Mortality and Morbidity Among Military Personnel and Civilians During the 1930s and World War II From Transmission of Hepatitis During Yellow Fever Vaccination: Systematic Review

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During World War II, nearly all US and Allied troops received yellow fever vaccine. Until May 1942, it was both grown and suspended in human serum. In April 1942, major epidemics of hepatitis occurred in US and Allied troops who had received yellow fever vaccine. A rapid and thorough investigation by the US surgeon general followed, and a directive was issued discontinuing the use of human serum in vaccine production.

The large number of cases of hepatitis caused by the administration of this vaccine could have been avoided. Had authorities undertaken a thorough review of the literature, they would have discovered published reports, as early as 1885, of postvaccination epidemics of hepatitis in both men and horses.

It would take 4 additional decades of experiments and epidemiological research before viruses of hepatitis A, B, C, D, and E were identified, their modes of transmission understood, and their genomes sequenced. (*Am J Public Health*. 2013;103:e16–e29. doi:10.2105/AJPH.2012.301158)

DURING WORLD WAR I, SIG-nificant infectious hepatitis epidemics (caused by microbes later identified as hepatitis A and E viruses, predominantly hepatitis A virus) occurred among British, French, German, and Romanian troops deployed in the Middle East and Balkan theaters of war. US troops were not deployed in these areas, and the US Army had far less experience with infectious hepatitis.[1]

Yellow fever vaccine development began in 1928.[2] The 17D strain of yellow fever vaccine was developed in 1937. On January 30, 1941, the US adjutant general ordered that all military persons stationed in tropical regions of the Western Hemisphere be vaccinated against yellow fever.[3] In March 1942, large outbreaks of hepatitis and jaundice occurred in Allied Army personnel previously vaccinated against yellow fever.[1]

Until May 1942, yellow fever virus was propagated in cell cultures with human serum, and vaccine was stabilized with serum to maintain viability. On April 15, 1942, the US surgeon general, upon determining that human serum could transmit hepatitis from donors to vaccine recipients, ordered the omission of human serum from yellow fever vaccine production.[4] No further cases of hepatitis were henceforth attributable to yellow fever vaccine.[3]

OBJECTIVES AND LITERATURE SEARCH

We undertook a systematic literature review to determine

1. cases of jaundice and hepatitis reported after yellow fever vaccination during the 1930s and World War II;
2. how decisions were made about the manufacture, testing, and use of yellow fever vaccine;
3. the effectiveness of the investigations by the military medical authorities;
4. whether a comprehensive search of the literature would have helped military authorities and their key advisers, such as the Rockefeller Foundation, realize the risks of hepatitis to the troops;
5. whether US experiences with yellow fever in Cuba and Panama were relevant in World War II;
6. whether US authorities' knowledge of Japanese war goals could have resulted in fewer troops receiving yellow fever vaccination; and
7. how long after World War II hepatitis B virus was identified.

We identified studies through electronic database searching (the Cochrane Library, MEDLINE, EMBASE, BIOSIS Previews, Global Health, CAB Abstracts, the Lilacs Database of Latin American and Caribbean literature) and military libraries in Australia, Canada, the United Kingdom, and the United States. We scanned reference lists of included articles and consulted experts to identify additional studies for inclusion in this review. Searches included all languages, and no date limits were applied. Search terms are available from the authors. All studies were independently read by 2 reviewers and included in this review if they reported data on risk factors associated with serious yellow fever vaccination adverse events.

FINDINGS

We identified 2415 abstracts of articles, 82 of which were selected for full text review. We identified 70 books and monographs and included 19 of them.

Jaundice and Hepatitis After Vaccination

Anaphylactic reaction after yellow fever vaccination occurs within minutes. The other serious adverse events, yellow fever–associated neurologic disease and yellow fever–associated viscerotropic disease, occur 14 to 30 days after vaccination. Jaundice or hepatitis more than 30 days after vaccination is not a result of serious yellow fever vaccine–associated adverse events.[5] Only 1 study of outbreaks in specific units of US troops provided a denominator[6]; others investigated epidemics of jaundice or hepatitis some time after the troops were vaccinated and provided no denominators[7–14] (Table 1). Three

TABLE 1—Episodes of Jaundice or Hepatitis More Than 30 Days After Yellow Fever Vaccination, 1930s and 1940s

Study	Location and Date of Study	Nonicterogenic Lots: No. Vaccinated With 17D	Nonicterogenic Lots: No. of Cases of Jaundice	Icterogenic Lots: No. Vaccinated With 17D	Icterogenic Lots: No. of Cases of Jaundice	Not Specified Whether Lots Nonicterogenic or Icterogenic: No. of Cases of Jaundice	Interval Between Vaccination and Jaundice or Hepatitis		No. of Deaths
Military Personnel: Studies With Denominator in Specific US Troop Formations or Bases									
Gauld[6]	US Third Division, Fort Ord, CA, 1942 ("Vaccinated Spring 1942")	14 635	112		1365 (associated with lots 367, 369, 370)		"Within a few months"	NI	
Gauld[6]	19th Regiment Combat Engineers, Fort Ord, CA, 1942 ("Vaccinated Spring 1942")				1458	95		NI	
Military Personnel: Studies Without Denominator in Specific US Troop Formations or Bases									
Badger[7]	US troops May–December 1942, mostly stationed in UK[a]	No jaundice associated with 67 of 80 lots; in 5 other lots jaundice attack rate < 1%.		8 lots all with jaundice attack rate ≥ 3%.	1318		12–18 wk	NI	
Benjamin and Hoyt[8]			200					NI	
de Veer and Matzne[9]	US troops, "A Naval Hospital," spring 1942				30		4 mo		1
Freeman[10]	US troops, 1942, Fort Belvoir, VA; Fort Sill, OK; Fort Lewis, WA. (Vaccinated December 30, 1941, through March 9, 1942)[b]			Stable number of troops on station, 18 000–19 000 (but no actual denominator stated). Text implies all received yellow fever vaccine with lots 284, 329, 350, 364, 368, 369.	700		12.3 wk	NI	
Hayman and Reed[11]	US Army troops at 4th "General Hospital," April–September 1942					405 (16 lots, not specified)	100.1 d (range 66–210)		2

Continued

TABLE 1—*Continued*

Sawyer et al.[12]	US Western Defense Command, West Coast Air Corps Training Center, Ninth Service Command, Fourth Army troops on army bases in western US. Jaundice began second week March 1942. Medical investigating team on site March 21, 1942.				10 284 (lots 331, 334, 335, 338, 340, 350–351, 367–369); 1569 (other lots)	13–16 wk	31
Turner et al.[13]	US troops, Camp Polk, LA (June–September 1942)				4083 (lot 369)	9–23 wk	14
Walker[14]	US Army, January 1–December 31, 1942				51 337 (lots 331, 334, 335, 338, 367, 368, 369)	2–4 mo	NI
			Summaries for US troops in Sawyer et al.,[15] JAMA,[1] and Paul and Gardner[16]				
Sawyer et al.[15]	US army troops (cases of jaundice in questionnaires and correspondence, surgeon general, March 7 to "end of 1942")	2 333 760 (98 lots with rate ≤ 2/1000)	2399 (rate = 1.02/1000)			60–150 d	1
Sawyer et al.[15]				433 080 (lots with jaundice rate = 10/1000 vaccinees: 307, 329, 331, 334, 335, 338, 367, 368, 369)	23 664 (rate = 54.6/1000)	60–150 d	23 (+ 2 deaths in which lot not designated and 3 in which no vaccination recorded)
Sawyer et al.[15]				187 760 (lots with jaundice rate = 3–9/1000 vaccinees: 316, 317, 319, 322, 340, 349, 350, 355, 356, 370)	708 (rate = 3.77/1000)	60–150 d	2
Sawyer et al.[15]	US Navy, 1942	446 938 (50 lots; includes 21 365 vaccinated with lots where lot number not stated, involving 58 cases of jaundice)	593	17 995 (lots 244, 316, 329, 334)	98 (31 of these in 200 troops vaccinated with lot 334; rate = 5.45/1000)	60–150 d	
			Rate = 1.33/1000				

Continued

TABLE 1—*Continued*

JAMA[16]	US troops January 1–July 4, 1942; vaccinations = "2 to 2.5 million";	jaundice/hepatitis = 28 585 (rate = 11.43/1000 of 2.5 million vaccinees); death rate = 0.025/1000 vaccinees						62
Sawyer et al.[15] (total for US Army and Navy)	Vaccinations = 3 419 533[c];	jaundice/hepatitis = 27 462 (rate = 8.03/1000); death rate = 0.0082/1000 vaccinees						28[d]
Paul and Gardner[1] (total for 1942)	Vaccinations = 7 million;	jaundice/hepatitis = 49 233 (rate = 7.033/1000); death rate = 0.012/1000 vaccinees						84
Military Personnel: Studies With Denominators in Specific UK Troop Formations or Bases								
MacCallum and Bauer[18]	UK troops, 1942				125 troops (batch 207KY)	46	56–172 d	NI
McArthur[19]	UK naval personnel, British Hospital Ship, November 1942				244 (110 hospital staff, 134 ship's staff)	46 (45 among hospital staff, 1 among ship's staff)	91–161 d	0
McArthur[19]	UK naval personnel, ("cases received from another establishment")	200	57					0
Military Personnel: Studies Without Denominators in Specific UK Troop Formations or Bases								
Findlay et al.[20]	UK Army, Air Force Naval personnel in West Africa August 1941 to September 1943					689	101.5 (1 case 26 d)	NI
Civilians in Brazil, Bolivia, Colombia, UK, Virgin Islands: Studies With Denominators								
Findlay and MacCallum[21]	UK civilians (in past 4.5 years before November 1937)	2200	48				2–7 mo	NI
Findlay and MacCallum[22]	UK civilians, 1932–1937	3100	89				Average 2–3 mo (range, 36 d to 7 mo)	NI

Continued

TABLE 1—Continued

Fox et al.[23]	Brazil, Bolivia, Colombia, 1939–1940	1 303 100	0	19 495 (304 with lot 467; 9604 with lot 489; 9587 with lot 494)	987 (82 from lot 467; 736 from lot 489; 150 from lot 494)	Lot 489 average 17,0.8 wk, lot 494 average 20.4 wk (range 1–2 to 80 wk)	22
Fox et al.[23]	Brazil, Bolivia, Colombia, 1939–1940	39 684 with 17 other lots	93			Average 27.8 wk (range 3–4 to 72 wk)	2
McCallum and Bauer[18]				58 civilian volunteers (batch 207KY)	9	73–99 d	NI
Oliphant[24]	Civilians, Charlotte Amalie, St. Thomas, Virgin Islands 1942[e]			11 358 (lot 331)	1669	Average 103 d (range 75–130)	NI
Oliphant et al.[25]	Institution, Virgin Islands			189 (of whom 60 were vaccinated with lot 361)	20 (of whom 14 were vaccinated with lot 361)	Average 12.3 wk	NI
Total civilians		1 379 184; jaundice/hepatitis cases: 2915 (rate = 2.11/1000); deaths: 24 (rate = 0.0174/1000)					

Note. NI = no information provided regarding whether there were or were not any deaths attributable to yellow fever vaccination. Some military units were not named (presumably for security reasons to avoid providing the enemy with estimates of decreases in effective troop strength), so overlap in data cannot be entirely verified. However, Sawyer and the National Library of Medicine provide overall estimates for 1942.

[a]Lot 368 had same attack in 2 widely separated units (1 was a coastal artillery unit in which men lived "in close proximity 24 hours/day," but none of the 51 men who did not receive yellow fever vaccine became jaundiced).

[b]January–March 1942 pre-epidemic period (jaundice rate = 0.01/1000/wk); April–October 1942 epidemic period; troops who had received yellow fever vaccine (jaundice rate = 1.40/1000/wk); nonvaccinated troops (0.01/1000/wk). There were 2 peak weeks: March 24–30 (troops who had received yellow fever vaccine; jaundice rate = 8/1000/wk) and June 23–29 (5.50/1000/wk).

[c]Sawyer et al.[15] reported that 6 861 820 troops received yellow fever vaccine January 1941 through April 1942 (US Army, 2 954 600; US Navy, 1 688 720; "Africa," 1 819 000; "miscellaneous," 399 500; but outcome data were only provided for the army and navy vaccines). After changing manufacture to exclude pooled serum, 4 million more doses were given to the end of 1942. The administration in Africa was after an extensive outbreak of yellow fever (May–December 1940) in the Nuba Mountains of Sudan with 1500 deaths, and the British government requested large amounts of vaccine.

[d]Sawyer et al.,[15] for the 31 deaths reported, verified that 28 had received yellow fever vaccine (for 2 the vaccine lot was not designated) and for 3 there was no recorded vaccination. He stated that the 3 physicians involved "made every effort to verify the diagnosis." Turner et al.,[13] for all 14 deaths reported, established acute severe liver failure as the cause of death, as did de Veer and Matzne[9] for the 1 case they reported.

[e]A 10% sample (n = 1198) in Charlotte Amalie, the principal city of St. Thomas, was surveyed and 159 (14.7%) had symptoms of hepatitis, whereas only 3 (1.9%) got hepatitis of the 159 unvaccinated individuals in the sample. By extrapolation, 1669 of the total vaccinated sample would have had hepatitis.

studies provided overall estimates of jaundice or hepatitis rates and of death rates (respectively, per 1000 vaccinees) after yellow fever vaccination for different periods in 1942: Sawyer et al.,[15] estimates of 8.03 and 0.0082 for March to December; an editorial in the *Journal of the American Medical Association*,[16] 11.43 and 0.025 for January through July; Paul and Gardner,[1] 7.033 and 0.012 for the whole of 1942. Sawyer et al.[15] identified 98 nonicterogenic yellow fever vaccine lots (2 333 760 doses, 2399 cases of jaundice or hepatitis; rate = 1.02 per 1000, with 1 death), 10 moderately icterogenic lots (187 760 doses, 708 cases; rate = 3.77 per 1000, with 2 deaths), and 9 highly icterogenic lots (433 080 doses, 23 664 cases; rate = 54.6 per 1000, with 23 deaths). The troops had been vaccinated 60 to 150 days before jaundice occurred. A review of icterogenic lots identified several blood donors with previous "catarrhal jaundice."[15] In contrast to US Army troops, in the US Navy, 446 938 individuals were vaccinated with low icterogenic lots (593 cases of jaundice or hepatitis; rate = 1.33 per 1000, with no deaths) and 17 995 with 4 icterogenic lots (98 cases; rate = 5.45 per 1000, with no deaths).[15]

Hospital admissions of US troops for infectious and serum hepatitis (the original name for what was later determined to be hepatitis) in 1942 through 1945 totaled 182 383. The cases in 1942 (n = 49 233), which were nearly all caused by yellow fever vaccination, were what would later be identified as hepatitis B, C, or D (most likely B). The rest of the cases (28 872 in 1943, 27 783 in 1944, and 76 495 in 1945) were a result of infectious hepatitis (i.e., what was later identified as hepatitis A and E).[1] This

was most likely hepatitis A because the incubation periods determined in the World War II outbreaks were consistent with hepatitis A, but hepatitis E cannot be excluded because infection by both viruses from common fecal-oral and waterborne spread would have been possible. Hospitalization for serum hepatitis averaged 49 days[17]; adverse events after yellow fever vaccination in 1942 thus immobilized troops equivalent to 2.5 divisions, with infectious hepatitis in 1943 and 1945 accounting for an additional 6.5 divisions. We identified a limited number of studies of UK troops[18–20] and civilians[18,21–25] (average rate of jaundice or hepatitis = 2.11 per 1000; Table 1). The vaccine for the United Kingdom was 17D supplied by the United States, but the British assigned "batch numbers" rather than lot numbers.

Decisions Regarding Yellow Fever Vaccine

Expecting that the United States would declare war, in 1940 Colonel James Simmons, of the Office of the Army Surgeon General, asked the Rockefeller Foundation to increase yellow fever vaccine production to vaccinate all US troops going to tropical areas.[3,26]

Wilbur Sawyer agreed on behalf of the Rockefeller Foundation to increase vaccine production, but advised that the US Public Health Service should also produce a vaccine to provide additional capacity (which was not produced until June 1, 1942, almost 6 months after the United States entered the war).[3] While Sawyer was in Europe advising the American Red Cross, the president of the Rockefeller Foundation, Raymond Fosdick, informed the surgeon general that the foundation could produce, free of charge, all the vaccine the forces needed.

Although a serum-free vaccine had already been developed and administered in Brazil, thus eliminating episodes of vaccine-associated jaundice, and was known to the Rockefeller Foundation, it had not yet been fully field tested. As a result, Wilbur Sawyer and Johannes Bauer decided to continue with the Rockefeller Foundation vaccine (using pooled serum from New York donors). Because it was expected that large numbers of troops might be moved rapidly between theaters of war, and it was not known whether Japan would invade areas at risk for yellow fever, the decision was taken by the US military authorities to vaccinate all US troops. By early April 1942, 7 million doses had been provided to US and British forces. Once serum-free vaccine was introduced after April 1942, there were no further reported cases of hepatitis after administration of yellow fever vaccination among American troops.[3,26]

Effectiveness of Military Investigations

Because the US military had been little affected by hepatitis during World War I and the interwar period, the military did not anticipate that this would be a major concern and made no specific provisions to address this issue.[1] Instead, the authorities focused their research efforts on other infectious diseases. Three separate army commissions—Measles and Mumps, Neurotropic Virus Disease, and Influenza, with staff from the Universities of Michigan, Pennsylvania, and Yale, respectively—were directed to assess the etiology and transmission of these 3 diseases and to search for pathogens. They conducted experiments on conscientious objectors and state prisoners in Connecticut, Michigan, New Jersey, and Philadelphia, demonstrating routes of infection for these diseases.[1]

As the jaundice epidemic began in March 1942, the surgeon general on March 20, 1942, instructed Sawyer, Johannes Meyer, and Monroe Eaton to report to the surgeon of the Western Defense Command. They flew to San Francisco on March 21 and conferred that evening with the medical staff there responsible for treating troops with jaundice. Data from questionnaires for each jaundice case were tabulated, and physical examination and laboratory investigations were performed on a sample of cases. On April 13, 1942, the team recommended to the surgeon general that vaccinations with lots numbered over 330 be stopped for 2 months while investigations continued.[12] On April 15, 1942, the surgeon general issued an order immediately stopping the use of all yellow fever vaccine manufactured by the Rockefeller International Health Division.[4] The number of cases of postvaccination jaundice or hepatitis dropped dramatically.[27] Sawyer's full report in 1944[15] reviewed the literature on postvaccination jaundice or hepatitis, examined vaccine manufacture methods, identified the numbers of troops vaccinated and cases of jaundice attributable to each vaccine lot, and reviewed the clinical and laboratory data from field studies, data on hepatitis and vaccination in civilians, and the history of serum donors. Although the histories of two thirds of the donors were missing, the report was able to conclude that "all highly icterogenic lots of vaccine apparently contained a certain amount of serum from persons who had suffered from an attack of jaundice sometime in the past," and that "such persons had become more or less permanent carriers," inferring an attack rate of 6%. The report also noted that there were donors who had given no history of jaundice, and concluded that the carrier rate in the population could therefore be higher.[15]

Of the 24 donors who provided serum to the highly icterogenic lots 367, 368, and 369, 1 had had an attack of catarrhal jaundice the previous year. Estimating that the 250 milliliters of serum this donor provided could have entered 250 000 doses, the conclusion was that his serum could be icterogenic at a concentration of 0.001 milliliters. The report concluded:

> This would seem an incredible concentration, especially 1 year after the attack of the diseases, and would suggest there are no neutralizing antibodies developed in this disease. . . . . Conditions somewhat similar are known to occur in . . . infectious anemia of horses, where virus has been shown to be present in the blood many years after the recovery from an attack.[15(p83)]

At that time, "icterogenic" was used to mean "causing jaundice," and "homologous serum jaundice" was used to describe jaundice associated with within-species transfusions of serum or blood. Sawyer's report discussed the research by Findlay and MacCallum in England and by Fox in Brazil, but his research focused on US troops. We have not been able to find a government order in the United Kingdom similar to that of the US surgeon general stopping the use of human serum in yellow fever vaccine.

Effectiveness of a Literature Search

The earliest jaundice epidemic (with symptoms of fever, vomiting,

and stiffness) was noted by Hippocrates in the 5th century BC on the island of Thassos.[28] Jaundice in armies was so common that the French called it *jaunisse de champs* (battlefield jaundice) and the Germans *Kriegsikterus* (war jaundice).[29] During the 19th century, jaundice was reported during most campaigns, including Napoleon's campaign in Egypt and the Crimean War. During the US Civil War, it has been estimated that there were 52 427 cases of jaundice in the Union Army (33 per 1000) with a fatality rate of 4.4 per 1000.[29] Havens reported a higher estimate of 71 691 cases.[30]

Jaundice as an adverse effect of vaccination was noted as early as 1885 by Lürman[31] and Jehn[32] (Table 2), and in 1923 by Flaum et al.[33] (who hypothesized a virus as the cause). Jaundice following vaccination of horses was noted in 1919 by Theiler[34] and in 1937 by Marsh.[35] In a key article in 1937, Findlay and MacCallum[21] confirmed that jaundice following yellow fever vaccination was not caused by yellow fever, and hypothesized a virus was the cause.[22,36,37] In 1938, jaundice was noted after measles vaccination.[9,39] Numerous attempts were made to classify types of jaundice and hepatitis, and to create appropriate terminology. In 1912, Cockayne concluded, "It is almost certain that two diseases or groups of diseases different in etiology have been described under the title of epidemic or infectious catarrhal jaundice."[40(p2)] He noted in "epidemic catarrhal jaundice" that the occupational groups most affected were butchers, soldiers, and sewermen. It was associated with contaminated food and water, and in Alexandria, Egypt, it most affected those living where

TABLE 2—Studies of Syringe-Mediated Outbreaks of Jaundice and Hepatitis, 1885–1942

1885: Lürman[31] reported vaccination against smallpox by 6 physicians in 3 separate buildings of 1289 workers in the Weser shipyard in Bremen with glycerinized human lymph ("obtained at third hand from a pharmacist"). They used 4 different brass capsules each containing about 100 doses. The lancet was cleansed with 1% carbolic solution by a police official after each vaccination. Within 2–8 months, 191 men became jaundiced whereas none of the 500 men vaccinated with lymph from a different source became jaundiced. None of the family members of workers became jaundiced, and Lürman could not implicate the drinking water or schnapps.

1885: Jehn[32] described the vaccination of 5 groups of patients by 5 different physicians. Varying numbers became jaundiced (141/500, 35/446, 14/243, 1/50 and 0/87) at intervals ranging from 2 to 8 months.

1909: Arsphenamine was introduced for the treatment of syphilis. Jaundice was a complication (but often ascribed to the toxicity of the drug).[28]

1919: Theiler[34] noted that in 1914, 27 (2%) of 1148 horses inoculated (mostly with vaccine and serum) against horse sickness developed the "staggers" with acute liver necrosis 62–78 d later; in 1916 in a group of army horses, 4%–5% of 1411 died, and 210 of another group of 1154 horses on various farms.

1923: Flaum et al.[33] attributed an epidemic of 34 cases of jaundice in Lund, Sweden (including 28 patients in a diabetic clinic) to daily blood tests in the laboratory with lancets. He noted long incubation periods averaging 131 days. The other patients' food was cooked in the same kitchen, but they did not become jaundiced. He identified an unknown infectious agent as the cause: "Solange das Virus unbekannt ist, dürfte die Frage nach der Art der Verbreitung des Ansteckungsstoffes schwer zu lösen sein. Doch ist in höchsten Grade bekmerkenswert, dass die Epidemie so gut wie ausschliesslich Diabetespatienten und Personen betraf, die mit solchen Patienten in Berührung kamen." (So long as the virus is unknown, it must be difficult to solve the manner in which the infectious material is spread. It is in the highest degree notable that the epidemic involved only diabetic patients and those who came into contact with them.)

1937: Marsh[35] reported after an outbreak of western equine encephalitis in Montana that 5193 horses were vaccinated with the Nevada strain and serum and 156 with serum alone. Of these, 89 developed hepatitis 32–92 days later, confirmed by autopsy, and with 90% mortality. The symptoms were very different from the sleepy symptoms of encephalitis, with tremors and icteric mucous membranes, and the horses were restless and pushed through obstacles causing lacerations. Marsh commented on the small percentage (1.5%) with hepatitis.

1937: Findlay and MacCallum[21] noted that 48 of the 2200 patients who received yellow fever vaccine in the preceding 2½ years developed jaundice 2–7 months later, with the symptoms of "infective hepatitis" with prolonged jaundice and pale stools. The symptoms could not be attributed to yellow fever as there was an almost complete absence of fever, headache, or backache; yellow fever virus could not be obtained from the blood; and yellow fever immune body titers did not increase. They considered an organism injected with the virus or serum: "If the virus were introduced with the serum it must be present in the serum of apparently healthy human beings both in England and South America and in the serum of monkeys and horses. . . . If a hypothetical virus pathogenic for man were directly injected with the virus or serum inoculum it is surprising that under 3 per cent. of persons developed symptoms. Although the presence of a hypothetical virus cannot entirely be excluded the evidence against it is very strong."

1938: Soper and Smith[36] in Brazil noted that in 1936 and 1937 30% of the patients vaccinated with the 17E strain of yellow fever vaccine (cultured in human serum) who also received monkey hyperimmune serum became jaundiced, and queried the role of the serum.

1938: Findlay and MacCallum[22] reviewed 3100 individuals who received yellow fever vaccine and immune serum 1932–1937 and noted 89 cases of jaundice 2–3 months later. They noted that "in the case of human beings there is a widely-spread disease—common infective jaundice—the symptoms of which closely parallel those of the jaundice following yellow fever immunization." They concluded: "Thus, although there is presumptive evidence that in the case of man post-inoculation jaundice is identical with common infective hepatic jaundice, absolute proof is not yet possible."

1938: MacNalty[38] noted that 37 of 191 children given measles convalescent serum became jaundiced and 7 died.

1938: Propert[39] reported that 7 children in a mental institution given measles convalescent serum on June 1, 1937 (to protect them as they had recently been in contact with measles cases) all became jaundiced 78–83 days later and 3 died.

1940: Findlay[37] reviewed all the cases of hepatitis after yellow fever vaccination and concluded that the cause was a virus and that "the only possible source of the agent appeared to be the pooled and filtered human serum which had been used in the tissue cultures." He also reviewed the literature to date on infectious hepatitis and noted a virus as the likely cause and necrosis of the parenchymatous cells of the liver.

sewage flowed into the sea. Conversely, he concluded that catarrhal jaundice was not spread by food or water because infectivity persisted during epidemics when soldiers were no longer permitted water but given tea, in regiments whose food and water came from different sources, and in regiments who were moved to different parts of the country. He also noted that in the Verdun garrison, although food and water were from a common source, the illness was confined to 1 battery, and that epidemics were more common among men in the same barracks, part of a camp or 1 corridor of a barracks, and among schoolchildren within 1 school or class or children sitting next to each other. He thus identified contaminated food and water and feces as the mode of transmission of epidemic catarrhal jaundice but stated that catarrhal jaundice was not spread by these routes. He made no conclusions about causal agents or incubation periods.

In 1914, Cockayne again tried to define types of jaundice. He described cases of epidemic catarrhal jaundice with "a prodromal period of malaise with pains in the head and limbs, the enlargement of the spleen, and the albuminuria."[41(p218)] He was still uncertain of the etiology but stated that

> [It] should be classed with measles and mumps as one of the specific infectious diseases due to an unknown organism. It is still an open question whether the disease is a local one of the bile-ducts and liver or a general blood infection. With growing knowledge many diseases formerly regarded amongst the former class are now placed in the latter.[41(p218)]

He noted that cases in children occurred in families or in those sitting next to each other in school. No other infections were present to explain the symptoms, and there were no reported cases of children in other school districts. He thus identified an infectious cause resembling measles or mumps and again noted transmission by close contact, but erred in inclining toward airborne transmission.

In 1916, Willcox reviewed cases of jaundice in troops in the Mediterranean campaign, again identifying 2 types of jaundice: (1) epidemic jaundice (the common type), with abdominal discomfort, anorexia, nausea, mild fever, body pains "all over," pale stools and dark urine, and enlargement of the liver and spleen, noting that "Usually in the moderately severe cases of epidemic jaundice two months, or even more, would elapse before the patient was fit to return to active duty"; (2) catarrhal jaundice, with anorexia, nausea, epigastric discomfort, general malaise, no fever, jaundice, pale stools and dark urine, slight enlargement of the liver but an impalpable spleen, noting that "the general symptoms were slight, except that depression and general weakness were marked, and it was usually several weeks before the patient was fit for duty."[42] Again, no causes or incubation periods were identified.

In 1923, Flaum et al. reported an outbreak of jaundice among diabetic patients in a clinic in Lund, Sweden, with an average incubation period of more than 3 months.[33] He attributed transmission to lancets and not food (the other patients' food was cooked in the same kitchen but they did not become jaundiced). Pickles observed epidemics in 1929 and 1935 in Yorkshire villages.[43] He noted that the incubation period was 26 to 35 days and that patients could be infective before they became symptomatic; he identified the contacts of 39 of the 118 affected cases. He also noted that wives infected husbands but not vice versa, but he assumed that transmission was by airborne droplets, not food preparation.

In 1937, Findlay and MacCallum[21] provided the most detailed hypothesis yet about the cause of hepatitis. They reviewed 52 cases of jaundice after 2200 individuals received yellow fever vaccine:

> [S]ome extraneous organism might have gained entrance when the yellow fever immune serum or the virus was injected. Since both the yellow fever immune serum and the virus suspension were filtered through Seitz filters and were bacteriologically sterile after filtration the hypothetical organism would almost certainly have to be a virus. If the virus were introduced with the serum it must be present in the serum of apparently healthy human beings both in England and South America and in the serum of horses and monkeys and it must not be killed by the addition of 0.2 per cent. tricresol and 0.2 per cent. ether.[21(p302)]

In 1938, Findlay and MacCallum[22] reviewed 89 cases of jaundice in 3100 individuals who had received yellow fever vaccine and cases of hepatitis in horses after immunization against grass sickness and equine hepatitis; they came to the same conclusion: that a virus was the cause. In 1940, Findlay continued Cockayne's distinction between infective hepatitis and catarrhal jaundice and concluded, "This long incubation [4 weeks] is suggestive of a virus infection for there are a number of virus diseases with incubation periods of many months."[37(p78)]

In 1942, Fox et al. reviewed 140 cases of hepatitis after vaccination with icterogenic lots of yellow fever vaccine in Brazil, as well as other cases of postvaccinal hepatitis in man since 1885 and in animals, and concluded, "Serum or lymph from apparently normal human sources may convey to other human beings . . . and from horses to other horses, an agent capable of provoking serious parenchymal liver disease."[23(p100)]

In 1942, the US Surgeon General's Circular Letter No. 95 noted that episodes of epidemic jaundice in US troops were not caused by yellow fever, that no yellow fever virus had been recovered from body materials, that experiments were under way to transmit "the disease" with materials from patients who had received icterogenic yellow fever lots, and that serum donor lists were being analyzed on the assumption that serum carried an icterogenic agent.[27]

Previous Experience in Cuba and Panama

Experiments by American physicians in the late 19th and early 20th centuries to identify the yellow fever vector were essential for the development of methods to control the spread of yellow fever and for production of a yellow fever vaccine before World War II. Henry Rose Carter's meticulous recording of the timing of visits to patients[44] with yellow fever in a Mississippi town during a yellow fever outbreak in 1898 identified the obligatory extrinsic incubation cycle:

> [Carter noticed] a strange pattern: there was usually a period of twelve days to three weeks between the appearance of the first case of yellow fever in a community, and subsequent cases apparently derived from it. . . . By carefully noting visitors to the house, he established that those who came in the first two weeks were fine, but thereafter, and even when the original patient was removed, there was a risk of infection. Not only did this point to an insect vector, but it also established that the virus

needed a period of "extrinsic incubation" inside the mosquito before it became dangerous. This neatly explained the failure of Finlay's experiments.[45(p286)]

During the war with Spain in 1898, the US Army in Cuba experienced a yellow fever epidemic within a month of landing.[46] Major William Gorgas controlled the epidemic by cleaning and disinfecting houses with bleach, and removing dead animals and rubbish from the streets.[46] Rates of yellow fever, typhoid, and dysentery declined until 12 000 Spanish workers without exposure to yellow fever arrived in August 1899, whereupon yellow fever rates rose and the cleansing strategy made no difference.[45]

Physicians on the US Yellow Fever Commission observed that a prisoner was infected with yellow fever a month after incarceration and died 6 days later, but no cell mates (even those who slept on his bunk) became ill. Walter Reed reasoned that an insect had bitten the prisoner and then flown out.[45] The doctors on the Yellow Fever Commission and US Army volunteers tested this transmissibility hypothesis by exposing themselves to *Aedes aegyptii* mosquitoes; James Carroll became seriously ill and Jesse Lazear died of yellow fever. The fomite hypothesis was disproved when a doctor and 3 volunteers lived in a mosquito-proof building for 20 days (sleeping on bedding soiled with the "black vomit" of previous yellow fever patients) and none got yellow fever.[45]

Reed, on behalf of the Yellow Fever Commission, formally reported that the female *A. aegyptii* transmitted yellow fever.[47,48] Gorgas then embarked on a comprehensive fumigation and sanitation program. The number of deaths from yellow fever declined from 300 in 1900 to 18 in 1901.[49]

In September 1904, Gorgas went to Panama to control the epidemics of yellow fever hampering construction of the canal. During the French period of construction (1881–1889) more than 22 000 had died, nearly all from infectious diseases, and deaths from yellow fever had included many nonimmune French nationals.[49] Gorgas realized that different programs were needed for yellow fever and malaria:

> The *Aedes aegyptii* mosquito, which carries yellow fever, required clear freshwater to breed and had a limited range of flight in the open air. It easily transmitted disease in urban areas, particularly ones with poor drainage, but it was also easy to eradicate. The *Anopheles* mosquito, on the other hand, ranged for hundreds of yards and bred in freshwater protected by algae and grass. Gorgas's antimalarial efforts therefore need to be extended to suburban and wilderness areas around the canal. . . . [A]ll tall grass was cleared and all pools of standing water were drained within 2 hundred yards of individual houses in the Canal Zone. Where this was impossible, workers sprayed oil to kill the mosquito larvae. Where oiling failed, Gorgas applied a specially designed larvicide. . . . The Sanitary Department 125 used 700 000 gallons of oil and 124 000 gallons of larvicide every year in the areas of treatment.[49(pp124–125)]

With information that *A. aegyptii* prefers to lay eggs in clean water in manmade containers, Gorgas oiled water surfaces weekly, fumigated houses and removed water storage jars, encountering obstacles:

> [U]sually tenants simply emptied water vessels at the back door while the inspector was entering at the front. . . . As most Panamanians were immune to yellow fever they felt little compulsion to assist in the eradication program.[45(p294)]

Gorgas solved the water jar problem by arranging to provide running water to the major towns in Panama.[44]

The last case of yellow fever was recorded in Panama City on November 11, 1905, and in Colón, Panama, on May 17, 1906. In the Canal Zone, the overall death rate from infectious disease decreased from 56.7 per 1000 in 1885 through 1889 to 8.7 per 1000 in 1920 through 1924.[49]

The experiences in Cuba and Panama were relevant to protecting Allied troops in World War II from yellow fever because vaccine development was prompted by the adverse effects on civilians of living in those places. For highly mobile combat troops, vaccination was the key intervention, as they would have been moving so rapidly that attempts to control mosquito breeding areas would have been futile. The sanitation methods Gorgas devised to control mosquito breeding areas were relevant for protection against malaria and yellow fever of troops in barracks in World War II.

Japanese War Goals and Yellow Fever Vaccination

Japanese expansionism began with the First Sino-Japanese War (1894–1895), when China was attacked and Korea, Formosa (Taiwan), and southern Manchuria were occupied. In 1928, the Japanese attacked the Chinese Army in Manchuria and established a puppet state of Manchukuo (which provided coal and shale oil).[50] In1937, China was again attacked by Japan; the United States objected and was no longer willing to supply 80% of the 100 000 barrels of oil Japan needed daily even before World War II. After attacking the US fleet at Pearl Harbor on December 7, 1941, Japan went on to occupy the Philippines, Malaya, French Indo-China, Burma, the Netherlands Indies (a key supplier of world oil), and Manchukuo, under the name "Greater Asia Co-Prosperity Sphere."[50] The Japanese planned that the Aleutian, Wake, and Marshall Islands would form the eastern defensive perimeter of their empire and hoped that US forces would exhaust themselves against Japanese defenses.[51,52]

The Japanese did not intend to send troops to South America or Africa.[53,54] However, US authorities were not sure how much the Japanese had learned from their catastrophic defeat in 1939 in Manchukuo by the Russian Army under Zhukov[50] (which was likened to the defeat Hannibal inflicted on the Romans at Cannae) or, with the expansionist General Tojo in charge of the government, how far they would extend their battle lines to enlarge the empire. Early in 1940, Lt. Col. James S. Simmons, needing to define army policy on yellow fever vaccination, consulted the National Research Council Advisory Committee on Tropical Diseases. According to Long, "On the basis of his suggestions the committee recommended, in June 1940, that military personnel going into areas where yellow fever was suspected to exist be immunized."[3(p306)] In January 1941, the surgeon general recommended to the adjutant general that all military personnel in tropical regions of the Western Hemisphere be vaccinated:

> [I]t was anticipated that troops would be sent to certain South American countries where exposure to yellow fever was a likelihood. In addition, the possibility of introduction of this disease into areas where it did not exist at the time was stressed.[3(p306)]

It was also expected that troops would be deployed worldwide:

> Early in 1941 . . . the war was being bitterly waged in Africa and, although Japan had not yet declared war against the Allies, the possibility of troop movements to and from Africa, India and the East . . . was unpredictable although certainly possible. In particular, attention was called to the possibility of introducing yellow fever from Africa into India . . . which . . . would have been an epidemic calamity of the first order.[1(423)]

After war was declared on Japan on December 8, 1941, the US Armed Forces decided to vaccinate all troops.

Sawyer published all the prewar yellow fever immunity surveys and was the world authority on endemic yellow fever regions (Table 3).[55,56] The literature contains no discussion as to whether the army authorities consulted Sawyer with respect to the benefits and risks of vaccinating all troops.

Time to Identify Hepatitis B Virus

The complete identification of types of viral hepatitis and genome sequencing was not realized until 4 decades after 1942. During World War II, the US Military conducted vaccination research through 3 commissions: Measles and Mumps (Joseph Stokes and John R. Neefe, University of Pennsylvania), Neurotropic Virus Disease (W. Paul Havens Jr. and John R. Paul, Yale University), and Influenza (Thomas Francis, University of Michigan). The researchers transmitted "Mediterranean epidemic hepatitis" to volunteers from well water contaminated by feces and duodenal fluid, or blood or feces from patients with acute hepatitis. They noted that the incubation period (18–25 days) was much shorter than that for "serum hepatitis" resulting from yellow fever vaccination (90 days); that seasoned troops (and Egyptian soldiers from large cities) had lower attack rates; and that although an attack conferred immunity 6 to 9 months later, an attack of "serum hepatitis" did not confer immunity from "Mediterranean epidemic hepatitis."[1] Serum hepatitis was transmitted to patients via injections of serum[18,25] and intranasal washings.[57]

In 1944, Sawyer et al.[15] published the definitive report on the 1942 hepatitis epidemic following yellow fever vaccination among US troops and concluded that jaundice was caused by the presence of an unknown filterable virus in the blood of apparently normal donors whose serum had been included in the yellow fever vaccine. When the serum was excluded, postvaccination jaundice ceased.

In 1943, jaundice was noted following measles vaccination with 2 icterogenic lots (K60 and K488).[58] The British Army used 20 weekly injections of neoarsphenamine to treat syphilis, and in 1944 Beattie and Marshall noted that 50% of vaccinees became jaundiced.[59] The hypothesis was that imperfectly sterilized syringes transmitted the agent causing jaundice. The solution was to issue each patient 1 syringe for the entire duration of therapy. In 1948, the British Army summarized the experiences of transfusions during the 1944 Normandy campaign: those who received plasma subsequently had higher rates of jaundice than those who received whole blood.[60] The conclusion was that because serum from many donors was pooled, serum from a single donor could be distributed in 500 bottles of plasma. Despite the marked dilution in 500 bottles, an icterogenic agent was nevertheless being transmitted.[60] In 1948, Havens noted that key research barriers remaining were the inability to transmit hepatitis from humans to animals (thus there was no animal model) and the lack of an immunologic test or laboratory animal to detect hepatitis disease and subclinical carriers.[61]

During the years 1946 to 1950, the US occupation troops in Germany experienced a 9.5% hepatitis rate. It was realized that since the 18th century, Germany

TABLE 3—Endemic Yellow Fever Areas Before World War II

Region/Sera Types	Year of Last Epidemic
Sera with yellow fever immunity (as tested by intraperitoneal protection test in mice) in any age group	
Mexico: 1089 sera: 9% of sera of those aged 10–14 y, 29% of those aged 15–19 y, and 43% of those aged > 20 y positive.	1921
West Indies, Cuba: 1177 sera: all those from persons aged < 20 y negative; 8.4% of those aged > 20 y showed immunity.	Barbados 1916, Cuba 1908, Jamaica 1905, Puerto Rico 1900, Trinidad 1914
Central America: 1182 sera: 7% of sera of those aged 15–19 y and 29% of sera of those aged > 20 y positive.	El Salvador 1924, Guatemala 1924, British Honduras 1924, Honduras 1921, Nicaragua 1919
From Senegal 3300 miles to upper reaches of White Nile in Sudan and southwards to northern Angola and Belgian Congo (16 degrees north to 6 degrees south).	
Sera with no yellow fever immunity in any age group	
Italy, Spain, Portugal, Canada, United States	Italy 1820, Spain 1890, US 1899
Australia, Ceylon, China, Java, India,[a] Malaya, Philippines, Syria	
Morocco, Algeria, Tunisia, Egypt,[b] Ethiopia, British Somaliland, Southern Rhodesia, Bechuanaland, Union of South Africa, Kenya,[c] Madagascar, Tanganyika,[d] Zanzibar	

[a]Two adults aged > 20 y in 1 city (Chingleput) showed immunity.
[b]Two adults in Assyut showed immunity.
[c]One person in Kisii showed immunity.
[d]One person in Mwanza showed immunity.
Source. Sawyer et al.[55,56] Data not published for Latin America.

had been a focus of hepatitis epidemics, especially Bavaria (the main area of US occupation apart from Berlin). Paul and Gardner concluded that the dispersion of troops in small towns led to troops being in contact with civilians from whom they acquired hepatitis, particularly from children who had high rates of subclinical infection.[62] Paul and Gardner also noted that US "institutions for mentally deficient individuals" had high rates of hepatitis resulting from close personal contact. The highest rates were in units with "individuals with the lowest mental capacity in which the poorest sanitation can be maintained."[62] Paul recommended that the high rates of infectious hepatitis among US troops could be reduced by not eating in German households or eating establishments, and serum hepatitis rates could be reduced by boiling all instruments and needles for 15 minutes before vaccines were administered.[63] In 1952, Kaufmann et al. noted an outbreak of viral hepatitis 23 to 36 days after a cook in a US battery mess contracted hepatitis, strongly suggesting contaminated food as the source of this epidemic of infectious hepatitis.[64]

After US troops landed in Korea in 1950, hepatitis epidemics began, with high rates among susceptible new recruits.[17] In 1953, the World Health Organization recommended clarifying hepatitis terminology by using hepatitis A for infectious hepatitis and hepatitis B for serum hepatitis, thus unlinking nomenclature from the transmission method.[65]

Two studies followed World War II veterans who had received yellow fever vaccinations. Stebbins traced 367 blood donors of serum used in 1942 in 9 icterogenic yellow fever vaccination lots; 23 (6.7%) had a history of jaundice, none within the 9 months before donation, leading to the conclusion that the donors were carriers.[66] Stebbins also verified that there were no infections in the farms that had provided eggs in which the yellow fever vaccine was grown, and that individuals who received other vaccines grown on eggs from these farms did not get hepatitis after vaccination.[66]

In 1987, Seeff et al. traced 567 veterans vaccinated during World War II.[67] In group 1 (who received yellow fever vaccine stabilized with human serum in 1942 and became jaundiced), 97% were positive for antibodies to hepatitis B virus; in group 2 (who received yellow fever vaccine but remained well), 76% had antibodies; in group 3 (who received the new serum-free yellow fever vaccine), 13% had antibodies. The prevalence of hepatitis A antibody was similar in all 3 groups; none were infected by the delta virus.

A series of transmission experiments and epidemiological investigations, together with serological and electron-microscopic characterizations, clarified the modes of transmission of hepatitis A, B, C, D, and E viruses; 40 years after World War II, their genomes were sequenced (Table 4). Current textbooks emphasize the overlap in symptoms between the 5 types of hepatitis:

> [A]ll types of viral hepatitis produce clinically similar illnesses. Modes of transmission overlap, however, and a clear distinction among the different types of viral hepatitis cannot be made solely on the basis of clinical or epidemiologic features.[97]

LIMITATIONS

There are several potential sources of bias in these studies of military personnel. (1) The studies in 1942 focused on hepatitis epidemics, which usually occurred 3 to 6 months after 17D vaccination. Denominators of numbers vaccinated were often not reported, although the total number of US troops who received yellow fever vaccination in 1942 is known. (2) Troops sent to distant theaters of war may have had cases of hepatitis that were not enumerated. (3) Hepatitis B, C, or D can be transmitted through intimate contact via small skin

TABLE 4—Hepatitis Viruses: Discovery, Incubation Period, Transmission, Clinical Severity, and Chronicity

Characteristic	HAV	HBV	HCV	HDV	HEV
Discovery[68-96]	1973: Virus visualized on immune electron microscopy; 1979: grown in mammalian cells; 1987: genome sequenced.[68-71]	1964: Identification of antigen in leukemia patients; 1967: identification of Australia antigen; 1979: genome sequenced.[72-76]	1974, 1975: Parenteral non-A non-B hepatitis identified; 1978: transmission to chimpanzees; 1989: virus cloned; 1989: antibody assay.[77-86]	1977: Detection of delta antigen; 1980: association of delta antigen with hepatitis B; 1980: transmission of delta antigen to chimpanzees; 1987: genome sequenced.[87-92]	1978: non-A, non-B hepatitis transmitted and identified during epidemic in Delhi; 1970: partial cloning; 1991: genome sequenced.[93-96]
Incubation, d,[97] range (mean)	15–45 (30)	30–180 (60-90)[a]	15–160 (90)	30–180 (60-90)	14–60 (40)
Onset[97]	Acute	Insidious or acute	Insidious	Insidious or acute	Acute
Clinical severity[97]	Mild	Occasionally severe	Moderate	Occasionally severe	Mild
Fulminant,[97] %	0.1	0.1–1	0.1	5–20	1–2 (20% in pregnant women)
Progression to chronicity[97]	None	1%–10% (90% of neonates)	75%–80%	Common (invariable in HDV superinfection)	None

Note. HAV = hepatitis A virus; HBV = hepatitis B virus; HCV = hepatitis C virus; HDV = hepatitis D virus; HEV = hepatitis E virus.
[a]In two thirds of hepatitis B patients, no identifiable percutaneous exposure is identified. Hepatitis B surface antigen (HbsAg) has been identified in almost every body fluid of infected persons, although saliva is less infectious than serum.

abrasions and by any body fluid, and it can be difficult to assess whether cases are caused by transmission from an infected individual or vaccination.

CONCLUSIONS

Our conclusions, as keyed to the stated objectives of the study, are as follows.

1. There were 49 233 cases of jaundice or hepatitis reported among US troops in 1942 after yellow fever vaccination that were attributable to the serum in which the vaccine was grown and suspended.
2. Although a serum-free vaccine was available, the decision was made to vaccinate all troops with the vaccine containing serum.
3. The investigations by the military medical authorities of the jaundice epidemic were rapid, thorough, and resulted in the correct advice to omit serum from vaccine.
4. A comprehensive search of the literature in all languages would have identified 2 different types of hepatitis, and substantial numbers of cases of jaundice or hepatitis after vaccination going back to 1885.
5. US experiences with yellow fever in Cuba and Panama were relevant in World War II for mobile troops in combat because they prompted later vaccine research, and the vector control measures developed were relevant to troops stationary in barracks.
6. The Japanese war goal was the occupation of Asian countries that had the resources needed by Japan, and it was unlikely they would occupy Latin American countries.
7. Two decades elapsed after World War II until hepatitis B virus was identified in leukemia patients.

The official history of the Medical Department of the US Army ironically concluded that

> As far as the effectiveness of yellow fever vaccine in American troops is concerned, there is little that can be said. No cases of yellow fever occurred. Neither was there appreciable exposure to the disease. Yellow fever did occur sporadically in the general areas in which some troops were stationed both in South America and in Africa. However, it is not known that the disease actually occurred in sufficiently close proximity to army installations so that exposure actually took place.[3(p311)] ■

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Contributors

R. E. Thomas read, analyzed, and performed data entry from English and foreign language articles, and wrote the drafts of the article and the final text. D. L. Lorenzetti performed the literature searches. R. E. Thomas and D. L. Lorenzetti wrote the study protocol and obtained World Health Organization ethics approval. R. E. Thomas, D. L. Lorenzetti, and W. Spragins applied inclusion–exclusion criteria to abstracts and selected full text studies for inclusion in the review. R. E. Thomas and W. Spragins extracted data from published sources.

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Note. The scientific independence of the researchers was at all times maintained. The sponsors did not participate in the collection, analysis, or interpretation of data or in the writing of the report.

References

1. Paul JR, Gardner HT. Viral hepatitis. In: Coates JB Jr, Hoff EC, Hoff PM, eds. *Preventive Medicine in World War II. Volume III. Personal Health Measures and Immunization.* Washington, DC: Dept of the Army; 1955:411–443.
2. Stock NK, Boschetti N, Herzog C, Appelhans MS, Niedrig M. The phylogeny of yellow fever virus 17D vaccines. *Vaccine.* 2012;30:989–994.
3. Long AP. Vaccination against yellow fever. In: Coates JB Jr, Hoff EC, Hoff PM, eds. *Preventive Medicine in World War II. Volume III. Personal Health Measures and Immunization.* Washington, DC: Dept of the Army; 1955:306–313.
4. Surgeon General, United States Army. Jaundice. *Circular Letter No. 45,* May 13, 1942.
5. Monath TP, Cetron MS, Teuwen DE. Yellow fever vaccine. In: Plotkin SA, Orenstein WA, Offit PA, eds. *Vaccines.* 5th ed. New York: Elsevier; 2008:chap 36.
6. Gauld RL. Epidemiological field. Studies of infectious hepatitis in the Mediterranean Theater of Operations. VIII. Relation between vaccine jaundice and hepatitis I. *Am J Hyg.* 1946;43(3):310–313.
7. Badger TL. Hepatitis following yellow fever vaccination. *Proc R Soc Med.* 1944;37:456–458.
8. Benjamin JE, Hoyt RC. Disability following postvaccinal (yellow fever) hepatitis. *J Am Med Assoc.* 1943;128(5):319–324.
9. De Veer JA, Matzne MJ. Postvaccinal (yellow fever) jaundice: report of fatal case. *U S Nav Med Bull.* 1944;42:1381–1387.
10. Freeman G. Epidemiology and incubation period of jaundice following yellow fever vaccination. *Am J Trop Med Hyg.* 1946;26(1):15–32.
11. Hayman JM Jr, Read WA. Some clinical observations on an outbreak of jaundice following yellow fever vaccination. *Am J Med Sci.* 1945;209:281–296.
12. Sawyer WA, Meyer KF, Eaton MD, Bauer JH, Putnam P, Schwentker FF. Jaundice in Army personnel in the Western Region of the United States and its relation to vaccination against yellow fever. Part I. *Am J Hyg.* 1944;39(3):337–430.
13. Turner RH, Snavely JR, Grossman EB, Buchanan RN, Foster SO. Some clinical studies of acute hepatitis occurring in soldiers after inoculation with yellow fever vaccine; with especial consideration of severe attacks. *Ann Intern Med.* 1944;20(2):193–218.
14. Walker DW. Some epidemiological aspects of infectious hepatitis in the US Army. *Am J Trop Med.* 1945;25:75–82.
15. Sawyer WA, Meyer KF, Eaton MD, Bauer JH, Putnam P, Schwentker FF. Jaundice in Army personnel in the Western Region of the United States and its relation to vaccination against yellow fever. Parts II, III & IV. *Am J Hyg.* 1944;40(1):35–107.
16. Editorial. Jaundice following yellow fever vaccination. *JAMA.* 1942;119(14):110.

17. Havens WP Jr. The military importance of viral hepatitis. *US Armed Forces Med J.* 1952;3(7):1013–1022.

18. MacCallum FO, Bauer DJ. Homologous serum jaundice transmission experiments with human volunteers. *Lancet.* 1944;243(6298):622–627.

19. McArthur NM. An epidemic of hepatitis. *J R Nav Med Serv.* 1944;30(1): 18–22.

20. Findlay GM, Martin NH, Mitchell JB. Hepatitis after yellow, fever Inoculation. Relation to infective hepatitis. II. Immunology and epidemiology. *Lancet.* 1944; 244(6316): 365–370.

21. Findlay GM, MacCallum FO. Note on acute hepatitis and yellow fever immunization. *Trans R Soc Trop Med Hyg.* 1937;31(3):297–308.

22. Findlay GM, MacCallum FO. Hepatitis and jaundice associated with immunization against certain virus diseases. *Proc R Soc Med.* 1938;31(7):799–806.

23. Fox JP, Manso C, Penna HA, Pará M. Observations on the occurrence of icterus in Brazil following vaccination against yellow fever. *Am J Hyg.* 1942;36(1): 68–116.

24. Oliphant JW. Jaundice following administration of human serum. *Bull N Y Acad Med.* 1944;20(8):429–445.

25. Oliphant JW, Gilliam AG, Larson CL. Jaundice following administration of human serum. *Public Health Rep.* 1943; 58(33):1233–1242.

26. Wilbur A. Sawyer Papers. Controlling disease during World War II, 1939–1944. Profiles in Science, National Library of Medicine. Available at: http://profiles.nlm.nih.gov/ps/retrieve/Narrative/LW/p-nid/139. Accessed May 28, 2012.

27. Surgeon General, United States Army. Circular Letter No. 95: the outbreak of jaundice in the army. *J Am Med Assoc.* 1942;126(1):51–53.

28. Martin NA. The discovery of hepatitis A: a military perspective. *J R Army Med Corps.* 2003;149(2):121–124.

29. Boughton CR. Jaundice and war: viral hepatitis and other causes of jaundice in times of war. *Health History.* 2002;4(2):41–56.

30. Havens WP Jr. Viral hepatitis. *Yale J Biol Med.* 1961;34:314–328.

31. Lürman A. Eine ikterusepidemie. *Berliner klinische Wochenschrift.* January 12, 1885:20–23.

32. Jehn J. Eine icterusepidemie in wahrscheinlichem Zusammenhang mit vorausgegangener revaccination. *Deutsche Medizinische Wochenschrift.* May 1885;11:339–340, 354–356.

33. Flaum A, Malmros H, Persson E. Eine nosocomiale ikterus-epidemie. *Acta Med Scand.* 1926;(suppl 16): 544–553.

34. Theiler A. Acute liver-atrophy and parenchymatous hepatitis in horses. In: *The Fifth and Sixth Reports of the Director of Veterinary Research. Department of Agriculture, Division of Veterinary Research.* (Pretoria: Union of South Africa Government Printing and Stationery Office; 1919):7–164.

35. Marsh H. Losses of undetermined cause following an outbreak of equine encephalomyelitis. *J Am Vet Med Assoc.* 1937;91:88–93.

36. Soper FL, Smith HH. Yellow fever vaccination with cultivated virus and hyperimmune serum. *Am J Trop Med.* 1938;18:111–134.

37. Findlay GM. Infective hepatitis and catarrhal jaundice. *J R Army Med Corps.* 1940;74:72–79.

38. MacNalty AS. Acute infectious jaundice and administration of measles serum. In: *Great Britain, Ministry of Health, On the State of the Public Health. Annual Report of the Chief Medical Officer of the Ministry of Health for the Year 1937. Publication No. 42.* London, UK: His Majesty's Stationery Office; 1938.

39. Propert SA. Hepatitis after prophylactic serum. *BMJ.* 1938;2:677–678.

40. Cockayne EA. Catarrhal jaundice, sporadic and epidemic and its relation to acute yellow atrophy of the liver. *Q J Med.* 1912;os6(1):1–29.

41. Cockayne EA. Epidemic catarrhal jaundice. *Lancet.* 1914;184(4743): 218–220.

42. Willcox WH. The epidemic jaundice of campaigns. *BMJ.* 1916;1:297–300.

43. Pickles WM. *Epidemiology in Country Practice.* London, UK: John Wright & Sons; 1939.

44. McCullough D. *The Path Between The Seas: The Creation of the Panama Canal 1870–1914.* New York, NY: Simon and Schuster; 1977:413.

45. Parker M. *Panama Fever.* New York, NY: Doubleday; 2007.

46. Craddock WL. The achievements of William Crawford Gorgas. *Mil Med.* 1997;162(5):325–327.

47. Reed W, Carroll J, Agramonte A, Lazear JW. The etiology of yellow fever—a preliminary note. *Public Health Papers and Reports.* 1900;26:37–53.

48. The United States Yellow Fever Commission (1900–1901). Available at: http://yellowfever.lib.virginiaedu/reed/cmmissioon.html. Accessed July 18, 2012.

49. Maurer N, Yu C. *The Big Ditch. How America Took, Built, Ran, and Ultimately Gave Away the Panama Canal.* Princeton, NJ: Princeton University Press; 2011.

50. Coox AD. *Nomonohan. Japan Against Russia, 1939.* Stanford, CA: Stanford University Press; 1985.

51. Viale CR. Prelude to war: Japan's goals and strategy in World War II. US Army Command and General Staff College, Fort Leavenworth, Kansas, School of Advanced Military Studies. May 17, 1988. Available at: http://www.dtic.mil/cgi-bin/GetTRDoc?Location=U2&doc=GetTRDoc.pdf&AD=ADA202272. Accessed July 9, 2012.

52. Coakley RW. World War II against Japan. In: *American Military History. Army Historical Series.* Washington, DC: Office of the Chief of Military History, United States Army; 1989:501–528.

53. Hoyt EP. *Yamamoto. The Man Who Planned Pearl Harbor.* New York, NY: McGraw-Hill Publishing Company; 1990.

54. Hiroyuki A. *The Reluctant Admiral: Yamamoto and the Imperial Navy,* trans. J. Bester. Tokyo, Japan: Kodansha International Ltd; 1979.

55. Sawyer WA, Whitman L. Yellow fever immunity survey of North, East and South Africa. *Trans R Soc Trop Med Hyg.* 1936;29:397–412.

56. Sawyer WA, Bauer JH, Whitman L. The distribution of yellow fever immunity in North America, Central America, The West Indies, Europe, Asia and Australia, with special reference to the specificity of protection tests. *Am J Trop Med.* 1937;17:137–161.

57. Findlay GM, Martin NH. Jaundice following yellow-fever immunization. Transmission by intranasal instillation. *Lancet.* 1943;241(6248):678–680.

58. Homologous serum jaundice: memorandum prepared by Medical Officers of the Ministry of Health. *Lancet.* 1943;1: 83–88.

59. Beattie J, Marshall J. The aetiology of post-arsphenamine jaundice. *BMJ.* 1944;1(4346):547–550.

60. War Office. *Jaundice Associated With Syphilis Treatment and With Blood Transfusion. Statistical Report on the Health of the Army 1943–1945.* London, UK: HMSO; 1948.

61. Havens WP Jr. Infectious hepatitis. *Medicine.* 1948;27(3):279–326.

62. Paul JR, Gardner HT. Epidemiologic aspects of hepatitis in US troops in Germany 1946–1950. *Am J Med.* 1950; 5:565–580.

63. Paul JR. Viral hepatitis preventive and clinical aspects. *Med Bull U S Army Eur Command Med Div.* 1951;8(10): 445–448.

64. Kaufmann GG, Sborov VM, Havens WP Jr. Outbreak of infectious hepatitis, presumably food-borne. *J Am Med Assoc.* 1952;149(11):993–995.

65. *Expert Committee on Hepatitis. First Report. TRS 62.* Geneva, Switzerland: World Health Organization; 1953.

66. Stebbins EL. Jaundice IV. Distant appraisal of yellow fever vaccine hepatitis. *Tex State J Med.* 1951;47:146–148.

67. Seeff LB, Beebe GW, Hoofnagle JH, et al. A serologic follow-up of the 1942 epidemic of post-vaccination hepatitis in the United States Army. *N Engl J Med.* 1987;316(16):965–970.

68. Feinstone SM, Kapikian AZ, Purcell RH. Hepatitis A: detection by immune electron microscopy of a viruslike antigen associated with acute illness. *Science.* 1973;182:1026–1028.

69. Provost PJ, Hilleman MR. Propagation of human hepatitis A virus in cell culture in vitro. *Proc Soc Exp Biol Med.* 1979;160:213–221.

70. Cohen JI, Ticehurst JR, Feinstone SM, Rosenblum B, Purcell RH. Hepatitis A virus cDNA and its RNA transcripts are infectious in cell culture. *J Virol.* 1987; 61:3035–3039.

71. Martin A, Lemon SM. Hepatitis A virus: from discovery to vaccines. *Hepatology.* 2006;43:S164–S172.

72. Blumberg BS, Alter HJ, Visnich SA. A new antigen in leukemia serum. *JAMA.* 1965;191:541–546.

73. Blumberg BS, Gerstley BJS, Hungerford DA, London WT, Sutaik AJ. A serum antigen (Australian antigen) in Down's syndrome, leukaemia and hepatitis. *Ann Intern Med.* 1967;66:924–931.

74. Blumberg BS, Sutnick AI, London WT, Millman I. Australia antigen and hepatitis. A comprehensive review. *CRC Crit Rev Clin Lab Sci.* 1971;2:473–528.

75. Dane DS, Cameron CH, Briggs M. Virus-like particles in serum of patients with Australia-antigen-associated hepatitis. *Lancet.* 1970;1:695–698.

76. Galibert F, Mandart E, Fitoussi F, Tiollais P, Charnay P. Nucelotide sequence of the hepatitis B virus genome (subtype ayw) closed in *E. coli. Nature.* 1979;281:646–650.

77. Prince AM, Brotman B, Grady GF, et al. Long-incubation post-transfusion hepatitis without serological evidence of exposure to hepatitis-B virus. *Lancet.* 1974;2:241–246.

78. Feinstone S, Kapikian AZ, Purcell RH, et al. Transfusion associated hepatitis not due to viral hepatitis type A or B. *N Engl J Med.* 1975;292:767–770.

79. Alter J, Purcell RH, Holland PV, et al. Transmissible agent in non-A, non-B hepatitis. *Lancet.* 1978;1:459–463.

80. Tabor E, Gerety RJ, Drucker JA, et al. Transmission of non-A, non-B hepatitis from man to chimpanzee. *Lancet.* 1978;1:463–466.

81. Choo QL, Kuo G, Weiner AJ, et al. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. *Science.* 1989;244: 359–362.

82. Kuo G, Choo QL, Alter HJ, et al. An assay for circulating antibodies to a major etiologic virus of human non-A, non-B hepatitis. *Science.* 1989;244:362–364.

83. Kato N, Hijikata M, Ootsuyama Y, et al. Molecular cloning of the human hepatitis C genome from Japanese patients with non-A, non-B hepatitis. *Proc Natl Acad Sci U S A.* 1990;87:9524–9528.

84. Kato N. Genome of human hepatitis C virus (HCV): gene organization, sequence diversity and variation. *Microb Comp Genomics.* 2000;5(3):129–151.

85. Seeff LB. The history of the "natural history" of hepatitis C (1968–2009). *Liver Int.* 2009;29(suppl 1):89–99.

86. Houghton M. The long and winding road leading to the identification of the hepatitis C virus. *J Hepatol.* 2009;51: 939–948.

87. Rizzetto M, Canese MG, Aricò S, et al. Immunofluorescence detection of a new antigen-antibody system (delta/anti-delta) associated with hepatitis B virus in liver and in serum of HBsAg carriers. *Gut.* 1977;18:997–1003.

88. Rizzetto M, Hoyer B, Canese MG, Shih JWK, Purcell RH, Gerin JL. Delta antigen: the association of delta antigen with hepatitis B surface antigen and ribonucleic acid in the serum of delta infected chimpanzees. *Proc Natl Acad Sci U S A.* 1980;77:6124–6128.

89. Rizzetto M, Canese MG, Gerin JL, London WT, Sly LD, Purcell RH. Transmission of the hepatitis B virus-associated delta antigen to chimpanzees. *J Infect Dis.* 1980;141:590–602.

90. Rizzetto M. Hepatitis D: thirty years after. *J Hepatol.* 2009;50:1043–1050.

91. Wang KS, Choo QL, Weiner AJ, et al. Structure, sequence and expression of the hepatitis delta (delta) viral genome [erratum appears in *Nature.* 1987;328:456]. *Nature.* 1986;323:508–514.

92. Taylor JM. Structure and replication of hepatitis delta virus RNA. *Curr Top Microbiol Immunol.* 2006;307:1–23.

93. Khuroo MS. Study of an epidemic of non-A, non-B hepatitis: possibility of another human hepatitis virus distinct from post-transfusion non-A, non-B type. *Am J Med.* 1980;68:818–823.

94. Khuroo MS. Discovery of hepatitis E: the epidemic non-A, non-B hepatitis 30 years down the memory lane. *Virus Res.* 2011;161(1):3–14.

95. Reyes GR, Purdy MA, Kim J, et al. Isolation of a cDNA from the virus responsible for enterically transmitted non-A, non-B hepatitis. *Science.* 1990; 247:1335–1339.

96. Tam AW, Smith MM, Guerra ME, et al. Hepatitis E virus (HEV): molecular cloning and sequencing of the full-length viral genome. *Virology.* 1991;185: 120–131.

97. Dienstag JL. Chapter 304: Acute viral hepatitis. In: Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Online. Featuring the Complete Contents of Harrison's Principles of Internal Medicine.*18th ed. Access Medicine from McGraw-Hill. Available at: http://accessmedicine.com/resourceTOC.aspx?resourceID=4. Accessed July 8, 2012.