COVID-19 and the blood sector: Risks, response measures and developments

Dragoslav Domanovic, ECDC, Keeping up with Reality and Quality: A Challenge for European Blood Establishments, EDQM, webinar 27-29 October 2020

Disclaimer: *These tables, histograms, maps and graphs are based on the available information at the time of publication, originating from several sources. Data completeness depends on the availability of information from the affected areas. All data should be interpreted with caution as the outbreak is evolving rapidly. In addition, due to the unavailability of date-of-onset data and different testing policies per country, these figures might not be reflective of the evolution of the epidemic.*

Human coronavirus taxonomy

Order: *Nidovirales*

Family: *Coronaviridae*

Sub-family	Genus	Sub-genus	Species	Sub-species
Orthocoronaviridae	*Alphacoronavirus*	*Duvinacoronavirus*	*HCoV-229*	
		Setracovirus	*HCoV-NL63*	
	Betacoronavirus	*Embecovirus*	*HCoV-HKU1*	
			Betacoronavirus 1	*HCoV-OC43*
		Merbecovirus	*MERS-CoV*	
		Sarbecovirus	*SARS-CoV*	
			SARS-CoV2	
	Deltacoronaviruus			
	Gammacoronaviruus			

Source: based on the International Committee on Taxonomy of Viruses (ICTV).

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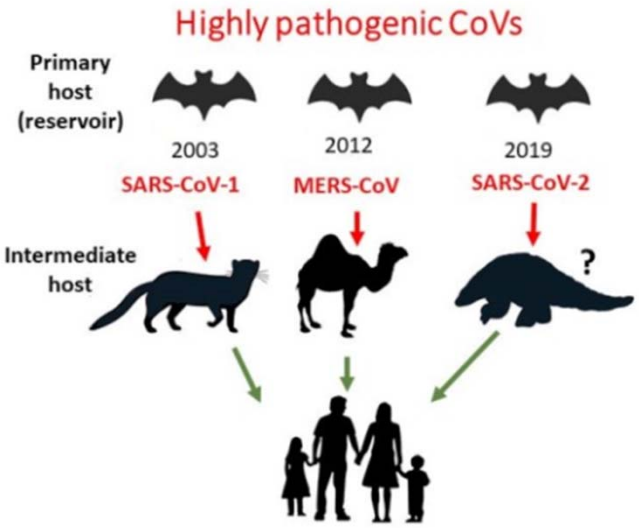
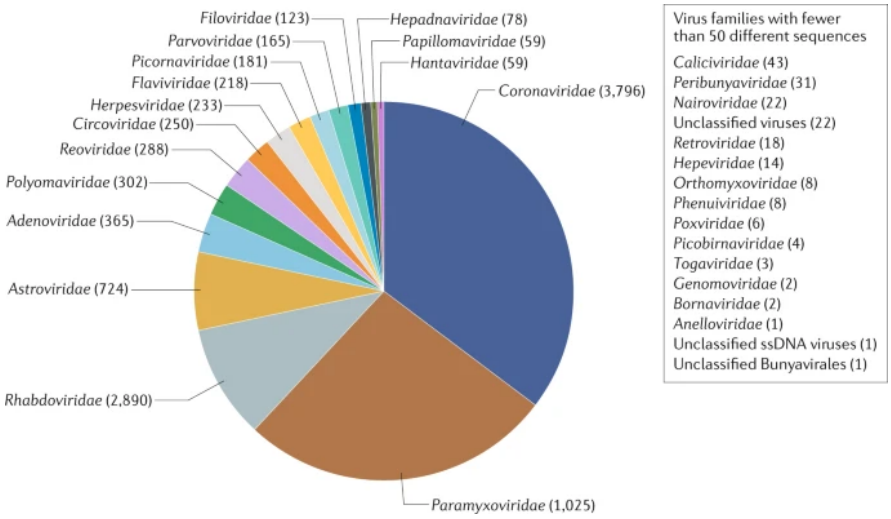
Highly pathogenic human corona viruses spill overs



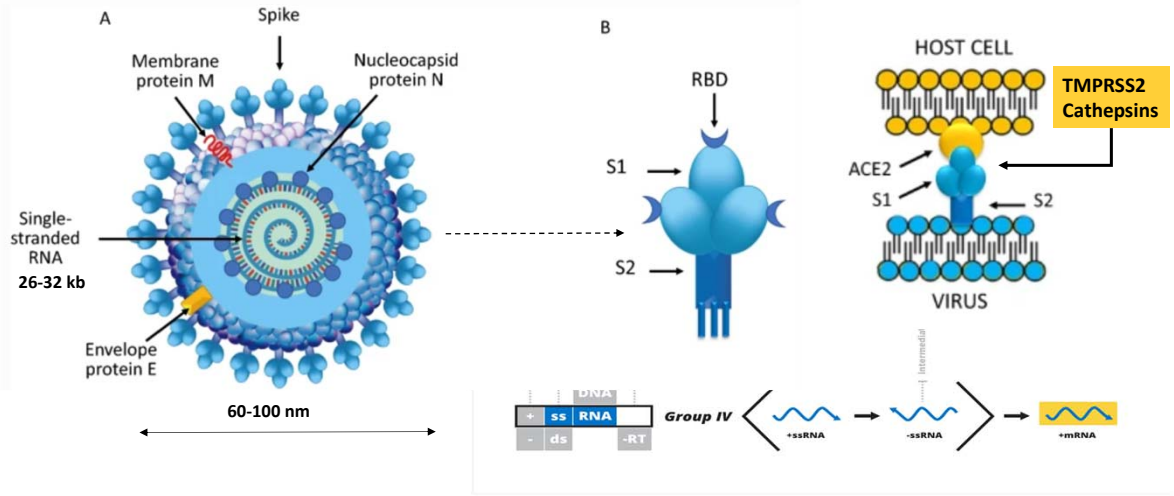
Shors, Teri. "Coronavirus." *AccessScience*, McGraw-Hill Education, May 2020.

Ongoing threat of bat-borne viral emergence



https://www.nature.com/articles/s41579-020-0394-z

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virion structure and cell entry



https://link.springer.com/article/10.1007/s15010-020-01486-5

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Epidemiological characteristics

Route of transmission -

- Human to human via respiratory droplets coughed or exhaled by infected persons, direct contact with an infected subject and by touching droplet-contaminated surfaces or objects and then touching the eyes, nose or mouth.

Viral RNA presence –

- Faeces, whole blood, serum, saliva, nasopharyngeal specimens, urine; ocular fluid, breast milk and in placental or foetal membrane samples. A correlation has been suggested between the isolation of viable virus and the initial viral RNA load (i.e. cycle threshold [Ct]).

Period of infectivity –

- Viral RNA levels appear to be highest at the time of symptom onset compared with later in the illness
- Viral shedding: in respiratory tract specimens 1-2 days before the onset of symptoms and it can persist for up to 8 days in mild cases, and for longer periods in more severe cases, peaking in the second week after infection. Prolonged viral RNA shedding - nasopharyngeal swabs (up to 67 days among adult patients) - faeces (more than one month after infection in paediatric patients).Late viral RNA clearance (≥15 days after illness onset), is associated with male sex, old age, hypertension, delayed admission to hospital, severe illness at admission, invasive mechanical ventilation, and corticosteroid treatment.
- **Infectious virus** has been detected up to day 8 post disease onset

Rates of transmission

- Vary by location and infection control interventions. Transmission from asymptomatic individuals (or individuals within the incubation period) has also been described (the extent remains unknown). Mathematical modelling studies (not peer-reviewed) have suggested that asymptomatic individuals might be major drivers for the growth of the COVID-19 pandemic

Basic reproduction number (R_0):

- Studies have estimated the R_0 = 2.2 (95% CI 1.4–3.9) and 2.7 (2.5–2.9) in an average **2.5**

CLINICAL FEATURES

Incubation period:

- Median incubation period: 5-6 days (range from 2-14 days).
- Modelling studies 2.3 days (95% CI, 0.8–3.0 days) up to 14 days

Pathology

- Histologic findings from the lungs include diffuse alveolar damage similar to lung injury caused by other respiratory viruses, such as MERS-CoV and influenza virus. A distinctive characteristic of SARS-CoV-2 infection is vascular damage, with severe endothelial injury, widespread thrombosis, microangiopathy and angiogenesis.

Spectrum of illness severity:

- Asymptomatic infections **-** frequency is unknown
- Symptomatic cases
  - Mild to moderate ~ 80 %.
  - Severe disease ~ 15 %.
  - Critical disease ~ 5 %.

Clinical symptoms

Most common symptoms

- headache (70.3%),
- loss of smell (70.2%),
- nasal obstruction (67.8%),
- cough (63.2%),
- asthenia (63.3%),
- myalgia (62.5%),
- rhinorrhoea (60.1%),
- gustatory dysfunction (54.2%)
- sore throat (52.9%).
- fever (45.4%)

Most common comorbidities

- hypertension, cardiovascular disease and diabetes (16.4%, 12.1% and 9.8%,)

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Disease severity

Serious and critical illness rates *

- ICU admission 10.9%,
- Acute respiratory distress syndrome (ARDS) 18.4%
- Mortality 4.3%,

COVID-19 serious complications:

- myocardial injury, arrhythmias, cardiomyopathy and heart failure, acute kidney injury often requiring renal replacement therapy, neurological complications such as encephalopathy, acute ischemic stroke, rare cases encephalitis, and coagulopathy presenting as thrombosis in various organs

Specific complications in children:

- Paediatric inflammatory multisystem syndrome (PIMS)

Long-term sequelae: fatigue and dyspnoea

* Zhang JJY, Lee KS, Ang LW, Leo YS, Young BE. Risk Factors of Severe Disease and Efficacy of Treatment in Patients Infected with COVID-19: A Systematic Review, Meta-Analysis and Meta-Regression Analysis. Clin Infect Dis. 2020 May 14.

Diagnostic tests

- Nucleic acid tests detect the presence of viral RNA. Typically, these use an amplification step based on RT-PCR.
- Antigen tests detect the presence of a viral antigen, typically part of a surface protein.
- Antibody tests detect the presence of antibodies generated against SARS-CoV-2. The three most used assays are enzyme-linked immunosorbent assays (ELISA), chemoluminescence assays (CLIA) and lateral flow assays (LFA). Neutralization Ab test.

Detection SARS-COV-2 RNA in Clinical Specimens by rRT-PCR of

Table. Detection Results of Clinical Specimens by Real-Time Reverse Transcriptase–Polymerase Chain Reaction

Specimens and values	Bronchoalveolar lavage fluid (n = 15)	Fibrobronchoscope brush biopsy (n = 13)	Sputum (n = 104)	Nasal swabs (n = 8)	Pharyngeal swabs (n = 398)	Feces (n = 153)	Blood (n = 307)	Urine (n = 72)
Positive test result, No. (%)	14 (93)	6 (46)	75 (72)	5 (63)	126 (32)	44 (29)	3 (1)	0
Cycle threshold, mean (SD)	31.1 (3.0)	33.8 (3.9)	31.1 (5.2)	24.3 (8.6)	32.1 (4.2)	31.4 (5.1)	34.6 (0.7)	ND
Range	26.4-36.2	26.9-36.8	18.4-38.8	16.9-38.4	20.8-38.6	22.3-38.4	34.1-35.4	
95% CI	28.9-33.2	29.8-37.9	29.3-33.0	13.7-35.0	31.2-33.1	29.4-33.5	0.0-36.4	

Abbreviation: ND, no data.

Preliminary results of first seroepidemiological population studies in EU/EEA and the UK from public sources, as of 30 June 2020

Country	Number (n)	Source of samples	Time of sampling (in 2020)	Laboratory method	Proportion of positive samples (%)
Austria	1,500	General population (Ischgl)	Week 17	n/a	42.4
	269	General population	Week 18	n/a	4.7
Belgium	3910: 1st collection 3391: 2nd collection	General population	Mid-April	EUROIMMUN IgG	2.9-6
Bulgaria	586	General population	Week 13-17	Orient Gene IgM/IgG	4.8
Czechia	26 549	General population	Week 18	Wantai rapid test	0.0-4.0
Croatia	1494	Industry workers	Week 17-18	n/a	1.2
Denmark	5 422	Blood donors	Week 18	EUROIMMUN Elisa	2.4
Finland	2 800	General population	Weeks 16-23	Fluorescence-based multiplex	1.0-4.3*
France	209	Pausi- symptomatic	n/a	In-house ELISA	29
	200	Blood donors	n/a	In-house ELISA	3
Luxembourg	1 862	General population	Weeks 17-19	EUROIMMUN IgG	1.97
Netherlands	7 361	Blood donors	Weeks 15-16	Wantai Elisa	2.7
Spain	60 983	General population	Weeks 18-19	Orient Gene IgM/IgG	5.0
	311	General population	Week 17	Rapid LFIA IgM/IgG	5.47
	634	GP patients	Week 18-19	Rapid LFIA IgM/IgG	38.4
Sweden	1 104	Residual sera	Week 18	n/a	3.7-7.3
	~400	Blood donors	Week 17-22	n/a	1.6-5.0
	1200	GP patients	Week 21	n/a	6.3
	500	General population (Norrbotten)	Week 22	EUROIMMUN IgG	1.9
UK (England)	7 694	Blood donors	Weeks 13-21	EUROIMMUN	8.5**
UK (Scotland)	500	Blood donors	Week 13	Pseudotype microneutralisation assay	1.0

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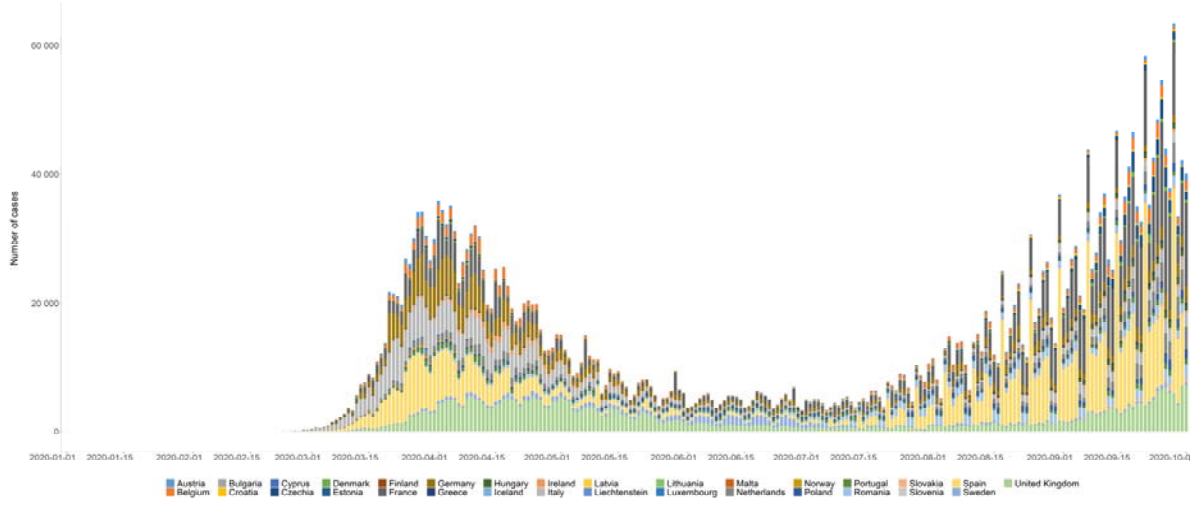
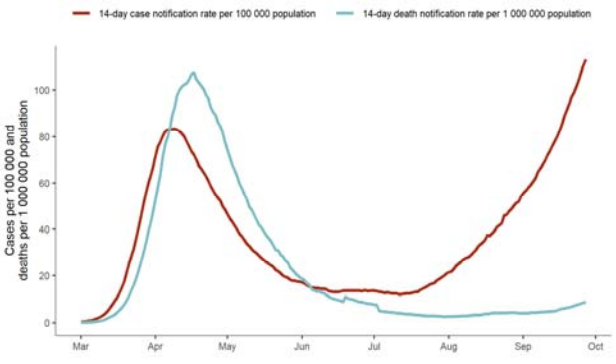
Distribution of laboratory-confirmed cases of COVID-19 in EU/EEA and the UK, as of 02 October 2020



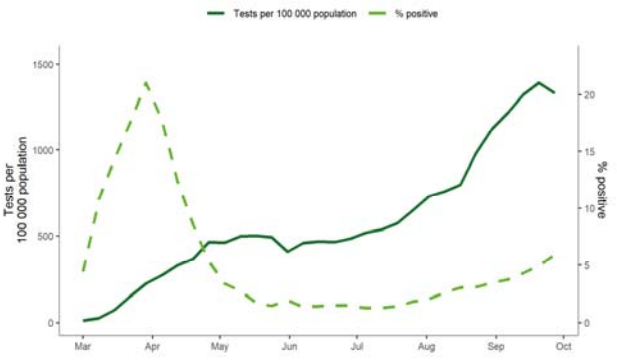
COVID-19 case and death notification rates, testing rates and test positivity, EU/EEA and the UK

EU/EEA and the UK: 14-day COVID-19 case and death notification rates, 1 March 2020 to 27 September 2020

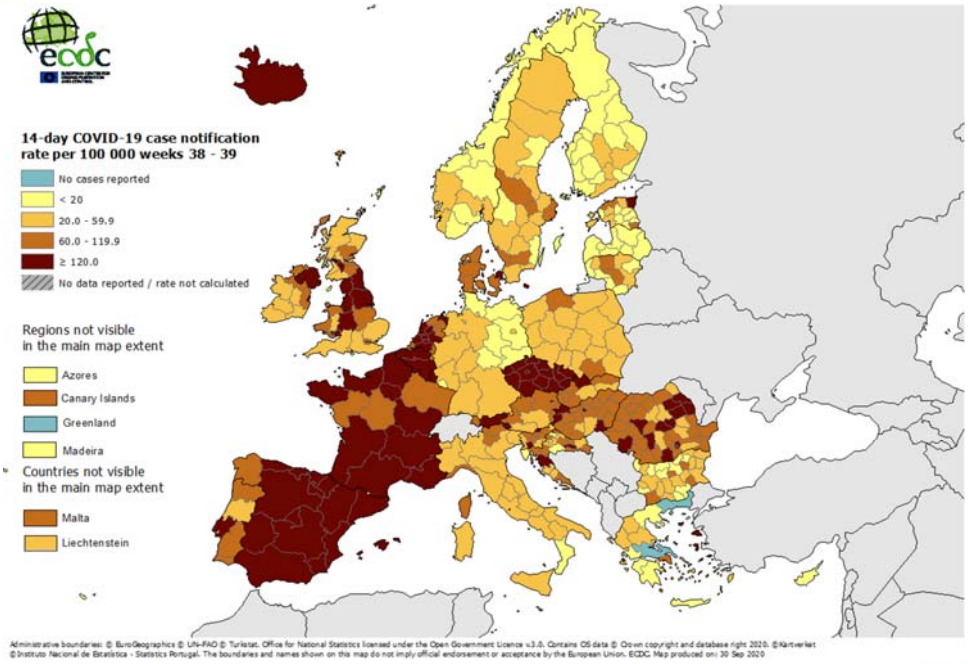


Source: ECDC Epidemic Intelligence

EU/EEA and the UK: testing rate and test positivity (%), 1 March 2020 to 27 September 2020



Source: TESSy and public websites. Data shown for countries submitting data up to 27 September 2020



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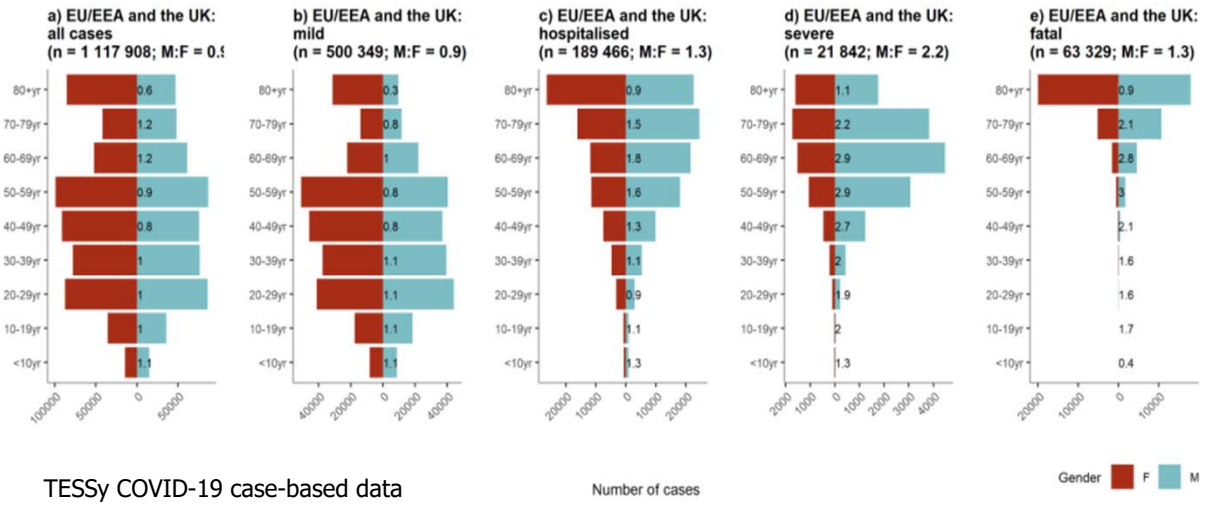
Age-sex distributions of all cases at different levels of severity in EU/EEA and UK



TESSy COVID-19 case-based data

https://www.ecdc.europa.eu/en/covid-19/surveillance/weekly-surveillance-report

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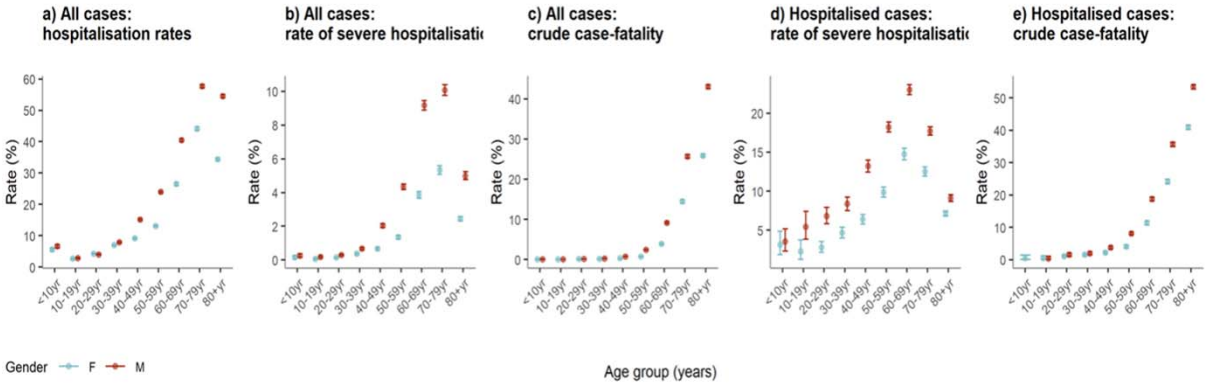
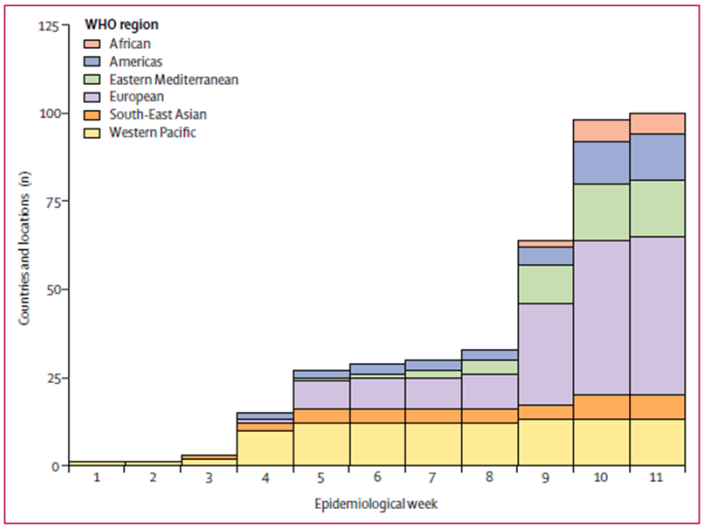
Age-sex-specific hospitalisation, severe hospitalisation and case fatality among all cases and hospitalised cases, EU/EEA and UK



https://covid19-surveillance-report.ecdc.europa.eu/

Spread of COVID-19 at the begging of the outbreak

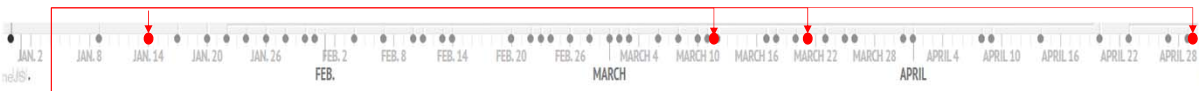
Countries and locations with confirmed cases of COVID-19, by WHO region and epidemiological week, from Dec 31, 2019, to March 10, 2020



- Compared with the SARS-CoV and MERS-CoV, SARS-CoV-2 spread more rapidly in the early weeks of the outbreak.
- Almost two-thirds of first cases in affected countries were in people reported to have recent travel from affected countries (China, Iran, and Italy).
- ECDC responded quickly by assessing the risk and recommending public health interventions including SoHO safety measures.

Dawood FS, et al. Observations of the global epidemiology of COVID-19 from the prepandemic period using web-based surveillance: a cross-sectional analysis. Lancet Infect Dis. 2020 Jul 29.

Timeline of the ECDC SoHO safety response



- 17 January 2020,
  ECDC First RRA - Cluster of pneumonia cases caused by a novel coronavirus, Wuhan, China. **Risks posed by COVID-19 to the safety of substances of human origin (SoHO) supply assessed and response measures recommended**.
- 12 March 2020,
  ECDC RRA sixth Update **- focus and priority in managing the national SoHO supply**
- 20 March 2020
  ECDC Technical document - **Coronavirus disease 2019 (COVID-19) and supply of substances of human origin in the EU/EEA**
- 29 April 2020,
  ECDC Technical document **Coronavirus disease 2019 (COVID-19) and supply of substances of human origin in the EU/EEA – First Update**
- ECDC regularly publishes RRA Updates including SoHO

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COVID-19 and supply of SoHO in the EU/EEA – First Update - Summary

Identified and assessed risks

- **Risk to the viral safety of SoHO**
  - Risk of SoHO-transmitted COVID -19 - THEORETICAL
- **Risk to the SoHO recipients**
  - Increased risk of transplant recipients
- **Risk to the staff in SoHO facilities,**
  - Increase risk of exposure
- **Risk to the sufficiency and sustainability of SoHO supply**
  - Major impact - increased risk of SoHO supply disruptions

Recommended risk mitigation measures

- Measures for each group of SoHO – PRECAUTIONARY
- Suggested options for patients and staff
- Emphasis on the Contingency plan activation/implementation

Second update planned in November 2020

Collection and distribution of blood and blood components in March and April 2019/2020 in 15 EU/EEA MS/Regions

Country/region	Collected blood and blood components (number of units)			Distributed blood and blood components (number of units)		
	03-04 2019	03-04 2020	Difference	03-04 2019	03-04 2020	Difference
Denmark**	32539	31031	-5%	39023	36670	-6%
Croatia	34358	26995	-27%	46331	39321	-18%
North. Ireland	8037	6820	-18%	7875	6747	-17%
Belgium FL*	52235	51503	-1%	51104	45530	-12%
Belgium W+B	66322	65962	-1%	62952	57624	-9%
Germany BWH	104581	104709	0%	95270	93996	-1%
Germany B	85098	78090	-9%	90341	83089	-9%
Republic of Ireland	20021	19959	0%	18711	16694	-12%
Lithuania	8248	7144	-15%	7266	6327	-15%
Luxemburg*	3686	3588	-3%	4323	4132	-5%
Latvia	9077	8365	-9%	14698	13842	-6%
Italy**	433277	402896	-8%	422544	367433	-15%
Slovenia	14051	11396	-23%	15693	13979	-12%
Portugal	31535.00	27689	-14%	32718	31109	-5%
Finland	33394	29273	-14%	-	-	-15%

*Plasma for fractionation excluded; ** Only Whole blood and red blood cells (+platelets in Denmark)

Median decrease in collections 9% (range 1% - 27%)

Median decrease in distribution 12% (1% - 18%)

Donation loss > Demand 4 c/r 27%
Donation loos = Demand 6 c/r 40%
Donation loss < Demand 5 c/r 33 %

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EMA Survey - potential impact of COVID-19 on supply of plasma and/or plasma-derived medicinal products

16 April 2020

A survey was sent to all 9 PMF-Holders/plasma fractionators in EU/EEA

Response rate

100% response rate, an additional response from a fractionator, until 2019, also PMF-H

Conclusions

- There are no reported shortages of plasma derived medicines at present.
- Some disruption in the supply of source plasma has been reported.
- All PMFs confirmed contingency plans in place to ensure little to no disruptions on the supply for the EU markets
- Monitoring plasma donation and availability of plasma derived medicines is essential to ensure that no critical shortages will take place in the future.
- New Survey planned in October 2020

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Impact of COVID-19 on corneal donation and distribution

Retrospective data Fondazione Banca degli Occhi del Veneto (FBOV) Venice, Italy

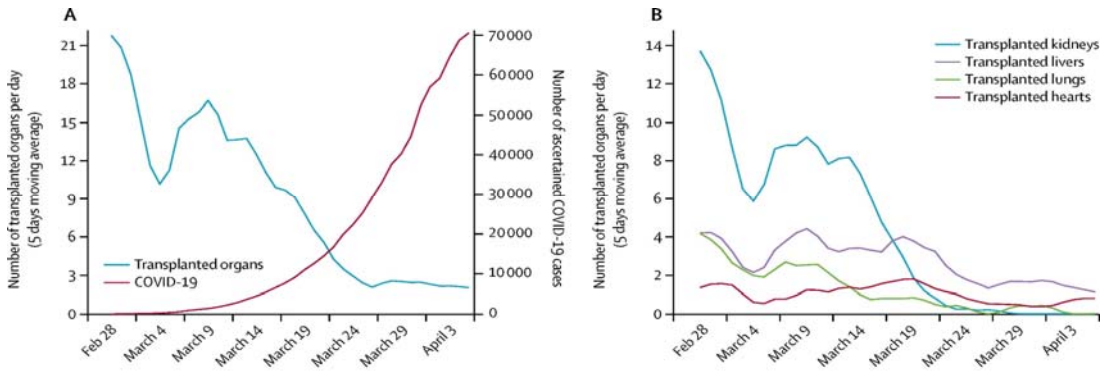
Observed period	Procurement	Distribution/Demand
09.04.19/20 – 08.05.19/20	-45% ($p < 0.0001$)	-61% ($p < 0.0001$)
11.05.19-20 -14.05. 19/20	-30% ($p = 0.4578$)	+14% ($p = 0.5065$)

- **Presence SARS-CoV-2 in tears – various preventive measures implemented**
- **Lock-down - reduction in the supply, retrieval and demand for corneal transplantation**
- **After lock-down - slow recovery of supply**

https://journals.sagepub.com/doi/full/10.1177/1120672120948746

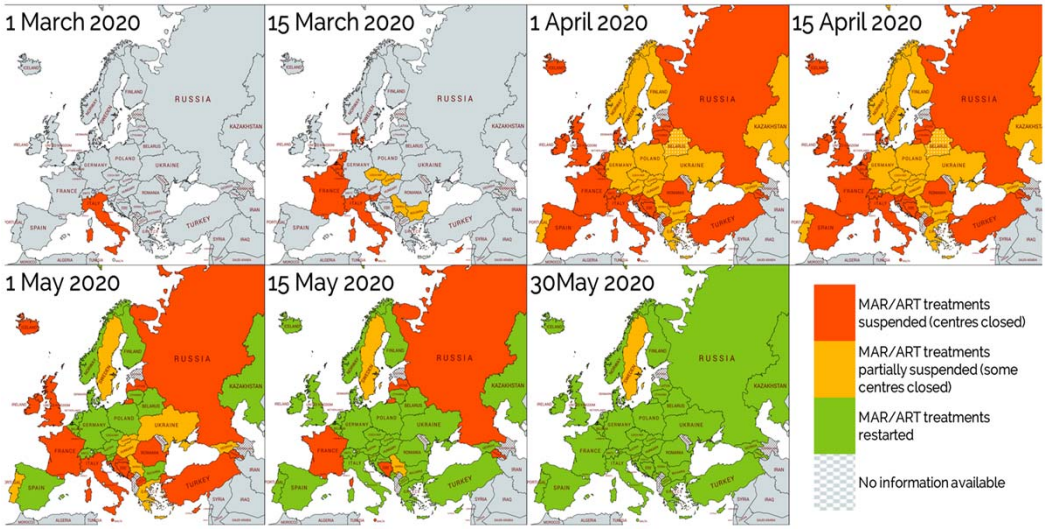
The Lancet 2020 395e95-e96

Organ procurement and transplantation during the COVID-19 pandemic in France (February-April 2020)



The Lancet. Volume 395 Issue 10237 Pages e95-e96 (May 2020) DOI: 10.1016/S0140-6736(20)31040-0

Overview of cessation and restart of MAR/ART activities in Europe between 1st of March and 30th of May 2020.



Hum Reprod Open, Volume 2020, Issue 3, 2020, hoaa035, https://doi.org/10.1093/hropen/hoaa035

OXFORD UNIVERSITY PRESS

EBMT COVID-19 registry; total cohort Outcome (preliminary data)

398 post-haematopoietic cell transplant (HCT) patients with COVID-19 from 20 countries

(Spain 150, UK 59, Italy 51, France 28, Sweden 17, Belgium 16, Netherlands 14, Saudi Arabia 12, Turkey 11, Germany 10, Israel 6, Portugal 5, Iran and Switzerland 4, Denmark and Czech republic 3, Ireland 2, Greece, Norway, and Poland 1):

- 250 allo HCT
- 137 auto HCT
- 11 CAR T

Clinical status	Number (%)
Died of COVID -19	83 (20.8%)
Alive and virus free	124 (31.1%)
Alive and clinically resolved	41 (10.3%)
Alive and virus positive	43 (10.8%)
Died of other causes	16 (4.0%)
No follow-up yet	91 (22.9%)

https://www.ebmt.org/covid-19-and-bmt

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Summary of COVID-19 impact on SoHO

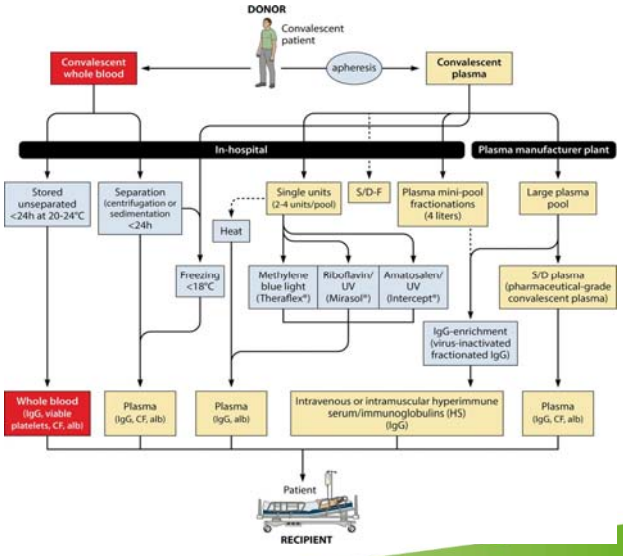
Since the beginning of the outbreak, no cases of COVID-19 transmission through SoHO have been reported

COVID-19 may affect the sufficiency and sustainability of SoHO supply by reducing donor availability, affecting the staff at SoHO facilities, changing demand for SoHO products, and limiting the provision or distribution of critical materials, equipment, and SOHO products.

Immunosuppressed transplant recipients are a high risk population for COVID-19

Convalescent plasma as a therapeutic option for COVID-19

- **Lack of effective therapy or vaccination**
- **Historical experiences**
- **Immediate availability and growing pool of convalescent patients**
- **Promising outcomes of initial case series and animal studies**



COVID-19 convalescent plasma therapy in EU/EEA

EUROPEAN COMMISSION
DIRECTORATE-GENERAL FOR HEALTH AND FOOD SAFETY

Directorate B - Health systems, medical products and innovation
B4 – Medical products: quality, safety, innovation

An EU programme of COVID-19 convalescent plasma collection and transfusion

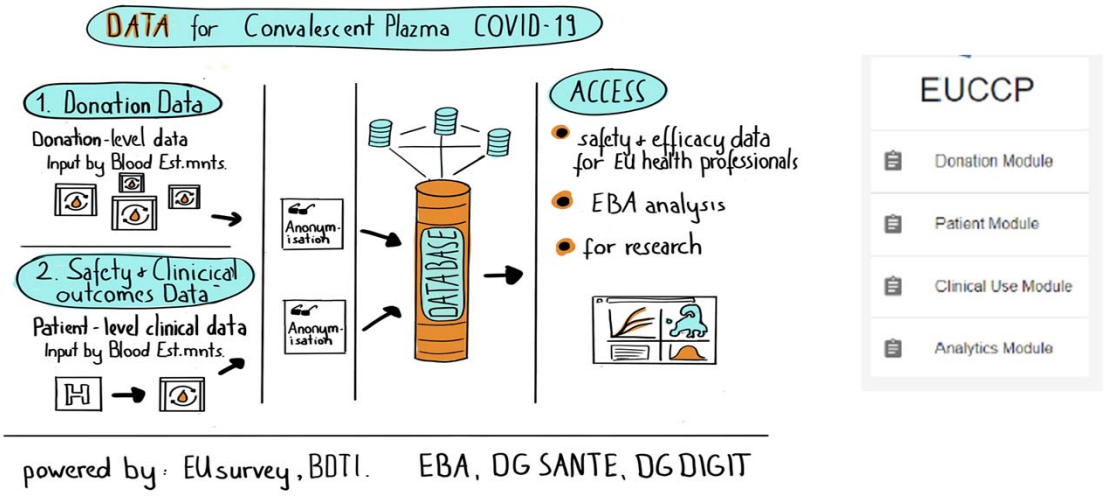
Guidance on collection, testing, processing, storage, distribution and monitored use

Endorsed by the Competent Authorities for Substance of Human Origin Expert Group (CASoHO E01718) following consultation of the competent authorities for blood and blood components and by the European Centre for Disease Prevention and Control.

- Authorisation of convalescent plasma collection,
- Testing, processing, storage and distribution
- Donor eligibility
- Collection, processing and storage
- Testing of donated plasma
- Distribution of COVID-19 convalescent plasma
- Data reporting and aggregation at the EU level

https://ec.europa.eu/health/sites/health/files/blood_tissues_organs/docs/guidance_plasma_covid19_en.pdf

EU CCP Database - COVID-19 convalescent plasma collection and transfusion in the EU



https://ec.europa.eu/health/blood_tissues_organs/covid-19_en#fragment0

EU CCP Platform – current data, accessed 27/09/2020

Country	# Requested	# Registered
Austria	3	2
Belgium	3	3
Bulgaria	2	2
Cyprus	1	1
Finland	1	1
France	2	2
Germany	4	4
Greece	1	1
Hungary	1	
Ireland	1	1
Italy	14	9
Malta	1	1
Netherlands	2	1
North Macedonia	1	1
Poland	1	1
Romania	1	
Spain	1	1
Sweden	3	3
Switzerland	1	1
United Kingdom	1	1
Total	**45**	**36**

Country	# Donations
Austria	16
Bulgaria	31
Finland	1
France	2555
Germany	47
Greece	1
Italy	518
Spain	800
Switzerland	48
Total	**4017**

Donors

- 72% male
- Median 28 days after end of symptoms

Collection, Process and Testing

- 99 % apheresis
- 653 mL col. Vol (Median)
- 90 % pathogen reduced
- 95 % processed in multiple units
- 90 % tested Elisa
- 50 % Sars-Cov2 SN Essay

https://www.euccp.dataplatform.tech.ec.europa.eu/

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Current status of CCP

Results from various types of clinical trials and expanded emergency use of COVID-19 convalescent plasma (CCP) showed the expected frequency of adverse transfusion reactions.

These studies also suggest that the transfusion of CCP containing a higher titre of neutralizing antibodies applied earlier in the clinical course is potentially effective in reducing the mortality of hospitalized non- intubated patients having the moderate or severe illness. CCP may also accelerate viral clearance, decrease progression into the critical phase of diseases and shorten the hospital stay of such COVID -19 patients.

The more evidence obtained in the randomized controlled trials is required to fully demonstrate the efficacy of CCP and to determine the indication, dosing and optimal CCP product characteristics.

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