

# Understanding the variability in responses to COVID-19 illness in older adults

August 20 2021, by Ciara O'shea

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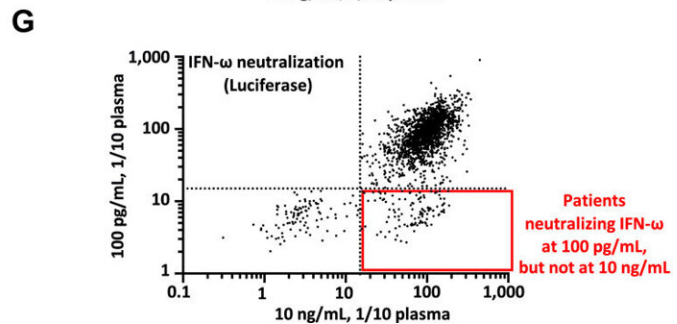
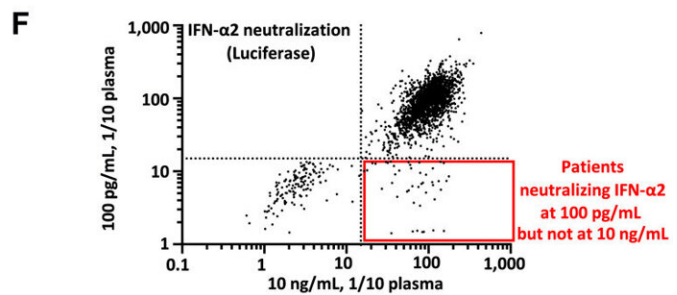
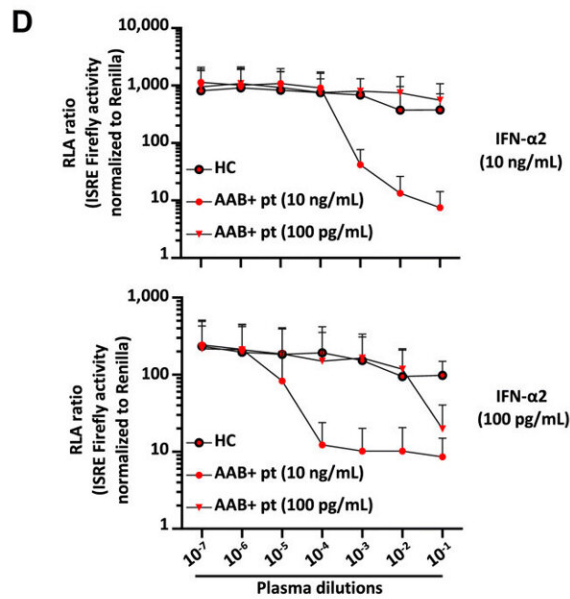
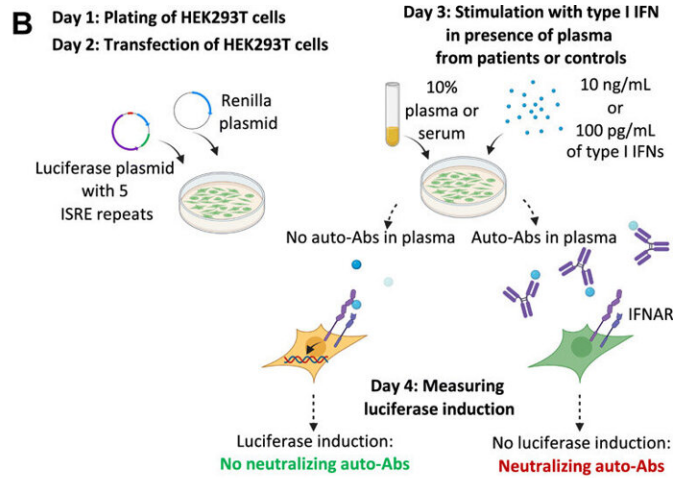
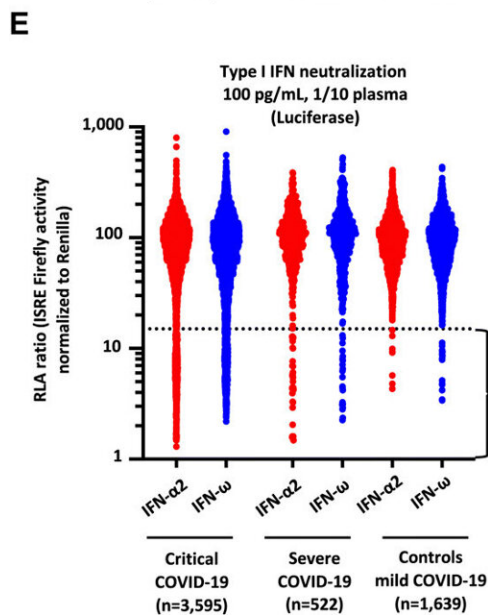
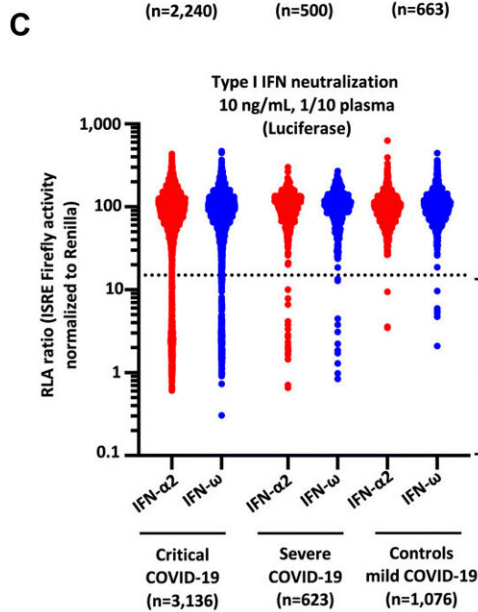
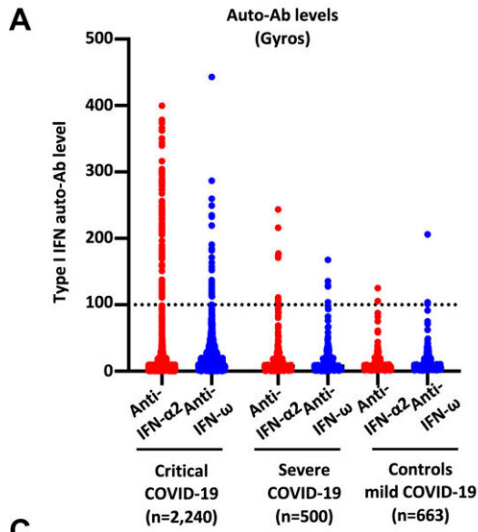


Fig. 1. Neutralizing auto-Abs against IFN- $\alpha$ 2 and/or IFN- $\omega$  in patients with life-threatening COVID-19. (A) Gyros (high-throughput automated ELISA) results for auto-Abs against IFN- $\alpha$ 2 and/or IFN- $\omega$  in patients with critical COVID-19 (N=2,240), severe COVID-19 (N=500), or asymptomatic/mild SARS-CoV-2 infection (N=663). (B) Schematic representation of the neutralization assay developed in HEK293T cells, using a luciferase system. ISRE: interferon-sensitive response elements. (C) Results for the neutralization of 10 ng/mL IFN- $\alpha$ 2 or IFN- $\omega$  in the presence of plasma 1/10 from patients with critical COVID-19 (N=3,136), severe COVID-19 (N=623), or controls with mild/asymptomatic infection (N=1,076). Relative luciferase activity is shown (ISRE dual luciferase activity, with normalization against Renilla luciferase activity) after stimulation with 10 ng/mL IFN- $\alpha$ 2 or IFN- $\omega$  in the presence of plasma 1/10. RLA: relative luciferase activity. (D) RLA after stimulation with IFN- $\alpha$ 2 at a concentration of 10 ng/mL or 100 pg/mL, with various dilutions of plasma from a positive control (from 1/10 to 1/107) neutralizing 10 ng/mL of type I IFNs (AAB+ pt, 10 ng/mL), a patient neutralizing 100 pg/mL of type I IFNs but not 10 ng/mL (AAB+ pt, 100 pg/mL), and a healthy control (HC). AAB: auto-Ab. Pt: patient. (E) Neutralization of 100 pg/mL IFN- $\alpha$ 2 or IFN- $\omega$  in the presence of plasma 1/10 from patients with critical COVID-19 (N=3,595), severe COVID-19 (N=522), or controls with asymptomatic/mild infection (N=1,639). (F) Plot showing luciferase induction after stimulation with 10 ng/mL or 100 pg/mL IFN- $\alpha$ 2, in the presence of plasma from patients with critical COVID-19. Dotted lines indicate neutralizing levels, defined as induction levels below 15% of the mean value for controls tested the same day. Patients with antibodies neutralizing both 10 ng/mL and 100 pg/mL IFN- $\alpha$ 2 are shown in the bottom left corner, whereas the patients in the bottom right corner had antibodies capable of neutralizing only 100 pg/mL IFN- $\alpha$ 2. (G) Plot showing luciferase induction after stimulation with 10 ng/mL or 100 pg/mL IFN- $\omega$ , for patients with critical COVID-19. Credit: DOI: 10.1126/sciimmunol.abl4340

Since the start of the COVID-19 pandemic in December 2019, more than 200 million people have been infected with SARS-CoV-2, resulting

in at least 4 million deaths, and probably closer to 7 to 9 million deaths worldwide. Interindividual clinical variability in the course of acute infection has been found to be vast, ranging from silent infection to rapid death.

Trinity researchers from the School of Medicine and Tallaght University Hospital have joined a large collaborative study, involving leading clinical research facilities from 38 countries internationally, to examine the reasons for this variability in morbidity and mortality in COVID-19 illness. The study is published in the journal *Science Immunology*.

This unique study explains a new mechanism that accounts for some of the variability in COVID-19 illness. The research has found that autoantibodies—antibodies that mistakenly target and react with a person's own tissues or organs—block a key mechanism in the antiviral immune response; the type 1 interferon response.

The type 1 interferon response is an immune mediator involved in antiviral protection and is a critical response in the body's ability to fight viral infections. This new research shows that the autoantibodies that neutralize the [interferon response](#), sharply increase in prevalence in patients over 60 years of age and underlie about 20% of all fatal COVID cases. Researchers believe that this may explain some of the variability that we see in COVID-19 illness in older people.

The presence of auto-antibodies in some individuals with critical COVID-19 illness was previously demonstrated by Paul Bastard (University of Paris, France) and Jean-Laurent Cassanova (Howard Hughes Medical Institute, NY, U.S.). Bastard and Cassanova have led this current collaborative study which demonstrates this key mechanism by which some individuals are more vulnerable to COVID-19 illness. These autoantibodies sharply increase with age and are present in about 4% of [older adults](#) aged >70 years of age in the general population,

partially explaining why older adults are so vulnerable to severe COVID-19.

## Key findings

- Auto-antibodies neutralizing type I interferons (a key immune defense mechanism) are present in 4% of adults aged 70 years or older and may account for up to 20% of COVID-19 deaths.
- Auto-antibodies are capable of neutralizing the body's own interferon anti-viral response.
- Auto-antibodies sharply increase after the age of 70 years.

The Irish contribution to this wider global research effort came from the inclusion of older individuals which were part a larger program of research at Trinity College Dublin and Tallaght University Hospital. The NH-COVAIR project is a longitudinal investigation of COVID-19 in Irish nursing home residents, examining the relationship between frailty, Clinical outcomes, immunophenotype, and vaccine response in nursing home residents.

The inclusion of this information into the larger global study is vital as older adults, and particularly those residing in nursing homes, are frequently excluded from research based on age or medical co-morbidity. This study, by demonstrating the striking increase in these autoantibodies after 70 years of age, emphasizes the need to not only include older adults in immunology research, but the need to study the variability in immune responses in older adults and in particular in those living with frailty, such as nursing home residents. By excluding older adults from research, this could mean the opportunity for key discoveries about immune system variability is lost.

## Implications for clinical care and treatment

The research presents several possibilities for clinical care and treatment of the COVID-19 illness. The identification of these auto-antibodies may inform clinicians about who is more susceptible to severe COVID-19 illness, who may benefit from early hospital admission and early treatment and who may benefit from therapy such as interferon-beta ( trials of nebulised interferon-beta are currently underway).

The Trinity team's ongoing NH-COVAIR study, is led by Dr. Adam Dyer, Professor Seán Kennelly and Dr. Nollaig Bourke, will aim to explore these responses further over the course of the next few years. This research emphasizes the need to include older people and those with advanced levels of frailty in basic scientific research.

Professor Seán Kennelly, Consultant Physician in Geriatric and Stroke Medicine, Department of Age-related healthcare, Tallaght University Hospital and Clinical Associate Professor in Medical Gerontology, Trinity College and co-author of the study said: "This important study explains why COVID-19 can have severe clinical consequences in some people but not others. We were delighted to ensure Tallaght University Hospital and Trinity College Dublin were represented amongst this international consortium of leading clinical research institutes. We are extremely grateful for the generous support of local nursing home residents, staff, and families who participated in this study."

Dr. Adam Dyer, ICAT Fellow & Specialist Registrar in Geriatric Medicine, Trinity College Dublin & Tallaght University Hospital and co-author of the study said: "The findings of this landmark study emphasize the need to explore immune-system variability in older adults. As clinicians, we see an immense variability in morbidity and mortality in older adults infected with this virus, and exploring the underlying immunological reasons why is an urgent unmet clinical need."

**More information:** Paul Bastard et al, Autoantibodies neutralizing

type I IFNs are present in ~4% of uninfected individuals over 70 years old and account for ~20% of COVID-19 deaths, *Science Immunology* (2021). [DOI: 10.1126/sciimmunol.abl4340](https://doi.org/10.1126/sciimmunol.abl4340)

Provided by Trinity College Dublin

Citation: Understanding the variability in responses to COVID-19 illness in older adults (2021, August 20) retrieved 18 June 2024 from <https://medicalxpress.com/news/2021-08-variability-responses-covid-illness-older.html>

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