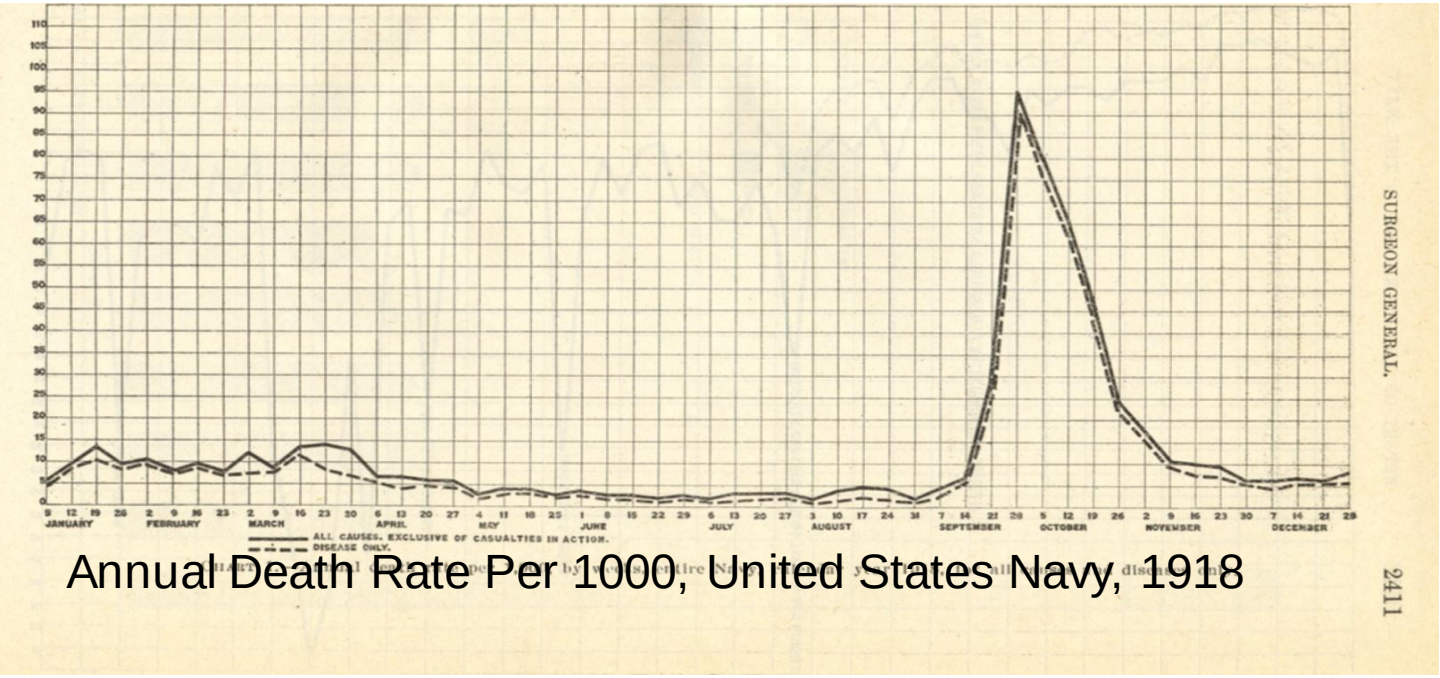
Update on Convalescent Plasma Therapy



Annual Death Rate Per 1000, United States Navy, 1918

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Notifications

- *The views expressed in this presentation are those of the author and do not necessarily reflect the official policy or position of the Department of the Navy, Department of Defense, nor the U.S. Government.*

- *The study protocol was approved by the Naval Medical Research Center Institutional Review Board in compliance with all applicable Federal regulations governing the protection of human subjects.*

- *This work was supported by funded by work unit W911QY-08-D-0022/DO 0011.*

Background

1. Convalescent Plasma and Serum has been used in the prophylaxis and treatment of pathogens in humans and in animal models.
   - H5N1 - Spanish flu - SARS - Measles - Hepatitis A
   - South American Hemorrhagic Fevers (Junin/Muchapo)
   - Diptheria - Orthopox (variola/vaccinia) - Many others
2. DoD personnel are at high risk for epidemics of infectious disease (natural or bioterror).
3. DoD currently collects and produces large volumes of blood products from military volunteers.
4. On June 7, 2007, Admiral D. C. Arthur (Ret), Surgeon General of the Navy, requested that the DHB evaluate and consider the use of convalescent plasma for the treatment of H5N1, pandemic influenza, and other infectious diseases for which inadequate therapies exist.

5. The DHB hosted a conference on convalescent plasma therapy on Feb 5 & 6, 2008 attended by representatives from:

- World Health Organization (WHO)
- Department of Defense (DoD)
- Department of Health and Human Services (HHS)
- Department of Homeland Security (DHS)
- Centers for Disease Control (CDC)
- National Institute of Health (NIH)
- Food and Drug Administration (FDA)
- Center for Biologics Evaluation and Research (CBER)
- Plasma Protein Therapeutics Association (PPTA)
- Non-profit blood donor centers
- National and international researchers, academicians and clinical care experts.

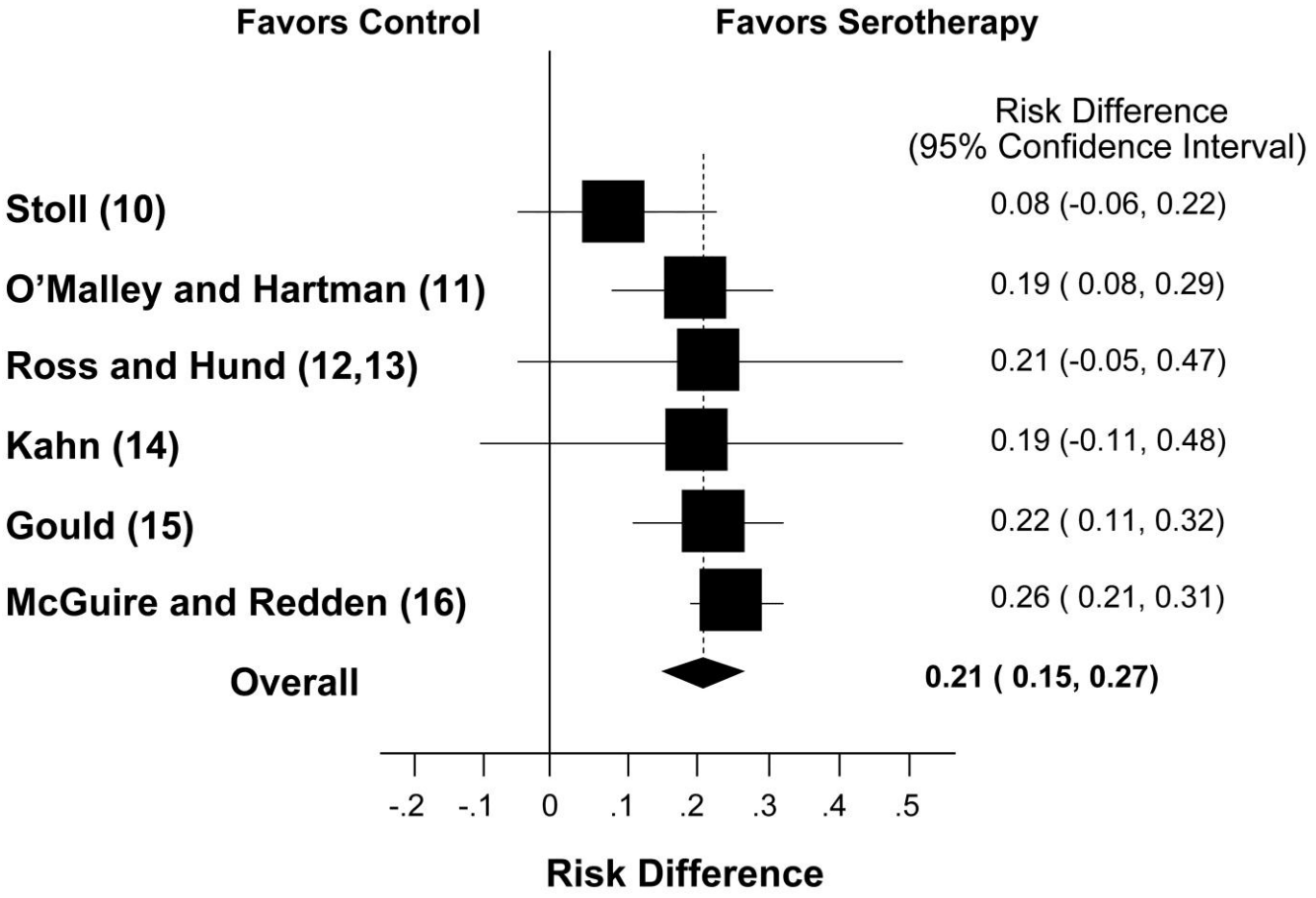
6. The DHB made recommendations on 14 May, 2008.
7. The DHB Pandemic Influenza Preparedness Subpanel met on 8 May, 2009 and endorsed the previous recommendations.
8. BUMED provided funding to NMRC to collect plasma from individuals that recovered from, or were vaccinated against, pH1N1.
8. NMRC is closely collaborating with NIAID on their IND(s) to produce Anti-Influenza A H1N1 2009 Plasma for use in a multicenter clinical trial.
9. Other Collaborators:
   - Navy Blood Program Office (BUMED)
   - Armed Services Blood Bank Center (ASBBC)
   - Naval Medical Center San Diego
   - Infectious Disease Clinical Research Program (USUHS)
   - Armed Services Blood Program (ASBP)

Convalescent Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment?

(Luke TC, Kilbane EM, Jeffries JL, Hoffman SL. Ann Int Med. Oct 17 2006. 145(8). 599-609)

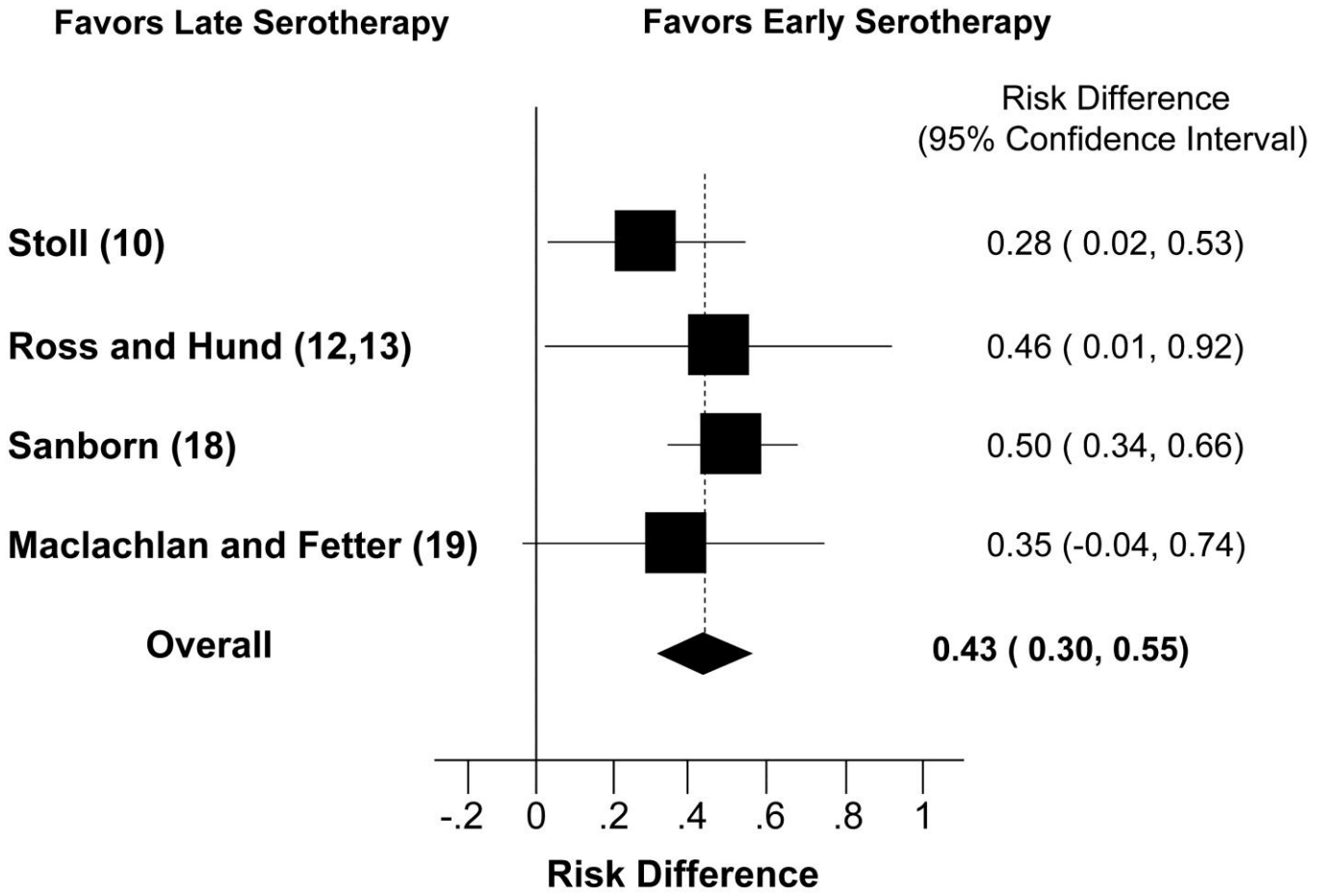
- 27 reports were found. Eight relevant studies involving 1703 patients met inclusion criteria. Treated patients were often selected because of more severe illness.
- The most common laboratory finding was leukopenia. The most common clinical finding was cyanosis and dyspnea.
- Convalescent whole blood, plasma or serum was obtained from donors one to 6 weeks after recovery from influenza.
- Patients typically received one or two treatments. The average amount of “plasma” in the treatment product was 100 to 150 milliliters (2 ml/kg).
- All eight studies reported a survival benefit.
- The authors concluded that the approach should be tested in well controlled clinical trials.

Absolute risk differences in mortality among patients treated with convalescent blood products and controls



The overall crude case-fatality rate was 16% (54 of 336) among treated patients and 37% (452 of 1219) among controls. The range of absolute risk differences in death was 8% to 26% (pooled risk difference, 21% [95% CI, 15% to 27%] between the treatment and control groups

Absolute risk difference in mortality among patients who received early (< 4 days) versus late treatment (>/= 4 days)



The overall crude case-fatality rate was 19% (28 of 148) for patients treated within 4 days of pneumonia complications and 59% (49 of 83) for patients treated at 4 days or later. The range of absolute risk difference in death was 26% to 50% (pooled risk difference, 41% [CI, 29% to 54%].

Treatment with Convalescent Plasma for Influenza A (H5N1) Infection

(Zhou B, Zhong N, Guan Y. New Engl J Med. 2007 Oct 4;357(14):1450-1.)

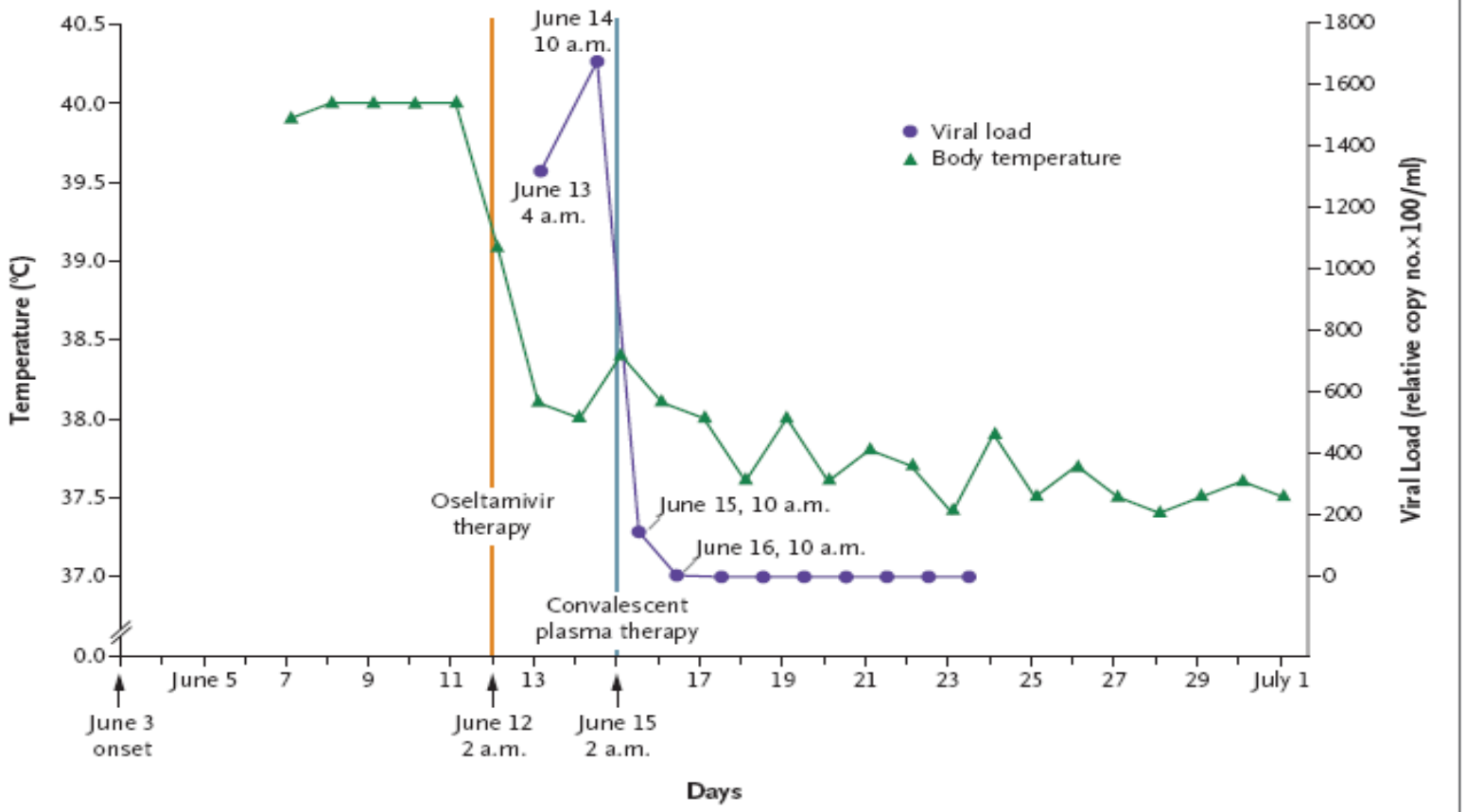


Figure 1. Influenza A (H5N1) Viral RNA Load in Tracheal Aspirates and the Patient's Response to Treatment.

The green line represents the patient's body temperature, and the purple line represents the viral load. The orange line represents the beginning of oseltamivir therapy, and the blue line represents the beginning of convalescent plasma therapy.

Other Publication(s)

- Luke TC, Casadevall A, Watowich S, Hoffman SL, Beigel JH, Burgess TH. **Hark Back: Passive Immunotherapy for influenza and other serious conditions**. *Crit Care Med* Apr 10 2010 Vol. 38, No. 3.
- World Health Organization, Blood Regulators Network: **Position paper on collection and use of convalescent plasma or serum as an element in pandemic influenza planning**. World Health Organization, July 9, 2009.
- Leider JP, Brunker PA, Ness PM. **Convalescent transfusion for pandemic influenza: preparing blood banks for a new plasma product?** Transfusion. 2010 Feb 11. [Epub ahead of print]
- Wu JT, Lee CK, Cowling BJ, Yuen KY. **Logistical feasibility and potential benefits of a population-wide passive-immunotherapy program during an influenza pandemic.** Proc Natl Acad Sci U S A. 2010 Feb 16;107(7):3269-74. Epub 2010 Feb 1.
- Wong HK, Lee Ck, Hung IF, Leung JN, Hong J, Yuen KY, Lin CK. **Practical limitations of convalescent plasma collection: a case scenario in pandemic preparation for influenza A (H1N1) infection**. Transfusion. 2010 Apr 15. [Epub ahead of print]

Average Monthly Donation of Whole Blood Units in the DoD for the Production of Packed Red Blood Cells, Platelets and Plasma

- Blood Products are the only licensed biological products that the DoD produces in its 22 blood banks:
  - 2009 monthly average: 12,262 RBC Units
  - 2010 monthly average: 11,645 RBC Units
  - Approximately 150,000 units per year
  - Could be substantially expanded by plasmapheresis capability.
- DoD has approximately 1.1 million active duty personnel
  - If 2% have severe influenza disease, then 20,000-40,000 units of convalescent plasma would be required.
  - Not dependent upon the production, allocation and delivery by the pharmaceutical industry or outside entity.

INDs for pH1N1 and Other Infectious Agents

- NIAID has an IND for the production of pH1N1 convalescent plasma.
  - NMRC is closely collaborating with NIAID
- NIAID has a plasmatherapy IND for severe pH1N1 in a multicenter trial.
  - MTF clinical sites via the IDCRP (USUHS) is planned.
  - pH1N1 activity is very low but will presumably increase in the fall
- The collaborative team and INDs could serve as a model for other "militarily" relevant diseases:
  - *Anthrax, Orthopox (Vaccinia), Adenovirus, Crimean-Congo Hemorrhagic Fever, etc*
  - *Lyophilized convalescent plasma is an application that could be explored*

Adenovirus

- Adenovirus is a significant respiratory disease in the recruit setting without adequate treatments.
  - Infrequent cause of severe disease and death
- The Naval Health Research Center has assays to determine serotype and antibody titer for adenoviruses (3, 4, 7, 14, 21, C (1,2))
  - Febrile Respiratory Illness (FRI) Surveillance Program
- The Naval Medical Research Center has an FDA approved methodology to label Fresh Frozen Plasma as a pH1N1 convalescent plasma product
  - Could be adapted for Adenovirus

pH1N1 Epidemic and Seasonal and Novel Influenza Vaccination at a Naval Facility

- 4400 students (18 – 24 years of age)
- 1200 Instructors, Officers, Support Personnel
- 23 May, 2009 H1N1 Index Case graduation week
- Students departed for summer training
- Late August/Early September Seasonal Influenza Vaccination (Flumist)
- 10 September, 2009 first confirmed case among students
- September–October 2009 pH1N1 Epidemic
- 7-8 December, Novel H1N1 Vaccination (Injectable)
- 20 November, 2009 and 17 April, 2010 for which de-linked stored serum samples were tested for HAI titer after routine blood drive

Hemagglutination Inhibition (HAI) Titers of 65 Fresh Frozen Plasma Units Obtained From a Routine Blood Drive at Navy Facility (17 November 2009)

HAI	A/California/7/2009 (pH1N1)	A/Brisbane/59/2007 (H1N1)	A/Uruguay/716/2007 (H3N2)
0	3	9	19
10	0	24	17
20	5	10	8
40	2	8	10
80	6	3	8
160	16	6	2
320	12	4	1
640	11	1	0
1280	10	0	0
Total ≥ 80 (%)	**55 (84 %)**	**14 (22 %)**	**11 (17 %)**

Hemagglutination Inhibition (HAI) Titers of 66 Fresh Frozen Plasma Units Obtained From a Routine Blood Drive at Navy Facility (20 April 2009)

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0	3	9	19
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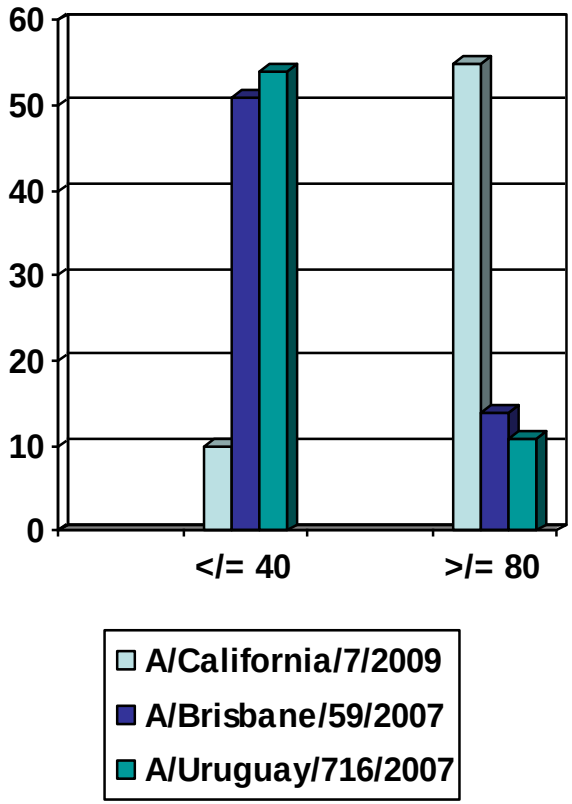
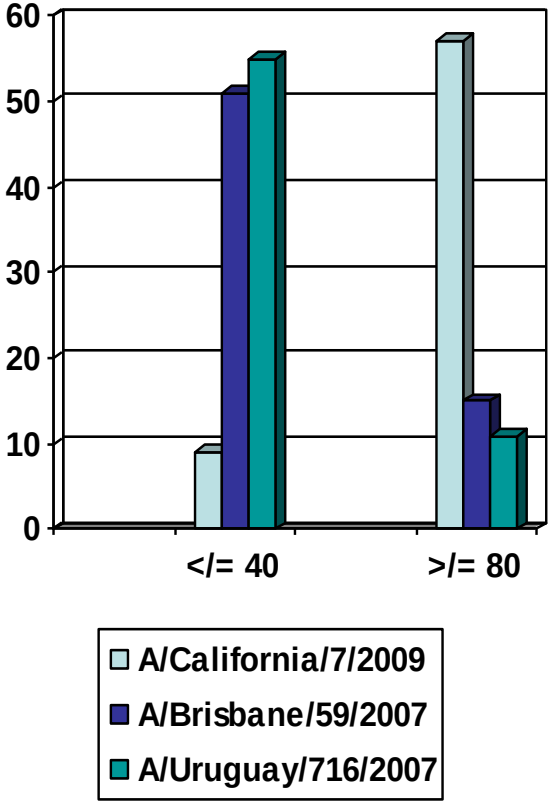
40	2	8	10
80	10	4	8
160	15	6	2
320	12	4	1
640	10	1	0
1280	10	0	0
Total ≥ 80 (%)	**57 (86 %)**	**15 (23 %)**	**11 (17 %)**

Distribution of HAI Titers From Routine Blood Drive at a Naval Facility

65 Samples, November, 2009



66 Samples, April, 2010



Anti-Influenza A H1N1 2009 Plasma with <u>FDA Approved Label</u>

Summary

- Convalescent plasma could be a primary or adjunct therapy for multiple pathogens
- NMRC and collaborators have developed and implemented a protocol to produce Anti-Influenza A H1N1 2009 Plasma under an IND
  - It could also produce seasonal H1 and H3 Convalescent Plasma (now)
- The pH1N1 experience will be informative for the evaluation and potential development of convalescent plasma for other militarily relevant diseases
  - Adenovirus, Anthrax, Orthopox, Crimean-Congo, etc
  - Concept has been introduced to industry, DoD, FDA and researchers
- DoD already produces large volumes of plasma
  - Plasma production is fast, “inexpensive”, and widely available
  - IVIG production is slower and not within DoD’s capability
- Resources and collaborations