

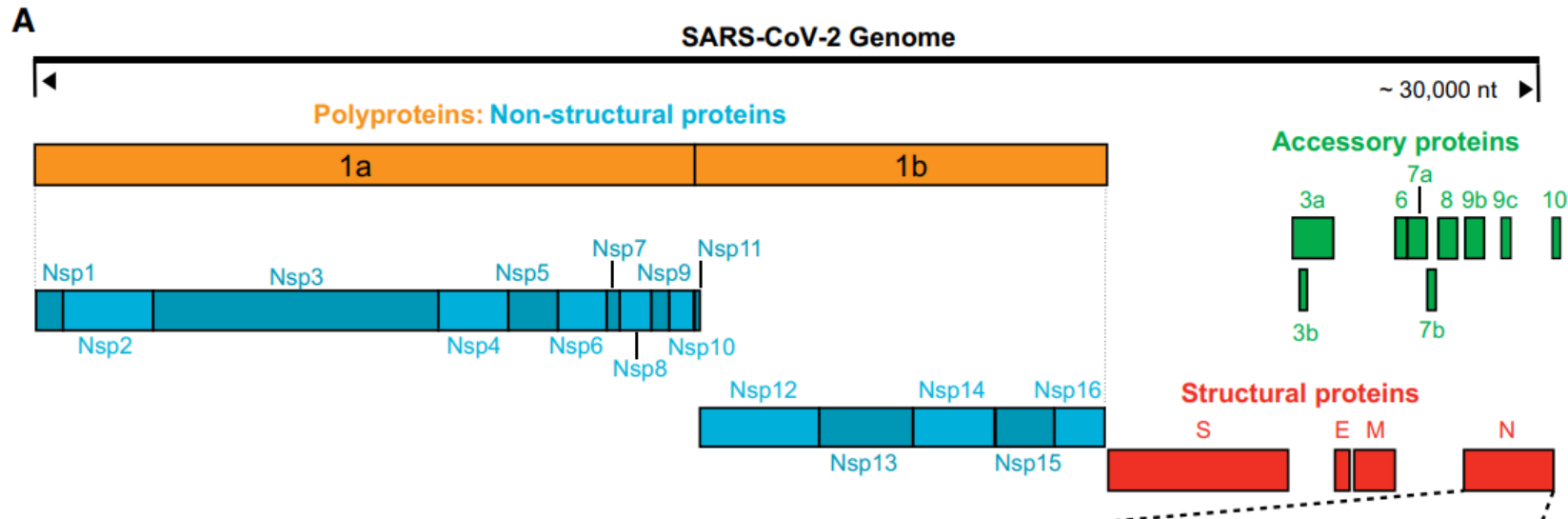
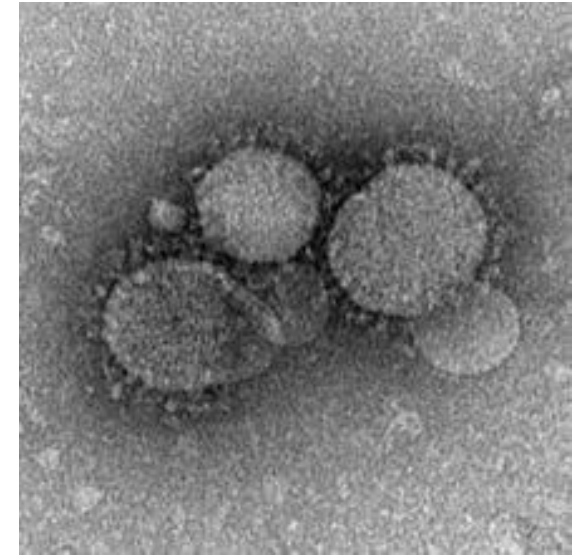
SARS-CoV-2 and Blood Safety

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**National Reference Centre for Transfusion Infectious
Risks – INTS**

IPFA/PEI Virtual Workshop 2021

SARS CoV-2

- genus : **betacoronavirus** (groupe 2) / subgenus : **sarbecovirus** - 50-140 nm enveloped virions, helicoidal nucleocapsid, trimeric flexible spike
- (+) single-stranded RNA genome, ~30 kb
- 4 structural, 16 non-structural and at least 9 accessory proteins



Peng, Y., et al. EMBO J. 2020 Oct 15;39(20):e105938. doi: 10.15252/embj.2020105938

Finkel, Y, et al. Nature 589, 125–130 (2021). <https://doi.org/10.1038/s41586-020-2739-1>

SARS-CoV-2 RBD / ACE2 receptor

The **receptor binding domain (RBD)** of the SARS-CoV-2 spike glycoprotein

- mediates viral attachment to ACE2 receptor
- is a major determinant of host range
- and a dominant target of neutralizing antibodies

Lungs++

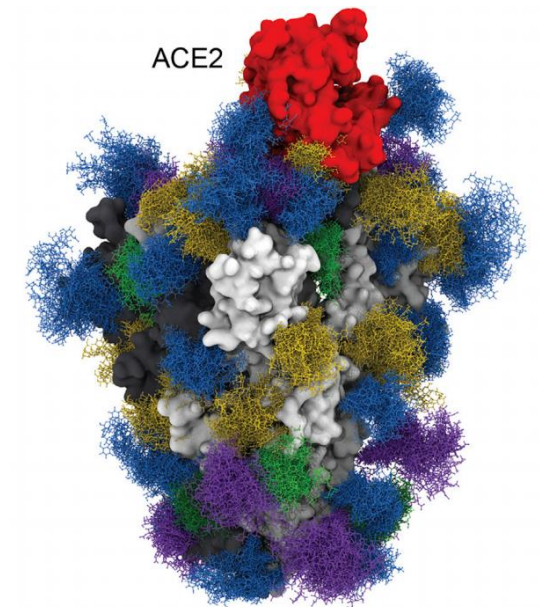
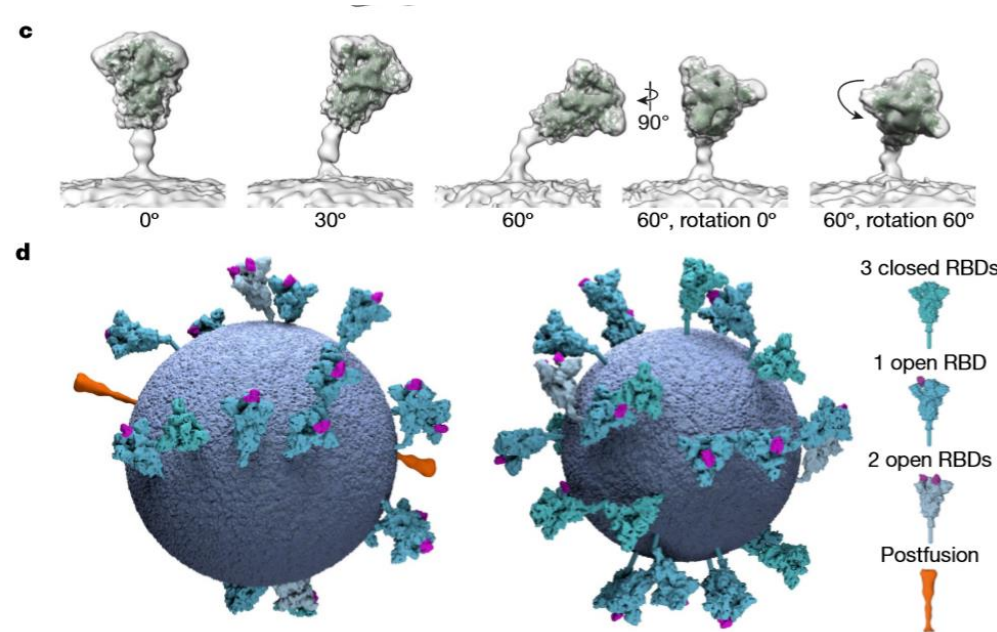
Enterocytes+

heart, muscles,

blood vessels,

peripheral blood

**haematopoietic stem
cells**



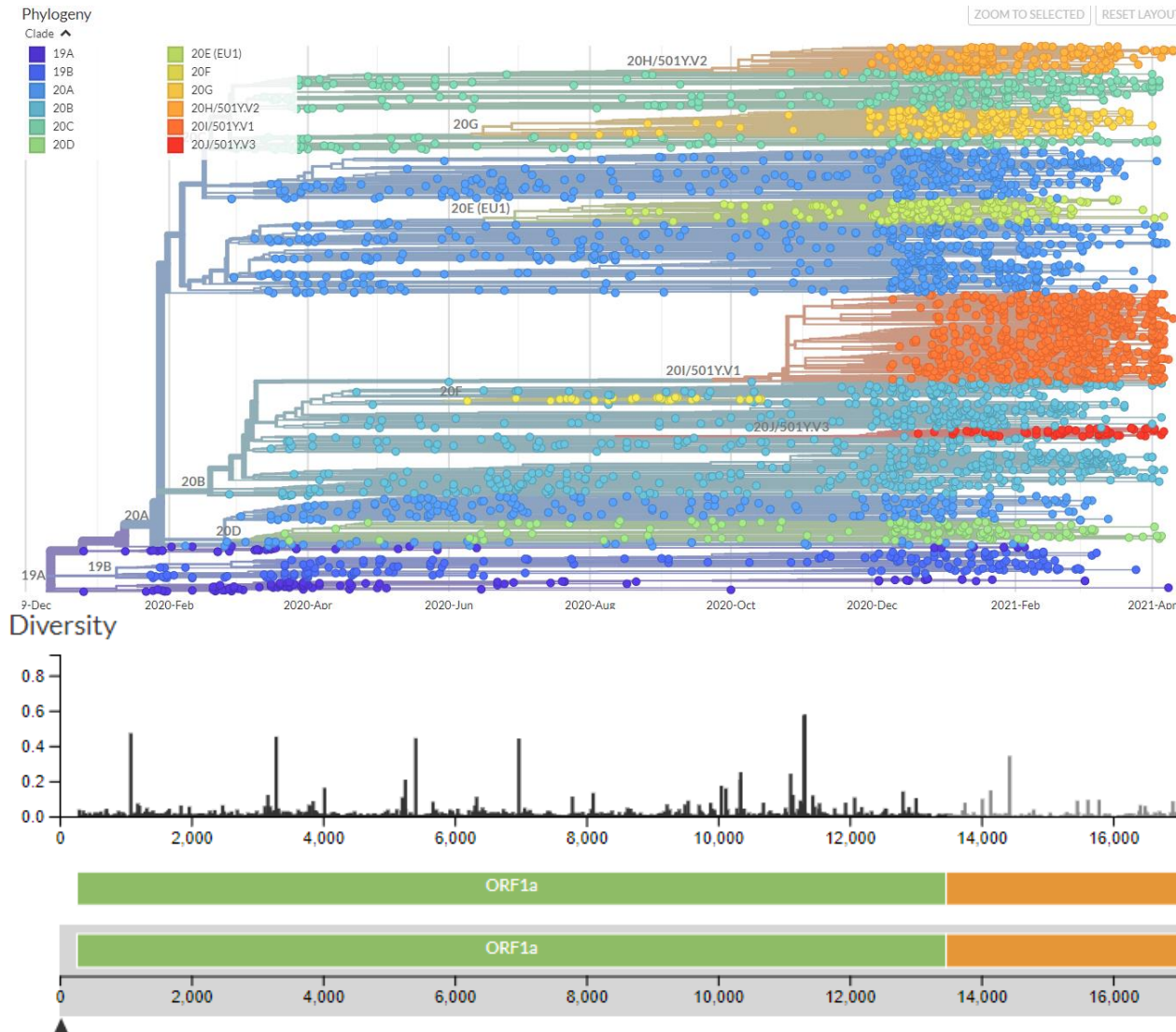
SARS-CoV-2 Spike Trimer

Salamanna F., et al. Front Med. 2020 Dec 3;7:594495. doi: 10.3389/fmed.2020.594495.

Ke Z., et al. Nature. 2020 Aug. doi.org/10.1038/s41586-020-2665-2

Zhao et al., 2020, Cell Host & Microbe 28, 586–601. <https://doi.org/10.1016/j.chom.2020.08.004>

SARS-CoV-2 genetic variability



- Estimation of mutation rate showed a median of 1.12×10^{-3} mut. per site-year (proofreading mechanism: nsp14-ExoN)

=> **Variants + recombinant strains**

- HIV : $1.2-3.4 \times 10^{-5}$ mut./site/round of replication

=> **Variants + recombinant strains**

- Influenza A/B : 2.0×10^{-6} and 0.6×10^{-6} mut./site/round of replication (+ reassortants)

=> **Variants + reassortant strains**

Nextstrain SARS-CoV-2. <https://nextstrain.org/ncov/global>

Koyama T. , et al. Bulletin of the World Health Organization 2020;98:495-504. doi: <http://dx.doi.org/10.2471/BLT.20.253591>

Li et al., Sci Adv. 2020 Jul 1;6(27):eabb9153. doi: 10.1126/sciadv.abb9153

SARS-CoV-2 Variants of Concern (VOCs)

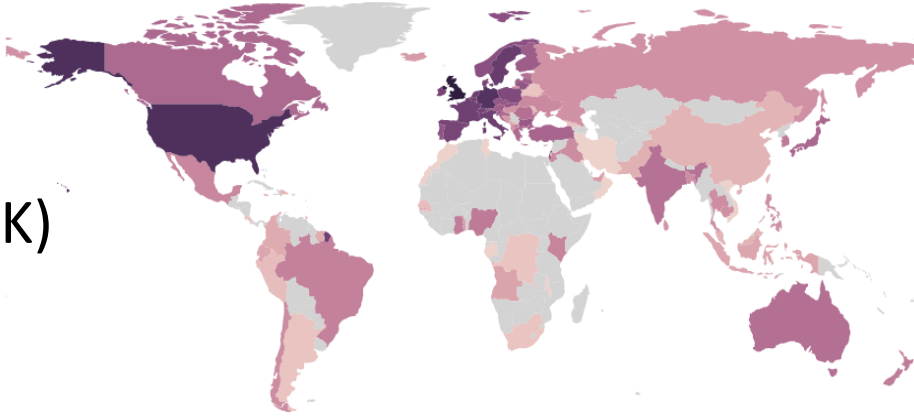
- increased transmissibility
- or more severe disease (increased hospitalizations or deaths),
- or significant reduction in neutralization (mAbs, post-vaccine sera, convalescent plasma)
- or diagnostic detection failures

name (PANGO lineage)	First detected	impact on transmissibility	impact on neutralization		RBD																
			mAb	convalescent plasma/pos-vaccin sera	Clade	Δ69/70	Δ144Y	S13I	W152C	K417N/T	N439K	L452R	Y453F	S477	E484K	Q493K	N501Y	A570D	D614G	H655Y	
B.1.1.7	UK	+50 %	minimal	minimal	20I	X	X										X	X	X		
P.1	Japan/Brazil	-	moderate	reduced	20J				X					X			X		X	X	
B.1.351	South Africa	+50 %	moderate	moderate	20H				X					X			X		X		
B.1.427	US-California	+20%	significant (not all)	moderate	20C						X								X		
B.1.429	US-California	+20%	significant (not all)	moderate	20C			X	X		X								X		

SARS-CoV-2 Variants of Concern (VOCs)

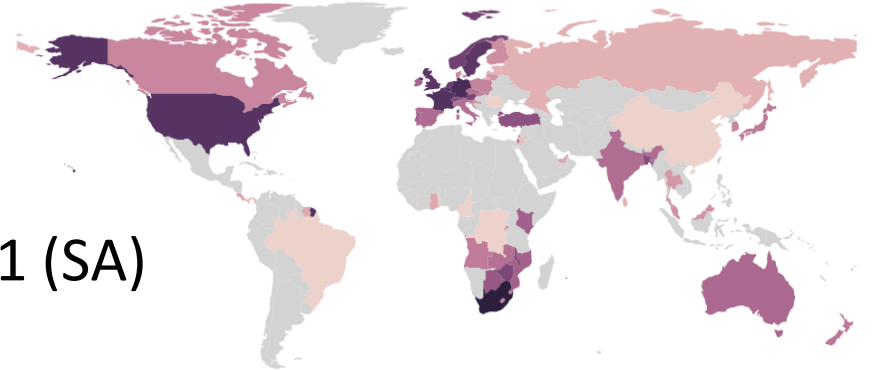
Max sequences
1 sequence
No variant record

B1.1.7 (UK)



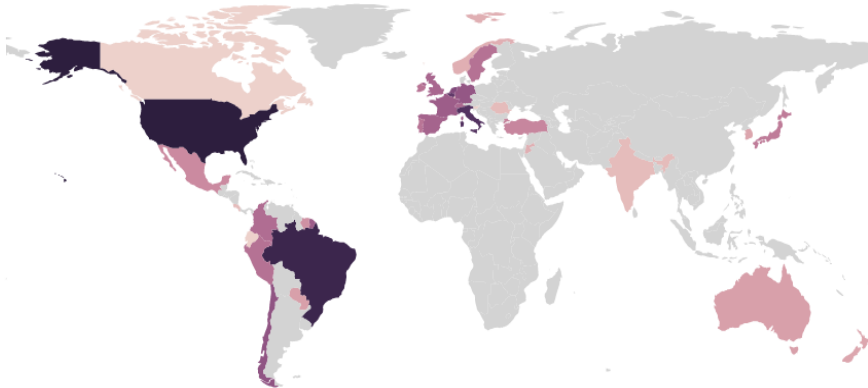
Max sequences
1 sequence
No variant record

B1.351 (SA)



Max sequences
1 sequence
No variant record

P.1 (BR)



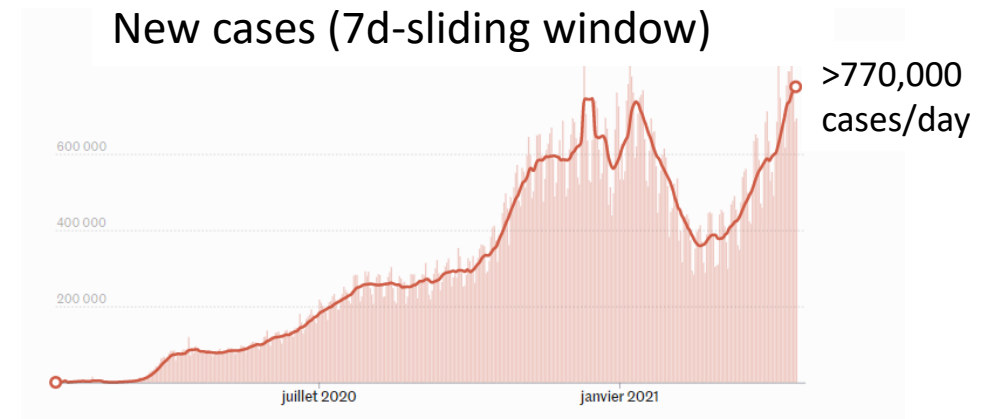
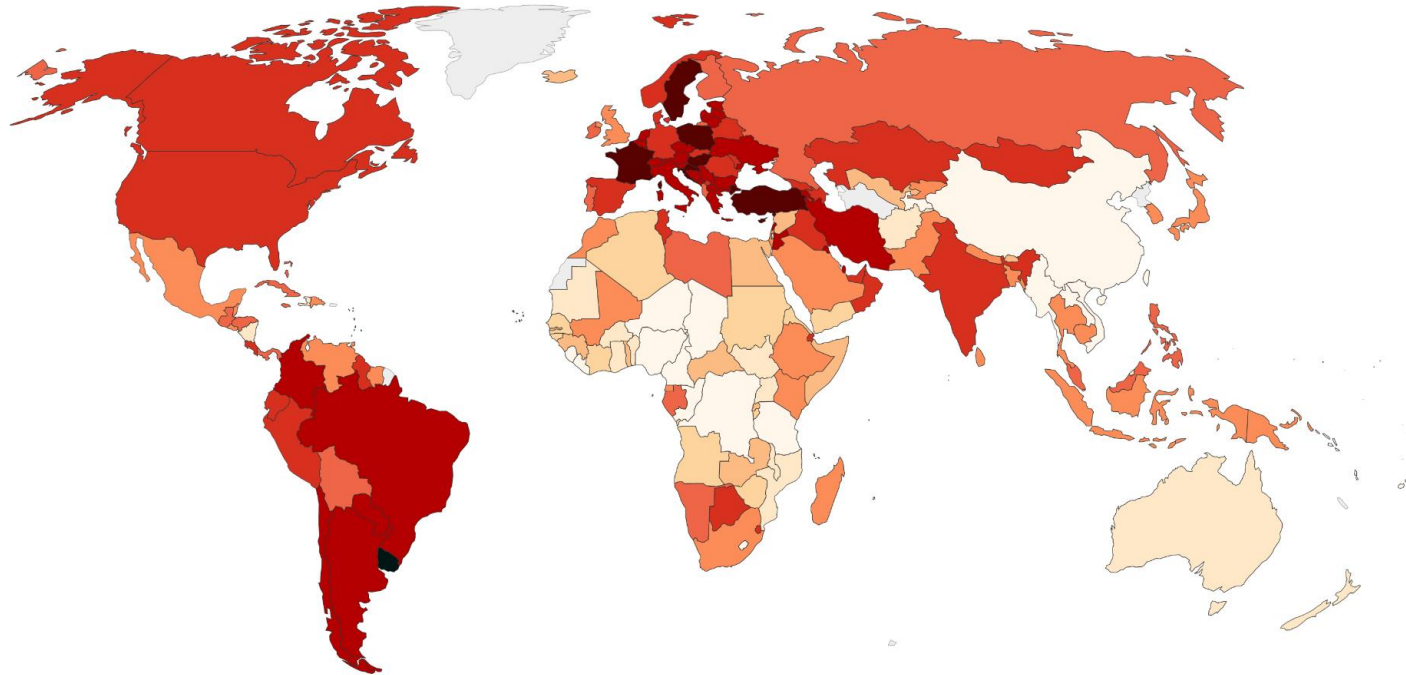
Weekly incidence - April 16, 2021

Daily new confirmed COVID-19 cases per million people, Apr 15, 2021

Shown is the rolling 7-day average. The number of confirmed cases is lower than the number of actual cases; the main reason for that is limited testing.

Our World
in Data

>139 M cases
> 2.9 M deaths



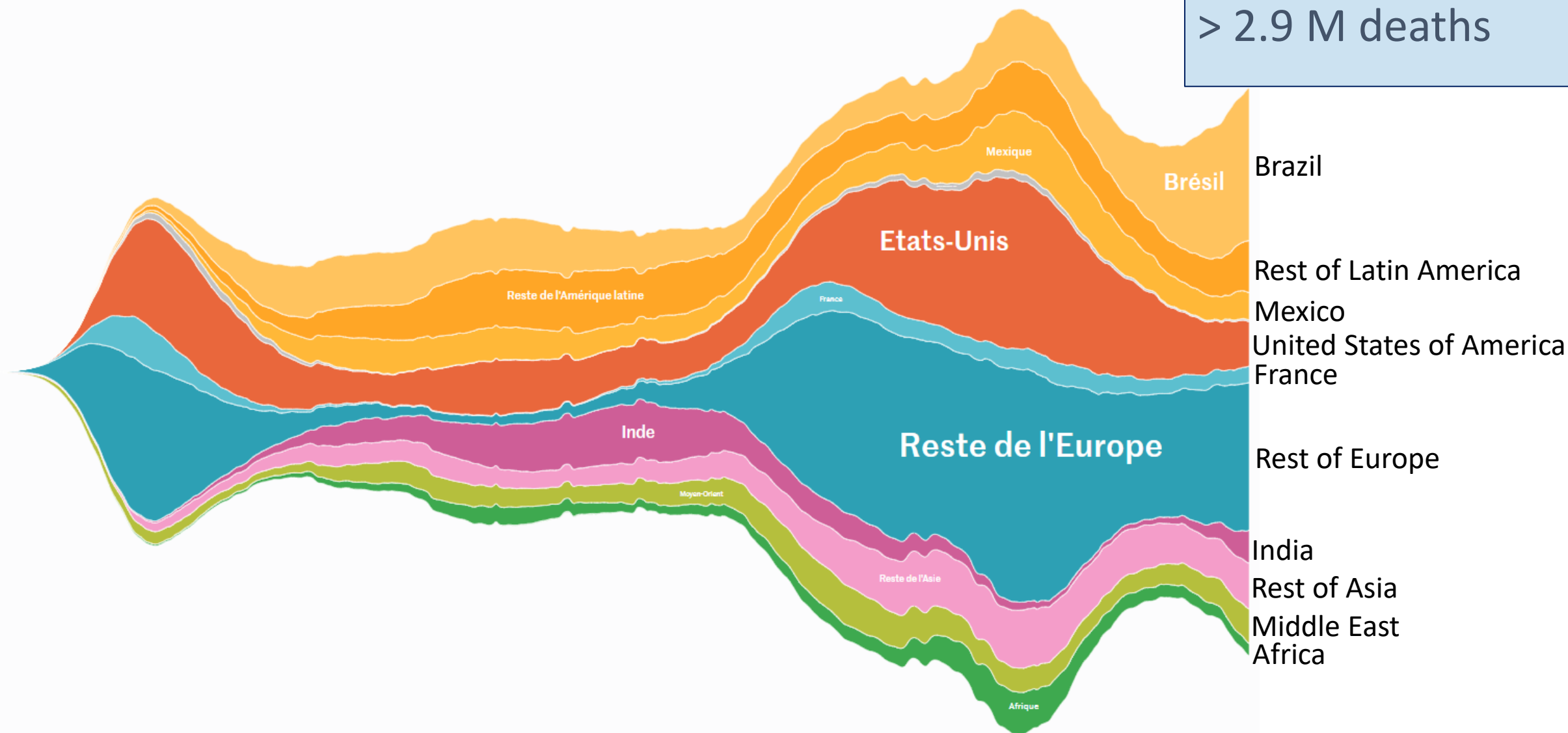
Source: Johns Hopkins University CSSE COVID-19 Data

CC BY

Source: Johns Hopkins University CSSE COVID-19 Data. CC BY

Death toll - April 16, 2021

>139 M cases
> 2.9 M deaths

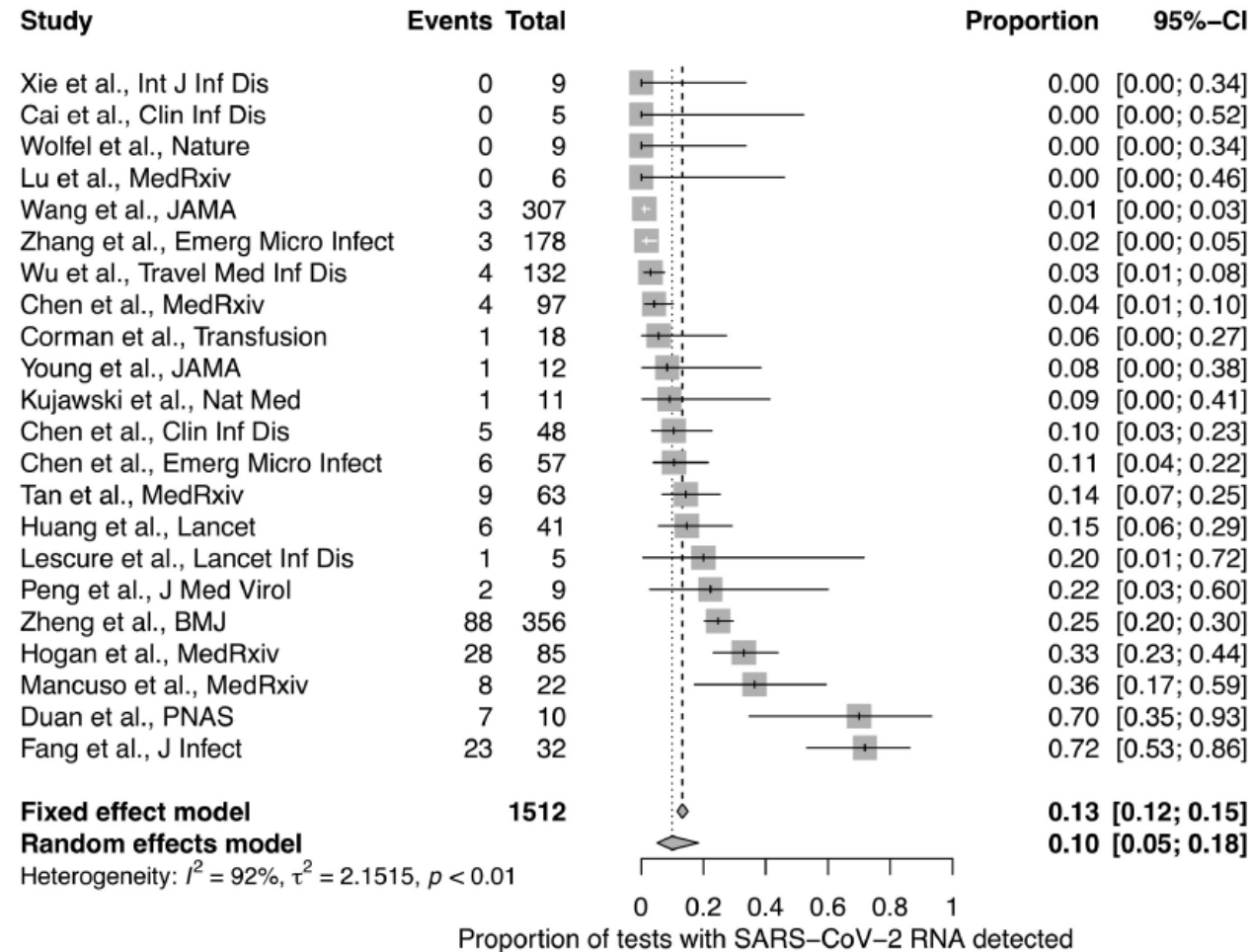


SARS-CoV-2: a potential threat to blood safety?

Are the criteria met ?

- presence of the agent (respiratory virus) in the blood of asymptomatic individuals?
 - ⇒ if so in an infectious form?
- survival of the agent during the processing and the shelf life of blood products?
- sensitivity to pathogen reduction?
- transmission of the agent via the haematogenous route?
- disease induced in the recipient of contaminated blood products?
- (impact of variants?)

SARS-CoV-2 RNAemia in clinical series



- Low
- Heterogenous (60-6000 cp/mL)
- Associated with increased risk of critical disease and death
- No evidence of infectious virus in RNA positive sera in cell culture

Figure 2. Prevalence of SARS-CoV-2 RNA in serum / plasma / whole blood samples from a systematic literature review. Point prevalence indicated for each study with confidence intervals showing citation and number of samples represented (Table 1).

SARS-CoV-2 RNAemia in blood donations

- **12** studies report prospective or retrospective screening of SARS-CoV-2 RNA in blood donations, or PDIs due to COVID-19
- **5** studies report RNAemia in pre- or asymptomatic blood donors
(n= **22** individuals in total)

1 st Author	Nb of donations involved or screened	Nb of SARS- CoV-2 RNA + plasma	Transfused blood products			Nb of recipients	Nb of positive recipient in nasopharyngeal swab	Comments	DOI
			RBC	PC	PLU				
➡ Busch*	257930	3	?	?	?	?	NA	15,000 MP16 + 3,000 MP6	M. Busch, TTID-WP ISBT personal communication 01/19/2021
➡ Busch*	284	9	?	?	?	?	?	284 PDI	
➡ Cappy	268	3	1	1	-	2	ND	3+ PDI	10.1182/blood.2020008230
Chang	7425	4	-	-	-	0	NA	1+PS /1+ RS /2+ PDI	10.3201/eid2607.200839
Chang	98 342	0	-	-	-	NA	NA	PS	10.1111/trf.15943
Cho	1	ND	-	1	-	1	0/1	PDI, case report	10.1016/j.jiph.2020.05.001
Gambacorti	7	ND	2	5	-	7	1/7	PDI, case reports	10.1016/j.transci.2021.103105
Kwon	7	0	3	6	-	7	0/3	7+ PDI	10.1111/vox.12925
Lee	1	0	-	1	-	1	0/1	PDI, case report	140.1111/tme.12724
Liapis	1	ND	1	1	-	1	0/1	PDI, case report	10.1007/s00277-020-04337-3
➡ Pham	700	1	-	-	-	NA	NA	PS	10.7326/L20-0725
Politis	1	ND	-	1	-	1	0/1	PDI, case report	10.1016/j.traccli.2020.10.007
➡ Waheed	690	2	2	-	-	2	0/2	RS	10.1055/s-0040-1716663
Total	365657	22	9	16	0	22			

*not published yet

RBC: red blood cell unit

PS: prospective screening

PC: platelet concentrate

RS: retrospective screening

PU: plasma unit

PDI: post-donation information

ND: not done

One-year COVID-19 experience of the French haemovigilance network

- Methods

- Outreach program on COVID-19 PDI in blood donors (national blood service, **EFS**)
- Detection of SARS-CoV-2 RNA with SARS-COV-2 R-GENE® PCR1 (BioMérieux)
- Confirmation: Pasteur Institute RT-PC (x3) / Aptima® SARS-CoV-2 assay (X5)
- Attempt to amplify and sequencing of positive samples: ARTIC PCR #77, 95
- Attempt to identify VOCs: ARTIC PCR #75, 76
- Attempt to isolate SARS-COV-2 on VERO E6 cells for each positive plasma

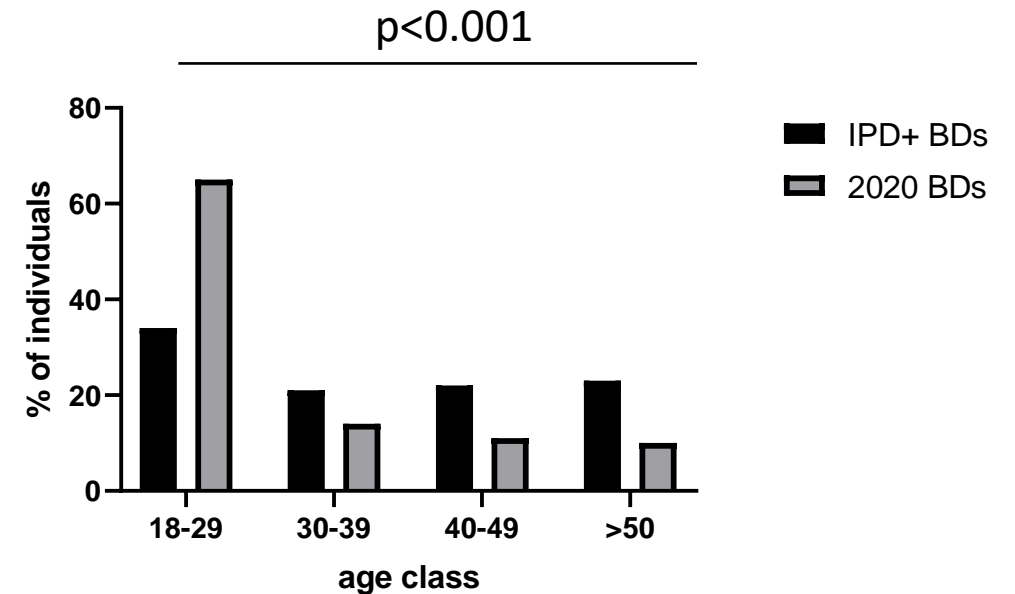
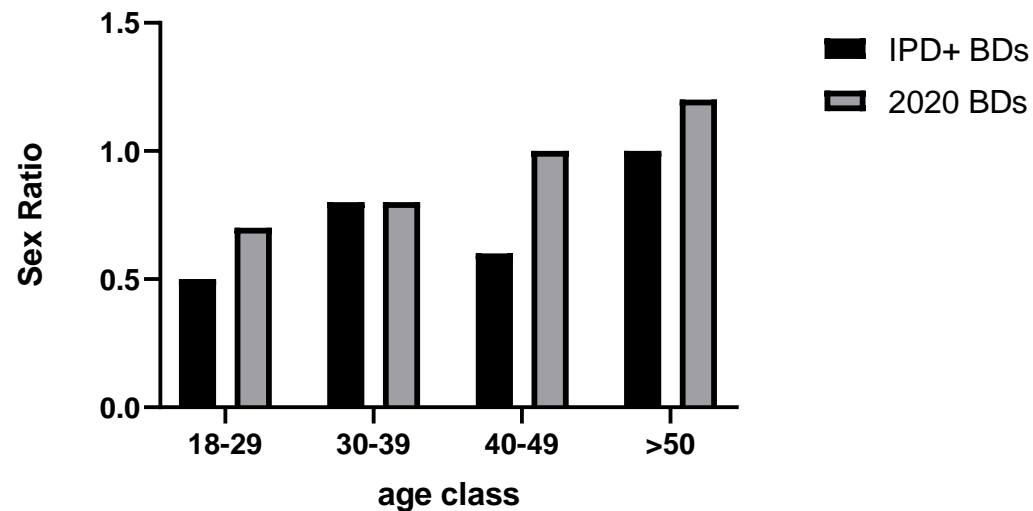
(NRC)

- First report (Cappy et al, Blood, DOI [10.1182/blood.2020008230](https://doi.org/10.1182/blood.2020008230))

- **268** blood donations with PDI => **3** (1.1 %) donations + for SARS-CoV-2 RNA in plasma
- **3** traceback investigations => **0/3** positive donations

PDIs - Population demographics

- 1092 donations investigated
 - **738 (68 %)** confirmed SARS-CoV-2+ (nasopharyngeal swabs)
 - **187 (17 %)** suspected SARS-CoV-2
 - **77 (7 %)** contact cases
 - **90 (8 %)** unknown status



PDIs - Detection of SARS-CoV-2 in BDs

- 1092 donations investigated
 - **37** donations positive with SARS-COV-2 R-GENE[®] assay PCR1
 - Ct between 36.5 and 41.4, in one target of the duplex PCR (FAM, NC)
 - **10** samples confirmed with another assays (RT-PCR, TMA and/or sequencing)
 - **7** samples confirmed by sequencing
 - All donations tested negative for Ab to SARS-CoV-2
 - Investigation of infectivity
 - **26** samples analysed in cell culture experiment
 - ⇒ RNAemia not associated with infectious SARS-CoV-2 (within the limitations of the assay) as already described in symptomatic individuals
- Andersson, M et al. Wellcome Open Res. 2020 Oct 12;5:181. doi: 10.12688/wellcomeopenres.16002.2.
- Confirmation of non-repeat samples (to be done)
 - COVID-seq / Illumina sequencing (98 amplicons)

Traceback investigations – 5 patients – 45 donations

- 5 patients, 5-67 years-old
- Received between 2 and 25 blood products
- 20 RBUs, 23 PCs
- None of the 45 traced-back repository samples tested + for SARS-CoV-2
- In particular, none of the RBUs (no pathogen reduction)

Traceback investigations: case report

- Case 1

- 5-yo patient, sickle-cell disease => HSCT (allograft)
- March 3-27: 21 APCs + 8 PPCs + 2 RBUs
- March 23: cough + March 28: fever and facial diplegia
- March 30: SARS-CoV-2 +
- April 1-30: ICU

- Parents: asymptomatic and SARS-CoV-2 neg
- Medical staff asymptomatic but not tested
- 2 COVID+ children in the same haematology unit

- Donations from 17 APCs + 8 PPC s + 2 RBUs tested neg for SARS-CoV-2
- accountability of blood donations excluded

Traceback investigations: case reports

- Case 2
 - October 20: 2 RBUs
 - October 23: lung infection + fever
 - October 28: patient died
 - No symptomatic and RT-PCR+ relatives
 - 2 donations tested neg for SARS-CoV-2

SARS-CoV-2: a potential threat to blood safety?

Are the criteria met ?

- presence of the agent (respiratory virus) in the blood of asymptomatic individuals? **YES, but only RNA is detectable**
⇒ if so in an infectious form? **No evidence in vitro**
- survival of the agent during the processing and the shelf life of blood products? **Not investigated**
- sensitivity to pathogen reduction? **YES (Azhar et al. Vox Sang 2020, Ragan et al., PlosOne 2020)**
- transmission of the agent via the haematogenous route? **No evidence according to lookback studies**
- disease induced in the recipient of contaminated blood products? **No reported transfusion transmission cases**
- (impact of variants ?) **Not investigated**

What has been done to avoid theoretical transmission by transfusion? (ecdc recommendations 10 dec 2020)

Precautionary measures only

Context	eligible for donation	measure
donors with active confirmed COVID-19	NO	quarantine (at least 14 days) after the end of symptoms
contact cases	NO	quarantine (at least 14 days)
donor returning from active zone	DEPENDING	if neg PCR-test when entering / quarantine (at least 14 days)
donor with positive SARS-CoV-2 serology	NO	quarantine (at least 14 days) if no symptoms
PDI within 14 days		discarding of donated blood and blood components, unless they have been treated with approved pathogen reduction technology

Not recommended: laboratory screening of blood donors (RNA or antigen) in the upper respiratory specimens

- transfusion-transmitted COVID-19 has not been reported
- published data show that blood-borne transmission of COVID-19 is unlikely

Conclusion

- No evidence of SARS-CoV-2 transmission by transfusion:
 - the risk remains theoretical
 - but precautionary measures are still in place
- The impact of the pandemic regarding blood transfusion is much higher on the blood supply !
- Blood donor population allowed/allows to:
 - better understand epidemiology of SARS-CoV-2 and its evolution (serosurveys) including the surveillance of VOCs
 - contribute to treatment (convalescent plasma)
 - evaluate diagnostic serological assays
 - constitute prospective cohorts for characterization of viral persistence and humoral and cellular immunity

Acknowledgements

