PASSIVE ANTIBODY THERAPIES: THEIR HISTORIC ROLE IN MEDICINE AND THEIR VALUE IN COVID-19

Nigel Paneth MD MPH
Michigan State University

Course in Frontiers in Emerging, Re-Emerging,
and Zoonotic Diseases, Magee-Women's Research Institute
and Ponce Health Sciences University

Ponce, Puerto Rico

February 17, 2026

This presentation can be found at
https://epibio.msu.edu/research/paneth.html

THIS TALK

I will cover four topics today

1. What is passive antibody and what are the three forms of passive antibody therapy?
2. A brief review of the historic use of passive antibodies in medicine.
3. The use (and misuse) of passive antibody therapy in COVID-19. I hope to convince you that convalescent plasma (CP) was indeed valuable, saving lives and hospitalizations when used correctly in COVID-19.
4. The possible use of passive antibody therapies in the next pandemic

WHAT IS PASSIVE ANTIBODY THERAPY?

1. Passive antibody therapy (also referred to as passive immunization) is the transfer of pre-formed antibodies to a recipient either to prevent or to cure disease.
2. It must be distinguished from active immunization, where vaccines stimulate the host immune system to produce antibodies and create immunologic memory.
3. Passive immunization provides only temporary protection.
4. Before the introduction of antibiotics, passive immunization was the major therapy for infectious disease.

THE THREE FORMS OF PASSIVE IMMUNIZATION

- CONVALESCENT PLASMA – Cell-free component of blood taken directly from recovering patients (presumed or shown to have neutralizing antibodies) for transfusion into sick or at-risk people. All plasma intended for direct transfusion into patients comes from voluntary contributions to blood banks.
- HYPERIMMUNE GLOBULIN – Concentrated antibody derived from thousands of people or from large animals stimulated to produce antibodies. Unlike plasma, HIG cannot be used for immediate infusion into patients, but must be processed. Made by plasma fractionating companies for profit.
- MONOCLONAL ANTIBODIES – Laboratory-engineered antibody targeted to specific proteins. Made by pharmaceutical companies.

HISTORICAL EVOLUTION OF PASSIVE ANTIBODY THERAPIES

1. CONVALESCENT PLASMA

   a) Passive antibody therapy in the form of antitoxins began in the 1890's but could only target organisms whose pathophysiology depended on toxins.

   b) Passive antibody therapy in the form of antisera, which targeted non-toxin producing organisms, began largely in the 1920's.

2. HYPERIMMUNE GLOBULINS

   Although used earlier (especially for antitoxins), technologies to more readily produce hyperimmune globulins were developed in the 1940's.

3. MONOCLONALS

   The first use of monoclonal antibodies to prevent or treat infectious diseases was in the 1990's

THE INVENTION OF ANTITOXIN

Behring and Kitasato demonstrated, in two papers in 1890, that serum from animals recovering from diphtheria and from tetanus had something in their serum that could prevent or cure the disease in susceptible animals.

The active agent was an antitoxin to toxins created by these bacteria. Behring in Germany and the Pasteur Institute in France mass-produced diphtheria antitoxin, and the technology was quickly adopted in the US, with several pharmaceutical companies and state and local health departments manufacturing antitoxins by 1900.

EFFECTIVENESS OF DIPHTHERIA ANTITOXIN

- Most assessments of diphtheria antitoxin were observational – treated vs untreated or time trends.
- The closest study to a randomized trial was a year-long trial in Copenhagen in which diphtheria antitoxin was administered on alternate days to new diphtheria admissions. 30 of 250 untreated patients died (12%) while 8 of 239 treated died (3.3%) a mortality reduction of 72%.
- The current WHO estimate of diphtheria antitoxin effectiveness is 76%.
- Time trends in diphtheria mortality after the introduction of antitoxin but before the vaccine was developed were also persuasive. If we had the diphtheria mortality of the 1890's - before antitoxin – we would lose some 400,000 lives a year, mostly children between ages 2 and 5.

TABLE 1: MAJOR ANTITOXINS AND THEIR EARLIEST HUMAN USE		
Disease	Organism	Year of first use in humans
Diphtheria	Cornybacterium Diphtheriae	1894
Scarlet Fever	Group A Streptococcus	1895*
Tetanus	Clostridium Tetani	1896**
Brucellosis	Brucella Abortus	1898
Shigella	Shigella species	1903
Gas gangrene	Clostridium Perfringens	1919**
Botulism	Clostridium Botulinum	1963

*Minimal use until the toxin was identified and an effective antoxin was made (Dick GF, Dick G:A Scarlet Fever Antitoxin:JAMA 1924;82:1246-1247)

** Tetanus toxoid was used effectively in WWI,and gas gangrene antitoxins, in WW II to treat infected war injuries.

EXPANDING THE REACH OF PASSIVE ANTIBODY THERAPY

MOVING FROM ANTITOXINS TO ANTISERA

DEVELOPMENT OF ANTISERA

- Antisera development faced greater biological challenges than did work on antitoxins.
- Toxins are chemicals and do not evolve or come in different strains.
- Early attempts to use antisera against non-toxin producing organisms were thus inconsistent.
- In the 1920's, the capacity to serotype important organisms, especially the pneumococcus, ushered in the antiserum era.

TREATING PNEUMOCOCCAL PNEUMONIA

- In the pre-antibiotic era, bacterial pneumonia, largely due to the pneumococcus, was a major cause of death. In the Boston City Hospital, where type-specific antiserum was pioneered, in the early 1930's 50% of all deaths were due to pneumococcal pneumonia.
- Quasi-randomized trials in the Boston City Hospital (e.g. alternate assignment of patients, treating one ward and not another) showed reductions of mortality of about 30% with type-specific antiserum. If treatment was initiated early, mortality was reduced by about 50%.
- Another pioneering institution for antiserum use in pneumococcal pneumonia, the Rockefeller Institute in NYC, used higher doses of antibody, and claimed better results.
- Timing of treatment and dosage are recurrent themes in passive antibody treatment to this day.

OTHER IMPORTANT ANTISERA

- BACTERIA
  - Antiserum reduced meningococcal meningitis mortality (at that time nearly 100%) to 31%, and to 18% if provided early (1910's).
  - Plague antiserum was shown in an RCT in India to lower mortality by 50% (1930's)
- VIRUSES
  - Polio immune globulin reduced mortality by nearly 80% (1950's)
  - In an RCT of CP in Argentine Hemorrhagic fever, mortality was 90% lower than in the control group (1980's).

OTHER DISEASES TREATED WITH ANTISERA

DEVELOPED BETWEEN 1906 – 1955

- Tularemia
- Invasive Haemophilus Influenza B
- Measles
- Mumps
- Influenza A
- Varicella
- Rabies

DEVELOPED BETWEEN 1984 - 2016

- MERS*
- SARS*
- Lassa Fever
- Ebola

*note that these two diseases are caused by coronaviruses.

END OF AN ERA

- The development of antibiotics in the 1930's/1940's greatly reduced use of passive antibody therapies. In the India plague trial where mortality was halved by antiserum, another trial arm showed that sulfa drugs lowered mortality by 70%.
- The polio immune globulin trial, with 50,000 enrollees in multiple US states and 80% effectiveness, was published less than a year before the announcement of the success of the Salk polio vaccine trial and was largely forgotten.
- Three other factors:
  - The complexity of antiserum therapy (obtaining matched serum, IV therapy) as compared to off-the-shelf antibiotics.
  - Inconsistency in results because of varying antibody levels in serum.
  - The not-for-profit status of blood banks, as contrasted to the resources of the pharmaceutical industry.

MOVING ON TO COVID-19

CCPP19 ORGANIZATIONAL ARRANGEMENTS THAT SPRUNG UP IN WEEKS

- A national group of several hundred physician-scientists dedicated to finding out whether convalescent plasma would be a good therapeutic option in COVID-19 was organized in March 2020.
- Initially, we held large scale weekly meetings by zoom (about 200 attendees)
- Need for communications led to the establishment of an-MSU supported website on March 26th with the assistance of Amazon Web Services.
- A seven-person leadership team was assembled which at first met by phone every evening, then steadily less frequently.

National convalescent plasma group https://ccpp19.org

Michael Joyner
Mayo Clinic

Arturo Casadevall
Johns Hopkins

Nigel Paneth
Michigan State

Brenda Grossman
Wash U

Jeffrey Henderson
Wash U

Lisse-anne Pirofski, Einstein

Shmuel Shoham
Johns Hopkins

ANTIBODY THERAPIES IN COVID-19

- HYPERIMMUNE GLOBULINS: In three of six small trials some evidence of effectiveness was seen. A consortium of US plasma fractionators collaborated and produced a hyperimmune globulin, but it did not show effectiveness in an RCT.
- MONOCLONAL ANTIBODIES were initially successful in lowering mortality when used early in the disease process, but viral evolution rendered them all ineffective towards the end of the pandemic.
- CONVALESCENT PLASMA: Effectiveness depended nearly entirely on time of administration and dosage of antibody. I will focus largely on the CP findings in the rest of this talk.

TWO KEY PRINCIPLES IN USING PASSIVE ANTIBODY THERAPY

1. DOSAGE. Unless measured, the amount of antibody in any given unit of convalescent plasma is unknown. Most randomized trials of convalescent plasma did not measure the antibody level of administered plasma.
2. TIMING. From the earliest days of antitoxins and antisera it has been known that passive antibody therapy only works if provided early in the course of illness. Several randomized trials of convalescent plasma treated hospitalized patients who had been ill for over a week.

IMPORTANCE OF EARLY TREATMENT

PNEUMOCOCCAL PNEUMONIA

"It is a fundamental principle in all serum therapy that to obtain the best results the serum must be given early in the disease"

Russell Cecil: Effects of very early serum treatment in pneumococcus type 1 pneumonia. JAMA 1937; 108: 689-692

DIPHTHERIA

DIPHTHERIA MORTALITY BY DAY OF ILLNESS ON WHICH ANTITOXIN TREATMENT WAS INITIATED IN 4,071 CHILDREN WITH DIPHTHERIA					
DAY	1	2	3	4	>4
MORTALITY	0.3%	1.7%	3.8%	12.4%	25.4%
Horace Hodes: "Diphtheria" in Holt's Disease of Infancy and Childhood. 11th ed. 1940, p. 1092					

THE FIRST EFFORT TO STUDY CONVALESCENT PLASMA – THE EAP

- The Expanded Access Program (EAP) was begun in March 2020 by the Director of Biologics of the FDA, Peter Marks MD, PhD (who also initiated the WARP SPEED program that led to the development of monoclonals and vaccines) to replace the system that required a separate request for CP to be submitted to the FDA for each patient.
- Dr. Marks asked Mayo Clinic to set up a database of all CP recipients in the US and required that they all be enrolled on that website. The Mayo clinic IRB approved this registry study on the same day the request was submitted.
- Michael J. Joyner MD, a physician-scientist at Mayo, was the PI, and the funding came from BARDA (Center for the Biomedical Advanced Research and Development Authority)
- The first EAP patient was enrolled on April 3rd, 10 weeks after the first COVID-19 case was reported in the US.

EAP FINDINGS

- From April to August 2020, the EAP enrolled over 100,000 patients from 44 states.
- Analyses of 20,000 patients showed that transfusion-related lung disease (TRALI), transfusion-associated cardiac overload (TACO), allergic reactions, hemolysis, and other reactions in total occurred in fewer than 5/1,000 patients.
- Remnant samples from the transfused plasma of 3,082 patients were retrieved from 54 blood banks and tested for antibody level to study outcomes of CP recipients in relation to the amount of antibody received.
- The FDA undertook a similar study using different samples and a different antibody test.

OUR FINDINGS IN THE EAP DATABASE

30-day mortality	NOT MECHANICALLY VENTILATED (N = 2,014)		MECHANICALLY VENTILATED (N = 1,017)	
ANTIBODY TITER*	RELATIVE RISK OF DYING	CONFIDENCE INTERVAL	RELATIVE RISK OF DYING	CONFIDENCE INTERVAL
High (top 20%)	**0.64**	(0.46–0.88)	0.95	(0.79–1.15)
Medium (middle 60%)	0.87	(0.70–1.09)	0.93	(0.72–1.19)
Low (lowest 20%)	1.0		1.0	

*VITROS ANTISARS-COV-2 IGG CHEMILUMINESCENT IMMUNOASSAY (Ortho-Clinical Diagnostics).
Source: Joyner MJ et al: N Engl J Med 2021 Mar 18;384(11):1015-1027

FDA FINDINGS IN THE EAP DATABASE

28-day mortality	ALL PATIENTS (2,817)	NOT INTUBATED (1,238)	NOT INTUBATED AGE LESS THAN 80 TREATED IN 1ST 72 HOURS (485)
ANTIBODY TITER*	RELATIVE RISK OF DYING		
HIGH TITER (highest 50%)	0.93	**0.84**	**0.71**
LOW TITER (lowest 50%)	1.0	1.0	1.0

*BROAD INSTITUTE NEUTRALIZING ANTIBODY
Source: https://www.fda.gov/media/142386/download

RESULTS OF THE EAP

- The antibody findings, combined with the safety data, convinced the FDA to declare the EAP over.
- On August 23rd, 2020, less than 5 months after the first EAP patient was enrolled, the FDA issued an emergency use authorization (EUA) for convalescent plasma use in in-patients.
- National use of CP increased substantially.
- But the adoption of CP in the US proved short-lived because of the publication of two large negative randomized trials in late 2020

THE PLACID TRIAL

Agarwal A et al: BMJ 2020 Oct 22:371:m3939

- 464 hospitalized patients across India with hypoxia and respiratory difficulty randomized to CP or usual care.
- Death or progression of respiratory dysfunction occurred in 18.7% of treated and 17.9% of controls RR = 1.04

HOWEVER

- Median duration of disease before transfusion was 12 days.
- The donor pool: "*most of the donors were young and only had mild disease.*"
- Neutralizing antibody "*values reported as less than 1:20 were considered as undetectable.*" One-third of donors had antibody levels below 1:20.
- The authors' conclusion: "*This suggests potentially no benefit of convalescent plasma collected from young survivors of mild covid-19 and administered to elderly patients with moderate or severe disease.*"

THE RECOVERY TRIAL:

Recovery Collaborative Group: Lancet. 2021 May 29; 397(10289):2049-2059 (pre-print available in December 2020)

THE TRIAL

- 11,558 hospitalized patients across the UK, 87% on oxygen. Plasma had acceptable antibody levels.
- Death occurred in 1,399/5,795 treated (24%) and in 1408/5763 (24%). RR = 1.00

HOWEVER,

- Median duration of disease before transfusion – 9 days.
- Patient population was very sick with nearly all on oxygen and an overall mortality rate of 24%
- Sub-groups indicating early illness tended to show greater mortality benefit with CP. For example:
  - Not on oxygen (RR = 0.83)
  - Not on steroids (RR = 0.78)

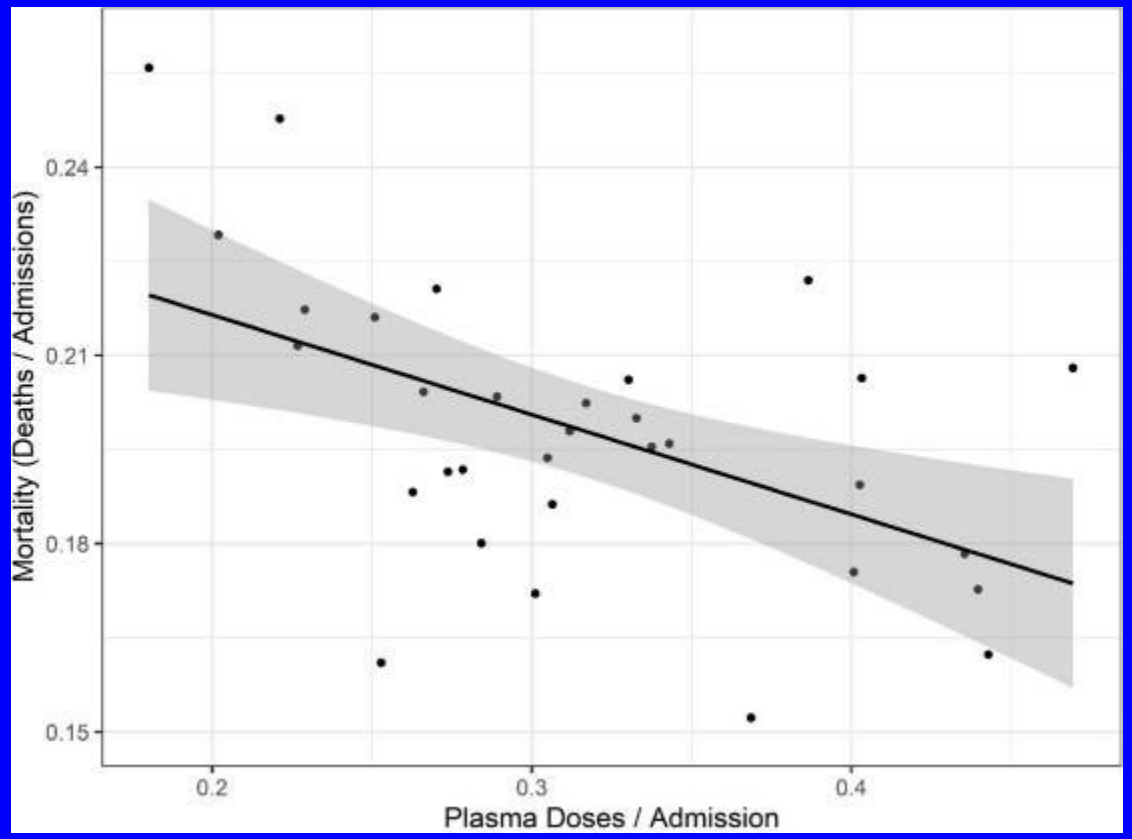
WHAT HAPPENED WHEN CONVALESCENT PLASMA WAS EXAMINED IN OUTPATIENTS?

1. Libster R et al N Engl J Med 2021 Feb 18;384(7):610-618
   - 160 outpatients > age 65 randomized to CP (with IgG titers > 1:1,000) or normal saline within 3 days of onset of symptoms.
   - End point of severe respiratory disease found in 16% of treated and 31% of controls, **RR = 0.52 (p <.05).**
   - If CP had IgG > 1:3,200, **RR = 0.27 (P < .01)**
   - 2 deaths and 2 ICU admissions in treated; 4 deaths and 6 ICU admissions in controls.
2. Sullivan D et al N Engl J Med 2022 May 5;386(18):1700-1711
   - 1,181 outpatients > age 18 randomized to CP or control plasma within 9 days of onset of symptoms.
   - 2.9% of CP recipients and 6.3% of controls were hospitalized. **RR = 0.46 (p=.005)**
   - If treated within 5 days of illness, 1.9% of CP recipients and 9.7% of controls were hospitalized. **RR = .20 (p = .002)**

ANALYSIS OF MORTALITY AND CONVALESCENT PLASMA USE

- The increase in CP use after the authorization of August 2020 and the subsequent decline in CP use constituted a natural experiment to assess the effect of CP on mortality.
- We were able to obtain the number of CP units dispensed weekly to hospitals by blood banks from *Blood Centers of America* and weekly hospital admissions for COVID from the CDC. From these data we estimated the fraction of patients treated with CP.
- CP use peaked in October 2020 with >40% of US hospital admissions being treated, but after the two negative trials appeared, CP use declined. By March 2021, only 10% of US hospital admissions were receiving CP.
- We then obtained COVID deaths by week from the CDC and examined weekly mortality per admissions for August 2020 – February 2021 in relation to CP use rates.

MORTALITY IMPACT OF CONVALESCENT PLASMA



Correlation of weekly deaths per admissions and COVID-19 CP doses per admissions.
R = −0.518 (p=0.0024).

R square = 0.268 indicating that CP use accounted for 27% of the variance in mortality in that period.

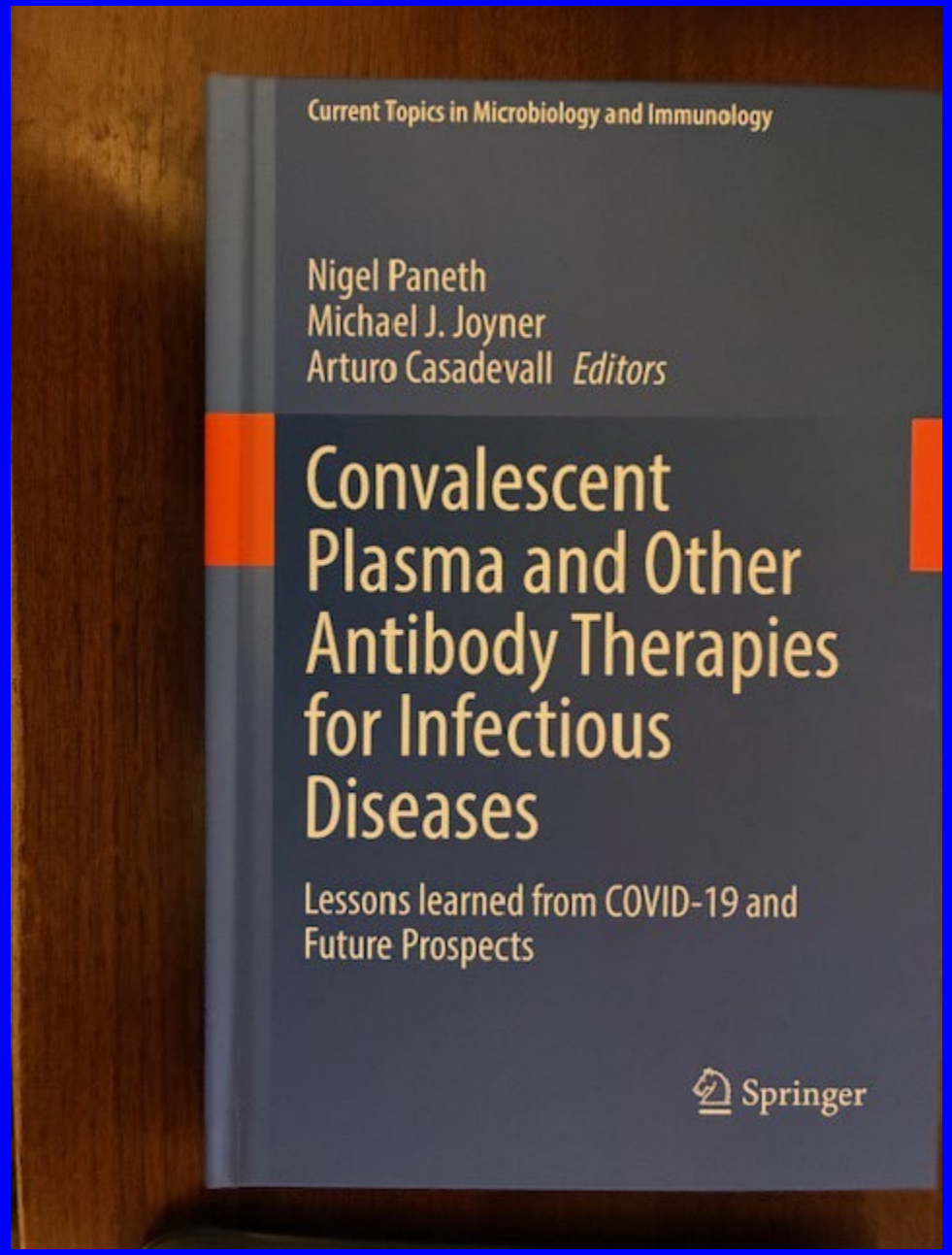
Source: Casadevall A et al: Convalescent plasma use in the USA was inversely correlated with COVID-19 mortality Elife. 2021 Jun 4;10:e69866.

DID CONVALESCENT PLASMA USE SAVE LIVES DURING THE COVID PANDEMIC?

- Depending on the assumptions modeled in stratified analyses, we estimated that CCP saved between 16,476 and 66,296 lives.
- Ideal use of CP (high titer plasma; outpatient or early inpatient use) might have saved as many as 234,869 lives and prevented 1,136,133 hospitalizations.
- Source: Dragotakes Q et al: Estimates of actual and potential lives saved in the US from the use of COVID-19 convalescent plasma. Proc Natl Acad Sci USA. 2024 Oct 8;121(41):e2414957121

The National Convalescent Plasma Project published some 100 papers on CP use in COVID-19.

We summarized much of this information in a volume published by Springer in September 2025.



PANDEMIC PLANNING INVOLVES EVERY COMPONENT OF THE HEALTH CARE SYSTEM

- Public health agencies: For disease detection, non-pharmaceutical measures (masking, crowd control).
- Pharmaceutical industry: Development of vaccines, monoclonals, anti-infective drugs, antibody tests.
- Plasma fractionators: Development of polyclonal immunoglobulins if possible.
- Clinical settings: Ensure facilities for isolating potentially infectious patients and providing outpatient IV treatment.
- Blood banks: Develop systems for obtaining and delivering convalescent plasma.
- **Academic medicine: Develop research systems – common IRB's, trial networks, funding sources– to efficiently study new interventions. Coordinate with pharma and plasma fractionators to develop new drugs and testing modalities.**

EFFECTIVE USE OF CONVALESCENT PLASMA

- In any epidemic with a new agent, an early tool, likely to be useful if used properly, is antibodies derived from survivors.
- Local blood banks must be ready to solicit donations from local survivors and used locally. Mortality was found to be higher in the EAP when the plasma source was > 150 miles from the patient.
- Outpatient facilities - including free-standing outpatient infusion centers - must be ready to provide convalescent plasma before hospitalization.
- State and federal regulatory authorities must make it feasible to use plasma on an emergency basis before formal approval, as in the EAP
- Resources will be needed to undertake trials because plasma is provided free and blood banks do not have the resources of pharmaceutical companies

THANK YOU VERY MUCH FOR LISTENING

I’M HAPPY TO TAKE QUESTIONS