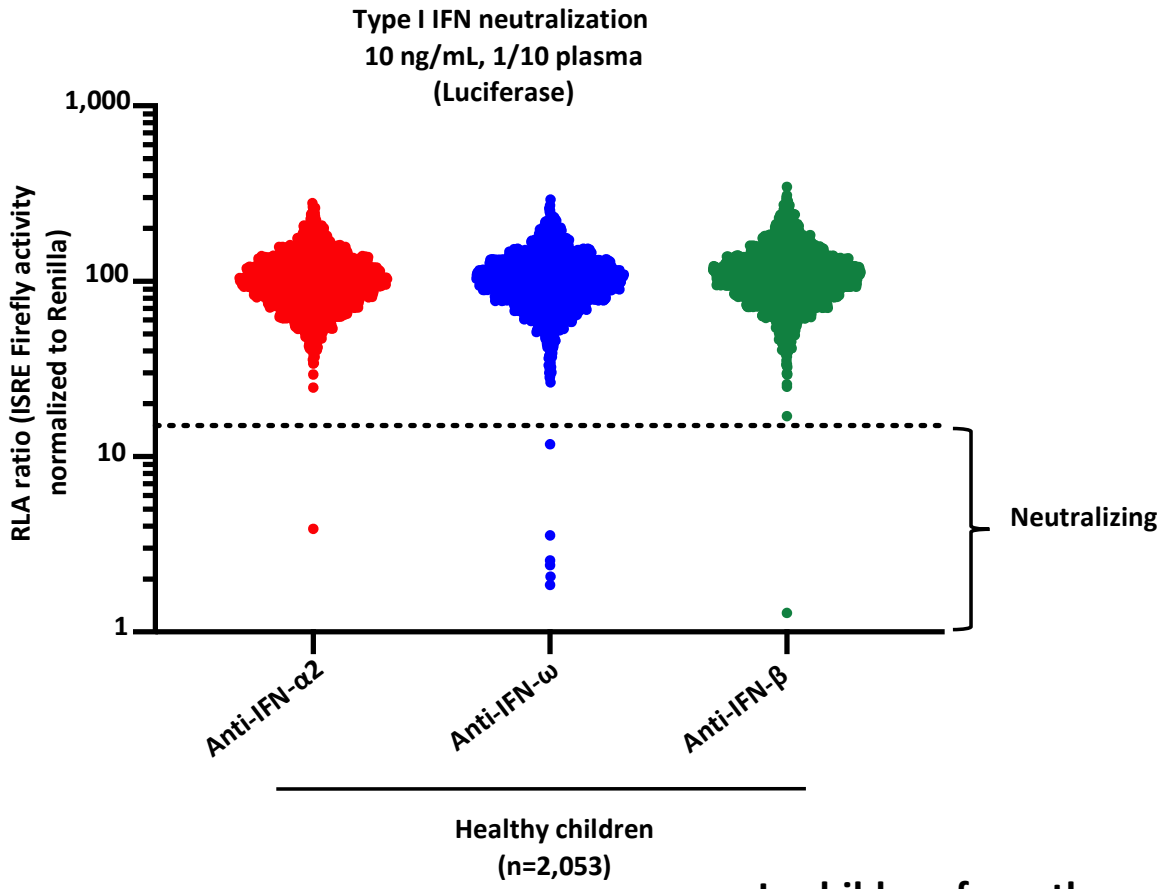
Children with auto-Abs to type I IFNs have been exposed to common pathogens

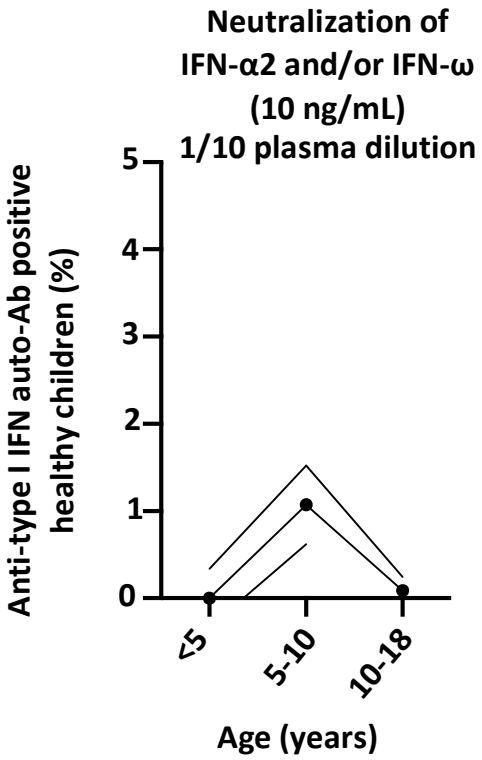


What is the prevalence in children from the general population?

Auto-Abs against type I IFNs in healthy uninfected children

> 2,000 healthy children
From Spain, Belgium, Canada, Estonia and Pakistan



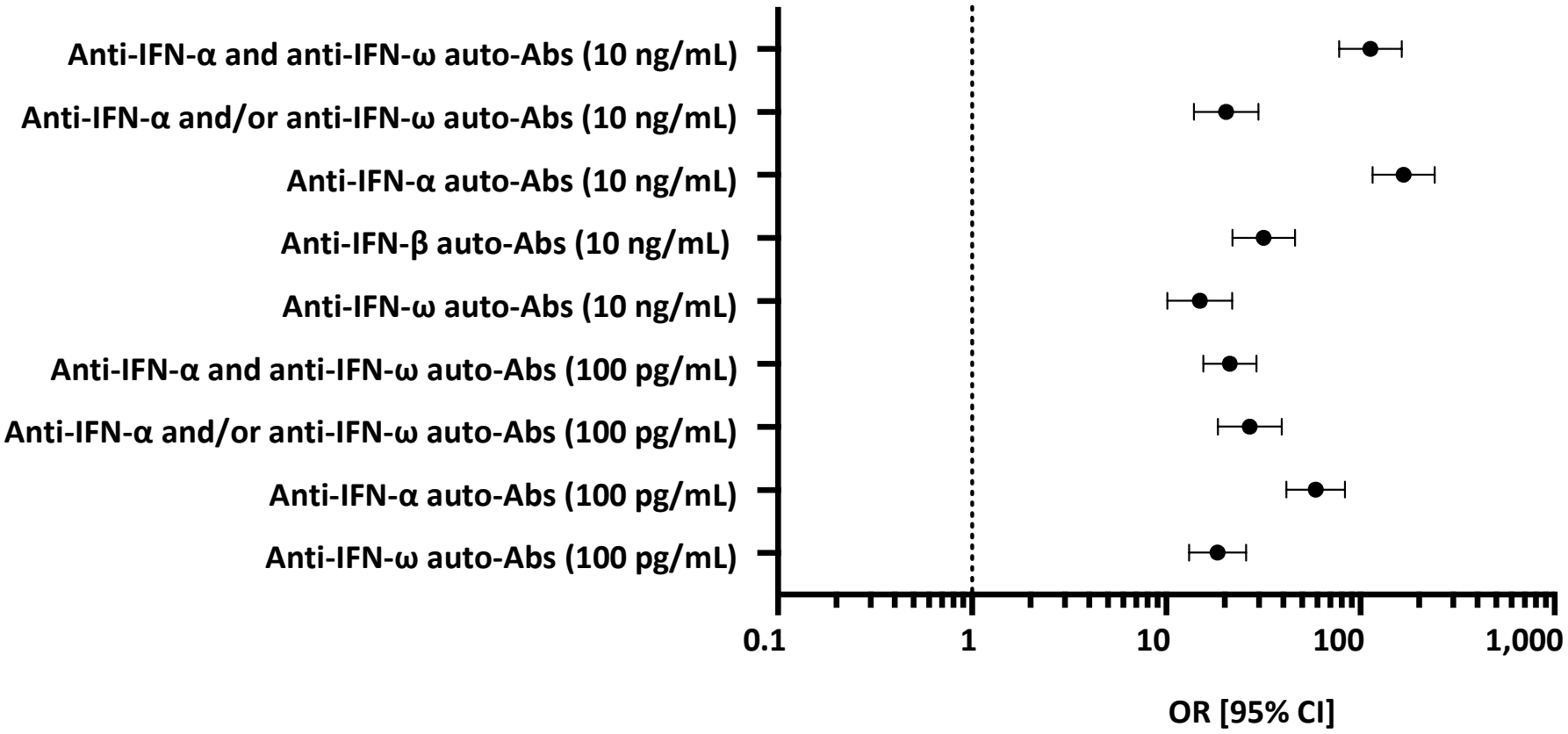


In children from the general population:
8 (0.36%) neutralize 10 ng/mL of IFN-α2, IFN-ω and/or IFN-β, and 2% neutralize 100pg/mL of IFN-α2 or IFN-ω

What is the risk of severe COVID-19 pneumonia in children with auto-Abs to type I IFNs ?

Bastard et al., *In preparation*

Risk of life-threatening COVID-19 pneumonia in children with neutralizing auto-Abs



	Proportion of pediatric patients with auto-Abs	*P*-value
Anti-IFN-α and anti-IFN-ω auto-Abs (10 ng/mL)	2.1%	5.3×10^{-5}
Anti-IFN-α and/or anti-IFN-ω auto-Abs (10 ng/mL)	3.7%	2.2×10^{-5}
Anti-IFN-α auto-Abs (10 ng/mL)	3.2%	1.7×10^{-6}
Anti-IFN-β auto-Abs (10 ng/mL)	1%	1.8×10^{-3}
Anti-IFN-ω auto-Abs (10 ng/mL)	2.6%	3.4×10^{-4}
Anti-IFN-α and anti-IFN-ω auto-Abs (100 pg/mL)	3.8%	7.4×10^{-4}
Anti-IFN-α and/or anti-IFN-ω auto-Abs (100 pg/mL)	10.1%	$< 10^{-13}$
Anti-IFN-α auto-Abs (100 pg/mL)	5.4%	1.2×10^{-9}
Anti-IFN-ω auto-Abs (100 pg/mL)	8.6%	1×10^{-17}

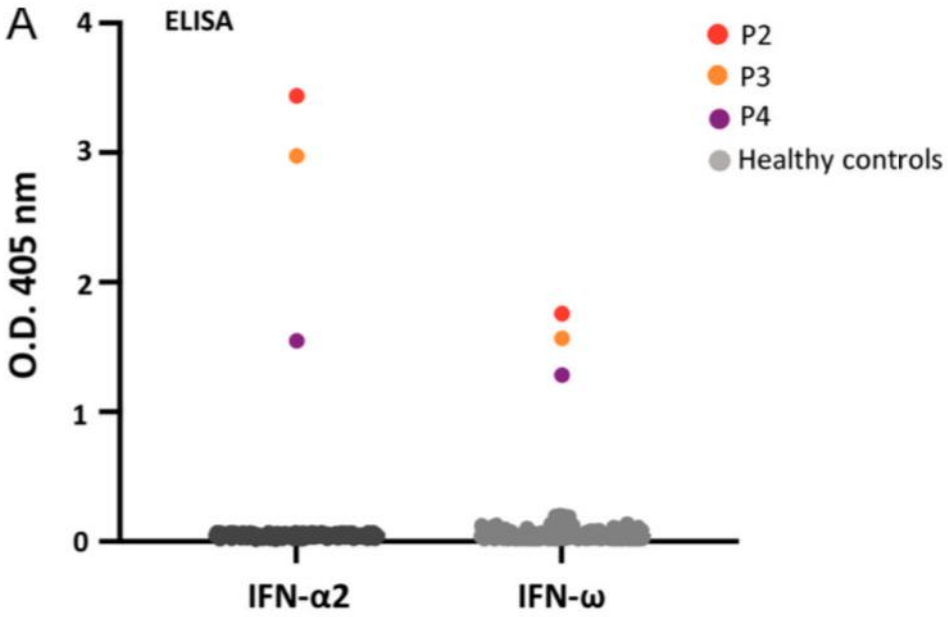
Can auto-Abs to type I IFNs underlie other viral diseases?

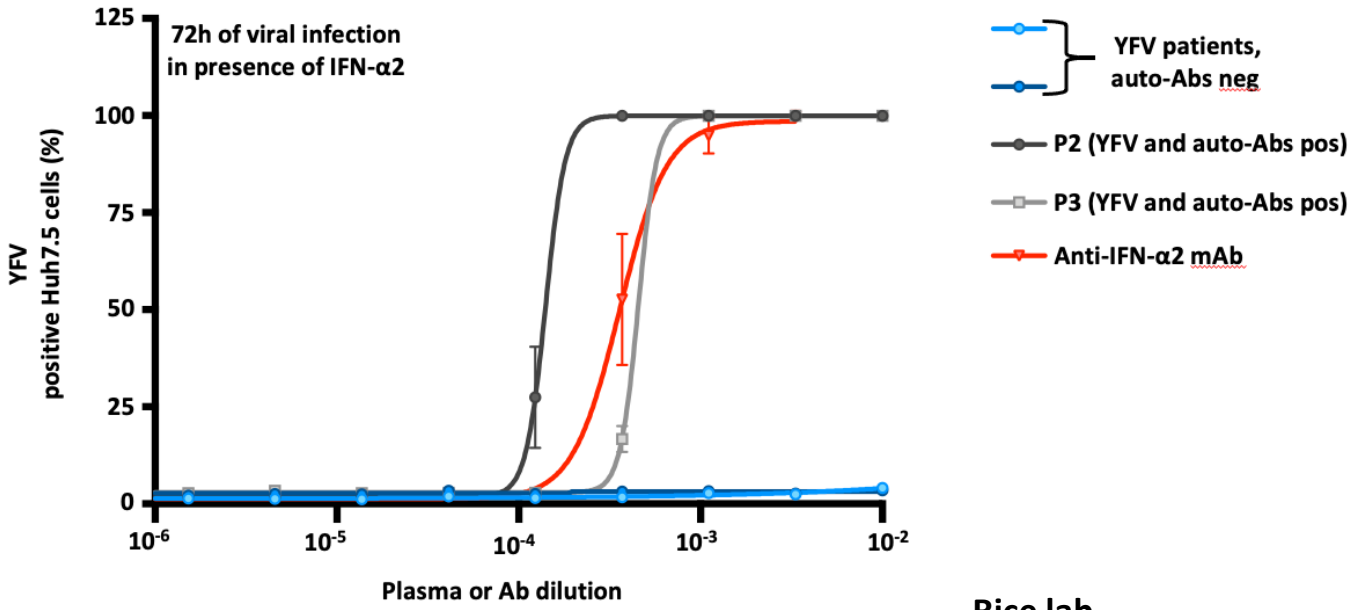
Auto-Abs to type I IFNs and adverse reactions to YFV vaccine

Risk groups of adverse reactions to the YFV vaccine:
(Seligman, *Vaccine*, 2014)

- Men > 55 years old
- Young women
- SLE patients
- Thymectomy (because of thymoma!)
- 2 young siblings with Addison's disease

➔ **Auto-Abs to type I IFNs**





Rice lab

Auto-Abs to type I IFNs underlie over a third of adverse events to live attenuated YFV vaccine

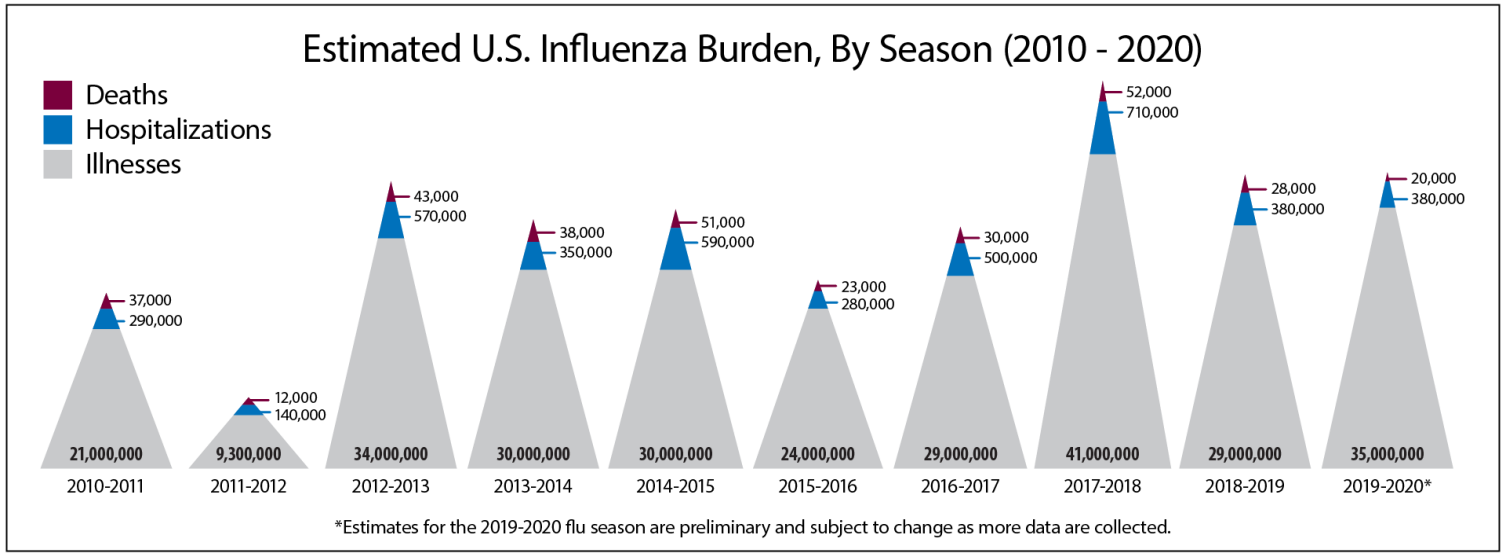
Bastard et al., *JEM-a*, 2021

➔ **And flu ?!**

Influenza pandemics and epidemics

1918

2010-2020

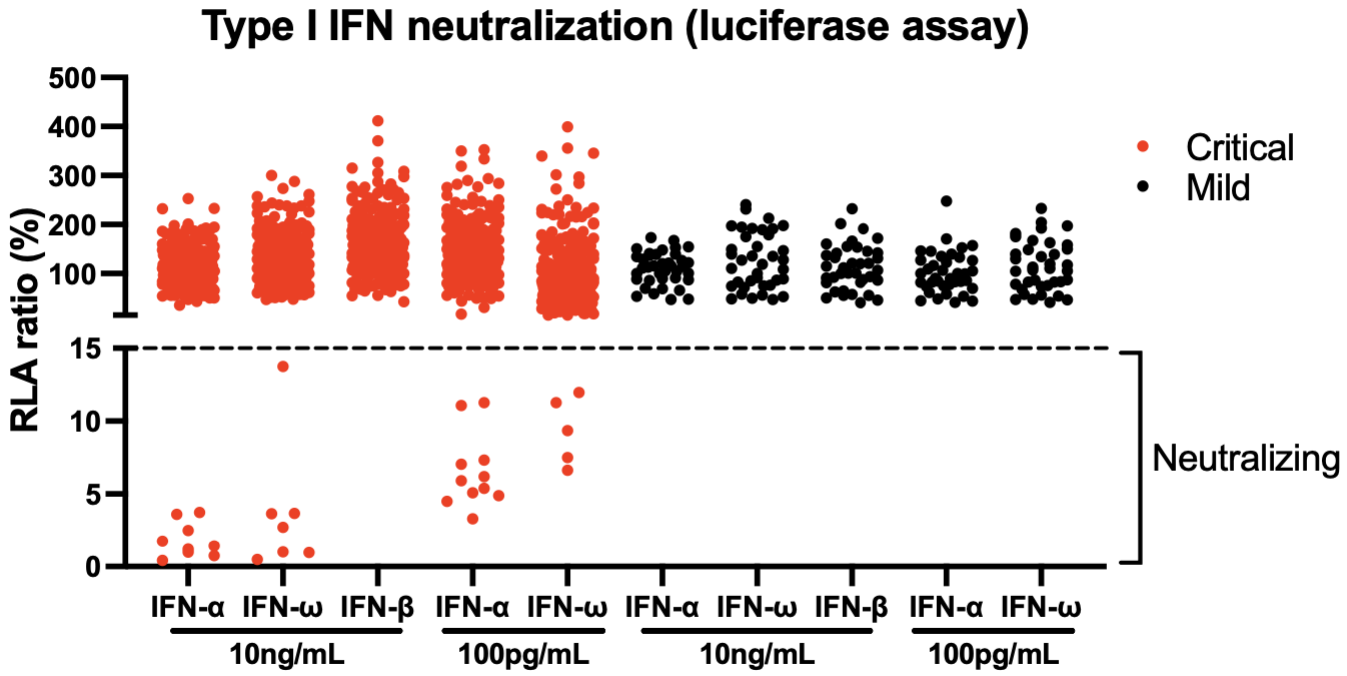


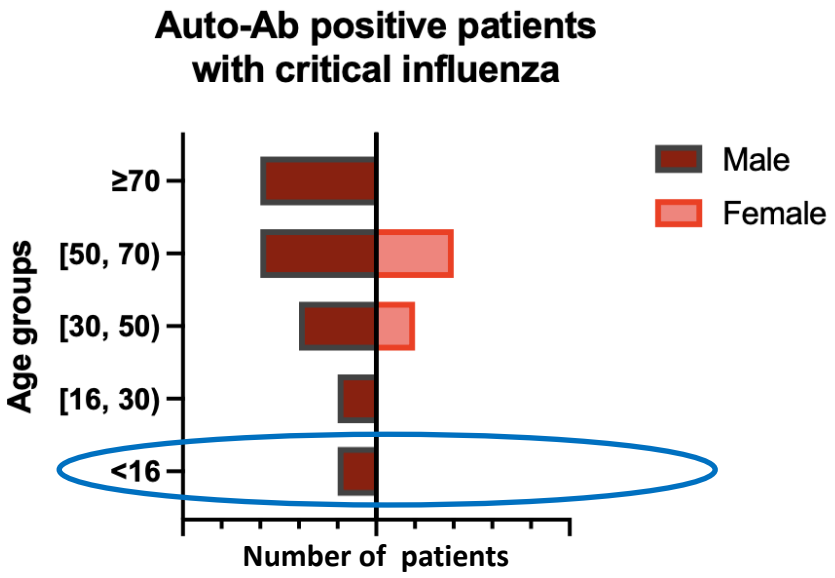
Increased risk of severe influenza in the elderly

Can auto-Abs to type I IFNs underlie severe influenza pneumonia?

Influenza division, Center for Disease Control
Otis Historical Archives National Museum of Health & Medicine

Auto-Abs to type I IFNs underlie critical influenza pneumonia



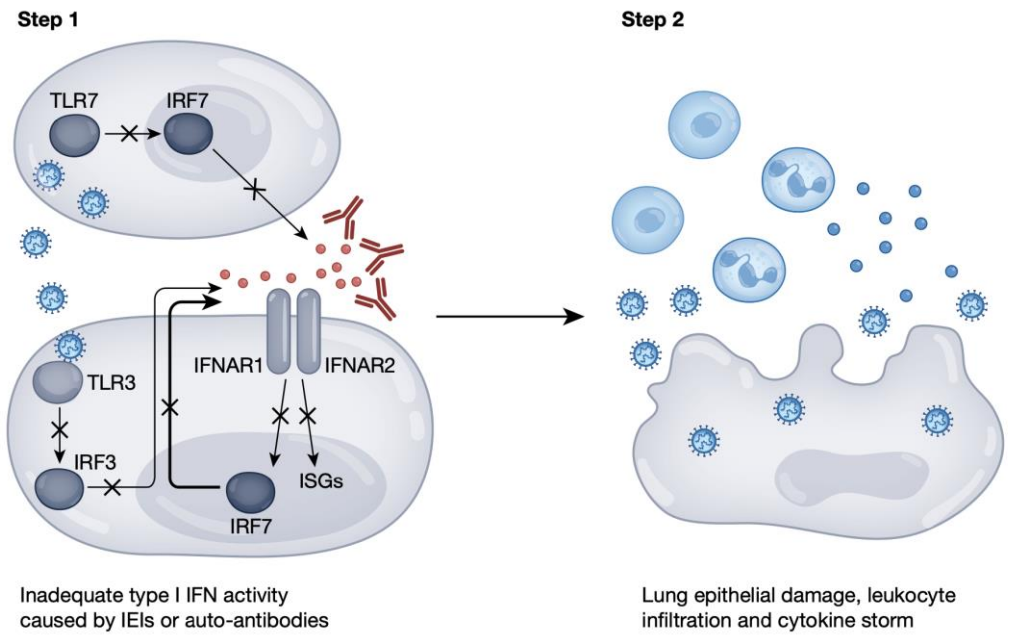


3 children
including 1 child with
hypomorphic RAG1 deficiency

Auto-Abs to type I IFNs can cause hypoxemic influenza pneumonia

Zhang et al., *J Ex Med*, 2022

Auto-antibodies to type I IFN immunity and immune dysregulation in critical COVID-19 (and beyond)



Zhang et al., *Nature*, 2022

Bastard et al., *Curr Op Immunol.*, 2022

Biological implications:

- **COVID-19: auto-immunity to intrinsic immunity**
- **Could explain the increased risk in the elderly**
- **But also some of the severe pediatric cases**

Clinical implications:

- **Diagnosis & screening (ELISA)**
- **Prevention: vaccination & boosters !**
- **Treatment: IFN-β, mAbs, antivirals, Ab depletion**

Many remaining questions:

- **Other viral infections?**
- **When to detect in children ?**
- **Other auto-immune diseases?**
- **What about in some malignancies?**
- **Specific treatments for the patients?**
- **Causes of the auto-Abs to type I IFNs?**

MERCI BEAUCOUP !

The physicians, the patients & their families
COVID Human genetic effort

Jean-Laurent Casanova, Laurent Abel

Adrian Gervais, Tom Le Voyer, Jérémie Rosain, Quentin Philippot
Aurélie Cobat, Anne Puel, Qian Zhang, Emmanuelle Jouanguy, Shen-Ying Zhang

Comité d'organization RIIP, Alexandre Belot, Olivia Boyer, et tout le comité scientifique
UIH-R: Unité d'Immuno-hématologie pédiatrique at Necker
Bénédicte Neven, Pierre Quartier, Stéphane Blanche, Alain Fischer, Despina Moshous, Martin Castelle, Brigitte Bader-Meunier, Romain Lévy

HGID lab in Paris and NY: Jérémy Manry, Anne Puel, Lucy Bizien, Vivien Béziat, Arnaud Fekkar, Bertrand Boisson, Jonathan Bohlen, Romain Lévy, Lazaro Lorenzo, Mélanie Migaud, Yoann Seeleuthner, Maya Chrabieh, Marie Materna, Yelena Nemirowskaya, Mark Woollett, Dana Liu

All friends & collaborators: Guy Gorochov, Pierre Tiberghien & EFS team, Isabelle Meyts, Sophie Assant, Helen Su, Luigi Notarangelo & NIH team, Eleftherios Michailidis, Charles M. Rice & team, Matthieu Mahevas, Aurélien Sokal, Constances cohort, 3-C cohort, French COVID

Imagine Institute: Stanislas Lyonnet, all the staff & teams at Imagine, &
Fondation Bettencourt-Schueller & **Fondation pour la recherche médicale**
Michelson Philanthropies & *Science* prize for Immunology & la Société Française de Virologie

imagine INSTITUT DES MALADIES GÉNÉTIQUES
Université de Paris
COVID HUMAN GENETIC EFFORT
hhmi Howard Hughes Medical Institute
NIH National Institutes of Health
SCIENTIA PRO BONO HUMANI GENERIS The Rockefeller University 1901

Merci beaucoup !

Picture by R. Doisneau

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