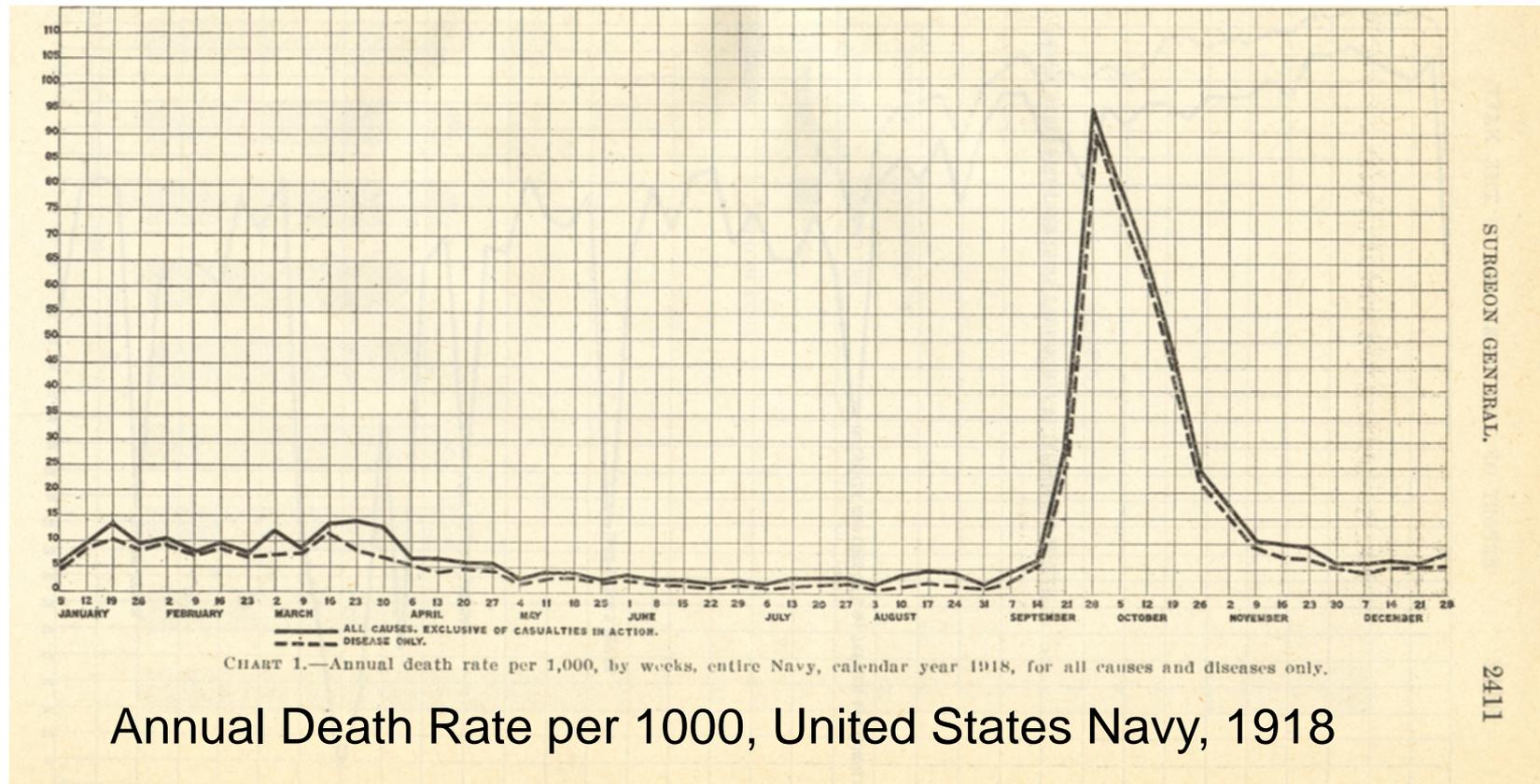


Meta Analysis: Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment?

Luke TC, Kilbane EM, Jackson JE, Hoffman SL.
Annals of Internal Medicine. 2006 Oct 17;145(8):599-609.



Topics

1. General Observations
2. Plasmatherapy
3. “Blood Products for Spanish Influenza-pneumonia.....”
4. Supporting Studies in Humans and Animal Models
 - Seasonal Influenza
 - H5N1
5. Conclusions

Pandemic Influenza Observations

- An effective vaccine will take months to develop and produce in quantity.
- Oseltamivir and other anti-virals will not be universally available and may not be effective.
- Supportive care – Access to ICU's, ventilators, antibiotics and medical care will be limited.
- Many people will not have access to any vaccine, anti-viral or other standard treatment.

Plasmatherapy

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) - Anthrax
 - Orthopox (variola/vaccinia) - Many others
2. Will likely be used in the future during outbreaks and epidemics.
3. No standardized methodology to study, collect and administer convalescent plasma for the treatment of current or new and emerging infectious diseases.

**Meta Analysis: Blood Products for
Spanish
Influenza Pneumonia: A Future H5N1
Treatment?**

Study Characteristics

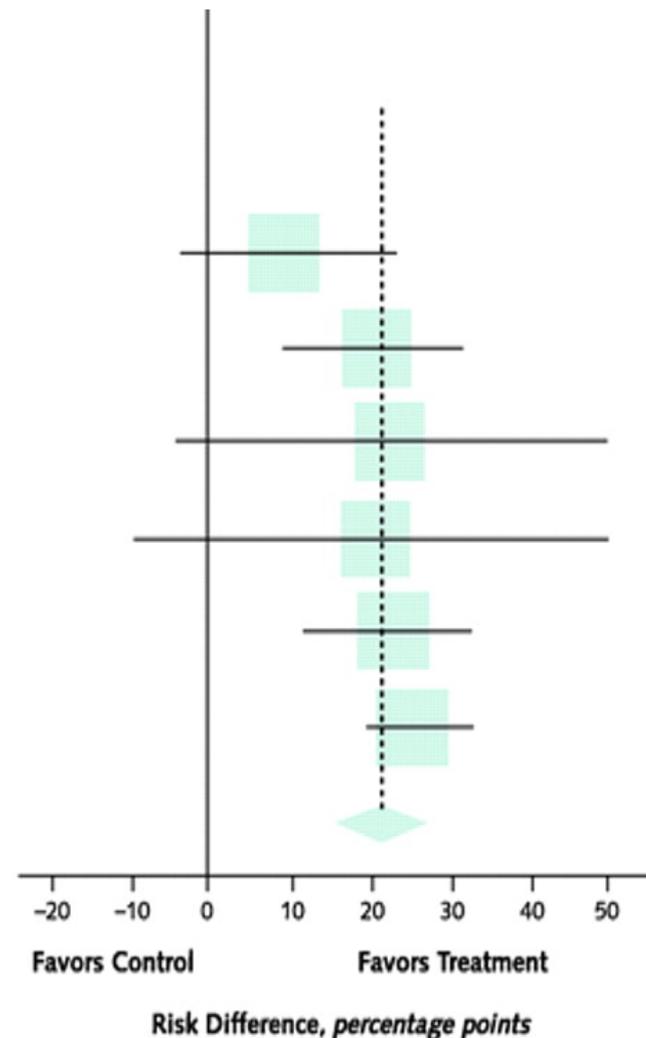
- **Background:** Studies from the Spanish influenza era reported that transfusion of influenza-convalescent human blood products reduced mortality in patients with influenza complicated by pneumonia.
- **Purpose:** To determine whether transfusion with influenza-convalescent human blood products reduced the risk for death in patients with Spanish influenza pneumonia.
- **Data Sources:** Manual search of prominent English-language journals from 1918 to 1925.
- **Study Selection:** Published English-language studies that had at least 10 patients in the treatment group, used convalescent blood products to treat Spanish influenza pneumonia in a hospital setting, and reported on a control or comparison group.
- **Limitations:** Studies had many methodological limitations by modern standards.

Findings

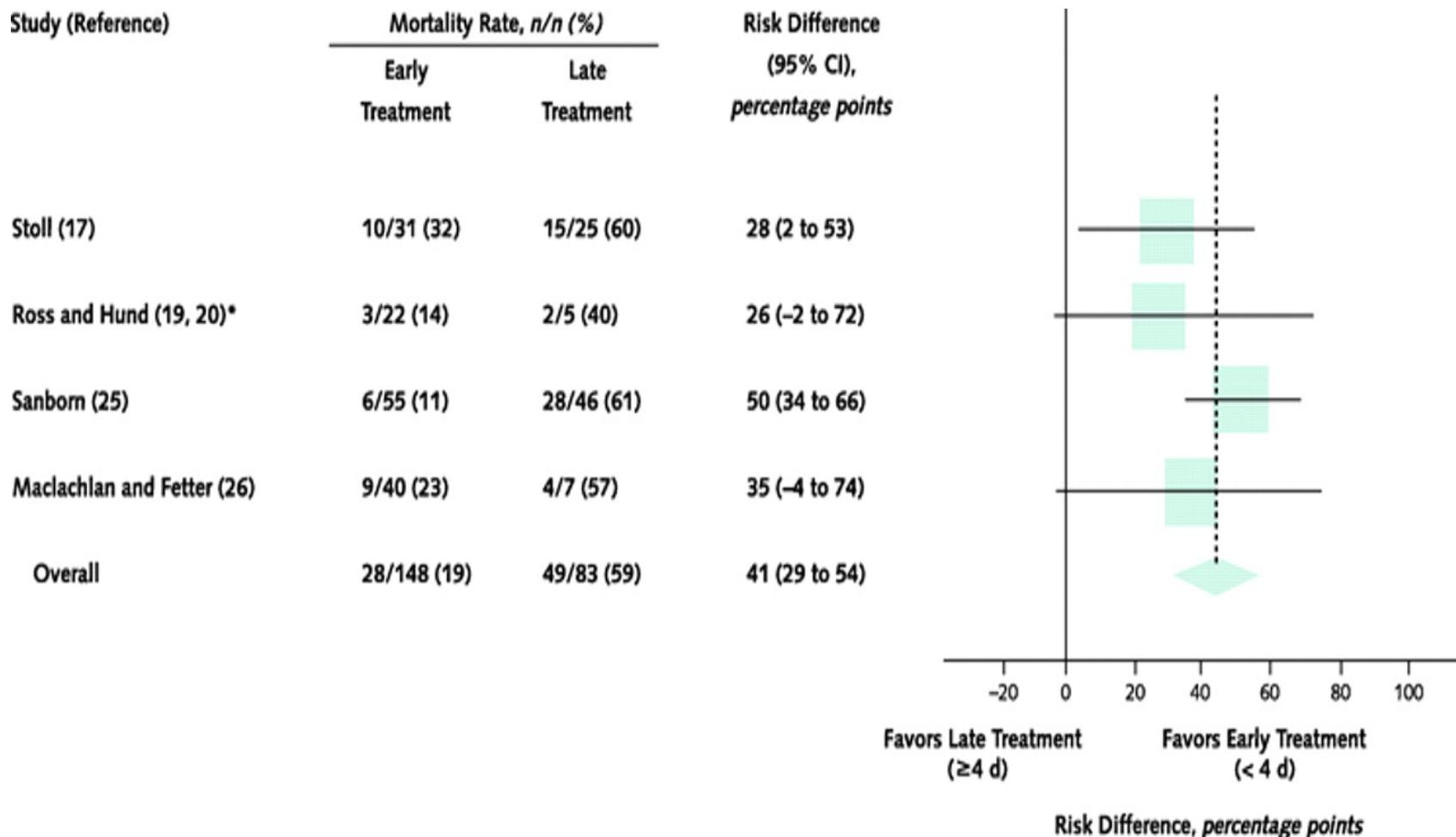
- 27 reports were found. Eight studies involving 1703 patients met inclusion criteria. Treated patients were often selected because of more severe illness.
- The most common laboratory finding was leukopenia. The most common clinical finding was cyanosis and dyspnea.
- Convalescent whole blood, plasma 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. Overall crude case-fatality rate was 16% (54 of 336) among treated patients and 37% (452 of 1219) among controls.

21% absolute risk difference in mortality among patients treated with convalescent blood products versus controls

Study (Reference)	Mortality Rate, <i>n/n</i> (%)		Risk Difference (95% CI), <i>percentage points</i>
	Treatment Group	Control Group	
Stoll (17)	25/56 (45)	201/379 (53)	8 (-6 to 22)
O'Malley and Hartman (18)*	3/46 (7)	28/111 (25)	19 (8 to 29)
Ross and Hund (19, 20)	6/28 (21)	9/21 (43)	21 (-5 to 47)
Kahn (21)	12/25 (48)	12/18 (67)	19 (-11 to 48)
Gould (22)	2/30 (7)	82/290 (28)	22 (11 to 32)
McGuire and Redden (23, 24)*	6/151 (4)	120/400 (30)	26 (21 to 31)
Overall	54/336 (16)	452/1219 (37)	21 (15 to 27)



41% ARD in mortality among patients who received early (< 4 days) versus late (> 4 Days) treatment



Other Outcomes

- **Clinical:** All 8 studies reported a clinical judgment that a distinct and beneficial improvement often occurred in treated patients after transfusion. The improvement was characterized by reductions in cyanosis, respiratory rate, nausea, vomiting, fever, malaise, or delirium within 2 to 24 hours after 1 or 2 transfusions. Improvements generally seen in those who received early treatment but also occurred in some who received late treatment.
- **Adverse events:** The most commonly reported adverse event was a brief "chill" reaction with a transient elevation in body temperature of 1° to 2°F 30 to 120 minutes after the transfusion. Serious complications relating to transfusion were rare.

Study Conclusions

- 1. Spanish influenza pneumonia patients who received transfusion with influenza-convalescent human blood products may have experienced a clinically important reduction in the risk for death.**
- 2. Convalescent human plasma could be an effective, timely, and widely available treatment for patients with H5N1 (or other new and emerging infectious disease) during outbreaks and pandemics, and this therapy should be studied in clinical trials.**

Study Conclusions

3. A central body of experts should be convened to consider plasma therapy and to make recommendations regarding a research strategy and the development of guidelines in the event that therapy is required before the research is completed.

Supporting Studies in Humans and Animal Models

- Seasonal Influenza
- H5N1 Influenza

Mouse Models for H1/H3 Influenza

- Mice with influenza-pneumonia (including immunodeficient nude and SCID mice) treated with MABs and convalescent serum with up to 100% survival (1 to 7 days after virulent challenge).
 1. Mozdzanowska et al. A pulmonary influenza virus infection in SCID mice can be cured by treatment with hemagglutinin-specific antibodies that display very low virus-neutralizing activity in vitro. *J Virol.* 1997 June; 71(6): 4347–4355.
 2. Kris et al. Passive serum antibody causes temporary recovery from influenza virus infection of the nose, trachea and lung of nude mice. *Immunology.* 1988 March; 63(3): 349–353.
 3. (Many others)

Human Plasmatherapy for Seasonal Influenza

- Soviet and German studies in 1950's and 60's on the prophylaxis and treatment of seasonal influenza/influenza-pneumonia with convalescent serum.
 - (see references Luke et al. Meta Analysis: Blood Products for Spanish Influenza Pneumonia: A Future H5N1 Treatment? 2006 Oct 17;145(8):599-609.)
- Recent Treatment of an H3 ARDS patient
 - Logtenberg SJ and Bilo HJ. Comments and Responses. Ann Int Med. 2006 Oct 17; 145(8): 599-609
 - Luke TC and Hoffman SL. Author Reply. Ann Int Med. 2006 Oct 17; 145(8): 599-609

Mouse H5N1 Antibody Therapy Studies

- Lu J, et al. Passive immunotherapy for influenza A H5N1 virus infection with equine hyperimmune globulin F(ab')₂ in mice *Respir Res.* 2006; 7(1): 43.
- Hanson BJ, et al. Passive immunoprophylaxis and therapy with humanized monoclonal antibody specific for influenza A H5 hemagglutinin in mice *Res Res.* 2006, 7:126.
- Simmons CP, et al. Prophylactic and therapeutic efficacy of human monoclonal antibodies against H5N1 influenza. *PLoS Med.* 2007 May;4(5):e178.
- Sandbulte MR et al. Cross-Reactive Neuraminidase Antibodies Afford Partial Protection against H5N1 in Mice and Are Present in Unexposed Humans. *PLoS Med.* 2007 February; 4(2): e59.

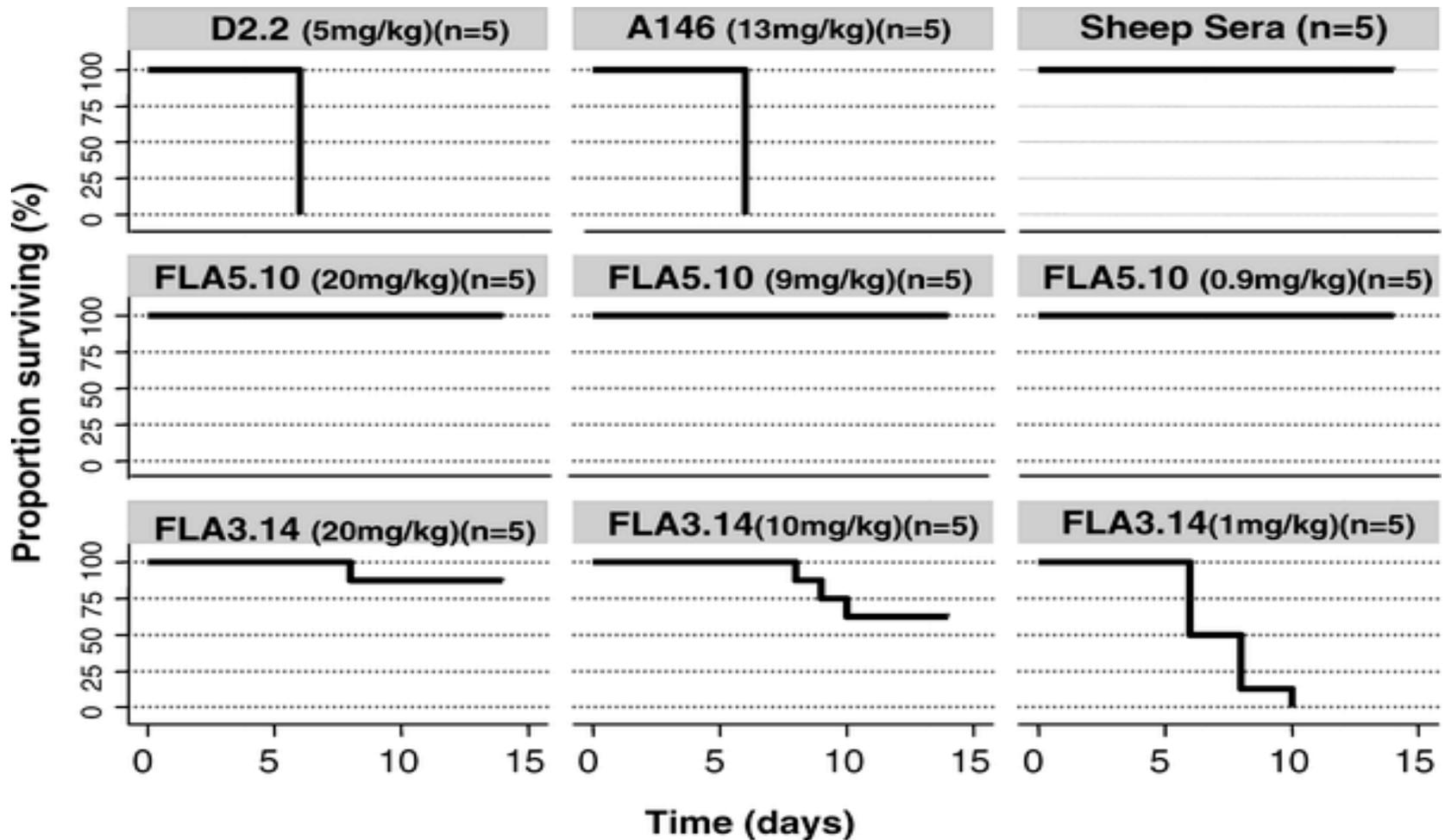


Figure 1. Passive Immunization and Survival after Challenge with A/Vietnam/1203/04 (H5N1). Dose of Sheep Sera (1 ml).

Simmons CP, et al. Prophylactic and therapeutic efficacy of human monoclonal antibodies against H5N1 influenza. PLoS Med. 2007 May;4(5):e178.

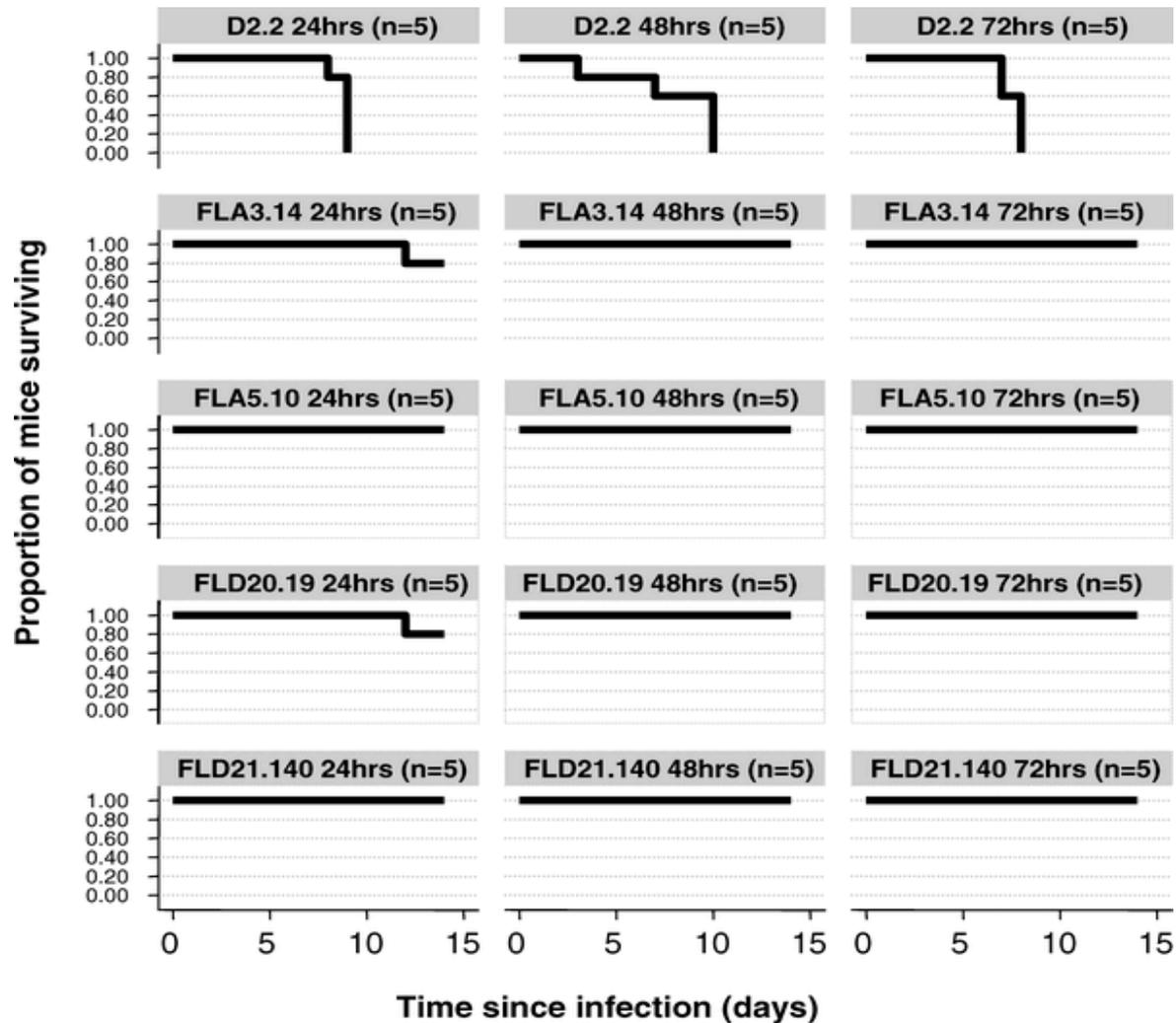


Figure 4. 50 mg/kg mAb Therapy and Survival in Mice with Established A/Vietnam/1203/04 (H5N1) Infection

Simmons CP, et al. Prophylactic and therapeutic efficacy of human monoclonal antibodies against H5N1 influenza. PLoS Med. 2007 May;4(5):e178.

Human Plasmatherapy for H5N1 Influenza

- Chinese treatment of H5N1 patients with convalescent plasma.
 - Zhou B, Zhong N, Guan Y. Treatment with convalescent plasma for influenza A (H5N1) infection. *N Engl J Med*. 2007 Oct 4;357(14):1450-1.
 - Kong LK, Zhou BP. Successful treatment of avian influenza with convalescent plasma. *Hong Kong Med J*. December 2006; Vol 12(6); 489.

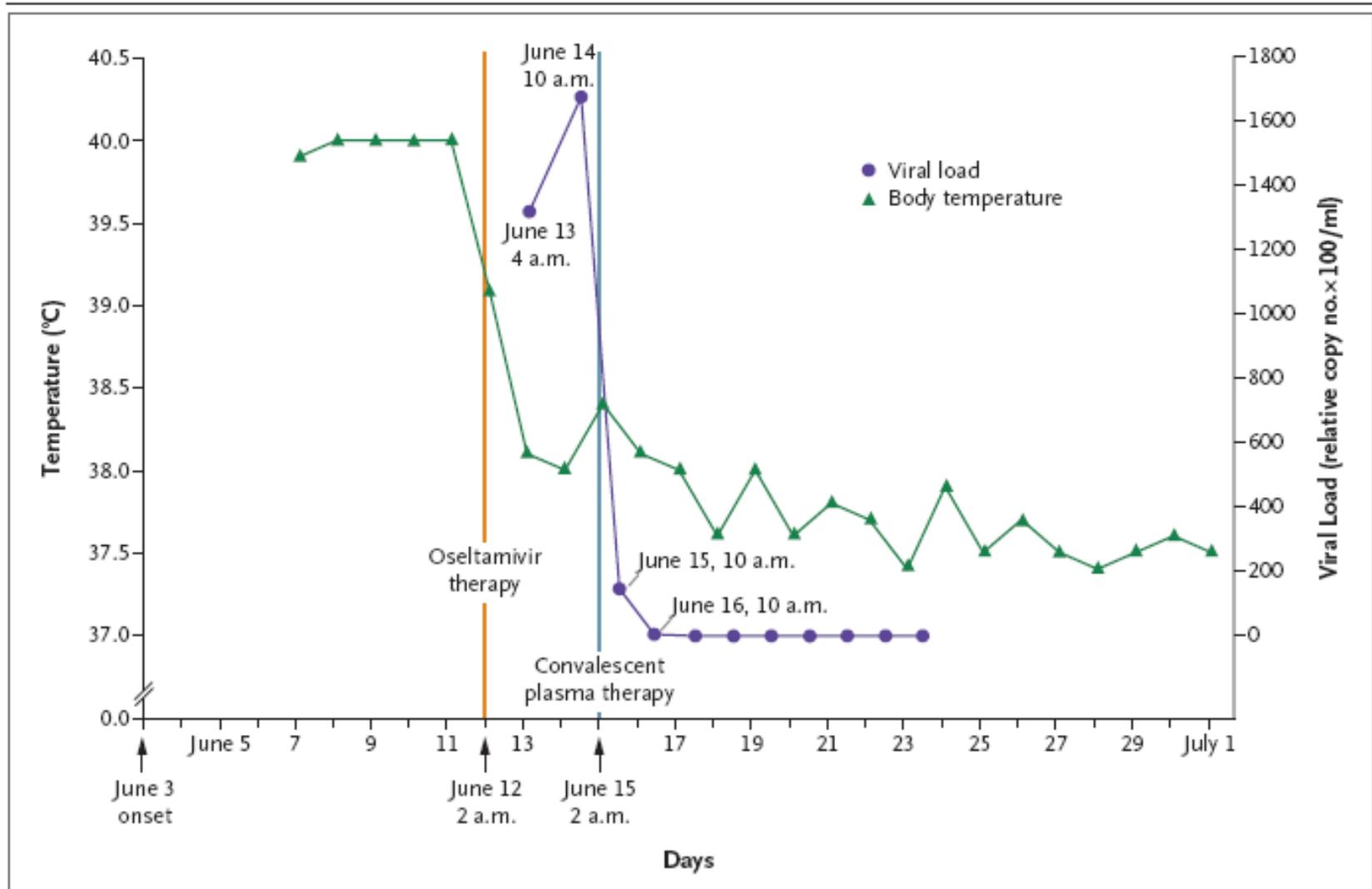
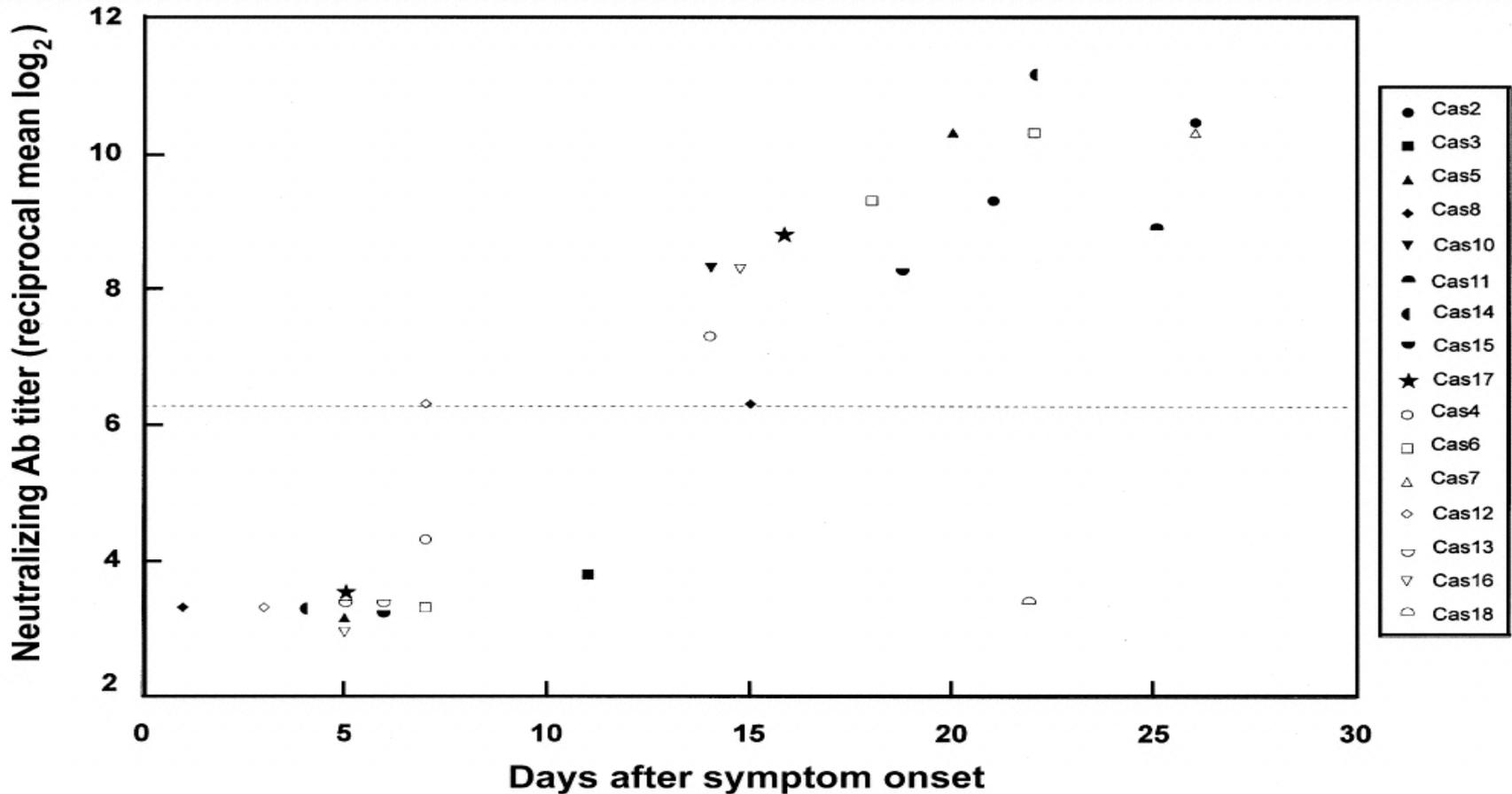


Figure 1. Influenza A (H5N1) Viral RNA Load in Tracheal Aspirates and the Patient's Response to Treatment.

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.

Kinetics of H5N1 serum neutralization antibody response



Katz, et al. Antibody Response in Individuals Infected with Avian Influenza A (H5N1) Viruses. *The Journal of Infectious Diseases* 1999;180:1763-1770

Modern Plasma Therapy

- Plasma is routinely acquired and safely used for the treatment of coagulopathies, other serious diseases, and for IVIG production.
- Current FDA regulations allow donors to donate 1000-1200 milliliters of plasma per week.
- A single donor could supply a quantity of plasma sufficient to treat multiple patients.
- Convalescent plasma could be an effective treatment for *seasonal* or *pandemic* “influenza-pneumonia” or other disease for which no good treatment exists.

Questions?