

Research Synthesis: Biosecurity Research and Development (R&D)

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Introduction

This work was undertaken to synthesize existing evidence on biomedical research and development (R&D) conducted by the military sector and/or relating to health security. The military is a known actor in technological or defence R&D, but its role in the (global) health R&D arena is not widely understood. The actors in biosecurity R&D have expanded beyond military agencies and evolved along with paradigms of health security.

This synthesis starts with a historical overview of military R&D, then turns to other health actors as they became increasingly involved in biosecurity R&D in recent years. The terms “biosecurity” and “biodefense” are often used for different purposes in different contexts but generally refer to “measures or protection against biological threats”. We use the term “biosecurity R&D” in this paper to refer to the development of medical products and strategies to address biological threats to security. The products are often referred to as “medical countermeasures (MCM)”, and include drugs, vaccines, and devices to diagnose, treat, prevent, or mitigate potential health effects of exposure to chemical, biological, radiological, and nuclear (CBRN) agents and emerging infectious diseases, such as pandemic influenza.¹ Biosecurity R&D aims to prepare for public health emergencies that impact national security, and are typically considered “mission-driven”, such as the Manhattan Project or the quest for penicillin.

The literature on biosecurity R&D is *considerable*^{*}, yet fragmented and dispersed. It includes both military and non-military entities as actors and focuses broadly on two areas: intentional use of CBRN agents to harm health, i.e., bioterrorism (CBRN) and unintentional spread of infectious diseases or pathogens of pandemic potential. Our literature search was limited to the English language. The literature we found focused predominantly on the United States (U.S.), which, therefore, is also the focus of this paper, unless stated otherwise.

¹ The term medical countermeasures also include technologies that might assist the development or use of medical countermeasures. CBRN agents can be natural, accidental, or intentional in origin.

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Search terms

Search was conducted using a combination of search mechanisms, mainly in English, with no specific time period of publication. Terms used include “military research”, “biodefense”, “biosecurity”, “bioterrorism”, “outbreaks”, “research and development”, “military medicine”, “health technologies”, “medical countermeasures”, and “emerging infectious diseases”.

Summary of the contents

The synthesis of the literature is organized into the following topics:

1. The historical context of biosecurity R&D
2. Actors and stakeholders in biosecurity R&D
3. Scope and prioritization of biosecurity R&D
4. Funding, incentives, and landscape of biosecurity R&D
5. Concluding remarks

Synthesis of the literature

1. The historical context of biosecurity R&D

Historically, biosecurity R&D is deeply intertwined with the military. Biomedical military research has often been claimed to be the engine of progress in medicine and surgery (Rasmussen, Reilly, and Baer 2014). Many critical medical milestones originated from the military experience, notably the triage system, wound dressing/management, antibiotic therapy, and various vaccines (Licina 2012). Military R&D typically falls under the mandate of “force health protection”, while any population health benefit is considered ancillary (Grabenstein et al. 2006).

Historically, the military has had a long-standing and well-established connection with infectious disease research, ranging from malaria to hepatitis, dengue to leishmaniasis. Disease-related morbidity, mortality, and disability that have had devastating consequences on armed troops are well documented, including the 1918 influenza pandemic which accounted for half of U.S. military casualties in Europe (Pages et al. 2010; Smallman-Raynor and Cliff 2004). Until World War II, the majority of deaths in military units engaged in combat were due to infectious diseases rather than direct combat injuries. Efforts to address these diseases gave rise to the discipline of “tropical medicine”, literally understood as “diseases of the warm climates” (Mostofi 1968; Yoeli 1972; Quail 2015; Beaumier et al. 2013). Medical army officers’ reports from stations worldwide represent some of the first epidemiological documentations of various illnesses (Mushtaq 2009). Expansion

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of colonial powers and empires between the 19th and 20th centuries brought about various scientific and medical breakthroughs, advancing tropical disease knowledge from basic pathogenesis and transmission to possible control measures (Hospenthal 2005). “Inoculation”, the basis of the vaccination concept, was first enacted in U.S. soldiers to prevent smallpox in 1777. In 1900, U.S. military personnel in Cuba identified a particular mosquito species as the vector transmitting yellow fever. The military also demonstrated the potential health benefits of large-scale malaria prevention campaigns, such as insecticide-treated nets and repellent (Kitchen and Vaughn 2007; Kitchen, Lawrence, and Coleman 2009). Military research stations abroad have enabled the establishment of overseas laboratory networks, which have provided an opportunity for the military to develop relations with communities in endemic countries and facilitate research collaborations (Gibbons et al. 2013).

The military contribution to the development of health tools spans across diagnostics, therapeutics, vaccines, and vector control. Vaccines are particularly attractive to the military as they can be administered pre-deployment and can have the indirect benefit of “herd immunity” (Grabenstein et al. 2006). Preventive measures are largely prioritized in many military operations as they offer advantages logistically and compliance-wise (Aronson, Sanders, and Moran 2006; Murray et al. 2007; Michel et al. 2014). At odds with the curative focus of the medical community at that time, the military research agenda was geared towards a more collective or public health approach (i.e., public health engineering, occupational health, and overall preventive interventions). Training in public health and tropical medicine were initially offered by military schools before slowly expanding to public and private universities in the mid-20th century. The contributions of U.S. military research were compiled in a 2005 supplement of the *Military Medicine* journal, covering: infectious diseases overall (Hospenthal 2005), vaccines (Artenstein et al. 2005), malaria (Ockenhouse et al. 2005), parasitic diseases (Crum et al. 2005), diarrhoeal diseases (Lim et al. 2005), bacterial zoonosis (Christopher et al. 2005), rickettsial diseases (Bavaro et al. 2005), sexually transmitted diseases (Rasnake et al. 2005), respiratory infections (Ottolini and Burnett 2005), hepatitis (Dooley 2005), viral hemorrhagic fever (Thomas, Lawler, and Endy 2005), and viral encephalitis (Charles H. Hoke 2005).

Table 1 below summarizes the numerous contributions of U.S. military to health technology development, focusing on human immunization (as key preventive method) from the 18th century to the present day.

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Table 1. Selective contributions of US military research to vaccination R&D (from the 18th century to November 2020)

Disease/ Agent	Year ^a	Product	Relevance and Contribution of US military research	Sources
Smallpox	1900s-present	Various vaccines	Smallpox was considered a highly contagious scourge of troops for centuries. Variolation (i.e., variola inoculation) began during the Revolutionary War, for the Continental army in 1777, with vaccination replacing this practise in 1812. The science of vaccinology advanced slowly through the 1800s; for most of the century, smallpox vaccine was the only vaccine available. Vaccination of US forces continued in WWI and WWII. While routine civilian smallpox vaccination programs stopped in the 1970s (after the disease was declared eradicated), the smallpox vaccine was routinely given to the US military members until 1984. After smallpox virus was determined to be a potential bioweapon threat in 2002, vaccination for select U.S. military personnel was resumed. A new generation smallpox vaccine was tested by USAMRIID and stockpiled as a strategic countermeasure.	(Grabenstein and Winkenwerder 2003)
Yellow fever	1900	V17D vaccine	Yellow fever causes epidemics associated with high mortality rates. The military established the Yellow Fever Commission, which confirmed the disease's mode of transmission, and military scientists contributed to early research on the 17D vaccine.	(Frierson 2010; Collins and Barrett 2017; Ratto-Kim et al. 2018)
Typhoid	1910s	Typhoid vaccine (oral live typhoid Ty21a vaccine) and antibiotic therapy	Typhoid fever caused by <i>Salmonella</i> bacteria caused devastating epidemics among troops for decades. The US military studied its epidemiology, transmission, and potential treatments, and modified the first typhoid vaccine developed in the UK, which was licensed in the US in 1914 and produced at the US Army Medical School. The US military also contributed to the more recently licensed oral typhoid vaccine (developed with Navy laboratories in Indonesia and Chile). Early case management (with chloramphenicol and ciprofloxacin) and rehydration techniques were also pioneered by the military.	(Gradmann, Harrison, and Rasmussen 2019; Kitchen and Vaughn 2007)
Tetanus	1940s	Tetanus toxoid vaccine	Wound tetanus was a major cause of morbidity and mortality until WWI. Passive immunization with tetanus antitoxin was relatively effective. However, it carried a risk of undesirable side effects, notably serum sickness, due to its equine protein content. The military researched and was the first to deploy a	(Ratto-Kim et al. 2018)

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Disease/ Agent	Year ^a	Product	Relevance and Contribution of US military research	Sources
			tetanus toxoid vaccine (licensed in the US in 1933) for large-scale use.	
Pneumo cocal disease	1940s	Pneumo cocal vaccine	Military scientists discovered <i>Streptococcus pneumoniae</i> (1880) and tested the first multivalent polysaccharide vaccine (not the newer conjugate vaccines against childhood pneumonia that are used in routine immunization today).	(Ottolini and Burnett 2005)
Influenza	1940s-present	Influenza vaccines	In the mid of 20 th century, military research was instrumental in preparation of the first whole-inactivated virus vaccine, as well as in investigations into the virus's antigenic drift and shift. The first bivalent influenza A and B vaccine was used to vaccinate troops in 1945. Outbreaks of influenza in 1957 and 1976 led to population-wide influenza vaccination campaigns. The US military has continued to study the influenza virus and attempt to develop a more effective vaccine, including monitoring new strains to ensure matching vaccine composition with circulating influenza strains.	(Hoyt 2006; Kitchen and Vaughn 2007)
Hepatitis B	1940s-present	HBV vaccine	Since the 1940s, military researchers have been studying hepatitis epidemiology and immunoprophylaxis, and have made advances in viral subtyping and demonstrated the protective effect of antibodies. The military then developed the first-generation HBV vaccine (licensed to Merck by US FDA in 1981), though now most available vaccines are recombinant types.	(Dooley 2005)
Hepatitis A	1940s-1990s	HepA vaccine	Recurrent outbreaks of Hepatitis A are linked to its fecal-oral route of transmission. In 1945, the US military played a role in demonstrating the efficacy of passive immunization with immunoglobulin. In 1986, WRAIR produced the first formalin-inactivated vaccine tested in humans. The Phase III trial of Hep A vaccine started in 1991 in Thailand, involving 40,000 participants and leading to the licensure of Havrix in 1995. The vaccine is the result of military collaboration with NIH and Smith Kline Beecham Biologics (now GSK).	(C. H. Hoke et al. 1992; Dooley 2005)
Japanese encephal i-tis (JE)	1940s-present	J.E. vaccine	There is a long history of military involvement in research on JE, starting with the virus's isolation in 1935 and continuing with studies of the ecological and epidemiological features of various outbreaks. The first formalin-inactivated vaccine from JEV-infected mouse brain was used until WWII despite	(Charles H. Hoke 2005; Grabenstein et al. 2006; Ratto-Kim et al. 2018)

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Disease/ Agent	Year ^a	Product	Relevance and Contribution of US military research	Sources
			suboptimal efficacy. Trials at military bases (including in Thailand and Japan) led to a new whole-virus vaccine licensed in 1992 and produced and distributed by BIKEN/Sanofi-Pasteur until 2005. Because of the ongoing threat of JE for military personnel stationed throughout Asia, the US military searched for second-generation JE vaccine preparations at WRAIR and with partners, leading to two additional vaccines: IXIARO® and IMOJEV®.	
Diphtheria	1950s	Diphtheria vaccine	Advantage of low-dose diphtheria toxoid for adults was demonstrated, which acted as a precursor to vaccine development.	(Artenstein et al. 2005)
Anthrax	1950s	Anthrax vaccine	A culture filtrate method was used to develop the first human vaccine (acellular) for <i>Bacillus anthracis</i> , it approved for use in the US as anthrax vaccine adsorbed (AVA) in 1965.	(Splino et al. 2005)
Adenovirus	1950s–present	Adenovirus vaccine	Adenovirus is one of the causes of Acute Respiratory Disease (ARD) with flu-like symptoms. In the 1950s military researchers identified the adenovirus types 4 and 7, and a formalin-inactivated vaccine was introduced in 1956, followed by live-attenuated vaccines in the 1960s-1970s. Wyeth Pharmaceuticals provided the vaccine for the US military until 1996 when production was halted. The vaccination program resumed in 2001 for military members, with a new producer (Barr Pharma).	(Kitchen and Vaughn 2007)
Rubella	1960s	Rubella vaccine	Military researchers isolated the rubella virus and created a live-attenuated viral vaccine (manufactured by Merck Sharp Dome), which was licensed in the US and served as the basis of a second-generation vaccine in the 1970s.	(Kitchen and Vaughn 2007)
Meningococcal disease	1960s/70s present	Meningo vaccines	Since the 19 th century, outbreaks had been commonly reported in military recruits. Military researchers helped describe immunologic responses to the bacteria and identified protective responses. Outbreaks and resistant strains led the military to develop the first polysaccharide immunogenic vaccine. Trial Phases I–III were conducted by the US military leading to a licensed vaccine for serogroup A and a combined serogroup A/C vaccine in 1970 and 1978, respectively. The serogroup C vaccine reached licensure, as well as other tetravalent vaccines (targeting A, C, Y, and W-135 serogroups) (manufacturing and licensure were handled by	(Grabenstein et al. 2006)

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Disease/ Agent	Year ^a	Product	Relevance and Contribution of US military research	Sources
			private companies, e.g., Menomune by Connaught Lab and Menactra by Aventis Pasteur). Military research into a vaccine for serogroup B meningococcus is ongoing.	
HIV	1980s-present	HIV vaccine	Military researchers looked into the potential immunogenicity of the virus's glycoprotein and continue to develop HIV vaccine candidates; the candidate RV144 was tested in a Phase 3 trial in Thailand through a partnership between the US Army, NIH, Royal Thai Army, Ministry of Health and Mahidol University. RV144 was the first, and remains the only, HIV efficacy trial to show protection, with vaccine efficacy of 31% at 42 months. However, it remains unlicensed and work continues to improve the vaccine.	(Ratto-Kim et al. 2018)
Malaria	1900s-present	Malaria vaccines	Malaria is one of the oldest priorities for the military and remains a challenge. Until WWII, the military strategy against malaria was primarily vector control. US DOD has been a leading investor in malaria drug and vaccine development, funding for which was reinvigorated by the Vietnam war and the spread of chloroquine resistance. WRAIR has worked on multiple malaria vaccine candidates for over 50 years. One approach spearheaded by WRAIR scientists, in collaboration with Smith Kline Beecham (subsequently GSK), resulted in the initial testing of the RTS,S malaria vaccine candidate. The vaccine is currently in pilot implementation after a large Phase 3 trial.	(Kitchen, Vaughn, and Skillman 2006; Teneza-Mora, Lumsden, and Villasante 2015)
Dengue	1950s-present	Dengue vaccines	US military personnel have dealt with dengue since the beginning of the 20 th century in the Spanish-American War. Given high attack rates and substantial burden of symptomatic illness – and no antiviral – the military has focused on vaccine development: the US army has researched a few candidate vaccines in partnership with GSK since the early 2000s. Trials are still ongoing for safer and more effective vaccines apart from those already licensed (e.g DengVaxia by Sanofi-Pasteur).	(Ratto-Kim et al. 2018)

^a This column refers to the time/decades/approximate year(s) considered as the start of military involvement and /or peak or R&D activities.

While the military was the primary actor engaged in biosecurity R&D for many years, as the nature, extent, and understanding of threats to health security evolved, the ecosystem expanded to include a broader range of actors. This

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evolution synchronously influenced the direction of military research. For example, the emergence of the Human Immunodeficiency Virus (HIV) and the ensuing AIDS pandemic was one such event. In the early 2000s, US intelligence agencies and, subsequently, the United Nations Security Council declared HIV/AIDS a national security threat and warned of instability due to the pandemic (United States. National Intelligence Council 2000; Feldbaum, Lee, and Patel 2006). According to Feldbaum et al. (2006), HIV necessitated public health investment from all sectors, including defence. The military, though it had been active in HIV prevention programs since the 1980s, subsequently expanded its dedicated research program for HIV/AIDS, including efforts to develop HIV vaccines.

Another turning point in the evolution of the biosecurity R&D system was the terrorist attack against the US on September 11, 2001 and the subsequent mailing of anthrax spores to US politicians the same year. An increased sense of vulnerability to terrorism in general, and to possible intentional dissemination of potentially fatal pathogens in particular, led to a surge in funding for infectious disease research (IoM 2002). In their review of the history of biological warfare and bioterrorism, Barras and Greub (2014) found that both were rare, but that incidents that did occur were well documented and often put forward as justification for resource allocation (Barras and Greub 2014).² The Severe Acute Respiratory Syndrome (SARS) outbreak in 2003 further highlighted the devastating consequences of epidemics in an increasingly globalized world and the lack of tools to prevent, detect, and respond to novel pathogens. Military research was considered an asset, a stepping stone, and a useful example for biosecurity R&D³ more broadly, especially against emerging diseases as biological threats (Ho, Hwang, and Lee 2014).

2. Actors and stakeholders in biosecurity R&D

2.1 US actors and structure for biosecurity R&D

Moss and Michaud's (2013) comprehensive report on the role of the US Department of Defense (DOD) in global health and infectious disease includes analysis of its sizeable medical R&D portfolio across various entities (Moss, K and

² For extensive discussions on bioweapons, including the grey areas of "offensive" or "defensive" biodefense research see: Studies of Military R&D and Weapons Development: Offensive/Defense Distinctions in BW Related Research: <https://fas.org/man/eprint/leitenberg/off-def.pdf>

³ "Bioterrorism" remains distinct from "naturally occurring disease" in intent and application, both are seen to require dedicated R&D. Biosecurity R&D programs' goals are explicitly devoted to "detect, prevent, and treat CBRN threats", with the "biological" portfolio covering both weaponized pathogens and disease outbreaks caused by "emerging and re-emerging" infectious diseases.

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Michaud 2013). The Army is designated to lead infectious diseases research within DOD with joint activity coordinated by the Military Infectious Diseases Research Program. Early-stage research is conducted mainly at the Walter Reed Army Institute of Research (WRAIR), the Naval Medical Research Center (NMRC), and the US Army Medical Research Institute of Infectious Diseases (USAMRIID). WRAIR and NMRC also conduct research overseas through divisions in Kenya, Thailand, Cambodia, Egypt, Ghana, Peru, and Singapore.⁴ These research centres and their field sites focus on “prevention, diagnosis, and treatment of naturally occurring disease causing microorganisms” and allow DOD staff and partners (including academics, WHO, host-country scientists) to conduct in-country research (Gibbons et al. 2013). The Infectious Disease Clinical Research Program (IDCRP) organizes trials in military hospital networks and collaborates with civilian researchers.

Non-health-specific defence R&D is conducted by the DOD's Defense Threat Reduction Agency (DTRA) and the Defense Advanced Research Projects Agency (DARPA). DARPA was established in 1958 and tasked “to make pivotal investments in breakthrough technologies for national security” (DARPA 2015). Its success in developing pivotal technologies, including the internet, navigation, space, and stealth technologies, are detailed in its 60th Anniversary Report (DOD 2018). The Biological Technological Office oversees DARPA's projects in the biomedical field (Mervis 2016). In 2017, it launched the Pandemic Prevention Platform (P3) program with the goal to create new medicines for emerging threats within 60 days, as a temporary ‘firebreak’; this work has now been extended to the COVID19 pandemic.⁵

Emerging diseases are also the target of the US Public Health Emergency Medical Countermeasures Enterprise (PHEMCE), an initiative launched in 2006 to coordinate efforts among multiple agencies developing and acquiring countermeasures. The partners include DOD, Department of Veterans Affairs (VA), Department of Homeland Security (DHS), and the Department of Agriculture (DA), led by the Department of Human and Health Services (HHS). Agencies including the Centers for Disease Prevention and Control (CDC), Food and Drug Administration (FDA), and National Institutes of Health (NIH) are also involved. The Biomedical Advanced Research and Development Authority (BARDA) was also

⁴ The US Army Medical Research Unit (USAMRU) in Kenya, and the Armed Forces Research Institute of Medical Sciences (AFRIMS) in Thailand are important for WRAIR's research on many infectious diseases. The Naval Medical Research Centre also performs research and conducts surveillance through its Naval Health Research Center (NHRC). Its units (NAMRUs) also allow in-country research on a number of infectious diseases.

⁵ In the COVID19 pandemic, DARPA P3 is funding four projects, including one in search of antibodies for treatment: <https://www.c4isrnet.com/coronavirus/2020/03/17/darpa-backed-pandemic-readiness-could-yield-results-by-july/>

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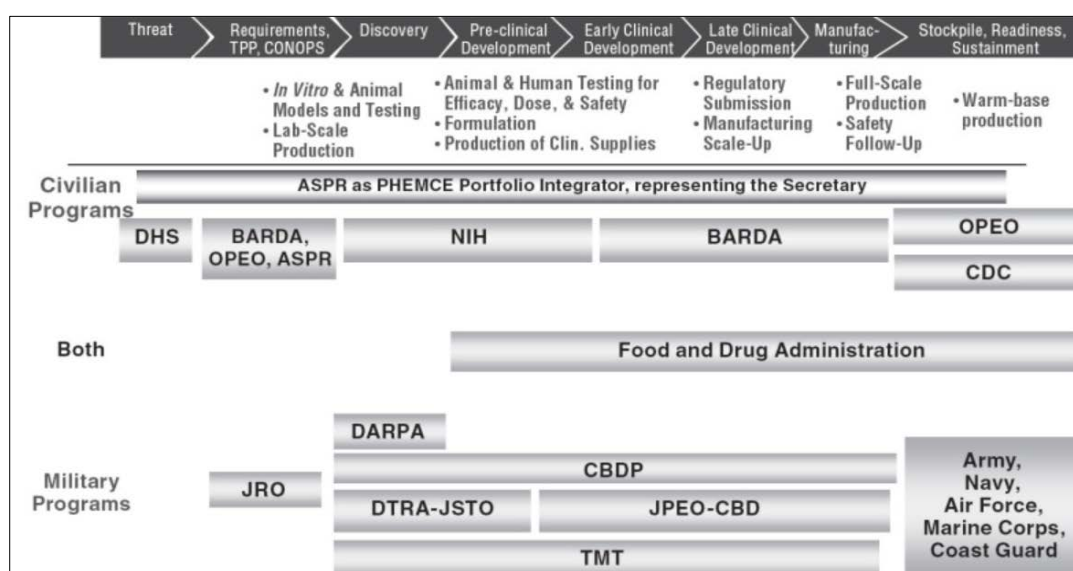
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created in 2006, following recommendations from a 2004 report on the need to have a dedicated agency for “end-to-end development of countermeasures” (National Research Council 2004). The DOD is responsible for addressing military threats, while BARDA, as a part of HHS, focuses on threats to the civilian population. These agencies also interact with civilian researchers and industry (see Figure 1). BARDA was designed to provide an integrated, systematic approach to the development and purchase of countermeasures for public health medical emergencies (BARDA 2019). In a 2017 review, BARDA was reported to have supported ~80 product candidates for multiple CBRN threat agents, procured and stockpiled 21 of these, with 6 products having received FDA approval/licensure for a CBRN-based indication (Larsen and Disbrow 2017) (see Table 4 further below for a summary of BARDA products to date).

Figure 1. Military and Civilian Role in the U.S. Biosecurity R&D Process



Legend: ASPR: Assistant Secretary for Preparedness and Response; BARDA: Biomedical Advanced Research Development Authority; CDC: Centers for Disease Control and Prevention; CBDP: Chemical and Biological Defense Program; CONOPS: Concept of Operations; DARPA: Defense Advanced Research Projects Agency; DHS: US Department of Homeland Security; DOD: Department of Defense; JPEO-CBD: Joint Program Executive Office for Chemical/Biological Defense; JRO: Joint Research Office; JSTO: Joint Science and Technology Office; NIAID: National Institute of Allergy and Infectious Diseases; NIH: National Institutes of Health; OPEO: Office of Preparedness and Emergency Operations; PHEMCE: Public Health Emergency Medical Countermeasures Enterprise; TMT: Transformational Medical Technology; TPP: Target Product Profile.

Source: National Research Council. 2011. *Protecting the Frontline in Biodefense Research: The Special Immunizations Program*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/13112>.

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2.2 Biosecurity R&D outside the U.S.

As noted in the introduction, we found limited literature available in English on biosecurity R&D conducted outside of the US. This section offers a non-exhaustive synthesis of the literature we found regarding other countries.

Many countries with a colonial history have played similar roles to the US in investing in infectious disease research (see **Section 1** above). As a part of the French Military Medical Service, the Military Biomedical Research Institute conducts research, often in partnership with civilian institutions, such as the Institut Pasteur network. In contrast, clinical research is usually undertaken in-house, i.e., in military hospitals (Binder 1999). There is a long history of British military being involved with research into infectious and tropical diseases since the 16th century; this fell under the umbrella of the Defence Medical Services for many years. Defense R&D in the UK is increasingly dependent on civilian agencies for its clinical, teaching, and research activities. Since the 2000s, the majority of defense funding for microbiology and infectious disease research has been given to civilian institutions (Bailey 2013; Herron and Dunbar 2018). Many countries maintain biomedical research entities that have historical ties to, or originated from, the military (Grant 1966). Examples include the Australian Army Malaria Institute, the Germany Institute of Virology in Marburg, and Russia's S.M. Kirov Military Medical Academy (Shanks et al. 2016). The life science branch of India's Defense Research and Development Organisation (DRDO), an umbrella organization for 51 military laboratories, focuses on the well-being of troops and technological innovation (Krishan, Kaur, and Sharma 2017).

For China, the history of military medicine spans centuries, and the military maintains a role in health services through the People's Liberation Army (PLA) (Fu 2014). Almost all its biosecurity-related research is government-funded. Huang (2011) reviewed the history of China's biodefense efforts since the set-up of the Military Medicine Institute in each military region (Huang 2011). Recent reforms in military research infrastructure resulted in an extensive network of 125 military hospitals and 15 research institutes under the umbrella of Academy of Military Medical Sciences (AMMS). Until the mid-1980s, the AMMS was devoted to research on biodefense against 'wartime special weapons' (i.e., atomic, biological, and chemical weapons). The Chinese military committed major resources in the 1990s to developing drugs for vector-borne diseases, including antimalarials such as benflumentol (lumefantrine), naphthoquine phosphate, and artemisinin (Chang 2016). The latter was a combination of efforts from the PLA's Research Institute and the China Academy of Traditional Chinese Medicine, in a military project called Project 523, an example of 'mission-oriented' R&D (Hsu 2006; Miller and Su 2011), which was later recognized with the award to Dr. Tu Youyou of part of the

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Nobel Prize in Medicine in 2015.⁶ According to Huang (2011), there was also increased attention to health security in China following the 2001 terrorist events in the US,⁷ although there was no significant shift in the research agenda insofar as specific disease agents were concerned (Huang 2011). China's Ministry of Health appears to handle only a small set of bioterrorism agents/diseases compared to the US. Liu et al. (2014) reviewed China's engagement in global health (including health security) over the years, and concluded that "China aspires to be a powerhouse in the discovery and production of new drugs and vaccines in global health," but no further details were offered (Liu et al. 2014).

3. Scope and prioritization of biosecurity R&D

Military research addresses many infectious diseases. The priorities have been those that cause outbreaks and threaten military personnel: (1) conditions that spread quickly in densely populated areas (respiratory and dysenteric diseases); (2) vector-borne diseases (disease carried by mosquitoes and other insects); (3) sexually transmitted infections (hepatitis, HIV, and gonorrhoea); and (4) diseases associated with biological warfare. Military research has built on its historical legacy and evolved with newer threats or "possible unknown biological disruption," currently specified in a priority list of pathogens⁸ (Russell and Gronvall 2012). In the US, such a list is established by DOD and partners, and the categorization is reviewed regularly and published by the CDC (see **Table 2** below). The US CDC list is the government's main public estimate of current biological threats and is expected to change over time.

The process to determine research priorities is complex, subject to budget and/or capacities, and may vary over time (Green et al. 2019). The level of R&D priority accorded to any particular target generally corresponds with the level of

⁶ The central government set up a panel of more than 500 medical military and civilian experts to develop new antimalarial treatments for soldiers. This was classified as a top-secret state mission named Project 523, after the date it was established 23 May 1967. Source: <https://www.who.int/bulletin/volumes/87/10/09-051009/en/>

⁷ Also in Huang (2011), search using "bioterror" (*shengwu kongbu*) as a key word search term for articles from the "China Academic Journals Full-text Database," which covers almost all academic journals published in China (in Chinese), found that prior to 2001 bioterrorism was rarely discussed, and post-2001 there was a significant increase in the number of publications. Of the articles that include "bioterror" in their key words since 1979, nearly 99% were published after 2001.

⁸ These would include several diseases that have re-emerged and caused global concern in recent years, such as Zika, SARS, Middle East Respiratory Syndrome (MERS) viruses, and Ebola. Following lessons from Ebola outbreaks (both 2014 and 2018), the WHO has published an R&D Blueprint. The Blueprint 2019 has listed the following as priority pathogens: Crimean-Congo hemorrhagic fever (CCHF), Ebola virus disease and Marburg virus disease, Lassa fever, MERS, SARS, Nipah and hantavirus diseases, Rift Valley fever (RVF), Zika and Disease X.

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(perceived) threat, but is also influenced by various factors, such as a disease’s geographical distribution, availability of control tools, transmission methods, and the historical impact (Michaud, Moss, and Kates 2012). In the US, although the military (DOD-led) and civilian (HHS-led) R&D efforts have somewhat different missions and priorities, the agencies have also recognized a shared interest in advancing the countermeasures pipeline. They have attempted to coordinate and integrate their needs better, in the form of an Integrated Portfolio for CBRN medical countermeasures (National Research Council 2011). A 2014 evaluation recommended that DOD improve the interagency process for setting priorities (U. S. Government Accountability Office 2014).

Table 2. List of priority pathogens, as identified by the US Centers for Disease Control (as of November 2020)

	Definition	Biological agents/pathogens
Category A	The US public health system and primary healthcare providers must be prepared to address various biological agents, including pathogens that are rarely seen in the United States. High-priority agents include organisms that pose a risk to national security because they can be easily disseminated or transmitted from person to person; result in high mortality rates and have the potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness.	<p>Anthrax (<i>Bacillus anthracis</i>)</p> <p>Botulism (<i>Clostridium botulinum</i> toxin)</p> <p>Plague (<i>Yersinia pestis</i>)</p> <p>Smallpox (<i>Variola major</i>)</p> <p>Tularemia (<i>Francisella tularensis</i>)</p> <p>Viral hemorrhagic fevers, including</p> <p>Filoviruses (Ebola, Marburg)</p> <p>Arenaviruses (Lassa, Machupo)</p>
Category B	Second highest priority agents include those that are moderately easy to disseminate; result in moderate morbidity rates and low mortality rates; and require specific enhancements of CDC’s diagnostic capacity and enhanced disease surveillance.	<p>Brucellosis (<i>Brucella</i> species)</p> <p>Epsilon toxin of <i>Clostridium perfringens</i></p> <p>Food safety threats (<i>Salmonella</i> species, <i>Escherichia coli</i> O157:H7, Shigella), Glanders (<i>Burkholderia mallei</i>)</p> <p>Melioidosis (<i>Burkholderia pseudomallei</i>)</p> <p>Psittacosis (<i>Chlamydia psittaci</i>)</p>

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		<p>Q fever (<i>Coxiella burnetii</i>) Ricin toxin from <i>Ricinus communis</i> (castor beans) Staphylococcal enterotoxin B Typhus fever (<i>Rickettsia prowazekii</i>) Viral encephalitis (alphaviruses, such as eastern equine encephalitis, Venezuelan equine encephalitis, and western equine encephalitis) Water safety threats (<i>Vibrio cholerae</i>, <i>Cryptosporidium parvum</i>)</p>
Category C	<p>Third highest priority agents include emerging pathogens that could be engineered for mass dissemination in the future because of availability; ease of production and dissemination; and potential for high morbidity and mortality rates and major health impact.</p>	<p>Emerging infectious diseases such as Nipah virus and hantavirus</p>

Source: CDC and NIAID; Available from <https://emergency.cdc.gov/agent/agentlist-category.asp> and <https://www.niaid.nih.gov/research/emerging-infectious-diseases-pathogens>. Last accessed on 01 November 2020.

In terms of health technology type, preventive measures predominate. Initially targeting specific diseases, wartime programs expanded the scope of the military's work in vaccines, which benefited both the military and civilians. One oft-cited example is the organizational purpose and efficiency of the commission organized by the US Army in 1941 to develop the first influenza vaccine, licensed by the FDA in two years (Hoyt 2006).⁹ The partnership between military and civilian actors, including the private sector and industrial partners, was considered vital and extended until the Cold War and beyond (Sarewitz 2011). Another example is the penicillin project, in which discoveries in military labs were further developed by pharmaceutical companies in close cooperation, and with transparent, regular scientific exchanges (Quinn 2013). The “generational” process of vaccine development (i.e., continual improvement, with newer version(s) that are safer, more effective, or more user-friendly) was performed by the industry, which

⁹ All health technologies designated for US troops must be approved by the FDA.

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further developed them for routine immunization.¹⁰ Hoyt (2006) argued that the collaboration between the military and industry partners accelerated vaccine innovation through the middle of the 20th century, with sustained cooperation even after the urgency and structure of wartime programs were dissolved. Maslow (2017) further attributed the strength of the military-industrial partnership to legal, economic, and political changes in the U.S during the 1970s -80s, such as the FDA's increasing authority in regulating vaccines and the emergence of biotechnology firms. Though the US DOD continues to pursue vaccines as a cost-effective solution (to prevent infectious diseases and protect combat-ready personnel), the industry is needed to manufacture them. However, vaccines that are marketed commercially have proven to be more attractive for the pharmaceutical industry, while some countermeasure vaccine candidates have languished in government labs (including the military) (Dembek et al. 2017; Trull, du Laney, and Dibner 2007).

Other than emerging infectious diseases, the US military has also prioritized malaria and HIV/AIDS, as evidenced by their continued vaccine efforts. Malaria poses a continuing threat to military operations in the regions of the world where it is endemic. Current malaria countermeasures include drug prophylaxis and treatment, vector control, and personal protection (topical repellents, clothing, and bed nets) – yet no vaccine has been licensed globally for adults. DOD institutions have contributed to the development of many widely-used antimalarial drugs: chloroquine, primaquine, mefloquine, doxycycline, atovaquone/proguanil, and, most recently, tafenoquine (Ockenhouse et al. 2005; Zottig et al. 2020; Kitchen, Lawrence, and Coleman 2009; Kitchen, Vaughn, and Skillman 2006). For HIV/AIDS, the DOD laboratories play a crucial role, alongside NIAID, in pursuing vaccine R&D since 1985 (Table 1). HIV remains a significant threat to US service members deployed overseas. Another increasingly important focus is antimicrobial resistance (AMR), which has come under increasing global attention.¹¹

As for diseases with importance beyond military concern, biosecurity R&D has gradually moved towards health technologies that can not only be used for emergencies but may also be beneficial in general medical care (e.g., burn care, radiation effects suffered by cancer patients, seizures, etc.) (Warfield and Aman 2016). As the occurrence of biological events is unpredictable, the idea of broad-spectrum technologies (multiplex or multi-use platforms; pathogen agnostic) that can be easily adjusted towards various pathogens and scaled up started to be

¹⁰ This has occurred for example with the Haemophilus influenzae type b (Hib), pertussis, pneumococcal, and hepatitis B vaccines.

¹¹ CARB-X was launched in 2016 as the world's largest public-private partnership dedicated to accelerating antibacterial research to tackle the global rising threat of drug-resistant bacteria, a collaboration between BARDA, NIAID/NIH and the UK Wellcome Trust.

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more actively pursued as a goal in biosecurity research (DeFrancesco 2004; Casadevall et al. 2008).

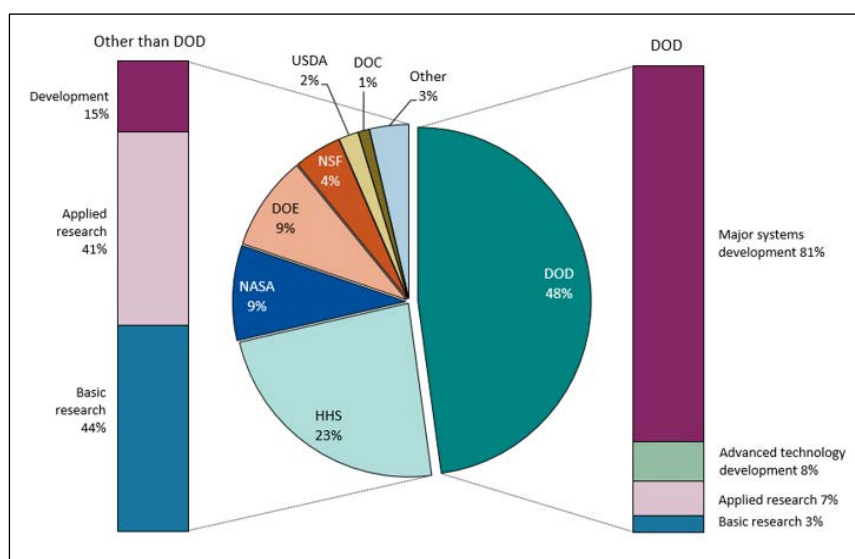
4. Funding, incentives and landscape of biosecurity R&D

4.1 Biosecurity R&D Funding at the US federal level

Internationally, global spending on R&D has been on the rise¹² (with the impact of Covid-19 still to be fully grasped). However, it is not straightforward to estimate investment in biosecurity R&D. This section synthesizes funding figures from various sources in the literature.

The US National Science Foundation reports on the federal R&D budget each year by department and purpose (summarized below in Figure 2).

Figure 2. Breakdown of US federal research and development budget, 2015*



*Total of R&D budget for 2015 amounted to 131.4 billion USD; Details may not add to total because of rounding.

Legend: DOC: Department of Commerce. DOD: Department of Defense; DOE: Department of Energy; HHS: Department of Health and Human Services; NASA: National Aeronautics and Space Administration; NSF: National Science Foundation; USDA: Department of Agriculture.

Source(s): National Science Foundation, National Center for Science and Engineering Statistics, Survey of Federal Funds for Research and

¹² OECD Main Science and Technology Indicators, 2018. <http://www.oecd.org/sti/msti.htm>. Accessed 18/08/2020

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Development, Science and Engineering Indicators 2018. Available from: <https://www.nsf.gov/statistics/2018/nsb20181/figures>

According to a 2019 report from the American Academy for the Advancement of Science, the federal R&D budget surged steeply after 2001, and despite a brief decline in 2010-2013 due to the financial crisis, has increased gradually again. Defence has long been a priority, accounting for almost half of federal R&D support, reaching \$51 billion in 2017 (“Report - S&E Indicators 2018 | NSF - National Science Foundation” n.d.). Basic and applied research is generally funded by nondefense agencies such as NIH or NSF. Although the DOD R&D budget focuses on the later stages of research (development/advanced manufacturing, facilities, procurement), military labs and DARPA also conduct more upstream research.

Disaggregated, specific funding data on biosecurity R&D is difficult to find, as it is funded through different programs in various agencies. Furthermore, there is no formal US government definition of what counts as biosecurity R&D, and activities may fall under broader categories such as “defense,” “global health,” “biosecurity,” or “EID”. **Table 3** provides a summary of funding data relevant for biosecurity R&D. As highlighted by the various figures and reporting methodologies in **Table 3**, it is difficult to find a single number that clearly represents total US funding for biosecurity R&D.¹³

Table 3. Selected US funding estimates relating to biosecurity R&D

Funding allocation*	Amount US\$ (billion)	Year	Source	Remark
US Defense R&D	55.4	2017	(Sargent Jr 2020)	Dated January 2020; total defense-related R&D, not only biosecurity-related and does not explicitly limit to DOD

¹³ An annual review reporting federal funding for health security programs is conducted by Johns Hopkins University Center for Health Security, published in the journal Health Security, for federal programs focused on prevention, preparedness, and response to attacks on civilians with biological agents and accidental releases of biological material. The latest one is available at: <https://www.liebertpub.com/doi/10.1089/hs.2018.0077>

The definitions used: Radiological and Nuclear Security: Federal programs focused on prevention, preparedness, and consequence management of radiological and nuclear terrorism and large-scale radiological accidents; Chemical Security: Federal programs focused on prevention, preparedness, and response to large-scale acute chemical exposures of civilian populations, both intentional and accidental; Pandemic Influenza and Emerging Infectious Diseases: Federal programs focused on preparedness and response to large, naturally occurring, and potentially destabilizing epidemics; and Multiple-Hazard and General Preparedness: Federal programs focused on multiple hazards or on building infrastructure and capacity to respond to large-scale health threats.

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Funding allocation*	Amount US\$ (billion)	Year	Source	Remark
US Global Health Security budget	0.55	2020	(KFF 2020)	From total 11 billion of US Global health funding, GH security represent 5%, while 48% for HIV, Global Fund (14%), maternal and child health (11%), T.B. (3%), NTD (1%)
US Government funding for Emerging Infectious Diseases R&D ^a	1.9	2014-2018	("Policy Cures Research Public Search" 2020)	From data visualisation in R&D Tracker collated by GFinder/PolicyCures. The US EID R&D funding in order of magnitude is for: NIH, BARDA, DOD, CDC, USAID
US Biodefense budget	60	2001-2011	(E. Hayden 2011)	Data is from Center for Biosecurity UPMC
TMT – DTRA	1.5	2006-2011	(E. C. Hayden 2011)	Data is from Center for Biosecurity UPMC
BioShield project	5.8	2004-2013	(Needham 2009)	Managed by DOD
BioShield	2.8	2014-2018	(Gotttron 2014)	Pandemic and All-Hazards Preparedness Reauthorization Act of 2013. BARDA gets \$415 million in annual appropriations to support advanced R&D
US DOD funding for health security	0.257	2019	(KFF n.d.)	The site created in 2014 allows tracking budget and resources related to health security, data for DOD available from 2006
PHEMCE budget	24.8	2017-2021	(US Dept of HHS n.d.)	The five-year funding total aggregates MCM-related spending estimates for NIH, BARDA, SNS, and FDA. Including details on spending plan and MCM achievements.
Civilian biosecurity budget	1.8			
Multiple hazard and general preparedness	7.62	2018	(Watson et al. 2018)	The paper is the latest (for FY 2019) in an annual series examining health security funding in the federal budget
Radiological/nuclear	2.38			
Chemical security	0.4			

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Funding allocation*	Amount US\$ (billion)	Year	Source	Remark
Pandemic influenza/EID programs	1.6			
<i>Total health security</i>	13.8			

Legend: BARDA: Biomedical Advanced Research Development Authority; CDC: Centers for Disease Control and Prevention; DOD: Department of Defense; FDA: Food and Drugs Administration; KFF: Kaiser Family Foundation; MCM: Medical Countermeasures; NIH: National Institutes of Health; PHEMCE: Public Health Emergency Medical Countermeasures Enterprise; SNS: Strategic National Stockpile; TMT-DTRA: Transformational Medical Technologies – Defense Threat Reduction Agency; UPMC: University of Pittsburgh Medical Center; US: United States of America.

^a For the scope of EID in Policy Cures Research, see <https://gfinderdata.policycuresresearch.org/pages/data-visualisations/usa>.

4.2 Push and pull incentives for biosecurity R&D in the US

In the last 20 years, the lack of licensed vaccines, diagnostics or therapeutics for many pathogens considered a priority threat has spurred the US government to mobilize various push and pull incentives to address the issue (National Research Council 2004). There is limited interest from the private sector to develop biodefense products, as typically there is high risk, and limited commercial markets until a large-scale outbreak actually occurs (Smith, Inglesby, and O’Toole 2003). Several of these pull and push incentives are briefly described here.

Project Bioshield was enacted in 2004 to ensure late-stage development, manufacturing, procurement, and stockpiling of strategic assets for public health emergencies. Managed by DOD, this program basically augments market incentives for companies by committing to advanced purchases, accompanied by tax incentives, intellectual property protection, and liability limits (Nolan et al. 2010; Trull, du Laney, and Dibner 2007). Matheny et al. (2007) reviewed several ‘push’ and ‘pull’ mechanisms to incentivize biosecurity product development, which includes government technology transfer, industrial collaboration, grants, prizes (e.g., DARPA Challenge), exclusivity and procurement contracts – each with its strength and weakness (Matheny et al. 2007). The system has developed many products (see **Table 4** below) but has not always been successful; a 2010 GAO report found that the firm VaxGen failed to deliver on an anthrax vaccine contract in 2006, while the FDA-licensed anthrax vaccine expired in the stockpile (GAO 2010).

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Table 4. Products developed by US BARDA (as of October 2020)

#	Medical Countermeasure	Threat Area	Company Sponsor	Year
1	H5N1 vaccine Antigen-alone formulation	Influenza	Sanofi Pasteur	2007
2	Fluzone® H1N1 influenza vaccine adult	Influenza	Sanofi Pasteur	2009
3	Fluvirin® H1N1 influenza vaccine	Influenza	Novartis	2009
4	FluMist® H1N1 influenza vaccine	Influenza	MedImmune	2009
5	FluLaval® H1N1 influenza vaccine	Influenza	GlaxoSmithKline	2009
6	Afluria® H1N1 influenza vaccine infants	Influenza	Commonwealth Serum Laboratories	2009
7	Afluria® H1N1 influenza vaccine adult	Influenza	Commonwealth Serum Laboratories	2009
8	XPERT FLU® H1N1 Influenza POC diagnostic	Influenza	Cepheid	2011
9	LIAT® Influenza A/B Rapid diagnostic Influenza A/B Rapid diagnostic	Influenza	Iquum / (Roche)	2011
10	Veritor® Influenza A/B Rapid diagnostic	Influenza	Becton Dickinson	2012
11	Simplexa® Point-of-care diagnostic device	Influenza	Focus/3M	2012
12	Flucelvax® Seasonal cell-based influenza vaccine	Influenza	Novartis	2012
13	Aura® Next generation portable ventilator	Influenza	Covidien	2012
14	Raxibacumab® Anthrax antitoxin	Anthrax	GlaxoSmithKline (formerly HGS)	2012
15	FluBlØk® Seasonal recombinant-based influenza vaccine	Influenza	Protein Sciences	2013
16	HBAT Botulinum heptavalent antitoxin	Botulism	Emergent (formerly Cangene)	2013
17	Q-PAN® H5N1 Pandemic influenza vaccine with adjuvant	Influenza	GlaxoSmithKline	2013
18	Sophia® Influenza A/B Rapid diagnostic	Influenza	Quidel (Nanogen)	2013

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#	Medical Countermeasure	Threat Area	Company Sponsor	Year
19	PharmaJet Needleless Flu Shot Stratis	Influenza	PharmaJet	2014
20	Rapivab® (peramivir) Influenza antiviral drug IV	Influenza	BioCryst	2014
21	Anthrasil™ (AIG) Anthrax antitoxin	Anthrax	Cangene	2015
22	Neupogen® (filgrastim) ARS anti-neutropenia cytokine	RAD/NUC	Amgen	2015
23	Neulasta (GM-CSFpeg) ARS anti-neutropenia cytokine	Rad/Nuc	Amgen	2015
24	BioThrax® (post-exposure prophylaxis indication)	Anthrax	Emergent	2015
25	Fluad (with adjuvant) Influenza vaccine for seniors	Influenza	Sequris (CSL – Novartis)	2015
26	Anthim Anthrax Monoclonal	Anthrax	Elusys	2016
27	Flucelvax Quadrivalent Influenza Virus Vaccine	Influenza	Seqirus	2016
28	Flucelvax Quadrivalent Influenza Virus Vaccine (Pediatric Indication)	Influenza	Seqirus	2016
29	Q-Pan H5N1 AS03-Adjuvanted Pandemic Influenza Virus Vaccine for Pediatrics	Influenza	GSK	2016
30	Flublok Quadrivalent Influenza Virus Vaccine	Influenza	Protein Sciences Corporation	2016
31	Vabomere (Carbavance)	BSA	MEDCO	2017
32	Rapivab® (peramivir) Influenza antiviral drug IV	Influenza	BioCryst	2017
33	Cobas LIAT C. Diff POC diagnostic	CBRN	Roche	2017
34	Roche LightMix Zika Molecular Diagnostic	Zika	Roche	2017
35	Leukine® (sargramostim) ARS anti-neutropenia cytokine	RAD/NUC	sanofi aventis	2018
36	ZEMDRI Plazomicin	BSA	Achaogen	2018
37	Procleix Zika Virus Assay	Zika	Hologic/Grifols	2018
38	Arestvyr®ST-246 (Tecovirimat) Smallpox antiviral drug	Smallpox	SIGA	2018
39	Xerava	BSA	Tetrphase	2018
40	Flucelvax Process 3.0	Influenza	Seqirus	2018
41	Seizalam	Chemical	Meridian	2018
42	RECELL	Burn	Avita	2018

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#	Medical Countermeasure	Threat Area	Company Sponsor	Year
43	QMS Plazomicin Immunoassay	BSA	Achaogen (Thermo Fisher)	2018
44	FluChip-8G Influenza A+B Assay	Influenza	InDevR	2019
45	InBios International Manual Zika IgM assay	Zika	InBios	2019
46	ADVIA Centaur® Zika test	Zika	Siemens	2019
47	Trilogy Evo Universal (K181170) ventilator	Influenza	Phillips	2019
48	Silverlon	Chemical	Argentum Medical	2019
49	IMVAMUNE® Smallpox MVA Vaccine	Smallpox	Bavarian Nordic	2019
50	Applied Biosystems™ Bacillus anthracis Detection Kit	Anthrax	Applied Biosystems	2019
51	OraQuick Ebola Rapid Antigen	Ebola	OraSure	2019

Sources: Data collated from BARDA <https://www.phe.gov/about/barDA/Pages/default.aspx> and <https://www.medicalcountermeasures.gov/barDA/>. Last accessed on 30 October 2020.

Regulatory measures such as the Emergency Use Authorization option and the Animal Efficacy Rule, were also established to accelerate biosecurity product development. The latter allows the FDA to approve products for “serious or life-threatening conditions caused by exposure to lethal or permanently disabling toxic biological, chemical, radiological, or nuclear substances” based on animal models alone.¹⁴ (Aebersold 2012; Gronvall et al. 2007). Another regulatory incentive was the addition of the ‘medical countermeasures’ category in 2016 to the Priority Review Voucher (PRV) mechanism. The PRV was created in 2007 to facilitate the development of drugs with insufficient commercial markets, typically rare paediatric and neglected tropical diseases.¹⁵ The PRV grants the sponsor a voucher that can be used for accelerated review of any subsequent new drug or biologic in development or be sold to the highest bidder.

The 21st Century Cures Act of 2016 included further efforts to accelerate biosecurity R&D. For example, it authorized BARDA to partner with entities that use venture capital practices and methods (U. S. Government Accountability Office 2020). Several examples include DOD's DeVenCi, the Army's OnPoint, Red

¹⁴ To date, only a small handful of products were approved based on the rule: J&J's Levaquin (levofloxacin) for plague and GSK's raxibacumab for inhalation anthrax in 2012, Cangene's antitoxin for botulism in 2013, and Bayer Healthcare's Avelox (moxifloxacin) in 2015 also for plague (although the drug is also approved for other diseases).

¹⁵ See Knowledge Portal on Innovation and Access to Medicines Research Synthesis on PRV: <https://www.knowledgeportal.org/priority-review-vouchers>

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Planet, or the CIA's In-Q-Tel¹⁶ – all of which are approaches to mobilize private funding for the early discovery stage (Institute of Medicine (US) Forum on Drug Discovery 2010). For countermeasures development, the government would invest in technology development by a company, and the return on investment is considered to be products. In 2018, BARDA launched the Division of Research, Innovation, and Ventures, for “transforming health security by connecting federal government, scientists and venture capital investors” (“DRIVE” n.d.). Since 2013, BARDA has also been given greater flexibility in providing grants, for example, through the establishment of partnerships through ‘Other Transactions Authority’ or Other Transaction Agreements (OTAs). OTAs allow BARDA to collaborate with large pharmaceutical companies or other consortia to address market failure in certain fields, for example in antibiotics development (Houchens and Larsen 2017). The main difference between OTAs and traditional contracts with the federal government is that they are generally exempt from federal procurement laws and regulations. The terms of all provisions of an OTA are considered negotiable including on intellectual property rights, therefore allowing the pharmaceutical companies to continue to pursue profits as usual (Schwartz and Peters 2019). OTAs are defined as transactions other than procurement contracts, grants, and cooperative agreement, and are regarded as being exempt from laws that protect taxpayers and that give the government rights in publicly-funded data and IP (KEI 2020).

Matheny et al. (2008) estimated costs and projections for the US biosecurity pipeline against selected HHS targets (e.g., anthrax vaccine, anthrax antitoxin, filovirus vaccine, filovirus antiviral, Junin virus antiviral, smallpox antiviral, broad-spectrum antibiotic against Gram-positives and Gram-negatives bacteria). Their analysis included only drugs and vaccines, and used various data sources to identify candidates (e.g., pharmaceutical and biotech companies’ press releases and quarterly and/or annual reports, news reports, US government agency reports and databases, and a 2006 biodefense market survey).¹⁷ On the basis of historical pharmaceutical success/failure rates, the probability of at least one approved product within the existing pipeline varied: 85% for an anthrax vaccine, 72% for an anthrax antitoxin, and 12% for an antibiotic (Matheny, Mair, and Smith 2008). The authors concluded that to yield at least a 90% probability of one approved product for each category, the pipeline and BARDA funding would need to both double.

¹⁶ DeVenCi (Defense Venture Catalyst Initiative) is a DOD program to increase awareness of emerging technologies developed outside traditional DOD procurement. OnPoint and In-Q-Tel provide funding for technologies that directly benefit its target but also have applicability in the commercial sector. Both models rely on the clear demand expressed by the respective government agencies. In-Q-Tel identifies and invests in companies developing these technologies.
¹⁷ From (Trull, du Laney, and Dibner 2007); and the previous year’s work: Trull, Laney & Dibner 2006. Biodefense Market Report: vaccines, therapeutics, and diagnostics for bioterror agents 2006 BioAbility/BioWorld Atlanta GA (June 2006) – not available in public domain.

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4.3 Landscape of biosecurity R&D

Russell and Gronvall (2012) reviewed US biosecurity R&D since 2001. The paper noted some progress, such as the simplification of the acquisition process and “smallpox readiness” (Russell and Gronvall 2012). However, various reviews have identified many issues, notably in leadership, coordination, and challenges in working across “the complex interagency, intergovernmental, and intersectoral biodefense enterprise” (U. S. Government Accountability Office 2014; IoM 2002). In 2011, the GAO found a lack of a broad, integrated national strategy that encompassed all stakeholders with biosecurity responsibilities; a national biodefense strategy was subsequently launched in 2018 (US Government Accountability Office 2011).

Trull et al. (2007) documented the global biosecurity market in 2006 by assessing commercial drug pipeline databases, government publication and websites, and pharmaceutical industry news to determine the stages of the products in development and comparing them against the CDC list of priority pathogens. They found 152 prophylactic vaccines, with 102 in preclinical development, 35 in Phase 1, 12 in Phase 2 and only three in Phase 3.¹⁸ As for vaccines, the therapeutic pipeline was dominated by products in preclinical development (129), with only 16 in clinical trials. The paper also reported that 189 entities were involved in a biosecurity program, with 95 groups spread over 19 countries that were developing vaccines, and 94 groups in 14 different countries developing therapeutics. Sixty-two percent of these groups were located in the US – partially due to the large number of pharmaceutical and biotech companies there, but also due to the availability of sources to identify and confirm their involvement in biosecurity product development. The authors also identified several challenges of biosecurity product development, including having to address multiple infections or serotypes from the same agent, rapidly changing public health priorities in infectious diseases, and necessary product attributes, such as the possibility of high-volume administration (Trull, du Laney, and Dibner 2007).

Milne et al. (2017) reported the results from the Tufts Center for the Study of Drug Development (CSDD) review of global medical countermeasure landscape from 2016 (C. Milne, Smith, and Chakravarthy 2017). There has been an expansion in terms of the number of products in the pipeline, as compared to 2008 (263 versus 592 in 2016) (see **Figure 3**). There has been rapid growth in the pipeline for influenza, Ebola (which caused major outbreaks in 2014 and 2018), and Zika (which caused a major outbreak in 2015-2016), but not for ‘biodefense only’ products, such as those for smallpox or anthrax. More than half of all MCMs in development (332

¹⁸ 24 for anthrax, 19 for smallpox, 13 for plague, 14 for viral encephalitis and 28 for avian influenza. For therapeutics in development, 155 products were identified, with similar distribution of targets (20 for smallpox, 18 for viral encephalitis, 17 for anthrax, 14 for SARS and 16 for avian influenza).

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products, 56%) are for just five indications, while the remaining 57 indications have a total of only 289 products, or 4.5 candidates on average per indication. The category of products that applied mainly to bioterrorism tends to be purchased in bulk by governments and is limited in terms of market growth after reaching a plateau of volume needed for stockpiles. The authors argued that the primary market drivers for the private sector thus would be the availability of government funding and the continued threat posed by various pathogens as reflected in the threats list.

The number of companies that are active in developing countermeasures also reportedly increased: from 133 in 2008 to 303 in 2016. The top five countries where these companies (generally small and medium enterprises (SMEs)) are based are the US (159 companies), China (33), UK (12), Canada (10), and Switzerland (10). The role of SMEs appears to be important: SMEs account for 86% of the countermeasures pipeline, although the majority are in early stage development.¹⁹ Only ~3% of products in development by the 25 biggest pharmaceutical companies are countermeasures, although their role increases in later-stage development (C. Milne, Smith, and Chakravarthy 2017; C.-P. Milne 2019). According to the same authors in a blog post on countermeasure development in Asia, China is the world's second most active country in terms of its countermeasure pipeline (with 52 products in development or 49% of the Asian pipeline) followed by South Korea, India, Japan, Malaysia, Thailand, and Singapore. In terms of priority, the top indications in the pipeline are rabies (23%), typhoid (9%), hepatitis A (9%), and Japanese encephalitis (7%). Notably, these indications do not necessarily overlap with the US CDC priority-pathogens list, underscoring that threats considered a priority in one region of the world may differ from those in another. When it comes to specific products, Li et al. (2020) described China's R&D for Ebola: total funding of up to CNY 44.05 million (USD 6.27 million), predominantly in the basic research phase (87.8%), resulting in the Ad5-EBOV vaccine and six Ebola-related products approved by the National Medical Products Administration of China (Li, Chen, and Huang 2020).

¹⁹ See Knowledge Portal on Innovation and Access to Medicines, Research Synthesis: Role of Small and Medium-sized Enterprises, 2019, available at: <https://www.knowledgeportal.ch/small-and-medium-enterprises>.

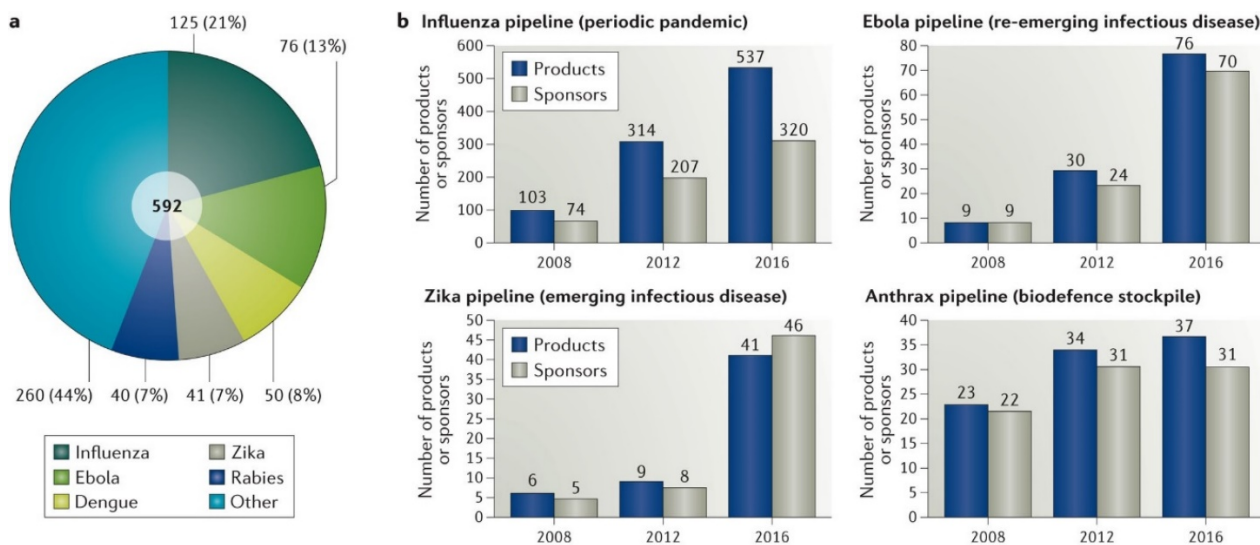
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Figure 3. The pipeline for medical countermeasures in 2016



Nature Reviews | Drug Discovery

a | Number of products in development for the most common medical countermeasure-related indications. b | Trends in the pipelines for selected medical countermeasures, illustrating the different drivers of product development.

Source: Milne, C., Smith, Z. & Chakravarthy, R. Landscape for medical countermeasure development. *Nat Rev Drug Discov* 16, 448 (2017). <https://doi.org/10.1038/nrd.2017.80> (Figure used with permission)

The G-FINDER project tracks annual investment in R&D for new products and technologies, including for EID, in which many of the diseases overlaps with biosecurity targets (Policy Cures Research, 2020).²⁰ Global funding for EID R&D is very narrowly focused on recent large-scale outbreaks, and the US government plays a dominant role in both product-specific and early-stage research. During the period of 2014-2018, there was an increase in EID basic research, which reached USD 886 million in 2018. The identified drivers were the Ebola and Zika epidemics, the establishment of the Coalition for Epidemic Preparedness Innovations (CEPI), and growing investment in ‘Disease X’ as an R&D priority. Overall EID funding in 2014-2018 was focused on vaccine R&D (51%), followed by basic research (17%), biologics (9.4%), and drugs (6.7%). The dominance of vaccine funding peaked in 2015, at the height of the West African Ebola epidemic, at nearly 70% of the global total, though this has since declined, reflecting the reactive nature of EID funding to date.

²⁰ Policy Cures Research defines EID as including the following disease groups: Ebola and Marburg, Zika, Lassa fever, Coronaviruses (Middle East Respiratory Syndrome and Severe Acute Respiratory Syndrome), Crimean-Congo Haemorrhagic Fever and Rift Valley Fever, Nipah and henipaviral diseases, Disease X and other non-disease-specific funding.

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5. Concluding remarks

This paper has offered a synthesis of the English-language literature on biosecurity R&D, and – reflecting the literature – has focused heavily on the US system. The overall approach for biosecurity R&D in the US can be summarized as: identifying current and future threats, setting priorities for countermeasure development, investing public funds directly in R&D by public and private actors, and providing incentives for private investment and R&D activity. The purpose, capacity, and financing of R&D for biosecurity influences the way R&D efforts are organized. Biosecurity R&D was built on a historical legacy of military R&D, with sustained investment from the government budget. The driver of continued military investment in R&D is civic duty and a mandate to protect national security. Private sector involvement in biosecurity R&D is heavily shaped by public funding, and legal, regulatory, technological, and financial incentives. Overall, increased awareness of the threat of emerging and re-emerging infectious disease outbreaks, seems to determine which countermeasures are a priority and how quickly they progress through the pipeline. The Covid-19 pandemic is likely to have profound impacts on national and global approaches to biosecurity R&D; this paper has offered a picture of the US pre-Covid-19 countermeasure R&D system, experiences from which are likely to shape policy debates in the years to come.

Research Limitations and Gaps

- Reviews of existing literature in languages other than English and covering other countries
- Insufficient studies on funding for biosecurity R&D
- Insufficient studies on outcomes of biosecurity R&D, and comparisons with time, success rates, and costs for other health technologies
- Insufficient empirical studies on the model of biosecurity R&D compared to other areas

Cited papers with abstracts

Aebersold, Paul. 2012. "FDA Experience with Medical Countermeasures under the Animal Rule." *Advances in Preventive Medicine* 2012. <https://doi.org/10.1155/2012/507571>.

Abstract: The Food and Drug Administration issued a final rule in May 2002 to permit the Agency to approve drugs or license biological products on the basis of animal efficacy studies for use in ameliorating or preventing serious or life-threatening conditions caused by exposure to lethal or permanently disabling

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toxic biological, chemical, radiological, or nuclear substances. Only two drugs were approved in the first nine years of the “Animal Rule” despite massive investment by the federal government since 2001 to stimulate development of medical countermeasures to biological threats. This article therefore examines the Food and Drug Administration reviews made public after approval of those two drugs and the public discussion at the Agency's Anti-Infective Drugs Advisory Committee of one biological product under development under the Animal Rule. Despite the paucity of approved drugs or licensed biological products as medical countermeasures, several investigational drugs have been placed in the National Strategic Stockpile for use as medical countermeasures, if needed.

Aronson, Naomi E., John W. Sanders, and Kimberly A. Moran. 2006. “In Harm’s Way: Infections in Deployed American Military Forces.” *Clinical Infectious Diseases* 43 (8): 1045–51. <https://doi.org/10.1086/507539>.

Abstract: Hundreds of thousands of American service members have been deployed to Afghanistan and Iraq since 2001. With emphasis on the common infections and the chronic infections that may present or persist on their return to the United States, we review the data on deployment-associated infections. These infections include gastroenteritis; respiratory infection; war wound infection with antibiotic-resistant, gram-negative bacteria; Q fever; brucellosis; and parasitic infections, such as malaria and leishmaniasis.

Artenstein, Andrew W., Jason M. Opal, Steven M. Opal, Edmund C. Tramont, Georges Peter, and Phillip K. Russell. 2005. “History of U.S. Military Contributions to the Study of Vaccines against Infectious Diseases.” *Military Medicine* 170 (4S): 3–11. <https://doi.org/10.7205/MILMED.170.4S.3>.

Abstract: The U.S. military has a long and illustrious history of involvement with vaccines against infectious diseases. For more than 200 years, the military has been actively engaged in vaccine research and has made many important contributions to the development of these products for use in disease prevention and control. Through the efforts of military researchers, numerous serious threats to the health of American troops and their families have been mitigated.

Bailey, Mark S. 2013. “A Brief History of British Military Experiences with Infectious and Tropical Diseases.” *BMJ Military Health* 159 (3): 150–57. <https://doi.org/10.1136/jramc-2013-000087>.

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Abstract: Infectious and tropical diseases have been a problem for British expeditionary forces ever since the Crusades. Outbreaks were especially common on Navy ships from the 16th to 18th centuries due to poor living conditions and travel to the tropics. However, since these occurred in small, isolated and controlled environments it meant that naval medical practitioners were able to keep detailed records and develop empirical approaches for their prevention. The first Royal Naval Hospitals were established in response to these diseases and Royal Navy doctors made valuable early contributions towards understanding them. Even larger outbreaks of infectious and tropical diseases occurred in the Army during the Napoleonic, Crimean and Boer Wars and throughout the colonial era, which strongly influenced the formation of the Army Medical Services including provision for teaching and research. The establishment of germ theory led to a golden era of discovery regarding these diseases and British Army doctors made numerous important contributions. Subsequent improvements in prevention, diagnosis and treatment reduced the mortality from infectious and tropical diseases during the World Wars, but they remained a significant problem in the non-European campaigns and also the numerous 'small wars' that followed. Even in the 21st century some of these diseases still cause outbreaks with significant morbidity and impact on deployments, but the military clinical and academic resources to deal with them are now much reduced. Preventive measures such as hygiene, sanitation, infection control, vaccination and chemoprophylaxis are invaluable, but history shows that these can become neglected over time and disrupted or overwhelmed during the early or most intense stages of military operations. This is why military specialists in infectious diseases, tropical medicine, sexual health, medical microbiology and communicable diseases control are still required.

BARDA. 2019. "The Power of Partnership: BARDA Ushers in 50th FDA-Approved Product for Health Security." ASPR Blog. 2019. <https://www.phe.gov/ASPRBlog/Lists/Posts/Post.aspx?ID=362>.

Abstract: not available.

Barras, V., and G. Greub. 2014. "History of Biological Warfare and Bioterrorism." *Clinical Microbiology and Infection* 20 (6): 497–502. <https://doi.org/10.1111/1469-0691.12706>.

Abstract: Bioterrorism literally means using microorganisms or infected samples to cause terror and panic in populations. Bioterrorism had already started 14

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centuries before Christ, when the Hittites sent infected rams to their enemies. However, apart from some rare well-documented events, it is often very difficult for historians and microbiologists to differentiate natural epidemics from alleged biological attacks, because: (i) little information is available for times before the advent of modern microbiology; (ii) truth may be manipulated for political reasons, especially for a hot topic such as a biological attack; and (iii) the passage of time may also have distorted the reality of the past. Nevertheless, we have tried to provide to clinical microbiologists an overview of some likely biological warfare that occurred before the 18th century and that included the intentional spread of epidemic diseases such as tularaemia, plague, malaria, smallpox, yellow fever, and leprosy. We also summarize the main events that occurred during the modern microbiology era, from World War I to the recent 'anthrax letters' that followed the World Trade Center attack of September 2001. Again, the political polemic surrounding the use of infectious agents as a weapon may distort the truth. This is nicely exemplified by the Sverdlovsk accident, which was initially attributed by the authorities to a natural foodborne outbreak, and was officially recognized as having a military cause only 13 years later.

Bavaro, Mary F., Daryl J. Kelly, Gregory A. Dasch, Braden R. Hale, and Patrick Olson. 2005. "History of U.S. Military Contributions to the Study of Rickettsial Diseases." *Military Medicine* 170 (4S): 49–60.
<https://doi.org/10.7205/MILMED.170.4S.49>.

Abstract: Rickettsial diseases have affected the military throughout history. Efforts such as those of the Joint U.S. Typhus Commission near the beginning of World War II and of military researchers since have reduced the impact of these diseases on U.S. and Allied forces. Despite the postwar development of effective antibiotic therapies, the newly emerging antibiotic-resistant scrub typhus rickettsial strains of the Asian Pacific region mandate continued research and surveillance. Similarly, tick-infested training areas in the United States and similar exposure abroad render the spotted fevers and the ehrlichioses problematic to deployed troops. The military continues to work on countermeasures to control the arthropod vectors, as well as actively participating in the development of rapid accurate diagnostic tests, vaccines, and improved surveillance methods. Several rickettsial diseases, including epidemic typhus, scrub typhus, the ehrlichioses, and the spotted fevers, are reviewed, with emphasis on the military historical significance and contributions.

Beaumier, Coreen M., Ana Maria Gomez-Rubio, Peter J. Hotez, and Peter J. Weina. 2013. "United States Military Tropical Medicine: Extraordinary Legacy, Uncertain Future." *PLOS Neglected Tropical Diseases* 7 (12): e2448.
<https://doi.org/10.1371/journal.pntd.0002448>.

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Abstract: Throughout the 20th century and into this new millennium, American troops in combat have been devastated by tropical infections. In response, the United States military has assembled an essential scientific and public health capability to combat these diseases. But the legacy of military tropical medicine now benefiting many aspects of global health is under threat.

Binder, Patrice. 1999. "Biomedical Research: Its Mission within the French Military Medical Service." *Military Medicine* 164 (5): 341–45.
<https://doi.org/10.1093/milmed/164.5.341>.

Abstract: The French Military Medical Service is organized as a distinct corps to support Army, Navy, and Air Force operations. This complex mission is accomplished through five operational components: (1) direct medical support of the force units; (2) hospital nursing and expertise; (3) biomedical research; (4) biomedical training; and (5) medical supply. Additionally, the French Military Medical Service is committed to humanitarian and civil medical support. Advanced biomedical research, particularly on infectious diseases and treatment of injuries, is actively pursued. Fundamental and applied research is needed to anticipate potential threats and improve medical support and care of French forces. The importance of biomedical research was recognized as necessary to develop technological improvements in rescue operations and to provide the military command with scientifically based advice. Biomedical military research has often been the engine of progress in medicine and surgery. Chief among those developments has been a special emphasis on infectious diseases and wound treatment.

Casadevall, Arturo, Susan A. Ehrlich, David R. Franz, Michael J. Imperiale, and Paul S. Keim. 2008. "Biodefense Research: A Win-Win Challenge." *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* 6 (4): 291–92.
<https://doi.org/10.1089/bsp.2008.1114>.

Abstract: Not available.

Chang, Zengyi. 2016. "The Discovery of Qinghaosu (Artemisinin) as an Effective Anti-Malaria Drug: A Unique China Story." *Science China Life Sciences* 59 (1): 81–88. <https://doi.org/10.1007/s11427-015-4988-z>.

Abstract: Not available.

Christopher, George W., Brian K. Agan, Theodore J. Cieslak, and Patrick E. Olson. 2005. "History of U.S. Military Contributions to the Study of Bacterial Zoonoses." *Military Medicine* 170 (4S): 39–48.
<https://doi.org/10.7205/MILMED.170.4S.39>.

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Abstract: Bacterial zoonoses have afflicted campaigns throughout military history, at times playing an important role in determining their outcomes. In addition, zoonotic bacteria are among the leading biological warfare threats. The U.S. military medical services have been at the forefront of research to define the basic microbiology, ecology, epidemiology, and clinical aspects of these diseases. This historical review discusses the military significance of plague, Q fever, anthrax, leptospirosis, bartonellosis, tularemia, and brucellosis and the U.S. military medical research counteroffensive. These contributions have ranged from basic molecular biology to elegant epidemiological surveys, from defining pathogenesis to developing new vaccine candidates. In an era of emerging diseases and biological weapons, the U.S. military will continue to lead a dynamic research effort to counter these disease threats.

Crum, Nancy F., Naomi E. Aronson, Edith R. Lederman, Janice M. Rusnak, and John H. Cross. 2005. "History of U.S. Military Contributions to the Study of Parasitic Diseases." *Military Medicine* 170 (4S): 17–29. <https://doi.org/10.7205/MILMED.170.4S.17>.

Abstract: U.S. military researchers have made major contributions to the discovery, diagnosis, treatment, and prevention of a number of parasitic diseases. We review the paramount U.S. military contributions to the understanding of leishmaniasis, filariasis, schistosomiasis, trypanosomiasis, gastrointestinal parasites, intestinal capillariasis, and angiostrongyliasis.

DARPA. 2015. "DARPA: Creating Breakthrough Technologies for National Security." <https://www.darpa.mil/attachments/CreatingBreakthroughTechnologiesforNationalSecurity%20Update.pdf>.

Abstract: Not available.

DeFrancesco, Laura. 2004. "Throwing Money at Biodefense." *Nature Biotechnology* 22 (4): 375–78. <https://doi.org/10.1038/nbt0404-375>.

Abstract: US funding for biodefense research continues on an upward trend, but some say the effort is misguided.

Dembek, Zygmunt F., Jerry L. Mothershead, Tesema Chekol, David B. Myers, Ronald G. Meris, Dana Meranus, and Aiguo Wu. 2017. "Operational Perspective of Lessons Learned From the Ebola Crisis." *Military Medicine* 182 (1–2): e1507–13. <https://doi.org/10.7205/MILMED-D-16-00074>.

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Abstract: Given its potential to quickly spread internationally and initially uncontrollable nature, the 2014 to 2015 Ebola outbreak has implications for global biosecurity. The Defense Threat Reduction Agency's Technical Reachback provided near real-time analysis and recommendations as outbreak-relevant events unfolded. Our review of often-conflicting or incomplete information was required to answer policy decision makers about the expanding Ebola epidemic, and enable the formulation of best-possible U.S. Department of Defense and Government response. Challenging questions often did not have obvious information available from which to provide a definitive answer. Nevertheless, through use of best-practice science and medicine, we provided timely and scientifically accurate weekly review for decision makers. Our comprehensive analyses included the nature of the outbreak, its global and national impact, contributing factors to this and future Ebola outbreaks, the U.S. Government and international response, and continuing interventions. We also provided guidance for Ebola transmission outside of West Africa, medical countermeasures, challenges with the international response, lessons learned, major constraints, and considerations for future preparedness. We believe an assessment of these events may help an improved response for future infectious disease outbreaks with global and national security implications.

DOD, US. 2018. "DARPA 1958-2018." 2018: Defence Advanced Research Project Agency. https://www.darpa.mil/attachments/DARAPA60_publication-no-ads.pdf.

Abstract: Not available.

Dooley, David P. 2005. "History of U.S. Military Contributions to the Study of Viral Hepatitis." *Military Medicine* 170 (4S): 71–76. <https://doi.org/10.7205/MILMED.170.4S.71>.

Abstract: Epidemic jaundice, although known by armies since ancient times, became a concern of the U.S. military only after outbreaks occurred during World War II. Early work by military investigators defined, for the first time, the existence of two different forms of hepatitis. Subsequently, investigators described the effective prevention of symptomatic hepatitis using immune serum globulin. Military researchers contributed to the isolation of and testing for the virus of infectious hepatitis, work that was then instrumental in the designing and fielding of a hepatitis A vaccine. Hepatitis B contributions included the elaboration of community-based epidemiology and description of the efficacy of immune serum globulin prophylaxis. Most recently, studies on hepatitis E defined the epidemiology, performed genomic sequencing, and developed a DNA vaccine currently being tested against the disease. Major

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research contributions to the understanding of and protection against viral hepatitis have been made by the military medical establishment over the past 60 years.

“DRIVE: Transforming Health Security” n.d. Accessed July 16, 2020.
<https://drive.hhs.gov/about.html>.

Abstract: Not available.

Feldbaum, Harley, Kelley Lee, and Preeti Patel. 2006. “The National Security Implications of HIV/AIDS.” *PLOS Medicine* 3 (6): e171.
<https://doi.org/10.1371/journal.pmed.0030171>.

Abstract: Feldbaum and colleagues look at evidence on the links between HIV and national security, and evaluate the risks and benefits of addressing HIV/AIDS as a national security issue.

Fu, Xiao-Bing. 2014. “Military Medicine in China: Old Topic, New Concept.” *Military Medical Research* 1 (1): 2. <https://doi.org/10.1186/2054-9369-1-2>.

Abstract: Military medicine is important in both war and peace. In China, military medicine plays a key role in supporting and maintaining health, in preventing injuries and diseases in military staff and in enhancing the military armed forces during war. Additionally, military medicine participates in actions such as emergency public health crises, natural disasters, emerging conflicts and anti-terrorist campaigns during peacetime. In this paper, we summary the current condition and achievements in military medicine in China and provide our perspective for its future.

Gibbons, Robert V., Ananda Nisalak, In-Kyu Yoon, Darunee Tannitisupawong, Kamchai Rungsimunpaiboon, David W. Vaughn, Timothy P. Endy, et al. 2013. “A Model International Partnership for Community-Based Research on Vaccine-Preventable Diseases: The Kamphaeng Phet-AFRIMS Virology Research Unit (KAVRU).” *Vaccine* 31 (41): 4487–4500.
<https://doi.org/10.1016/j.vaccine.2013.07.082>.

Abstract: This paper describes an international collaboration to carry out studies that contributed to the understanding of pathogenesis, diagnosis, treatment, and prevention of several diseases of public health importance for Thailand and the United States. In Kamphaeng Phet Province, Thailand, febrile syndromes, including encephalitis, hepatitis, hemorrhagic fever, and influenza-like illnesses, occurred commonly and were clinically diagnosed, but the etiology was rarely confirmed. Since 1982, the Kamphaeng Phet Provincial Hospital, the Thai Ministry

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of Public Health, and the US Army Component of the Armed Forces Research Institute of Medical Sciences, along with vaccine manufacturers and universities, have collaborated on studies that evaluated and capitalized on improved diagnostic capabilities for infections caused by Japanese encephalitis, hepatitis A, dengue, and influenza viruses. The collaboration clarified clinical and epidemiological features of these infections and, in large clinical trials, demonstrated that vaccines against Japanese encephalitis and hepatitis A viruses were over 90% efficacious, supporting licensure of both vaccines. With the introduction of Japanese encephalitis vaccines in Thailand's Expanded Program on Immunization, reported encephalitis rates dropped substantially. Similarly, in the US, particularly in the military populations, rates of hepatitis A disease have dropped with the use of hepatitis A vaccine. Studies of the pathogenesis of dengue infections have increased understanding of the role of cellular immunity in responding to these infections, and epidemiological studies have prepared the province for studies of dengue vaccines. Approximately 80 publications resulted from this collaboration. Studies conducted in Kamphaeng Phet provided experience that contributed to clinical trials of hepatitis E and HIV vaccines, conducted elsewhere. To provide a base for continuing studies, The Kamphaeng Phet-AFRIMS Virology Research Unit (KAVRU) was established. This paper reviews the origins of the collaboration and the scientific observations made between 1982 and 2012.

Gottron, Frank. 2014. "The Project BioShield Act: Issues for the 113th Congress," June, 24.

Abstract: In 2004, Congress passed the Project BioShield Act (P.L. 108-276) to provide the federal government with new authorities related to the development, procurement, and use of medical countermeasures against chemical, biological, radiological, and nuclear (CBRN) terrorism agents. However, the government still lacks countermeasures against many of the CBRN terrorism agents determined by the government to pose the greatest threat. Congress is likely to consider whether modifications of these authorities or new authorities would help address remaining gaps.

Link: <https://fas.org/sgp/crs/terror/R43607.pdf>

Grabenstein, John D., Phillip R. Pittman, John T. Greenwood, and Renata J. M. Engler. 2006. "Immunization to Protect the US Armed Forces: Heritage, Current Practice, and Prospects." *Epidemiologic Reviews* 28 (1): 3–26. <https://doi.org/10.1093/epirev/mxj003>.

Abstract: Americans serving with the US Armed Forces need protection from the dangerous infections that they can contract during training, based on

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occupation, during overseas deployment, or because of underlying health status. For over 230 years, the military health-care system has immunized troops to protect them personally and to help them accomplish their missions. Military researchers have invented, developed, and improved vaccines and immunization delivery methods against more than 20 diseases. This article consolidates content from several previous historical reviews, adds additional sources, and cites primary literature regarding military contributions and accomplishments. Discussion emphasizes smallpox, typhoid fever, tetanus, influenza, meningococcal disease, adenovirus, yellow fever, pneumococcal disease, and anthrax. Delivery issues include documentation, simultaneous immunization, seroscreening, safety surveillance, jet injection, and cold-chain management. Immunization policies for each major US conflict are described. Military immunization programs need to be individualized on the basis of personal contraindications and prior immunity. The proper conduct of military immunization programs respects the need for detailed education of military personnel, maximizes quality in immunization delivery, and supports quality clinical care to prevent and treat adverse events after immunization. Military immunization programs maintain the health of soldiers, marines, sailors, airmen, and coast guardsmen, the resources most critical to military success.

Grabenstein, John D., and William Winkenwerder. 2003. "US Military Smallpox Vaccination Program Experience." *JAMA* 289 (24): 3278–82. <https://doi.org/10.1001/jama.289.24.3278>.

Abstract: **CONTEXT:** The United States recently implemented smallpox vaccination of selected military personnel in a national program of preparedness against use of smallpox as a biological weapon. The resumption of smallpox vaccinations raises important questions regarding implementation and safety. **OBJECTIVE:** To describe the US military smallpox vaccination program. **DESIGN:** Descriptive study of the vaccination program from its inception on December 13, 2002, through May 28, 2003. **SETTING:** US Department of Defense (DoD) fixed and field medical treatment facilities on multiple continents and ships at sea. **SUBJECTS:** US service members and DoD civilian workers eligible for smallpox vaccination. **MAIN OUTCOME MEASURES:** Numbers of vaccinations and rates of vaccination exemptions, symptoms, and adverse events. Data were collected via reports to headquarters and rigorous surveillance for sentinel events. **RESULTS:** In 5.5 months, the DoD administered 450 293 smallpox vaccinations (70.5% primary vaccinees and 29.5% revaccinees). In 2 settings, 0.5% and 3.0% of vaccine recipients needed short-term sick leave. Most adverse events occurred at rates below historical rates. One case of encephalitis and 37 cases of acute myopericarditis developed after vaccination; all cases recovered. Among 19 461 worker-months of clinical contact, there were no cases of transmission of vaccinia from worker to patient, no cases of eczema vaccinatum or progressive

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vaccinia, and no attributed deaths. CONCLUSIONS: Mass smallpox vaccinations can be conducted safely with very low rates of serious adverse events. Program implementation emphasized human factors: careful staff training, contraindication screening, recipient education, and attention to bandaging. Our experience suggests that broad smallpox vaccination programs may be implemented with fewer serious adverse events than previously believed.

Gradmann, Christoph, Mark Harrison, and Anne Rasmussen. 2019. "Typhoid and the Military in the Early 20th Century." *Clinical Infectious Diseases* 69 (Supplement_5): S385–87. <https://doi.org/10.1093/cid/ciz672>.

Abstract: Background: In the decades following the discovery of the bacillus causing typhoid, in 1880, understanding of the disease formerly known as enteric fever was transformed, offering new possibilities for prevention. Gradually, measures that aimed to prevent infection from human carriers were developed, as were inoculations designed to confer immunity against typhoid and paratyphoid fevers. These were initially introduced in European armies that were regularly ravaged by typhoid, especially garrisons stationed in the colonies. This article reviews the research undertaken in the armed forces and the measures that they implemented in the years up to and during the First World War. Methods: The article is based on an analytical review of scientific literature from the early 19th century, focusing on the United Kingdom, Germany, and France. Results: The armies of the United Kingdom, Germany, and France undertook important work on the transmission of typhoid in the years between 1890 and 1918. Many preventive measures were introduced to deal with the spread of typhoid but these varied between the 3 countries, depending largely on their political traditions. Inoculation was particularly successful in preventing typhoid and greatly reduced the number of casualties from this disease during the First World War. Despite this, it proved difficult to prevent paratyphoid infection, and debates continued over which vaccines to use and whether or not immunization should be voluntary. Conclusions: By the end of the First World War, the value of inoculation in preventing the spread of typhoid had been proven. Its successful implementation demonstrates the importance of vaccination as a public health intervention during times of conflict and social upheaval.

Grant, Robert P. 1966. "National Biomedical Research Agencies: A Comparative Study of Fifteen Countries." *Minerva* 4 (4): 466–88. <https://doi.org/10.1007/BF02207979>.

Abstract: Not available.

Green, Manfred S, James LeDuc, Daniel Cohen, and David R Franz. 2019. "Confronting the Threat of Bioterrorism: Realities, Challenges, and Defensive

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Strategies." *The Lancet. Infectious Diseases* 19 (1): e2–13.
[https://doi.org/10.1016/S1473-3099\(18\)30298-6](https://doi.org/10.1016/S1473-3099(18)30298-6).

Abstract: Global terrorism is a rapidly growing threat to world security, and increases the risk of bioterrorism. In this Review, we discuss the potential threat of bioterrorism, agents that could be exploited, and recent developments in technologies and policy for detecting and controlling epidemics that have been initiated intentionally. The local and international response to infectious disease epidemics, such as the severe acute respiratory syndrome and west African Ebola virus epidemic, revealed serious shortcomings which bioterrorists might exploit when intentionally initiating an epidemic. Development of new vaccines and antimicrobial therapies remains a priority, including the need to expedite clinical trials using new methodologies. Better means to protect health-care workers operating in dangerous environments are also needed, particularly in areas with poor infrastructure. New and improved approaches should be developed for surveillance, early detection, response, effective isolation of patients, control of the movement of potentially infected people, and risk communication. Access to dangerous pathogens should be appropriately regulated, without reducing progress in the development of countermeasures. We conclude that preparedness for intentional outbreaks has the important added value of strengthening preparedness for natural epidemics, and vice versa.

Gronvall, Gigi Kwik, Dennis Trent, Luciana Borio, Robert Brey, Lee Nagao, and on behalf of the Alliance for Biosecurity. 2007. "The FDA Animal Efficacy Rule and Biodefense." *Nature Biotechnology* 25 (10): 1084–87.
<https://doi.org/10.1038/nbt1007-1084>.

Abstract: Not available.

Hayden, Erika. 2011. "Biodefence since 9/11: The Price of Protection." *Nature* 477 (7363): 150–52. <https://doi.org/10.1038/477150a>.

Abstract: Not available.

Hayden, Erika Check. 2011. "Pentagon Rethinks Bioterror Effort." *Nature* 477 (7365): 380–81. <https://doi.org/10.1038/477380a>.

Abstract: Not available.

Herron, Jonathan, and James Dunbar. 2018. "The British Army's Contribution to Tropical Medicine." *Clinical Medicine* 18 (5): 380–83.
<https://doi.org/10.7861/clinmedicine.18-5-380>.

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Abstract: Infectious disease has burdened European armies since the Crusades. Beginning in the 18th century, therefore, the British Army has instituted novel methods for the diagnosis, prevention and treatment of tropical diseases. Many of the diseases that are humanity's biggest killers were characterised by medical officers and the acceptance of germ theory heralded a golden era of discovery and development. Luminaries of tropical medicine including Bruce, Wright, Leishman and Ross firmly established the British Army's expertise in this area. These innovations led to the prevention of many deaths of both military personnel and civilians. British Army doctors were instrumental in establishing many of the teaching facilities that we now consider to be global leaders in tropical medicine. The impact of the Army in this field has certainly been significant in the past and its contribution continues to this day.

Ho, Zheng Jie Marc, Yi Fu Jeff Hwang, and Jian Ming Vernon Lee. 2014. "Emerging and Re-Emerging Infectious Diseases: Challenges and Opportunities for Militaries." *Military Medical Research* 1 (1): 21. <https://doi.org/10.1186/2054-9369-1-21>.

Abstract: The communal nature of living and training environments, alongside suboptimal hygiene and stressors in the field, place military personnel at higher risk of contracting emerging infectious diseases. Some of these diseases spread quickly within ranks resulting in large outbreaks, and personnel deployed are also often immunologically naïve to otherwise uncommonly-encountered pathogens. Furthermore, the chance of weaponised biological agents being used in conventional warfare or otherwise remains a very real, albeit often veiled, threat. However, such challenges also provide opportunities for the advancement of preventive and therapeutic military medicine, some of which have been later adopted in civilian settings. Some of these include improved surveillance, new vaccines and drugs, better public health interventions and inter-agency co-operations. The legacy of successes in dealing with infectious diseases is a reminder of the importance in sustaining efforts aimed at ensuring a safer environment for both military and the community at large.

Hoke, C. H., L. N. Binn, J. E. Egan, R. F. DeFraités, P. O. MacArthy, B. L. Innis, K. H. Eckels, et al. 1992. "Hepatitis A in the US Army: Epidemiology and Vaccine Development." *Vaccine* 10 (January): S75–79. [https://doi.org/10.1016/0264-410X\(92\)90550-4](https://doi.org/10.1016/0264-410X(92)90550-4).

Abstract: Control of hepatitis A has been an important concern for US military forces in war and peace. Immune serum globulin, although effective, is exceedingly cumbersome to use. The prevalence of antibody against hepatitis A is decreasing in young American soldiers, putting them at risk of hepatitis A

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during deployment. The US Army has been an active participant in development of hepatitis A vaccine. The first successful cell-culture-derived, formalin-inactivated hepatitis A vaccine was developed at the Walter Reed Army Institute of Research. This prototype vaccine was shown, in 1986, to be safe and immunogenic for humans. Since then we have evaluated the following issues related to the use of inactivated hepatitis A vaccines in military populations. Immunogenicity of vaccine derived from the CLF and HM175 strains; immunogenicity of hepatitis A vaccine given by jet injector; immunogenicity of hepatitis A vaccine when given with hepatitis B vaccine; immunogenicity when given in shortened schedules; safety and immunogenicity in Thai children; and efficacy under field conditions in the tropics. The hepatitis A vaccines which we tested are safe and highly immunogenic. Immunization by jet gun confers immunity equivalent to immunization by needle. Hepatitis A vaccine is equally potent when given with hepatitis B vaccine. Data on rapid immunization schedules and efficacy are under evaluation. We conclude that hepatitis A vaccine is a major improvement in our ability to prevent hepatitis A in soldiers.

Hoke, Charles H. 2005. "History of U.S. Military Contributions to the Study of Viral Encephalitis." *Military Medicine* 170 (4S): 92–105.
<https://doi.org/10.7205/MILMED.170.4S.92>.

Abstract: The viral encephalitides represent 15% (9 of 62) of the infectious diseases identified by the Armed Forces Medical Intelligence Center as being of U.S. military operational importance. Japanese encephalitis, tick-borne encephalitis, Venezuelan equine encephalitis, Eastern equine encephalitis, Western equine encephalitis, West Nile fever, rabies, St. Louis encephalitis, and Murray Valley (Australian) encephalitis are included on the Armed Forces Medical Intelligence Center threat list. This article reviews the U.S. military contributions to the prevention and control of the first seven of these.

Hospenthal, Duane R. 2005. "History of U.S. Military Contributions to the Understanding, Prevention, and Treatment of Infectious Diseases: An Overview." *Military Medicine* 170 (4S): 1–2.
<https://doi.org/10.7205/MILMED.170.4S.1>.

Abstract: The contributions of U.S. military and affiliated civilian personnel to the advancement of mankind's understanding, prevention, and treatment of infectious diseases are innumerable. This supplement of *Military Medicine* has been produced by the Armed Forces Infectious Diseases Society (AFIDS) to review and highlight the accomplishments of U.S. Department of Defense military and civilian researchers in this field of study. Contributions by U.S. Armed Forces investigators to better the health of the world are documented in the 11 articles that follow.

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Houchens, C, and J Larsen. 2017. "The Role of the Biomedical Advanced Research and Development Authority (BARDA) in Promoting Innovation in Antibacterial Product Development." *Economics and Innovation* (blog). February 8, 2017. <http://resistancecontrol.info/2017/the-role-of-the-biomedical-advanced-research-and-development-authority-barda-in-promoting-innovation-in-antibacterial-product-development/>.

Abstract: The Biomedical Advanced Research and Development Authority (BARDA) initiated a program in 2010 to address antimicrobial-resistant bacterial infections. Since then, BARDA has established several public-private partnerships aimed at the development of new antibacterial drugs and diagnostic platforms.

Hoyt, Kendall. 2006. "Vaccine Innovation: Lessons from World War II." *Journal of Public Health Policy* 27 (1): 38–57. <https://www.jstor.org/stable/3879064>

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 18 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.

Hsu, Elisabeth. 2006. "Reflections on the 'Discovery' of the Antimalarial Qinghao." *British Journal of Clinical Pharmacology* 61 (6): 666–70. <https://doi.org/10.1111/j.1365-2125.2006.02673.x>.

Abstract: Artemisinin, qinghaosu, was extracted from the traditional Chinese medical drug qinghao (the blue-green herb) in the early 1970s. Its 'discovery' can thus be hailed as an achievement of research groups who were paradoxically successful, working as they were at the height of a political mass movement in communist China, known in the West as the Cultural Revolution (1966–1976), a period that was marked by chaos, cruelty and enormous suffering, particularly, but by no means only, among the intelligentsia. On the one hand, China's cultural heritage was seen as a hindrance to progress and Mao set out to destroy it, but on the other hand he praised it as a 'treasure house', full of gems that, if adjusted to the demands of contemporary society, could be used 'for serving the people' (wei renmin fuwu). The success of the 'task of combating malaria' (kang nüe ren wu), sometimes known as 'task number five hundred and twenty-three', depended crucially on modern scientists who took seriously knowledge that was

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recorded in a traditional Chinese medical text, *Emergency Prescriptions Kept up one's Sleeve* by the famous physician Ge Hong (284–363).

Huang, Yanzhong. 2011. "Managing Biosecurity Threats in China." *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* 9 (1): 31–40. <https://doi.org/10.1089/bsp.2010.0060>.

Abstract: The author assesses 3 major biosecurity threats that China faces: biowarfare, bioterrorism, and biocrimes. He maintains that China has not yet articulated a coherent strategy to effectively tackle the challenges.

Institute of Medicine (US) Forum on Drug Discovery. 2010. *Partnerships and Alternative Business Models. The Public Health Emergency Medical Countermeasures Enterprise: Innovative Strategies to Enhance Products from Discovery Through Approval: Workshop Summary*. National Academies Press (US). <https://www.ncbi.nlm.nih.gov/books/NBK50752/>.

Abstract: As discussed above, there are several examples of successful medical countermeasures development under the Orphan Drug Act. Nonprofit disease research organizations and venture philanthropy groups are a force behind much of the progress in orphan product development. These organizations were primarily founded by patients because there was not enough research focus on their particular disease area (IOM, 2009). Their model is to derisk the research. Many of these groups are partnering successfully with industry, approaching biotechnology companies directly and offering funding for research in their area of interest. Margaret Anderson of FasterCures described two new rare disease-related activities that, if implemented effectively, may also serve as an opportunity for improved medical countermeasure development—the Cures Acceleration Network (CAN) and the Therapeutics for Rare and Neglected Diseases (TRND) program.

Institute of Medicine (US). 2002. *Protecting Our Forces: Improving Vaccine Acquisition and Availability in the U.S. Military*. <https://doi.org/10.17226/10483>.

Abstract: Infectious diseases continue to pose a substantial threat to the operational capacity of military forces. *Protecting Our Forces* reviews the process by which the U.S. military acquires vaccines to protect its warfighters from natural infectious disease threats. The committee found that poorly aligned acquisition processes and an inadequate commitment of financial resources within the Department of Defense vaccine acquisition process – rather than uncleared scientific or technological hurdles – contribute to the unavailability of some vaccines that could protect military personnel and, implicitly, the welfare and security of the nation. *Protecting Our Forces* outlines ways in which DoD

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might strengthen its acquisition process and improve vaccine availability. Recommendations, which include combining all DoD vaccine acquisition responsibilities under a single DoD authority, cover four broad aspects of the acquisition process: (1) organization, authority, and responsibility; (2) program and budget; (3) manufacturing; (4) and the regulatory status of special-use vaccines.

KEI. 2020. "Other Transaction Agreements: Government Contracts That May Eliminate Protections for the Public on Pricing, Access and Competition, Including in Connection with COVID-19." KEI Briefing Note 2020:3. <https://www.keionline.org/wp-content/uploads/KEI-Briefing-OTA-24June2020.pdf>.

Abstract: Not available.

KFF. 2020. "Breaking Down the U.S. Global Health Budget by Program Area." KFF. March 12, 2020. <https://www.kff.org/global-health-policy/fact-sheet/breaking-down-the-u-s-global-health-budget-by-program-area/>.

Abstract: Not available.

———. n.d. "U.S. Global Health Budget Tracker & Resources." KFF. Accessed November 16, 2020. <https://www.kff.org/interactive/u-s-global-health-budget-tracker/>

Abstract: This budget tracker provides regularly updated information on U.S. government funding for global health. It includes historical trends and tracks funding levels throughout the appropriations process. Data can be customized by fiscal year, sector, and U.S. agency.

Kitchen, Lynn W., Kendra L. Lawrence, and Russell E. Coleman. 2009. "The Role of the United States Military in the Development of Vector Control Products, Including Insect Repellents, Insecticides, and Bed Nets." *Journal of Vector Ecology* 34 (1): 50–61. <https://doi.org/10.1111/j.1948-7134.2009.00007.x>.

Abstract: Arthropod-borne diseases such as malaria, dengue, scrub typhus, and leishmaniasis continue to pose a significant threat to U.S. military forces deployed in support of operational and humanitarian missions. These diseases are transmitted by a variety of arthropods, including mosquitoes, ticks, chiggers, sand flies, and biting midges. In addition to disease threats, biting arthropods can cause dermatitis, allergic reactions, and sleep loss; therefore, monitoring of vector impact and integrated use of personal protective measures (PPM) and methods to reduce the vector populations are needed to protect service

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members. The U.S. military has played a vital role in vector identification tools and the development and testing of many of the most effective PPM and vector control products available today, including the topical repellent DEET and the repellent/insecticide permethrin, which is applied to clothing and bed nets. Efforts to develop superior products are ongoing. Although the U.S. military often needs vector control products with rather specific properties (e.g., undetectable, long-lasting in multiple climates) in order to protect its service members, many Department of Defense vector control products have had global impacts on endemic disease control.

Kitchen, Lynn W., and David W. Vaughn. 2007. "Role of U.S. Military Research Programs in the Development of U.S.-Licensed Vaccines for Naturally Occurring Infectious Diseases." *Vaccine* 25 (41): 7017–30. <https://doi.org/10.1016/j.vaccine.2007.07.030>.

Abstract: U.S. military physicians and researchers have collaborated in the development of eight U.S.-licensed vaccines since 1934, when product efficacy requirements were added to product safety requirements mandated in 1902. These vaccines include influenza (1945), rubella (1969), adenovirus types 4 and 7 (1980), meningococcus A, C, Y, W-135 (1981), hepatitis B (1981), oral typhoid (1989), Japanese encephalitis (1992), and hepatitis A (1995). Current efforts include new adenovirus and Japanese encephalitis vaccines, and vaccines to prevent dengue, diarrhea due to enterotoxigenic *E. coli*, *Campylobacter*, and *Shigella*, malaria, hemorrhagic fever with renal syndrome, scrub typhus, meningococcus type B, and HIV infection. All vaccines currently administered to U.S. military forces must be licensed by the U.S. Food and Drug Administration (FDA).

Kitchen, Lynn W., David W. Vaughn, and Donald R. Skillman. 2006. "Role of US Military Research Programs in the Development of US Food and Drug Administration--Approved Antimalarial Drugs." *Clinical Infectious Diseases: An Official Publication of the Infectious Diseases Society of America* 43 (1): 67–71. <https://doi.org/10.1086/504873>.

Abstract: US military physicians and researchers helped identify the optimum treatment dose of the naturally occurring compound quinine and collaborated with the pharmaceutical industry in the development and eventual US Food and Drug Administration approval of the synthetic antimalarial drugs chloroquine, primaquine, chloroquine-primaquine, sulfadoxine-pyrimethamine, mefloquine, doxycycline, halofantrine, and atovaquone-proguanil. Because malaria parasites develop drug resistance, the US military must continue to support the creation and testing of new drugs to prevent and treat malaria until an effective malaria vaccine is developed. New antimalarial drugs also benefit civilians residing in and traveling to malarious areas.

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Krishan, Kewal, Baljinder Kaur, and Anshula Sharma. 2017. "India's Preparedness against Bioterrorism: Biodefence Strategies and Policy Measures." *Current Science* 113 (09): 1675. <https://doi.org/10.18520/cs/v113/i09/1675-1682>.

Abstract: Bioterrorism is a realistic threat to the security and well-being of all countries. Significant legal and biodefence measures must be taken to prevent the production and use of deadly biological weapons. Previous bioterror incidences, dense population and congenial climatic conditions of India, make it vulnerable to bioterrorism threats. This review provides a comprehensive picture of the potential biothreats to the country, the existing laws and policies to counteract such incidences with a strong need for their implementation, and biodefence strategies for preparedness and protection, to make India a bioterror free nation.

Larsen, Joseph C., and Gary L. Disbrow. 2017. "Project BioShield and the Biomedical Advanced Research Development Authority: A 10-Year Progress Report on Meeting US Preparedness Objectives for Threat Agents." *Clinical Infectious Diseases* 64 (10): 1430–34. <https://doi.org/10.1093/cid/cix097>.

Abstract: The Biomedical Advanced Research and Development Authority (BARDA) conducts the advanced research and development and procurement of vaccines, therapeutics, and diagnostics for chemical, biological, radiological, and nuclear (CBRN) threats, pandemic influenza, and emerging infectious diseases. Since its inception in 2006, BARDA has played a critical role in partnering with industry to advance candidates in development toward US Food and Drug Administration (FDA) approval and then procuring them for potential use in a public health emergency. A decade into its existence, we now reflect on how BARDA has improved the preparedness posture of the United States against CBRN threat agents. BARDA has stockpiled or is the process of stockpiling 21 products for potential use in public health emergencies. Six products have achieved FDA approval or licensure. For several threat agents, the entire repertoire of medical countermeasures that have been procured and stockpiled should serve as a substantial deterrent to their future use in an attack.

Li, Chao, Jing-Yi Chen, and Yang-Mu Huang. 2020. "Challenges and Opportunities for China Entering Global Research and Development for Emerging Infectious Diseases: A Case Study from Ebola Experience." *Infectious Diseases of Poverty* 9 (1): 27. <https://doi.org/10.1186/s40249-020-00643-0>.

Abstract: BACKGROUND: China has emerged as a powerful platform for global pharmaceutical research and development (R&D) amid the 2014 Ebola outbreak.

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The research and development impact of developing countries on prevention and control of infectious disease outbreaks has long been underestimated, particularly for emerging economies like China. Here, we studied its research and development progress and government support in response to Ebola outbreak by timeline, input, and output at each research and development stage. This study will contribute to a deeper understanding of the research and development gaps and challenges faced by China, as well as providing evidence-based suggestions on how to accelerate the drug development process to meet urgent needs during future outbreaks. **METHODS:** Data were obtained from the National Nature Science Foundation of China database, PubMed database, Patent Search System of the State Intellectual Property Office of China, National Medical Products Administration, national policy reports and literature between Jan 1st, 2006 and Dec 31st, 2017. An overview of research funding, research output, pharmaceutical product patent, and product licensed was described and analyzed by Microsoft Excel. A descriptive analysis with a visualization of plotting charts and graphs was conducted by reporting the mean \pm standard deviation. **RESULTS:** China has successfully completed the research and development of the Ebola Ad5-EBOV vaccine within 26 months, while the preparation and implementation of clinical trials took relative long time. The National Nature Science Foundation of China funded CNY 44.05 million (USD 6.27 million) for Ebola-related researches and committed strongly to the phase of basic research (87.8%). A proliferation of literature arose between 2014 and 2015, with a 1.7-fold increase in drug research and a 2.5-fold increase in diagnostic research within 1 year. Three years on from the Ebola outbreak, six Ebola-related products in China were approved by the National Medical Products Administration. **CONCLUSIONS:** China has started to emphasize the importance of medical product innovation as one of the solutions for tackling emerging infectious diseases. Continuing research on the development of regulatory and market incentives, as well as a multilateral collaboration mechanism that unifies cross-channel supports, would advance the process for China to enter global R&D market more effectively.

Licina, Derek. 2012. "The Military Sector's Role in Global Health: Historical Context and Future Direction." *Global Health Governance* 6 (1). <http://blogs.shu.edu/wp-content/blogs.dir/109/files/2012/12/VOLUME-VI-ISSUE-1-FALL-2012-The-Military-Sector%E2%80%99s-Role-in-Global-Health-Historical-Context-and-Future-Direction.pdf>.

Abstract: The military sector's role in global health has gained visibility in recent years following its disaster responses to the South Asian Tsunami of 2004 and the earthquake that hit Haiti in 2010, in addition to humanitarian assistance activities conducted throughout the world. What is less clear is the overall contribution of the military sector to global health outcomes through direct and indirect investments. These investments range from medical research and

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development to peacekeeping operations while providing normative, technical assistance, and coordinating roles. Focusing efforts where required, as identified in international agreements such as the Geneva Conventions, and expanding multilateral organizations (e.g., the International Congresses of Military Medicine and Global Uniformed Services Task Force) may improve near term efficiencies. A collective international military global health financing mechanism to support these efforts is also necessary. Through further enhancement of existing structures, the military sector's current role can become more efficient and effective in supporting the global good. The health and security of individuals and states throughout the world deserve nothing less.

Lim, Matthew L., Gerald S. Murphy, Margaret Calloway, and David Tribble. 2005. "History of U.S. Military Contributions to the Study of Diarrheal Diseases." *Military Medicine* 170 (4S): 30–38.
<https://doi.org/10.7205/MILMED.170.4S.30>.

Abstract: Diarrhea, a scourge upon humanity since preliterate times, has been the particular nemesis of military forces. The Armed Forces of the United States have been in the forefront in the diagnosis, treatment, and prevention of diarrheal illness. U.S. military scientists and physicians implemented the first mandatory typhoid inoculation program, contributed to advances in water chlorination, and pioneered the use of antibiotics for typhoid fever. U.S. Navy physicians refined the intravenous treatment of cholera, reducing the death rate from 20% to less than 1%. Their studies of electrolyte and fluid balance in cholera, and the subsequent development of oral rehydration therapy for cholera and other diarrheal illness, have saved millions of lives worldwide. U.S. Army researchers refuted the desquamation theory of cholera pathogenesis, isolated the cholera exotoxin, and developed improved cholera vaccines. U.S. Army and Navy researchers pioneered the use of antibiotics for the treatment of typhoid fever, made major contributions to the treatment of dysentery, developed algorithms for the treatment of traveler's diarrhea, and continue active development of traveler's diarrhea and dysentery vaccines. U.S. military diarrheal research has directly contributed to the welfare of hundreds of millions of people.

Liu, Peilong, Yan Guo, Xu Qian, Shenglan Tang, Zhihui Li, and Lincoln Chen. 2014. "China's Distinctive Engagement in Global Health" 384: 13. doi: 10.1016/S0140-6736(14)60725-X

Abstract: China has made rapid progress in four key domains of global health. China's health aid deploys medical teams, constructs facilities, donates drugs and equipment, trains personnel, and supports malaria control mainly in Africa and Asia. Prompted by the severe acute respiratory syndrome (SARS) outbreak in

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2003, China has prioritised the control of cross-border transmission of infectious diseases and other health-related risks. In governance, China has joined UN and related international bodies and has begun to contribute to pooled multilateral funds. China is both a knowledge producer and sharer, offering lessons based on its health accomplishments, traditional Chinese medicine, and research and development investment in drug discovery. Global health capacity is being developed in medical universities in China, which also train foreign medical students. China's approach to global health is distinctive; different from other countries; and based on its unique history, comparative strength, and policies driven by several governmental ministries. The scope and depth of China's global engagement are likely to grow and reshape the contours of global health.

Matheny, Jason, Michael Mair, Andrew Mulcahy, and Bradley T. Smith. 2007. "Incentives for Biodefense Countermeasure Development." *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* 5 (3): 228–38. <https://doi.org/10.1089/bsp.2007.0030>.

Abstract: Therapeutics and vaccines are available for only a fraction of biological threats, leaving populations vulnerable to attacks involving biological weapons. Existing U.S. policies to accelerate commercial development of biodefense products have thus far induced insufficient investment by the biopharmaceutical industry. In this article, we examine the technical, regulatory, and market risks associated with countermeasure development and review existing and proposed federal incentives to increase industrial investment. We conclude with several recommendations. To increase industry's engagement in biodefense countermeasure development, Congress should expand BioShield funding, giving HHS the flexibility to fund a portfolio of biodefense countermeasures whose revenues are comparable to those of commercial drugs. Congress should establish tradable priority review vouchers for developers of new countermeasures. A National Academy of Sciences or National Biodefense Science Board should formally evaluate incentive programs and a government-managed "Virtual Pharma," in which HHS contracts separate stages of research, development, and production to individual firms.

Matheny, Jason, Michael Mair, and Bradley Smith. 2008. "Cost/Success Projections for US Biodefense Countermeasure Development." *Nature Biotechnology* 26 (9): 981–83. <https://doi.org/10.1038/nbt0908-981>.

Abstract: Not available.

Mervis, Jeffrey. 2016. "What Makes DARPA Tick?" *Science* 351 (6273): 549–53. <https://doi.org/10.1126/science.351.6273.549>.

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Abstract: Founded in 1958 in the aftermath of Sputnik, the Defense Advanced Research Projects Agency (DARPA) is supposed to make sure the U.S. military holds a technological edge over its enemies. Over the decades since, it has earned a reputation for using out-of-the-box thinking to solve what defense officials like to call "DARPA-hard" problems. The key to its success, say dozens of people who have worked for or with DARPA, is its cadre of program managers. Some call them DARPA's "secret sauce." Although they typically stay for only 4 to 5 years, they can have an enormous impact on the agency because of a combination of autonomy, authority, and ample resources that is rare in government. The stellar reputation of this small but mighty defense agency rests on the unparalleled clout of its program managers.

Michaud, Josh, Kellie Moss, and Jen Kates. 2012. "THE U.S. DEPARTMENT OF DEFENSE AND GLOBAL HEALTH: TECHNICAL VOLUME," 45. KFF. <https://www.kff.org/wp-content/uploads/2013/01/8358-t.pdf>

Abstract: This technical volume accompanies the Kaiser Family Foundation report The U.S. Department of Defense and Global Health, providing more detailed information on select topics covered in the report. This volume is divided into two sections: 1. Appendix A: organization charts and descriptions for DoD offices engaged in global health-related activities, by DoD component, as well as for key organizations relevant to DoD's global health-related activities; and 2. Appendix B: key guidance and policy documents governing and guiding DoD's global health-related activities.

Michel, R., J. P. Demoncheaux, M. A. Créach, C. Rapp, F. Simon, R. Haus-Cheymol, and R. Migliani. 2014. "Prevention of Infectious Diseases during Military Deployments: A Review of the French Armed Forces Strategy." *Travel Medicine and Infectious Disease, Occupational and Military Travel Medicine*, 12 (4): 330–40. <https://doi.org/10.1016/j.tmaid.2014.07.001>.

Abstract: Military personnel in operations have always paid a high toll to infections. In the 21st century some of these diseases still cause outbreaks with significant morbidity and impact on deployments. The new configuration of the French Armed Forces requires the permanent preparedness of deployable units. During deployments, soldiers are at least exposed to the infectious diseases that are observed in travellers, but with a potentially severe impact for the combatting strengths and a risk for cancelation or failure of the operational durability. The most common disabling infections during military deployments are faeco-oral transmitted diseases including diarrhoea. Preventing infectious diseases during deployments is of great concern and the French medical service has established a strategy based on different components; risk assessment and preparation, immunizations, protective measures and chemoprophylaxis, health

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education, health surveillance, outbreak investigations and medical tracking. In this review, the authors present the context of deployment of the French Armed Forces, the main health risks they are exposed to and develop the key points of the force health protection strategy, focused on infections related to military deployments.

Miller, Louis H., and Xinzhuan Su. 2011. "Artemisinin: Discovery from the Chinese Herbal Garden." *Cell* 146 (6): 855–58. <https://doi.org/10.1016/j.cell.2011.08.024>.

Abstract: This year's Lasker DeBakey Clinical Research Award goes to Youyou Tu for the discovery of artemisinin and its use in the treatment of malaria—a medical advance that has saved millions of lives across the globe, especially in the developing world.

Milne, Christopher, Zachary Peter Smith, and Ranjana Chakravarthy. 2017. "Landscape for Medical Countermeasure Development." *Nature Reviews Drug Discovery* 16 (7): 448–448. <https://doi.org/10.1038/nrd.2017.80>.

Abstract: Medical countermeasures (MCMs) encompass biologics, drugs or devices that may be used for biodefence against biological, chemical or radiological bioweapons, or in the event of naturally occurring emerging and re-emerging diseases, or natural disasters. Since 2008, the Tufts Center for the Study of Drug Development (CSDD) has routinely explored the R&D landscape for MCMs. Here, we present the findings of CSDD's most recent review, completed in 2016.

Milne, Christopher-Paul. 2019. "The Changing Landscape for New Drug Development: Medical Countermeasures (MCMs) as a Case Study." In *Curious 2018: Future Insights in Science and Technology*, edited by Ulrich A.K. Betz, 47–68. Cham: Springer International Publishing. https://doi.org/10.1007/978-3-030-16061-6_7.

Abstract: This chapter is comprised of materials adapted from previous publications authored by the Center for the Study of Drug Development at Tufts University School of Medicine (Tufts CSDD) over a ten-year period from 2010 through 2019. In addition, there are occasional infusions of updated commentary to "connect the dots" of how we got to where we are today. These publications may be requested from Tufts CSDD (if originally published in-house) or through the usual channels for requesting articles published in the public domain (permission to reprint the articles having been granted, where required). The text of the chapter is structured basically in a chronological fashion beginning with Tufts CSDD analysis of the early era of MCM evolution as a sub-sector from

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various extant therapeutic areas. It then chronicles the changes to the R&D paradigm in response to the challenges that emerged for both MCMs and biopharma in general. Finally, it ends with an exploration of the devolution of the MCM sub-sector back into its roots in the infectious disease area as an increase in actual outbreaks as well as other signals of global vulnerability to pandemic threats have minimized the MCM emphasis on biodefense against a wide range of CBRN agents in favor of public health tactics to address humankind's maladaptation to a world in which it is constantly assailed by its microbial competitors and symbionts, or to novel public health crises of its own making.

Moss, K, and J Michaud. 2013. "The U.S. Department of Defense and Global Health: Infectious Disease Efforts." <https://www.kff.org/global-health-policy/report/the-u-s-department-of-defense-and-global-health-infectious-disease-efforts/>.

Abstract: This report provides an overview of DoD's work pertaining to infectious diseases, looking at how activities are organized internally and ways they are coordinated with other U.S. government (USG) agencies and external partners. It focuses on the force health protection areas of medical research and development, health surveillance, and personnel education and training programs in infectious diseases, as well as to support the growing area of partnership engagement activities with partner countries. It identifies the various DoD funding streams for infectious disease efforts and spotlights DoD's work to address two of global health's key infectious disease challenges, HIV/AIDS and malaria, and DoD and USG funding supporting these efforts.

Mostofi, F K. 1968. "Contributions of the Military to Tropical Medicine." *Bulletin of the New York Academy of Medicine* 44 (6): 702–20.

Abstract: Not available.

Murray, Clinton K., Lynn L. Horvath, Charles D. Ericsson, and Christoph Hatz. 2007. "An Approach to Prevention of Infectious Diseases during Military Deployments." *Clinical Infectious Diseases* 44 (3): 424–30. <https://doi.org/10.1086/510680>.

Abstract: The US military conducts missions that range from major ground combat operations to disaster and humanitarian relief efforts. A primary goal of military medical professionals is disease prevention, which can be made more difficult in the context of short preparation times and prolonged deployment duration. The military uses a 6-component approach to deployment medicine, emphasizing preparation, education, personal protective measures, vaccines, chemoprophylaxis, and surveillance in an attempt to prevent infectious diseases.

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Many of the components of military deployment medicine are applicable to civilian disaster relief and humanitarian missions.

Mushtaq, Muhammad Umair. 2009. "Public Health in British India: A Brief Account of the History of Medical Services and Disease Prevention in Colonial India." *Indian Journal of Community Medicine* 34 (1): 6. <https://doi.org/10.4103/0970-0218.45369>.

Abstract: The evolution of public health in British India and the history of disease prevention in that part of world in the 19 th and early 20 th century provides a valuable insight into the period that witnessed the development of new trends in medical systems and a transition from surveys to microscopic studies in medicine. It harbors the earliest laboratory works and groundbreaking achievements in microbiology and immunology. The advent of infectious diseases and tropical medicine was a direct consequence of colonialism. The history of diseases and their prevention in the colonial context traces back the epidemiology of infectious diseases, many of which are still prevalent in third world countries. It reveals the development of surveillance systems and the response to epidemics by the imperial government. It depicts how the establishment of health systems under the colonial power shaped disease control in British India to improve the health of its citizens.

National Research Council. 2004. *Giving Full Measure to Countermeasures: Addressing Problems in the DoD Program to Develop Medical Countermeasures Against Biological Warfare Agents*. Washington, DC: The National Academies Press. <https://doi.org/10.17226/10908>.

Abstract: In recent years, substantial efforts have been initiated to develop new drugs, vaccines, and other medical interventions against biological agents that could be used in bioterrorist attacks against civilian populations. According to a new congressionally mandated report from the Institute of Medicine and National Research Council of the National Academies, to successfully develop these drugs, vaccines, and other medical interventions against biowarfare agents, Congress should authorize the creation of a new agency within the Office of the Secretary of the U.S. Department of Defense. The committee recommended that Congress should improve liability protections for those who develop and manufacture these products, to stimulate willingness to invest in new research and development for biowarfare protection. Giving Full Measure to Countermeasures also identifies other challenges—such as the need for appropriate animal models and laboratories equipped with high-level biosafety protections—that will require attention if DoD efforts to develop new medical countermeasures are to be successful.

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———. 2011. *The U.S. Medical Countermeasures Enterprise and Recent Reviews and Current Operation of the Special Immunizations Program. Protecting the Frontline in Biodefense Research: The Special Immunizations Program*. National Academies Press (US).
<https://www.ncbi.nlm.nih.gov/books/NBK209349/>.

Abstract: The Special Immunizations Program (SIP) remains a distinct but small component, but it is part of the overall U.S. military and civilian medical countermeasures (MCM) enterprise, so its effectiveness must be considered in this broader framework.

Needham, John. 2009. "PROJECT BIOSHIELD." GAO-09-820. GAO.
<https://www.gao.gov/new.items/d09820.pdf>.

Abstract: The Project BioShield Act of 2004 (BioShield Act) increased the federal government's ability to procure needed countermeasures to address threats from chemical, biological, radiological, and nuclear agents. Under the BioShield Act, the Department of Health and Human Services (HHS) was provided with new contracting authorities (increased simplified acquisition and micropurchase thresholds, and expanded abilities to use procedures other than full and open competition and personal services contracts) and was authorized to use about \$5.6 billion in a Special Reserve Fund to procure countermeasures. Based on the BioShield Act's mandate, GAO reviewed (1) how HHS has used its purchasing and contracting authorities, and (2) the extent to which HHS has internal controls in place to manage and help ensure the appropriate use of its new authorities. To do this work, GAO reviewed contract files and other HHS documents, including internal control guidance, which GAO compared with federal statutes and federal internal control standards.

Nolan, John M., Emad U. Samad, Lawrence F. Jindra, and Stephen G. Brozak. 2010. "Seeking Innovation: Incentive Funding for Biodefense Biotechs." *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* 8 (4): 365–72. <https://doi.org/10.1089/bsp.2010.0044>.

Abstract: In the current venture capital climate, it is easier to secure funding for late-stage, next-in-class therapeutic agents than for early-stage opportunities that have the potential to advance basic science and translational medicine. This funding paradigm is particularly problematic for the development of "dual-use" biothreat countermeasures such as antibiotics, vaccines, and antitoxins that target pathogens in novel ways and that have broad public health and biodefense applications. To address this issue, we propose the creation of the Drug Development Incentive Fund (DDIF), a novel funding mechanism that can stimulate the development of first-in-class agents that also possess the

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capability to guard against potential biothreats. This program would also support greater synergies between public funding and private venture investment. In a single act, this organization would secure science of national importance from disappearing, invest in projects that yield significant public health returns, advance the promises of preclinical and early phase research, revitalize biopharmaceutical investment, and create valuable innovation-economy jobs.

NSF - National Science Foundation “Report - S&E Indicators 2018 | Chapter 4 | Research and Development: U.S. Trends and International Comparisons,.” n.d. Accessed August 18, 2020.

<https://www.nsf.gov/statistics/2018/nsb20181/report/sections/research-and-development-u-s-trends-and-international-comparisons/recent-trends-in-federal-support-for-u-s-r-d>.

Abstract: One of the federal government's most significant roles in supporting the U.S. R&D system is the regular stream of funding it has provided for R&D activities conducted by both federal entities (agency intramural laboratories/facilities and FFRDCs) and external, nonfederal organizations such as businesses and academic institutions. Fifteen federal departments and a dozen other agencies engage in and/or provide funding for R&D in the United States (Table 4-15). Historically, the majority of the yearly federal funding total is accounted for by the R&D activities of a relatively small group of departments and agencies: Department of Defense (DOD); Department of Health and Human Services (HHS, primarily the National Institutes of Health [NIH]); Department of Energy (DOE); National Aeronautics and Space Administration (NASA); National Science Foundation (NSF); Department of Agriculture (USDA); and Department of Commerce (DOC).

Ockenhouse, Christian F., Alan Magill, Dale Smith, and Wil Milhous. 2005. “History of U.S. Military Contributions to the Study of Malaria.” *Military Medicine* 170 (4S): 12–16. <https://doi.org/10.7205/MILMED.170.4S.12>.

Abstract: More so than any other infectious disease, malaria has all too often affected the conduct of military operations in war and in some cases has disproportionately influenced the outcome. From Napoleon’s defensive action at Walcheren, to the Union Army’s attempts to take control of the Mississippi River at Corinth and Vicksburg, to the dreadful numbers of malaria casualties suffered by U.S. Marines on the islands of Efate and Guadalcanal during World War II and more recently in Liberia in 2003, malaria has extracted a heavy toll. In this article, we summarize a few of the significant contributions to malaria control by U.S. military personnel throughout its history. We review examples of scientific achievements, medical breakthroughs, and lessons learned from preceding wars that continue to drive the quest for effective antimalarial therapies and

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preventive vaccines. This review is by no means comprehensive or complete but serves as a testament to the skill, courage, self-sacrifice, and devotion to duty of the many who have faithfully served their country in the past and to those today who continue the struggle against this disease.

Ottolini, Martin G., and Mark W. Burnett. 2005. "History of U.S. Military Contributions to the Study of Respiratory Infections." *Military Medicine* 170 (4S): 66–70. <https://doi.org/10.7205/MILMED.170.4S.66>.

Abstract: History reveals a tremendous impact of respiratory pathogens on the U.S. military, dating back to the time of the Revolutionary and Civil Wars, during which 90% of casualties were for nonbattle injury, including several respiratory illnesses such as measles, whooping cough, and complicated pneumonia. The devastating impact of the influenza pandemic at the end of World War I led to a more proactive approach to research into the etiologies and potential preventive measures for such diseases. The development of the Armed Forces Epidemiological Board, with its subordinate commissions, coincided with the massive mobilization for World War II. Efforts of the board during and after the war led to significant progress against many common pathogens, such as the landmark studies of group A Streptococcus among young trainees at Warren Air Force Base, which led to the development of highly effective prophylactic and therapeutic strategies to prevent rheumatic fever. Military pediatricians contributed greatly to this work, as well as subsequent investigations into both the pathogenesis of and prophylactic therapy for a variety respiratory pathogens, including pertussis and respiratory syncytial virus. The momentum of this work continues to this day, among researchers from all three military branches.

Pages, F., M. Faulde, E. Orlandi-Pradines, and P. Parola. 2010. "The Past and Present Threat of Vector-Borne Diseases in Deployed Troops." *Clinical Microbiology and Infection* 16 (3): 209–24. <https://doi.org/10.1111/j.1469-0691.2009.03132.x>.

Abstract: From time immemorial, vector-borne diseases have severely reduced the fighting capacity of armies and caused suspension or cancellation of military operations. Since World War I, infectious diseases have no longer been the main causes of morbidity and mortality among soldiers. However, most recent conflicts involving Western armies have occurred overseas, increasing the risk of vector-borne disease for the soldiers and for the displaced populations. The threat of vector-borne disease has changed with the progress in hygiene and disease control within the military: some diseases have lost their military significance (e.g. plague, yellow fever, and epidemic typhus); others remain of concern (e.g. malaria and dengue fever); and new potential threats have appeared (e.g. West Nile encephalitis and chikungunya fever). For this reason,

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vector control and personal protection strategies are always major requirements in ensuring the operational readiness of armed forces. Scientific progress has allowed a reduction in the impact of arthropod-borne diseases on military forces, but the threat is always present, and a failure in the context of vector control or in the application of personal protection measures could allow these diseases to have the same devastating impact on human health and military readiness as they did in the past.

Policy Cures Research | Public Search. Data visualization, USA. 2020.
<https://gfinderdata.policycuresresearch.org/pages/data-visualisations/usa>

Abstract: Not available.

Policy Cures Research, G-FINDER data portal. 2020. "LANDSCAPE OF EMERGING INFECTIOUS DISEASE RESEARCH AND DEVELOPMENT: PREVENTING THE NEXT PANDEMIC." https://s3-ap-southeast-2.amazonaws.com/policy-cures-website-assets/app/uploads/2020/10/30095357/EID_Report.pdf.

Abstract: This report is divided into five main parts:

- 1) funding by disease group provides analysis of the funding for each of the priority pathogen families, ordered on the basis of total funding, including a breakdown of funding by product, funding across the various individual diseases and multi-disease categories, and major providers of funding;
- 2) funding by product type examines the division of global funding across vaccines, therapeutics, basic research and vector control and lays out the sources and allocation of funding within each product category;
- 3) funding to intermediaries lists the major providers and recipients of intermediary funding and analyses their contributions;
- 4) funders of emerging infectious disease R&D recognises the major providers of EID funding, by sector, nation and organisation, and summarises the distribution of public, private and philanthropic funding across the different disease groups; and
- 5) discussion, where we summarise our main conclusions from an analysis of five years of EID funding data and identify the key lessons for policy makers.

Quail, Geoffrey. 2015. "The Debt Tropical Medicine Owes to the Military." *Journal of Military and Veterans Health* 23 (3): 18.

Abstract: Prior to the twentieth century, infectious diseases took a heavy toll of troops and civilians from western countries posted to tropical locations. Indeed, it was generally recognised that in most prolonged campaigns the victorious side was the one experiencing the lesser number of medical casualties.

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Examples of wastage of soldiers of European nations are numerous. Even as late as the mid nineteenth century little had changed, with disastrous medical casualties being experienced in the Crimean and South Africa (Boer) Wars and in 1915 illness accounted for eight times as many casualties as trauma in the concluding months of the Gallipoli campaign.

Quinn, Roswell. 2013. "Rethinking Antibiotic Research and Development: World War II and the Penicillin Collaborative." *American Journal of Public Health* 103 (3): 426–34. <https://doi.org/10.2105/AJPH.2012.300693>.

Abstract: Policy leaders and public health experts may be overlooking effective ways to stimulate innovative antibiotic research and development. I analyzed archival resources concerning the US government's efforts to produce penicillin during World War II, which demonstrate how much science policy can differ from present approaches. By contrast to current attempts to invigorate commercial participation in antibiotic development, the effort to develop the first commercially produced antibiotic did not rely on economic enticements or the further privatization of scientific resources. Rather, this extremely successful scientific and, ultimately, commercial endeavor was rooted in government stewardship, intraindustry cooperation, and the open exchange of scientific information. For policymakers facing the problem of stimulating antibiotic research and development, the origins of the antibiotic era offer a template for effective policy solutions that concentrate primarily on scientific rather than commercial goals.

Rasmussen, Todd E., Patricia A. Reilly, and David G. Baer. 2014. "Why Military Medical Research?" *Military Medicine* 179 (8S): 1–2. <https://doi.org/10.7205/MILMED-D-14-00245>.

Abstract: The challenging circumstances that confronted military caregivers during the years of war in Afghanistan and Iraq established the imperative for military-oriented medical research. The burden of injury and illness resulting from this long period of combat operations, and the unique clinical and logistical considerations it engendered provide a compelling rationale for requirement-driven, well-coordinated medical research. Also referred to as "gap" driven and programmed, military trauma research is specifically aimed at providing readily deployable solutions to reduce morbidity and mortality from war-related injury.

Rasnake, Mark S., Nicholas G. Conger, C. Kenneth McAllister, King K. Holmes, and Edmund C. Tramont. 2005. "History of U.S. Military Contributions to the Study of Sexually Transmitted Diseases." *Military Medicine* 170 (4S): 61–65. <https://doi.org/10.7205/MILMED.170.4S.61>.

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Abstract: Sexually transmitted diseases have posed a threat to military service members throughout history. Among these diseases, syphilis, gonorrhea, and human immunodeficiency virus infections have accounted for the most significant morbidity and mortality rates in the U.S. military. In response, military researchers have made significant contributions to the treatment and prevention of these diseases. We review the impact of these diseases through the history of the U.S. Armed Forces and review selected sexually transmitted disease-oriented publications of U.S. military researchers.

Ratto-Kim, Silvia, In-Kyu Yoon, Robert M. Paris, Jean-Louis Excler, Jerome H. Kim, and Robert J. O’Connell. 2018. “The US Military Commitment to Vaccine Development: A Century of Successes and Challenges.” *Frontiers in Immunology* 9. <https://doi.org/10.3389/fimmu.2018.01397>.

Abstract: The US military has been a leading proponent of vaccine development since its founding. General George Washington ordered the entire American army to be variolated against smallpox after recognizing the serious threat that it posed to military operations. He did this on the recommendation from Dr. John Morgan, the physician-in-chief of the American army, who wrote a treatise on variolation in 1776. Although cases of smallpox still occurred, they were far fewer than expected, and it is believed that the vaccination program contributed to victory in the War of Independence. Effective military force requires personnel who are healthy and combat ready for worldwide deployment. Given the geography of US military operations, military personnel should also be protected against diseases that are endemic in potential areas of conflict. For this reason, and unknown to many, the US military has strongly supported vaccine research and development. Four categories of communicable infectious diseases threaten military personnel: (1) diseases that spread easily in densely populated areas (respiratory and dysenteric diseases); (2) vector-borne diseases (disease carried by mosquitos and other insects); (3) sexually transmitted diseases (hepatitis, HIV, gonorrhea); (4) diseases associated with biological warfare. For each category, the US military has supported research that has provided the basis for many of the vaccines available today. Although preventive measures and the development of drugs have provided some relief from the burden of malaria, dengue and HIV, the US military continues to fund research and development of prophylactic vaccines that will contribute to force health protection and global health. In the past few years, newly recognized infections with zika, Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS) viruses have pushed the US military to fund research and fast track clinical trials to quickly and effectively develop vaccines for emerging diseases. With US military personnel present in every region of the globe, one of the most cost-effective ways to maintain military effectiveness is to develop vaccines against prioritized threats to military members’ health.

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Russell, Philip K., and Gigi Kwik Gronvall. 2012. "U.S. Medical Countermeasure Development Since 2001: A Long Way Yet to Go." *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* 10 (1): 66–76. <https://doi.org/10.1089/bsp.2012.0305>.

Abstract: The U.S. government has taken significant steps toward developing and acquiring vaccines, drugs, and other medical countermeasures (MCMs) to protect and treat the population after a biological attack. In contrast to 2001, there is now a procedure for the Department of Health and Human Services (HHS) to develop, license, and stockpile MCMs for civilian use. Another major accomplishment is smallpox preparedness: There is now an adequate supply of vaccine for every person in the U.S., and there is an alternative vaccine meant for immunocompromised people and those with close contact with them. In spite of these and other accomplishments, the U.S. government MCM effort has been criticized by federal advisory committees, National Academy of Sciences reports, a congressional commission, and outside analysts who state that the efforts lack central leadership and accountability and that the pace of progress has been slow. A clear operational strategy for using MCMs, which would guide their development and acquisition, is also lacking. In this article, we review key areas of progress made since 2001 to develop and acquire MCMs, and we summarize what we judge to be the most critical and often mentioned areas where improvements are needed.

Sarewitz, Daniel. 2011. "Science Agencies Must Bite Innovation Bullet: Before Research Can Rebuild the US Economy It Must Learn from the Prosperous Heyday of the Military-Industrial Complex, Says Daniel Sarewitz." *Nature* 469 (7337): 137–38.

Abstract: In January's State of the Union address, President Barack Obama said that the United States had reached "our generation's Sputnik moment", and to respond to international competition he placed science and innovation at the centre of his policy agenda. Amid extraordinary budget pressures, he has called for a US\$7-billion (11.6%) increase in government spending on research for 2012 to help "rebuild" the economy. More money for science is always welcome, but can it deliver on the president's promises? Not necessarily. The post-Sputnik research enterprise that delivered innovation and prosperity is not the same as the one the President is counting on today.

Sargent Jr, John. 2020. "Government Expenditures on Defense Research and Development by the United States and Other OECD Countries: Fact Sheet." Fact Sheet R45441. Washington, D.C.: Congressional Research Service. <https://fas.org/sgp/crs/natsec/R45441.pdf>.

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Abstract: Research and development (R&D) has played a central role in the national security of the United States and its allies. R&D creates the foundation for new and improved technologies that underpin a wide range of applications. These applications include advanced weapons and systems that provide intelligence, medical treatments, and troop support. For more than 70 years, U.S. defense-related R&D has delivered breakthroughs in computing, communications, networks, satellites, fighter and bomber aircraft, aircraft carriers, submarines, tanks, tactical and strategic missiles, nuclear weapons, drones, advanced materials, autonomy, and other weapons and technologies. Military and policy analysts broadly agree that investments in R&D can provide substantial technological advantages against potential adversaries. This fact sheet provides data on government defense R&D funding of the United States and other countries of the Organisation for Economic Co-operation and Development (OECD).

Schwartz, Moshe, and Heidi M Peters. 2019. "Department of Defense Use of Other Transaction Authority: Background, Analysis, and Issues for Congress," CRS, 48.

Abstract: not available.

Shanks, G Dennis, Michael D Edstein, Qin Cheng, Steve Frances, John Aaskov, Ken Lilley, Robert Cooper, Ivor Harris, and Alyson Auliff. 2016. "Army Malaria Institute - Its Evolution and Achievements Fifth Decade: 2006-2015" 24 (1): 20. <https://jmvh.org/article/army-malaria-institute-its-evolution-and-achievements-fifth-decade-2006-2015/>

Abstract: As the Army Malaria Institute entered its fifth decade, its research mission expanded and matured. Five research departments were engaged in assessing a variety of malaria drugs, molecular biology, field, clinical and diagnostic studies while arbovirus vaccines and molecular epidemiology topics were studied. Internal and external reviews of the Army Malaria Institute (AMI) were conducted indicating that AMI should remain within the Joint Health Command and eventually change its name to better reflect its role within the entire Australian Defence Force and with infectious diseases beyond malaria. AMI's deployment capability is intended to be emphasised by the evolution of a separate identifiable unit involving the uniformed members. How AMI should manage its quasi-academic status as well as external research funds has not been determined yet. As AMI's Fiftieth Anniversary approaches in mid-2016, it is clear that the on-going threat of infectious diseases to the ADF will mean that the Institute will continue to evolve its structure and functions into the future.

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Smallman-Raynor, Matthew R., and Andrew D. Cliff. 2004. "Impact of Infectious Diseases on War." *Infectious Disease Clinics* 18 (2): 341–68. <https://doi.org/10.1016/j.idc.2004.01.009>.

Abstract: In his classic book *The Epidemics of the Middle Ages*, Hecker paints an apocalyptic picture of the association between war and infectious diseases. These "unfettered powers of nature" are "inscrutable in their dominion; destructive in their effects; stay the course of events; baffle the grandest plans; paralyze the boldest flights of the mind; and when victory seemed within their grasp, have often annihilated embattled hosts with the flaming sword of the angel of death".

Smith, Bradley T., Thomas V. Inglesby, and Tara O'Toole. 2003. "Biodefense R&D: Anticipating Future Threats, Establishing a Strategic Environment." *Biosecurity and Bioterrorism: Biodefense Strategy, Practice, and Science* 1 (3): 193–202. <https://doi.org/10.1089/153871303769201842>.

Abstract: not available.

Splino, Miroslav, Jiri Patocka, Roman Prymula, and Roman Chlibek. 2005. "Anthrax Vaccines." *Annals of Saudi Medicine* 25 (2): 143–49. <https://doi.org/10.5144/0256-4947.2005.143>.

Abstract: Anthrax, an uncommon disease in humans, is caused by a large bacterium, *Bacillus anthracis*. The risk of inhalation infection is the main indication for anthrax vaccination. Pre-exposure vaccination is provided by an acellular vaccine (anthrax vaccine adsorbed or AVA), which contains anthrax toxin elements and results in protective immunity after 3 to 6 doses. Anthrax vaccine precipitated (AVP) is administered at primovaccination in 3 doses with a booster dose after 6 months. To evoke and maintain protective immunity, it is necessary to administer a booster dose once at 12 months. In Russia, live spore vaccine (STI) has been used in a two-dose schedule. Current anthrax vaccines show considerable local and general reactogenicity (erythema, induration, soreness, fever). Serious adverse reactions occur in about 1% of vaccinations. New second-generation vaccines in current research programs include recombinant live vaccines and recombinant sub-unit vaccines.

Teneza-Mora, Nimfa, Joanne Lumsden, and Eileen Villasante. 2015. "A Malaria Vaccine for Travelers and Military Personnel: Requirements and Top Candidates." *Vaccine, Malaria Vaccines 2015*, 33 (52): 7551–58. <https://doi.org/10.1016/j.vaccine.2015.10.004>.

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Abstract: Malaria remains an important health threat to non-immune travelers with the explosive growth of global travel. Populations at high risk of acquiring malaria infections include once semi-immune travelers who visit friends and relatives, military forces, business travelers and international tourists with destinations to sub-Saharan Africa, where malaria transmission intensity is high. Most malaria cases have been associated with poor compliance with existing preventive measures, including chemoprophylaxis. High risk groups would benefit immensely from an efficacious vaccine to protect them against malaria infection and together make up a sizable market for such a vaccine. The attributes of an ideal malaria vaccine for non-immune travelers and military personnel include a protective efficacy of 80% or greater, durability for at least 6 months, an acceptable safety profile and compatibility with existing preventive measures. It is very likely that a malaria vaccine designed to effectively prevent infection and clinical disease in the non-immune traveler and military personnel will also protect semi-immune residents of malaria-endemic areas and contribute to malaria elimination by reducing or blocking malaria transmission. The RTS,S vaccine (GlaxoSmithKline) and the PfSPZ Vaccine (Sanaria Inc) are the leading products that would make excellent vaccine candidates for these vulnerable populations.

Thomas, Stephen J., James V. Lawler, and Timothy P. Endy. 2005. "History of U.S. Military Contributions to the Study of Viral Hemorrhagic Fevers." *Military Medicine* 170 (4S): 77–91. <https://doi.org/10.7205/MILMED.170.4S.77>.

Abstract: The viral hemorrhagic fever viruses represent a unique group of viruses that can produce large outbreaks of both animal and human disease and produce severe, highly fatal, human illnesses. The viral hemorrhagic fever viruses display a great deal of diversity in their genetic organization, vectors for transmission, and geographic distribution. They share common features in being able to induce a great deal of cellular damage and to elicit an immune response among humans that can result in severe hemorrhage, coagulopathy, shock, and death. The characteristics of the viral hemorrhagic fever viruses as arthropod-borne or rodent-borne viruses that can result in human illnesses with high morbidity and mortality rates make these viruses a unique threat, historically, currently, and in the future, to deployed soldiers around the world. In response to this threat, U.S. military scientists have been world leaders in the development of knowledge on the viral hemorrhagic fever viruses, from extensive fieldwork in areas in which these viruses are endemic, outbreak investigations of epidemics, and careful clinical studies elucidating the pathogenesis of severe disease. Defining the disease threat and creating practical countermeasures through the development of drugs and vaccines has been the major mission of military scientists and has resulted in numerous candidate vaccines currently in animal and human clinical trials.

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Trull, Melanie C., Tracey V. du Laney, and Mark D. Dibner. 2007. "Turning Biodefense Dollars into Products." *Nature Biotechnology* 25 (2): 179–84. <https://doi.org/10.1038/nbt0207-179>.

Abstract: Five years after the US anthrax attacks, and more than two years after BioShield legislation was ratified, a survey reveals that biodefense funding has thus far produced only a handful of products for clinical development.

U. S. Government Accountability Office. 2011. "National Preparedness: Improvements Needed for Acquiring Medical Countermeasures to Threats from Terrorism and Other Sources," no. GAO-12-121 (October). <https://www.gao.gov/products/GAO-12-121>.

Abstract: What GAO Found. Through PHEMCE, HHS laid out its CBRN medical countermeasure development and acquisition priorities in 2007 in a publicly available plan based primarily on two types of CBRN risk assessments one from the Department of Homeland Security (DHS) and one from HHS but HHS has not updated the plan as intended. The 2007 plan outlined spending for these priorities through 2013, when special federal funding for countermeasure acquisition will expire. HHS invested about \$1.9 billion in development and \$2.4 billion for acquisition of countermeasures to fulfill these priorities from fiscal year 2007 to fiscal year 2010. Since 2007, DHS and HHS have continued to assess the risks that CBRN agents pose to national security and public health, and HHS has reassessed decisions on the quantities and types of medical countermeasures needed. However, HHS has not updated its plan, as it had intended to do biennially, to indicate whether any priorities have changed. Further, HHS has not provided specific information on anticipated budget priorities for countermeasure acquisition--information desired by companies to help them decide whether to invest in product development. HHS has begun to address most recommendations from its August 2010 review of PHEMCE and of HHS's countermeasure activities, but HHS has not developed an adequate strategy to monitor implementation.

U. S. Government Accountability Office. 2014. "Biological Defense: DOD Has Strengthened Coordination on Medical Countermeasures but Can Improve Its Process for Threat Prioritization," no. GAO-14-442 (May). <https://www.gao.gov/products/GAO-14-442>.

Abstract: From fiscal years 2001 through 2013, the Department of Defense (DOD) received over \$4.3 billion in total funding (in constant fiscal year 2013 dollars) to research, develop, and make available medical countermeasures that respond to biological threat agents. Of that \$4.3 billion, approximately \$3.75 billion was for the research and development of new medical countermeasures.

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———. 2020. “Public Health Preparedness: HHS Has Taken Some Steps to Implement New Authority to Speed Medical Countermeasure Innovation,” no. GAO-20-601R (July). <https://www.gao.gov/products/GAO-20-601R>.

Abstract: The COVID-19 pandemic and other infectious disease outbreaks have raised concern about the nation's ability to prevent, respond to, or mitigate potential public health emergencies. Congress allowed the Department of Health and Human Services (HHS) to partner with a private, nonprofit entity to work on this problem.

United States. National Intelligence Council. 2000. “National Intelligence Estimate: The Global Infectious Disease Threat and Its Implications for the United States.” *Environmental Change and Security Project Report*, no. 6: 33–65. <https://www.wilsoncenter.org/publication/national-intelligence-estimate-the-global-infectious-disease-threat-and-its-implications>

Abstract: Infectious diseases are a leading cause of death, accounting for a quarter to a third of all deaths worldwide. The spread of infectious diseases results from both human behavior such as lifestyle choices, land-use patterns, increased trade and travel, and inappropriate use of antibiotic drugs, as well as mutations in pathogens. These excerpts from a January 2000 National Intelligence Estimate highlight the rising global health threat of new and reemerging infectious diseases. The National Intelligence Council argues that the infectious disease threat will complicate US and global security over the next 20 years. These diseases will endanger US citizens at home and abroad, threaten US armed forces deployed overseas, and exacerbate social and political instability in key countries and regions in which the US has significant interests, according to the report.

US Dept of HHS. n.d. “PHMCE Multi Year Budget 2017-2021.” Accessed November 16, 2020. <https://www.phe.gov/Preparedness/mcm/phemce/Documents/phemce-myb-2017-21.pdf>.

Abstract: The Public Health Service (PHS) Act, as amended by the Pandemic and All-Hazards Preparedness Reauthorization Act of 2013 (PAHPRA), requires the Office of the Assistant Secretary for Preparedness and Response (ASPR) to lead the development of a coordinated five-year budget plan for medical countermeasure (MCM) development and to update the plan annually. This Public Health Emergency Medical Countermeasures Enterprise (PHEMCE) Multiyear Budget Report (MYB) is the fourth submission in response to that requirement. This report includes the multiyear budgets for the Department of

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Health and Human Services (HHS) entities, or their divisions, that are members of the PHEMCE: the National Institutes of Health (NIH), ASPR's Biomedical Advanced Research and Development Authority (BARDA), the Strategic National Stockpile, and the Food and Drug Administration (FDA).

Warfield, Kelly L., and M. Javad Aman. 2016. "Role of Small Biotechnology Companies in the Fledgling Biodefense Vaccine Industry." *Expert Review of Vaccines* 15 (9): 1079–82. <https://doi.org/10.1586/14760584.2016.1168702>.

Abstract: Since Edward Jenner introduced immunization with cowpox in the late eighteenth century for smallpox prevention, vaccines have saved countless lives and trillions of dollars in public health and related expenditures. At the same time, a 40-billion-dollar-worldwide vaccine market has been created that is dominated by a few large pharmaceutical companies [1]. While the Food and Drug Administration (FDA) lists 80 licensed vaccine products [2], the number of diseases (22 pathogens or their toxic products) targeted is much smaller due to multiple competing products for high-value markets. This is a sobering reminder that successful vaccine development is a colossal undertaking plagued with risks and requires companies with a strong financial backbone as well as extensive experience and infrastructure.

Watson, Crystal, Matthew Watson, Daniel Gastfriend, and Tara Kirk Sell. 2018. "Federal Funding for Health Security in FY2019." *Health Security* 16 (5): 281–303. <https://doi.org/10.1089/hs.2018.0077>.

Abstract: This article is the latest in an annual series analyzing federal funding for health security programs. We examine proposed funding in the President's Budget Request for FY2019, provide updated amounts for FY2018, and update actual funding amounts for FY2010 through FY2017. Building health security for the nation is the responsibility of multiple agencies in the US federal government, as well as that of state, tribal, territorial, and local governments and the private sector. This series of articles focuses on the federal government's role in health security by identifying health security-related programs in public health, health care, national security, and defense and reporting funding levels for that ongoing work. This article is the latest in an annual series analyzing federal funding for health security programs. It examines proposed funding in the President's Budget Request for FY2019, provides updated amounts for FY2018, and updates actual funding amounts for FY2010 through FY2017. This series focuses on the federal government's role in health security by identifying health security-related programs in public health, health care, national security, and defense and reporting funding levels for that ongoing work.

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Yoeli, M. 1972. "The Evolution of Tropical Medicine: A Historical Perspective." *Bulletin of the New York Academy of Medicine* 48 (10): 1231–46.

Abstract: not available.

Zottig, Victor E., Katherine A. Carr, John G. Clarke, Moshe J. Shmuklarsky, and Mara Kreishman-Deitrick. 2020. "Army Antimalarial Drug Development: An Advanced Development Case Study for Tafenoquine." *Military Medicine* 185 (Supplement_1): 617–23. <https://doi.org/10.1093/milmed/usz304>.

Abstract: Malaria is classified as a top-tier infectious disease threat associated with a high risk for mortality among U.S. service members deployed overseas. As malarial drug resistance degrades the efficacy of current gold standard drugs for malarial prophylaxis and treatment, it is vitally important to maintain a robust drug pipeline to discover and develop improved, next-generation antimalarial prevention and treatment tools. The U.S. Army Medical Materiel Development Activity (USAMMDA) manages the medical product development of the malarial drug tafenoquine for malarial prophylaxis to address the threat to U.S. service members. Tafenoquine is an effective prophylactic drug against all parasite life cycle stages and all malaria species that infect humans. Thus, it provides broad capabilities in a single drug for malarial prophylaxis and treatment. Partnerships with industry are a crucial part of USAMMDA's medical product development strategy, by leveraging their drug development experience and manufacturing capabilities to achieve licensure and commercial availability. Additionally, these partnerships capitalize on expertise in the commercial market and help ensure that USAMMDA successfully translates a Department of Defense capability gap into a commercially available product. This article will highlight the strategies used to move this critical antimalarial drug through the development pipeline.

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ⁱ * For the purposes of this review, we have established three categories to describe the state of the literature: thin, considerable, and rich.

- Thin: There are relatively few papers and/or there are not many recent papers and/or there are clear gaps
- Considerable: There are several papers and/or there are a handful of recent papers and/or there are some clear gaps
- Rich: There is a wealth of papers on the topic and/or papers continue to be published that address this issue area and/or there are less obvious gaps

Scope: While many of these issues can touch a variety of sectors, this review focuses on medicines. The term “medicines” is used to cover the category of health technologies, including drugs, biologics (including vaccines), and diagnostic devices.

Disclaimer: The research syntheses aim to provide a concise, comprehensive overview of the current state of research on a specific topic. They seek to cover the main studies in the academic and grey literature, but are not systematic reviews capturing all published studies on a topic. As with any research synthesis, they also reflect the judgments of the researchers. The length and detail vary by topic. Each synthesis will undergo open peer review and be updated periodically based on feedback received on important missing studies and/or new research. Selected topics focus on national and international-level policies, while recognizing that other determinants of access operate at sub-national level. Work is ongoing on additional topics. We welcome suggestions on the current syntheses and/or on new topics to cover.

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