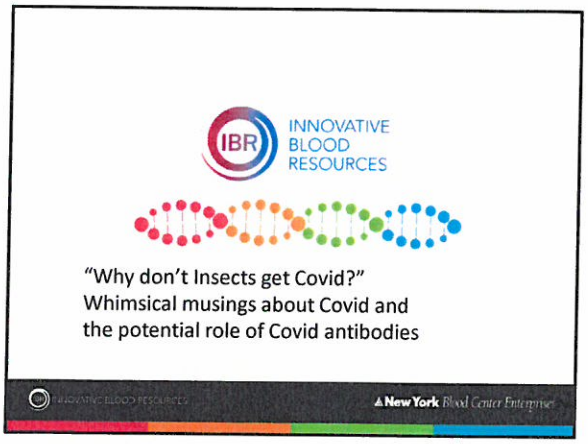
IBR
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BLOOD
RESOURCES
"Why don't Insects get Covid?"
Whimsical musings about Covid and
the potential role of Covid antibodies
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1


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BLOOD CENTERS
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Community Blood Bank
Blood Bank
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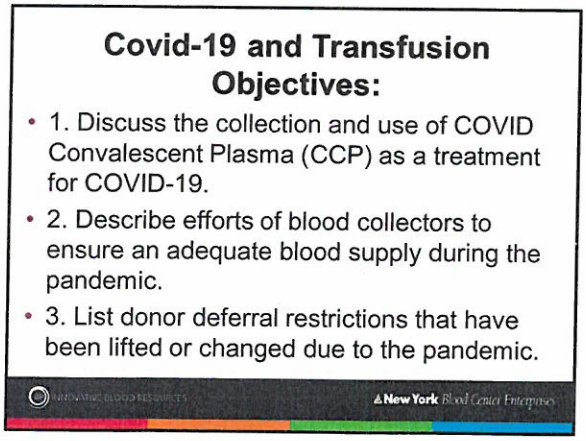
2


Covid-19 and Transfusion
Objectives:
• 1. Discuss the collection and use of COVID Convalescent Plasma (CCP) as a treatment for COVID-19.
• 2. Describe efforts of blood collectors to ensure an adequate blood supply during the pandemic.
• 3. List donor deferral restrictions that have been lifted or changed due to the pandemic.
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3

?????

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4

"Cereal" dilutions!

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5

7 human coronaviruses

229E
NL63
OC43
HKU1

Endemic "common cold" coronaviruses

SARS
MERS
SARS-CoV-2

"Bad" coronaviruses

Louis M. Katz MD CMO, Mississippi Valley Regional Blood Center
Chair, AABB TTD Committee Adj Clin Prof, Infectious Diseases:
Carver College of Medicine, Iowa City

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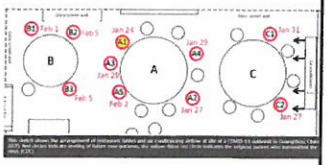
Covid-19: Community acquisition

- Elegant epidemiologic investigation documented transmission within a restaurant with most contacts becoming symptomatic from 3-7 days



7

SARS-CoV-2 as Transfusion transmitted infectious disease (TTID)?

- Theoretically possible?
  - Its RNA can be amplified from patient blood
  - Presence of infectious virus not established
  - No respiratory viruses, including human coronaviruses, provide a precedent for TTI
- Routine donor screening practices will prevent symptomatic donors from giving
- Asymptomatic donors are our main concern
- Plasma derivatives should be safe
- So, how precautionary must we be??

8

Risk-benefit considerations

- "…transmission of a respiratory virus by transfusion is very unlikely to result in an infection in the transfused patient although… the possibility of transmission has to be considered …"*
- *Balance donor deferrals for protecting the blood supply with an estimate of any negative impact on the adequacy of the blood supply.*

*WHO. Maintaining a safe & adequate blood supply during pandemic influenza: Guidelines for Blood Transfusion Services. 2011.

9

What is the rate of asymptomatic infection?

- Diamond Princess cruise ship epidemic:
  - 3011 PCR tests of 3707 passengers & crew PCR tested for SARS-CoV-2 as of 20 Feb at end of quarantine
    - 621 PCR positive specimens (20.6%)
    - 318 (51%) of confirmed passengers & crew asymptomatic *at time of specimen collection*
      - https://www.niid.go.jp/niid/en/2019-ncov-e/9407-covid-dp-fe-01.html

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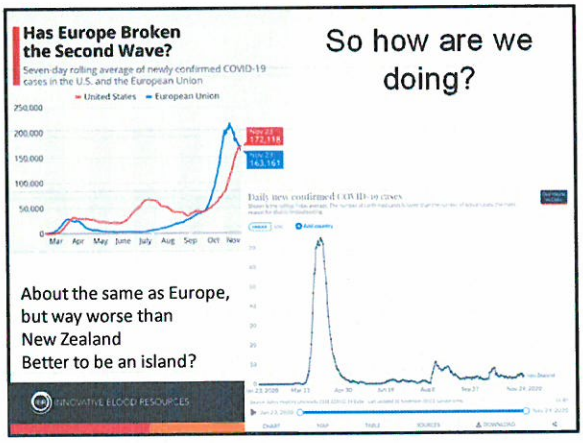
So how are we doing?



About the same as Europe, but way worse than New Zealand
Better to be an island?

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Experts agree: comprehensive testing, case tracking and quarantine are key to getting epidemic under control

US COVID-19 testing rate declines as cases top 4.7M

The daily number of COVID-19 tests administered across the US dropped 3.6% to 750,000 over the past two weeks -- possibly due to frustrations with long lines and delayed results -- even as deaths continue to increase and confirmed infections surpassed 4.7 million. Concerns about reduced testing prompted experts at Harvard's Global Health Institute to call for distribution of $1 saliva-based antigen tests to all Americans for regular testing, an approach they say would detect five times more COVID-19 infections than the existing system, even though the paper-based tests have lower accuracy.

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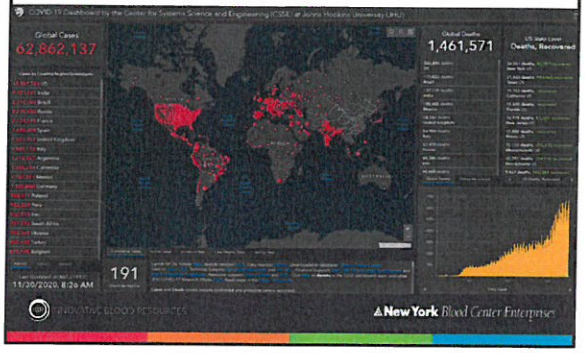
Hopkins Covid-19 world map



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Convalescent Plasma Therapy

1st Nobel prize in Medicine (1901) to Emil von Behring for transfer of antibodies from one person to another – using convalescent plasma to mitigate symptoms of influenza!

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Controlled CCP trials

Evidence favouring the efficacy of convalescent plasma for COVID-19 therapy
Michael J. Joyner https://doi.org/10.1101/2020.07.29.20162917

Table

Table 1 | Case Fatality Rates in Hospitalized COVID-19 Patients

Study	Location	Convalescent Plasma Survivor	Convalescent Plasma Non-Survivor	Convalescent Plasma Mortality	Control Survivor	Control Non-Survivor	Control Mortality	Statistics OR	Statistics P
Randomized Clinical Trials (RCT)									
Li et al. [7]	Wuhan, CHN	43	9	16%	26	12	24%	0.59	0.30
Ghebhaan et al. [8]	NLD	37	6	14%	32	11	26%	0.47	0.19
Rasheed et al. [10]	IRQ	20	1	5%	20	3	29%	0.13	0.06
Fixed Effect Model [a]		103	16	13%	80	31	28%	0.46	0.03
Matched Consuls									
Hegenius et al. [12]	Washington, USA	18	2	10%	14	6	30%	0.28	0.13
Liu et al. [11]	New York, USA	35	5	13%	116	36	24%	0.44	0.11
Perotti et al. [13]	Pava, ITA	43	3	7%	16	7	30%	0.18	0.01
Abolghasemi et al. [14]	IRN	58	17	15%	58	16	24%	0.54	0.10
Fixed Effect Model [a]		184	27	12%	204	69	25%	0.41	0.001
Controlled studies Fixed Effect Model [a]		284	42	13%	284	100	26%	0.43	<0.001
Case Series									
Salazar et al. [15]	Texas, USA	24	1	4%	--	--	--	--	--
Hartman et al. [16]	Wisconsin, USA	37	4	13%	--	--	--	--	--
Duan et al. [17]	Wuhan, CHN	10	0	0%	--	--	--	--	--
Martinez-Resendez et al. [18]	Monterrey, MEX	8	0	0%	--	--	--	--	--
Total		69	5	7%	--	--	--	--	--

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Hopkins/Mayo Clinical Trial

Study Agent: SARS-CoV-2 convalescent plasma (1-2 units; ~300-600 mL at neutralization antibody titer *>1:160.*

Primary Efficacy Objective: Reduction in progression of oxygenation and ventilation support.
Primary Endpoint: Avoidance of ICU admission.
Secondary endpoints: Cardio-circulatory arrest (at any time), Transfer to ICU, Type and duration of respiratory support (and other ICU support)in ICU, ICU mortality and LOS, Hospital mortality and LOS, Ventilator-free days, 28 day mortality

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Joyner EAP CCP trial closed 8/28/20

- April –July > 40K patients treated
- Analyzed by time from diagnosis to CCP, severity at time of CCP, antibody strength and over time.
- Confounding variables included better outcome, earlier administration and larger volumes over time
- Benefit observed with higher Ab titer, earlier administration and ? Larger volume, but are these simply markers for later enrollment?!

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So Does CCP work?: Maybe

- Multiple randomized controlled trials of CCP given after severe symptoms (intubated, 7+ days after symptom onset) fail to find benefit
- Case controlled (Eric Salazar, Houston) and randomized controlled (Argentina) indicate that if given very early (first 2-3 days before intubation) a benefit is seen

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Negative Randomized Trials

- Agarwal BMJ (2020) > 400 patient with "moderate" Covid respiratory symptoms randomized to 2 doses of 200+ml CCP vs Placebo.
  - No benefit in 28 day mortality observed
- Simonovich NEJM 11/24/20 A Randomized Trial of Convalescent Plasma in Covid-19 Severe Pneumonia
  - > 200 treated, >100 controls.
  - ***Median time from the onset of symptoms to enrollment in the trial was 8 days***
  - At day 30 day, no significant difference was noted between the convalescent plasma group and the placebo group
- CONCLUSIONS
  - No significant differences were observed in clinical status or overall mortality

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But early Rx seems better ?

- Eric Salazar: Houston Case controlled study.
  - Patients receiving CCP in first 44 hours did better
- Libster, Argentina: Prevention of severe COVID-19 in the elderly by early high titer plasma
- **Conclusions.** Early administration of high-titer convalescent plasma against SARSCoV2 to mildly ill infected seniors reduced COVID-19 progression.

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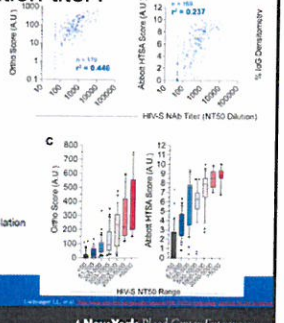
So how does Ortho COVID antibody test correlate with neutralization titer?

NYC Convalescent Plasma Donor Antibody Levels (n=300)

- VSV-S and HIV-S NAb assays
  - 83% and 93% donors NAb positive
  - Highly variable titers (<1:50 - >1:2000)
    - Median: 1:390 – 1:450
    - 9% - 11% w/ >1:2000
    - 52% - 56% <1:500
- NAb correlation better with Ortho Total (Spike) vs. Abbott (NC)
  - Ortho has a higher dynamic range and tests for antibodies to the Spike protein = better correlation



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FDA- Emergency Use Authorization (EUA)

- Allows use of CCP in hospitalized patients
- After 2/1/21 will require labelling as high titer vs. low titer currently defined as Ortho IgG only assay signal/cutoff ratio ≥ 12. This roughly correlates with Broad Institute Covid neutralization titer of 1:250. Data being obtained and submitted on alternative assays.
- Only 1/3 to ½ of current CCP meets this titer

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Ethical Approach to CCP distribution: Fairly and efficiently allocate very scarce supplies of convalescent plasma to maximize opportunities to learn about its value in the treatment of hospitalized patients with COVID-19

- **Priority 1 Patients: The patients receiving the highest priority for allocation of CCP are:** Patients within three days of diagnosis who are 1) on advanced respiratory support (high flow nasal cannula, CPAP, or BIPAP) but not mechanical ventilation; or 2) on supplemental oxygen only.
- **Priority 2 Patients:** Patients who would be transfused between four and seven days of diagnosis who are 1) on advanced respiratory support (high flow nasal cannula, CPAP, or BIPAP) but not mechanical ventilation; or 2) on supplemental oxygen only.
- **Priority 3 Patients**: If facilities have met the needs of the first and second priority groups of patients, facilities should then allocate CCP based on the following criteria:
- Patients more than 7 days from diagnosis who: are on advanced respiratory support, or are on supplemental oxygen, mechanical ventilation or ECMO.
- **Prioritization of critical workers with high occupational risk of exposure to SARS-CoV-2**
- Critical workers with high occupational risk of exposure should receive priority in allocation of some scarce health resources for two primary reasons. See "Guidance Regarding The Prioritization Of Critical Workers In High Risk Settings Prioritization Of Key Workers For Allocation Of Scarce Health Resources During The Covid-19 Pandemic" for background and specifics on implementation.

Supply	Track A – Key Workers with "medium" or "high" risk of occupational exposure	Track B – General Population
Extreme scarcity	Priority 1 Priority 2	Priority 1
Moderate scarcity	Priority 3	Priority 2
Some scarcity		Priority 3
Adequate supply	No rationing	No rationing

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Logistics

- Who is paying for all of this?
  - BARDA has agreed to retroactively reimburse blood collection centers on Mayo eIND and now some pediatric treatments (<100)
  - BARDA has also agreed to cover cost of building 300K unit "strategic reserve"
    - Where are units stored?
    - Do blood centers have capacity to store this many units
    - Will FDA allow > 1 year expiration date?

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Other Ab therapies

- Hyperimmune globulins
  - Prepared from plasma collected by blood centers, plasma centers
  - More consistent and likely much higher dose
  - IM vs IVIG?
- Monoclonal antibody cocktails
  - Already in clinical trial

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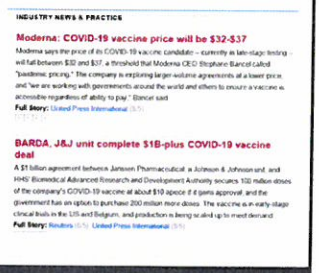
Vaccines?

US already funding multiple manufactures with many BILLIONS of dollars to expedite development

Priorities in roll out and logistics of vaccinating 300+ million people challenging



INDUSTRY NEWS & PRACTICE

Moderna: COVID-19 vaccine price will be $32-$37

Moderna says the price of its COVID-19 vaccine candidate – currently in late-stage testing – will fall between $32 and $37, a threshold that Moderna CEO Stephane Bancel called "pandemic pricing." The company is exploring larger-volume agreements at a lower price, and "we are working with governments around the world and others to ensure a vaccine is accessible regardless of ability to pay," Bancel said.

Full Story: United Press International

BARDA, J&J unit complete $1B-plus COVID-19 vaccine deal

A $1 billion agreement between Janssen Pharmaceutical, a Johnson & Johnson unit, and HHS' Biomedical Advanced Research and Development Authority secures 100 million doses of the company's COVID-19 vaccine at about $10 apiece if it gains approval, and the government has an option to purchase 200 million more doses. The vaccine is in early-stage clinical trials in the US and Belgium, and production is being scaled up to meet demand.

Full Story: Reuters United Press International

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Sustainability of regular blood supply

- Most blood collection agencies rely heavily on mobile drives, especially those at schools
  - ARC annual collection from HS => 20%
  - No HS, church, business drives Ides of March till June
  - Still not back to full blood drive schedule

27

So the FDA was trying to help

(But public doesn't understand it takes time to implement these changes!)

- Deferrals dropped to 3 months:
  - MSM
  - Malarial Travel
  - Tattoos/piercings (non-state licensed)
- vCJD
  - Eliminated 5 year residence in Europe deferral or 6 months on US military base
  - Maintained transfused in UK/France or 3 mo residence

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Mid-March our donor world changed

- Schools closed, Church services stopped and business sent employees to work at home.
- Many blood centers collect 50-80% of donors on mobiles and these were stopped
- Frantic calls yielded a bit too much blood which lasted the 8 weeks but predictably inventories were depleted by the time (semi) elective surgeries restarted in May/June

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Blood donor site accommodations

Donation by appointment only

Further space donation chairs and cleaning between donations.

Masks for all donors and staff

Temp checks (with horribly non-specific) forehead scanners before entering

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Current inventory woes

- CCP collections distract from regular collections
  - Staff pulled to recruit, collect CCP donations
  - Plasma collection on various devices, (Alyx, Trima) makes them and their collection kits less available for regular collection
- Usage which fell by >30% has now returned to 80-90% and continues to increase. But collection opportunities at schools/churches/business have not rebounded
- Staff are equally affected by COVID as their communities and either due to exposure or underlying conditions may be unable to work
- Although higher unemployment might make recruiting easier, it is very difficult to hire and train staff in this setting. Furthermore, most centers put hiring freezes in place or let some staff go when future demand uncertain.

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Meanwhile our donor base is aging

Independent of Covid, the volunteer blood donor base in the US (and developed world) is aging. Inability to get younger donors post high school to donate and increased population of older patients will inevitably result in supply/demand imbalances developing

Graph below shows high dependence upon high school drives (females yellow, males red 2019)

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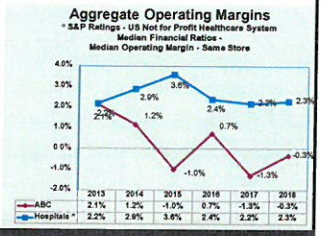
We're nonprofits but there is a limit!

- Meanwhile several of our hospitals have approached us to reduce pricing (one requesting 20%) because they were no longer making money
  - Blood collection agencies haven't been breaking even in a while!



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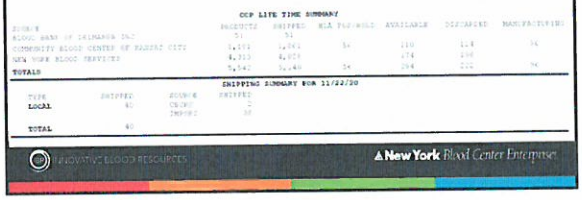
On a happy note…

- To date, CBCKC has shipped over 5000 CCP units and has ~300 in inventory, so virtually all of our customers are getting immediate service when these units are requested!



CCP LIFE TIME SUMMARY

SOURCE	RECEIVED	SHIPPED	WEB FULFILLED	AVAILABLE	DISCARDED	MANUFACTURING
BLOOD BANK OF DELMARVA INC	51	51				
COMMUNITY BLOOD CENTER OF KANSAS CITY	3,171	3,043	5%	110	114	5%
NEW YORK BLOOD SERVICES	4,313	4,054		274	198	
TOTALS	7,535	7,148	5%	384	312	5%

SHIPPING SUMMARY FOR 11/22/20

TYPE	SHIPPED	SOURCE	SHIPPED
LOCAL	40	CBCKC	5
		IMPORT	35
TOTAL	40		

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