Vaccine Innovation: Lessons from World War II

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ABSTRACT

World War II marked a watershed in the history of vaccine development as the military, in collaboration with academia and industry, achieved unprecedented levels of innovation in response to war-enhanced disease threats such as influenza and pneumococcal pneumonia. In the 1940s alone, wartime programs contributed to the development of new or significantly improved vaccines for 10 of the 28 vaccine-preventable diseases identified in the 20th century. This article examines the historical significance of military organizations and national security concerns for vaccine development in the United States.

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WORLD WAR II VACCINE DEVELOPMENT PROGRAMS

World War II research and development programs generated many medical and technological innovations and the United States Surgeon General's Office (SGO) and the Office of Scientific Research and Development (OSRD) published volumes on their wartime achievements. The most celebrated wartime innovations include the development of blood substitutes such as plasma, the mass production of penicillin, and the development of insect repellents and insecticides, most notably DDT (1). Less noted, yet no less valuable to the future of public health, were wartime contributions to vaccine development. All told, these programs contributed to the development of new or significantly improved vaccines for 10 of the 28 vaccine-preventable diseases identified in the 20th century (A new vaccine is defined as the first safe and effective vaccine licensed to prevent a disease for which no form of active immunity was previously available).

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Under the auspices of the SGO and the OSRD, members of the military, academia, and industry came together to develop the first licensed vaccines for influenza, pneumococcal pneumonia, and plague. They developed an entirely new typhus vaccine after establishing that the former vaccine had lost potency and, in conjunction with the War Research Service (WRS), developed the first botulinum toxoid, and the first Japanese encephalitis vaccine. They also made significant improvements to the existing yellow fever, cholera, smallpox, and tetanus vaccines. Improvements to the safety of the smallpox and tetanus vaccines in particular facilitated the wider use of these vaccines in the general population after the war, making a significant contribution to public health.

Why were vaccine development efforts so much more productive during this period than any other period in the 20th century? In part, a sense of national urgency to defend against war-enhanced disease threats fostered unprecedented levels of federal support and a spirit of collaboration between military, industrial, and academic scientists. Additionally, targeted research and development programs administered under the federal government provided a governance structure that productively channeled this spirit of cooperation. However, the third and most underappreciated source of innovation derived from the participation of the military itself.

World War II vaccine development programs paired industrial vaccine developers with lead users of vaccine technologies – the military. Close collaboration with lead users typically fosters high rates of innovation because it provides the developer with valuable insights about product development and user needs (2). Working within the context of wartime urgency and governance structures, the military was well-equipped to furnish the vaccine industry with the tools it required to develop an exceptional number of new and improved vaccines.

Prewar Preparations

On the eve of World War II, the federal government began to make unprecedented investments in infectious disease research and vaccine

development through intra- and extra-mural projects conducted through the OSRD and the Army SGO. Funding for US Army medical research alone increased more than 100 percent between 1940 and 1942. The department received a total of $16,000 for 1940 and was slated for a total of $37,000 in 1942 (3). Federal investments were driven by the fear that another world war would generate new natural and intentional disease threats. This fear was predicated, in part, on the military's experience with the influenza pandemic at the close of World War I, which claimed between 20 and 50 million lives worldwide (4). Military populations had been particularly hard hit. According to one estimate, influenza accounted for nearly 80 percent of the war casualties suffered by the US Army during World War I (5–7). Dr. Thomas Francis Jr, chairman of a commission that coordinated research on the influenza vaccine during World War II described the manner in which war and disease had become connected in the minds of military planners after 1918: "The appalling pandemic of 1918 in the last months of the exhausting conflict of World War I, with massive mobilization of armies and upheaval of civilian populations, has irrevocably linked those two catastrophes. It demonstrated that virulent influenza may be more devastating to human life than war itself … the onset of another war inevitably recalled the specter of 1918 and the possibility that … [it] would again result in the epidemiologic conditions which would heighten the severity of influenza to a catastrophic level" (8,9).

Fears of deliberate disease also drove federal investments in biodefense research and development. War planners in the SGO reasoned that, "the devastation wrought by the natural partnership of war and pestilence has scarred the face of history so deeply that it is only logical that military men in search of offensive weapons should consider the intentional use of disease producing agents" (10). In devising a defense strategy, war planners often did not distinguish between the threat of natural and intentional forms of disease, in part because the distinction was difficult to make. The Spanish Influenza pandemic of 1918, for example, had been so severe, so unprecedented, and so devastating to US troops in particular, that a number of Office of Strategic Services (OSS) intelligence reports intimated that the Germans had deliberately unleashed the disease (11).

Military planners shared Dr. Francis's concern that a new war would unleash another influenza pandemic along with other natural and perhaps intentional infectious diseases. Dr. James Simmons, Chief of the Preventive Medicine Division in the SGO, was an early proponent of initiating a program to defend against biological threats. While stationed in Panama in 1934, he became so "impressed with the hazard of yellow fever and its possible intentional introduction that he prepared an informal plan to counteract such a move in the event of war" (12). In January 1941, fearing that yellow fever might be used against US troops for military purposes, Simmons recommended mandatory yellow fever vaccinations for all servicemen in tropical stations.

Pearl Harbor

The bombing of Pearl Harbor in 1941 brought a new sense of urgency to biodefense planning that had been underway since 1940. Under a heightened sense of fear and uncertainty regarding Axis activities, federal planners launched into full-scale offensive and defensive preparations for biological warfare. The effects of urgency were not, however, limited to the activities of the federal government. Government officials received many offers of assistance from industrialists and scientists in the civilian sector. Many of the ideological and practical barriers to closer collaboration between industrial, military, and academic institutions collapsed under the threat of war. Industry opposition to low-margin contracts, academic opposition to disrupted research and teaching schedules, and government and military opposition to a technocratic reorganization of the nation's research and development apparatus diminished under a common threat. Alfred Newton Richards, Chair of the Committee on Medical Research (CMR), which coordinated many vaccine development projects under the auspices of OSRD, marveled at the "unselfish zeal, cooperative spirit, and the competence with which our civilian investigators, laying aside more agreeable pursuits, entered into the attack on problems whose solution was vital to our fighting forces … . Never before, we believe, has there been so great a coordination of medical scientific labor" (13).

Intramural and extramural research projects were administered through the Army SGO, the civilian-led OSRD, and in some cases,

the civilian-led WRS. Members of the organizing WBC committee agreed from the start that defensive and offensive biological programs must be kept nominally, if not institutionally, separate. The SGO would administer defensive research programs and the WRS would direct offensive research. The Preventive Medicine Division of the SGO directed research programs through an international network of laboratories and through the Army Medical Graduate School (AMS) in Washington DC. The research branch of the AMS became the Walter Reed Army Institute of Research (WRAIR) in 1955. These programs were chiefly concerned with the diagnosis, prevention, and treatment of typhoid dysentery, typhus, and syphilis. In 1941, the Secretary of War, Henry Stimson, also created a Board for the Investigation and Control of Influenza and other Epidemic Diseases, or what was later known as the Army Epidemiology Board (AEB). In 1949, when the board became responsible for the Navy and the Air Force, it was renamed the Armed Forces Epidemiology Board. Also administered through the Preventive Medicine Division, this seven-member board directed 10 commissions of 100 civilian scientists to conduct research on diseases of military importance. These commissions enlisted the top infectious disease specialists in the United States, from universities, hospitals, public health labs, and private research foundations to conduct epidemiological surveys and to develop and test preventive measures against diseases such as influenza, meningitis, encephalitis, acute respiratory diseases, measles, mumps, pneumonia, typhus, and rickettsial diseases. The Board oversaw Commissions on Acute Respiratory Diseases, Air-Borne Infections, Epidemiological Survey, Hemolytic Streptococcal Infections, Influenza, Measles and Mumps, Meningococcal Meningitis, Neurotropic Virus Diseases, Pneumonia, and Tropical Diseases.

With the exception of the Respiratory Disease Commission, which had a laboratory at Fort Bragg, North Carolina, the War Department contracted civilian scientists to conduct research at their home institutions on a part-time basis. According to Dr. Bayne-Jones, Deputy Chief of the Preventive Medicine Division during the war, AEB contracts were designed to permit the Army to outsource research it was not qualified to perform and to gain access to "valuable services and facilities in the leading institutions in the country" (14).

Vaccine development projects were also coordinated under the OSRD's CMR through contracts to civilian scientists. The CMR was created by executive order in June of 1941 to supplement the efforts of the National Defense Research Committee. Together these two committees formed the OSRD. The CMR was created to tap expertise within the Division of Medical Sciences (DMS) at the National Research Council (NRC) because the NRC was not a government agency and by law could not obtain congressional funding to administer a large-scale contract research program.

Research and development (R&D) priorities were set under the auspices of the Division of Preventive Medicine in the Army SGO according to the scientific feasibility and the strategic military importance of the vaccine. Both the AEB and the CMR had access to outside scientific and medical expertise through advisory committees and professional networks. Outside experts often played an important role, vetting development projects for scientific feasibility before they received military sponsorship.

The AEB and CMR also worked closely with military planning committees to align what was feasible with what was needed. Individual members of the CMR, for example, held joint membership in the Division of Preventive Medicine in the SGO, in the Navy Bureau of Medicine and Surgery, the AEB, the CWS, the Office of the Quartermaster General, and in the Office of the Air Surgeon. In this manner, the CMR ensured that military needs were well articulated and accounted for in all R&D planning sessions.

Once R&D priorities had been set, most scientific, technical, and operational decisions lay with the commission directors contracted through the AEB and the principle investigators under the CMR. This practice was consistent with one of Vannevar Bush's (Director of OSRD) principles of research management, a practice that he often referred to as "giving a man his head". He argued that "this is more than a matter of scientific freedom, important though that principle is … it is entirely possible to give a man his head and yet to specify by agreement with him his objectives" (15). In this manner, scientists were given free reign to pursue vaccine development within the design parameters established through the SGO.

The programs also benefited from simple, direct reporting relationships between the scientists and the individuals within the

SGO, AEB, and CMR possessing the highest level of professional expertise and program authority. In each case, vaccine development programs placed operational program authority with those individuals who had the greatest professional expertise. This top-down management structure eliminated intervening layers of bureaucracy and contributed to speed and efficiency.

Pneumococcal Capsular Polysaccharide Vaccine

The pneumococcal capsular polysaccharide vaccine was one of the most radical innovations to come from World War II vaccine development programs. Not only did this vaccine target a previously unpreventable disease, but it also used an entirely new method to confer immunity. However, as was the case with most World War II vaccine development successes, a basic understanding of both the pathogen and the disease had already been well established before the US entered the war.

In 1927, Wolfgang Casper and Oscar Schieman published research in a Berlin medical journal demonstrating that vaccines made from purified pneumococcal capsular polysaccharides would immunize mice against infection from the pneumococcal strains used to make the vaccine. This article offered the first evidence that substances other than proteins could have antigenic properties. The concept of a capsular vaccine was preferable to whole-cell vaccines because the polysaccharide capsules alone are incapable of causing infection. Thomas Francis, Walter Tillet and Lloyd Felton at the Rockefeller Institute in the 1930s, conducted a series of laboratory and clinical studies to demonstrate the immunogenic properties of pneumococcal capsular polysaccharides. Their research identified the particular antigens on polysaccharide capsules responsible for inducing an immune response, and determined how to isolate and purify these antigens to produce a vaccine. Pilot vaccines were tested during the 1930s on volunteers in the West Coast Civilian Conservation Corps (16–18). These studies provided early evidence that types I and II polysaccharide vaccines offered sufficient levels of safety and efficacy.

Industry and academia lost interest in the development of a pneumococcal vaccine after the antibiotic sulfapyridine was introduced in 1939. Physicians began to substitute sulfonamides for the

previously widely used pneumococcal antisera. Sulfonamides were less expensive, easier to administer, and considered safer and more effective against a wide spectrum of pneumococci. All efforts to develop a new vaccine to induce active immunity would likely have come to a halt if the military had not had a continued interest in population-based preventive measures. Vaccines remained more attractive to the military for the simple reason that an effective vaccine would reduce the overall number of sick days for the armed forces more effectively than therapeutic measures. To this end, the AEB formed the Commission on Pneumococcal diseases to continue the search for a vaccine.

Thus, well before the wartime pneumococcal commission convened, the scientific feasibility of a vaccine had been established through previous efforts to purify polysaccharide capsules and to demonstrate their antigenic properties. The remaining challenge was organizational in nature. It consisted of coordinating the expertise and activities of the scientists, engineers, epidemiologists, and physicians to identify which serotypes were most prevalent in military populations, and to develop, scale-up, and test a vaccine containing these serotypes.

The pneumococcal commission conducted a survey of the most prevalent pneumococcal types in the military to determine the optimal composition for vaccine development. With this information in hand, Dr. Michael Heidelberger, a Colombia-trained immunochemist and a member of the AEB commission, supervised the production of purified polysaccharide at the pharmaceutical plant of E.R. Squibb and Sons. As large lots of purified polysaccharides became available, Dr. Heidelberger performed a series of small-scale clinical studies to determine the optimal dosage of polysaccharide required to obtain and sustain a sufficient immune response.

Once Dr. Heidelberger established consistent production standards and optimal dosages, the AEB was ready to test the efficacy of this new vaccine more broadly. The crowning achievement of wartime clinical research occurred under the auspices of the AEB, when Dr. MacLeod performed the first double-blind randomized clinical trial of a quadravalent pneumococcal vaccine for the military (19). The study enrolled over 17,000 men at the Army Air Force Technical School between 1944 and 1945, half of whom received the vaccine and the other half received a placebo. At the end of a

7-month observation period, four men in the experimental group contracted pneumonia, whereas 26 men in the control group contracted the disease. Dr. Heidelberger recalled that "the entire study, so beautifully organized and monitored under Colin MacLeod's direction, showed that epidemics of pneumococcal pneumonia in closed populations could be terminated within two weeks after vaccination with the polysaccharides of the causative types" (20). This study, according to Dr. Heidelberger, set the standard for all future clinical trials (20).

Influenza Vaccine

As with the pneumococcal vaccine, much of the scientific groundwork for an influenza vaccine was laid before the US entered World War II. In 1933, Patrick Laidlaw, at the National Institute for Medical Research in London, isolated a filterable virus from a patient with influenza and determined that this agent produced flu-like symptoms in a ferret. This agent became known as influenza type A. In 1940, Thomas Francis first isolated the type B strain of influenza. In the early 1940s Dr. Macfarlane Burnet in Australia developed methods for growing the virus in developing chick embryos. By 1941, several virologists had determined ways to quantify and titrate influenza-specific antibodies. Thus, by the time the SGO formed the Influenza Commission in 1941, investigators had already established the etiology of the disease and developed methods for the isolation, cultivation, and purification of the components for an influenza vaccine. Once the scientific feasibility of the vaccine had been determined, targeted research and development of an influenza vaccine proceeded apace. The remaining tasks consisted of determining methods to scale up the vaccine for industrial production and to evaluate it for safety and efficacy before it could be administered to the armed forces.

Thomas Francis, as director of the Influenza Commission, worked in concert with contracted CMR scientists and industry to develop a vaccine. The CMR issued contracts to investigate technical aspects of influenza vaccine development. Under these contracts, investigators determined conditions for improving virus yields from embryonated eggs and methods for improving titration accuracy, plus ultracentrifuge and electrophoresis purification. In particular, investigators

determined that fractionation with a Sharples centrifuge offered the best method for concentrating and purifying the virus on a large scale, far larger than the previously used elution and precipitation methods (21,22).

By 1945, CMR's production methods were accepted by the Army as an alternative to red cell absorption and elution methods that were used in 1944. Industry began widespread adoption of CMR production guidelines by mid 1945 and expanded production to meet civilian markets by early 1946. CMR's Sharples centrifuge purification techniques were considered state of the art in the industry until the 1960's, when zonal centrifugation technologies were transferred from military labs to commercial industry.

As new methods for vaccine production became available, Dr. Francis worked with industry to adopt and refine these methods to improve the potency and purity of vaccine lots for clinical trials. In particular, the AEB consulted with Parke Davis, Lilly, Lederle, Sharp and Dohme, and E.R. Squibb and Sons to produce sample lots of the vaccine. Dr. Francis would then test these lots in his own laboratory at the University of Michigan and provide feedback to industry in an effort to develop uniform standards for potency and purity.

Once a suitable vaccine had been developed and produced in large lots, the SGO authorized a large-scale clinical trial of the influenza A vaccine within the Army Specialized Training Program Units (ASTP). Dr. Francis conducted field studies with the vaccine under the auspices of the AEB to provide the first reliable proof of safety and efficacy. He observed that field trials at military installations afforded an ideal opportunity to assess the efficacy of the early vaccines developed by the AEB Influenza Commission; the installations "were stable populations and subject to constant, uniform observations. It was possible to obtain participation of entire units so that vaccinated persons and controls could be properly designated rather than depending upon the less desirable and unpredictable use of volunteers" (23).

Together with the CMR, industry, and the SGO, Dr. Francis and his team standardized the production procedures, record systems, observation procedures, and the viral and serological tests that would permit the uniform clinical study of more than 12,500 members of ASTP groups across the country. These men were

vaccinated in October and November of 1943, just weeks before an influenza epidemic hit the nation.

By early January, the influenza board was able to provide the first conclusive evidence of an efficacious vaccine against epidemic influenza A. In light of these findings, the SGO recommended the acquisition of 10,000,000 doses of the vaccine for the US Army in the event of another outbreak (24). Thus, the first influenza vaccine became available for general administration within the military within 2 years of initiating the research and development program.

In 1945, the AEB had an opportunity to demonstrate efficacy of the B-strain vaccine as well, when a wave of influenza B passed through the US Naval and ASTP units in November and December, which were already under observation at the University of Michigan and Yale University. The AEB was able to compare hospital admission rates between vaccinated and unvaccinated groups to demonstrate efficacy of the vaccine.

Anthrax Vaccine

Not all wartime vaccine development projects were highly successful. The experiences of Dr. Louis Julianelle at the Public Health Research Institute in New York City illustrate the problems that beset some development projects. Contracted by the WRS to investigate the bacteriological and immunological aspects of anthrax, Dr. Julianelle found himself challenging pre-existing knowledge of the disease more quickly than he could build from it. He began by testing the effectiveness of commercial antisera, only to conclude that these antisera could not mitigate anthrax infections. He subsequently determined that sulfa drugs were useless as well. Penicillin, however, was effective in high doses. As penicillin was in short supply, he then attempted, without success, to develop vegetative, capsular, and spore vaccines.

Dr. Julianelle reported to the WRS that "text-book accounts all indicated that the subject was pretty well closed as far as immunization, and specific serum therapy was concerned. It came a good deal as a surprise to discover how incomplete or unreliable was indeed the existing knowledge. Consequently, it has been necessary to rework a number of the more fundamental phases of

"N" [code for anthrax] with the result that progress has been slow and the lag period of relearning prolonged" (25).

In the absence of a clear understanding of development needs, the anthrax vaccine development program yielded to less efficient, and more flexible bottom-up decision-making processes characteristic of basic research programs.

Dr. Julianelle's experience was characteristic of many WRS vaccine development projects. While the WRS mimicked OSRD's administrative structure and targeted research strategies, it had a less impressive record in vaccine development. Botulinum toxoid was the only human vaccine to come out of the WRS program. This was due in part to the secrecy restrictions placed on research, which prevented investigators and administrators from engaging in the same level of information sharing that was possible in unclassified vaccine development programs. More significantly, WRS investigators lacked a basic scientific understanding of the pathogens under study because they were often asked to work with more exotic, low-incidence organisms such as coccidioides, brucellosis and tularemia that had not been extensively and systematically studied by the general scientific community. As Dr. Julianelle discovered, it was neither possible nor desirable to exercise top-down control on vaccine development projects before a basic scientific understanding of the disease and organism had been established. A poor scientific understanding of biological warfare diseases under investigation undercut targeted R&D objectives and demoralized WRS participants.

LESSONS FROM WORLD WAR II VACCINE DEVELOPMENT PROGRAMS

Top-down Governance

World War II vaccine development programs highlight the value of governance structures that enrolled military, academic, and industrial scientists under project managers with defined development goals. While the threat of war contributed to the initial collaborative arrangements that fueled World War II vaccine development programs, the governance structure of these programs ensured their success.

Vaccine development requires contributions from a variety of disciplines ranging from epidemiology, pathology, immunology, bacteriology, and virology, to bioprocess engineering. Wartime development programs united individuals with this diverse range of expertise under a clear objective: to develop, test, scale-up, and manufacture a set of specified vaccines. The top-down organization of these programs permitted the rapid integration and application of existing knowledge to vaccine production. This organizational structure accelerated traditional technology transfer, as the OSRD, SGO, and WRS were in a position to transfer people, technology, and ideas to the projects that needed them most. Top-down administrative structures also ensured that research objectives met military needs. Research and military objectives were so well coordinated, in fact, that some vaccines were developed for specific military missions. The botulinum toxoid, for example, was developed for D-Day in response to OSS reports that the Germans may have loaded V-1 rockets with the toxin. Similarly, the Japanese encephalitis vaccine was developed in anticipation of a land invasion of Japan.

When the underlying scientific principles were well established, these programs were able to develop and deliver a large number of pragmatic vaccine innovations in a short time. Difficulties arose whenever a program attempted to apply its top-down governance structure to projects that required more than the straightforward application of previous findings. As the anthrax vaccine development effort demonstrated, anthrax research was in its infancy and the project would have benefited from the bottom-up, investigator-initiated structure that fosters basic scientific research.

In 1945, James Conant, former director of NDRC under Vannevar Bush and then president of Harvard University, gave a succinct summary of the method and rationale behind OSRD's successful ventures. In a letter to the editor of the *New York Times* he wrote, "There is only one proven method of assisting the advancement of pure science – that of picking men of genius, backing them heavily, and leaving them *to direct themselves*. There is only one proven method of getting results in applied science – picking men of genius, backing them heavily, and *keeping their aim on the target chosen*. OSRD … had achieved its results by the second procedure which is applicable to government-financed research in war time because the

targets can be chosen with a reasonable degree of certainty… .its objective was not to advance science but to devise and improve instrumentalities of war" (26).

As Conant's comments suggest, the success of World War II vaccine development programs was due less to scientific breakthroughs than to the ability of these programs to distill and apply existing knowledge for new vaccine candidates. In many cases, the basic knowledge required to develop a new vaccine had been available since the 1930's. Barriers to the development of these vaccines were therefore not scientific but organizational in nature. These barriers were best overcome by the coordination provided by targeted research and development programs.

Lead Users

The World War II experience also reveals the value of the military as a vaccine development partner for academia and industry. While the military made important contributions to product development through their targeted governance structure, much of their value as a development partner stemmed from their status as a lead user of vaccines. Lead-users refer to "organizations or individuals that are ahead of market trends and have needs that go far beyond those of an average user" (27). The military had, and continues to have, vaccine performance needs that exceed those of the general population. In addition to the need to defend themselves against the threat of biological weapons, military personnel have greater than average protection needs for natural diseases.

In nearly every war prior to World War II, more men in the US Armed Forces have died from disease than from battle wounds (28). As one historian observed: "more than one great war has been won or lost not by military genius or ineptitude, but simply because the pestilence of war – from smallpox and typhoid to cholera, syphilis, diphtheria, and other scourges – reached the losers before they infected the winners" (29). Whether at peace or at war, military settings foster high rates of infectious disease. Training camps and battlegrounds bring men from different geographical regions into close contact with one another. These men are often stressed, exhausted, and may be wounded. Camp conditions breed new

diseases and magnify the effects of common diseases, boosting their incidence and spread (30). For the military, therefore, fighting disease is, and always has been, equally important, to fighting the enemy.

Military organizations have long-respected the importance of effective disease control to military success. American armed forces have pursued vaccine-mediated defensive measures since the Revolutionary War. Smallpox was cited as a factor in the failure of the Continental Army to capture Quebec. In an effort to protect against similar future losses, General Washington gave orders for the variolation of his entire army in 1777. Military organizations continued to suffer tremendous losses from infectious diseases in the Civil War and later in the Spanish-American War, where the ratio of disease to battle casualties was approximately five to one. Typhoid fever accounted for the majority of disease casualties, with 20,738 reported cases in the Spanish-American War. Severe losses inspired the US Army to sponsor the research of Major Fredrick Russell, who succeeded in developing the first effective typhoid fever vaccine several years after the war.

Scientists and physicians working in military contexts had extensive experience with communicable disease and they were able to provide clear direction on research objectives and development needs, as was the case, with the pneumococcal and influenza vaccines. They were particularly adept at helping academic scientists and industry to bridge the "basic-applied" gap between basic knowledge of which pathogens cause which diseases and the mechanics of how to develop and manufacture vaccines. Unlike their academic counterparts, scientists working in the military context often shared industry's product development orientation. They were skilled at isolating and culturing pathogens, and developing pilot lots of vaccine for testing. In this manner, they were strong where industry was weak. Once military-contracted scientists were able to develop vaccine candidates, industrial engineers and scientists applied their talents to scale-up production for large-scale testing and licensing. Working together, military-academic-industrial development teams overcame hurdles that would have thwarted development if each group had worked in isolation.

Scientists and physicians working in military contexts were also skilled at identifying new diseases in military populations and

determining their etiology. As they were treating demographically homogenous populations that ate, slept, and worked under similar environmental conditions, they were quicker to identify population level characteristics of new and familiar diseases than were civilian scientists and physicians.

Military installations, with advanced record-keeping systems and high disease rates within controlled populations, offered both a testing ground and a market for new vaccines. One member of the SGO Preventive Medicine Division noted that "the practitioner of military preventive medicine has at his disposal information on morbidity of a quality not available in any other social organization; records of admission to hospital and quarters are a part of the military system. These data permit sound evaluation of non-effectiveness and of the reasons for discharge for medical disability" (31). Under these conditions, the AEB was able to provide the first reliable demonstration of the safety and efficacy of the newly developed plague, botulinum toxoid, Japanese encephalitis, pneumococcal, and influenza vaccines.

Even in the absence of well-planned clinical trials, the widespread use of a vaccine in military populations often offered *de facto* evidence of safety and efficacy. For example, the military experienced such high rates of safety and presumed efficacy with their tetanus vaccine that, in the absence of formal clinical trials, in 1944, the American Pediatric Association recommended the routine use of the vaccine in the general population.

The military's experience also revealed problems and guided improvements to vaccines before they were administered to the general population. Pre-war versions of the tetanus vaccine were highly reactogenic but in-house research conducted by the SGO Preventive Medicine Division identified peptones in the vaccine broth as the likely culprits for the allergic reactions. In response to this finding, the SGO contracted Dr. Mueller at Harvard Medical School to develop a synthetic alternative to broths containing peptones. Industry adopted the new process formula and began to fill military contract orders.

Similarly, widespread use of the yellow fever vaccine at the beginning of the war revealed the dangers of using human serum to stabilize vaccines, as many lots of the vaccine contained hepatitis B-contaminated serum. In response to the military's experience, the

PHS developed a safer, non-serum-based version of the vaccine in 1942.

Despite their proven safety and efficacy, many of the vaccines that came out of World War II development programs were commercial failures. The military often encouraged industry to develop vaccines well before commercial markets could support industry participation. In many cases, such as with Japanese encephalitis and yellow fever vaccines, US market needs never caught up with military needs. The civilian market for these vaccines was, and remains, small due to the low incidence of these diseases in North America. The market is therefore limited to travelers and a handful of laboratory workers. In other cases, such as the pneumococcal vaccine, the civilian demand did eventually catch up with the military demand as antibiotic resistance spread, but it was too late for industry to recoup their financial losses. Civilian doctors, who prefer therapeutic to preventive measures as a general rule, became convinced of the efficacy of antibiotics in treating pneumococcal infections. Squibb, which had invested millions in new plants to produce the vaccine, could no longer afford to stay in the pneumococcal vaccine business, and, in 1954, the company terminated the production of the vaccines. Two AFEB members, Dr. Robert Austrian and Dr. Jerome Gold, revived interest in pneumococcal vaccine development when they produced evidence that on average 17% of the patients died from bacteremic pneumococcal infections despite early treatment with antibiotics such as penicillin. Due in part to this research and growing evidence of antibiotic resistance, commercial interest in pneumococcal vaccines resumed by the 1970s, but it was far too late for Squibb to recover from its financial losses. It is notable, therefore, that industry managed to develop these vaccines in the absence of specific in-house capabilities and significant commercial incentives for vaccine development. In each case, direct contributions from World War II vaccine development programs played a significant role.

In sum, World War II vaccine development programs generated high rates of innovation in part because they were able to harness war-wrought urgency to develop new vaccines under an effective governance structure for product development and in part because they leveraged the military's talent for vaccine development. The World War II experience highlights the value of targeted R&D for

generating biomedical countermeasures of high national security importance within a short time frame. These programs were noteworthy, not for their ability to generate new scientific insights, but for their ability to consolidate and apply existing knowledge to a set of clearly defined and prioritized development objectives. The World War II experience also highlights the value of the military as a lead-user of vaccines of national security importance. As a lead user, the military anticipated problems with existing vaccines and vaccine candidates, and they were able to predict future vaccine needs. Unlike their academic counterparts, military research scientists often had an interdisciplinary product development orientation and were able to provide early-stage vaccine development expertise. In this role, the military proved particularly well suited to help industry bridge the gap between early- and late-stage vaccine development. Pairing the complementary skills of military and industrial research scientists in this manner, wartime development programs generated an unprecedented number of vaccine innovations.

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