Annals of Internal Medicine | Review

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

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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. Treatments for H5N1 influenza are unsatisfactory, and convalescent human plasma containing H5N1 antibodies could be an effective therapy during outbreaks and pandemics.

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 English-language journals from 1918 to 1925. Citations from retrieved studies were also searched.

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.

Data Extraction: Two investigators independently extracted data on study characteristics, outcomes, adverse events, and quality.

Data Synthesis: Eight relevant studies involving 1703 patients were found. Treated patients, who were often selected because of more severe illness, were compared with untreated controls with influenza pneumonia in the same hospital or ward. 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 mortality between the treatment and control groups was 8% to 26% (pooled risk difference, 21% [95% CI, 15% to 27%]). The overall crude case-fatality rate was 19% (28 of 148) among patients who received early treatment (after <4 days of pneumonia complications) and 59% (49 of 83) among patients who received late treatment (after ≥4 days of pneumonia complications). The range of absolute risk differences in mortality between the early treatment group and the late treatment group was 26% to 50% (pooled risk difference, 41% [CI, 29% to 54%]). Adverse effects included chill reactions and possible exacerbations of symptoms in a few patients.

Limitations: Studies were few and had many methodologic limitations. No study was a blinded, randomized, or placebo-controlled trial. Some pertinent studies may have been missed.

Conclusions: Patients with Spanish influenza pneumonia who received influenza-convalescent human blood products may have experienced a clinically important reduction in the risk for death. Convalescent human H5N1 plasma could be an effective, timely, and widely available treatment that should be studied in clinical trials.

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The world is bracing for a potential H5N1 influenza pandemic. During the Spanish influenza pandemic, an estimated 30% of the world's population became ill and 50 million people died (1). An H5N1 influenza pandemic could be equally or more severe. Unfortunately, effective vaccines will be difficult to produce before a novel human pandemic strain emerges and will take substantial time to manufacture and distribute in quantity. It is sobering that the world's annual production capacity for influenza vaccine is 300 million doses (2)—enough for 4.5% of the world's population. These facts have caused some governments to develop response plans to pandemic influenza that involve creating antiviral stockpiles and increasing the capacity to handle surges in the need for medical care.

Patients with H5N1 influenza often develop a fatal case of acute respiratory distress syndrome or multiple organ dysfunction syndrome that is similar to the syndromes reported in patients with Spanish influenza who developed pneumonia-like complications (3–5). To treat patients with H5N1 influenza, the World Health Organization recommends hospitalization with early use of oseltamivir and supportive care (3). Despite these treatments, 30% to 80% of hospitalized patients with H5N1 influenza have died, and an oseltamivir-resistant virus has developed in some patients (3, 4). A case series report of Vietnamese patients with H5N1 influenza suggested that "supportive care may be the only option available" (4). Even if more effective standard pharmaceutical treatments are produced, it is unlikely that sufficient quantities will be rapidly or widely available because of financial, logistical, and health care delivery limitations.

Passively delivered anti-influenza antibodies in convalescent human plasma obtained from H5N1 survivors may offer a novel treatment approach and possible solution to these problems. Passive antibodies have been used to prevent or treat such diseases as rabies, measles, hepatitis B, cytomegalovirus, and respiratory syncytial virus (6), and convalescent human plasma may have efficacy in the treatment of severe acute respiratory syndrome (7, 8). The

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Context

Studies of Spanish influenza that evaluated effects of transfusion with influenza-convalescent blood products might offer insights regarding potential treatments for H5N1 influenza.

Contribution

This review of 8 controlled studies published in English-language medical literature between 1918 to 1925 found that transfusion with influenza-convalescent human blood products may have reduced risk for death in hospitalized patients with Spanish influenza complicated by pneumonia. Transfusions caused some chill reactions.

Cautions

Studies had many methodologic limitations.

Implications

Studies from the Spanish influenza era support the idea that convalescent human H5N1 plasma could be an effective, accessible treatment that should be studied in clinical trials.

—The Editors

modern plasmapheresis systems in many hospitals and blood collection centers currently produce large volumes of plasma for treating coagulopathies and other conditions (9, 10). The same infrastructure, personnel, and regulatory framework could produce convalescent plasma for the treatment of H5N1 influenza. To help assess the potential treatment efficacy of convalescent plasma in reducing mortality in current patients with H5N1 influenza, we conducted a review of studies from the Spanish influenza era that used influenza-convalescent human blood products to treat patients with Spanish influenza complicated by pneumonia ("influenza pneumonia").

METHODS

Data Sources and Searches

We developed and followed a protocol for the literature review and also followed standard reporting guidelines (11). The medical literature during the 1920s was not centrally indexed in an electronic or text database. Two authors first conducted a preliminary survey and study of the original medical literature published about Spanish influenza. This was done to gain an understanding of the scientific concepts, research methods, medical practices, and vocabulary used during that era to aid in the development of our review and search strategy. Subsequently, 1 author conducted a manual review of the indexes of the following medical journals from 1918 to 1925: *Journal of the American Medical Association*, *Boston Medical and Surgical Journal* (now *New England Journal of Medicine*), *British Medical Journal*, *Canadian Medical Association Journal*, *Lancet*, *Archives of Internal Medicine*, *The Military Surgeon* (United States), and *Naval Medical Bulletin* (United States).

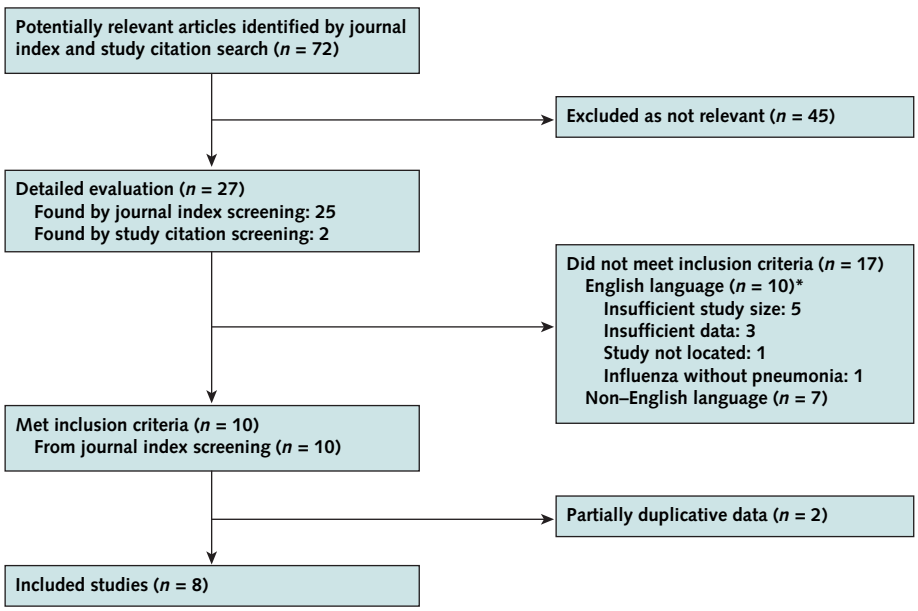
We searched 3 terms in the journal indexes: *influenza, serotherapy,* and *pneumonia*. We then searched subindexes or article titles that were listed under the 3 categories for any of the following terms: *influenza, serotherapy, pneumonia, serum, plasma, blood, bronchopneumonia, convalescent, intravenous*, and *transfusion*. Potentially relevant articles were obtained and reviewed. We also reviewed references of relevant articles. Of note, many of the source journals provided an indexed abstract section of articles drawn from other English-language and non–English-language journals. Original articles on our topic were often published as an abstract by other journals, and the articles often cross-referenced each other. For practical reasons, including feasibility and resource constraints, we limited our searches to years in which relevant studies were likely to be published.

Study Selection

Two authors selected studies published in an English-language medical journal that met inclusion criteria defined a priori (**Figure 1**). Studies had to have used convalescent whole blood, plasma, or serum obtained from humans who had recovered from Spanish influenza as the treatment product and had to indicate the type, route, and volume of the product that was used. The treatment and control groups had to have included hospitalized patients with a diagnosis of influenza complicated by pneumonia, and investigators had to report mortality rates. The treatment group had to include at least 10 patients. The control group had to receive standard care and could not be assigned to receive, as a group, an alternative experimental therapy, such as an equine-derived antipneumococcus serum. Studies had to be conducted in a hospital setting during the Spanish influenza pandemic of 1918 to 1920. We excluded studies if they were reported only as an editorial, commentary, or abstract or as a translated synopsis of a non–English-language study.

Our rationale for the detailed inclusion and exclusion criteria was as follows. Hospitalized patients were likely to have had very severe illness and a more reliable diagnosis of influenza pneumonia than were patients whose illness was diagnosed and treated by general practitioners in the home. Although strains of Spanish influenza probably circulated before 1918 and certainly did so after 1920, the accuracy of a diagnosis of Spanish influenza pneumonia was likely to be reasonably good during years when herd immunity was low, the virus was virulent, and large epidemics occurred. Because scientific concepts, research methods, medical practices, and vocabulary have changed markedly since 1920, we restricted our analysis to articles that we could carefully scrutinize and for which we could reasonably reliably determine the primary clinical condition of patients, the treatment that was given, and characteristics of the treatment and control groups.

Figure 1. **Flow diagram of trial identification and selection.**



*Most of these studies were excluded on the basis of multiple criteria.

Data Extraction and Quality Assessment

Two authors independently extracted data about study characteristics, outcomes, adverse events, and quality. Disagreements were resolved by consensus. The quality of each study was assessed by using a 27-item checklist that was developed to assess the methodologic quality of randomized and nonrandomized studies of health care interventions (12). The quality scores could range from 0 to 27, with higher scores indicating better quality.

Data Synthesis and Analysis

We used as the principal measure of effect the range of absolute risk differences in death between the treatment and control groups. We conducted a planned subgroup analysis of mortality among patients who received early treatment (after <4 days of illness) compared with those who received late treatment (after ≥ 4 days). We also calculated overall crude case-fatality rates and pooled absolute risk differences in death by using the random-effects model of DerSimonian and Laird (13). Heterogeneity was assessed visually by using Galbraith plots (14) and statistically by using the I^2 statistic (15). To exclude the possibility that any one study was excessively influencing the results, we conducted a sensitivity analysis by excluding each study one at a time. We used the method of Egger and colleagues (16) to assess for statistical evidence of possible publication bias. All analyses were performed by using Stata software, version 9.1 (Stata Corp., College Station, Texas).

Role of the Funding Source

No funding was received for this review.

RESULTS

Study Selection and Evaluation

We searched hundreds of titles in the topic indexes and retrieved 72 manuscripts for screening (**Figure 1**). Many of these studies focused on the isolation and identification of the "influenza" bacillus or known bacterial pathogens or used various animal-derived antipneumococcus serums or other preparations for treatment. In 27 reports, influenza-convalescent human blood products were used to treat patients with Spanish influenza, with or without pneumonia complications. Of these, 8 studies described in 10 reports met all of our inclusion criteria (17–26). No included study was identified solely from the citation review. We excluded 17 articles that were small case reports, were incomplete or noninterpretable, were written in a non-English language, or involved only patients with uncomplicated influenza (27–43).

Tables 1 and **2** show details from these studies, which ranged in size from 43 to 551 patients. The methodologic quality of the studies was poor, and the mean quality score was 11. No study was a randomized trial. Neither physicians nor patients were blinded to treatment status; placebo, sham, or alternative experimental treatments (such as equine-derived antipneumococcus serum) were not used in the control groups. Dosages, volumes, and administration schedules of convalescent blood products were not standardized. Patients were often selected for the treatment on the basis of a more serious clinical illness. Control groups

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Table 1. **Characteristics of 8 Studies That Assessed the Effect of Convalescent Blood Products on Mortality in Patients with Spanish Influenza Pneumonia***

Study (Reference)	Dates of the Study	Location	Sample†	Treatment Group Characteristics	Control Group Characteristics‡	Day of Convalescent Serum Donation
Stoll (17)	September 1918–early 1919	Walter Reed General Army Hospital, Washington, DC	Primarily adult soldiers	56 seriously ill patients with influenza pneumonia selected for treatment (70% had a distinctly bad prognosis)	All other patients with influenza pneumonia admitted to the hospital (n = 379)	≥10 days after fever abatement
O'Malley and Hartman (18)	September–December 1918	Naval Hospital, Washington, DC	Primarily adult sailors and some civilian employees	46 patients with influenza pneumonia selected for treatment	All other patients with influenza pneumonia admitted to the hospital (n = 111)	4–10 days after resolution of symptoms
Ross and Hund (19, 20)	November 1918	Emergency Naval Hospital, Mare Island, California	Adult male employees of a naval industrial facility	28 seriously ill patients with influenza pneumonia selected for treatment (some were moribund)	21 patients with influenza pneumonia concurrently matched for a similar clinical condition	3 days–6 weeks after resolution of symptoms
Kahn (21)	September–October 1918	Army Hospital, Camp Zachary Taylor, Louisville, Kentucky	Adult soldiers	25 seriously ill patients with influenza pneumonia selected for treatment (majority had distinctly bad prognosis; some were moribund)	18 patients with influenza pneumonia concurrently matched, but with a more favorable clinical impression	<1 week after fever abatement
Gould (22)	October 1918	Naval Hospital, Brooklyn, New York	Adult sailors	30 consecutive patients with influenza pneumonia admitted to a specific ward	All other patients with influenza pneumonia admitted to the same hospital ward (n = 290)	Several days after fever abatement
McGuire and Redden (23, 24)	October–November 1918	Naval Hospital, Chelsea, Massachusetts	Primarily adult sailors and some civilians	151 seriously ill patients with influenza pneumonia selected for treatment	All other patients with influenza pneumonia admitted to the hospital (n = 400)	Average of 10 days after fever abatement
Sanborn (25)	December 1918–May 1919	Boston City Hospital, Boston, Massachusetts	Civilians	101 consecutive seriously ill patients with influenza pneumonia referred for treatment (includes 9 pregnant women, 2 of whom died after miscarriage)	Treatment group patients treated early (n = 55) compared with patients treated late (n = 46)	3–60 days after fever abatement
Maclachlan and Fetter (26)	October 1918	Mercy Hospital, Pittsburgh, Pennsylvania	Primarily adult soldiers and some civilians	47 seriously ill patients with influenza pneumonia selected for treatment (some were moribund)	Treatment group patients treated early (n = 40) compared with patients treated late (n = 7)	After recovery

* All studies were nonrandomized studies with comparison groups. Follow-up ended with the patient's death or discharge from the hospital. IV = intravenous.
† Patients were primarily 17 to 45 years of age.
‡ Standard care for the control groups was not defined.
§ Patients in the treatment and control groups developed secondary bacterial pneumonias and infections.
‖ Reported post-transfusion clinical improvements included reduced cyanosis, dyspnea, respiratory rate, fever, nausea, vomiting, malaise, or delirium within 2 to 24 hours.

Table 1—**Continued**

Type of Influenza Convalescent Blood Product	Administration, Timing, and Number of Doses	Transfusion-Related Adverse Events§	Clinical and Laboratory Notes‖
Serum: pooled and nonpooled Blood: nonpooled, ABO matched	IV; serum, 100–150 mL; blood, 300–400 mL: unknown timing; 1–6 doses (50% received 1 dose)	16% of treated patients had a chill, shake, and temporary increase in body temperature (1 patient had hyperpyrexia to 107°F after a blood transfusion); transfusion reaction possibly hastened death in 4 seriously ill patients	Early transfusions generally resulted in distinct improvement in clinical signs and symptoms; patients had leukopenia at diagnosis with increasing leukocyte counts after transfusion
Plasma: pooled and nonpooled, non–ABO matched	IV; average dose, 125 mL; 1–4 doses every 12 h (majority received 1 or 2 doses)	75% of treated patients experienced a slight or frank chill with a temporary increase in body temperature; transfusion "may" have aggravated serious symptoms in terminally ill patients	Early transfusions generally resulted in distinct improvement in clinical signs and symptoms; patients had leukopenia at diagnosis
Blood: ABO matched	IV; 250–500 mL; 1–3 doses every 12–24 h (>90% received 1 dose)	Transfusion recipients "frequently" had a chill reaction; a single use of unmatched blood resulted in anticipated anaphylaxis (the patient was treated with epinephrine and survived); 1 patient had post-transfusion hyperpyrexia to 107 °F	Early transfusions generally resulted in a distinct improvement in clinical signs and symptoms; patients had leukopenia at diagnosis with increasing leukocyte counts after transfusion (see Table 2)
Serum: pooled, non–ABO matched	IV; 100 mL; 1–3 doses every 24 hours (majority received 2 doses)	Not reported	Transfusions can result in distinct improvement in clinical signs and symptoms; some patients were noted to have leukopenia
Serum: nonpooled, non–ABO matched	IV; serum from 200–250 mL of blood; a transfusion from a second donor was given if no improvement occurred	Transfusion recipients experienced no "untoward" effects	Early transfusions generally resulted in distinct improvement in clinical signs and symptoms; all patients had leukopenia at diagnosis
Serum: pooled and nonpooled, non–ABO matched	IV; 100–250 mL; 1–7 doses every 8–16 hours (>60% received 1 dose)	Treated patients "infrequently" experienced a chill and temporary increase in body temperature; 1 case of jaundice and phlebitis was related to transfusion	Early transfusions generally resulted in distinct improvement in clinical signs and symptoms; fever ended 1.83 days after transfusion (a decided shortening compared with controls); the majority of patients had leukopenia or a normal leukocyte count at diagnosis
Serum: pooled, non–ABO matched	IV; adults, 100 mL; children, 50 mL: 1–6 doses every 24 h (80% received 1 or 2 doses).	10% of the treated patients experienced a mild chill reaction	Early transfusions generally resulted in distinct improvement in clinical signs and symptoms; fever ended in 1 or 2 days in treated survivors; patients had leukopenia at diagnosis
Blood: non–ABO matched	IV; 75–100 mL; 1–4 doses (majority received 1 or 2 doses)	"Some" treated patients developed a chill reaction with a temporary increase in body temperature; rapid infusion could ["can"] exacerbate cyanosis and dyspnea in critically ill patients	Early transfusions generally resulted in distinct improvement in clinical signs and symptoms; patients had leukopenia (3000–5000 cells/mL) at diagnosis

were formed from all other patients with influenza pneumonia who were admitted to the same hospital or ward or were "matched" for similar or lesser clinical severity. "Standard care" that was delivered to controls was not clearly defined. Blood product donors were screened for recent influenza disease and had no history of syphilis and a negative result on a Wasserman test. Follow-up continued until death or discharge from the hospital, and no study reported that any patient was lost to follow-up. Deaths in treated patients were ascribed to late transfusion, the hopeless condition of some moribund patients when they first received transfusion, a preexisting medical condition, or development of a fatal secondary bacterial infection after full or partial recovery.

Patients were primarily previously healthy adult men 17 to 45 years of age. Diagnoses were made clinically, although chest radiography was occasionally used. Leukopenia was a common laboratory finding. The diagnosis of influenza complicated by pneumonia included 3 overlapping modern diagnostic entities: influenza pneumonia, the acute respiratory distress syndrome, and secondary bacterial pneumonia. The investigators were aware that they were treating virulent influenza with an unusual spectrum of pneumonic complications, but the exact cause and pathogenesis were unclear, because the influenza A virus was not discovered until 1931 and the acute respiratory distress syndrome was not a well-defined or recognized clinical entity in the early 20th century.

Trials included in the subanalysis of early treatment versus late treatment ranged in size from 33 to 147 patients. Transfusion was not withheld in any study for the purpose of evaluating mortality among late-treated patients. Rather, late treatment was the result of delayed presentation by the patient or a shortage of blood products.

Mortality Outcomes

Six studies reported survival benefits with treatment (17–24). 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%]; $Q = 7.0$; $I^2 = 29.3\%$) between the treatment and control groups (**Figure 2**). We found no evidence of statistical heterogeneity ($P = 0.22$) nor any statistical suggestion of possible publication bias ($P = 0.25$ [Egger test]). No individual study exerted an unusual or undue influence on our results.

Four studies reported the time delay between presentation with pneumonia complications and initiation of treatment (17, 19, 20, 25, 26). All 4 studies that compared early versus late treatment reported survival benefit with early treatment. 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%]; $Q = 2.76$; $I^2 = 0\%$) between patients treated early and patients treated late (**Figure 3**). There was no evidence of statistical heterogeneity ($P = 0.43$) nor any statistical suggestion of possible publication bias ($P = 0.23$ [Egger test]). No individual study exerted an unusual or undue influence on our results.

Only 2 trials (17, 19, 20) reported sufficient data to compare both early and late treatment groups with a control group. The mortality rates among patients treated within 4 days compared with controls were 32% (10 of 31) versus 53% (201 of 379) (17) and 14% (3 of 22) versus 43% (9 of 21) (19, 20). The mortality rates among patients treated on or after the fourth day compared with controls were 60% (15 of 25) versus 53% (201 of 379) (17) and 40% (2 of 5) versus 43% (9 of 21) (19, 20).

Adverse Events

Seven studies provided information on transfusion-related adverse events (17–20, 22–26) (**Table 1**). One study did not provide information on adverse events (21). The most commonly reported mild adverse event was a brief "chill" reaction with a transient elevation in body temperature by 1 to 2 °F 30 to 120 minutes after the transfusion. The rates of the chill reaction were reported as 16% (17), 75% (18), or 10% (25) of patients, or as "frequent" (19, 20) or "infrequent" (23, 24) or seen in "some" patients (26). The different rates of this minor transfusion-like reaction may be due to the variable reactogenicity of the blood product used (serum, plasma, or whole blood). One study reported that transfusions had no "untoward" effects (22). Five studies reported moderate to severe transfusion-related adverse events. Three studies reported that serious exacerbations of symptoms soon after transfusion could have "hastened death" in 4 seriously ill patients (17), "may" have occurred in some terminally ill patients (18), and could ["can"] have occurred in critically ill patients if the infusion was too rapid (24). One study reported a case of "anticipated anaphylaxis" after transfusion with non–ABO-matched blood, which was administered because no matched donor was available and the patient's condition was critical (the patient survived) (19, 20). Two studies each reported a case of hyperpyrexia to 107 °F shortly after transfusion (17, 19, 20). One study reported a case of phlebitis and generalized jaundice (23, 24). The overall rate of moderate to serious transfusion-related adverse events from studies (17, 19, 20, 23, 24) that provided quantifiable data was 4% (9 of 235 patients). Fatal and nonfatal adverse events related to underlying disease were reported in the treatment and control groups and included secondary bacterial pleurisies, empyemas, pneumonias (commonly hemolytic streptococcus), septicemia, meningitis, and undifferentiated delirium and psychosis.

Other Outcomes

All 8 studies reported a clinical judgment that a distinct and beneficial improvement often occurred in treated

Table 2. **Supplementary Data on Clinical and Laboratory Findings**

Study (Reference)	Study Group Diagnosis	Experimental End Point	Experimental Group			Control/Comparison Group			Notes
			Intervention	Patients with Study Outcome, *n/n (%)*	Findings	Intervention	Patients with Study Outcome, *n/n (%)*	Findings	
Stoll (17)	Influenza pneumonia	Post-transfusion improvement	Convalescent serum at 3.9 days (average)	23/32 (72)	–	Convalescent serum at 5.4 days (average)	4/24 (17)	–	2 groups of patients received early or late treatment; the early treatment group had a higher rate of post-transfusion clinical improvement
						Normal serum	5/28 (18)	–	28 patients were treated (early?) with "normal" noninfluenza convalescent serum; 4 showed improvement
Ross and Hund (19, 20)	Influenza pneumonia	Average leukocyte count on days 1 and 4	Convalescent serum	28*	Day 1: 5020 cells/mL Day 4: 11 790 cells/mL	Standard care	21*	Day 1: 4800 cells/mL Day 4: no change (range, 3000–6000 cells/mL)	Treated patients had a daily increase in leukocyte count and rapid resolution of fever; controls had no change in leukocyte count through day 4 and had prolonged fever; duration of fever was calculated from the time of first influenza illness until death or abatement of fever
		Average duration of fever			9.5 days			15 days	
McGuire and Redden (23, 24)	Influenza (no pneumonia)	Fever at 24 hours	Convalescent serum	0/3 (0)	–	Normal serum	5/5 (100)	–	Patients were randomly assigned to receive 100 mL of convalescent serum intravenously or 100 mL of "normal," noninfluenza convalescent serum intravenously; at 24 hours, patients who received influenza convalescent serum had a normal temperature and patients who received "normal" serum had the same or higher temperature; the 5 patients who received normal serum then received influenza convalescent serum and were afebrile within 24 hours

* Total number of patients.

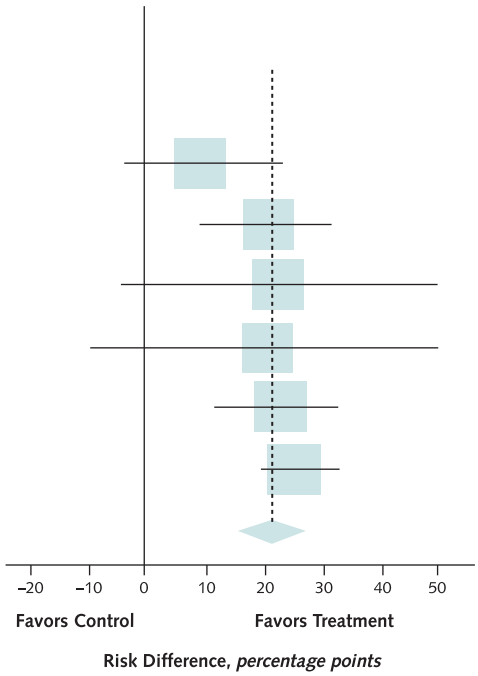
patients after transfusion (**Table 1**). The improvement was characterized by reductions in cyanosis, respiratory rate, nausea, vomiting, fever, malaise, or delirium within 2 to 24 hours after 1 or 2 transfusions. Distinct improvements were generally noted in patients who received early treatment but also occurred in some patients who received late treatment. One of the studies (17) reported that patients who received early treatment had a beneficial post-transfusion response (23 of 32 [72%]), whereas those who received late treatment (4 of 24 [17%]) or "normal" serum (5 of 28 [18%]) did not (**Table 2**). One study (19, 20) reported that 28 patients in the treatment group had more rapid resolution of fever (average duration, 9.5 days) and an increase in leukocyte count (average increase 3 days after transfusion, 7000 cells/mL) compared with 21 controls (average duration of fever, 15 days; no change in leukocyte count) (**Table 2**). In 1 study (23, 24), 8 patients with uncomplicated influenza were randomly allocated to receive influenza-convalescent serum (3 patients) or "normal" serum (5 patients) (**Table 2**). Twenty-four hours after transfusion, the 3 patients who received influenza-convalescent serum were afebrile, whereas the 5 patients who received normal serum had the same or higher body temperature. The 5 patients who received normal serum then received influenza-convalescent serum and were afebrile in 24 hours.

Data from Excluded Studies

Most excluded studies (**Appendix Table**, available at www.annals.org) reported that use of influenza-convalescent blood products was beneficial (27–29, 32–43). One large study at a U.S. Army recruit training hospital investigated the use of influenza-convalescent serum in patients with Spanish influenza but not pneumonia (27). The treatment group consisted of 26 patients with influenza who were selected on the basis of highest fever and clinical severity of illness and were compared with a control group of 219 concurrent patients with uncomplicated influenza. Compared with controls, treated patients had faster resolution of fever (average, 3.6 days vs. 5.8 days), fewer cases of pneumonia (1 of 26 treated patients [4%] vs. 30 of 219 controls [13.7%]), and fewer deaths (0 of 26 patients vs. 6 of 219 patients [3%]). In a published discussion forum, 2 commentators purported that this treatment approach was not beneficial on the basis of their experience (30, 31). It was unclear whether these commentators were treating bac-

Figure 2. **Absolute risk differences in mortality among patients treated with convalescent blood products and controls.**

Study (Reference)	Mortality Rate, *n/n (%)*		Risk Difference (95% CI), *percentage points*
	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)



Results favor treatment with convalescent blood products ($z = 7.1$; $P < 0.001$), and there was no statistical evidence of large heterogeneity ($Q = 7.0$; $I^2 = 29.3\%$; $P = 0.22$). The pooled estimate should be interpreted with caution and should not be generalized to other strains of virulent influenza without further study. Percentages have been rounded to the nearest whole integer. *In 2 studies with low mortality rates in the treatment group, the majority of patients were treated within 48 hours after pneumonia complicating influenza was diagnosed (18, 23, 24). McGuire and Redden (23, 24) reported a range of mortality rates of 30% to 60% among controls, and 30% was used in the analysis.

terial pneumonia or influenza pneumonia, and their commentaries lacked a complete description of important factors.

Discussion

Our analysis suggests that patients with Spanish influenza pneumonia who received transfusion with influenza-convalescent human blood products may have experienced a clinically important reduction in the risk for death and improvements in clinical signs and symptoms. Adverse effects included chill reactions and possible exacerbations of symptoms in a few seriously ill patients. Our subanalysis indicates that early treatment (after <4 days of pneumonia complications) was superior to late treatment (after ≥4 days of pneumonia complications). The mortality rate among controls and late-treated patients appeared similar and is consistent with the modern recognition that early definitive therapy for pneumonia and hypoxia is clinically important. Although we calculated a pooled estimate of possible effect, we urge caution in the interpretation of the summary estimate and do not think that it should be generalized to other virulent influenza strains without further study.

Our biological hypothesis for why mortality and morbidity may have been reduced is that the virus was neutralized by anti-influenza antibodies in the blood product. Rapid viral clearance would halt further replication and the stimulus for the cytokine cascade that is responsible for the acute respiratory distress syndrome. Reductions in the mortality rate may have also resulted from fewer secondary cases of bacterial pneumonia, empyema, and septicemia. Several human and animal studies (44–58) have reported protection with use of passively acquired anti-influenza antibodies and provide support for this hypothesis. Successful treatment of a pulmonary influenza virus infection in severe combined immunodeficiency mice with hemagglutinin-specific antibodies with very low virus-neutralizing activity in vitro (51) and in H5N1-infected mice with equine-derived H5N1 F(ab) fragments (52) provides direct evidence that anti-influenza antibodies are therapeutic in a model of severe disease.

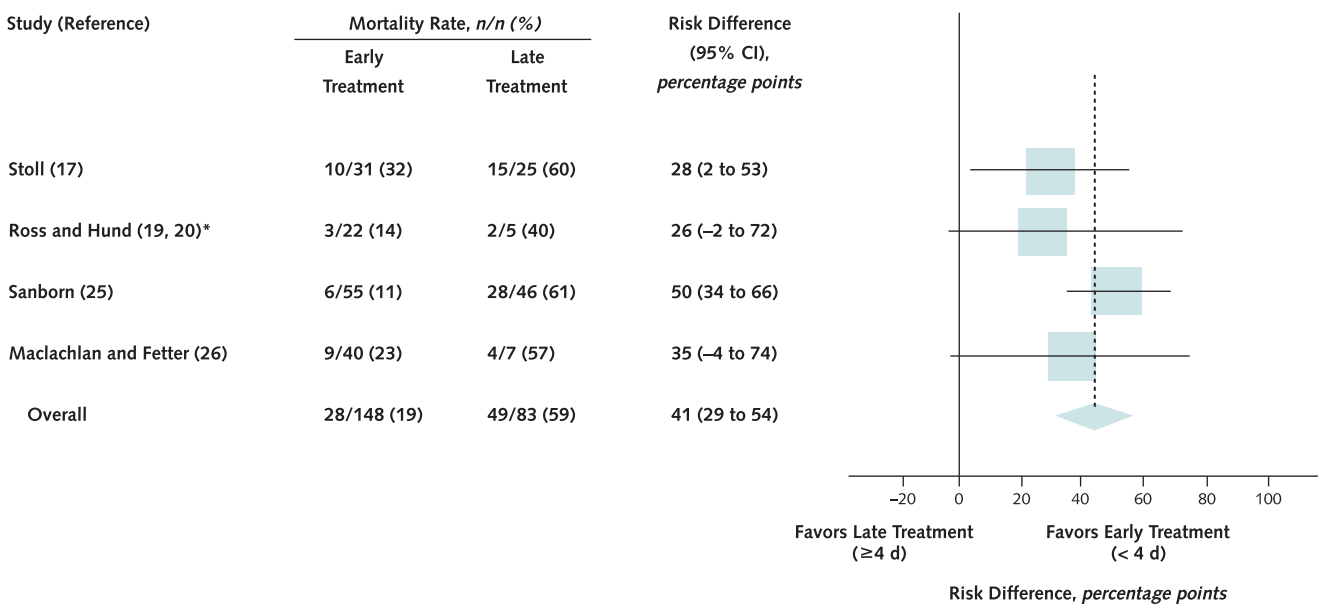
Our findings are provocative, but our review has important limitations. Studies were few, and the size of most was small. The medical and research practices of the 1920s are archaic by current standards. None of the studies was a blinded, randomized, or placebo-controlled trial. Treated patients were often selected on the basis of having more severe illness, and treatment regimens were not standardized. Although the Egger test did not detect statistical evidence of possible publication bias, this test is not a fool-

proof measure of publication bias, particularly when few studies are found. Moreover, we could not acquire and analyze every study. World War I coincided with the most intense waves of the Spanish influenza pandemic, and wartime censorship, death, or illness of investigators and rapid demobilization of drafted physicians may have prevented the publication of negative (or positive) studies. Therefore, publication bias may be present. Although survival or death while under direct observation for this acute and highly fatal disease is an easily determined dichotomous outcome that is resistant to misclassification, bias is always a concern in studies that are not randomized or blinded. For these reasons, we cannot establish a definitive judgment regarding the efficacy of this form of therapy for Spanish influenza and other virulent avian-like influenza strains (59).

However, current treatment options for H5N1 patients are unsatisfactory. In the event of a severe pandemic, antiviral agents, antibiotics, and intensive care medicine may be rationed or not available to most severely ill patients. Modern plasmatherapy may be an effective and practical health care delivery alternative. Large volumes of plasma are currently produced by existing hospital-based plasmapheresis and blood collection centers (60, 61), and U.S. Food and Drug Administration regulations (62) allow individuals to donate 1000 to 1200 mL of plasma per week. A single H5N1 convalescent donor could provide a weekly volume of plasma sufficient to treat multiple patients with H5N1 influenza. Donation is safe and entails few adverse events because the cellular components of the blood are returned to the donor under sterile conditions, and risks should not increase for convalescent donors. Locally produced plasma from convalescent donors or early vaccine recipients could be immediately effective in the event of a virulent influenza epidemic or other disease for which no good treatment exists. Plasma could also be processed into a frozen plasma product or a hyperimmune γ-globulin product and shipped to other regions for use during outbreaks or pandemics.

Current human H5N1 outbreaks are small, sporadic, and geographically distant. The comprehensive study of this treatment will probably require a global approach because a series of underpowered, nonstandardized, and nonrandomized case studies will not conclusively demonstrate or disprove efficacy. A central body of experts should be convened to consider H5N1 plasma therapy and to make recommendations regarding a research strategy and possibly treatment guidelines in the event that therapy is required before the research is completed. A standardized protocol could be created and then submitted by a consortium of international investigators to local or national investigational review boards. This effort would also aid in preparation of an application for an investigational new drug to such national regulatory agencies as the U.S. Food and Drug Administration. As a point of discussion, existing transfusion practices could be used to administer acute

Figure 3. **Absolute risk difference in mortality among patients who received early versus late treatment with convalescent blood products.**



Results favor treatment with convalescent blood products ($z = 6.50$; $P < 0.001$), and there was no statistical evidence of heterogeneity ($Q = 2.76$; $I^2 = 0\%$; $P = 0.43$). The pooled estimate should be interpreted with caution and should not be generalized to other strains of virulent influenza without further study. Percentages have been rounded to the nearest whole integer. *The treatment day of a fatal case could not be determined and was excluded from analysis of early versus late treatment (19, 20).

convalescent plasma to patients with H5N1 infection, in quantities of at least 1 to 2 mL/kg of body weight (9, 62). Larger treatment volumes may be necessary if the donor has been convalescent for a significant period owing to a reduced antibody titer. The information in **Table 1** forms the basis for this interim recommendation. According to the investigators (17, 18, 21, 23–25), plasma from 3 or more donors may be more consistently potent. Studies in animal models infected with H5N1 and H1N1 Spanish influenza strains (59, 63) could provide additional information in advance of a completed human trial.

In conclusion, patients with Spanish influenza pneumonia who received transfusion with influenza-convalescent human blood products may have experienced a clinically important reduction in the risk for death. Convalescent human H5N1 plasma could be an effective, timely, and widely available treatment for patients with H5N1 influenza during outbreaks and pandemics, and this therapy should be studied in clinical trials.

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Appendix Table. **Data from Excluded Studies***

Study (Reference)	Country	Study Group Diagnosis	Experimental Group		Control/Comparison Group		Notes
			Intervention	Patients with Study Outcome, *n/n (%)*†	Intervention	Patients with Study Outcome, *n/n (%)*†	
Francis et al. (27)	United States	Influenza (no pneumonia)	Convalescent serum	Death: 0/26 (0) Pneumonia: 1/26 (4)	Standard care	Death: 6/219 (3) Pneumonia: 30/219 (14)	All soldiers with influenza admitted to the hospital from 1–15 February 1920; treatment group was selected for highest fever and clinical severity and received 50–100 mL of serum intramuscularly immediately (most patients received 1 or 2 injections); the treatment group had rapid postinoculation improvement in signs and symptoms; the control group had a typical clinical course; average duration of fever: 3.6 days in the experimental group, 5.8 days in the control group
Redden (28)	United States	Influenza pneumonia	Convalescent serum	16/100 (16)	None	None	A series of patients referred for treatment who received an average of 120 mL of serum IV; the majority was treated early and required a single transfusion; 13 deaths were among late-treated patients (≥ 4 days); 3 deaths occurred among 13 pregnant women in their second or third trimester; rapid post-transfusion improvement occurred in most survivors
Jacobaeus (29)	Sweden	Influenza pneumonia	Convalescent serum	Unknown/70	Unknown	Unknown	Patients received 20–40 mL of serum IV (the majority received 1 to 3 transfusions); treatment seemed effective in patients with early cases but not in those with terminal cases
Lord (30)	United States	Influenza pneumonia	Convalescent serum	6/23 (26)	Standard care	3/25 (12)	Patients received an unknown volume of serum (IV?); the investigator stated, "There may have been extenuating circumstances in the treated cases"
Locke (31)	United States	Pneumonia with influenza	Convalescent serum?	10/25 (40)	Standard care	10/25 (40)	Case–control study of patients with "pneumonia with influenza" matched on "type" of disease; in that era, bacterial pneumonia was categorized as type 1 through 4 (by sputum and culture), and it is unclear what condition was treated; the treatment group may have received 120 mL of convalescent serum IV; the study found no benefit but also noted no adverse effects
Bass and Ervin (32)	United States	Influenza pneumonia	Convalescent whole blood	18/55 (33)	Unknown	Unknown	Patients received an unknown volume of whole blood or serum (IV?); the most severely ill patients in the wards were selected for treatment; treatment had marked value, but early administration was important
Simici (33)	Romania	Influenza pneumonia	Convalescent whole blood	4/24 (17)	Unknown	Unknown	Patients received 20 mL of whole blood (IV?); survivors had rapid improvement in signs and symptoms
Holst (34)	Sweden	Influenza pneumonia	Convalescent serum	7/20 (35)	Unknown	Unknown	Patients received 10–30 mL of serum intramuscularly; 10 patients had prompt improvement and survived; 10 patients had no immediate improvement; 7 patients died
Lesne et al. (35)	France	Influenza (no pneumonia)	Convalescent plasma	0/8 to 20? (0)	Unknown	Unknown	Patients received an unknown volume of convalescent plasma (IV?)
Ehrenberg and Barkman (36)	Sweden	Influenza pneumonia Influenza (no pneumonia)	Convalescent serum	2/8 (25) 0/12 (0)	Unknown Unknown	Unknown Unknown	Patients received 40 mL of convalescent serum IV

Continued on following page

Appendix Table—**Continued**

Study (Reference)	Country	Study Group Diagnosis	Experimental Group		Control/Comparison Group		Notes
			Intervention	Patients with Study Outcome, *n/n (%)*†	Intervention	Patients with Study Outcome, *n/n (%)*†	
Bang (37)	Norway?	Influenza pneumonia	Convalescent serum	2/10 (20)	Unknown	Unknown	Patients received a small amount of serum by an unknown route
Bogardus (38)	United States	Influenza pneumonia	Convalescent whole blood	2/6 (33)	None	None	Patients received an unknown volume of whole blood (IV?); 1 patient died within 12 hours; treated survivors had rapid improvement in signs and symptoms
Huff-Hewitt (39)	England	Influenza pneumonia	Convalescent serum	0/3 (0)	None	None	Patients received 15 mL of serum by an unknown route (IV?); all patients had rapid improvement in clinical signs and symptoms
		Influenza (no pneumonia)		0/1 (0)	None	None	
Miller and McConnell (40)	United States	Influenza pneumonia	Convalescent serum	0/3 (0)	None	None	2 children (8 and 11 years of age) and 1 woman received 6–13 mL of serum IV; the children had rapid improvement in signs and symptoms; the woman had gradual improvement
Brown and Sweet (41)	United States	Influenza pneumonia	Convalescent whole blood	0/2 (0)	None	None	1 woman in the third trimester (in labor; she gave birth to a living child) and 1 man received 60 mL of matched whole blood (IV?); both patients were treated on the third day of illness; transfusion resulted in rapid decrease in body temperature and pulse and increased leukocyte count
Carlyle (42)	England	Influenza pneumonia	Convalescent serum	0/1 (0)	None	None	A youth received 15 mL of serum by an unknown route and had gradual improvement in signs and symptoms
Liebmann (43)	Germany (?)	Influenza pneumonia	Unknown	Unknown	Unknown	Unknown	Treatment may have been beneficial

* Abstracted data were obtained from an excluded study, commentary, abstract, or translated synopsis of a non–English-language article. IV = intravenously.
† The experimental end point was death unless otherwise indicated. Percentages have been rounded to the nearest whole integer.