Military Relevance of Vaccine-Preventable Infectious Diseases

Subjects: Primary Health Care

Contributor: Roberto Biselli , Roberto Nisini , Florigio Lista , Alberto Autore , Marco Lastilla , Giuseppe De Lorenzo , Mario Stefano Peragallo , Tommaso Stroffolini , Raffaele D'Amelio

The military worldwide have always been challenged with the issue of infectious diseases, which may deeply influence the outcome of battles/wars. The military are particularly exposed to the risk of infectious diseases for a series of reasons, including the community life, often in precarious environmental conditions regarding the hygiene of water and food supply, sanitation, the traumatism with contaminated wounds, and the possibility to be exposed to extreme temperatures and to diseases unknown in their country of origin, for which no natural immunization has, therefore, been developed.

the military infectious diseases passive immunization vaccines

1. Smallpox

Smallpox was a feared infectious disease caused by one of two virus variants, *Variola major* and *Variola minor*, belonging to the genus *Orthopoxvirus*. Smallpox was characterized by an incubation period of 10–14 days, a transmission mainly through respiratory route [1], and symptomatology with fever, general malaise and a vesicular, and then pustular, skin rash. Historically it manifested with periodical epidemics. The disease was declared eradicated in 1980, following an aggressive vaccination campaign driven by the WHO [2]. It was highly contagious, with an average lethality of 15–30%, ranging from 1% in the case of variola minor up to more than 97% in the case of hemorrhagic smallpox. In the attempt to reduce the consequences of smallpox, the practice of variolation was reported starting from the tenth century in China, and probably in India. Variolation is the inoculation of the secretion of a smallpox lesion taken from a mild case in a susceptible subject to protect him/her from natural smallpox. This practice was in use for a long-time, even though burdened by relatively high mortality, of the order of 0.33%, but up to 3%, which was, however, markedly lower than the average lethality of the natural infection, approximately 16% [3]. The relevance of smallpox for the outcome of wars was demonstrated during the independence war of the American colonies against the British Army (1775–1783) and later in Europe during the Franco-Prussian war (1870–1871). In the former war in 1777, General George Washington ordered the variolation of the Continental Army after losing many soldiers because of smallpox, 1800 out of 7000 only in the last 2 weeks of May 1776 [4]. In 1796, Edward Jenner, an English physician, based on the observation that the milkmaids were protected from smallpox because of hand lesions contracted during the milking of cows affected by cowpox, decided to take the secretion of a cowpox lesion and inoculate it into a boy, who was later challenged with smallpox, to which he was protected.

This same experiment was repeated in 22 other volunteers, always with successful results, which were published in 1798 [5]. At the beginning of the nineteenth century in most European countries and the USA, vaccination was adopted, to become compulsory for infants in Bavaria (1807), Denmark (1810), Norway (1811), Bohemia and Russia (1812), Sweden (1816), Hanover (1821), and Great Britain (1853) [2]. Similar to most other infectious diseases, precarious hygienic conditions, as observed in war periods, facilitate the spreading and severity of infection; thus, the military all over the world immediately applied prophylaxis for this dreadful disease, in some countries well before the application to the general population. This was the case for Italy, where the smallpox vaccine became compulsory for the military nearly 30 years earlier than for the general population, for which smallpox vaccination was made compulsory for all newborns in 1888 [6]. Despite that the vaccination for the military in Prussia was mandatory since 1831 [1], it was only offered to the general population in Germany, whereas it was only made mandatory following the Franco-Prussian war in 1870–1871. However, the Prussian army was well protected during the smallpox outbreak; smallpox was nearly non-influent for the Prussian soldiers (only 278 soldiers died), whereas the French soldiers, for whom vaccination was compulsory but revaccinations were not systematically carried out [7], had 23,400 deaths because of smallpox; thus, the smallpox epidemic was one relevant factor for deciding the outcome of the war [8]. In 1811, Napoleon introduced the smallpox vaccination for the army recruits [9], whereas for the general population, the vaccination was promoted, offered for free to indigent individuals, but never made mandatory by law [10]. In 1806, the ruler of Lucca and Piombino, Elisa Bonaparte, Napoleon's sister, mandated the vaccination of newborns and adults. In 1853, the Compulsory Vaccination Act introduced the mandatory smallpox vaccination for infants in England and Wales. However, due to the military organization, the relevance for the military to fight infectious diseases, and the lower relevance in the military of the no-vax opinion groups, the application of vaccination in the military was generally earlier and better implemented than in the corresponding civilian population.

In 1980, the WHO declared smallpox eradicated, after the last case of natural smallpox occurring in Somalia in 1977, and recommended vaccination interruption, considering that the risk of adverse events was higher than the risk of smallpox infection. However, in some countries, the military continued to be immunized, as a prevention for the possible use of smallpox as a biological agent on a population that was not protected anymore. The fear of the possible use of smallpox as a biological weapon became more pressing after the episode of anthrax sent by mail; thus, USA President Bush ordered that the health workers and the military were compulsorily immunized. However, vaccination was interrupted after having vaccinated approximately 500,000 military subjects and 40,000 health workers, for the relatively high frequency of adverse events [11]. Nonetheless, the last North Atlantic Treaty Organization (NATO) document on the vaccinations for the military in the 30 NATO countries reports that 3/25 countries that have reported their military vaccination schedule, still maintain smallpox vaccine for selected categories of personnel [12]. New, less reactogenic, tissue-culture-based live attenuated, and subunit smallpox vaccine formulations are studied for the risk that smallpox may be used as a biological weapon [13], or for protection against naturally occurring monkeypox. Moreover, by collecting the blood of the immunized people, it was possible to produce specific polyclonal Ig, which were protective and could be used in emergencies, with significantly lower adverse events than the vaccine [11]. Thus, despite smallpox having been eradicated since 1980,

the interest for the military is still great, in light of its possible use as a biological weapon, of category A. The military contribution is the worldwide early military vaccination, which may have contributed to its eradication.

2. Typhoid Fever

Typhoid fever is a serious infection caused by *Salmonella typhi*, a Gram-negative bacterial microorganism, which may infect through ingestion of contaminated water or food. The disease is characterized by high fever, headache, gastralgia, diarrhea or constipation, hepato-splenomegaly and possible complications, such as intestinal perforation. In the pre-antibiotic era, mortality was as high as 20%. Salmonella has three antigens, the O and H antigens, thermostable and thermolabile, respectively, and a third antigen Vi, for virulence. The diagnosis may be carried out by stool culture, blood culture and serologically, by the search for specific anti-O and anti-H antibodies. Some people may become chronic carriers of *S. typhi*, continuing to release bacteria in their stools, thus spreading the disease. Typhoid fever is a classic example of an infectious disease spreading in unfavorable hygienic conditions, with lack of access to safe water and food, as may be observed during the war. This, joined with the severe clinical picture and the relatively high lethality, makes the disease of great interest to the military. In addition to the environmental prophylaxis, the search for an effective vaccine has registered the activity of military researchers from Germany, Great Britain, France, Italy, and the USA. The development of the typhoid vaccine has been traditionally attributed to Almroth Wright, Professor of Pathology at the British Army Medical School at Netley, even though documents prove that Wright, appointed by the Director of the Army Medical Service to develop a typhoid vaccine and worried to be unable to comply, was reassured after knowing the results obtained by Prof. Richard Pfeiffer in Germany about the development of a typhoid vaccine [14][15]. Pfeiffer, a military doctor of the German Army, was seconded to the Laboratory of Robert Koch at the University of Berlin, and applied with success to bacteriology and immunology, by observing that a heated *S. typhi* culture, inoculated subcutaneously in man, could induce antibody-mediated agglutination. These data were described by Pfeiffer and Kolle in 1897 [16]. In 1896, Wright published a paper that was not focused on typhoid vaccination [17], while his paper on typhoid vaccination was contemporaneous to the paper of Pfeiffer and Kolle in 1897 [18]. However, independently of who was the first, this activity witnesses the interest of the military in preventing this dreadful disease. The first chance to test the vaccine's effectiveness was the Anglo-Boer War in southern Africa in 1899, during which the British Army used early forms of the typhoid vaccine. Among 14,626 immunized British soldiers, 1417 contracted typhoid fever and 163 died, with an attack rate of 9.7% and a case fatality rate of 11.5%. Conversely, 48,754 cases of typhoid fever occurred among 313,618 unimmunized soldiers, and 6991 died, with an attack rate of 15.5% ($p < 0.0000001$ vs. the attack rate of immunized soldiers), and a case fatality rate of 14.34% ($p = 0.002965$ vs. lethality of immunized soldiers) [19]. However, the golden test for proving the vaccine effectiveness of the typhoid vaccine in preventing typhoid fever was World War I (WWI) trench warfare during which all the infectious diseases favored by poor hygiene, such as typhoid fever, could easily spread. The British Army decided, therefore, that troops should be vaccinated, but, contrarily to Germany, France, and Italy, which imposed the compulsory vaccination, the British Army, for the strength of anti-vaccine movements that had obtained exemption from the smallpox vaccine, could not decide for the mandatory typhoid vaccination, but only for a warm vaccine recommendation. Nonetheless, the percentage of vaccinated soldiers was 94%, and the vaccine effectiveness was clearly demonstrated; among the

604,420 vaccinated, 570 typhoid cases and 34 deaths were observed versus 295 cases and 89 deaths among the 38,580 non-vaccinated [20]. The incidence of typhoid in the British Army during the Anglo-Boer War was 285 per 1000, while in WWI, it fell to <1 per 1000 [21]. Moreover, the British Army, under the guidance of Col. David Harvey, could develop a trivalent vaccine against *S. typhi* and *S. paratyphi* A and B (TAB), able to better protect against enteric infections during the war in France. This vaccine was introduced in 1916 [22]. In the same period, the Italian microbiologist Aldo Castellani, Director of Government Clinic for Tropical Diseases, Colombo, Ceylon, later full Professor of Tropical and Sub-Tropical Diseases, University of Rome, and physician in the Italian Navy with the rank of General, developed and successfully experimented the combined killed TAB vaccine [23], by promoting its use on the military during WWI. The TAB vaccine, combined with the tetanus toxoid (TABTe), was used in the Italian military until the second half of the 1980s, when it was replaced by a new live oral vaccine [24], following a comparative study between the two vaccines, which showed lower reactogenicity of the oral vaccine associated with good immunogenicity, even at mucosal level [25].

A few years later, in France and the USA, military researchers prepared inactivated typhoid vaccines, which have been largely and successfully used during WWI. In France, the military medical doctor Hyacinthe Vincent, in collaboration with André Chantemesse, a medical researcher of the Pasteur Institute, developed a typhoid vaccine, able to control the typhoid epidemic, which had provoked more than 65,000 cases among the French troops in the period ranging between September 1914 and May 1915 [26][27]. Meanwhile in the USA, Major Frederick Russell, who had visited the laboratories of Wright and Pfeiffer, developed a whole cell typhoid vaccine, heat and chemically inactivated, similar to the vaccine of Wright and Pfeiffer, which became compulsory for the US Army and Navy in 1911. By using this vaccine for the 4,100,000 USA military during WWI, only approximately 2000 cases of typhoid fever have been observed with 227 deaths [28]. The US Army had an incidence of typhoid fever of 142 per 1000 in 1898, which fell to <1 per 1000 during WWI [29].

In conclusion, the first typhoid vaccines, all developed by military researchers, even though reactogenic and incompletely protective, showed a satisfying protection in the unfavorable hygienic conditions of the trench warfare such as of the one of WWI. During the 1970s, a new live attenuated oral typhoid vaccine was developed from a wild-type *S. typhi* strain Ty2 made defective from the galactose-epimerase gene and Vi antigen by chemical mutagenesis [30]; it was approved in Europe in 1983 and in the USA in 1989. A Vi polysaccharide injectable typhoid vaccine was developed in the 1970s and is used in many world countries. Moreover, in the second half of the 1980s, the Vi polysaccharide–protein conjugate was also developed [31]. The conjugate vaccine, in which the Vi polysaccharide is linked to a protein matrix, which may be represented by tetanus toxoid, or diphtheria toxoid, or CRM197 (a recombinant, avirulent analogous of diphtheria toxin) or recombinant exotoxin A of *Pseudomonas aeruginosa*, compared to the plain polysaccharide vaccine, allows a T-independent antigen to be transformed into a T-dependent one, thus eliciting memory cells. However, despite that it represents a more effective vaccine than the plain polysaccharide, the conjugation process is complex and expensive; thus, it has currently only been approved in endemic countries, such as India and Nepal [32].

Currently, with the improvement of hygienic conditions, typhoid fever has virtually disappeared in developed countries; thus, in the military of many developed countries, such as Italy, typhoid vaccination is only compulsory

for troops deployed abroad, in developing countries with unfavorable epidemiological situations. The WHO estimates an annual incidence of 11–20 million typhoid cases and annual deaths of 128,000–161,000, mainly occurring in developing areas of Africa, the Americas, Southeast Asia and Western Pacific regions [33]. Typhoid vaccination is present in all the 25 NATO countries out of 30, which have reported the vaccination schedule for the military. In 18 countries, the used vaccine is the inactivated one, whereas in the remaining seven, it is the live attenuated one. In none of these 25 countries vaccination is it addressed to the whole military personnel, but analogous with Italy, it is addressed to selected categories only [12]. The first vaccine development was uniquely carried out by the military, and it was crucial in disease containment. *S. typhi* has been included among the biological agents, category B [34].

3. Tetanus

Tetanus is a potentially lethal disease caused by the anaerobic microorganism *Clostridium tetani*, which produces a neurotoxin toxin (tetanospasmin). The severe symptomatology of the disease is characterized by spastic palsy, due to the inhibition of the inhibitory neurotransmitters of nerve terminals of lower motor neurons, the nerves activating voluntary muscles [35]. The spores of *C. tetani* are resistant in the soil; thus, the wounds with necrotic parts contaminated by topsoil are at particular risk of developing the infection. In absence of therapy, the disease is virtually always lethal. Emil Adolf von Behring, a German military physician expert in disinfection, joined the Robert Koch's Institute of Hygiene in 1890, after leaving the Army. In that period, in France with Louis Pasteur and in Germany with Robert Koch, microbiology and immunology were emerging. In particular, the Koch's Laboratory collected many scientists around, including Behring, Richard Pfeiffer who with Kolle and Wright in Great Britain, will share credit for developing the typhoid vaccine, Paul Ehrlich, bacteriologist, and immunologist, Shibasaburo Kitasato, who isolated the *C. tetani*. Behring and Kitasato, in December 1890, published one paper describing that the inoculation of sterilized cultures of tetanus in rabbits induced the appearance of antitoxins in the blood, as proven by the inoculation of this immune blood in mice that resulted protected by a challenge with tetanus [36]. A week later, Behring published another paper to extend this observation to diphtheria as well [37]. Based on these premises, Behring inoculated the serum of a previously immunized animal to diphtheria toxin in an eight-year-old boy with severe diphtheria, who later had a full recovery. The lethality rate of diphtheria in the following 10 years decreased from 50% to 13% [38]. This represented the birth of passive immunization, which has later been applied to different clinical contexts, including the recently set up of monoclonal antibodies to severe acute respiratory syndrome coronavirus (SaRS-CoV-2). For the relevance of this discovery, Emil von Behring was awarded the first Nobel Prize for Physiology or Medicine in 1901, "*for his work on serum therapy*, *especially its application against diphtheria*, *by which he has opened a new road in the domain of medical science and thereby placed in the hands of the physician a victorious weapon against illness and death*" [39]. The test case for demonstrating the effectiveness of anti-tetanus hyper-immune animal serum was WWI, during which contaminated wounds were frequently complicated by tetanus. Considering that the vaccine was not developed yet, the only protective weapon, in addition to a thorough wound toilet, was the hyper-immune serum, which appeared more effective in prophylaxis than in therapy, as reported in the UK experience. Among 2,032,142 wounded British soldiers, 2385 were tetanus cases, with an incidence of 1.17:1000 [40]. The case-fatality rate among the 1437 cases of tetanus

occurring in England was 34.8%, ranging from over 70% to less than 20% according to the tetanus severity. The case-fatality rate was higher in the British troops stationed in France (71.3%) than in England [40]. The use of hyper-immune serum as therapy could poorly influence the outcome; instead, the prophylactic use was probably responsible for the reduction of incidence from 9 per 1000 in September to 1.4 per 1000 in December and for the reduction of the case-fatality rate from 85%, which was the average pre-serum observed case-fatality rate, to 47%, which resulted from joining together the British cases of tetanus observed in England and the French war theater [40]. In 1914, the lethality rate for tetanus in the German Army ranged from 75% to 100% [41]. In the Italian Army, tetanus was negligible, with an incidence of 0.5 per 1000 (it was 10 per 1000 in the Russo-Japanese War) and a mortality rate of 1:33,000 [42].

In 1923, a veterinarian of the Pasteur Institute, Gaston Ramon, by exposing tetanus and diphtheria toxins to 0.5% formaldehyde and heat, was able to eliminate their virulence, while maintaining their antigen power, thus paving the way for the respective vaccines to be prepared. The transformed toxins were denominated by Ramon anatoxins, and, in 1926, profiting from the close collaboration between the Institute Pasteur Network and the French Military Medical Service, the military medical doctor Christian Zoeller collaborated with Ramon to improve the vaccines for tetanus and diphtheria. These vaccines were studied in the military population, and a few years later, they became compulsory for the military, diphtheria in 1931 and tetanus in 1936 [43]. The tetanus vaccine became compulsory in the military of other countries before the start of WWII, in Italy in 1938, and in the USA in 1940 [28]. As WWI was the test case to analyze the effectiveness of anti-tetanus hyper-immune serum, WWII was the test case to analyze the effectiveness of the tetanus toxoid vaccine. In WWI, the incidence of tetanus in the US Army was 13.4 per 100,000 wounded and injured versus 0.44 per 100,000 in WWII [44], over thirty-fold lower; thus, definitively demonstrating the high effectiveness of the tetanus toxoid vaccine.

Although nearly 100 years have elapsed since the tetanus vaccine development by Ramon, no substantial modifications have been introduced in this vaccine preparation, which has remained the same. A certain degree of reactogenicity observed in the 1940s has been attributed to some peptones formed during the process of toxoid preparation, which have been removed [44]. In developed countries, the disease has virtually disappeared; however, in most military vaccination programs, tetanus vaccine is present [45]. The tetanus vaccine is included in the military vaccination program of all the 25 NATO countries, which have reported the respective vaccination schedule out of the 30 ones, 23 of which for the whole personnel and in another two for selected categories [12]. In Italy, the tetanus toxoid vaccine was included in the vaccination program for infants only in 1968, thirty years later than for the military. The relevance of military vaccination as a public health measure for tetanus prevention was witnessed in Italy and France, until the conscription was present in both countries, by the unbalanced epidemiological situation of the few cases of tetanus annually reported, which were characterized by a marked preponderance of old females, who were not covered by vaccination because it was not administered during the military service, which was only compulsory for males, nor in infancy, because it was not introduced in the infant vaccination schedule yet [43]. Currently, an open issue is the durability of vaccine-induced antibodies and thus the right timing for booster administration to maintain the protective antibody levels without risking hyper-immunization [46][47][48]. The military contributed to the discovery of passive immunotherapy and to the collaboration to vaccine development.

4. Diphtheria

Diphtheria is an infectious disease caused by the toxigenic strains of the Gram-positive *Corynebacterium diphtheriae*, of which three main biotypes exist: gravis, intermedius, and mitis. The infection is localized in the high airways, where the toxin causes rhinitis, pharyngitis, and laryngitis. The toxin may induce myocarditis and polyneuropathy; the disease is generally observed in <15-year-old boys and the case-fatality rate is 5–17% [49]. Diphtheria has been described in the sixteenth and seventeenth centuries in Spain, with recurrent epidemics in the eighteenth century in the USA, in the nineteenth and twentieth in Europe and more recently even in Asia and Africa. The etiologic agent was identified by Edwin Klebs in 1883 and was cultured by Friedrich Löffler, who demonstrated the toxin as well, whereas the progress in passive and active immunization is parallel to the one of tetanus, and it has been reported above in the paragraph of tetanus.

Considering that in non-vaccinated subjects, the disease is generally observed in <15-year-old boys, diphtheria is not apparently of military interest. However, the military must travel to different world countries, and if they are exposed to the etiologic agent in conditions of insufficient immune protection, they may be infected and become carriers, thus spreading the infection. This appears to have been the case for the start of a diphtheria epidemic occurring in the period 1990–1995 in the newly independent states of the former Soviet Union, where 47,808 cumulative cases of diphtheria occurred, 1746 of which were fatal [50]. A cluster of diphtheria infection was described in the members of a military construction battalion in Moscow in 1990. It must be considered that the Soviet troops had been present, in the period 1980–1989, in Afghanistan, which reported to the WHO 13,628 cases of diphtheria in the same period. Considering that the notification system for infectious diseases in the former Soviet Union was completely separated between military and civilian populations, civilian health authorities were not immediately aware of these diphtheria cases occurring in the military; thus, the actions for limiting the infection spreading were late and largely ineffective [50]. However, the causes for the spreading of the infection were largely unknown, but a high rate of unimmunized children and waning immunity in adults was certainly present; thus, even in the armies of developed countries, where diphtheria has been eradicated, particular attention to maintaining the antibody levels above the threshold for protection has become mandatory. In Italy, diphtheria booster was added to the compulsory vaccination schedule for the military after demonstration of the relatively low percentage of recruits with protective antibody levels [51]. However, even though in the military much attention has been paid to the need to maintain protective antibody levels for diphtheria, a survey made up among the military medical services of 52 world countries showed that the tetanus vaccine was present in the compulsory vaccine program for the military in 45/52 (87%), whereas diphtheria was only present in 30/52 (58%) [45]. Currently, the diphtheria vaccine is included in the military vaccination program of all 25 NATO countries, which have reported the respective vaccination schedule out of the 30, 22 of which are for the whole personnel and the other three for selected categories [12]. The outbreak of diphtheria in the newly independent states of the former Soviet Union in the 1990s is a clear example of how the military may become involuntary carriers of disease; thus, the military health authorities should not only combat infectious diseases for assuring the operational readiness but even closely collaborate with civilian health authorities in order to prevent possible military-mediated outbreaks. The complete separation of civilian and military notification systems for infectious diseases in the former Soviet Union was instead an example of a flawed organization, which has allowed the happening of such a dramatic event.

5. Pertussis

Pertussis is a highly contagious infectious disease, known for many centuries, caused by the Gram-negative coccobacillus *Bordetella pertussis*, which was isolated and cultivated by Jules Bordet and Octave Gengou in 1906 [52]. The most relevant symptom is whooping cough, which may be accompanied by inflammation of the high airways and may be complicated by apnea, pneumonia, rib fractures, insomnia, hospitalization, and rarely death [53]. The disease was generally observed in infancy, but in the last 20–30 years, it has even been observed in adults [53], thus acquiring an interest for the military, considering that in many countries, limited outbreaks in the military have been described [54][55][56][57][58]. In the Italian military, a study carried out in the 1990s showed that more than 90% of subjects had specific cell-mediated and antibody immunity to *B. pertussis* and that symptoms suggestive of pertussis were absent in the military [59].

Two types of vaccines are available, the first one is whole-cell, older, and inactivated, whereas the second vaccine, developed in the 1970s, but practically available since the 1990s, is acellular, recombinant and may only contain one, two, or three of the main virulence factors of the microorganism, represented by the pertussis toxin, the pertactin, and the filamentous hemagglutinin. The whole-cell vaccine is more reactogenic, however, it seems quite more effective and able to provide more durable protection. Both vaccines are combined with tetanus and diphtheria, in a trivalent diphtheria/tetanus/pertussis (DTP) or diphtheria/tetanus/acellular pertussis (DtaP). Pertussis is now, in both the USA and Europe, particularly present in adults, who represent the major reservoir for the infection [60]. Currently, 21/25 countries reporting the vaccination military program among the 30 countries considered in the document of the NATO standardization agreement for vaccination of 2021 declare having pertussis included in the program, in 18 countries for all the military personnel, in two out of the remaining three countries for selected categories (deployable, alert, risk personnel) and in one country for recommendation only [12]. The use of the trivalent DTP/DtaP vaccine in the military is a relevant measure of public health, particularly in the countries with conscription because maintaining a high level of immunity reduces the microorganisms' circulation.

6. Tuberculosis (TB)

TB is a severe disease, whose infectious nature was demonstrated by the French military physician Jean-Antoine Villemin in 1865, and which was published in 1868 [61], through inoculation of material from infected humans to laboratory rabbits. TB is caused by *Mycobacterium tuberculosis*, discovered in 1882 by Robert Koch, who was awarded the Nobel Prize for Physiology or Medicine in 1905 [62]. The microorganism is transmitted through airways and may induce, after an average period of 3–9 months up to two years [63], either a latent or active disease, generally at lung level, but, more rarely, everywhere in the body. It is estimated that one-third of the world population is infected, the large majority with a latent infection and a minority, which in 2011 was represented by 8.7 million cases, with active infection, and 1.4 million deaths [64]. In 1895, a French military physician, Albert Calmette, who founded the Pasteur Institute in Saigon and later directed the Pasteur Institute in Lille, started his studies on tuberculosis and, together with the veterinarian Camille Guérin, developed a live attenuated vaccine for

TB, which was successfully tested for the first time in 1921 [65]. This vaccine uses attenuated *Mycobacterium bovis* and is known as Bacillus Calmette–Guérin (BCG), after the names of its discoverers.

Similar to many other infectious diseases, TB spread increases in unfavorable environmental conditions, such as insane housing, overcrowding or hypo-nutrition, that characterize poverty and occur during wars, but community life may also favor TB spreading [66]. In the US military, the epidemiology of TB has been analyzed since the Civil War (1861–1865) up to the last wars in Iraq and Afghanistan. TB was more frequent in the military up to WWI and lower than in the civilian population in the following years [67]. During the American Civil War, the morbidity rate for TB was 924/100,000 and the mortality rate 261/100,000, whereas during the Spanish–American War (1898) the mortality rate was slightly reduced to 197/100,000, and during WWI, the morbidity rate increased up to 1168/100,000, with a higher prevalence of cases among soldiers who had remained in the USA compared with those who were deployed to Europe [66]. With WWII, lung X-ray was extensively employed to improve the screening before enrollment, thus preventing new cases coming from the contagion with infected comrades. From WWII, the influence of war on the epidemiology of TB seems inapparent, even when the wars occurred in countries endemic to TB, such as Korea, Iraq, and Afghanistan; the epidemiological curve of incidence continued to descend, until 0.4/100,000 in 2012, which represents a value eight-fold lower than in the USA civilian population [67]. However, a crucial point for reducing the cases of active TB in the military is to identify with the highest possible precision the subjects with latent TB among the applicants for military service during the pre-enrollment medical screening, for these cases to be adequately treated before enrollment, thus preventing the possible development of active TB as a consequence of the stress of the military life [68]. In the UK, the situation is quite different, considering that TB still presents a morbidity rate of 12.3/100,000 in the general population, mainly due to immigrants from high-endemicity countries (70/100,000 among immigrants versus 4/100,000 of UK-born people), but even dependent on risk factors, such as smoking, alcohol consumption, immunosuppression, and concomitant diseases, such as HIV infection and diabetes. The situation is similar in the UK military, in which historically at the end of the nineteenth century, TB represented the first cause of medical discharge from active service (300/100,000 in 1891). In the first half of the twentieth century, the situation improved by showing a reduction of approximately 50% (an average of 150/100,000), a behavior that was observed during WWII and even afterward, up to half a century. In the second half of the century, a series of initiatives were taken, including pre-enrollment screening, the diagnosis and treatment of latent TB infections and the offer of BCG to skin-negative subjects who had not received BCG in infancy. Based on a careful study, it emerged that the risk of TB was higher in older veterans who entered the Army before the implementation of preventive measures [69]. In Italy, a study carried out on over 2000 soldiers in the 1990s found a prevalence of latent infections (tuberculin-positive, asymptomatic subjects) of over 6% [70], a percentage not dissimilar from the percentage of the US Army in the same period [71]. Based on this result, in 2001, the norm of article 10 of Act 1088/1970 requiring that all skin-negative soldiers would have been vaccinated with BCG at enrollment was cancelled. The reactogenicity and the uncertain protection induced by BCG in adults [72] did not justify its administration in the presence of a relatively reduced prevalence. Moreover, in 2005, the conscription in Italy was abolished, thus deeply modifying the socio-epidemiology in the military. In addition to a numerical reduction of the military personnel, even the community life was reduced and only maintained during the training and operational periods, thus reducing the occasions for infections spreading.

The lung TB in the period 1986–1997 in the Italian military had an annual incidence ranging from 8 to 13.5/100,000, higher than that observed in the age- and sex-matched civilian population, with an average annual incidence of 10.4/100,000 [73], whereas in the period 2008–2018, the annual incidence was always lower than 1/100,000, except for in 2013 and 2017, when it was 1.68/100,000 and 2.1/100,000, respectively, with an annual average incidence of 0.675/100,000 and a reduction of 15.4-fold. Only six NATO countries maintain the BCG for the military; however, in only two countries, it is administered to the whole military personnel; in one, it is only recommended, and in the last three, it is administered to selected categories of personnel, who are exposed as a consequence of occupational risk or deployed in high-risk areas [12]. A rising problem is the multi-drug-resistant TB (MDR-TB), caused by isoniazid- and rifampin-resistant *Mycobacterium tuberculosis*; this issue has been considered of awareness for the military, not only because of the difficulties in the treatment of patients with MDR-TB but also because drug-resistant *Mycobacterium tuberculosis* is a pathogen included among the biological agents, category C in the Centers for Disease Control and Prevention (CDC) classification, and studies aimed at counteracting its infection are of strategic interest. In conclusion, even for TB, the role of military physicians in the demonstration of the infectious nature of the disease and the prophylactic vaccine, as well as in its epidemiology, especially in wartime, witnesses the interest of the military and the contribution the military provided.

7. Meningococcal Meningitis

Meningococcal meningitis is a serious, potentially lethal, and invalidating disease, caused by the Gram-negative microorganism *Neisseria meningitidis*, which is transmitted through airborne droplets and was identified by Weichselbaum in 1887 [74]. Based on the chemical characteristics of the polysaccharide capsule of the microorganism, 13 serogroups are known, six of which may induce invasive meningococcal disease (IMD) in humans, A, B, C, W_{135}, Y, and X. It is estimated that the annual global cases of IMD are at least 1,200,000 and the annual global deaths 135,000 [75]. In the pre-vaccine period, the highest disease prevalence was observed in infants and people living in communities, particularly in the first days of community life, such as college students and the military. Hence, the particular interest of the military in this dreadful disease and the successful efforts in identifying the protective role of specific antibodies, the type of immune response, and a vaccine, by the researchers of the Department of Bacteriology of the Walter Reed Army Institute of Research (WRAIR) in the 1960s [76][77][78][79][80]. Meningococcal meningitis has been described as a severe disease in the military since the nineteenth century both in peacetime and wartime. It struck the Prussian Army in 1806–1807, the French Army in Algeria in 1840, different European countries and the USA, which were particularly hit during the American Civil War (1861–1865), and, since 1875, it has spread worldwide [81]. During WWI and WWII, meningococcal meningitis was a relevant problem for all armies. In the first year of WWI, 150/100,000 meningococcal meningitis cases occurred in the US Army, with a case-fatality rate of 39%, whereas during WWII 14,000, cases were described in the US Army; however, the case-fatality rate was reduced to 4%, as a consequence of early diagnosis and the availability of anti-bacterial drugs [82]. During WWII, the only available treatment was sulfa drugs, discovered in 1937, but by the first half of the 1960s, most meningococci were resistant to the sulfa drugs [83]. Thus, the search for an effective vaccine was pushed by the awareness that the most effective preventive tool was active immunization. The C polysaccharide vaccine, introduced in 1972 in the US Army, provided 87% of protection [84];

this vaccine was in 1979 replaced by the bivalent A + C, and in 1983 by the tetravalent (A, C, W_{135}, and Y). Compared with the pre-vaccine era, the vaccine introduction reduced morbidity by over 90%, whereas the case-fatality rate did not result to be significantly modified, always remaining around 7% [82]. In Italy, the burden of meningococcal meningitis in the military became particularly relevant during the 1980s (in 1985, an incidence of 17/100,000 cases, 92% serogroup C, and in 1986, an incidence of 7/100,000, 95% serogroup C, were observed, compared with an incidence of 0.8/100,000 in the general population [85][86]); thus, the bivalent A + C vaccination was introduced since 1 January 1987. Vaccination was effective in reducing the burden of meningococcal meningitis A and C, showing an effectiveness of 91.2% [85][87], an immunogenicity of 84% and 91% of protective seroconversion for polysaccharides A and C, respectively, with the appearance of mainly oligoclonal specific antibodies, and safety [88]. In 1991, the tetravalent polysaccharide $ACW_{135}Y$ vaccine was introduced, recently largely replaced by the protein–conjugate formulation. However, the tetravalent polysaccharide vaccine maintains its validity because of its good immunogenicity and the long durability of induced antibody response, which were recently examined at 9 months [89] and 5 years [90]. In the French military, the vaccine was introduced in 1996, and 2 years later, its protective effectiveness was calculated to be 100% [91]. Currently, the tetravalent vaccine $ACW_{135}Y$ is included in the vaccination program of 24/25 NATO countries which have replied out of the 30, in 10 countries for the whole military personnel and in the other fourteen for selected categories [12].

A vaccine based on polysaccharide antigen could not be pursued only for meningococcal polysaccharide B, considering that polysaccharide B has a chemical structure close to human brain polysaccharide, thus resulting in being poorly immunogenic or, even worse, auto immunogenic [92]. Therefore, the approach for obtaining an effective anti-B vaccine was long, laborious, and not based on the use of polysaccharides as antigens; rather, through the innovative approach of reverse vaccinology, a recombinant protein vaccine was achieved only in 2005 [93]. This vaccine proved to be mildly moderately reactogenic in infants, particularly when administered in association with other vaccines; however, it was proven that the concurrent administration of paracetamol significantly reduced reactogenicity without interfering with the immune response [94]. Due to the relative rarity of IMD, not many significative studies on efficacy in the pre-registration phase have been carried out, however, the vaccine has been approved based on its immunogenicity [94]. The effectiveness in preventing IMD has been demonstrated in the real-world [95]. Vaccination with meningococcal B vaccine has been included in the national immunization program (NIP) of the UK, Ireland, and Italy; 12 European Member States have made an assessment to include the vaccine in the NIP, three are recommending the vaccine without reimbursement, whereas five are not recommending, as of March 2015 [96]. Only 5/25 NATO countries, which had reported the respective military vaccination program, declare having meningococcal B vaccine included in their vaccination program for the military; in two cases the vaccine is only recommended, whereas in the remaining three, it is compulsory for selected categories of military personnel [12]. Even though sporadic cases are still observed, the vaccine introduction induced a substantial reduction of IMD in both civilians and militaries [97]. In Italy, the anti-meningococcal polysaccharide vaccine has been introduced in the compulsory vaccination program for the military thirty years before its availability for free in infants; however, the meningococcal B vaccine has been freely offered to infants since 2017, and it has not been included in the vaccination schedule for the military yet.

8. Hepatitis A

Hepatitis A is a disease caused by an RNA virus (HAV), transmitted via the fecal–oral route, by contaminated water and food, that easily spreads in poor hygienic conditions and overcrowding. It was so largely widespread in the military, both in peacetime and mainly in wartime, that it was even known as “camp jaundice” [98]. In 2019, the global annual infections were estimated to be 158,944,000, an increase of nearly 14% compared with 1990, and the annual deaths were 39,280 [99]. Poor hygienic conditions and overcrowding as risk factors for the military were present in the literature up to 1990, whereas in more recent times, the major risk factor for the military has been the deployment to countries of high endemicity [100]. One epidemiological study in Italy in the decade 1987–1997 revealed a similar incidence in the military and the age- and sex-matched civilian population [73]. Moreover, a study carried out in the Italian military in 2003 documented that Italy passed from a prevalence of 66.3% positive subjects for anti-HAV antibodies in 1981 to 5.3% in 2003, thus from high to low HAV endemicity in 20 years, with the military reflecting the epidemiology of the general population [101]. A similar behavior of anti-HAV seroprevalence was even observed in the French military [102]. In the Italian military, the annual incidence in the period 1986–1997 ranged from 5 to 60/100,000, with an average annual incidence of 17.5/100,000 [73], whereas in the period 2008–2018, it ranged from 0.35 to 0.66/100,000, an average annual incidence of 0.5/100,000, a reduction of 35-fold. In 1953, for the first time, the definition of hepatitis A and hepatitis B, to identify the infectious (shorter incubation time, fecal-oral transmission, better prognosis) versus the serum-transmitted (higher incubation time, serum transmission, worse prognosis) hepatitis, respectively, was reported by an expert committee of the WHO [103]. However, until 1942, when an outbreak of acute viral hepatitis involving nearly 50,000 US Army personnel following yellow fever vaccination [104], no clear idea that at least two types of hepatitis could occur was still present: only the study of this outbreak, and the clarification that the outbreak was not due to a side effect of yellow fever vaccine, but to the preparation of the vaccine with human serum contaminated with virus hepatitis, has allowed a better comprehension of acute hepatitis to be achieved.

A disease with the characteristics of epidemic or infectious jaundice was described during the British–American War of 1812, but especially during the American Civil War, when 87,326 cases of jaundice were recorded by the Medical Corps of the Union Army [105]. In WWI, epidemic jaundice represented a relevant problem for the French, British, and German armies, whereas this was not the case for the US Army, and in WWII, the US Army registered over 180,000 cases of infectious jaundice, with a case-fatality rate of 0.3% [106]. However, following the occupation of Italy and Germany, where infectious jaundice was endemic, the US military registered an increase in cases, which in Italy reached the incidence of 37/1000 and in Germany continued even after the end of the war [97]. This observation allowed the first epidemiological studies to be carried out by US researchers in a newly established hepatitis center in Bavaria [96]. During the Korean War in 1950–1951, in a country of high endemicity, the cases of jaundice in the troops hospitalized or isolated were over 4000 [106].

During WWII, US military researchers demonstrated the protective role of the pooled gamma-globulin plasma fraction against epidemic jaundice [107]. During the Korean War, a randomized double-blind study driven by US military researchers on intramuscular IgG administration to soldiers could establish that the passively immunized subjects resulted protected from hepatitis A, B, and non-A non-B for 6 months [108]. Even though passive

immunization has been used for a long time for the protection of travelers and military personnel, more recently an inactivated vaccine was developed by US researchers of WRAIR in collaboration first with Robert Purcell at the National Institute of Health [NIH] and later with SmithKline Beecham (SKB), now GlaxoSmithKline. This vaccine proved to be safe, immunogenic, and highly protective (94% after two doses) in a large phase III study in Thailand on approximately 20,000 individuals and 20,000 controls who had received hepatitis B vaccine [109]; based on these results, the vaccine was approved by the Food and Drug Administration (FDA) in 1995 [97]. The vaccine, administered in two doses 6 months apart not only demonstrated to be highly immunogenic but even effective, by inducing a long, probably a life-long, protection. The persistence of anti-hepatitis A antibodies following vaccination is so long that in a recent study, the durability of vaccine-induced antibodies could not even be calculated because the curve representing mean antibody titers was slightly ascending in joining the levels found at 9 months and 5 years post-vaccination [90]. HAV vaccine has been introduced in the military vaccination program of all 25/30 NATO countries, which have reported the vaccination program for the military: in 12/25 countries, the vaccination is indicated for all the military personnel and in the remaining 13 countries for selected categories [12]. Currently, HAV infection, which has historically represented a real obstacle to the operational readiness of the military, does not represent a problem for the military anymore, not even when deployed to high endemicity countries. The military contribution in the fight against hepatitis A has been crucial for epidemiology, the demonstration of protection by passive immunization with human immunoglobulins, and vaccine development.

9. Hepatitis B

Hepatitis B is a disease caused by a DNA virus (HBV), which may cause either acute or chronic disease. Chronic disease may eventually induce liver cirrhosis and/or hepato-carcinoma. The disease is highly contagious and may be transmitted by contaminated blood and blood derivatives, sexual route and perinatally. The diagnosis may be made by identifying: the surface antigen (HBsAg) of the virus released in biological fluids; the antibody response to viral antigens (serum antibodies to the viral core (HBcAb), surface (HBsAb), and/or envelope (HBeAb) antigens); or by amplification of viral genes by polymerase chain reaction (PCR) at serum and hepatic levels. It is estimated that, worldwide, approximately 2 billion people have come in contact with HBV [110] and the WHO estimates that in 2019, 296 million people were living with chronic HBV infection; each year 1,500,000 new infections and 820,000 deaths occur, the majority from severe sequelae of hepatitis B, such as cirrhosis and hepatocarcinoma [111]. This blood-borne disease is of interest for the military, considering that wounds may be a source of contagion and whole blood transfusions are used as resuscitation tools, consequently, the need that the soldiers are “walking blood banks”, thus free of blood-borne viruses, such as HBV, hepatitis C virus (HCV), human immunodeficiency virus (HIV) types I and II, and human T-cell lymphotropic virus (HTLV) types I and II, is imperative [112].

A pre-enrollment screening for blood-borne viral infections to prevent admission to the military seems, therefore, the best preventive measure. However, in a survey carried out by the WHO in 1998 in over half of the countries reporting to the WHO (107/193), only 76 replied; of these, 53 declared having a central military laboratory to perform the screening of the recruits, 27/53 (51%) for HIV, 17/53 (32%) for HBV and 7/53 (13%) for HCV [45]. Currently, the situation is probably improved, even in consideration that in 1991 in different world countries, the

compulsory HBV vaccination for infants was introduced; thus, in the last decade, the applicants for military service had generally been vaccinated in infancy. The vaccine, which was made available as plasma-derived in the first half of the 1980s, and, since 1986 as recombinant, is effective and, after having completed the whole vaccination cycle (three administrations), provides a long, probably life-long, protection [113]. Moreover, in 24/25 NATO countries hepatitis B vaccine is present, in 15 for the whole personnel and in 9 for selected categories [12]. However, in some NATO countries, in which the access to HBV vaccination in infant age has been delayed, the prevalence of serum HBV infection markers was still quite high in the first decade of this century [114][115].

The combined influence of entry screening, awareness of the risk of infection due to sexual activity as a consequence of the HIV infection prevention programs, and vaccination has determined a rate of infection slightly lower in the US military (0.23%) than in the corresponding civilian population (0.3–0.5%) [116]. The influence of vaccines may be inferred by the significant difference between the rate observed in the older cohort, born before 1979, generally not vaccinated, and the rate observed in the younger cohort, born in or after 1979, generally vaccinated, 0.39% vs. 0.13%, respectively (p = 0.016, Yates corrected, two tails, χ^2). Conversely, the influence of social factors and fear of HIV infection may be observed in the dramatic decline, in less than a decade, of HBV markers in two Italian military populations of approximately 5000 individuals each, the first from the Italian Navy analyzed in 1981 and the second from the Italian Air Force analyzed in 1990. HbsAg and HbcAb were 3.4% and 16.8%, respectively, in 1981, whereas they declined to 1.6% and 5.8%, respectively, in 1990 [117]. Even a study of incidence in the same period on approximately 1300 Italian students at a military school located in the Italian region with the highest prevalence of HBV infection, followed-up for eight months, showed seroconversion to HBV markers of only two subjects (0.24/100 person-years of exposure), thus witnessing a low spreading of HBV markers among the Italian recruits [118]. In the Italian military in the period 1986–1997, the annual incidence of HB ranged from 7 to 33/100,000, with an average annual incidence of 19/100,000 [72], whereas in the period 2008–2018, only four cases have been reported, an annual incidence ranging from 0.32 to 0.65/100,000 cases, an average of 0.44/100,000, a 43-fold reduction. This epidemiological situation and the consideration that currently the cohorts of recruits have been previously vaccinated when entering the military life are at the basis of the decision of the Italian military health authorities to eliminate the HBV vaccine from the military vaccination schedule, thus avoiding an expensive, useless, and unjustified booster.

10. Poliomyelitis

Poliomyelitis is a severe disease caused by an enterovirus, of which three types, 1, 2, and 3, are known. The disease may be transmitted through the nasopharynx, through an oral–oral way, by feces, or through a fecal–oral way, and after infection, the virus enters the bloodstream. This virus is highly contagious, and up to 100% of households may be infected, but in 95%, the infection runs asymptomatically or pauci-symptomatically, whereas in the remaining 5%, the symptoms are characterized by fever, headache, fatigue, nausea, vomiting, and neck stiffness, for meningitis. In some subjects, the virus, which has a marked neurotropism, localizes at the spinal level, most frequently in the anterior horn cells of the cord, thus eventually determining an asymmetric flaccid paralysis, particularly in the arms. More rarely, the virus may localize at the bulbar level, thus compromising vital functions,

such as circulation and respiration, with consequent high mortality [119]. The case-fatality rate of paralytic cases was 2–5% for children and 15–30% for adults [120]. The disease in the pre-vaccine era was largely widespread worldwide; in 1956, the inactivated trivalent vaccine developed by Jonas Salk was introduced, whereas in 1962, it was largely replaced by the oral, living, vaccine developed by Albert Sabin [119]. The use of vaccines has allowed the disease spread to be dramatically reduced; however, in 1988, the WHO decided to start an eradication campaign with the objective to eliminate the disease by the year 2000. Despite that the eradication campaign could not achieve eradication by 2000, the 350,000 estimated cases in 1988 were reduced to 3000 in the year 2000 [121]. Currently, the viral types 2 and 3 have been declared eradicated; thus, the wild virus is only type 1, which is still present in Afghanistan and Pakistan, where in the last years, it has even increased [122], and sporadic cases are reemerging in other politically unstable countries and sometimes sites of conflicts, such as Syria, Iraq, Cameroon, Equatorial Guinea, Ethiopia, Kenia, Nigeria, and Somalia [123]. In the process of eradication, in addition to the difficulties created by war and political instability, a further complication derives from the fecal elimination of a vaccine virus in countries where the oral, living vaccine is, or was, used. The live attenuated vaccine virus may revert to virulence; thus, being able of induce paralytic polio in vaccine recipients, particularly in those with immunodepression [122]. All these difficulties may delay the date of eradication; consequently, vaccination should be maintained at least until eradication.

Although the disease has been known for a long time, with the first evidence identified approximately 1500 years BCE, poliomyelitis did not induce outbreaks until the end of the nineteenth century, when outbreaks of infantile paralysis occurred in Scandinavia and the USA [124]. The disease was not considered relevant for the military, because it scarcely occurred in adults, and even during WWI, no outbreaks were described, despite the poor hygienic conditions and sanitation. However, in the interwar period, the cases of poliomyelitis in adults increased, and in the course of WWII, the US military registered 1023 cases with over 20% of deaths [125]. Out of the 1023 cases, 446 occurred in the troops who remained in the USA, whereas 577 occurred in the troops deployed overseas, in particular in Egypt, Italy, and the Philippines. Although these figures do not appear so high if compared with another severe, “military”, infectious disease such as meningococcal meningitis, for which 14,000 cases were described during WWII with a case-fatality rate of 4%. Polio had over 20% of mortality, 42% of discharge for disability and was the infectious disease with the highest number of lost days, with only 34% of infected military returning to duty, figures not comparable with other infectious diseases [125]. Nonetheless, polio has never been considered a “military” infectious disease, and vaccination is maintained only to make the military ready to be deployed everywhere, even in countries such as Afghanistan, where wild poliovirus is still circulating, and yearly cases due to poliovirus type 1 are notified. Out of the 25/30 NATO countries reporting the vaccination program for the military, all maintain an inactivated polio vaccine, 16 for all the military personnel and nine for selected categories [12]. The vaccine-induced antibodies are well stimulated by inactivated vaccine even though the priming is carried out with oral vaccine [122], and their durability above the threshold for protection has been calculated in 10–20 years for anti-type 1 and 3 antibodies [90], data in line with the literature [126]. Maintaining the anti-polio inactivated booster for the military creates ulterior protection to prevent the possibility that soldiers returning from a mission to endemic areas become involuntary carriers of wild poliovirus; moreover, it is a relevant measure of

public health, because it reduces the viral circulation, thus contributing to the eradication campaign of the Global Polio Eradication Initiative.

11. Measles

Measles is a disease caused by a virus derived from the agent of the cattle rinderpest, which adapted to humans 5000–10,000 years ago [127]. It is air-borne transmitted and is highly contagious (one infected person may infect on average 9–18 susceptible individuals, more than the smallpox virus, which may infect 5–7 susceptible individuals, and influenza, which may infect 2–3 susceptible subjects). The disease is characterized by fever, cough, coryza, maculopapular rash, and conjunctivitis; however, the virus is carried by lymphocytes and may localize in the lymphoid tissue and everywhere in the body, with possible severe complications, such as pneumonitis, keratoconjunctivitis, and encephalitis. The infection of lymphocytes causes a transitory immunodepression, and the measles virus was the first infectious agent for which induced immunodepression was demonstrated. The Nobel Laureate John Franklin Enders developed the first live attenuated vaccine in 1960 [72]. Measles was responsible for over 2 million deaths annually in the pre-vaccine era, but even now, it is still responsible for over 100,000 deaths per year. In 2015, the global annual cases were estimated to be over 9,700,000 (only 245,928 cases reported), and the global annual deaths were 134,200 [128]. Despite the RNA genome being generally characterized by a high rate of mutations, both the wild virus and vaccine strains are stable, making it not necessary to update the vaccine to a newly circulating mutated virus, as required for the influenza vaccine. The inclusion of this live attenuated vaccine in the Expanded Program of Immunization (EPI) in 1980 contributed to the reduction of measles morbidity and mortality, particularly in areas such as Sub-Saharan Africa, with the highest morbidity and case-fatality rate [129]. Measles eradication by a global immunization program is in theory possible, as the vaccine is effective and no animal reservoir is known. However, the deadline of 2010 for its eradication set by WHO in the European region was not respected, and to date, measles prevalence is still quite high (11%) in this area, whereas in some countries, an increase was reported after 2010 [129][130]. Various causes can be hypothesized for this failure, including the vaccine hesitancy caused by the publication and diffusion on mass media of the false association of measles/mumps/rubella (MMR) vaccination with autism, which led many parents to not vaccinate their children [72].

Measles has represented a relevant problem, even for the military, particularly up to the twentieth century. For example, in the American Revolutionary War and the American Civil War, measles was one of the main causes of death among the soldiers [28]. During the whole Civil War, measles caused 67,763 cases and 4246 deaths (case-fatality rate of 6.27%) in the Union Army [131]. The case-fatality rate was 6% and 11% for white and black soldiers, respectively [132]. A reduction in the impact of measles on the US military in the war was observed in the following years. The morbidity in the Union Army in the first 2 years of war (1861–1862) was 56/1000, with a case-fatality rate of 2/1000 [133]. Morbidity (42/1000) and mortality (0.45/1000) caused by measles decreased in the first 2 years (1898–1899) of the Spanish–American War. In 2 years of WWI (1917–1918), the reported morbidity was 28/1000 and the mortality 0.7/1000. The progressive reduction of morbidity and mortality was confirmed in WWII when over 300,000 admissions to hospitals were registered for measles, mumps, rubella, and varicella [28], but a limited number of US soldiers died of measles. Finally, during the Vietnam War, no death to measles was registered

among US soldiers. The progressive reduction of cases and deaths for measles cannot be explained by medical progress, considering that no immunoglobulins or antibiotics for the possible bacterial super-infections, nor vaccines, were still available in the first phase of observed reduction. A possible explanation that has been proposed for this phenomenon is the epidemiological isolation of recruits. In the nineteenth and first years of the twentieth century, the majority of soldiers were enrolled from rural, isolated areas, where the possibility to acquire measles and natural immunization in infancy was scarce. Overcrowded barracks, tents and battle camps forced young men coming from different areas of the country to live in close contact, creating the best conditions for viral spread among susceptible individuals upon the emergence of new cases [132]. Measles, in the first part of the last century, was mainly complicated by bacterial pneumonia, more often caused by *Streptococcus haemolyticus*, currently known as *Streptococcus pyogenes*, largely present in apparently healthy carriers, and able to induce pneumonia, and sometimes empyema, in a respiratory tree already damaged by measles virus [134]. In 1915, the Highland Division of the British Army suffered a measles outbreak associated with scarlet fever; out of 529 soldiers with measles, 65 died, a case-fatality rate of 12%, greater than that observed during the American Civil War [135]. In 1917, measles and pneumonia were responsible for 30% of all USA deaths in the troops [28]. This same paradigm of a bacterial super-infection on a viral disease was repeated in 1918 with the Spanish influenza pandemic, whose high mortality was largely dependent on the bacterial super-infection, with severe cases of pneumonia, which were frequently lethal in the pre-antibiotic era. Conversely, prior to the twentieth century, measles-associated deaths were mainly due to lethal gastrointestinal complications and a hemorrhagic illness known as black measles [136].

Even in the post-vaccine era, the military, due to the high contagiousness of the disease and the community life, which is characteristic of the military population, seem to be more exposed to measles than the general population, as observed in Italy in the period 1986–1997 [73], and France in 2011 [137]. This observation pushed the military medical authorities in Italy and in France to introduce the compulsory measles vaccination in the trivalent formulation MMR, which was developed by Dr. Maurice Hilleman in Merck, after leaving WRAIR (in Italy, it was introduced in the military vaccination program in 1998 [24], whereas only in 1999 was vaccination offered for free to infants, to become compulsory only at the end of 2017, following a large measles outbreak in January of the same year [138]). In Italy, the effectiveness was found to be 95% [138], and even the immunogenicity was good, considering that 96% of vaccinees showed post-vaccine protective antibody levels [123]. However, the high prevalence of pre-vaccine antibody positivity, probably due to natural immunization [123], induces to believe that pre-vaccine screening may be the best policy to adopt, such as in the USA [28]. In Italy, in the period 1986–1997, measles annual incidence ranged from 70 to 1300 cases per 100,000, with an average annual incidence of 671/100,000 versus an annual incidence ranging from 0.33 to 4.2/100,000 in the period 2008–2018, an average annual incidence of 1.31/100,000, and a 512-fold reduction. This epidemiological situation probably reflects not only the effectiveness of MMR, which was introduced in 1998, but even the socio-environmental transformation due to the passage, in 2005, from the mandatory conscription to the professional army. This resulted in a reduction of occasions of disease transmission, consequent to the reduction of the number of military personnel, but mainly to the marked reduction of the requirement for the soldiers to live in barracks, a rule that has remained limited to training or operational military personnel. Currently, 23/25 NATO countries reporting the military vaccination program maintain the measles vaccination, in 18 countries for all the military personnel and in five for selected

categories of personnel [12]; in all these countries, the administered vaccine is the trivalent MMR. Despite that measles responds well to the vaccine, such that it does not represent a severe risk for public health in most countries anymore, the eradication process is quite hard to reach, even in some European countries [139]; thus, guard must remain high, even because there is the awareness that the disease-induced protection is lifelong, whereas the vaccination-induced protection is not, and currently, there is an open discussion on how many boosters are needed, in addition to the two already accepted vaccine administrations [140], for maintaining protection in the different environmental conditions [123]. The military are particularly exposed because of being a close community and because of operational activity, which may put them in contact with under-vaccinated populations where the virus is still highly circulating; thus, it should be desirable that the military is always updated with this vaccination, even by periodical checks, which may verify the state of immunization [141]. However, a measles outbreak has been recently reported even in a highly vaccinated population [142].

12. Mumps

Mumps is a disease caused by the Mumps virus, a member of the *Paramyxoviridae* family in the genus *Rubulavirus* that naturally infects only humans. Mumps generally has mild clinical course, characterized by swelling of salivary glands, especially parotid, accompanied by fever, headache, and malaise, but complications such as aseptic meningitis in up to 10%, orchitis in approximately 25% of post-pubertal male subjects, pancreatitis, deafness in approximately 4% of subjects, and rarely encephalitis, which may induce permanent disabilities or even death, may occur [143]. The infection is transmitted with moderate-high effectiveness by respiratory route, is only observed in humans, and has an incubation time of 2–4 weeks with a clinical course of 1–2 weeks [144]. A live attenuated vaccine has been developed in the 1960s [145]; it may contain different viral strains, with major or minor reactogenicity/efficacy, and it is generally administered in a combined formulation, similar to MMR. One mostly used strain, because of its safety and efficacy, is named Jeryl Lynn, after the daughter of Dr. Maurice Hilleman, who isolated the virus from her throat and prepared the attenuated vaccine strain.

In the eighteenth century, mumps was known and occurred worldwide, particularly in crowded environments such as in schools, colleges, prisons, and military barracks [146], with an annual incidence of >100/100,000 [143]. However, in the military, an even higher incidence of 6000/100,000 was observed [147]. In the first year of WWI in the USA, mumps spread explosively when recruits coming from rural areas or cities of the USA were assigned together in military barracks [148][149]. Recruits from rural areas perhaps had fewer probabilities compared to recruits from cities to come in contact with infectious agents and acquire natural immunization at infancy; thus, they were more susceptible to this and other viral infections. The epidemics followed a periodical trend, with a period of approximately 3 years and a higher peak during WWII [150]. In the USA, mumps vaccine was initially made available in 1967 to specific categories; then, from 1968 to 1977, it was gradually extended to all children of 12 months of age. The annual mumps incidence from 88/100,000 in 1968 decreased to 2.5/100,000 in 1982 with a net reduction of 97% [150]. Despite two periods of mumps resurgence in the decade 1983–1992 and in the 15-year 1993–2008 period, generally occurring in schools and colleges of rural USA populations, no resurgence was observed in the military, probably for the vaccination policy of the military with MMR since 1991. A crucial point is

the choice of the vaccine, considering that some vaccine strains are effective but poorly attenuated, such as Urabe Am9, which was responsible in the Italian military for a post-vaccine outbreak due to the vaccine strain, as molecularly demonstrated [151]. The vaccine-induced mumps for scarce vaccine strain attenuation may possibly be one of the reasons for finding 70% of mumps vaccine efficacy, compared with 95% of vaccine efficacy for measles and rubella [152]. However, the mumps vaccine effectiveness is quoted ranging from 69% to 88% [153], and a mumps outbreak has been reported in a French military Parachuting Unit in 2013, in the majority vaccinated with two MMR doses, characterized by a high attack rate, ranging from 21.6% to 25% [154]. The mumps occurrence in highly vaccinated populations is a well-known phenomenon even in other countries [155][156], and different hypotheses have been proposed for its interpretation, including early waning of immunity or antigenic variance that may reduce the efficacy of the vaccine against new circulating strains, as frequently observed with influenza vaccine [156]. Another crucial point is the number of boosters that should be administered for maintaining antibody levels above the threshold for protection. Currently, it has been established that in countries where two vaccine doses at approximately five years of distance are administered in infancy, immunization is protective with an effectiveness of over 99% of disease reduction, a percentage higher than that observed in the countries where vaccination schedule is based on only one vaccine administration [143]. However, the need for further booster(s) is still a matter of discussion and has not been established yet. Only one mumps case has been reported in the Italian military in the decade 2008–2018, an incidence of 0.32/100,000; thus, it has virtually disappeared, whereas, in the period 1986–1997, when the MMR was lacking in the compulsory vaccination schedule for the Italian military, it ranged from 25 to 65/100,000 cases, an average annual incidence of 45.5/100,000 [73]. The ratio of reduction is over 142-fold; however, for this dramatic reduction, the same considerations spent for measles on the passage in Italy from mandatory conscription to professional army in 2005 are valid. Considering that the administered vaccine is MMR, among the 25 NATO countries reporting the respective military vaccination schedule, the mumps vaccine, similar to measles, is administered in 23 countries, in 18 of them for the whole military and in five for selected categories [12].

13. Rubella

Rubella is a viral disease caused by *Rubivirus rubellae*, a member of the genus *Rubivirus*, with a generally mild clinical course, rash and lymphadenopathy, mainly at nuchal level. The major complication of rubella is fetus infection, which may provoke miscarriage or congenital rubella syndrome (CRS), a severe condition characterized by congenital ocular, hearing, heart, brain, or endocrine disabilities [157]. Despite that an effective live attenuated vaccine has been developed by Dr. Maurice Hilleman in the 1960s [158], CRS is still present with approximately 100,000 cases per year [157]. The disease has no animal reservoir, has an effective vaccine and has been eradicated in the Americas since 2009 and in Great Britain; thus, it is an optimal candidate for global eradication, even in consideration of its lower transmissibility compared with measles, provided that a suitable percentage of herd immunity, which may range from <70% to >90% according to the different world areas, is achieved and maintained [157].

The interest of rubella for the military is not only witnessed by the outbreaks observed in wartime and peacetime, but even and especially by the fact that the virus was first identified and isolated by military researchers of the WRAIR in the US Army recruits in 1961 [159]. The rubella vaccine was adopted in the US Army in 1972 [28]. The effect of vaccine introduction in reducing rubella cases was dramatic. In the three years before vaccine introduction, the number of rubella cases notified in the USA was 47,745, whereas in 2005, the CDC announced that endemic rubella was eradicated in the USA [106]. In the Italian military, rubella showed an over four-fold incidence increase in the period 1991–1995 compared with the period 1976–1980 (1150/100,000 vs. 280/100,000, respectively), with an annual incidence ranging from 50/100,000 to 2300/100,000 in the period 1986–1997 and an average annual incidence of 936/100,000 [73], whereas in the period 2008–2018, only 11 cases have been registered, 10 of which were in 2008, an incidence of 3.32/100,000, and one in 2013, an incidence of 0.33/100,000, and an average annual incidence of 1.825/100,000, a reduction of 512-fold. However, for this dramatic reduction, the considerations spent for measles and mumps on the passage in Italy from mandatory conscription to professional army in 2005 should be taken into account. Even for rubella, the situation in the NATO countries is identical to the situation reported for measles and mumps, with 18 countries using MMR for the whole personnel and five for selected categories of military personnel [12]. MMR vaccination in the military is a relevant measure of public health even in countries where MMR is provided in infancy, where, acting as a booster, it contributes to reducing viral circulation.

14. Varicella

Varicella or chickenpox is a disease caused by a DNA herpesvirus that generally induces a mild disease, characterized by fever, malaise, and vesicular erythema. The disease has high transmissibility, with an R0 estimated at around 10–12 [160], by airborne route of the virus coming from skin vesicles [161]. Varicella only occurs in humans and is present at global level, with an average annual incidence of 13–16/1000, but greater than 100/1000 in the <9-year-old children [161]. However, this epidemiological pattern is generally observed in temperate areas, because in tropical areas, the adult age is more frequently represented [161]. The clinical course tends to be self-limiting in children, whereas it may be complicated in adults in pregnancy, in which varicella may cause fetal malformations (congenital varicella syndrome) in approximately 1% if infection occurs in the first two trimesters, and in immunosuppressed people, in whom it may be responsible for death in up to 15–18% [161][162]. In 1974, Takahashi developed a live attenuated vaccine [163], which has been shown to be safe and effective. Its systematic use with two doses has deeply modified the disease epidemiology, with a reduction of over 95% of incidence, hospitalizations, and deaths in children in the USA [161].

Varicella is highly contagious; thus, it has represented a problem for the military in the pre-vaccine era, in analogy to measles, rubella, mumps, and pertussis. Even though most recruits are protected when they join the military, nonetheless, some dozen cases occur each year, as in Israel [164], considering that vaccine-induced seroprotection seems to be lower than disease-induced protection [165]. In some countries, a marked increase in varicella infection has been observed in the military between the 1970s and the 1980s [166] or between the 1970s and 1990s [73]. In the Italian military in the period 1986–1997, the annual incidence ranged from 800 to 1900/100,000 cases with an

average annual incidence of 1300/100,000 [73], whereas it ranged from 2.4 to 12.6/100,000 in the period 2008–2018 with an average annual incidence of 7.29/100,000, a reduction of 178-fold. This seems more a probable expression of the transformation of the military service in Italy than of the effect of vaccination, considering that in 2005, compulsory conscription was substituted with the professional army. In Italy, similar to many other countries, even though vaccination is mandatory, in practice, it is only administered to those who do not refer having suffered the disease or carried out vaccination in infancy, a method that does not appear as reliable, particularly in the presence of negative history [167]. Moreover, vaccination is applied in only 10/25 NATO countries reporting the military vaccination schedule, in half of which is either compulsory for all the military personnel or compulsory/recommended for selected categories of personnel [12]. Finally, in some countries, the percentage of susceptible recruits to varicella is quite high, of the order of 50% in the current period [162]. In conclusion, despite the availability of a safe and effective tool for varicella prevention, it appears that the vaccine is not as largely used in the military and, even when it is used, the policy to limit vaccine administration to those lacking documentation of infant vaccination or disease may reduce its impact on disease prevention. This may probably explain why the reduction rate of varicella is lower than the reduction rate of measles and rubella in the Italian military.

15. Influenza

Influenza is an acute respiratory disease that is transmitted by respiratory route, characterized by fever, cough, myalgias, and a generally benign clinical course of approximately 2–8 days. However, sometimes, particularly in children less than 5 years of age, older adults, subjects with underlying diseases, and in pregnant women, influenza may be complicated, mainly by pneumonia and even by multi-organ failure, with possible hospitalization and death [168]. The WHO estimates that annually approximately 1 billion people become infected with seasonal influenza, with approximately 3–5 million severe influenza and 300,000–500,000 deaths [169]. The etiological agent is a highly mutant RNA virus, of which four types are known, A, B, C, and D, the first being responsible for epidemics and pandemics, and the most severe clinical forms [170]. All four types may be found in humans and other animal species, such as swine, horses, dogs, seals, bats, and the largest reservoir, represented by wild aquatic birds [171]. The virus A expresses in its surface two proteins, hemagglutinin (H), responsible for the infection, through the attachment to the corresponding receptors on respiratory cells, of which 18 subtypes are currently known, and neuraminidase (N), responsible for detachment from cell to infect other cells, of which 11 subtypes are known [171]. Type B, which may be responsible for epidemics, C, which has been associated with mild symptoms, and D, which has not been associated with pathology in humans, may be found in animals and humans. Currently, two A strains are circulating, H1N1 and H3N2, and two B subtypes, B/Yamagata and B/Victoria [170]. Hemagglutinin and neuraminidase, as first observed by Dr. Maurice Hilleman at WRAIR in 1957 [4], undergo annual slight antigenic modifications, defined “drifts”, and periodic marked antigenic transformations, defined “shifts”, which are responsible for pandemics since the immune system does not recognize the brand-new antigen. In 1918, a terrible influenza pandemic, called “Spanish flu” started inside the USA military, at the training camps of recruits of the American Expeditionary Force (AEF), due to the strain H1N1, which was responsible for an estimated infection of one-third of humankind and death of approximately 50 million subjects, with a case-fatality rate of over 2.5% vs. 0.1% observed in other pandemics [172]. In 1957, a new pandemic, due to the strain H2N2,

defined as “Asian flu”, was responsible for approximately 1.5 million deaths, followed in 1968 by a new pandemic, due to the strain H3N2, defined as “Hong Kong flu”, which was responsible for approximately 1 million deaths. Finally, in 2009, a new pandemic, due to a swine strain H1N1, was responsible for an estimated 300,000 deaths [173].

The “Spanish” influenza pandemic was the worst. It deeply hit the military, at the beginning the US military, and afterward the military and the civilian populations of other countries, including different European countries, Africa, India and Asia, Australia and New Zealand [174]. However, the rate of infection was always higher in the military than in the corresponding civilian population [175]. This pandemic developed along three successive waves, starting in spring 1918 with a relatively mild disease and then proceeding to fall and winter–spring 1919 with two highly lethal waves. The high lethality was observed not only in the extreme life’s ages, as in other influenza epidemics or pandemics, but also in young adults. This wide distribution of lethality had a dramatic demographic and economic impact on the working and productive sectors of the interested population, higher than the war itself [172]. The virulence of the influenza virus was unique, unprecedented, and never observed afterward [176], but many other causes may have contributed to the extraordinary severity of the pandemics in wartime, including overcrowding, undernutrition, and stress due to the war, thus making the disease spread and the bacterial super-infection with consequent pneumonia easier. The high case-fatality rate, in general, and for young adults in particular, remains without an answer, despite several, careful studies [176]. In 1918, two months before the armistice of November, a peculiar event occurred that will never be repeated: the simultaneous outbreak of influenza and malaria in the Egyptian Expeditionary Force in Palestine, in which out of 315,000 soldiers, 773 died from malaria and 934 from influenza–pneumonia. Disease victims outnumbered those due to combat by over 37 to 1. Moreover, out of 40,000 men of the Desert Mounted Corps, 19,652 sick soldiers were evacuated due to malaria from *Plasmodium falciparum*, a condition that caused the interruption of combat operations [177]. However, the US military tolerated a high influenza pandemic burden in 1918–1919, such that their engagement in studying and preventing influenza was witnessed by establishing, in 1941, the Board for the Investigation and Control of Influenza and Other Epidemic Diseases in the Army, which evolved into the Army Epidemiological Board in 1944 and the Armed Forces Epidemiological Board (AFEB) in 1949 [107]. This structure supported the studies for the development of the influenza vaccine [178][179], which was tested on the military. Starting in 1943, army personnel were immunized against virus A, prior to the licensure to Parke Davis, in order to prevent possible influenza outbreaks during troop mobilization [107]. Moreover, AFEB supported real-world studies of vaccine effectiveness in the military [180][181][182][183][184][185]. Influenza virus is highly mutant, and the immunization success is closely dependent on the matching between the circulating and the vaccine viral strains; thus, the WHO has organized a network of collaborating laboratories, in order to early identify the circulating strain and give precise indications to the industry for the seasonal vaccine preparation [186]. The US military participates in such a network with the Armed Forces Health Surveillance Center, Division of Global Emerging Infections Surveillance and Response System (AFHSC-GEIS), which supports at least 52 national influenza centers and other country-specific influenza, regional and US-based, emerging infectious disease reference laboratories (44 civilian, 8 military) in 46 countries worldwide for surveillance and response [187]. Even the French military has implemented a surveillance system for influenza, called the military influenza surveillance system (MISS), as further evidence of the relevance of influenza to the military [188].

Finally, even the Italian Armed Forces have organized an Influenza Surveillance System in coordination with the civilian Influenza Surveillance Network (Influnet), driven by the Italian National Institute of Health. All these activities aim to contrast a fearsome infectious disease, which, even though did not recur with the high virulence of the Spanish flu pandemic, has shown an easy capability of spreading in favorable environmental conditions, such as those encountered in the military [186]. However, although influenza is considered a threat to the military, flu vaccination was only compulsory in the US military, on the basis of a WHO survey [45][186]. More recently, influenza vaccination has become present in the military vaccination program of 24/25 NATO countries that report the vaccination program for the military; however, in only nine countries for the whole military personnel, two of these nine countries uniquely recommend [12]. The relatively scarce use of immunization for influenza in the military is probably a consequence of the relatively poor effectiveness of the influenza vaccine in young adults [189], which is parallel to vaccine immunogenicity [123].

16. Adenovirus

Adenoviruses are a group of over 50 serotypes of a DNA virus, which may be transmitted by respiratory route, conjunctiva (in case of contact with contaminated hands), and fecal–oral route. They may induce acute respiratory disease, conjunctivitis, and gastrointestinal infections. Premises for epidemics are environmental conditions characterized by community life with overcrowding, a situation often encountered in the military, particularly the recruits, who are exposed especially in the first 3–5 weeks of training [190]. A new virus, later denominated adenovirus [191], was identified in the first half of the 1950s by Dr. Hilleman and Dr. Werner at WRAIR [192]. It was later recognized that adenovirus includes different serotypes and that types 4 and 7 were particularly implicated in acute respiratory disease in the military [106]. Adenoviruses were later recognized as the main etiological agent of acute respiratory disease in the military, with up to 80% of infected and 20% of hospitalized subjects [193]. Dr Hilleman developed a formalin-inactivated bivalent vaccine including serotypes 4 and 7, which was successfully tested for safety and efficacy, showing to be safe and over 90% effective, and was licensed in 1958. However, due to the risk of contamination by the oncogenic virus SV40, the license was retired in 1963 [4]. New live oral vaccines for serotypes 4 and 7 were developed in the 1960s by a group of military researchers led by Col. Edward Buescher and were tested in the military [4]. These vaccines proved to be safe, highly immunogenic, and protective [194][195] and were regularly administered to the US recruits on the first day of their arrival at the training camps starting in 1971 [4]. However, in 1996, this vaccination was interrupted, as the vaccines were not produced anymore by the unique manufacturer; thus, the US Department of Defense made a contract with another manufacturer [107], and in 2011, vaccination of the military was resumed [196], with a dramatic decline of febrile respiratory illness and of adenovirus respiratory infections, which decreased 100-fold [197]. This vaccine is licensed by the FDA for US military personnel, ages 17 through 50, who may be at higher risk for infection from these two adenovirus types [12]. Although the issue of adenovirus respiratory infection has been deeply studied by the US military, it has been reported in the military of other countries since the 1970s until now [198][199][200][201][202][203]. However, among the 25 NATO countries reporting vaccination schedules for the military, only one country reports that adenovirus vaccination is recommended for all recruits [12]. This is probably due to the adenovirus epidemiology in these countries, frequently involving serotypes for which vaccine is not available. Moreover, the relevance itself of the

problem may be overlooked by the lack of pathognomonic symptomatology and the difficult access to molecular and/or serological diagnosis.

17. Coronavirus Disease 2019 (COVID-19)

Coronavirus disease 2019 (COVID-19) is a potentially lethal respiratory disease, first described in China at the end of 2019 and still ongoing, caused by an RNA coronavirus (SARS-CoV-2, because similar to the SARS-CoV described in China in 2003), with high contagiousness, so that in a few weeks from the first description, it was declared a pandemic by the WHO [204][205]. As of 23 May 2022, it has caused 525,618,514 total cases and 6,277,339 total deaths, thus showing an average global attack rate of 6.78% and case-fatality rate of 1.19% (https://coronavirus.jhu.edu/map.html (accessed on 21 July 2022)). From the same data bank, the post-vaccine average annual new cases and deaths have been calculated. The average values of new cases and deaths referred to a 28-day period occurring in the last year (2021–2022) and were multiplied by 13 to refer to the length of one year; the results were 195,044,798 annual new cases and 650,702 annual deaths. Compared with the dreadful Spanish flu of more than a century ago, the attack rate and the case-fatality rate of COVID-19 are markedly lower, considering that in the Spanish flu, the estimated attack rate was as high as approximately 30% [206], and the estimated lethality 50 million deaths [207]. Nonetheless, the current pandemic is representing a great challenge for all the countries and the respective health services, which are overwhelmed by the high number of patients who are hospitalized, particularly in intensive care units, for the more severe cases, during the acute phases of the pandemic. The response to the pandemic by research was unprecedented and could develop and make available in less than one-year effective vaccines [208], monoclonal antibodies, and anti-viral agents, even though the great variability of the RNA virus has generated viral variants of concern, more aggressive and/or more transmissible, which may make the disease control uncertain. In the research for an effective vaccine, the Chinese military had an early and relevant role [209][210]. Although the pandemic is still ongoing and has not been eradicated nor transformed into an endemic disease, the vaccine's effectiveness, especially against severe disease and its complications, including hospitalizations and death, is definitively demonstrated [211].

The military are exposed to the infection not only for their community life but even for the direct management of the pandemic for its control, which offers a variety of opportunities for exposure to the virus [212]. However, even though the military are particularly exposed to the virus and their rate of infection may significantly differ or not from the civilian population, they are expected to overcome the disease without complications, considering that they are generally young and in good health [213]. A comparison between the study of the COVID-19 outbreak in the aircraft carrier Theodore Roosevelt and the cruise ship Diamond Princess is a clear demonstration of the statement above. Theodore Roosevelt is a ship with a crew of 4779 members, 1271 of whom have been found to be serologically confirmed COVID-19 infected (26.6%) and 60 had suspected COVID-19 for suggestive symptomatology, in the absence of positive serology. Out of these 1331 (27.85%) confirmed and suspected COVID-19 infected subjects, 23 (1.73%) have been hospitalized, 4 (0.3%) needed intensive care, and one died [214]. Diamond Princess is a cruise ship that started a cruise on 20 January 2020 with approximately 3700 passengers and crew members, during which an outbreak of 712 COVID-19 infected subjects occurred (19.24%, $p < 0.0000001$ vs. Theodore

Roosevelt), with 36 (5%, $p = 0.00003448$ vs. Theodore Roosevelt) hospitalized, and 13 (1.83%, $p = 0.00001793$ vs. Theodore Roosevelt) deaths [215]. The significant difference in the attack rates, higher in the military ship, is probably related to the tighter available spaces for sleeping in the military ship, compared to the more comfortable cabins of the Diamond Princess, where social distancing and isolation are easier to reach, whereas the higher rates of hospitalization and death in the Diamond Princess is probably related to the military being young and in good health. Last year, another outbreak occurred on another US Navy ship, with a crew of approximately 350 members. The infected crew members were 22 (attack rate 6.3%), all were fully vaccinated and, although symptomatic, no severe cases were observed, none were hospitalized and no death occurred [216]. This observation is a testimony of the effectiveness of the vaccine on hospitalizations and deaths and of the limited protection against infection, in the presence of the aggressive viral Delta variant. A similar observation has been made on vaccinated British military personnel deployed to Western Africa. A total of 15 out of 26 soldiers had symptomatic, but not severe, COVID-19 infection, despite being fully (11) or partially (4) vaccinated [217]. Even the infection-induced protection is not absolute, as demonstrated in Marine Corps recruits, who are admitted to the basic training after a quarantine period and a baseline negative quantitative polymerase chain reaction (qPCR) and a serological test for specific antibodies. The risk of infection in the seropositive recruits was five-fold lower than that of the seronegative recruits, thus underlining marked, but not absolute, infection-induced protection [218]. The relevance of the community life to the infection spread has even been clearly demonstrated in non-embarked personnel, such as Marine Corps recruits before being admitted to basic training. They had to follow a 2-week quarantine period at home followed by 2 weeks on a college campus, during which the recruits were asked to wear masks and to adopt social distancing. At the end of this second 2-week period, approximately 2% of recruits were SARS-CoV-2 positive by qPCR, thus underlining the relevance of community life for the infection rate, despite the right and checked behavioral control measures [219]. Even in the Bolivian military, the rate of infection is higher than in the civilian population (2.5% vs. 1.26%, $p < 0.0000001$), whereas the rate of mortality is significantly lower (1.9% vs. 6.19%, $p < 0.0000001$) [220]. The rate of infection even in the Brazilian military is higher than in the civilian population [221], whereas the opposite is observed in the Korean military [222], thus confirming that the rate of infection may depend on many variables, including the coverage of the vaccination in the military compared with the general population. Moreover, despite the vaccine's effectiveness against severe disease, the protection against infection seems to be quite limited, in particular for some types of viral variants of concern; thus, the research is actively engaged in developing more effective vaccines, possibly a "universal" vaccine [223], such as the one that is desirable to obtain even for influenza [224]. However, despite that no documents are yet available on the vaccination coverage of the military in all the countries of the world, it may be hypothesized that in all countries, the military have been considered a category to be primarily vaccinated, such as health care workers and vulnerable patients. The COVID-19 pandemic has the characteristic of profoundly interfering with societal functioning and stability, even for the relevant sequelae of the acute disease (so-called long COVID-19) that may be observed in over one-third of the subjects [225] and may markedly reduce fitness to work [226], thus fully justifying the marked interest of the military for COVID-19 and their involvement in the management of the pandemic, in the picture of close civil–military collaboration in several world countries [227].

18. Pneumococcus

Streptococcus pneumoniae is a Gram-positive diplococcus, whose discovery was independently described in the same year, 1881, by the US Major George Sternberg [228][229] and Louis Pasteur [230][231]. *S. pneumoniae* is potentially fatal, being able to induce, in addition to otitis media, sinusitis, and bronchitis, invasive pneumococcal disease (IPD), including pneumonia, meningitis, febrile bacteremia, and death. More than 90 different serotypes are known, based on the antigenic characteristics of the polysaccharide capsule, which induces neutralizing antibodies. This makes the search for a fully protective vaccine difficult, considering that the polysaccharide vaccines, either plain or conjugated to a protein matrix, are only protective for the included serotypes, and a vaccine including all the serotypes is impossible to realize [232]. However, the search for alternative vaccines, based on the inactivated whole cell or purified proteins, has demonstrated that they are safe and immunogenic, at cellular and humoral levels [233], but less effective than expected; thus, the only approved vaccines are plain or conjugated polysaccharide ones, which have been demonstrated to be able to reduce the nasopharyngeal carriage, a necessary step for reducing IDP [232].

S. pneumoniae is the main etiological agent of community-acquired pneumonia, responsible for nearly a quarter of them [234]. The military are sensitive to the problem of pneumococcal pneumonia, considering that in WWI they had to observe the dreadful and quite invariably fatal pneumonia complicating measles and Spanish influenza. The US military, therefore, tested in 1945 the first hexavalent pneumococcal polysaccharide vaccine and observed a reduced incidence of pneumonia and pneumococcal carrier rates [107]. Despite this successful experience, the pneumococcal vaccine was scarcely used and later withdrawn from the market [235], due to the higher confidence placed at that time in the newly available antibiotics compared to vaccines to deal with the pneumococcal disease issue [236]. More recently, the US military organized a large randomized, double-blind, placebo-controlled effectiveness study of the pneumococcal polysaccharide 23-valent vaccine for reducing pneumonia in healthy military trainees. However, the results of this large and well-performed study on more than 150,000 recruits did not show any protective effect of the polysaccharide vaccine, whose routine use in healthy military trainees was, therefore, not recommended [237]. Currently, only 8/25 NATO countries report that the respective vaccination programs for the military included the pneumococcal vaccine; in one country, it is intended for all the military personnel, whereas among the other seven, it is only recommended in four, and only considered for selected categories in the remaining three [12]. This confirms that the issue of pneumonia prevention is far from being completely resolved with the currently available vaccines.

19. Rabies

Rabies is an almost invariably fatal disease, caused by an RNA virus, which is largely present in many feral mammal animals, including dogs, cats, skunks, raccoons, and bats, and it is transmitted to humans by bites, scratches, and contact with skin lesions or mucosae. The virus, once transmitted, retrogradely proceeds along the peripheral nerves toward the medulla and the brain, where, after an incubation time generally ranging from 20 to 90 days, it induces encephalomyelitis, which manifests with severe symptomatology, characterized by difficulty in swallowing and hydrophobia, and either an encephalitic (furious) or paralytic (dumb) form, in 80% and 20% of cases, respectively [238]. The WHO estimates that globally there are at least 55,000 deaths each year from rabies,

especially in Asia and Africa [239]. No effective therapy exists, but an effective inactivated vaccine and passive immunotherapy with human rabies immunoglobulins (RIGs) are available. In case of bite and suspected infection, post-exposure prophylaxis (PEP) may be administered as soon as possible, by cleansing the wound and inoculating human RIGs at 20 IU/kg around the wound [240], and by administering four vaccine doses intramuscularly in two weeks (0, 3, 7, and 14 days) for minor contacts [241].

Despite that the military are not actively engaged in rabies research, rabies is a disease of military interest, in particular for deployed active service members [242]. In the US Armed Forces in the period 2011–2018, 22,709 animal bites were reported, which is an average of eight animal bites per day [243]. Animal bites with consequent rabies have been observed during the Vietnam war [244]. After the Vietnam war, rabies was still a problem in the Philippines, where in 1984, 315 potential rabies exposures were managed and 79 of them received PEP [245]. The British Army had to manage 62 animal bites when deployed to Bosnia–Herzegovina in 1995–1996 [242]. The possible shortage of RIGs may heavily influence the outcome of an at-risk animal bite in deployed personnel; thus, pre-exposure prophylaxis by active immunization has been considered to avoid the need of administering RIGs in the PEP [241]. All 25 NATO countries reporting the military vaccinating program include rabies vaccine for selected military categories; however, in three countries, rabies vaccine is only recommended [12].

20. Yellow Fever

Yellow fever is a potentially lethal disease caused by an RNA flavivirus, which is transmitted by the bite of infected mosquitoes of the species *Aedes aegypti* and *Hemagogus*, endemic in Sub-Saharan Africa and tropical Central and South America [71]. The case-fatality rate of the disease is estimated at approximately 35%; modeling studies have estimated in 2013 the burden of yellow fever in 84,000–170,000 cases with 29,000–60,000 deaths [246]. The incubation period is 3–6 days, and the disease may run asymptomatic or with a mild, not specific, symptomatology, with fever, myalgia, backache, headache, loss of appetite, nausea or vomiting, for 3–4 days. Most patients heal from the infection, whereas a few patients may enter a toxic phase one day after the end of symptomatology, with multi-organ failure, icterus and bleeding from the nose, mouth, eyes or stomach; half of these patients die within 7–10 days [246].

Yellow fever was endemic in Africa, and in the sixteenth century, it traveled to the Americas, following the slave trade, thus becoming endemic in the coastal areas of Central and South America and even in the southern and eastern coast of North America to Boston. From 1668 to 1893, over 135 epidemics of yellow fever occurred in the USA. In 1793, an epidemic of yellow fever killed 10% of the Philadelphia population and in 1878, another epidemic killed 20,000 people in the Mississippi valley [247]. At that time, nothing was known about the biology of the disease and the way it is transmitted. At the start of the Spanish–American war in 1898, the US troops were decimated by yellow fever in Cuba. Thus, the Surgeon General of the US Army, Gen. George Miller Sternberg, organized a Yellow Fever Commission, coordinated by Major Walter Reed, and composed of Majors James Carroll, Aristides Agramonte, and Jesse Lazear, with the duty of clarifying the way of transmission of the disease in order to prevent infection spreading [247]. The Commission went to Cuba to begin its activity in June 1900. It started by verifying the etiological hypothesis proposed by the Italian microbiologist Giuseppe Sanarelli, who in 1897, announced to have

found the etiological agent of yellow fever, which was named *Bacillus icteroides*. The commission ruled out this hypothesis and then focused its activity on taking into account the work of Carlos Finlay, a Cuban physician who had suggested a transmission through the mosquito *Aedes aegypti* by performing specific experiments on human volunteers, which were unsuccessful. Finlay tried to expose healthy volunteers to the bite of mosquitoes 2–6 days after the mosquitoes had bitten a patient with yellow fever; however, he never succeeded in observing a clear case of infection transmission. The reason was clarified over 10 years later by the observations of the US physician Henry Rose Carter in 1898, relative to the “extrinsic incubation” of yellow fever in the mosquito, which was calculated in approximately 2 weeks. The Yellow Fever Commission thus repeated Finlay’s experiments, by taking into account the “extrinsic incubation” time of Carter and succeeded in demonstrating the transmissibility of the etiological agent by mosquitoes, thus providing scientific evidence to Finlay’s hypothesis. Considering that there is not an animal model for yellow fever, the commission used healthy human volunteers, including the same members of the commission and one of its members, Jesse Lazear, who died in 1900, at the age of 34 years [248]. The observations of the Yellow Fever Commission were published in 1901 (JAMA 1901;36: 431–40), and the Major physician US Army William C Gorgas, responsible for health in Cuba, received the disposition to free Havana of mosquitoes. His work was excellent because in 90 days, he transformed the epidemiological situation of Havana, in which one case of yellow fever per day was described on average from 1762 to 1901, whereas after mosquito disinfestation, it was free of the disease [247]. Thus, the fight against yellow fever was won in this phase by the US military.

The viral etiological agent was only isolated in 1927 from a sick man in Ghana. A live vaccine, attenuated by 200 subcultures of this virus, designated 17D strain, was developed in the 1930s by Theiler and Smith [249]; Theiler was awarded the Nobel Prize for Physiology or Medicine in 1951 [72]. The vaccine is generally safe, highly immunogenic and protective for long periods, considering that the presence of neutralizing antibodies has been found after 30–35 years from vaccination [250]. Currently, all 25 NATO countries reporting the respective military vaccination program include yellow fever vaccine, in 24 for selected categories, whereas in one country for all the military personnel. With the use of the vaccine, yellow fever does not represent a problem for the military at the global level anymore [12]. Yellow fever virus has been included among the possible biological agents, category C [34].

21. Japanese Encephalitis (JE)

Japanese encephalitis (JE) is a potentially lethal disease caused by an RNA flavivirus transmitted by the bite of infected *Culex* mosquitoes, in particular *Culex tritaeniorhynchus*; however, even other mosquito species may be vectors. The virus is endemic in large parts of South, South-East Asia and the Western Pacific, including an estimated population of over 3 billion people, particularly in rural areas, where the risk factor is living in proximity of rice fields and pig rearing [251]. It is estimated that the annual JE cases are 67,900, with 13,600–20,400 deaths. The infection may run asymptomatic in most patients; in one case out of 250 infections, the disease is severe. After an incubation period of 4–14 days, symptomatology starts with high fever, chills, myalgias, headache, and mental confusion; however, opisthotonos and even acute flaccid paralysis may occur. The disease occurs preferentially in

children <10 years, in whom it is generally more severe. The case-fatality rate of the severe disease is 20–30%, and approximately 30% of the survivors present permanent neurologic or psychologic disabilities [252].

The interest for the US military started during WWII; in 1942, a research team was established at WRAIR, with the duty of developing a vaccine for JE [242]. Even Major Albert Sabin received by the Commission on Neurotropic Virus Diseases of the Army Epidemiological Board the task to develop a JE vaccine [107]. The vaccine was a formalin-inactivated JE virus cultured in the brains of mice; it was used on 250,000 US soldiers during the war, starting in 1945, after an outbreak of JE in the US military stationed in Okinawa [107]. Albert Sabin had the opportunity to study and describe this outbreak and the use of the vaccine [253]. Even after the war, Albert Sabin and the US military collaborated with Japanese researchers for studying together the JE vaccine [254]. The US military suffered a relevant outbreak of 300 cases of JE in 1950 among the US troops stationed in Korea during the Korean War, although the US military were all vaccinated, and 16 lethal cases were observed [242]. Even during the Vietnam War, cases of JE in the US Air Force personnel were described [242], however, no reduction of US force fighting strength was observed [255]. Following the Korea outbreak, which had demonstrated the poor protection provided by the first used vaccine, the army interrupted the vaccination of the US military assigned to the Far East Command [107]. At the end of the 1950s, researchers of WRAIR working in Japan contributed to providing new knowledge on JE ecology [256]. The studies for the development of a new vaccine resumed in the 1980s, led by the CDC; however, the conclusive phase III studies were carried out in Thailand, under the leadership of Col. Charles Hoke, of the US Army Medical Component, Armed Forces Research Institute of Medical Sciences (AFRIMS) in Bangkok, Thailand, during which a monovalent (Nakayama strain) and bivalent (Nakayama and Beijing-1 strains) vaccine were studied in comparison with placebo. The results showed 91% of efficacy for both monovalent and bivalent vaccines [257][258]. It could be carried out due to the previous research at AFRIMS of the military researcher Donald Scott Burke, who had set up a diagnostic test for anti-JE IgM in serum and liquor [259][260]. Another study was carried out by the WRAIR researchers on 538 US soldiers with monovalent JE vaccine, which confirmed the safety and the high immunogenicity of the vaccine and ruled out the possible interference with a previous yellow fever vaccination, another flavivirus [261]. In 2005, the production of the mouse brain-derived JE inactivated vaccine was discontinued by the manufacturing company because it was considered too reactogenic and poorly immunogenic [262]. Currently, in the USA, the only approved vaccine is IXIARO (JE-VC), which is a Vero cell-culture-derived inactivated vaccine [263]. However, even live and recombinant live vaccines are available [252][261]. Twenty-one out of the twenty-five NATO countries report that the military vaccination program includes the JE vaccine for selected categories of personnel [12]. The Italian military soldiers participating in the INTERFET (International Force to East Timor) mission in 1999 were vaccinated with the monovalent (Nakayama strain) mouse brain-derived JE vaccine, without side effects. However, some of them were infected by the dengue virus, and the previous vaccination with the JE vaccine has been considered partly cross-protective even for dengue [264].

22. Tick-Borne Encephalitis (TBE)

Tick-borne encephalitis (TBE) is a disease caused by an RNA flavivirus transmitted by the bite of ticks. The virus is present in many animals, such as wild rodents, deer, boar, dog, fox, sheep, cattle, and bat, and is transmitted to

humans by ticks of the family *Ixodidae*, in particular *Ixodes Ricinus* and *Ixodes persulcatus*. Humans are a dead-end host and may even be infected by alimentary route, by eating raw contaminated dairy. Three subtypes of the virus are responsible for the respective diseases that are endemic in central, eastern and northern Europe (western subtype), eastern Europe, Russia and northern Asia (Siberian subtype), and eastern Russia as well as some parts of China and Japan (far eastern subtype) [265]. Although two-thirds of the cases are asymptomatic, the disease caused by the western subtype has a biphasic pattern, with a first phase characterized by nonspecific symptomatology (fever, myalgia, headache, fatigue, nausea) and a second phase, following a free interval, by meningoencephalitis, myelitis or paralysis, whereas the far eastern subtype is associated with a monophasic disease. Moreover, the European disease is milder (mortality 0.5–2%, and neurological sequelae up to 10%) than the disease caused by the far eastern subtype, which has a mortality of up to 20% and a higher prevalence of permanent neurological sequelae [266]. The diagnosis may be made by molecular or serological approaches. However, virus identification by molecular methods is poorly used because the viremia is present for a short time, and the reliability of serological tests is reduced for the possible cross-reaction among different flaviviruses. There is no available treatment, whereas an inactivated vaccine from a cell-cultured virus has been shown to be safe and protective in over 95% of recipients after three-dose administration [265]. The annual world cases of TBE are approximately 10,000–12,000 [267], whereas in Europe, over 3000 annual TBE cases are hospitalized [268]. The disease tends to be more frequent in males than in females in Europe and more severe in >50–60-year-old subjects, who are less responsive to the vaccine [265][269][270].

The interest for the military of TBE is linked to the country where the military live or are deployed to, whether TBE is endemic or not. The US military, which started to be interested in TBE in the mid-1980s [271], vaccinated the troops deployed to Bosnia in 1996 with an accelerated schedule (0, 7, and 28 days instead of 0, 1–3, and 9–12 months) of TBE vaccine in order to be readily protected; 80% of seroconversion rate was observed after the third vaccine dose, and the vaccine proved to be safe, with only 7/3981 (0.18%) vaccinees reporting self-limited symptoms. However, the infection risk was relatively low, considering that only 4/959 (0.42%) unvaccinated soldiers seroconverted [272]. Among the 25 NATO countries reporting the respective vaccination schedule for the military, twenty-two include the TBE vaccine, six of these countries (all European where TBE is endemic) provided to the whole military personnel, and in the other sixteen, only to selected categories [12]. The TBE virus has been included among biological agents, category C [34].

23. Human Papillomavirus (HPV)

Human papillomavirus (HPV) is a DNA virus, which infects epithelial basal cells, at cutaneous and mucosal levels, and may induce different cutaneous and mucosal lesions and even cancers. There are more than 100 serotypes, some of which may cause cervix, anal, penile, and oropharynx cancers, with serotypes 16 and 18 being the most frequently implicated in cancers. However, even serotypes 31, 33, 45, 52, and 58 may be considered high risk for cancer induction, whereas serotypes 6 and 11 are generally associated with anogenital warts, such as condyloma acuminatum, and are considered low-risk HPV [273]. The main way of HPV transmission is through sexual intercourse; thus, the military worldwide are at special risk [274], hence their interest in HPV, even considering that a

safe and effective HPV vaccine is currently available. Three recombinant vaccines are available, the bivalent (16 and 18 serotypes), the tetravalent (6, 11, 16, and 18 serotypes), and the nine-valent (6, 11, 16, 18, 31, 33, 45, 52, and 58 serotypes). It may be calculated that with bivalent and tetravalent vaccines, the protection against cancer is approximately 70%, whereas it increases to approximately 90% with the nine-valent one [72]. Only one NATO country reports HPV mandatory vaccination in the military schedule, whereas in the other six countries, the vaccination is only recommended [12]. A longitudinal study in the US military showed that 14.6% of male recruits were HPV positive for serotypes 6, 11, 16 or 18 at entry and 34.2% of those originally negative for these serotypes seroconverted to one or more of them after 10 years [275]. However, more recently, an epidemiological survey on genital HPV infections developed during a 9-year long follow-up, between 1 January 2012 and 31 December 2020, has shown a significant reduction of infection for both genders, female service members from 261.2/10,000 to 163.1/10,000 person-years (37.5% of reduction) and male service members from 40.6 to 16.9/10,000 person-years (66.1% of reduction), a decrease that has been attributed, at least in part, to the introduction of a vaccine for females in 2006 and for males in 2010, which, even though it is not mandatory, is encouraged and offered to service members [276]. In a relatively low number of countries (76/195, 39%), the HPV vaccine has been introduced as mandatory and in most cases for young females, with a gradient of application ranging from 10% for low-income countries to 69% for high-income countries, thus clearly indicating the negative influence of poverty on the possibility of introducing this relatively expensive vaccine. The global HPV vaccination coverage is estimated to be as low as 12.2% [277]. Australia was the first country to organize, in 2007, an eradication program of the cancer of the cervix [278]. Despite that the fight against cervical cancer is a priority considering the high number of annual cases and deaths, especially in low-income countries [277], and for this reason, the vaccination campaign has mainly been addressed to young girls before starting sexual activity, the vaccination of the males should also be considered to prevent male cancers [279].

HPV vaccination in the military could contribute to the reduction of HPV-related cases of cancers if mandatory, considering that the military are at a higher risk of infection than the matched civilian population, and the simple recommendation of vaccination cannot reach critical coverage, considering the stigma linked to the sexually transmitted diseases [280][281]. Moreover, a cost-effectiveness estimate allows one to compare the care cost per case of anal cancer of USD 52,700 or 146,100 per case of oropharyngeal cancer versus USD 450 for HPV vaccination [282]. Thus, this hesitancy in making HPV vaccination mandatory for the military is quite surprising, and it diverges from the historical behavior of the military, that for many infectious diseases has generally anticipated the general population in vaccine research and application. Probably, this was the expression of a different time, in which infectious diseases could heavily influence the outcome of battles and war more than the combat capacity. Moreover, HPV is not acutely incapacitating, considering that it may induce deferred neoplastic disease. However, a larger vaccine use, especially in countries with compulsory conscription, may represent a relevant measure of public health.

24. Cholera

Cholera is a bacterial disease that can be transmitted through water or food contaminated with *Vibrio cholerae*, 01 and 0139 serogroups, endemic in 50 countries and able to induce epidemics. It is estimated that annually 1.3–4 million people become infected, resulting in 21,000–143,000 annual deaths [283]. Seven pandemics since 1817 spread from Asia to all over the world. Right rehydration may lower the mortality from over 50% to 0.2% [284]. The prevention consists of water sterilization and sanitation. Cholera was first reported by the British military in 1770 [285]. Similar to all the infectious diarrheal syndromes linked to poor hygienic conditions, it has always been considered a threat by the military. In 1855, during the Crimean War, the Piedmont–Sardinia expeditionary force was deeply hit by cholera; 2728/18,000 military personnel fell ill with cholera, an attack rate of 15%, and 1230 died, a case-fatality rate of 45% [286]. A live vaccine against cholera was first developed by Jaime Ferran in Spain [287], but it was ultimately the vaccine developed by the German scientist Wilhelm Kolle in 1896, using heat-inactivated cholera bacilli, that came into general use and that served as a model for cholera vaccines for the next century [288]. As a military physician and hygienist during WWI, Kolle was highly successful in vaccination against cholera. This vaccine was widely used during WWI in the military, such as by the Italian Army when, in August 1915, cholera broke out in the Italian troops deployed along the Isonzo river. The anti-cholera mass vaccination of the military was then ordered and subsequently extended to civilians residing in closely affected areas. This approach allowed the containment of the epidemic, which remained almost confined to the military community and only marginally affected the civilian population. In 1915, the observed cases were 14,000, whereas they were reduced to only 170 in 1916 [289]. These data demonstrate that vaccination campaigns can be carried out safely even during the epidemic phases, helping to provide useful information to the scientific world to better understand the effectiveness of this vaccine. However, this vaccine was painful and did not give long-lasting immunity.

Furthermore, it is worth noting the contributions of US military investigators on the front lines of cholera research. The US Navy's involvement with cholera began in Cairo, Egypt, during the 1947 cholera epidemic, when the commander of the Naval Medical Research Unit (NAMRU) 3, Robert A. Phillips, made some interesting observations. He established that the stools of patients with cholera were isotonic with their blood [290] and did not contain proteins; thus, allowing him to argue that no mucosal damage was present [285]. This observation allowed the rehydration of patients by infusion of isotonic electrolyte solutions to be possible, as even confirmed in a cholera outbreak in Bangkok Thailand, where Phillips applied his method [291]. This rehydration method allowed the mortality of cholera to be reduced from 20–30% to less than 1%; thus, saving a large number of lives. Later, in 1961 in Manila, Phillips discovered that isotonic electrolyte solutions containing glucose could be orally administered to rehydrate patients with cholera and other diarrheal diseases. This further observation made the rehydration method accessible even to developing countries for its lower cost, thus allowing millions of lives to be saved in the past several decades [285]. Richard Finkelstein, a civilian working at WRAIR, isolated the cholera exotoxin, which he called cholerogen, in 1963 [292].

Finally, the US military contributed to developing and testing improved cholera vaccines. Col. Jose Sanchez and colleagues, from WRAIR [293], and even in collaboration with the US Navy Medical Research Institute Detachment —Lima, Peru [294], studied a killed, whole-cell, vaccine plus recombinant cholera toxin B subunit (WC/rBS), and Col. David Taylor and other colleagues from WRAIR contributed to basic science research into a live attenuated O139 *Vibrio cholerae* vaccine prototype [295][296].

In addition, the US Department of Defense contributed to basic science research into a live attenuated cholera vaccine at the Armed Forces Research Institute of Medical Sciences in Bangkok [297] and at the Indonesian US NAMRU in Jakarta [298], respectively.

While considering the advances in the development of vaccines, also due to the contribution of the military, cholera is still a major global health problem in unsanitary conditions. Current cholera vaccines, represented by a two-dose killed whole cell monovalent (01) plus recombinant cholera B subunit of cholera toxin (WC-rBS), a two-dose killed whole cell bivalent (01 and 0139) (WC), and a single-dose live oral attenuated vaccine (CVD-103 HgR), are safe, feasible to use and represent a public health tool in the prevention of the disease, along with hygiene measures [299]. Currently, such as for typhoid fever, in the military of most NATO countries (21/25), including Italy, cholera vaccination is present in the vaccination schedule, but only for the troops deployed to at-risk epidemiological countries [12]. *V. cholerae* has been included among the possible biological agents, category B [34].

25. Leptospirosis

Leptospirosis is a potentially fatal bacterial disease caused by *Leptospira*, an aerobic bacterium containing in its structure a lipopolysaccharide similar to the one found in Gram-negative bacteria [300]. *Leptospira* is present in different wild and domestic animals; however, the main reservoir for human infections is *Rattus norvegicus* [301]. *Leptospira* is excreted in rat urine; thus, contaminating soil and water. Humans are accidental hosts, who may be infected through the trans-cutaneous or trans-mucosal passage, profiting from cuts or abrasions of the skin or conjunctival and/or oral mucosae [302]. Leptospirosis is therefore an occupational zoonosis; the most exposed worker categories are sewage workers, farmers in rainy areas and the military, particularly during exercises in marshy soils. The disease may be mild and self-limited; however, in some subjects and with some serovars, the disease may be severe, as in the case of Weil's disease, caused by serovars of the *icterohaemorrhagiae* serogroup, in which the mortality is over 10%, or the severe pulmonary hemorrhage syndrome, which may have a case-fatality rate of over 50% [302]. Annually leptospirosis is estimated to be responsible for 1.03 million clinical cases with 58,900 deaths [303].

The etiological agent was discovered in 1915 by Japanese [304] and German [305][306] physicians, whereas the severe form of the disease had been described by Weil in 1886 [307]. However, the disease was present before and in the seventeenth century in New England, and in the eighteenth and nineteenth centuries in Europe, illnesses with the characteristics of leptospirosis had been described, particularly by military doctors [308]. Leptospirosis is a disease of interest for the military, because it is frequently associated with the military, both in wartime, considering the precarious hygienic conditions, particularly in humid trench warfare, and in peacetime, for training in standing water [309]. It was described during the second independence war in Italy in 1859 [308], during WWI and WWII, and the Vietnam War [296]. In the summer of 1942, there was an outbreak of febrile exanthem at Fort Bragg, which involved 40 US soldiers and recurred in the summer of 1943 and 1944, whose etiology was only clarified in 1952 by Major US Army William Gochenour and colleagues following isolation of *Leptospira autumnalis* [310]. In the same year, Major Gochenour and colleagues were able to diagnose as leptospiral meningitis an outbreak of "aseptic meningitis" occurring in 1949 in US soldiers serving in Okinawa [311]. In the 1980s, Dr. Ernest T. Takafuji from

WRAIR and colleagues were able to successfully test the efficacy of chemoprophylaxis with doxycycline against leptospirosis on US soldiers training in field exercises in the Panama Canal [312]. Although an inactivated whole-cell vaccine has been available for more than a century, it is largely used in animals, whereas it is rarely used in humans, despite its effectiveness, due to its specific protection only against single serovars (Spirolept®, produced by Sanofi-Pasteur, only protects against *Leptospira icterohaemorrhagiae*), the quite heavy schedule, characterized by three subcutaneously administered doses followed by biannual boosters, and its reactogenicity [301][313]. Although information about the number of world countries adopting the leptospirosis vaccine for the military is lacking, among NATO countries, only two consider leptospirosis vaccination in occupationally exposed military personnel [12].

26. Dengue

Dengue is the most prevalent arthropod-borne viral disease [314], responsible for an estimated 390,000,000 annual infections, a quarter of which are symptomatic [315]. The virus is an RNA flavivirus, of which four serotypes (1, 2, 3, and 4) are known, and is transmitted by the same vector of yellow fever virus, *Aedes aegypti*; however, in some geographical regions, other vectors, such as *Aedes albopictus* and *Aedes polynesiensis*, may even transmit the virus [316]. The infection may run completely asymptomatic, whereas in an estimated 25% of cases, it may induce non-specific fever, dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. Dengue hemorrhagic fever is frequently observed in children and dengue shock syndrome, if severe, may be responsible for death in 9.3%, but up to 47%, of cases with profound shock [317]. Dengue is of interest to the military because it is highly prevalent at the global level and may heavily reduce the operational readiness of the soldiers, even though the annual mortality is estimated to be quite low, 12,000, mainly occurring among children [318]. In a recent quantitative algorithm to quantify the burden of infectious diseases for the US military, dengue ranks third, after malaria and bacterial diarrhea [319]. Moreover, the prevention of dengue consists of the defense from the vector, considering that a satisfying vaccine registered in many world countries is still lacking. Although different types of vaccines are under study, including the live recombinant ones, inactivated, subunits with the envelope (E) protein alone or together with the precursor of the membrane (prM), only one tetravalent recombinant live on a YF17D backbone has been licensed in Mexico in December 2015, with the name Dengvaxia® [320]. Afterward, other endemic countries registered this product with their respective regulatory authorities. This vaccine is administered according to a 0/6/12-month schedule and has the highest efficacy of 76.9% against serotype 4 and the lowest of 43% against serotype 2. However, the cumulative efficacy was substantially higher, 78.2%, in people already exposed to dengue compared to naïve [320]. In different projects for vaccine and monoclonal antibodies development, the US military, at WRAIR and Naval Medical Research Center (NMRC), are involved as further evidence of the interest in dengue for the military [320][321][322]. In addition to the diagnostic problem for the cross-reaction with other flaviviruses and the possible cross-protection between different flaviviruses [323][324], for dengue virus only the issue of antibody-dependent enhancement (ADE) has been described, which is the facilitated antibody-mediated viral entry into the cells through the FcγR [316]. ADE has been considered as the main reason for the waning, after approximately 2 years from an infection with a dengue serotype, of the cross-protection against the other three serotypes (heterotypic protection), whereas the homotypic protection is lifelong [320], in line with the long

persistence of protective antibodies [325]. After the waning of heterotypic protection, people are more exposed to severe forms of dengue by heterologous serotypes [326]. This peculiar behavior of humoral anti-dengue immunity has to be taken into account when developing a dengue vaccine.

The US military have reviewed the burden of dengue from the American–Spanish War, through the Philippines, where they could observe that the disease more easily occurred in urban than in rural areas and that reinfection was not rare. During WWII, dengue occurred in many war theaters, particularly in the South Pacific, New Guinea and the Philippines; in the Vietnam War, the diagnosis moved from clinically to laboratory made, and finally in the Philippines again, Somalia, and Haiti [327]. During this long period, the engagement of the US military was continuous, mainly in the etiology and diagnosis, with a relevant contribution of the former Major Albert Sabin, and prevention through indirect measures, whereas the involvement in the research for an effective vaccine is more recent, probably for historical underestimation of the military significance of dengue [328][329]. Even the French military exert dengue surveillance for their overseas departments and territories endemic for dengue, where annually, 25,000 French soldiers are present, thus replacing the lack of a local epidemiological surveillance system [330]. However, in addition to the US, French and British military, who have a long historical tradition of being present at the global level in endemic areas, the military of all the world's countries may be challenged with the dengue problem during peace-keeping operations in endemic areas [264]. Currently, US military researchers are still actively engaged in the search for a safer and more effective vaccine than Dengvaxia®, which has not been licensed by the FDA [330]. Dengvaxia® may induce severe dengue in seronegative recipients of any age >9 years [331]. Moreover, the efficacy against serotypes 3 and 4 is good, whereas it is moderate to serotype 1 and marginal to serotype 2 [331].

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