# The risk of COVID-19 death is much greater and age-dependent with type I IFN autoantibodies

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# Abstract

SARS-CoV-2 infection fatality rate (IFR) doubles with every five years of age from childhood onward. Circulating autoantibodies neutralizing IFN-α, IFN-ω, and/or IFN-β are found in ~20% of deceased patients across age groups. In the general population, they are found in ~1% of individuals aged 20-70 years and in >4% of those >70 years old. With a sample of 1,261 deceased patients and 34,159 uninfected individuals, we estimated both IFR and relative risk of death (RRD) across age groups for individuals carrying autoantibodies neutralizing type I IFNs, relative to non-carriers. For autoantibodies neutralizing IFN-α2 or IFN-ω, the RRD was 17.0[95% CI:11.7-24.7] for individuals under 70 years old and 5.8[4.5-7.4] for individuals aged 70 and over, whereas, for autoantibodies neutralizing both molecules, the RRD was 188.3[44.8-774.4] and 7.2[5.0-10.3], respectively. IFRs increased with age, from 0.17%[0.12-0.31] for individuals <40 years old to 26.7%[20.3-35.2] for those ≥80 years old for autoantibodies neutralizing IFN-α2 or IFN-ω, and from 0.84%[0.31-8.28] to 40.5%[27.82-61.20] for the same two age groups, for autoantibodies neutralizing both molecules. Autoantibodies against type I IFNs increase IFRs, and are associated with high RRDs, particularly those neutralizing both IFN-α2 and -ω. Remarkably, IFR increases with age, whereas RRD decreases with age. Autoimmunity to type I IFNs appears to be second only to age among common predictors of COVID-19 death.


# Introduction

There have already been more than 250 million SARS-CoV-2 infections and at least five million deaths from COVID-19 worldwide. Interindividual clinical variability in the course of infection with SARS-CoV-2 is immense, ranging from silent infection in about 40% of cases to acute respiratory distress syndrome in ~3% of cases[1-3]. Death occurs in ~1% of cases[4]. Age is the strongest epidemiological predictor of COVID-19 death, with the risk of death doubling every five years of age from childhood onward[4,5]. Men are also at greater risk of death than women[3,6]. The COVID Human Genetic Effort[7] has shown that type I interferon (IFN) immunity is essential for protective immunity to respiratory infection with SARS-CoV-2[8-11]. We have reported that inborn errors of Toll-like receptor 3 (TLR3)-dependent type I IFN immunity can underlie life-threatening COVID-19 pneumonia in a small subset of patients[11]. Biochemically deleterious mutations of eight genes were found in 23 patients with critical COVID-19 (3.5% of 659 patients), including 18 patients under 60 years old. Remarkably, four patients, aged 25 to 50 years, had autosomal recessive (AR) deficiency of IFNAR1 or IRF7. Two other patients with AR IFNAR1 or TBK1 deficiency were independently reported[12,13]. The penetrance of those defects is unknown, but it is probably higher for AR than for autosomal dominant disorders. We then reported that X-linked recessive TLR7 deficiency accounted for 1.8% of cases of life-threatening COVID-19 in men under 60 years old[10,14]. The penetrance of this disorder is apparently high but incomplete, especially in children. Deficiencies of IFNAR1 and IRF7 blunt type I IFN immunity across cell types, whereas defects of the TLR3 and TLR7 pathway preferentially affect respiratory epithelial cells and plasmacytoid dendritic cells, respectively[10,15].

We have also reported the presence of autoantibodies (auto-Abs) neutralizing high concentrations (10 ng/mL, with plasma diluted 1/10) of IFN-α2 and/or IFN-ω in about 10% of patients with critical COVID-19 pneumonia but not in individuals with asymptomatic or mild infection[9]. This finding has already been replicated in 13 other cohorts[16-29]. We then detected auto-Abs neutralizing lower, more physiological concentrations (100 pg/mL, with plasma diluted 1/10) of IFN-α2 and/or IFN-ω in 13.6% of patients with life-threatening COVID-19, and 18% of deceased patients[8]. The proportion of male patients was greater in patients with auto-Abs than in patients without auto-Abs[8,9]. In addition, 1.3% of patients with critical COVID-19 had auto-Abs neutralizing IFN-β (10 ng/mL, with plasma diluted 1/10), most without auto-Abs neutralizing IFN-α2 or IFN-ω. The prevalence of auto-Abs neutralizing IFN-α2 and/or IFN-ω in the general population increased with age, from 0.18% for 10 ng/mL and 1% for 100 pg/mL in individuals between 18 and 69 years old to 3.4% for 10 ng/mL and 6.3% for 100 pg/mL for individuals over 80 years old[8]. The prevalence of auto-Abs against IFN-β did not increase with age. The crude odds ratios (ORs) for critical COVID-19 as opposed to asymptomatic or mild infection in auto-Ab carriers relative to non-carriers ranged from 3 to 67, depending on the type I IFNs recognized and the concentrations neutralized[8]. At least 12 lines of evidence strongly suggest that auto-Abs against type I IFNs are strong determinants of COVID-19 death (Table 1). The specific impact of these auto-Abs on COVID-19 mortality according to age and sex remains unknown and is of major interest, as both the prevalence of these auto-Abs and the risk of death increase with age and are higher in men. Here, we estimated the relative risk of COVID-19 death (RRD) and the SARS-CoV-2 infection fatality rate (IFR) for type I IFN auto-Ab carriers relative to non-carriers, by sex and age category.

# Methods

## Study design

We enrolled 1,261 patients aged 20 to 99 years old who died from COVID-19 pneumonia, and 34,159 controls from the adult general population from whom samples were collected before the COVID-19 pandemic, as previously described[8]. All subjects were recruited according to protocols approved by local institutional review boards (IRBs). Auto-Ab determinations were performed as described by Bastard *et al.*[8,46], and were classified as neutralizing high concentrations (10 ng/ml) of IFN-α2, -ω, or –β, or low concentrations (100 pg/ml) of IFN-α2, or –ω (Additional Methods).

## RRDs and IFRs for carriers of neutralizing autoantibodies

We estimated the RRD in individuals carrying auto-Abs neutralizing type I IFNs relative to non-carriers, using large samples of patients who died from COVID-19 and of individuals from the general population. For each combination of auto-Abs, a Firth's bias-corrected logistic regression model, including auto-Ab status, sex and age was fitted (Supplementary Table 1). For assessments of the effect of age and sex on the RRD due to auto-Abs, we added auto-Abs*sex and auto-Abs*age interaction terms to the Firth's logistic regression model (Additional Methods). We estimated the IFR for carriers of neutralizing auto-Abs

infected with SARS-CoV-2 ($IFR_{AAB}$) following Bayes' theorem, and using the age-dependent prevalence of auto-Abs in deceased patients and in the general population together with the reported age-specific IFR[4] as detailed in Additional Methods.

# Results

## Patients and controls

We estimated the RRD of individuals carrying auto-Abs neutralizing type I IFNs relative to non-carriers by Firth's logistic regression, using large samples of 1,261 patients who died from COVID-19 and 34,159 individuals from the general population from whom samples were collected before the pandemic. In this study design, in which controls are sampled from the baseline population regardless of disease status, the ORs obtained by logistic regression approximate to the RR in the absence of the assumption of rare disease[47] (see Additional Methods). For auto-Abs neutralizing low concentrations (100 pg/mL) of IFN-α2 and/or IFN-ω, we used 1,121 patients who died from COVID-19, and 10,778 individuals from the general population (Table 2).

Assessments of auto-Abs neutralizing high concentrations (10 ng/mL) of IFN-α2 and/or IFN-ω were available for 1,094 deceased patients, and 34,159 individuals from the general population (Table 2). We also had assessments of auto-Abs neutralizing 10 ng/mL IFN-β for a subsample of 636 deceased patients and 9,126 individuals from the general population (Table 2). RRD was estimated by means of Firth's bias-corrected logistic regression, considering death as a binary outcome and adjusting for sex and age in six classes (20-39, 40-49, 50-59, 60-69, 70-79, ≥80 years). For assessment of the effect of age and sex on RRD, we added auto-Abs*age and auto-Abs*sex interaction terms to the logistic model (see Methods and Additional Methods).

## RRD for carriers of auto-Abs neutralizing low concentrations of type I IFNs

We first estimated the RRD for individuals carrying auto-Abs neutralizing low concentrations of IFN-α2 or IFN-ω. As expected, increasing age and maleness were highly significantly associated with greater risk of COVID-19 death (*P* values $\leq 10^{-16}$, Supplementary Table 1). Different age classes were used to test the interaction with the presence of auto-Abs, and the best fit was obtained with a two-age class model (20-69 and ≥70 years, Supplementary Table 2) with a significant effect of the auto-Abs*age interaction term (*P* value = $4\times10^{-6}$). The RRD associated with auto-Abs did not vary significantly with sex (*P* value = 0.81). These interaction results are fully consistent with the distribution of RRD according to age (Fig. 1A) and sex (Fig. 1B), with a clear decrease in RRD after the age of 70 years, and no sex effect. Overall, the RRD for individuals carrying auto-Abs neutralizing IFN-α2 or IFN-ω decreased from 17.0 [95% CI: 11.7-24.7] before the age of 70 years to 5.8 [4.5-7.4] for individuals ≥70 years old (Fig. 2A, Supplementary Table 3). We then applied the same strategy to other combinations of auto-Abs neutralizing low concentrations of

IFN, and observed similar age effects on RRDs (Supplementary Table 1). The presence of auto-Abs neutralizing both IFN-α2 and IFN-ω was associated with the highest RRD, estimated at 188.3 [45.8-774.4]) for individuals under the age of 70 years and 7.2 [5.0-10.3] for those over 70 years old (Fig. 2A, Supplementary Table 3).

### RRD for carriers of auto-Abs neutralizing high concentrations of type I IFNs

We then estimated the RRD for the presence *versus* the absence of auto-Abs neutralizing high concentrations (10 ng/mL) of type I IFN. The effect of age on RRD was similar to that observed with auto-Abs neutralizing low concentrations of type I IFN, with the use of two age classes providing the best fit (Supplementary Table 2 and 4). The RRDs associated with auto-Abs neutralizing high concentrations of type I IFNs were higher than those associated with auto-Abs neutralizing low concentrations, and also decreased with age (Fig. 2B, Supplementary Table 5). The RRD for carriers of IFN-α2 or IFN-ω auto-Abs decreased from 62.4 [38.4-101.3] before the age of 70 years to 6.8 [5.1-9.2] after the age of 70 years, whereas carriers of auto-Abs against both IFN-α2 and IFN-ω had the highest RRD, estimated at 156.5 [57.8-423.4] and 12.9 [8.4-19.9] for subjects <70 years and ≥70 years old, respectively (Fig. 2B, Supplementary Table 5). Interestingly, auto-Abs neutralizing high doses of IFN-β had the lowest RRD before 70 years (7.0 [2.2-22.4]), with no significant age-dependent association (*P* value = 0.37).

### IFR in individuals carrying auto-Abs neutralizing low concentrations of type I IFNs

We then estimated the IFR in SARS-CoV-2-infected individuals carrying auto-Abs neutralizing low concentrations of type I IFNs. According to Bayes' theorem, $IFR_{AAB}$ can be expressed as a function of the age-dependent prevalence of auto-Abs in deceased patients and in the general population together with the reported age-specific IFR[4] (see Supplementary Information). For all combinations of auto-Abs, the $IFR_{AAB}$ was much higher than the overall IFR. Figure 3 illustrates this much higher IFR for carriers of auto-Abs neutralizing low concentrations of IFN-α2 or IFN-ω; it exceeded 1% and 10% for subjects over the ages of 40 and 60 years, respectively. Considering other combinations of auto-Abs, the highest $IFR_{AAB}$ was observed for carriers of auto-Abs neutralizing both IFN-α2 and -ω, reaching 40.5% [27.8-61.2] in individuals over 80 years old (Fig. 4A and Supplementary Table 6). $IFR_{AAB}$ values were similar for all other combinations of auto-Abs. For example, the $IFR_{AAB}$ for individuals carrying auto-Abs neutralizing either IFN-α2 or -ω ranged from 0.17% [0.12-0.31] in individuals under 40 years old to 26.7% [20.3-35.2] in individuals over 80 years old. An exception was noted for the $IFR_{AAB}$ of carriers of anti-IFN-α2 auto-Abs, which was 1.8 to 2.6 times higher than that for carriers of auto-Abs neutralizing IFN-α2 or -ω in subjects under 60 years old.. The $IFR_{AAB}$ was also generally higher in male subjects than in female subjects, particularly in individuals carrying auto-Abs neutralizing both IFN-α2 and -ω (~2.7 times higher) (Supplementary Fig. 1).

### IFR in individuals carrying auto-Abs neutralizing high concentrations of type I IFNs

The age-, sex- and type I IFN-dependent patterns of $IFR_{AAB}$ observed for carriers of auto-Abs neutralizing high concentrations of IFN-α2 and/or -ω were similar to those previously obtained for carriers of auto-Abs neutralizing low concentrations of these molecules, but with higher values. For example, $IFR_{AAB}$ ranged from 3.1% [1.3-20.8] before 40 years of age to 68.7% [42.5-95.8] in those over 80 years old for carriers of auto-Abs neutralizing high concentrations of both IFN-α2 and -ω (Fig. 4B, Supplementary Table 7). $IFR_{AAB}$ values were ~5 times higher in male than in female subjects, across all age groups and auto-Abs combinations (Fig. 2). For carriers of auto-Abs neutralizing IFN-β (tested only at high concentration), $IFR_{AAB}$ was lower (by a factor of six to 71) than for individuals under the age of 80 years with auto-Abs neutralizing IFN-α2 and/or -ω. It ranged from 0.04% [0.01-0.16] for individuals under the age of 40 years to 2.2% [0.2-9.3] for the 70-79 years age group. In the oldest age-class, $IFR_{AAB}$ was 31.0% [2.4-88.1], similar to that for carriers of auto-Abs against IFN-α2 or -ω, albeit with a large confidence interval.

# Discussion

In this study, we estimated RR from the general population[47] to obtain the RRDs associated with auto-Abs. We also used IFR values previously reported for the general population[4] to estimate $IFR_{AAB.}$ We report high RRDs for carriers of auto-Abs neutralizing type I IFNs, ranging from 2.6 for auto-Abs neutralizing IFN-β (high concentration) in subjects over 70 years old to >150 for auto-Abs neutralizing both IFN-α2 and IFN-ω in subjects under 70 years old. For all types of auto-Abs, RRDs were three to 26 times higher in subjects under 70 years old than in older individuals. This is consistent with the increasing prevalence of auto-Abs in the general population with age (~1% under 70 years of age and >4% over 70 years of age), whereas the proportion of deceased patients with these auto-Abs is stable across age categories (~15-20%). The lower RRD observed in the elderly may be partly explained epidemiologically, by the larger contribution of other mortality risk factors, such as comorbid conditions, which become more frequent with increasing age. At the cellular level, aging is associated with immunosenescence, which may contribute to a defective innate and adaptive response to SARS-CoV-2 infection, thereby conferring a predisposition to severe COVID-19[48]. At the molecular level, global type I IFN immunity in the blood (plasmacytoid dendritic cells) and respiratory tract (respiratory epithelial cells) has been shown to decline with age[49-52]. These epidemiological, cellular, and molecular factors probably overlap. Thus, despite their increasing prevalence with age, auto-Abs against type I IFNs make a decreasing contribution to the risk of COVID-19 death with age due to the progressive development of additional age-dependent risk factors, including other mechanisms of type I IFN deficiency. However, for the very same reasons, $IFR_{AAB}$ increases dramatically with age in patients with auto-Abs, reaching 68.7% for carriers of auto-Abs neutralizing high concentrations of both IFN-α2 and -ω.

RRD and $IFR_{AAB}$ varied considerably with the IFNs recognized and the concentrations neutralized by auto-Abs. For most combinations involving auto-Abs against IFN-α2 and/or –ω, the neutralization of low concentrations was associated with a lower RRD and a lower $IFR_{AAB}$ than the neutralization of high concentrations, suggesting that residual type I IFN activity may be beneficial in at least some patients. Blood IFN-α concentrations during acute asymptomatic or paucisymptomatic SARS-CoV-2 infection typically range from 1 to 100 pg/mL[8]. In addition, the presence of auto-Abs neutralizing both IFN-α2 and IFN-ω was associated with the highest RRD and $IFR_{AAB}$ values. Interestingly, IFN-α2 and IFN-ω are encoded by two genes, *IFNA2* and *IFNW1*, that have been shown to have evolved under strong selective constraints[53], consistent with their neutralization being harmful to the host. In addition, patients with auto-Abs against IFN-α2 have been shown to neutralize all 13 IFN-α subtypes[8,9], rendering any potential IFN-α redundancy inoperative[8,9]. Accordingly, the $IFR_{AAB}$ values for carriers of auto-Abs against IFN-α2 were higher than those for carriers of auto-Abs against IFN-ω in subjects under 60 years of age. In older age groups, this difference tended to disappear, consistent with the lower impact of auto-Abs in the elderly, as discussed above. Finally, auto-Abs neutralizing IFN-β were less common, and associated with lower RRD and $IFR_{AAB}$ values (by about one order of magnitude) than auto-Abs against IFN-α2 and/or IFN-ω, in all age groups except the over-80s. This less deleterious effect of auto-Abs neutralizing IFN-β is consistent with a mouse study showing that the blockade of IFN-β alone does not alter the early dissemination of lymphocytic choriomeningitis virus[54]. Overall, auto-Abs against type I IFNs are associated with very high RRD and IFR values, and the magnitude of this effect is much larger than that of other known common risk factors apart from age, such as maleness (Fig. 4), comorbidities, or the most significant common genetic variant on chromosome 3, all of which have been associated to life-threatening COVID-19 with ORs of about 2[3].

Despite the lower prevalence of these auto-Abs in younger than in older individuals, the much higher $IFR_{AAB}$ observed in individuals with these auto-Abs suggests that the testing of infected individuals in all age groups is warranted. Particular attention should be paid to patients, especially children, with known autoimmune or genetic conditions associated with the production of auto-Abs against type I IFNs. Early treatments could be provided[55], including monoclonal antibodies[56], new antiviral drugs, and/or IFN-β in the absence of auto-Abs against IFN-β[57,58]. Rescue treatment by plasma exchange is a therapeutic option in patients who already have pneumonia[30]. A screening of uninfected elderly people could be considered, given that these auto-Abs are found in 4% of individuals over 70 years old. Carriers of auto-Abs should be vaccinated against SARS-CoV-2 as a priority, and should benefit from a booster, whatever their age, and ideally from a monitoring of their antibody response to the vaccine. They should not receive live-attenuated vaccines, including the yellow fever vaccine (YFV-17D) and anti-SARS-CoV-2 vaccines based on the YFV-17D backbone[46]. In cases of SARS-CoV-2 infection, vaccinated patients should be closely monitored. As SARS-CoV-2 vaccination coverage increases and mortality due to COVID-19 decreases over time, it will be important to re-evaluate the risk of fatal COVID-19 in vaccinated individuals with and without auto-Abs. It is currently unclear whether these auto-Abs impair antibody responses to vaccines, and whether a vaccine-triggered antibody response can overcome type I IFN deficiency in response to

large or even medium-sized viral inocula. Finally, further investigations are required to determine the contribution of these auto-Abs to other severe viral diseases, and to elucidate the mechanisms underlying their development, which may be age-dependent. In the meantime, auto-Abs against type I IFNs should be considered as a leading common predictor of life-threatening COVID-19 after age, as their detection has a much greater predictive value for death, and, by inference, hospitalization and critical COVID-19, than sex, comorbidities, and common genetic variants (Fig. 3).

## Declarations

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# Conflict of Interest Disclosures

J.-L.C. is an inventor on patent application PCT/US2021/042741, filed 22 July 2021, submitted by The Rockefeller University, which covers diagnosis of, susceptibility to, and treatment of viral disease and viral vaccines, including COVID-19 and vaccine-associated diseases. M.C.N. is an inventor on patent application PCT/US2021/070472 submitted by The Rockefeller University that covers neutralizing anti–SARS-CoV-2 antibodies and methods of the use thereof. M.C.N. reports being on the Scientific Advisory Board of Celldex and Frontier Biotechnologies. R.P.L. reports being a non-executive director of Roche.

# Availability of data and materials

All the data are available in the manuscript or in the Supplementary Materials. Plasma, cells, and genomic DNA are available from J.-L.C. under a material transfer agreement (MTA) with The Rockefeller University or the Imagine Institute. Huh-7.5 cells are available on request from C.M.R. under an MTA with The Rockefeller University and Apath LLC. The materials and reagents used are almost exclusively commercially available and nonproprietary. Materials derived from human samples may be made available on request, subject to any underlying restrictions concerning such samples.

# Code availability

Access to the code is available from the authors on request for noncommercial, academic and research use only.

# Group Information

Lists of members of the HGID Lab, COVID Clinicians, COVID-STORM Clinicians, NIAID Immune Response to COVID Group, NH-COVAIR Study Group, Danish CHGE, Danish Blood Donor Study, St. James's Hospital, SARS CoV2 Interest group, French COVID Cohort Study Group, Imagine COVID-Group, The Milieu Intérieur Consortium, CoV-Contact Cohort, Amsterdam UMC Covid-19 Biobank Investigators, COVID Human Genetic Effort, CP-COVID-19 Group, CONSTANCES cohort, 3C-Dijon Study, Cerba Health-Care, Etablissement du Sang study group consortia are available in the Supplementary Information.

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# Tables

**Table 1. Lines of evidence suggesting that auto-Abs against type I IFNs are strong determinants of the risk of life-threatening COVID-19.**

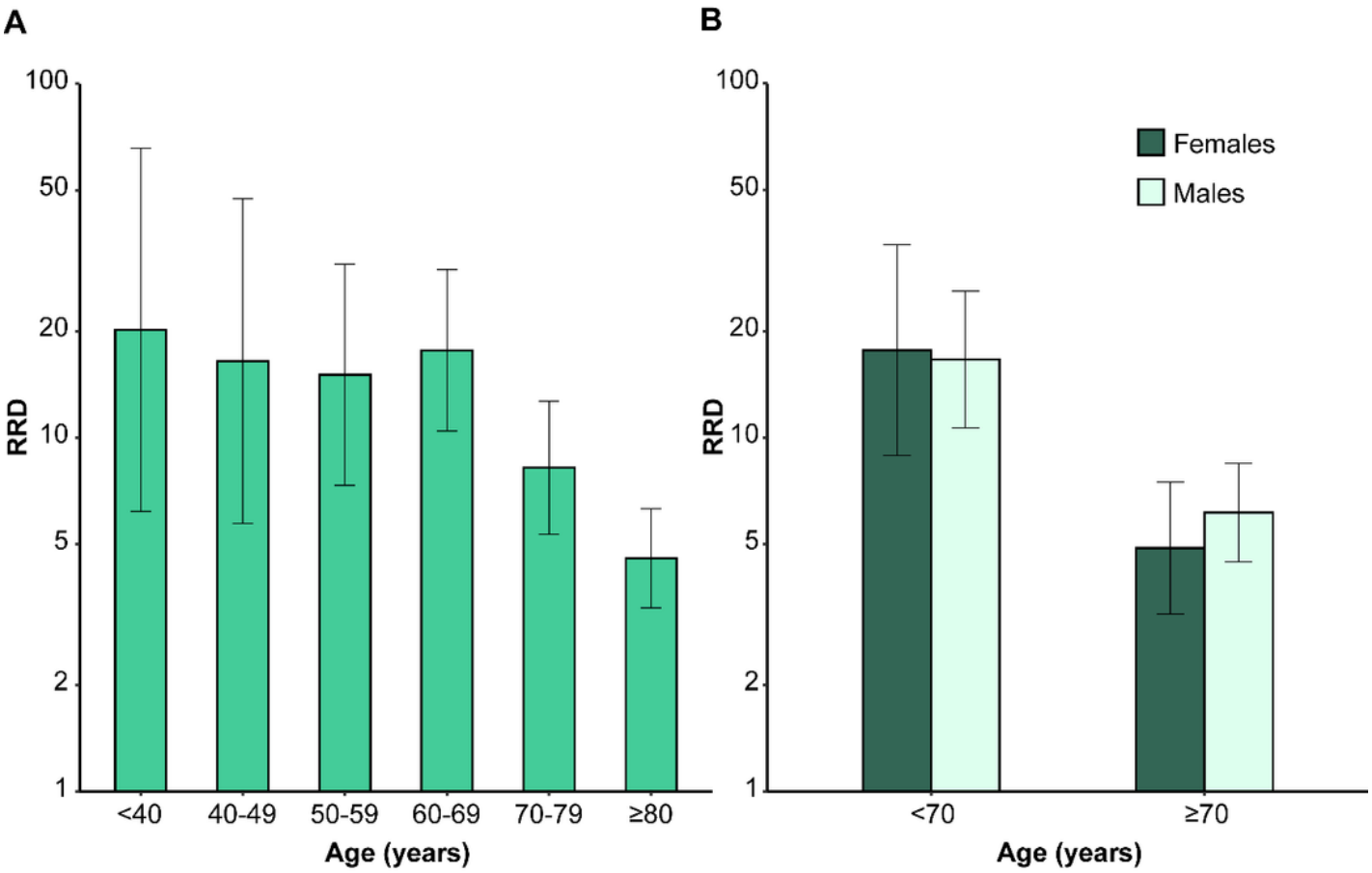
| Evidence | Examples | References |
|---|---|---|
| Auto-Abs against type I IFNs are present before SARS-CoV-2 infection | In patients for whom a sample collected before the COVID-19 pandemic was available, the auto-Abs were found to pre-exist infection | 30 |
| | These auto-Abs are found in the uninfected general population, and their prevalence increases after the age of 65 years | 8 |
| Auto-Abs are associated with COVID-19 severity | Patients with inborn errors underlying these auto-Abs from infancy onward (e.g. APS-1) have a very high risk of developing critical COVID-19 pneumonia | 30 |
| | The population of patients with critical disease includes a higher proportion of individuals producing these auto-Abs than the population of patients with silent or mild infection (ORs depending on the nature, number, and concentrations of type I IFN neutralized) | 8 |
| | The results concerning the proportions of critical cases with auto-Abs against type I IFNs have already been replicated in >15 different cities (Americas, Europe, Asia) | 16-29 |
| Auto-Abs against type I IFNs neutralize host antiviral activity | These auto-Abs neutralize the antiviral activity of type I IFNs against SARS-CoV-2 *in vitro* | 9 |
| | These auto-Abs are found *in vivo* in the blood of SARS-CoV-2-infected patients, where they neutralize type I IFN | 31 |
| | These auto-Abs are found *in vivo* in the respiratory tract of patients, where they neutralize type I IFN | 32-34 |
| | A key virulence factor of SARS-CoV-2 *in vitro* is its capacity to impair type I IFN immunity | 35 |
| | Animals with type I IFN deficiency develop critical disease, including animals treated with mAbs that neutralize type I IFNs | 36 |
| Auto-Abs against cytokines are clinical phenocopies of the corresponding inborn errors | Patients with auto-Abs against type I IFNs are phenocopies of IFNAR1$^{-/-}$, IFNAR2$^{-/-}$, and IRF7$^{-/-}$ patients with critical COVID-19 pneumonia | 11 |
| | Patients with auto-Abs against IL-6, IL-17, GM-CSF, and type II IFN are phenocopies of the corresponding inborn errors and underlie staphylococcal disease, mucocutaneous candidiasis, nocardiosis, and mycobacterial diseases, respectively | 37-45 |

**Table 2. Characteristics of the general population cohort and of the cohort of patients who died from COVID-19, by age, sex and autoantibody status**

| Characteristics | Neutralization 100 pg/mL | | Neutralization 10 ng/mL | |
|---|---|---|---|---|
| | General Population (*N*=10,778) | Deceased Patients (*N*=1,121) | General Population (*N*=34,159) | Deceased Patients (*N*=1,094) |
| **Male – no. (%)** | 5,429 (50.4)[a] | 821 (73.2) | 17,859 (52.3) | 805 (73.5) |
| **Mean age[a] ±SD – yr** | 62.3 ±17.2 | 70.7 ±13.0 | 52.7 ±18.2 | 70.6 ±13.1 |
| **Age distribution – no. (%)** | | | | |
| 20-39 yr | 1,251 (11.6) | 17 (1.5) | 9,102 (26.6) | 15 (1.4) |
| 40-49 yr | 1,459 (13.5) | 43 (3.8) | 5,403 (15.8) | 47 (4.3) |
| 50-59 yr | 1,736 (16.1) | 144 (12.8) | 6,414 (18.9) | 152 (13.9) |
| 60-69 yr | 2,475 (23.0) | 307 (27.4) | 6,881 (20.1) | 289 (26.4) |
| 70-79 yr | 1,790 (16.6) | 307 (27.4) | 3,721 (10.9) | 296 (27.1) |
| ≥80 yr | 2,067 (19.2) | 303 (27.0) | 2,638 (7.7) | 295 (27.0) |
| **Auto-Ab – no. of carriers (%)** | | | | |
| IFN-α2 and IFN-ω | 65 (0.6) | 102 (9.1) | 45 (0.1) | 75 (6.8) |
| IFN-α2 or IFN-ω | 246 (2.3) | 203 (18.1) | 181 (0.5) | 130 (11.9) |
| IFN-α2 | 151 (1.4) | 140 (12.5) | 117 (0.3) | 118 (10.8) |
| IFN-ω | 160 (1.5) | 165 (14.7) | 109 (0.3) | 87 (8.0) |
| IFN-β[b] | NA | NA | 24 (0.3) | 6 (0.9) |

SD standard deviation.
NA not available.
[a]Age is given in years and corresponds to age at the time of recruitment for members of the general population cohort (controls) and age at death for COVID-19 patients.
[b]IFN-β neutralization experiments were performed only for a concentration of 10 ng/mL, on 9,126 individuals (49.5% male, mean age 60.6 years) from the general population and 636 COVID-19 patients (71.1% male, mean age 72.9 years).

# Figures




## Figure 1

**Relative risks of death associated with auto-Abs neutralizing low concentrations of IFN-α2 or -ω, by age and sex.** RRDs for individuals with auto-Abs neutralizing low concentrations of IFN-α2 or IFN-ω relative to individuals without such auto-Abs, by age and sex. RRDs are displayed on a logarithmic scale (A) for six age classes, and (B) for male and female subjects under and over the age of 70 years. Vertical bars represent the 95% CI.

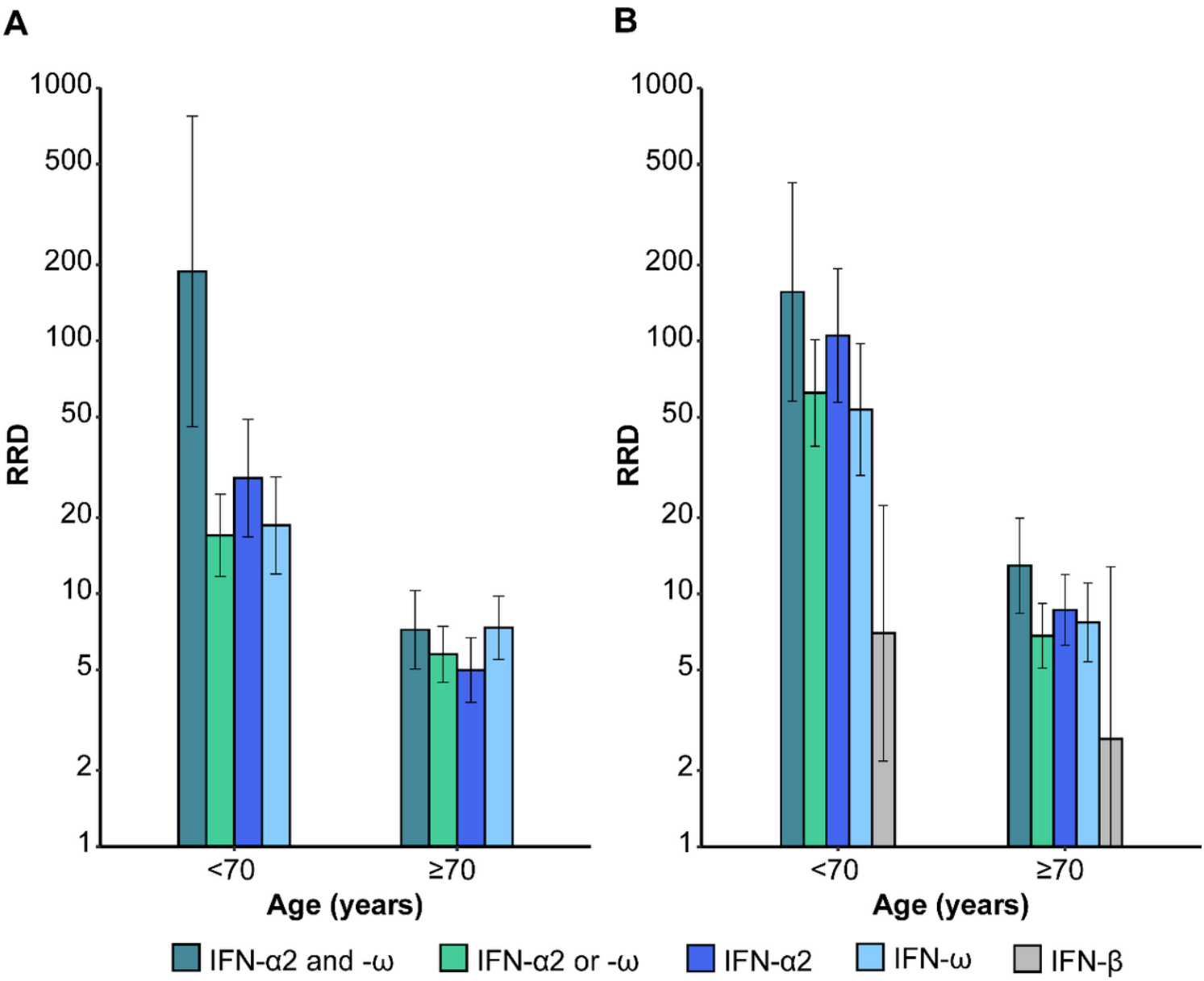



**Figure 2**

**Relative risks of death associated with auto-Abs neutralizing various combinations of type I IFNs, by age.** RRDs for individuals with auto-Abs neutralizing different combinations of type I IFNs relative to individuals without such auto-Abs, by age. RRDs are displayed on a logarithmic scale for individuals under and over 70 years of age with (A) auto-Abs neutralizing low concentrations of IFN-α2 and IFN-ω, IFN-α2 or IFN-ω, IFN-α2, IFN-ω, and (B) auto-Abs neutralizing high concentrations of IFN-α2 and IFN-ω, IFN-α2 or IFN-ω, IFN-α2, IFN-ω and IFN-β, relative to individuals without such combinations of auto-Abs. Vertical bars represent the 95% CI.

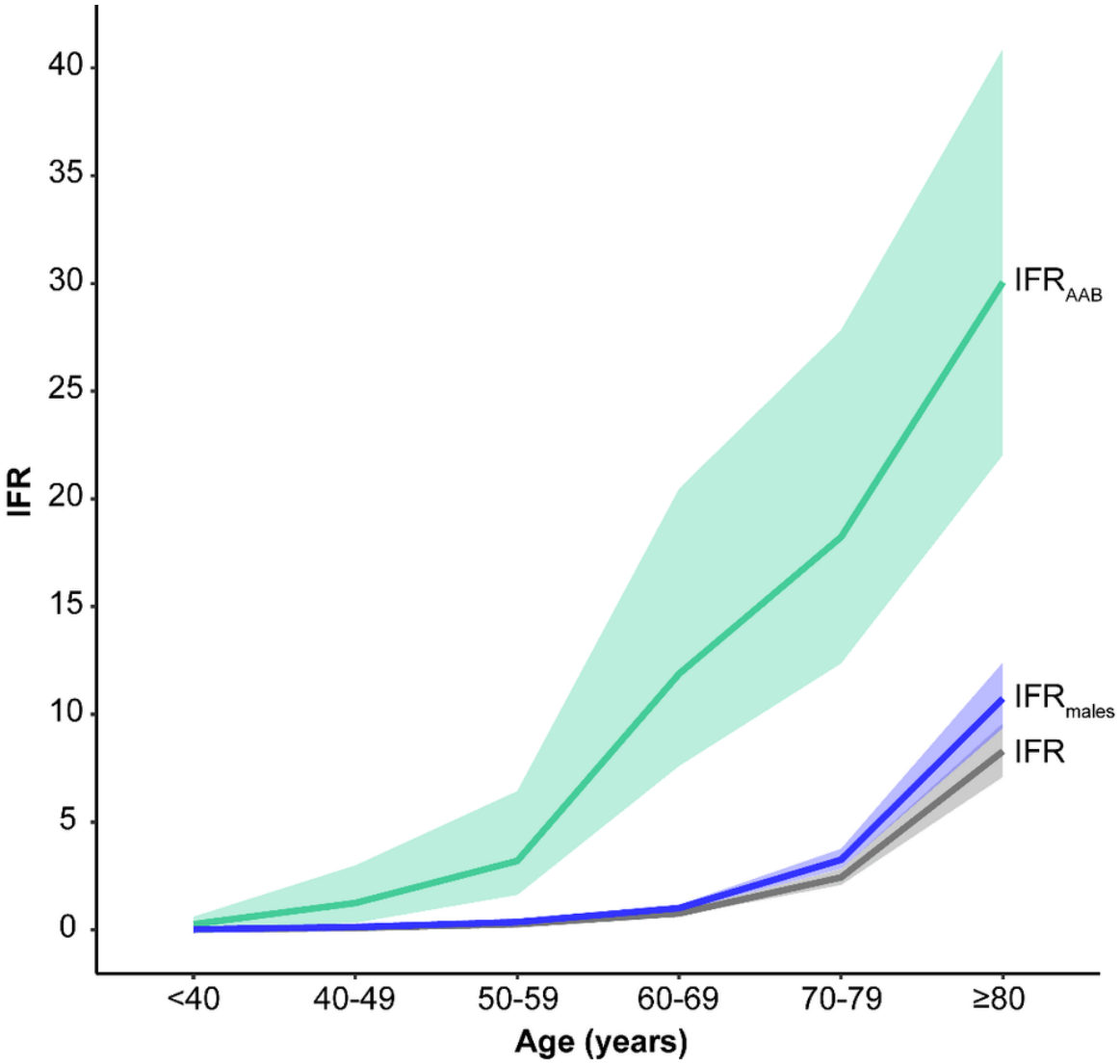



**Figure 3**

**SARS-CoV-2 infection fatality rates by age.** IFRs are provided in the general population for both sexes (gray) and for males only (blue) using the data of O'Driscoll et al. [4]; $IFR_{AAB}$ (green) are shown for individuals carriers of auto-Abs neutralizing low concentrations of IFN-α2 or IFN-ω. Auto-Abs against type I IFNs are associated with high RRDs and strongly increase IFR, to a much greater extent than maleness, and by inference than other classical common risk factors providing ORs of death similar to maleness (around 2) such as some comorbidities, or the most significant common genetic variant on chromosome 3[3].

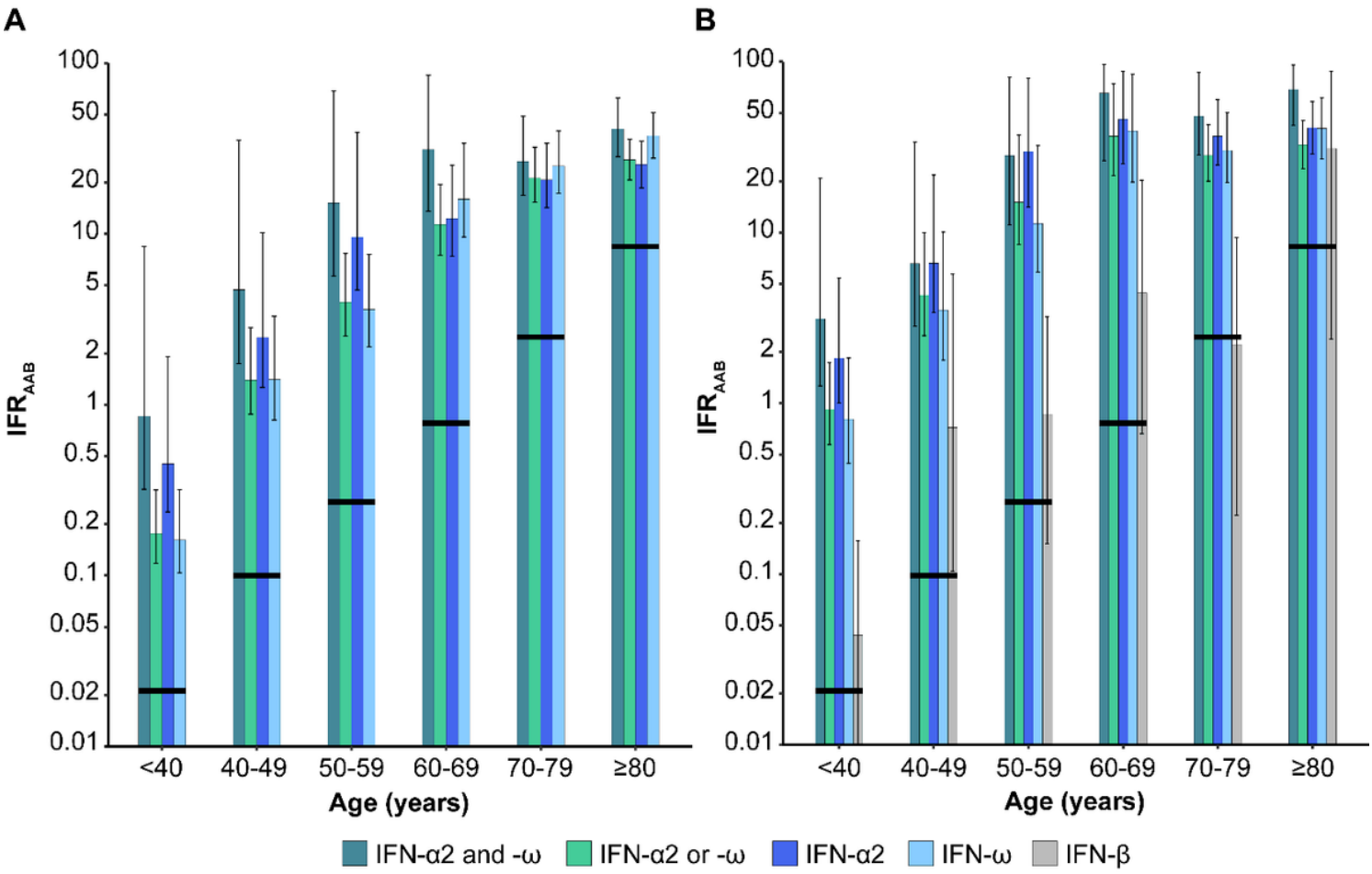



**Figure 4**

**SARS-CoV-2 infection fatality rates for carriers of various combinations of neutralizing auto-Abs, by age.** $IFR_{AAB}$ values (%) are displayed, on a logarithmic scale, by age, for individuals with (A) auto-Abs neutralizing low concentrations of IFN-α2 and IFN-ω, IFN-α2 or IFN-ω, IFN-α2, IFN-ω, and (B) auto-Abs neutralizing high concentrations of IFN-α2 and IFN-ω, IFN-α2 or IFN-ω, IFN-α2, IFN-ω and IFN-β. Vertical bars represent the 95% CI. Horizontal black lines represent the IFR provided by O'Driscoll *et al*[4].

# Supplementary Files

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