Antibodies and COVID

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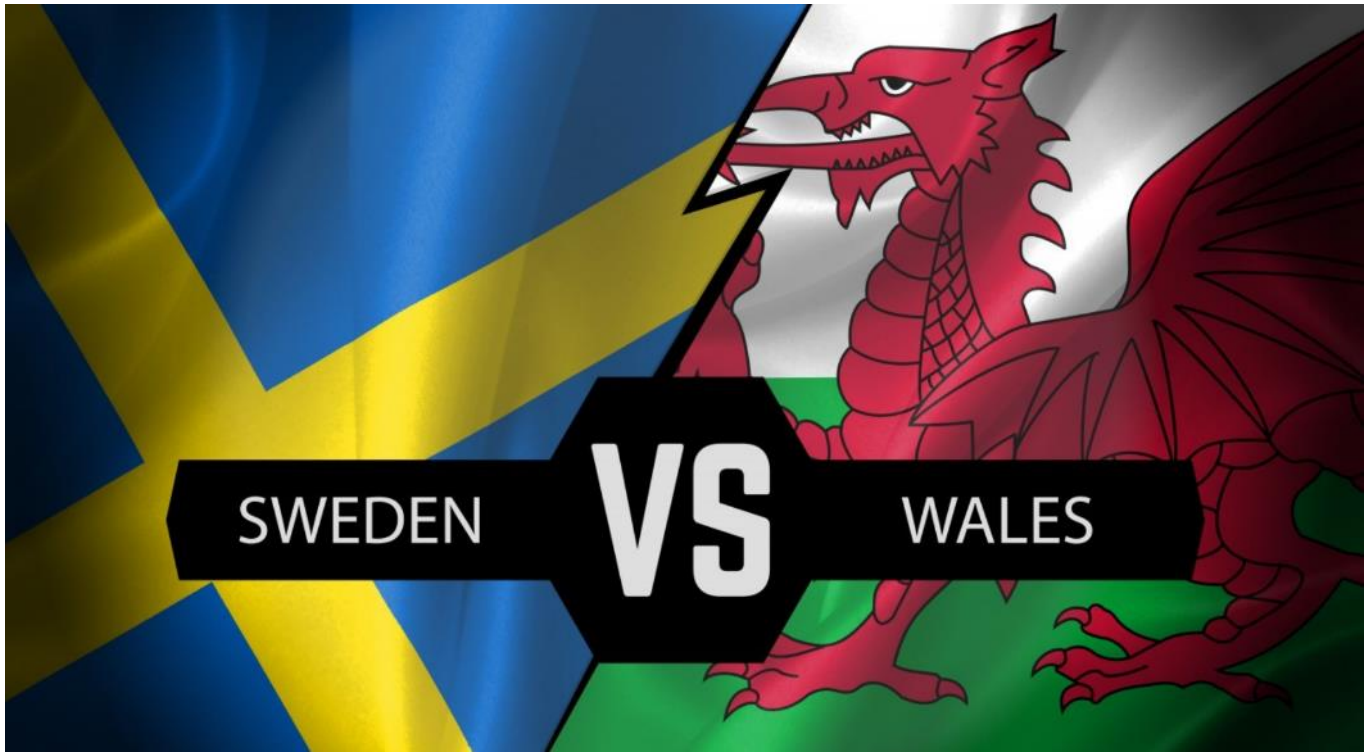
Content

- Sweden vs Wales approach to COVID
- PID data
- XLA data
- Cohort Data
- Secondary and COVID
- Pregnancy and COVID
- Persistent COVID
- Conclusions



Shielding Policy for Clinically Extremely Vulnerable

Shielding Policy – 118000

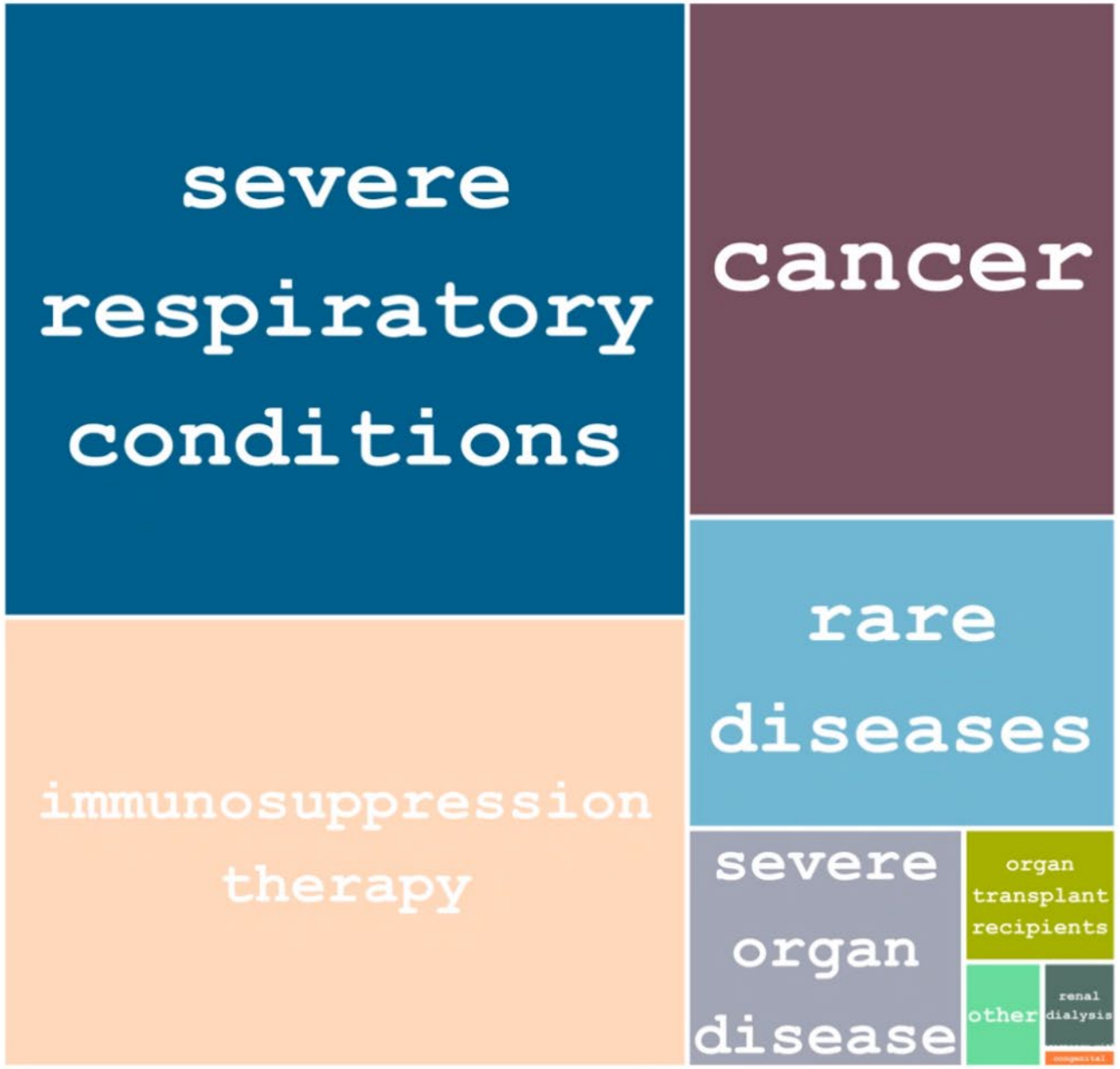
EVITE Study

Clinical Vulnerability Category

Reason for being on the shielded list:

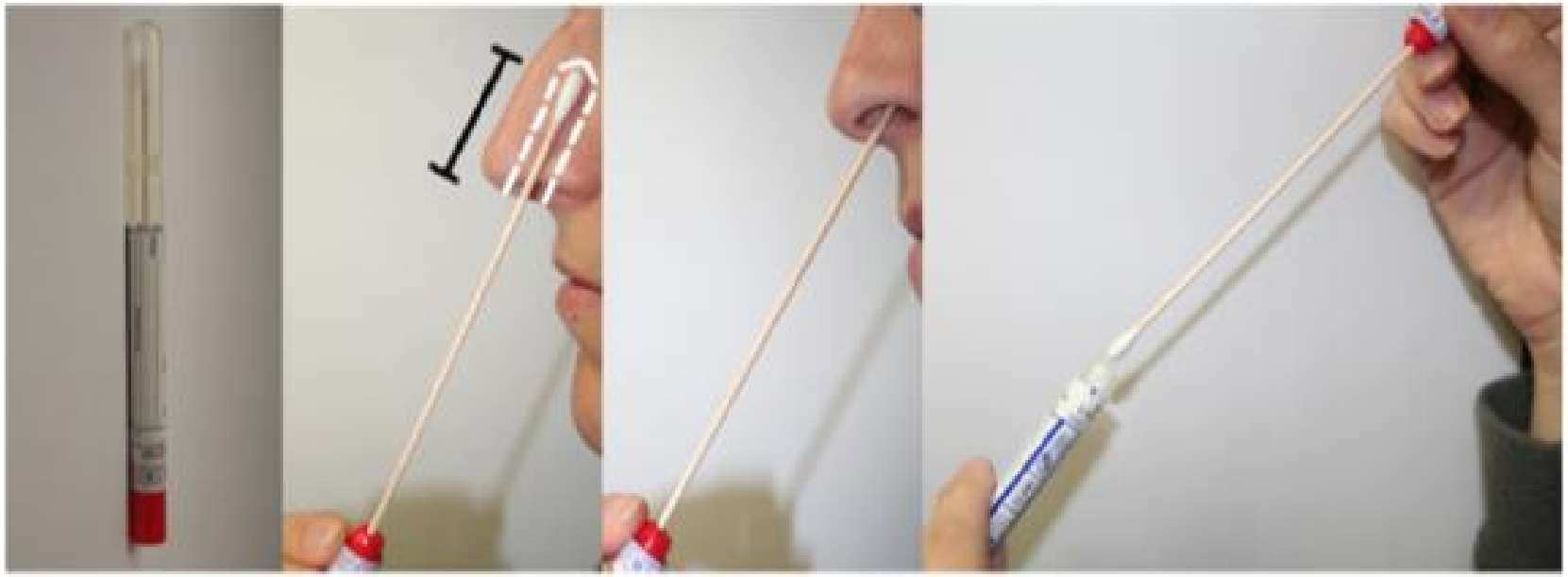
	n	%
severe respiratory conditions	41744	35.5%
immunosuppression therapy	30493	25.9%
cancer	21926	18.7%
rare diseases	13223	11.2%
severe organ disease	6542	5.6%
organ transplant recipients	2019	1.7%
other	822	0.7%
renal dialysis	635	0.5%
pregnancy with congenital heart disease	139	0.1%

** where persons have multiple records on the shielding list, the record with the earliest date of being known to be shielding was used to categorise clinical vulnerability*



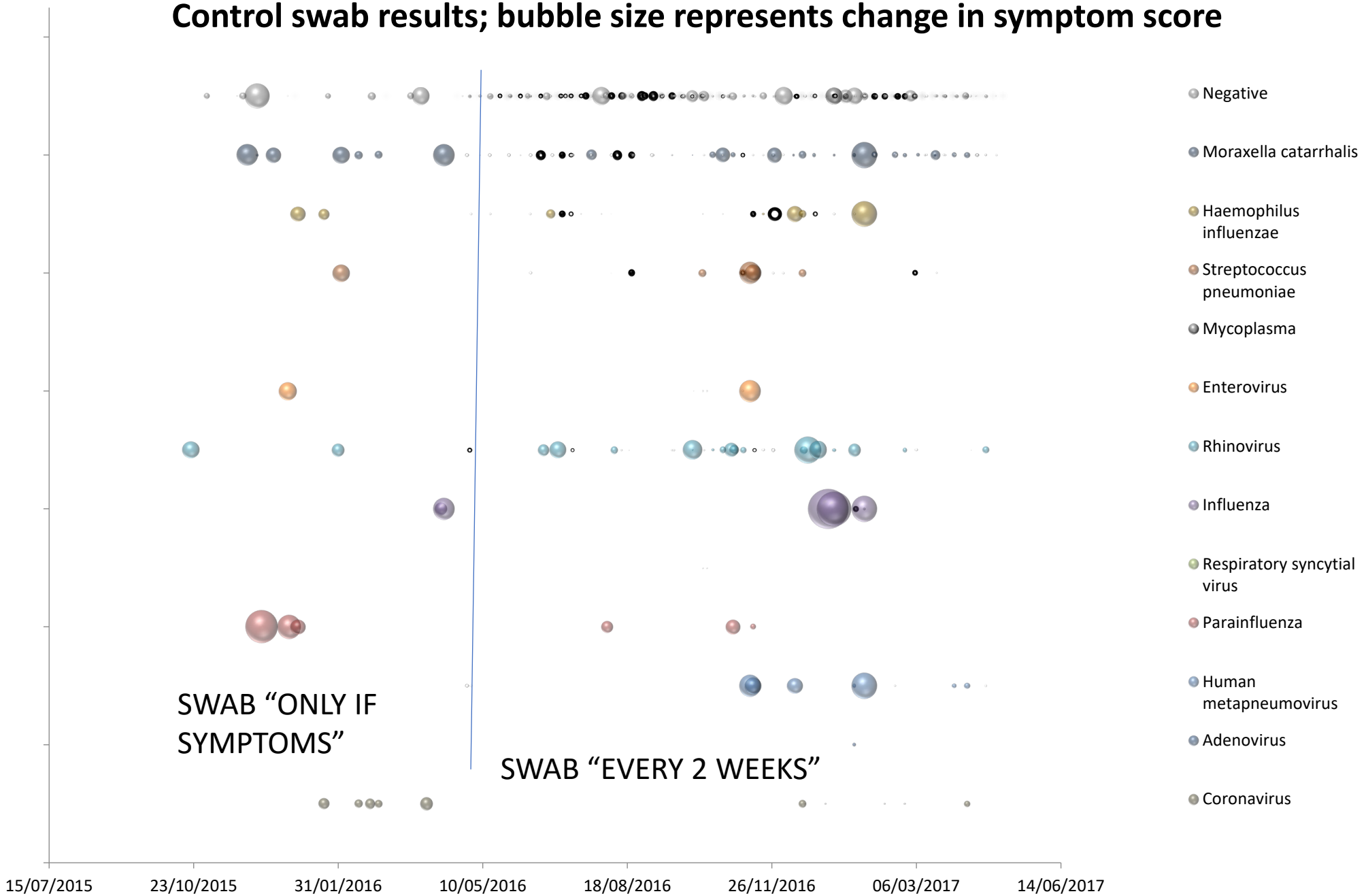
Non Pharmaceutical Interventions (NPIs)

BIPAD – ‘the North remembers’

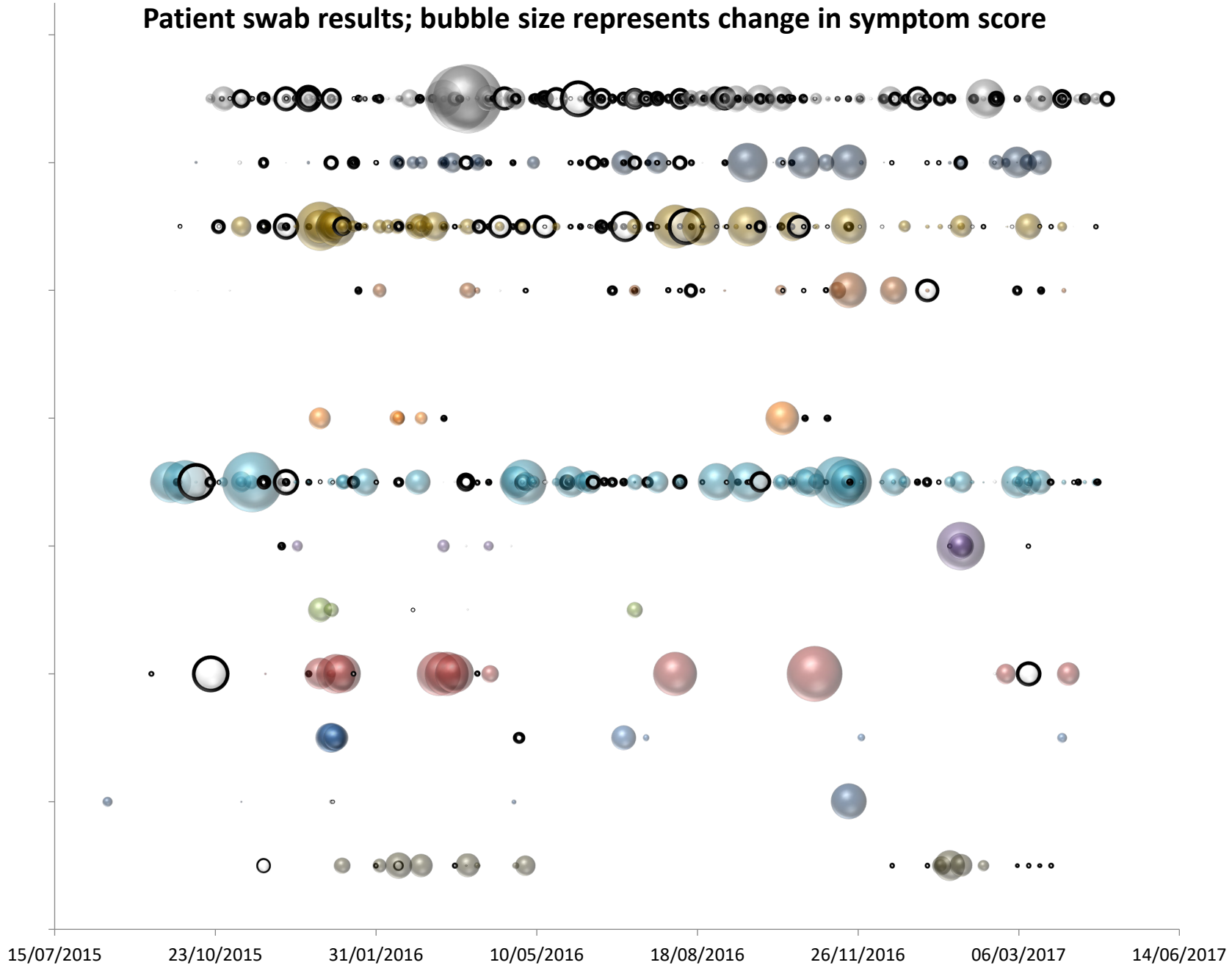


1: Take swab by the red end. **Twist** and remove swab from container.	2: **Insert** white bud end into nostril by 1 inch (2-3cm) and rub against the inside of the nose.	3: **Repeat** this using the <u>same</u> swab in the <u>other</u> nostril. Touch **firmly** – almost so you want to sneeze.	4: **Replace** the swab within the original container. Take care not to touch anything else as this might result in contamination. Return swab and diary by post within 24 hours

Control swab results; bubble size represents change in symptom score



Patient swab results; bubble size represents change in symptom score



- Negative
- Moraxella catarrhalis
- Haemophilus influenzae
- Streptococcus pneumoniae
- Mycoplasma
- Enterovirus
- Rhinovirus
- Influenza
- Respiratory syncytial virus
- Parainfluenza
- Human metapneumovirus
- Adenovirus
- Coronavirus

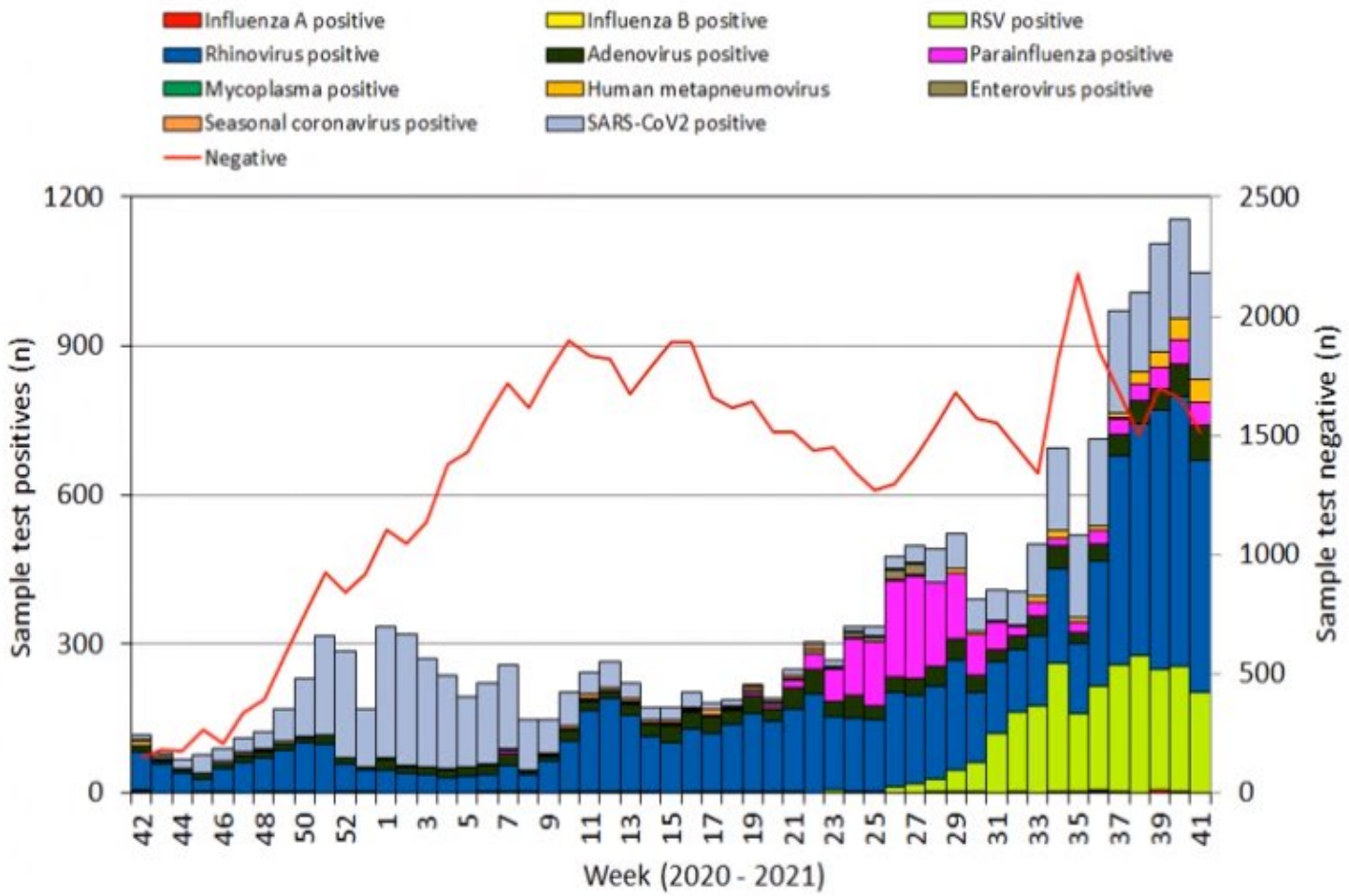
What happened next?

BUT…

Weekly Influenza & Acute Respiratory Infection Surveillance:

Specimens submitted for virological testing for hospital patients and non-sentinel GPs

Week 42 2020 to Week 41 2021



Winter is coming..
Back

- Does not include data for patients tested SOLEY for SARS- CoV2
- Summarises individual test results – patients positive for multiple infections within a given week will appear multiple times.

Other impacts of Shielding

- JAK3 SCID – 41yr old female
- Non conditioned sibling HSCT aged 6 wks
- On IgRT
- Shielded for 2 years, worked from home
- Very worried about going out
- Vaccinated x2
- Spike and nucleocapsid antibodies negative
- Spike and nucleocapsid T cells positive

COVID & PID Severity

- **Infection Fatality Rate**
- UK Population 2.95%
- PID on IgRT 16.3%
- CVID 18.3%
- SID 27.2 %
- **Median Age of Death**
- UK Population 83 yrs
- PID on IgRT 57 yrs

- 326 cases with PID or SID UKPIN registry
- Overall cohort mortality 16.9%
- Risks – age, comorbidities, low lymphocyte count at baseline <1
- Caveats – access to specific therapies was not always available

Shields AM JACI 2021, Metys I JACI 2021, Shields AM et al 2021 submitted

England response to Ig shortages

- **Tiers 1- 4** increasing **Shortage Pressure**. In Tier 4 Central allocations and distribution by the national team will be implemented – ie centralised
- **Clinical Severity – single axis**
- Grade 4 - Solely and immediately dependent on Immunoglobulin for life-threatening disease
- Grade 3 - Dependent on Immunoglobulin in the long term, but **delayed** treatment or **temporary reduction** in dose unlikely to pose life-threatening risk
- Grade 2 - As for Grade 3, but no evidence of reviews/dose optimisation
- Grade 1 - Immunoglobulin treatment supportive but not essential - ?multivitamin

Multispecialty Rating of Evidence-Based Conditions for Intravenous Immunoglobulin Therapy Using a 3-Axis Prioritization Algorithm

Jordan S. Orange, MD, PhD; Matt Johnson, BA; Barb Lennert, RN, BSN, MAOM; Katarzyna Shields, PharmD, MBA, BCOP, BCPS; Michael Eaddy, PharmD, PhD

Ronapreve Policy

- Use in PCR positive, seronegative patients who require admission to hospital to manage their COVID
- Short supply – approx. 4 doses per Health Board per day
- Risk of exclusion if IgRT becomes positive
- Quality and durability of endogenous vaccine responses may not be the same in ID

COVID and XLA lessons from a monogenic antibody deficiency

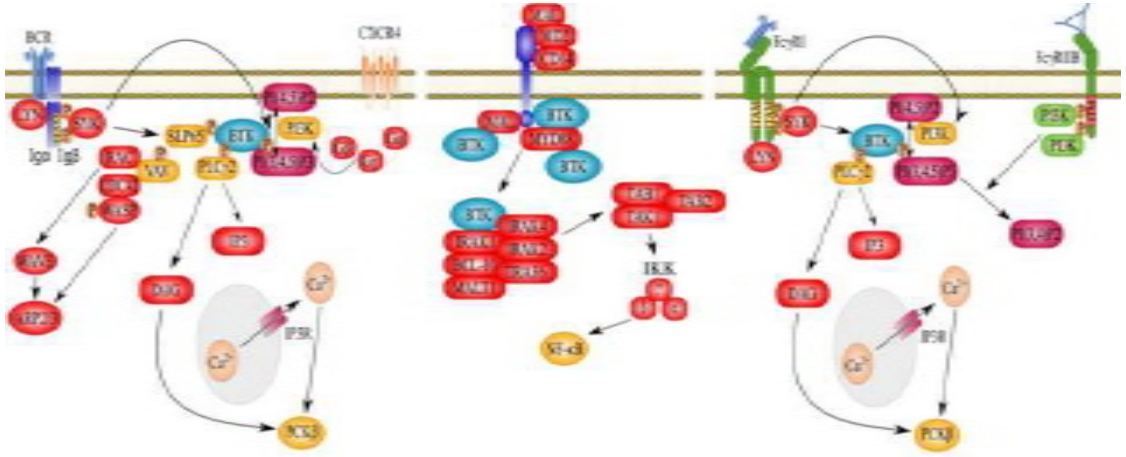
- Viral as well as bacterial susceptibility
- Chronic meningoencephalitis – Echovirus 11 Coxsackie B 5
- Severe Herpes group viruses before adequate IgRT
- Vaccine associated paralytic polio
- Persistent Rhinovirus longer than 4 months
- Chronic Type 2 norovirus requiring TPN and HSCT

- Role for antibody in viral defence (caveat other roles of BTK)

Ponsford MJ Curr Opp Allergy & Clin Imm 2021, Kainulainen L JACI 2010, Shillitoe BMJ J Clin Immunol 2021

Is XLA protective from severe COVID?

- No anti-SARS-CoV-2 antibodies – but no anti-IFN antibodies either
- BTK – wide haematopoietic expression neuts, DC, NK, macrophages & myeloid monocytes
- Roles in BCR, CXCR4, FcγR, TLR and NLRP3 signaling including thrombo-inflammation in platelets
- Role in macrophage activation and IL-6 production



Ponsford MJ Curr Opp Allergy & Clin Imm 2021, Kainulainen L JACI 2010, Shillitoe BMJ J Clin Immunol 2021

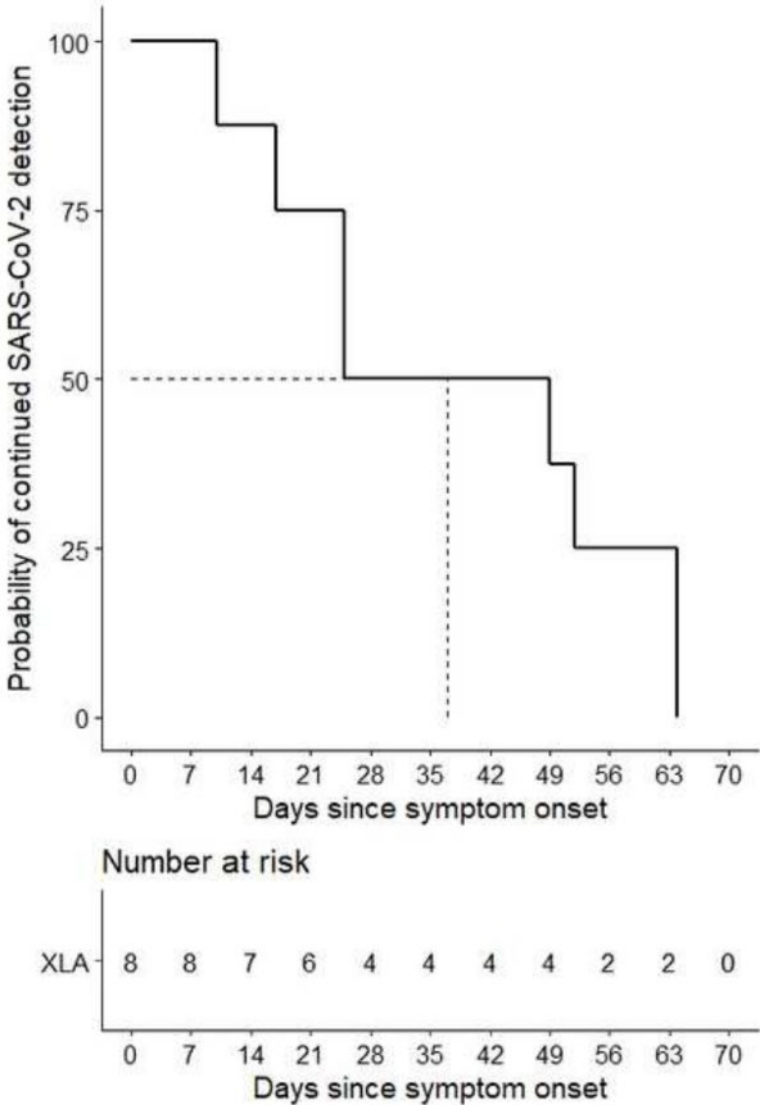
Outcomes of COVID in XLA patients

- Age reported in 23/28 - median 30.5yrs (5-55)
- Asymptomatic presentation 2/24 (8%)
- Fever (80%), cough (50%), SOB (38%)
- 79% (22) admitted to hospital
- 73% of those admitted received supplemental oxygen
- Median stay was 22d (11-73)
- 3 admitted to ICU
- 1 death (4%)

Ponsford MJ Curr Opp Allergy & Clin Imm 2021, Kainulainen L JACI 2010, Shillitoe BMJ J Clin Immunol 2021

Outcomes of COVID in XLA patients

- In contrast to earlier reports, this series suggests that XLA patients are at risk of severe COVID
- Protracted COVID is common in XLA
- XLA patients can mount an antiviral T cell response
- Viral evolution in protracted COVID remains a concern

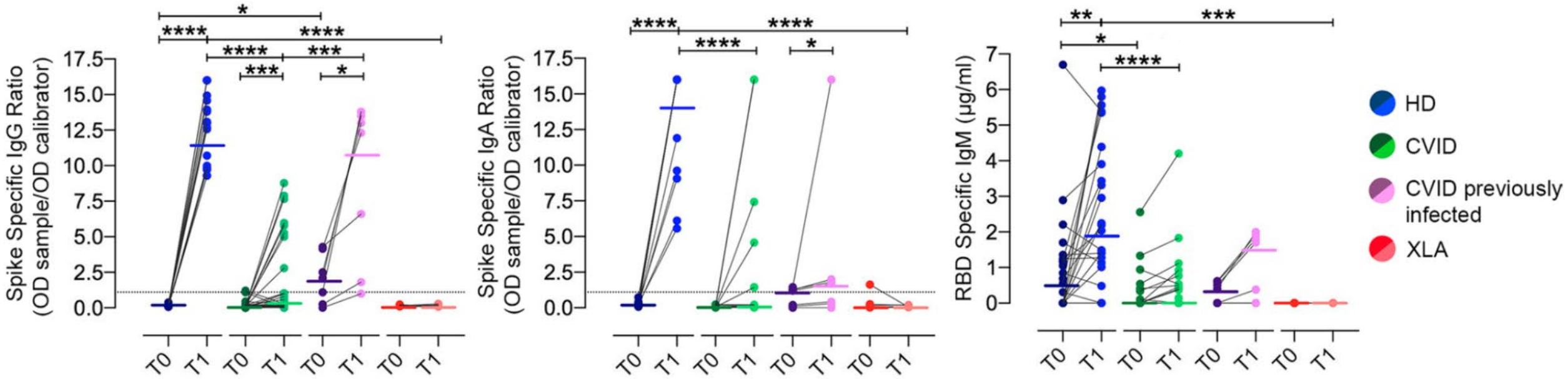


Ponsford MJ Curr Opp Allergy & Clin Imm 2021, Kainulainen L JACI 2010, Shillitoe BMJ J Clin Immunol 2021

Immunodeficiency Cohort Analysis

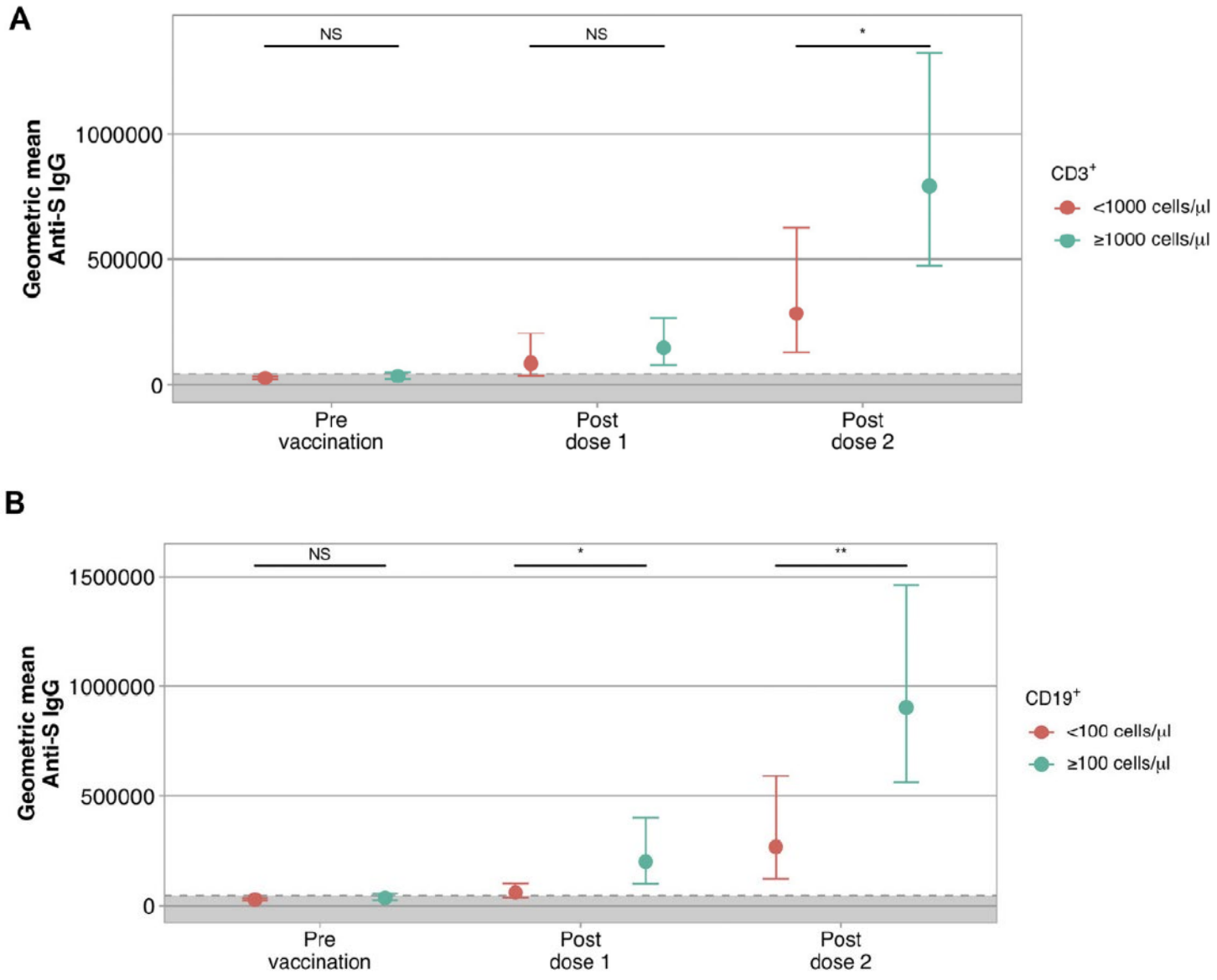
- Studies to date
  - Hagin D JACI 2021 – 26 adults Pfizer 18/26 Ab, 19 T
  - Romano C Ann Allergy Asthma Imm - 5 CVID Pfizer 4/5 Ab
  - Freeman A JACI 2021 83 IEI Pfizer & Jannsen – 85% lower with ritux and T cells <1000
  - Salinas A JoCI 2021 41 CVID 6 XLA Pfizer CVID 20% Ab, 70% T
  - Squire J JoCI 2021 25 PID – safety data
  - Bloomfield M JoCI 2021 – 7 STAT1 GoF safety and responses on ruxolitinib

IgG, A and M Responses



Salinas A JoCI 2021

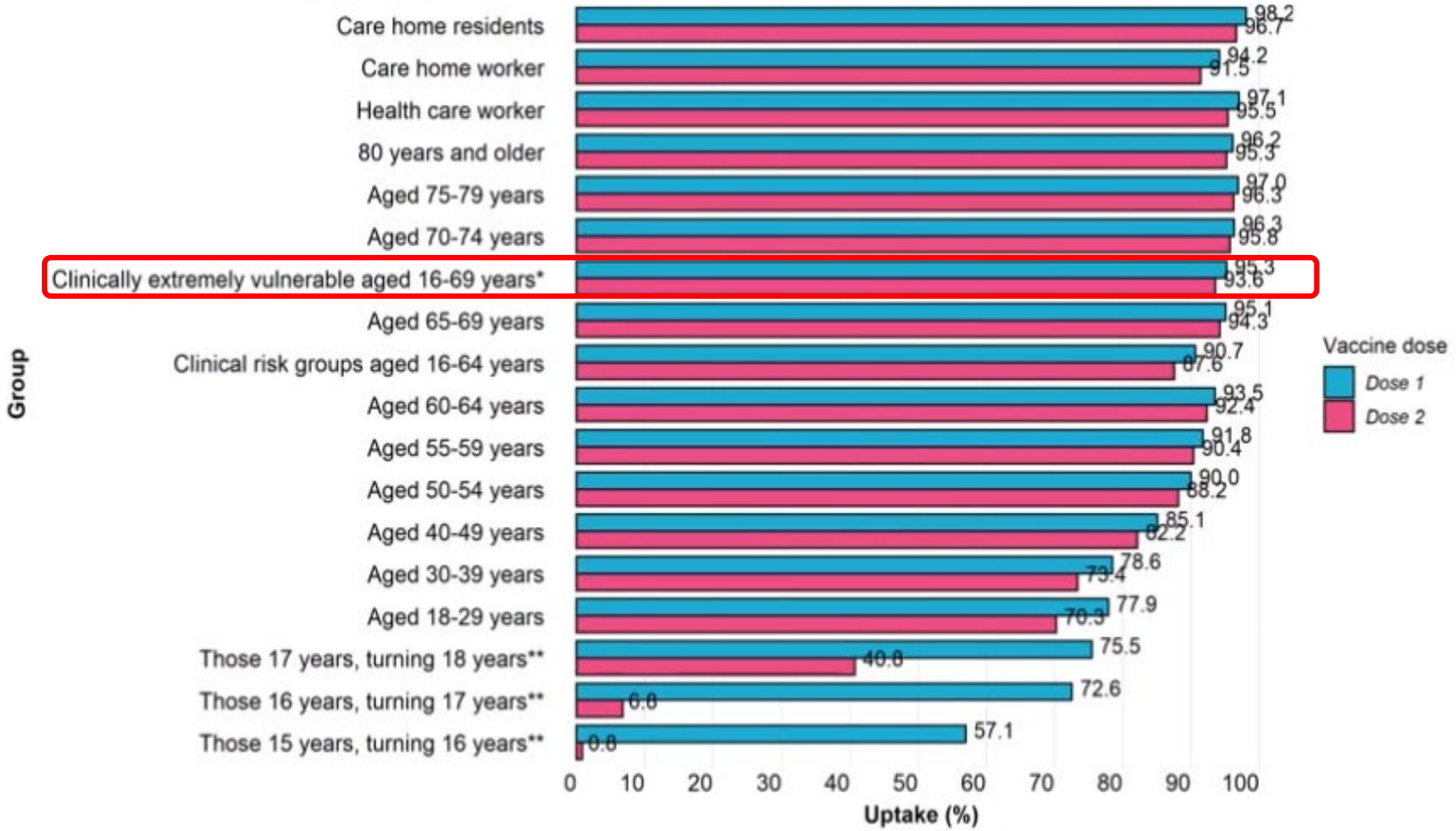
Incrementation with Low T and Low B cells



Freeman A JACI 2021

COVID-19 Vaccination Coverage by age and risk group, Wales

As at: 21/10/2021



Vaccination rates in > 16 yr olds

1 Dose: 93%
2 Dose: 86%

Uptake figures now exclude data on those who have died from any cause.

Newborn DBS COVID Antibody Testing

- DBS Testing Established – Euroimmun Spike antibodies tested
- Anonymous testing of 1 week per month (600/month)
- November 2020 – November 2021
- Reflects maternal antibody via placental FcRn transfer
- Rationale – serosurvey of maternal antibodies

Development of a high-throughput SARS-CoV-2 antibody testing pathway using dried blood spot specimens.
Moat SJ et al. Ann Clin Biochem. 2021 Mar;58(2):123-131.

Confidence building Advice

Pregnancy

For COVID-19 VACCINE

Use only if potential benefit outweighs risk. The MHRA and PHE advise that patients should be informed about the risks and benefits of vaccination, and that safety data in pregnancy is limited.

- And don’t forget the infertility
- Microchips
- And potential harm to the baby

Pregnancy and COVID

- Pregnancy itself represents a risk factor for severe COVID
- Increased further by pre-existing conditions – DM, HTN, BMI >25, age >35, social deprivation and BAME
- Pregnant women with symptomatic COVID have a 24% chance of preterm deliver <37 weeks and 11% perinatal death
- 32% of all women 16-49yrs receiving ECMO in ICU are pregnant

JAMA Pediatrics | Original Investigation

Maternal and Neonatal Morbidity and Mortality
Among Pregnant Women With and Without COVID-19 Infection
The INTERCOVID Multinational Cohort Study

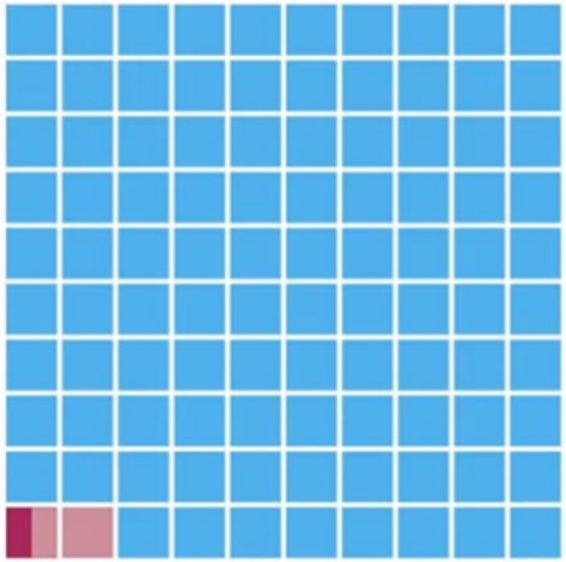
Vaccination Status in hospital admissions for COVID

UKOSS
UK Obstetric Surveillance System

MBRRACE-UK
Mothers and Babies: Reducing Risk through Audits and Confidential Enquiries across the UK

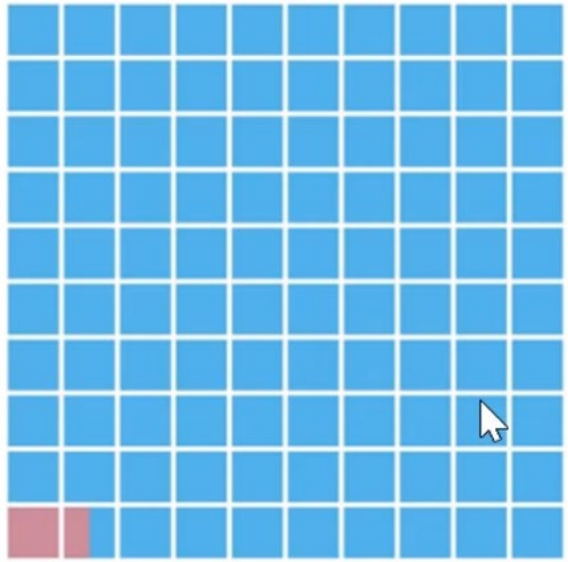
1st February 2021 to 30th September 2021

1714 pregnant women admitted to hospital with symptomatic COVID



98.1% unvaccinated
1.5% one dose
0.4% two doses

235 of whom (14%) were admitted to intensive care



98.7% unvaccinated
1.3% one dose

Changes its mind

News

NHS encourages pregnant women to get COVID-19 vaccine

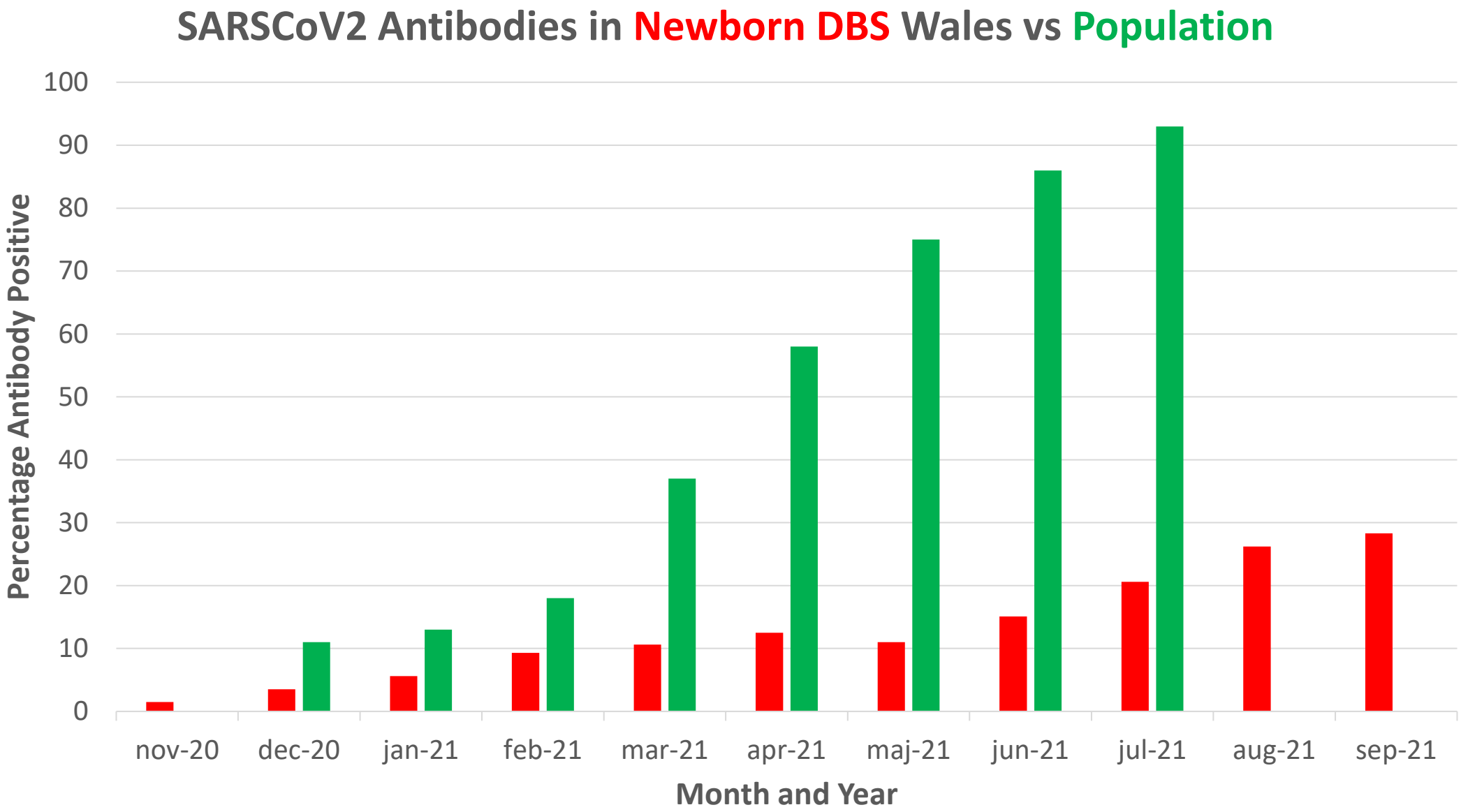
11 October 2021

The NHS is encouraging pregnant women to get the COVID-19 vaccine as new data shows that nearly 20 per cent of the most critically ill COVID patients are pregnant women who have not been vaccinated.

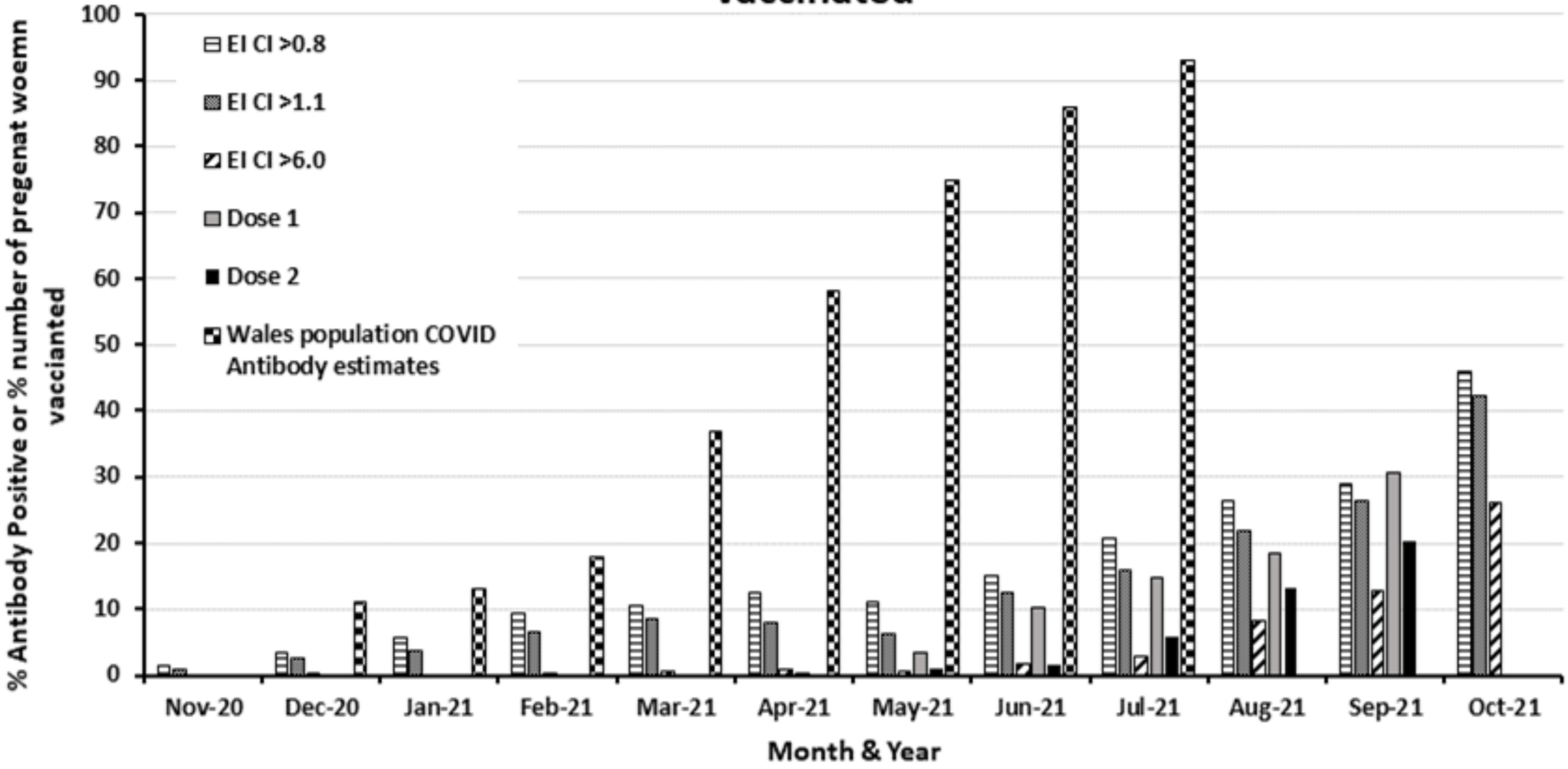
Since July, one in five COVID patients receiving treatment through a special lung-bypass machine were expectant mums who have not had their first jab.

Out of all women between the ages of 16 and 49 on ECMO in intensive care, pregnant women make up almost a third (32 percent) – up from just 6 per cent at the start of the pandemic, March 2020.

Results


SARSCoV2 Antibodies in Newborn DBS Wales vs Population
Percentage Antibody Positive
100
90
80
70
60
50
40
30
20
10
0
nov-20
dec-20
jan-21
feb-21
mar-21
apr-21
maj-21
jun-21
jul-21
aug-21
sep-21
Month and Year

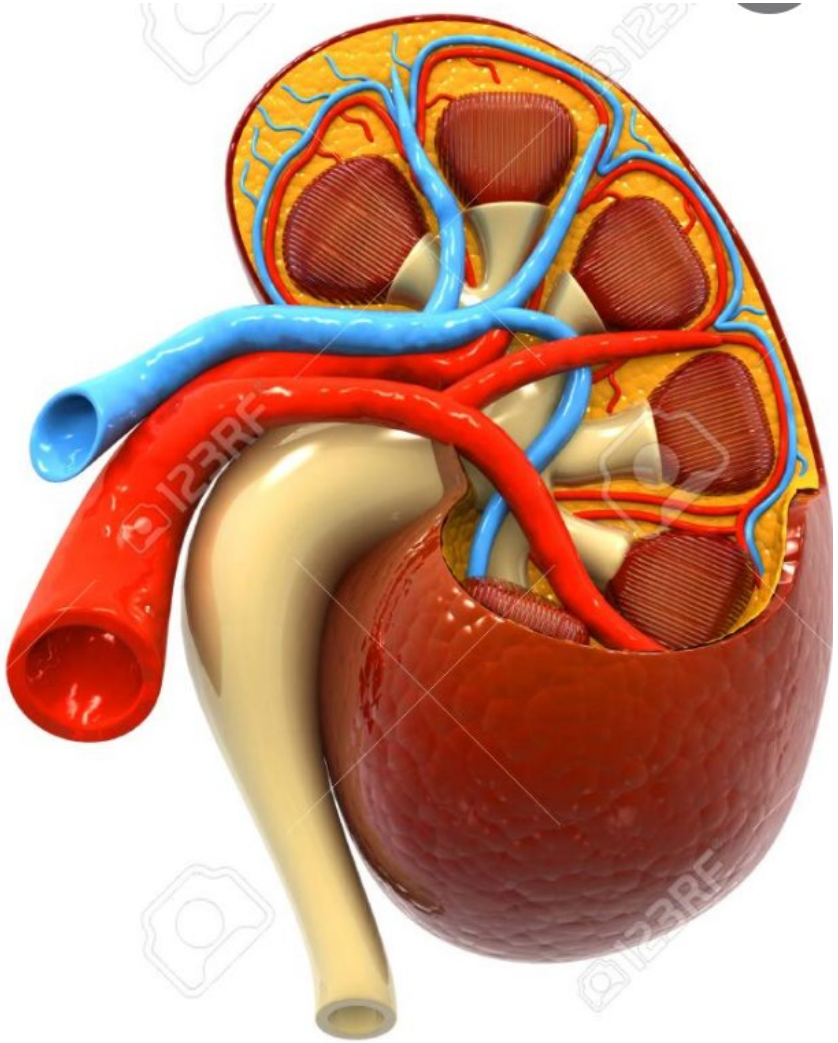
SARSCoV2 Antibodies in Wales Newborn DBS samples vs Wales population estimates for Ab status and number of pregnant women vaccinated

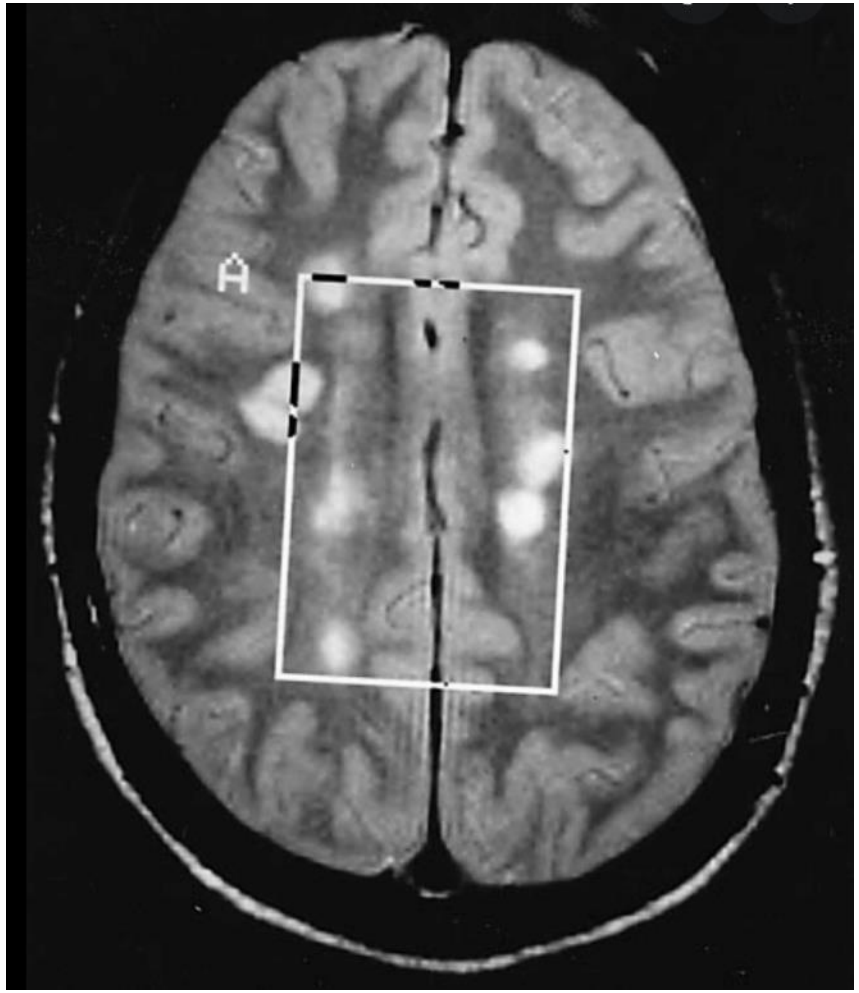


Newborn DBS COVID Antibody Testing

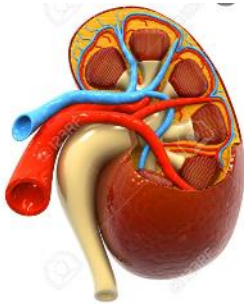
- Neonatal DBS testing allows a ‘real time’ assessment of maternal COVID serostatus
- This reflects both natural infection and vaccination uptake
- There remains a significant gap between the population seropositivity and that for pregnant women with slow catch up
- Potential risk for pregnant mothers as their other children return to school
- DBS testing avoids the need for patient travel, blood bottles, phlebotomy, OPD and nosocomial exposure
- Future work could assess both N and S antibody levels in DBS and response to policy and practical interventions to improve vaccine uptake in this group

Secondary Immunodeficiency





Renal Transplantation ENLIST Study

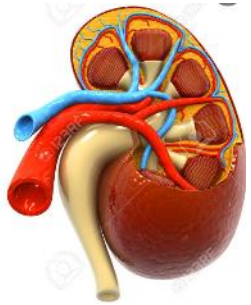


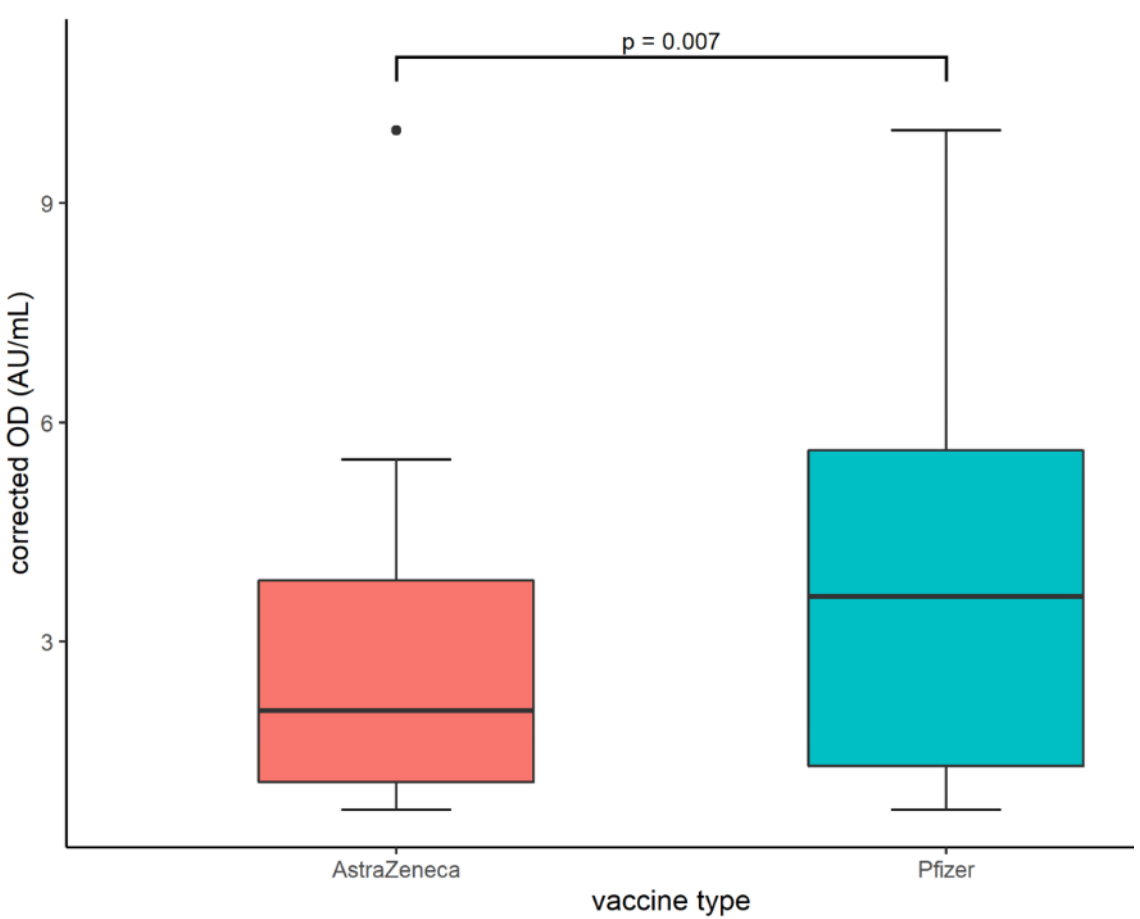
- 920 Renal Tx patients recruited with at least 1 dose
- 454 with data after second dose (225 AZ & 229 Pfizer)
- Responses AZ 47% & 49.8% Pfizer
- Excluding non responders AZ 2.06 vs Pfizer 3.62 AU/ml p=0.007
- All serious post vaccine infections occurred in non seroconverters

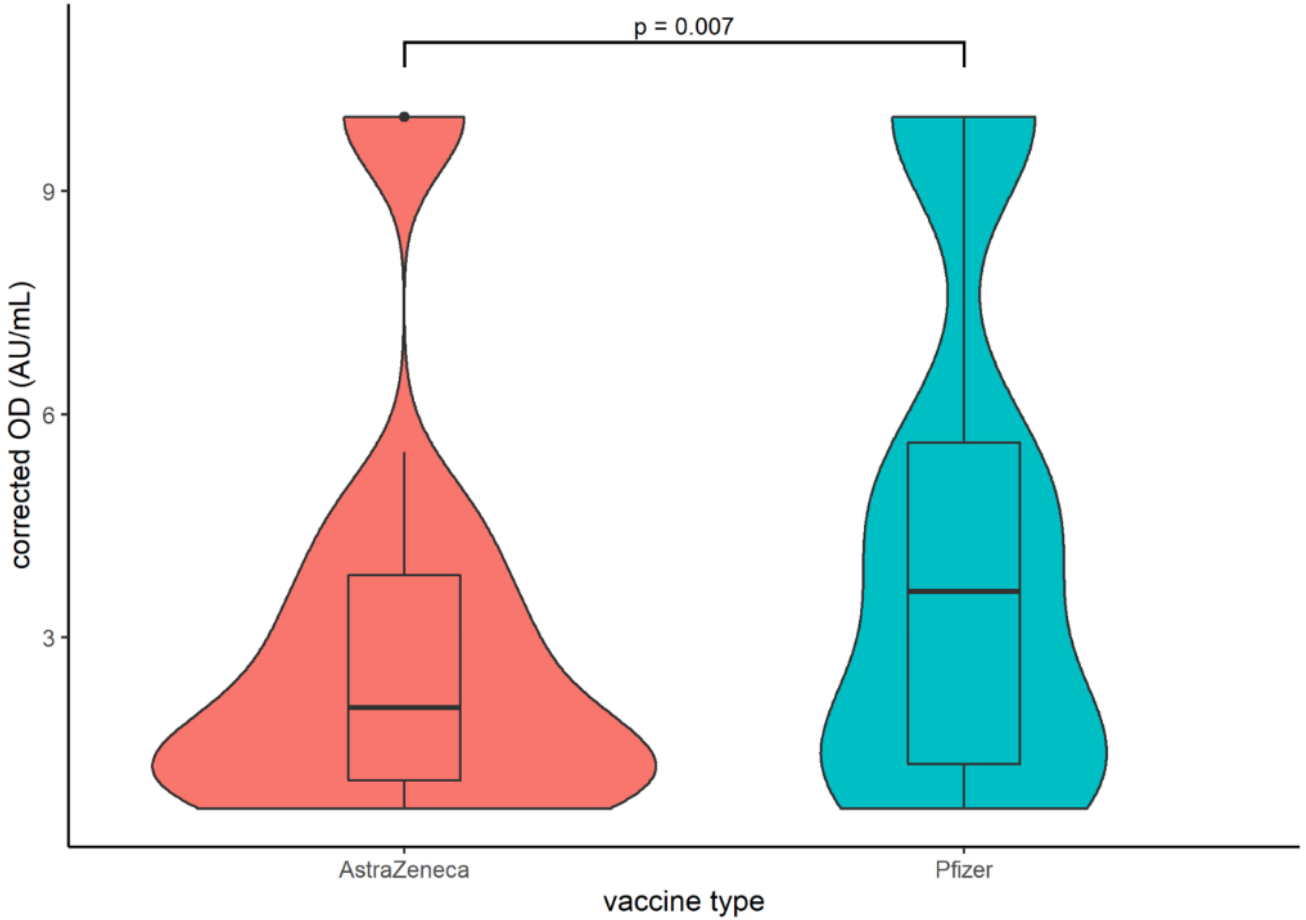
	β	95% Confidence Interval for β		P-value
		Lower bound	Upper bound	
Recipient Age	-0.03 (-0.17)	-0.05	-0.01	0.001
Transplant duration (<6m vs >6m)	-0.69 (0.07)	-1.69	0.3	0.17
Mycophenolate (No vs Yes)	-1.18 (-0.19)	-1.8	-0.55	<0.001
Induction immunosuppression (ATG vs Alemtuzumab)	0.121	-0.144	0.387	0.370
Prednisolone (No vs Yes)	-0.13 (-0.2)	-0.67	0.42	0.6
Type of vaccine (AZ vs Pfizer)	0.65 (0.12)	0.10	1.2	0.02
Gender group (M vs F)	0.58 (0.10)	0.03	1.14	0.04
Race group (Caucasians vs Asians)	0.84 (0.07)	-0.28	1.9	0.14

Asderakis A - submitted

Response after 2 doses by vaccine type



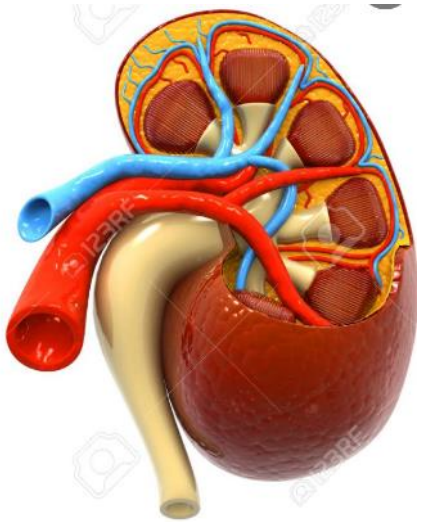


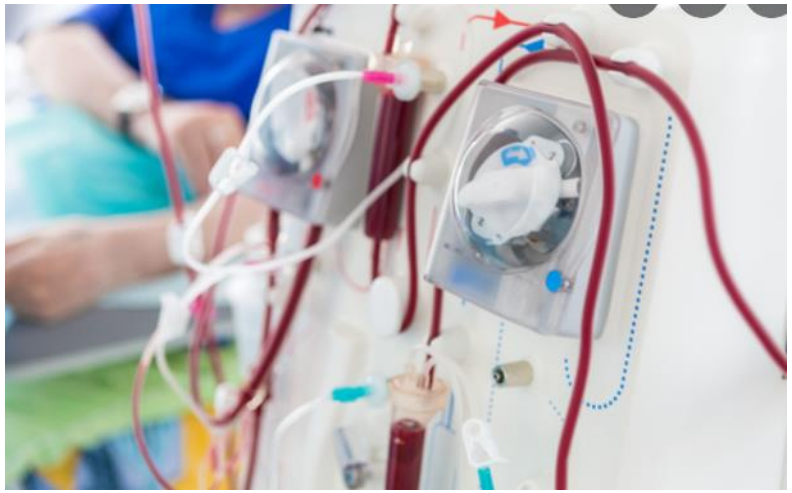


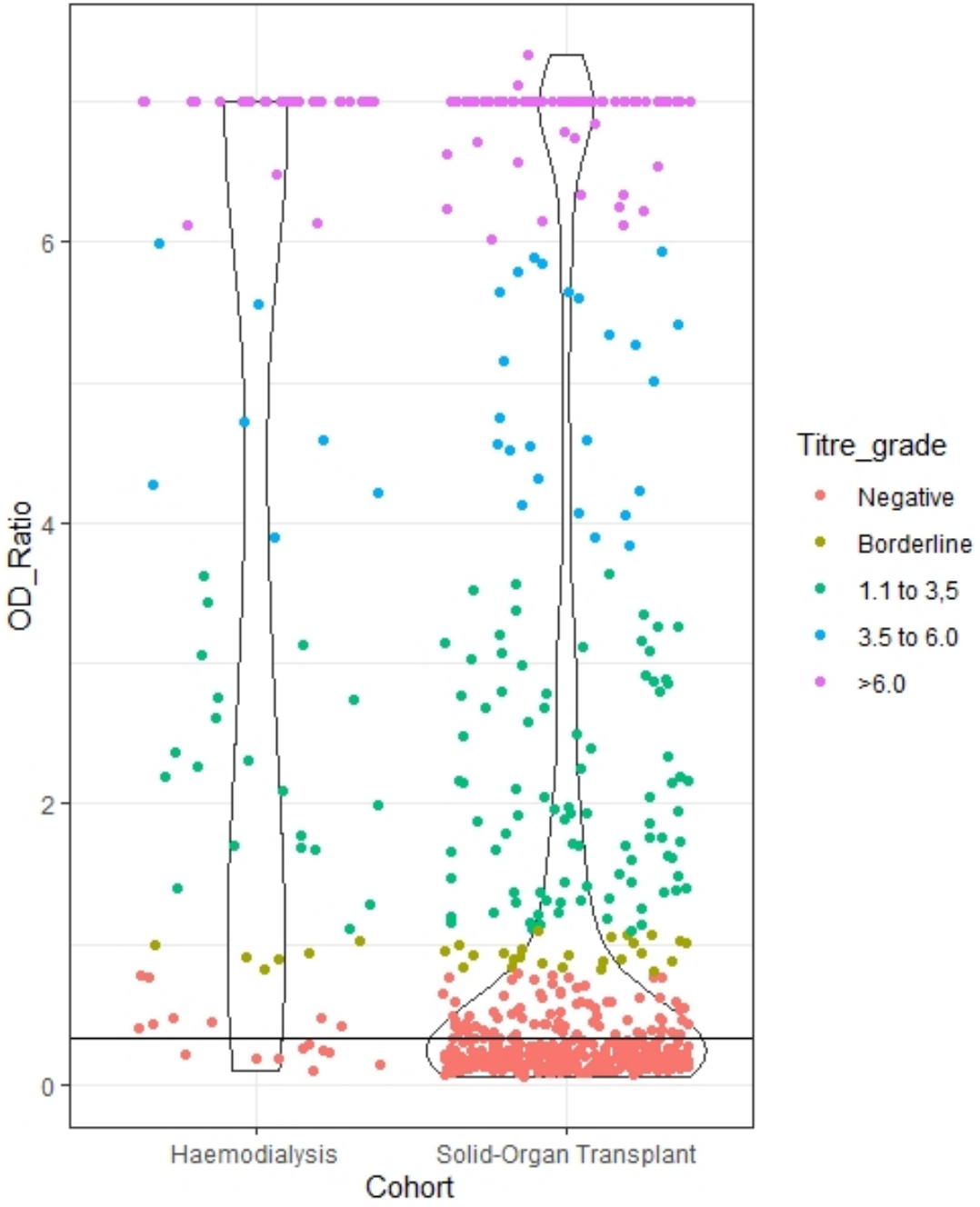
Asderakis A - submitted

Renal Transplant vs Dialysis

- Responses in Dialysis patients are less impaired than in renal transplantation







Asderakis A – in preparation

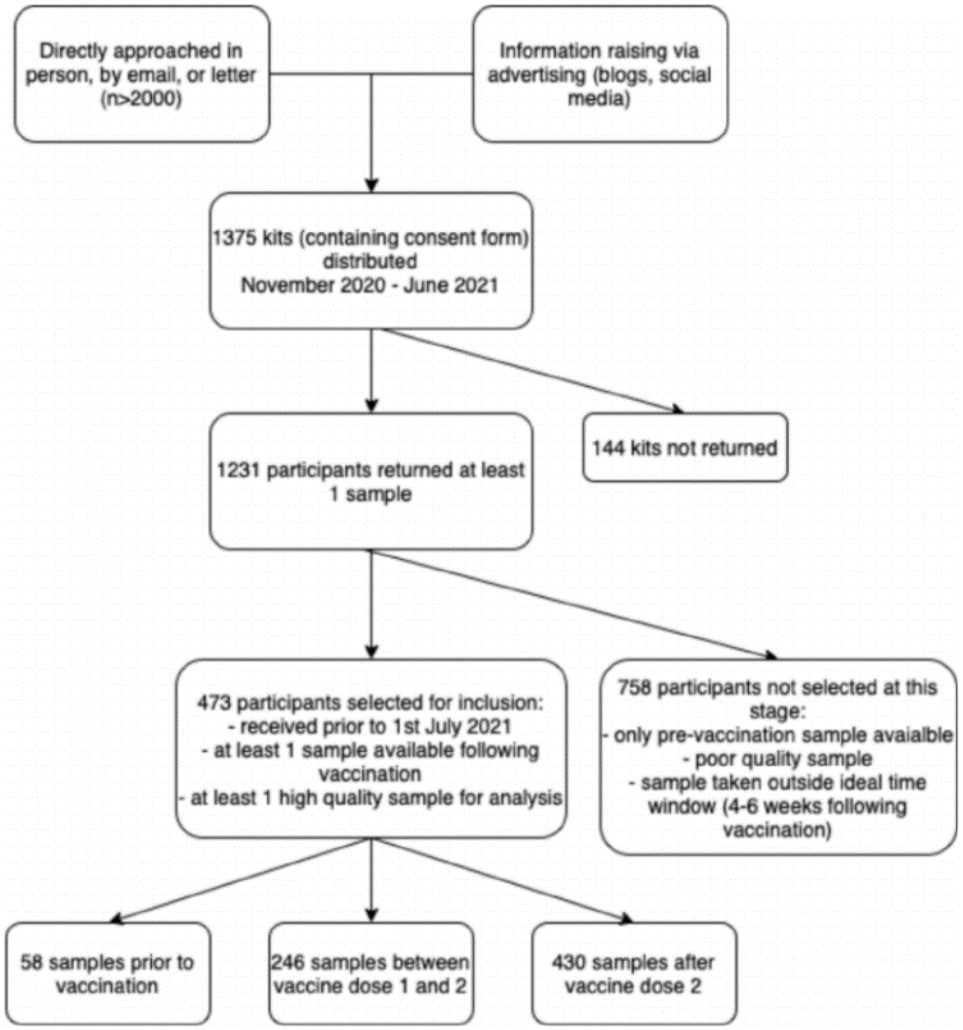
Multiple Sclerosis

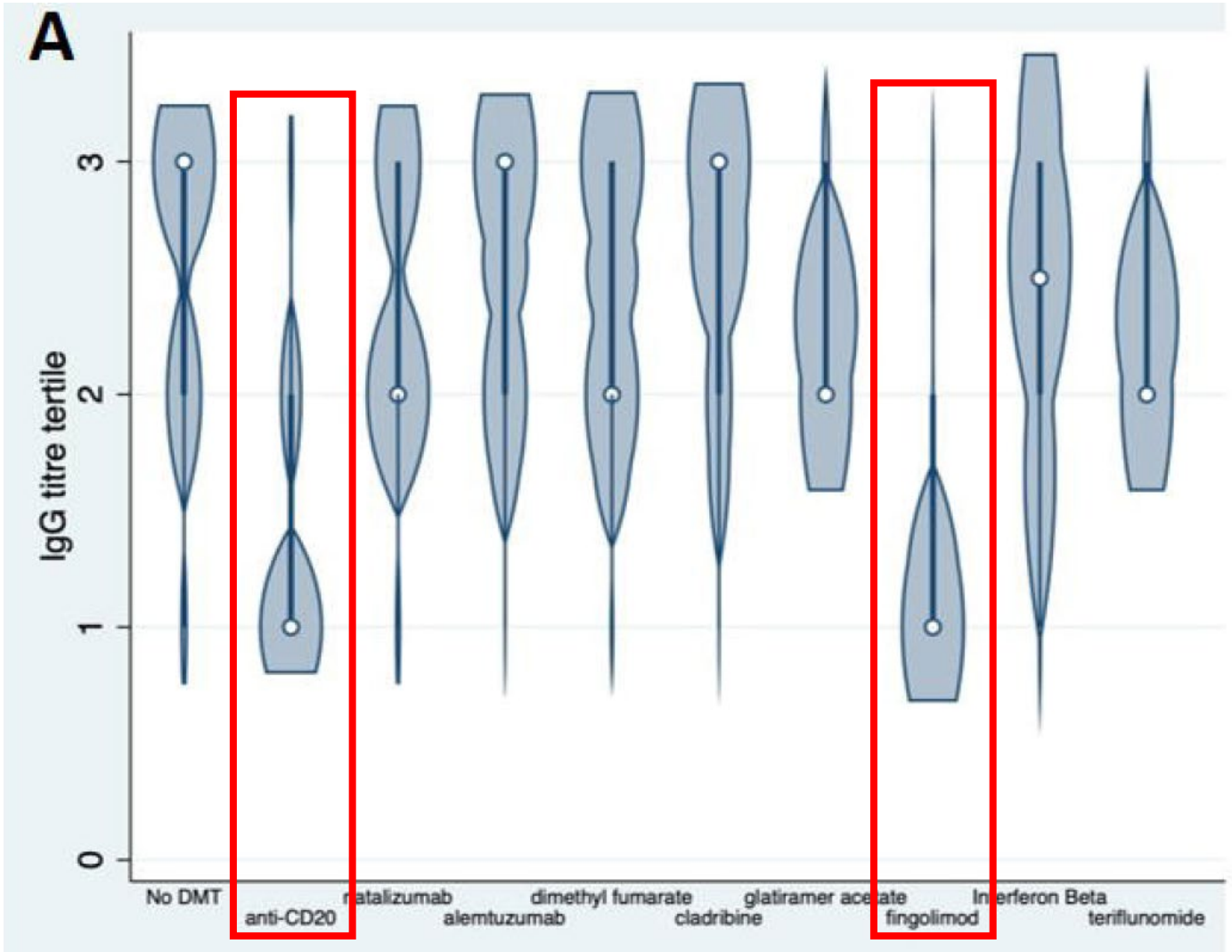
COVID-19 **DRiE**D BLOODSPOT **A**NTIBODY **M**EASUREMENT STUDY (DREAM)

- MS patients tend to receive sequential monotherapies
- 473 people from 5 centres provided one or more DBS and questionnaire
- Disease and drug history information extracted from medical records
- DBS were analysed for anti-SARSCoV2 RBD antibodies and partitioned
- Patients on no disease modifying therapy were used as controls
- Odds ratios for seroconversion and quantitative vaccine response by therapy
- Regression modelling to explore vaccine timing, type, age, lymphocyte count, and duration on therapy

Tallantyre EC Ann Neurol 2021 , Moat SJ Ann Clin Biochem 2021

Multiple Sclerosis





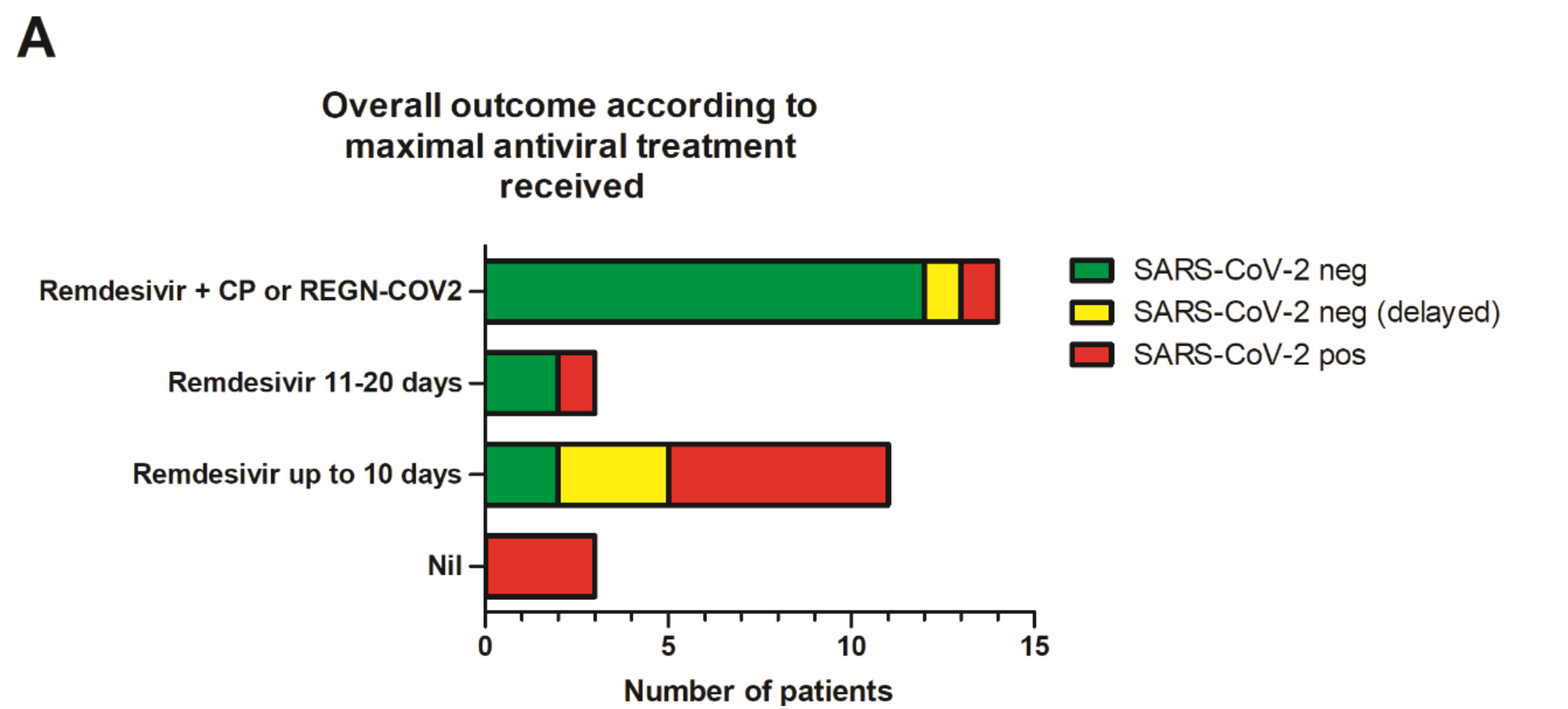
Tallantyre EC Ann Neurol 2021 , Moat SJ Ann Clin Biochem 2021

Persistent COVID in Immunodeficiency

- UK Survey – 31 cases median age 49yrs
- Commonest ID – Antibody deficiency with profound reduction in B cells inc XLA 55%, SAD inc prior rituximab 45%
- Median duration of disease 64 days max 300 days
- Individual patients experienced up to 5 episodes of illness
- Remdesivir monotherapy was associated with viral clearance in 30.4%
- Remdesivir and CPT was associated with viral clearance in 92.8%
- Patients on no treatment did not clear the virus

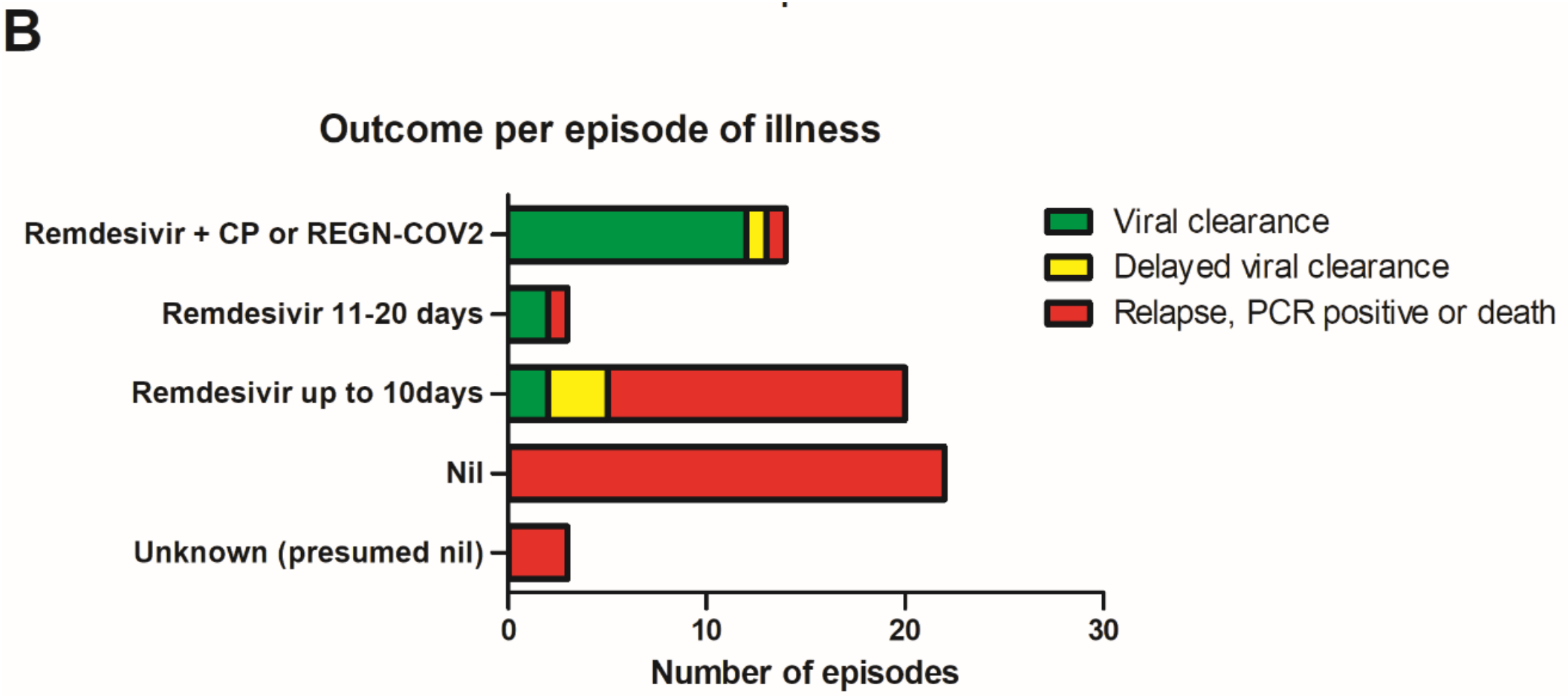
Lowe D et al JACI in press

Persistent COVID in Immunodeficiency



Lowe D et al JACI in press

Persistent COVID in Immunodeficiency



Lowe D et al JACI in press

Persistent COVID in WAS

- 37 yr old Optometrist with a molecular diagnosis of WAS
- PMH – splenectomy for thrombocytopenia, eczema, recc infections, early bronchiectasis, asthma and persistent molluscum
- Suboptimal vaccine response to polysaccharide and conjugated antigens with reduced CSMB
- SCIg 8g/L with trough 12-15g/L
- Prior HKU-1 coronavirus 12 months previously

Bradley R et al JoCI 2021

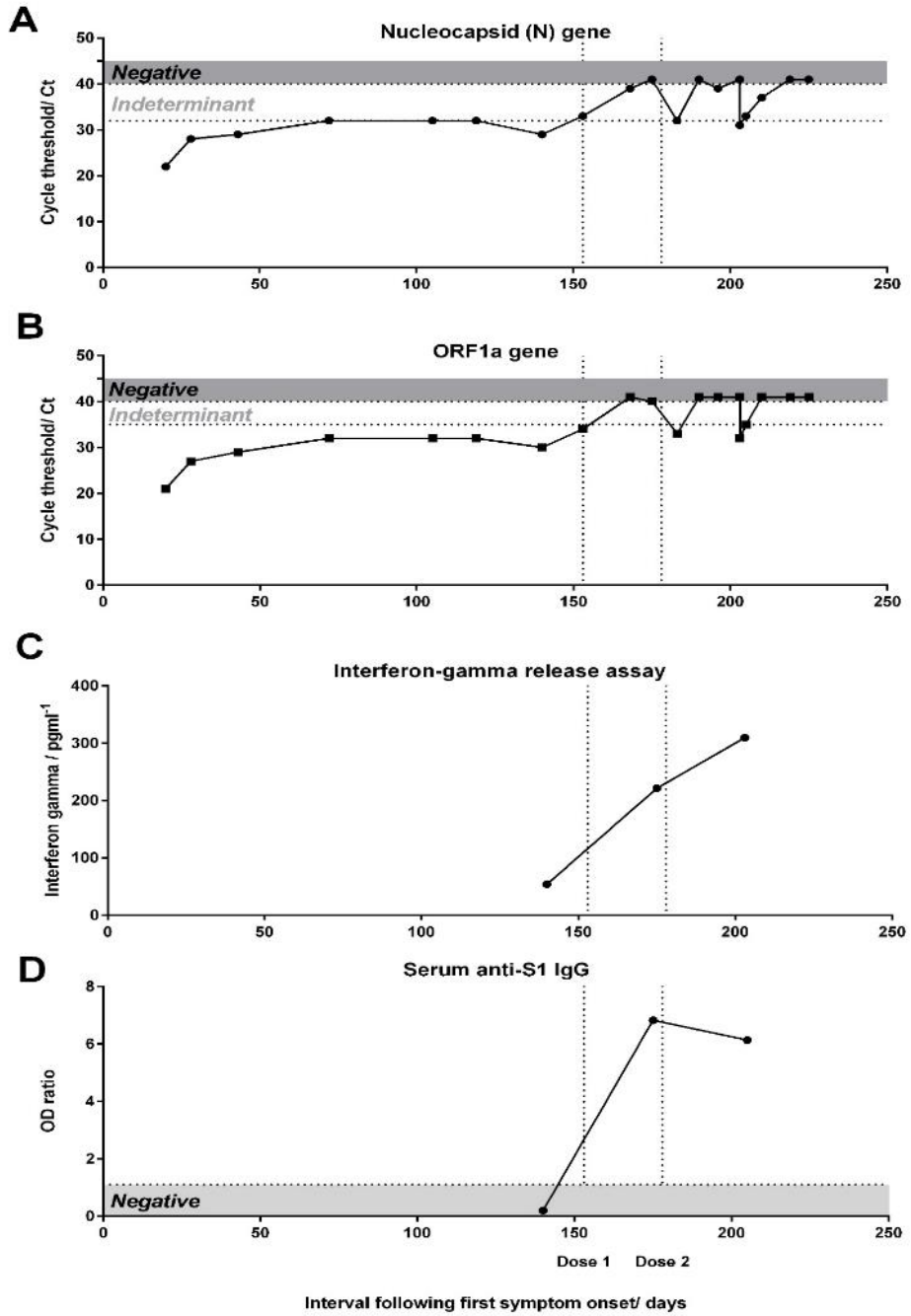
Persistent COVID for 218 days in WAS

- Anosmia, ageusia, cough, dyspnoea, fatigue
- Progressed to an atypical relapsing illness with chest tightness, dyspnoea, poor concentration & fatigue every fourth week
- Oxygen saturation >96%, CRP <12
- Monitored on Immunology Virtual Ward
- CT at Day 153 showed small airway inflammatory changes with widespread bilateral basal tree-in-bud and centrilobular micro-nodularity

Bradley R et al JoCI 2021

Therapeutic Vaccination

- CPT and mAb not clinically available
- 2 doses of Pfizer mRNA vaccination given 1 month apart
- Mild flu like symptoms only
- Pre and post antibody and T cell response assessment
- Enhanced antibody and T cell responses 14d after vaccination



Bradley R et al JoCI 2021

Conclusions

- Antibodies are a key component of the response to COVID with reduction in viral load & collaboration with T cell responses
- ID is a significant risk factor for worse outcomes
- Responses in both PID and SID are impaired and heterogeneous but many do respond
- Prior knowledge of antibody response enables precision medicine
- ID patients may present with atypical and persistent infection
- Advocacy and working together with our patients is key given the clash of ideologies – one size fits all vs individualized precision medicine
- There is more light with improved access to therapies (antibody, early, sc, vaccine, antivirals, molnupiravir, new agents) for our patients
- And much still to learn