

Corona Convalescent Plasma: from whom and when

Hans Vrielink, MD, PhD

Unit of Transfusion Medicine
Sanquin Blood Supply

h.vrielink@sanquin.nl

Blood and Beyond



Conflicts of interest / disclosures

- None

Outline

- COVID-19
- Why CCP / immunoglobulins could be of help
- How to get CCP / immunoglobulins
- Experiences with use of CCP in patients



**Corona Convalescent Plasma:
from whom and when**

Hans Vrielink, MD, PhD

Unit of Transfusion Medicine
Sanquin Blood Supply
h.vrielink@sanquin.nl



Blood and Beyond

The background of the slide features a pattern of stylized virus particles. These particles are depicted as light blue, spherical structures with numerous thin, radiating lines representing surface proteins or spikes. They are scattered across the slide, with a higher concentration in the upper right quadrant. The overall color scheme is a gradient of blue and purple.

COVID-19



Y.R.O.M. the Former Yugoslav Republic of Macedonia
The former Republic of Serbia, Bosnia, Bulgaria is the capital, the republics regarding the status
the former name is not recognized, most of the embassies are based in Belgrade, Serbia
U.A.E. United Arab Emirates

155,631,113

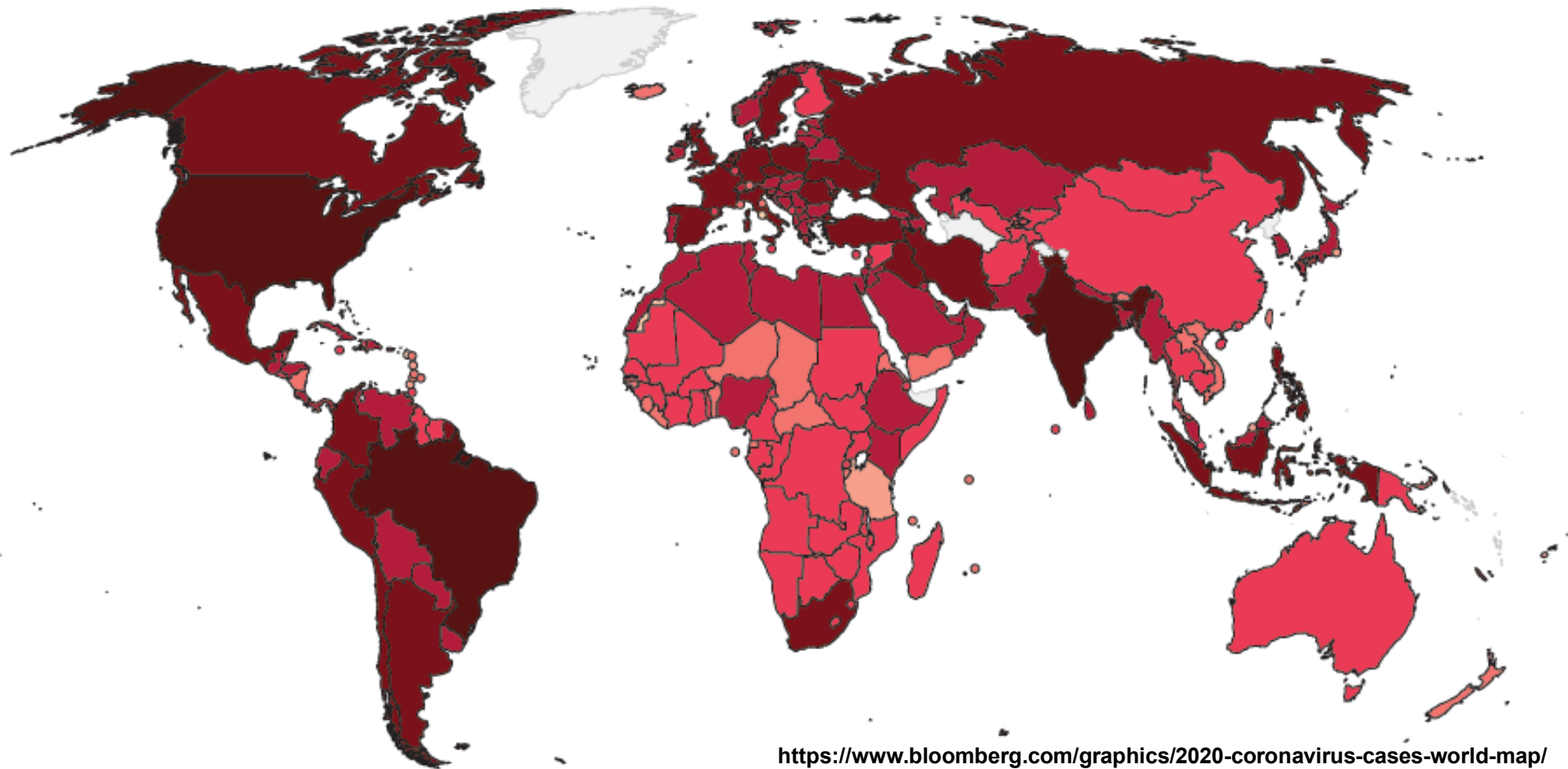
Confirmed cases worldwide

3,251,647

Deaths worldwide

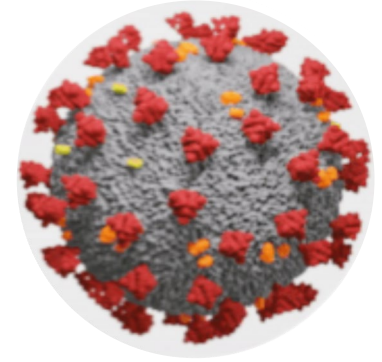
Jurisdictions with cases confirmed as of 7 mei 2021 04:20 CEST

1-99 100-999 1,000-9,999 10,000-99,999 100,000-999,999 1,000,000-9,999,999 10 million or more



Corona viridae

- Enveloped
- Single-stranded RNA
- Spikes on surface
- 2 sub-families, 5 genera, 26 sub-genera, and 46 species



<https://en.wikipedia.org/wiki/Coronaviridae>

Coronaviridae

- Orthocoronavirinae

Alphacoronavirus

Betacoronavirus

Middle East respiratory syndrome-related coronavirus (MERS-CoV)

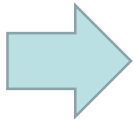
Severe acute respiratory syndrome-related coronavirus 1 (SARS-CoV-1)

Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2, COVID-19)

Deltacoronavirus

Gammacoronavirus Brangacovirus Goose coronavirus CB17

- Lentovirinae



Corona viridae

Coronaviridae

- Orthocoronavirinae

Alphacoronavirus

Betacoronavirus

Middle East respiratory syndrome-related coronavirus (MERS-CoV)

Severe acute respiratory syndrome-related coronavirus 1 (SARS-CoV-1)

Severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2, COVID-19)

Deltacoronavirus

Gammacoronavirus Brangacovirus Goose coronavirus CB17

- Lentovirinae

Common cold corona viruses

- 229E
- NL63

- OC43
- HKU1

Symptoms SARS-CoV-2 infection

- Fever / chills
- Cough
- Sputum production
- Shortness of breath to severe dyspnea
- Respiratory distress

(94%)

“common cold” to severe pneumonia

Symptoms SARS-CoV-2 infection

- Fever / chills (94%)

- Cough

- Sputum production

- Shortness of breath to severe dyspnea

- Respiratory distress

“common cold” to severe pneumonia

- Fatigue

- Muscle / body aches

- Neurologic (headache, altered mentality)

- New loss of taste or smell (65%)

- Sore throat

- Congestion / runny nose

- Nausea / vomiting

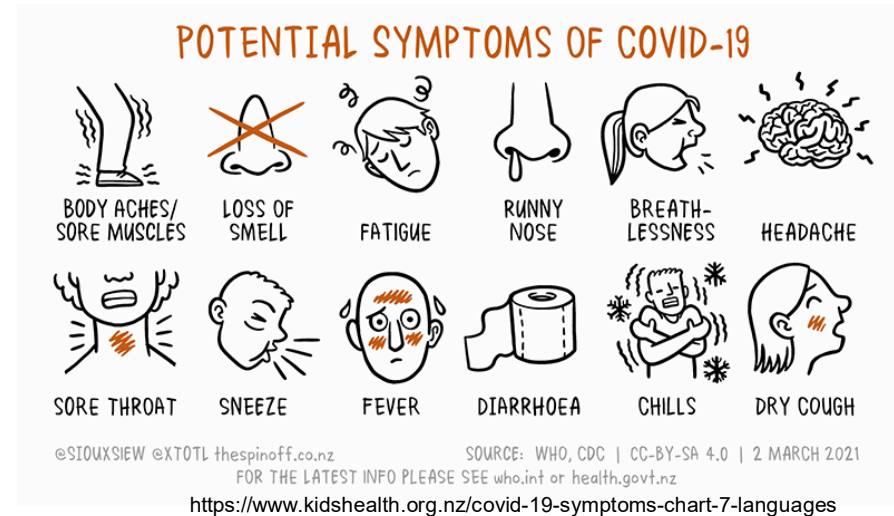
- Diarrhea

- Malaise

- Clotting disorders

SARS-CoV-2

Affects the respiratory system
with minimal symptoms



But, rapid onset of

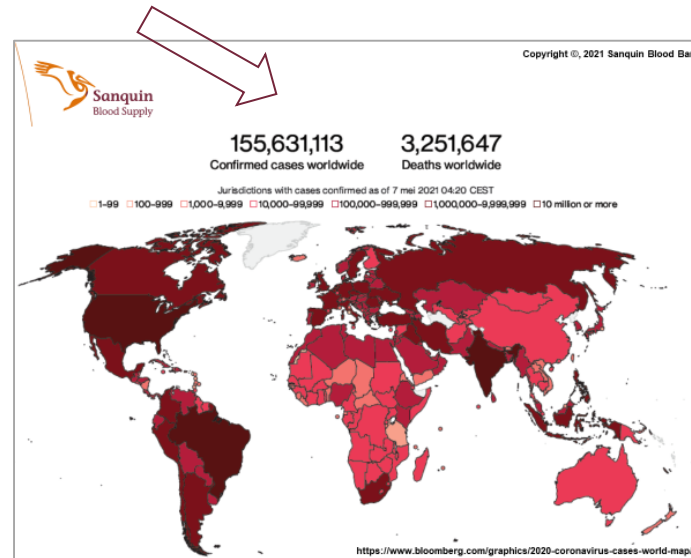
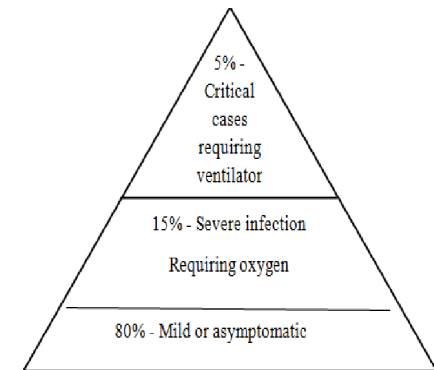
- Acute Respiratory Distress Syndrome (ARDS)
 - Caused 70% of the mortality in COVID-19 patients
- Multi-Organ Failure (MOF)
- Significant coagulation disturbances

Chang JC. Thromb J 2019;17:10.

Chang JC. Clin Appl Thromb Hemost 2019;25.

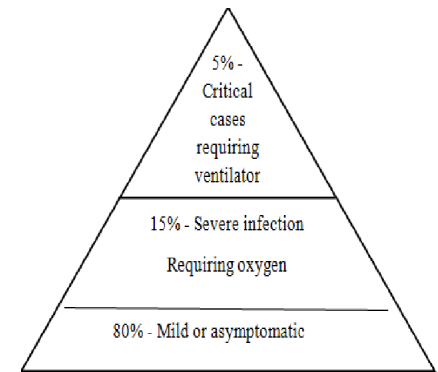
COVID-19

- Presentations of SARS-CoV-2-infection
 - asymptomatic/mild symptoms (81%)
 - severe (14%)
 - critical illness (5%)
 - (and mortality (2,3%))

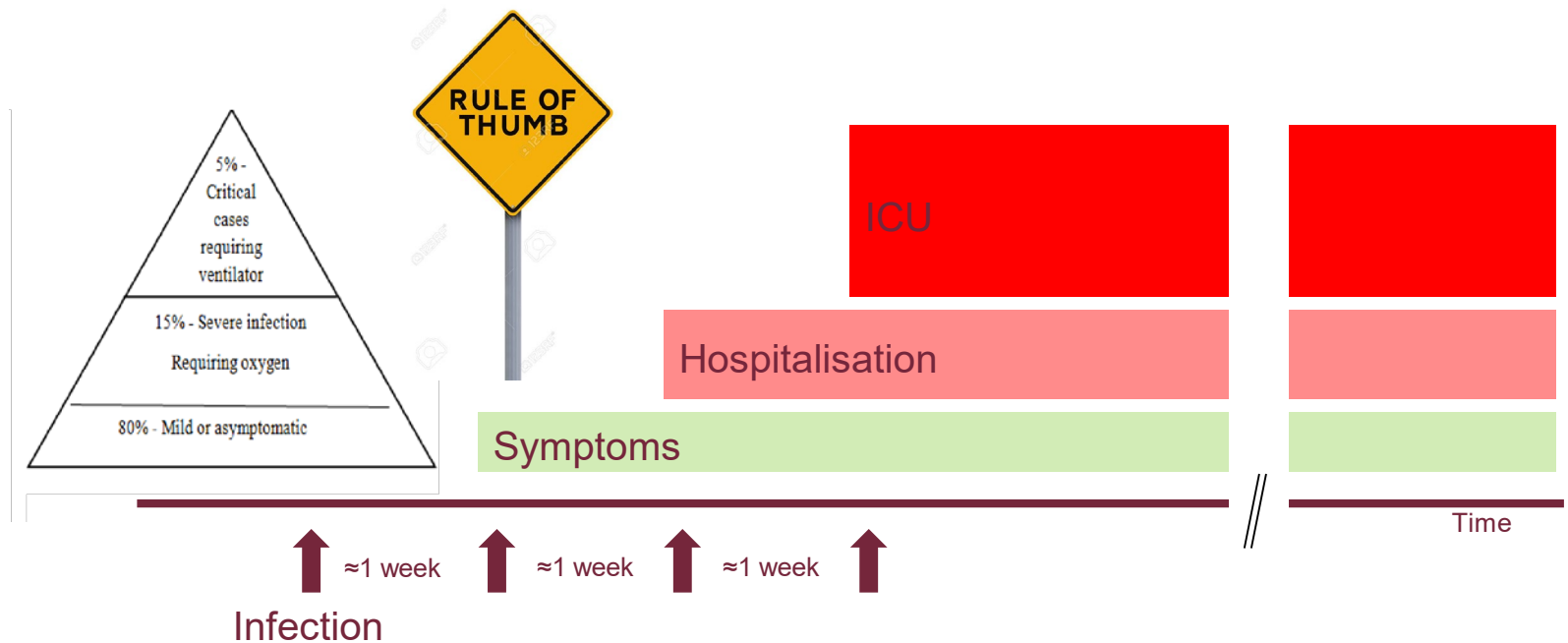


COVID-19

- Presentations of SARS-CoV-2-infection
 - asymptomatic/mild symptoms (81%)
 - severe (14%)
 - critical illness (5%)
 - (and mortality (2,3%))
- The mean incubation period is 5.1 days (2-14 days after exposure)
(97.5% developed symptoms within 11.5 days)



Timeline





February – March 2020

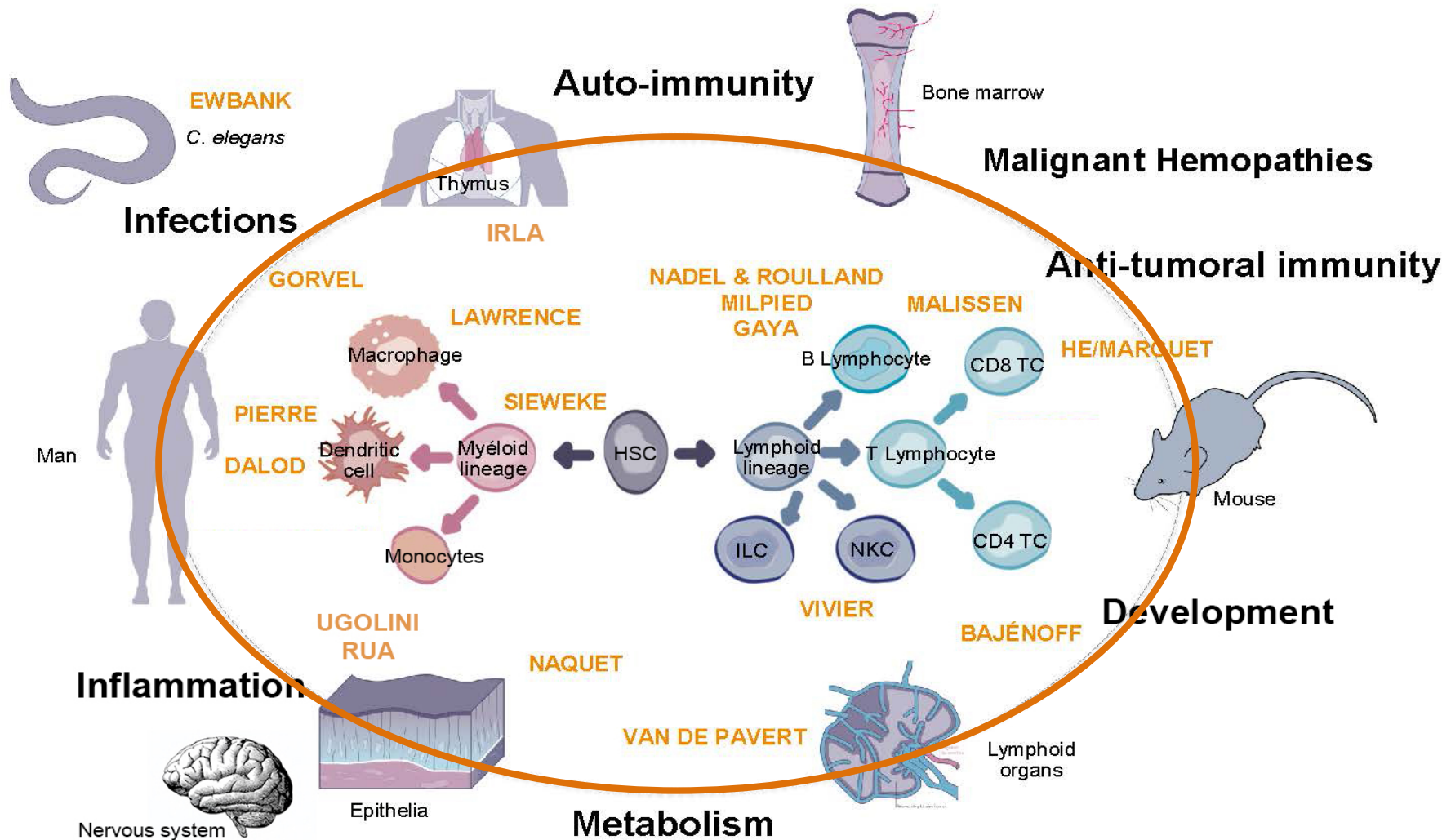
Copyright ©, 2021 Sanquin Blood Bank



Immunology



Immunology in all its states

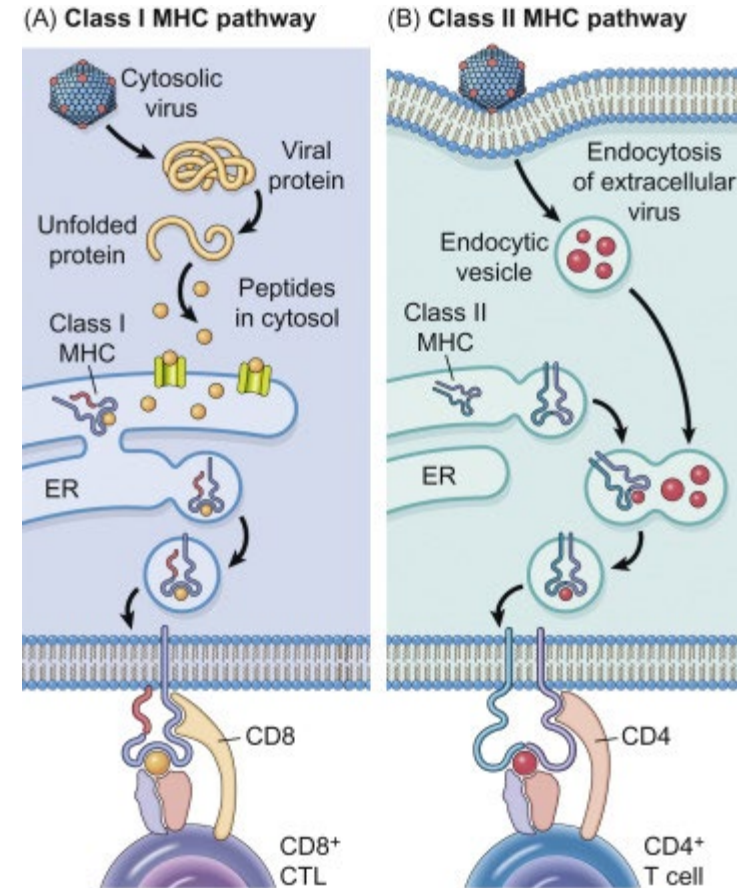


Lymphocytes

- B-lymphocytes
- T-Lymphocytes
 - Antibody production & assist activation T-cells
 - T-helper (CD4+ve) → activate and regulate B-cells
 - CD8+ve → viruses and tumor cells
 - $\gamma\delta$ T-cell → first line of defense
 - Regulatory T-cells → prevents autoimmunity and back regulation to normal
 - Natural killer cells → viruses and tumor cells

Infection with virus

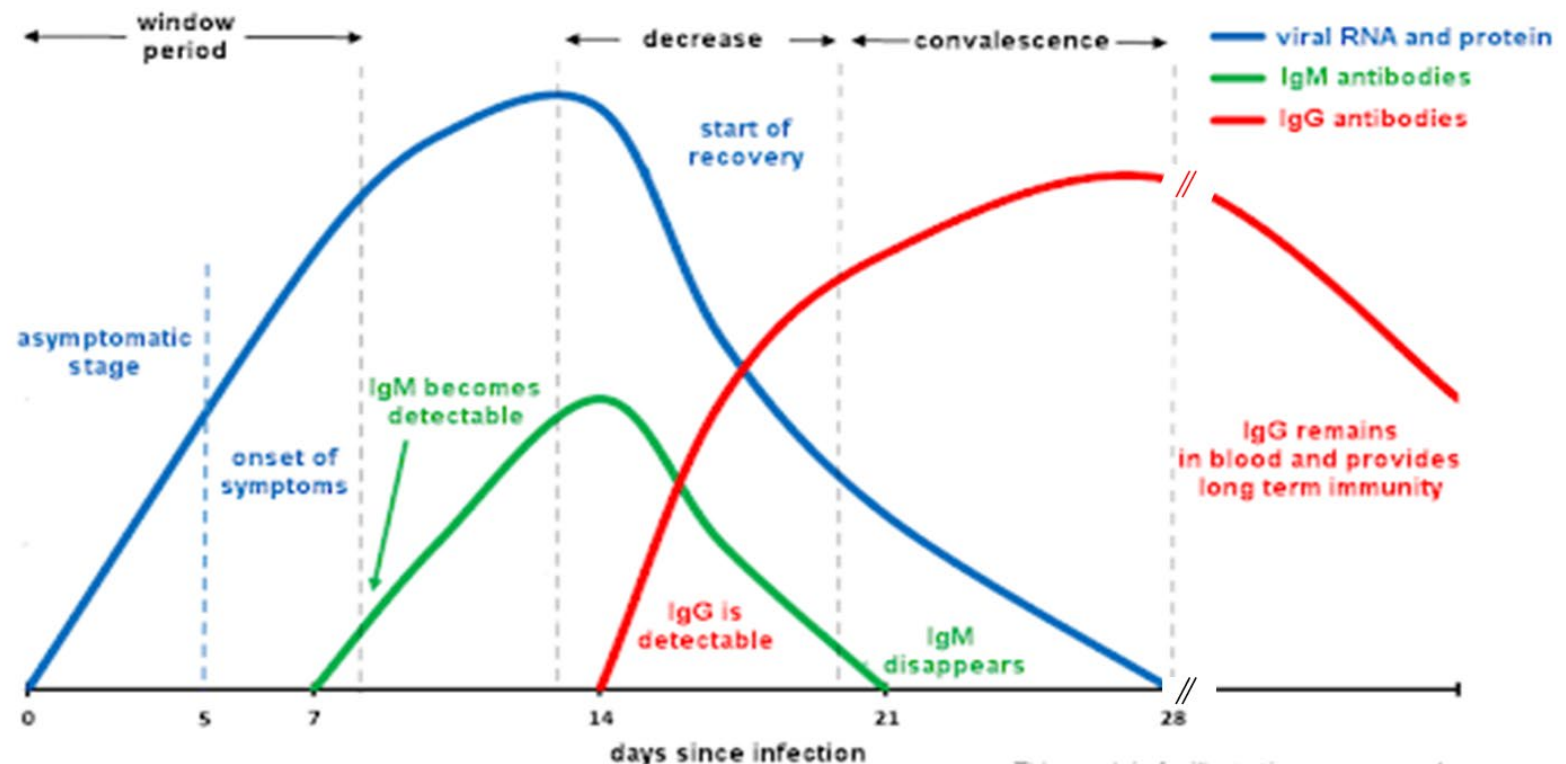
- Virus attacks / enters cell
 - Activation MHC-I pathway
 - Cytotoxic T-cell
 - NK-cell
 - Activation MHC-II pathway
 - T_{helper}
 - Activation B-cells
 - Production of interferons
- Release and production of cytotoxic factors
 - Perforins
 - Granzymes
 - Granulysin
 - Cytokines



<https://www.sciencedirect.com/science/article/pii/B9780128009468000040>

B-cell activation

Directly and / or T-cell caused
→ Production of immunoglobulins



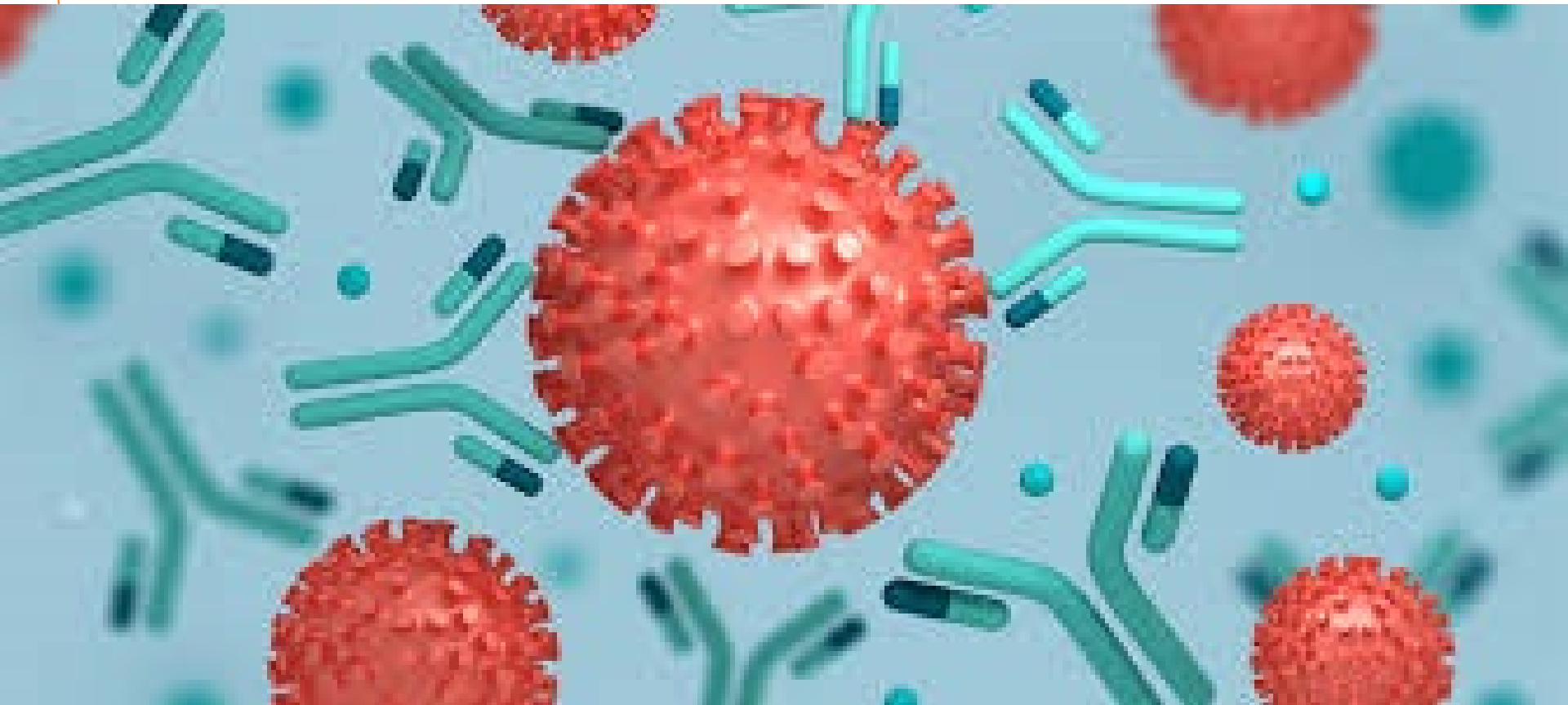
Adapted from: <https://www.traveldoc.com/covid-19-antibody-testing-available/>

This graph is for illustration purposes only

Immunoglobulins

- Neutralization of the virus
- Agglutination of viruses
- Activation of phagocytosis
- Activation of complement system

Can Corona Ig be used in COVID-19?



Antibody therapy?

The Nobel Prize in Physiology or Medicine 1901

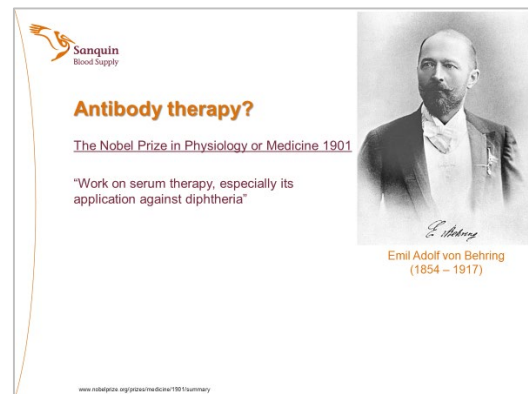
“Work on serum therapy, especially its application against diphtheria”



Emil Adolf von Behring
(1854 – 1917)

Covid convalescent plasma

- SARS-CoV-1
 - MERS-CoV (Middle East Respiratory syndrome)
 - Ebola
 - SARS-CoV-2?
- COVID-19



Why?

Corona Convalescent plasma

Infusion of plasma from people who've recovered from COVID-19

- Lower viral load
- Shorter hospital stay
- Lower mortality

Long Chen, Lancet 2020:398-400

Corona Convalescent plasma



SARS-CoV-2 antibodies
needed.....

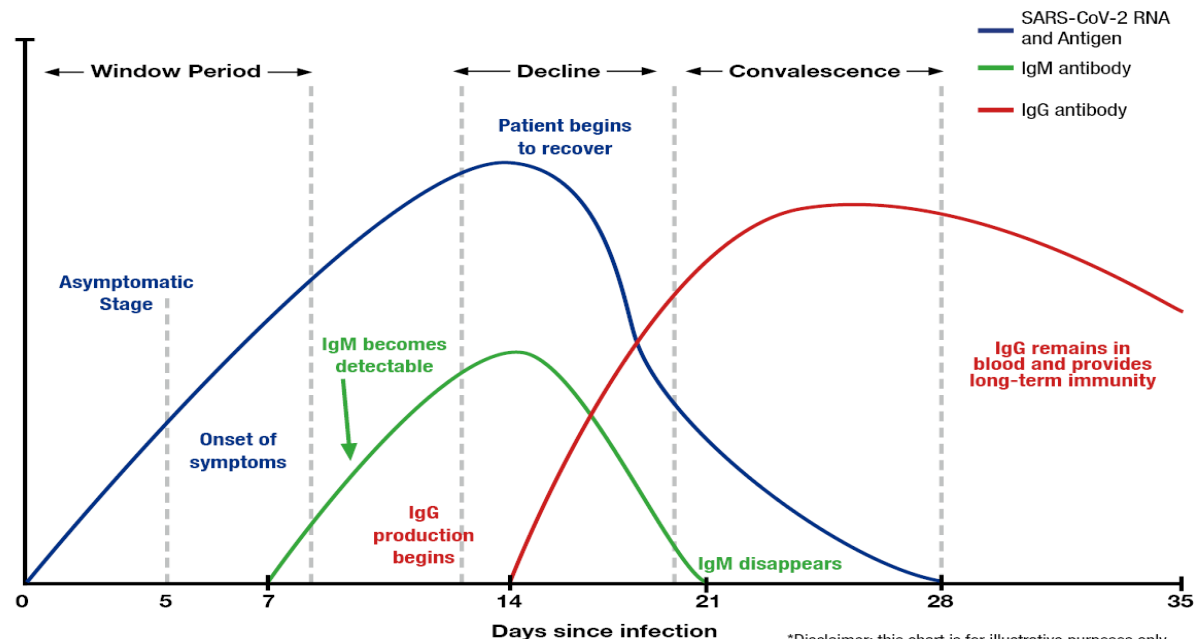


Anti-SARS-CoV-2 donation

• Plasmadonors needed

Donation must be safe for

- Donor
- Operators and colleague donors
- Recipient



Anti-SARS-CoV-2 donor: donor safety

- Donor safety

Donor must be recovered from the infection

→ 14 – 28 days after relieve of symptoms



<https://pharmaphorum.com/news/does-my-cough-sound-like-covid-there-could-be-an-app-for-that/>

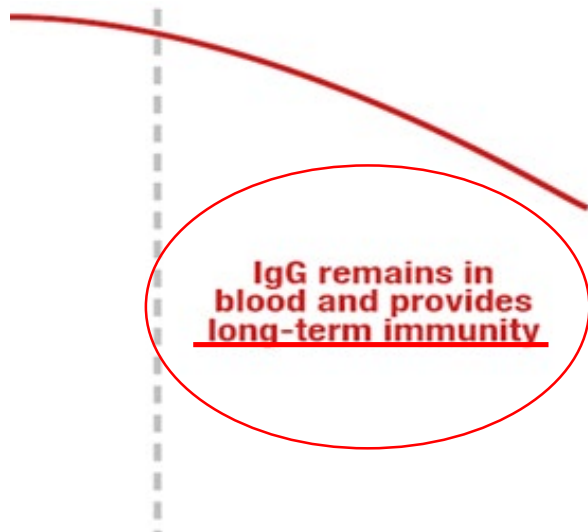
Anti-SARS-CoV-2 donor: operator/donor safety

- Infectivity?

PCR needed?

→ PCR positive, but after recovery of symptoms ≠ infectious

→ other individuals safe?



Social distancing (1.5 m)
Capacity reduction donor center



Anti-SARS-CoV-2 donor: patient safety

- Convalescent plasma

SARS-CoV-2 : not considered transfusion transmitted

Donor frequently first-time donor → more TTI

No HLA / HNA antibodies → TRALI risk

Documented PCR positive donor

High titer of neutralizing antibodies



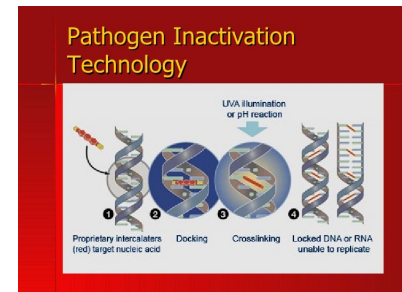
Off label use

<https://www.fda.gov>

Who should receive the plasma?

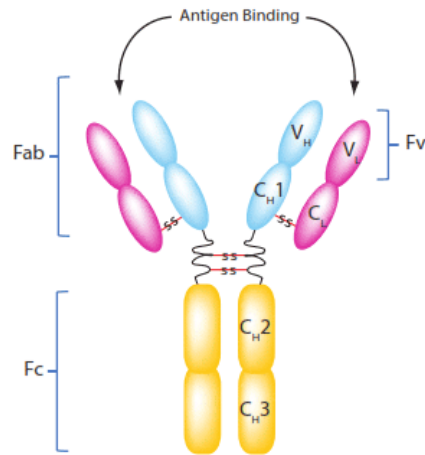
Severe ill patients

Ethical committee approved study



Mendoza:
<https://www.slideshare.net/specialclass/blood-transfusion>

General Antibody Schematic

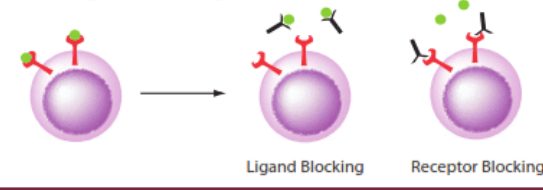


<https://www.bio-connect.nl/functional-antibodies/cnt/page/3649>

- Highly trained technicians
- Labour intensive
- Time consuming

Different Types of Antibody Functionality

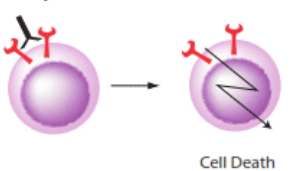
Blocking/Neutralizing



Activation/Induction



Depletion



Serial dilutions of test sera

Addition of virus

First incubation

Addition of cells

Second incubation

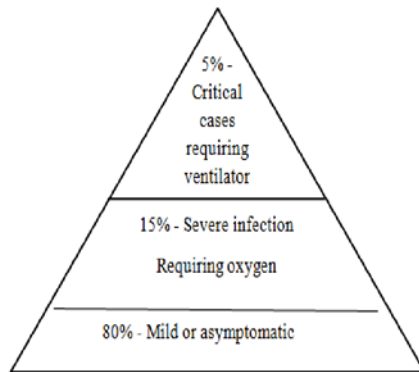
Plate reading



<https://www.quora.com/What-is-a-virus-neutralization-test-and-how-is-it-conducted>

SARS-CoV-2 and antibodies

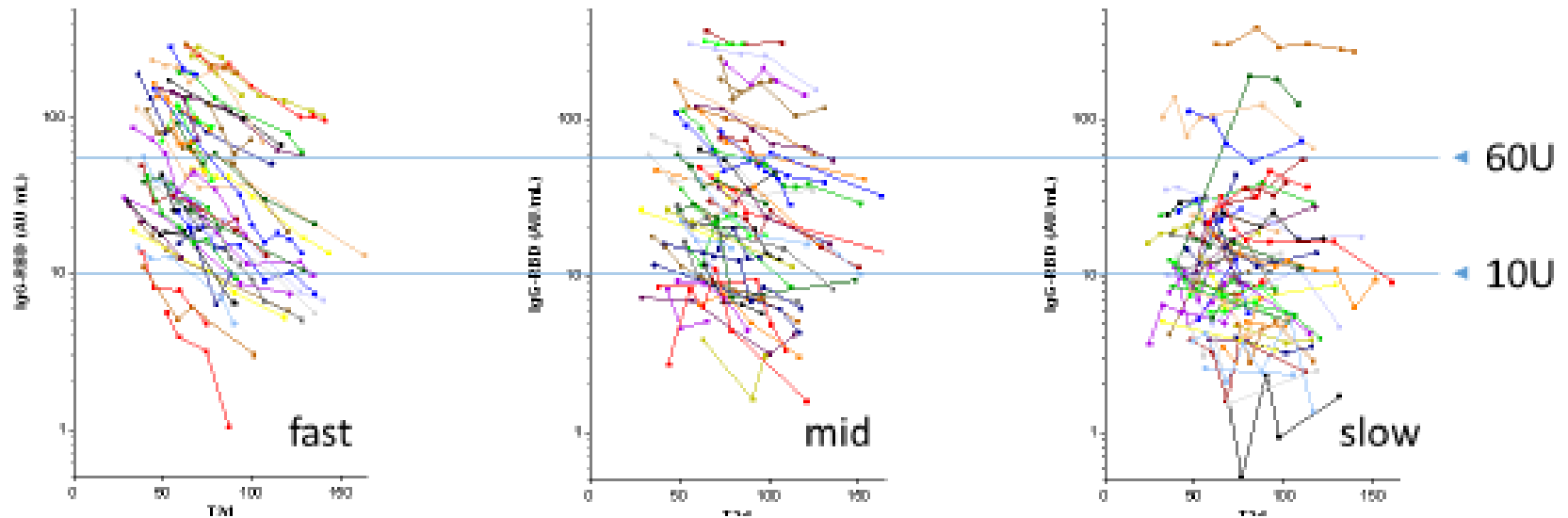
Donors in the Netherlands



- 80-85% no to only very mild symptoms
- 15-20% severe symptoms; hospitalization needed
- 7.5% ICU

Also less antibodies ?
How long are Ab present?

SARS-CoV-2 IgG



Theo Rispens: personal communication

SARS-CoV-2 Immunoglobulins

- Covid Convalescent plasma
- Hyperimmune IgG



Photo: Sanquin Blood Supply; credits Kick Smeets



Photo: Sanquin Blood Supply

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

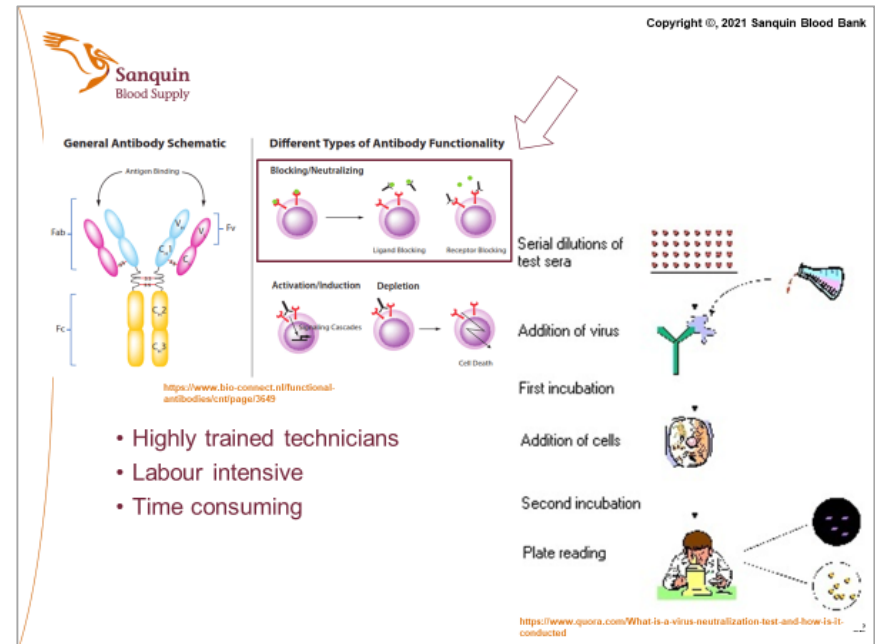
Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

Libster, et al. January 6, 2021 NEJM.org.

Many trials are ongoing

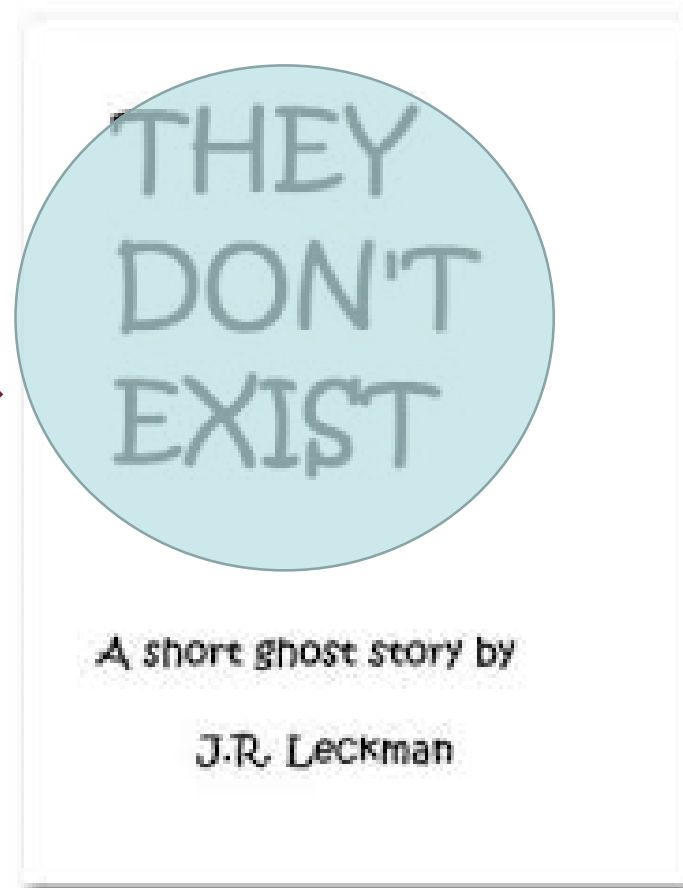
Guidelines

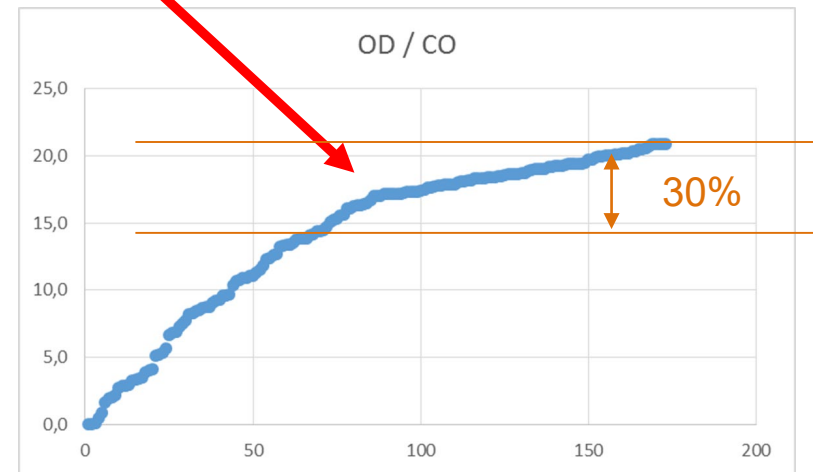
- nSARS-CoV-2 antibody titer should be above $\geq 1:80-160$)



Standardization in SARS-CoV-2 antibody test?

International System of Units - SI	
K	▶ kelvin (<i>temperature</i>)
m	▶ meter (<i>distance</i>)
A	▶ ampere (<i>electric current</i>)
s	▶ second (<i>time</i>)
mol	▶ mole (<i>amount of substance</i>)
kg	▶ kilogram (<i>mass</i>)
cd	▶ candela (<i>intensity of light</i>)



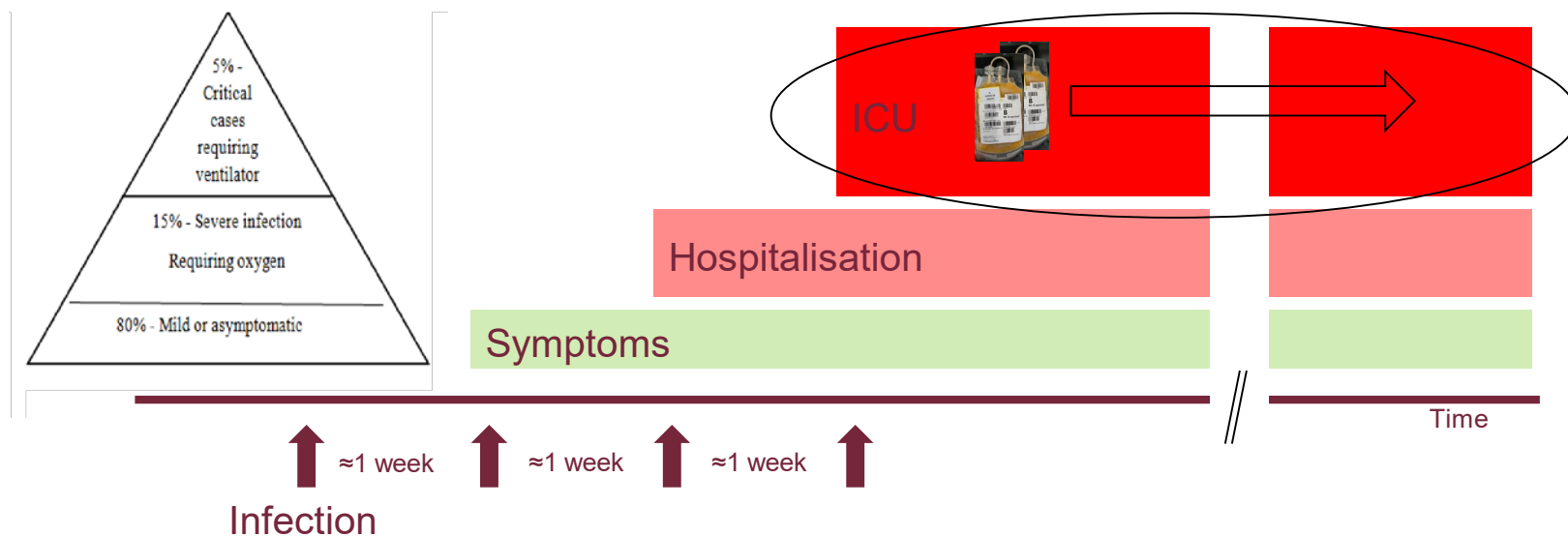


aSARS-CoV-2 IgG (AU/mL)

- High
- Normal
- Lacking

When in COVID-19

Timeline



Corona convalescent plasma

Studies

- Randomized controlled studies
- Observational studies
- Case reports



<https://sterkfamilylaw.com/staying-optimistic/>

Corona convalescent plasma

FDA

“Totality of the evidence suggests that the benefits of convalescent plasma would outweigh its risks”

→ Emergency Use Authorization.

NIH

The data are insufficient to recommend for or against the use of convalescent plasma.

Infectious Diseases Society of America and AABB

The use of convalescent plasma be limited to clinical trials; critically ill patients and those in the ICU are unlikely to benefit from transfusions of CCP

Corona convalescent plasma

In general: no clear benefits of CCP transfusions in the course of severe COVID-19



Li L, et al. JAMA 2020; 324:460-70.

Salazar E, et al. Am J Pathol 2020; 190: 2290-303.

Agarwal A, et al. BMJ 2020;371: m3939.

Gharbharan A, et al. <https://doi.org/10.1101/2020.07.01.20139857>

Simonovich VA, et al. N Engl J Med. DOI: 10.1056/NEJMoa2031304.

Avendaño-Sola C, et al. September 29, 2020 (<https://www.medrxiv.org/content/10.1101/2020.08.26.20182444v1>).preprint.

Joyner MJ, et al. August 12, 2020 (<https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1>).preprint.

Katz. NEJM Febr 2021.

SARS-CoV-2

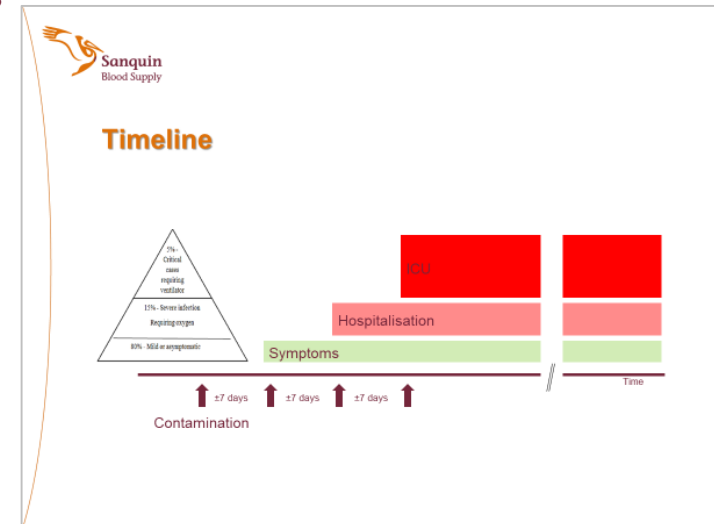
Affects respiratory system with minimal symptoms

But, rapid onset of

- Acute Respiratory Distress Syndrome (ARDS)
 - Caused 70% of the mortality in COVID-19 patients
- Multi-Organ Failure (MOF)
- Significant coagulation disturbances

Chang JC. Thromb J 2019;17:10.

Chang JC. Clin Appl Thromb Hemost 2019;25.



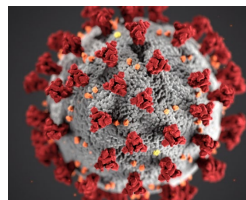
Contamination with virus

- Virus attacks / enters cell
 - Activation MHC-I pathway
 - Cytotoxic T-cell
 - NK-cell
 - Activation MHC-II pathway
 - T_{helper}
 - Activation B-cells
 - Production of interferons

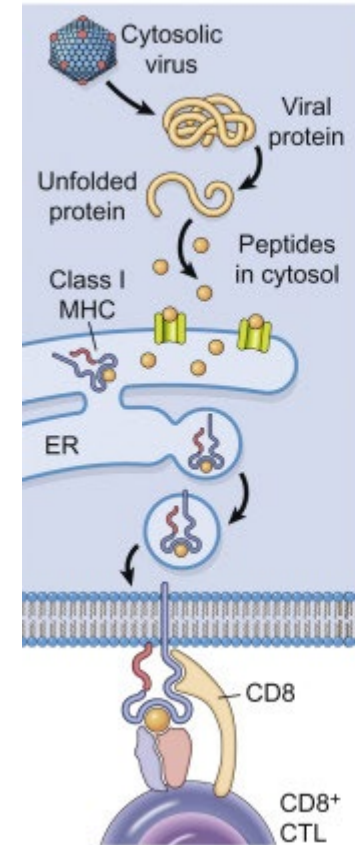
Release and production of cytotoxic factors

• ...

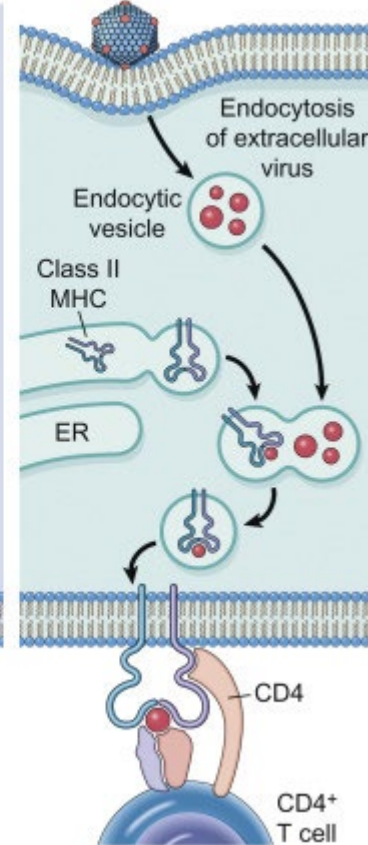
• **Cytokines**



(A) Class I MHC pathway



(B) Class II MHC pathway



<https://www.sciencedirect.com/science/article/pii/B9780128009468000040>

SARS-CoV-2

Cytokine Release Syndrome / Cytokine Storm

- pathological inflammatory reaction at local and systemic level following infections.
- thought to play a role in disease severity as well as in patient mortality.

Davidson S, et al. *J Interferon Cytokine Res* 2015; 35: 252-64.

Ye Q, et al. *J Infect* 2020; 80: 607-13.

Cytokine Release Syndrome / Cytokine Storm

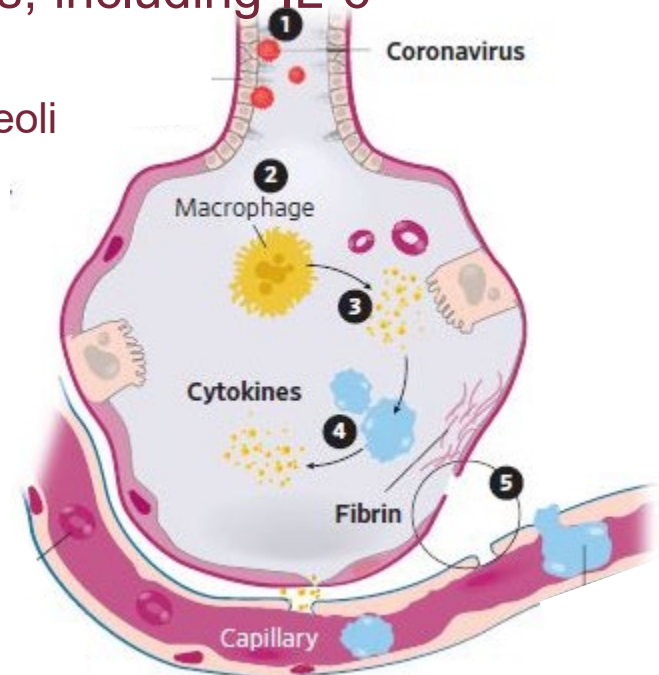
SARS-COV-2 → Infection of the respiratory system

- Activation of the innate immune system

- CD14+ and CD16+ monocytes, T-helper and cytotoxic T-cells

→ release of large numbers of cytokines, including IL-6

- Increase vascular permeability
 - Migration of fluid and blood cells into the alveoli
 - Dyspnea and respiratory failure
 - Tissue damage (with organ-failure)



Adapted from: The Wall Street Journal

Corona convalescent plasma

No clear benefits of CCP transfusions in the course of severe COVID-19

CCP should be used as early as possible in the course of infection (preferably within 3 days after diagnosis) in order to achieve the best outcomes.

Li L, et al. JAMA 2020; 324:460-70.

Salazar E, et al. Am J Pathol 2020; 190: 2290-303.

Agarwal A, et al. BMJ 2020;371: m3939.

Gharbharan A, et al. <https://doi.org/10.1101/2020.07.01.20139857>

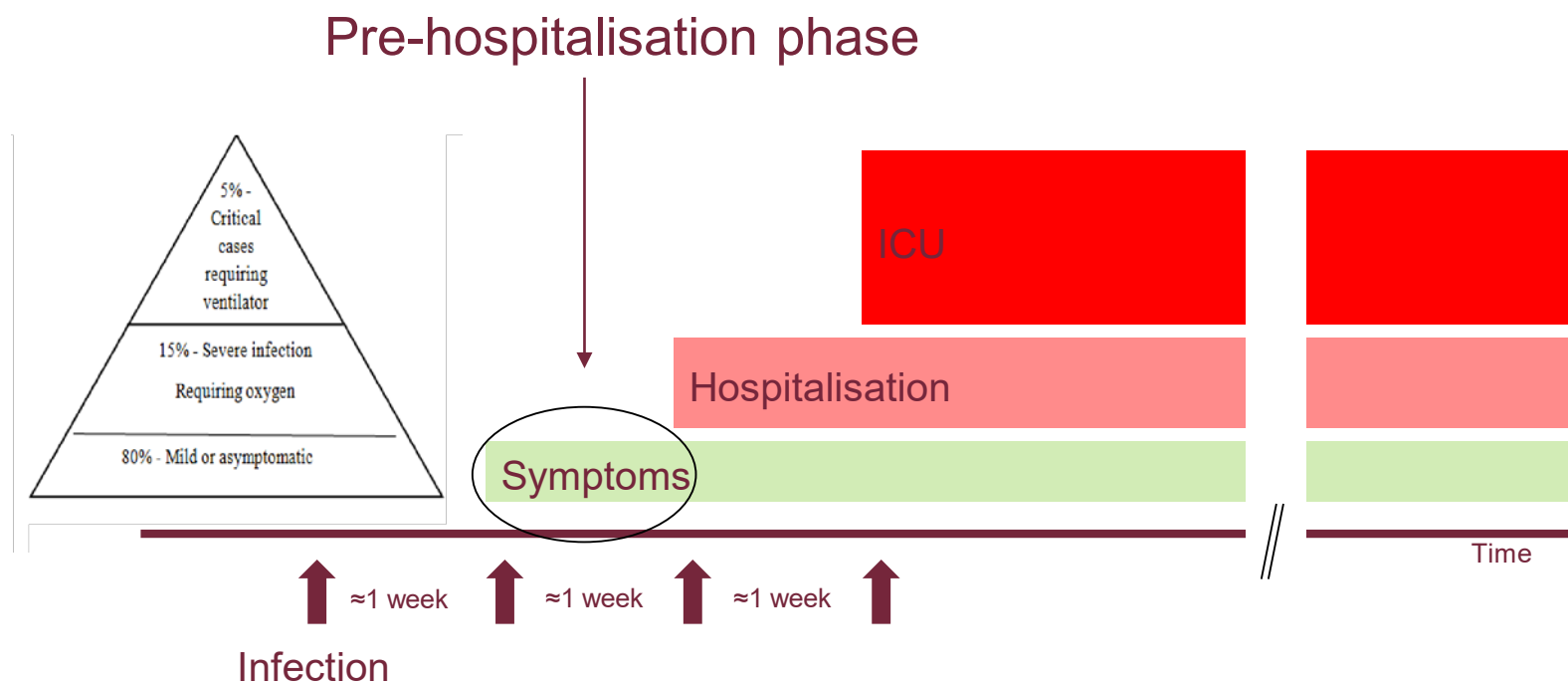
Simonovich VA, et al. N Engl J Med. DOI: 10.1056/NEJMoa2031304.

Avendaño-Sola C, et al. September 29, 2020 (<https://www.medrxiv.org/content/10.1101/2020.08.26.20182444v1>).preprint.

Joyner MJ, et al. August 12, 2020 (<https://www.medrxiv.org/content/10.1101/2020.08.12.20169359v1>).preprint.

Katz. NEJM Febr 2021.

Timeline



Immunoglobulins

- Neutralization of the virus
- Agglutination of viruses
- Activation of phagocytosis
- Activation of complement system



<https://www.webmd.com/cold-and-flu/ss/slideshow-immune-system>



Infection

The NEW ENGLAND JOURNAL *of* MEDICINE

ORIGINAL ARTICLE

Early High-Titer Plasma Therapy to Prevent Severe Covid-19 in Older Adults

Libster, et al. January 6, 2021 NEJM.org.

Many trials are ongoing

Is this all we can do with



SARS-CoV-2 Immunoglobulins

- Covid Convalescent plasma
- Hyperimmune IgG



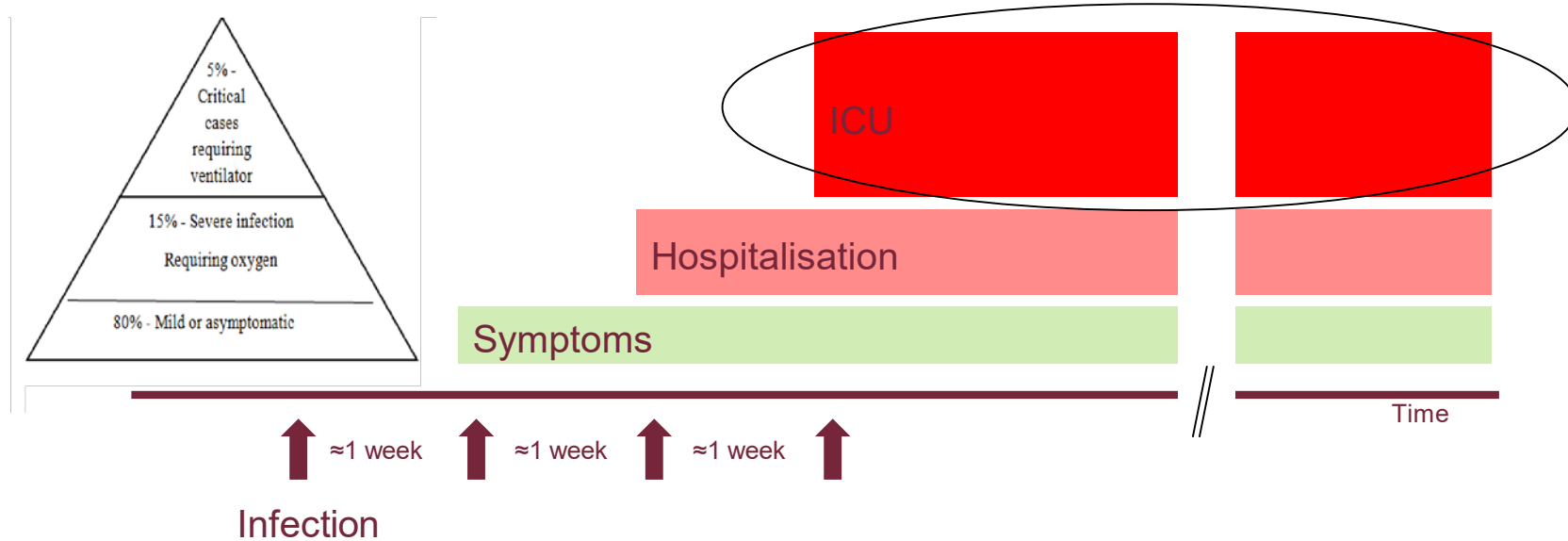
Photo: Sanquin Blood Supply; credits Kick Smeets



Photo: Sanquin Blood Supply



Timeline



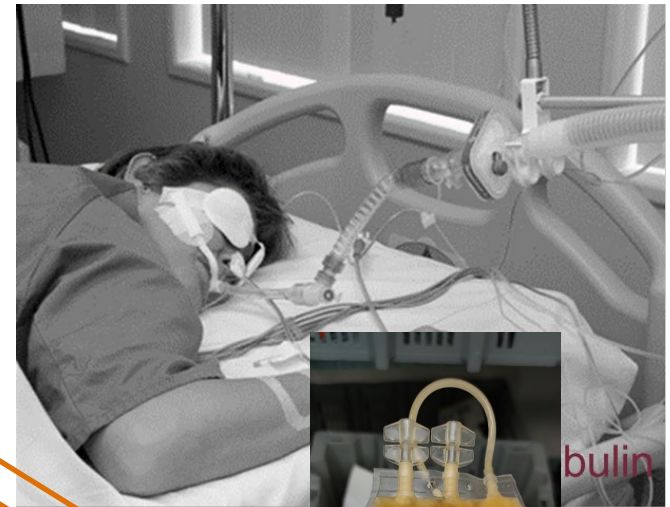


Immune system is needed

SARS-CoV-2 antibodies in COVID-19

Immune compromised patients

- Lymphoma's
- Leukemia's
- Hypo gammaglobulinaemia
- Stem cell transplant
- Organ transplant
-
- Immune suppression therapy
- Rituximab therapy
-



In conclusion

- Achieving CCP is challenging
- The data are insufficient to recommend for or against the use of convalescent plasma.
- No clear benefits of CCP transfusions in the course of severe COVID-19.
- CCP should be used as early as possible in the course of infection.
- Could be of use in immune compromised patients
- Hyperimmune Ig (COVIg) as preventive tool?



Photo: Hans Vrieling April 2021

Thank you for your attention