A Review of the Current Status of Anthrax Medical Countermeasures

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Anthrax, the disease resulting from infection with the zoonotic bacterium Bacillus anthracis, has a high potential for use as an agent of biological terrorism and warfare, and has in fact been used for both. Given its relative high mortality rate in untreated humans, e ective medical treatments and prophylactics are essential. This brief review will summarize the current state of medical countermeasures (MCM) for treating individuals exposed to anthrax as well as preventing the disease from manifesting.

Anthrax; Vaccine; Monoclonal antibodies; Bioterrorism

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e disease anthrax results from infection with the zoonotic, aerobic, gram-negative, endospore-forming bacterium *Bacillus anthracis*. Anthrax occurs primarily as cutaneous, gastrointestinal, and inhalational forms [1]. e cutaneous form is the most common natural infection (approximately 95% of human cases) and usually results from exposure to animals or animal products. Gastrointestinal anthrax is very rare, and inhalational anthrax accounts for approximately 5% of human cases. More recently, the much less common injection anthrax and welder's anthrax forms have been described [2].

Inhalational infection with B. anthracis occurs via introduction of the spores, followed by germination into the vegetative form of the bacterium which produces several characteristic toxins. e initial presentation (Stage I) of infection is characterized by nonspeci c u-like symptoms which last hours to days. Lacking treatment during Stage I, the disease progresses to a fulminant form of infection (Stage II) which is associated with fever, dyspnea, diaphoresis, massive lymphadenopathy, and stridor [3]. Chest X-rays at this stage show mediastinal widening (characteristic) and pleural e usion. Individuals with Stage II disease are unlikely to recover, with death resulting from massive organ failure [4].

B. anthracis produces three polypeptides which combine in binary form to produce lethal toxin (LT) or edema toxin (ET); the genes encoding all three antigens are found on the pXO1 plasmid. ese toxins are responsible for the symptoms and lethality of anthrax. Protective antigen (PA) is the receptor binding component of both LT and ET and is responsible for delivery of these toxin complexes into the target cell. LT is a zinc metalloproteinase that cleaves the N-terminus of several mitogen-activated protein kinase kinases, and which induces an atypical vascular collapse (not endotoxin shock). ET is a calmodulin-dependent adenylate cyclase that a ects many di erent cell-signaling pathways and is associated with hemorrhaging lesions in many organs [5]. e endospores of B. anthracis are extremely resistant to environmental degradation; this property, coupled with the rapidly virulent nature of the inhalational form of the disease as well as the initial non-speci c signs which might be confused with less severe conditions, makes anthrax a near-ideal biological weapon (Goel, 2015). Consequently, anthrax has been utilized as a weapon or an agent of terrorism for several years and was a component of the biological warfare arsenals of multiple countries [6].

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Given the obvious importance of preventing and treating anthrax infections to human health and national security, a robust armamentarium of MCM to prevent and treat anthrax is necessary [7-

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03-July-2023, Manuscript No. jbtbd-23-105474; 05-July-2023, PreQC No. jbtbd-23-105474 (PQ); 20-July-2023, QC No. jbtbd-23-105474; 24-July-2023, Manuscript No. jbtbd-23-105474 (R); 31-July-2023, DOI: 10.4172/2157-2526.1000338

House RV (2023) A Review of the Current Status of Anthrax Medical Countermeasures . J Bioterr Biodef, 14: 338.

label use of amoxicillin as the preferred PEP agent if the anthrax strain is proven to be susceptible to that drug (Committee on Prepositioned Medical Countermeasures for the Public; Institute of Medicine, 2011). Since strains of anthrax have demonstrated resistance to these approved drugs, several other antibiotics are under investigation as potential MCM including moxi oxacin, linezolid, meropenem, and cyclic lipopeptides such as daptomycin; to date, none of these antibiotics have been approved by the FDA for treatment or PEP of anthrax [11].

While antibiotics represent the rst line of MCM response to anthrax, their use is reactive rather than proactive; to adequately prepare for potential large-scale events involving anthrax dissemination, vaccines are required. Although anthrax had been used o ensively in the past, following the so-called "Amerithrax" event of 2001, there was a renewed interest in developing and approving anthrax vaccines for the general population [12-13]. Currently, there are only two anthrax vaccines being administered in the West, namely Anthrax Vaccine Absorbed (AVA) which is approved in the United States and Anthrax Vaccine Precipitated (AVP) which is approved in the UK (Clark and Wolfe, 2020), although multiple investigators are evaluating additional anthrax vaccine candidates [14-15]. In addition, a modi cation of the AVA vaccine, Anthrax Vaccine Absorbed, Adjuvanted (AV7909) is in advanced development. ese vaccines are described brie y below.

development for several years; however, they are all still in early development and none have been approved for human use. Whereas many/most MCM for anthrax focus on PA, some investigators believe that this is short-sighted since the interaction of LT and ET are multifaceted. Accordingly, investigators are evaluating a wide variety of target including – but not limited to - inhibitors of binding domains on anthrax toxin receptors (TEM8 or CMG2), inhibitors of furin PA_{83} cleavage, inhibitors of PA_{63} oligomerization and prepore formation, inhibitors of LF and EF attachment to the PA oligomer, inhibitors of endosomal pore formation and translocation of LF and EF, and inhibitors of the intracellular enzymatic e ects of LF [27, 28].

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Passive immunization, also referred to (somewhat inaccurately) as “instant immunity” refers to protection against/treatment of infection by administering pre-formed antibody speci c for antigens associated with the infection [29]. Passive immunization has the advantage of providing rapid (although perhaps not “instant”) neutralization of

of 2023. Obiltoxaximab is supplied to the SNS in the US. In addition, in April 2022 Heat Biologics announced that it had nalized a contract with the Canadian government to deliver ANTHIM® to Canada's National Emergency Strategic Stockpile under a procurement contract totaling CAD $7.9 million.

At present, Raxibacumab and Obiltoxaximab are the only mAbs approved for treatment and PEP of anthrax and are likely to remain so. In 2021 a Justi cation and Approval for Other an Full and Open Competition stated: "FDA does not anticipate another product entering the market in the next 5-10 years as there is no market outside of the USG for such which dissuades vendors from investing hundreds of millions of dollars with no potential return." e justi cation further states: "Due to the expense and intensive time investments needed to bring a new anthrax antitoxin to market, it is not anticipated that the USG will invest in the creation of an additional anthrax antitoxin in the near future." [Award of Anthim (Obiltoxaximab) 600mg/6ml for Injection (Accessed from SAM.GOV Oct 24, 2022. Although both mAbs have been approved by the FDA using the Animal Rule (and Obiltoxaximab was approved by the European Union), neither has been used to treat inhalational anthrax following human exposure. Studies are ongoing by various investigators to further elucidate the full e ectiveness of these MCM [46-48].

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In May of 2022, BARDA published its Strategic Plan 2022-2026: Fortifying the Nation's Health Security. Although this Strategic Plan lays out a wide-ranging series of goals for BARDA, there is sparce mention of acquisition of MCM, including those for anthrax. However, the Department of Health and Human Services' 2022 Justi cation of Estimates for Appropriations Committee included line items for Anthrax ($10 million), stating that "FY 2022 funding will support assessment of delivery approaches that may enable a next-generation anthrax vaccine that can provide protection a er a single dose." Additionally, a line item for Anthrax Antitoxins ($1 million) was included to "support ongoing analytical studies designed to evaluate extended stability of existing anthrax antitoxins.

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In 1998 Congress appropriated funds for the CDC to acquire a stockpile of vaccines and pharmaceuticals to address biological and chemical threats. e program was originally called the National Pharmaceutical Stockpile (NPS) program; however, as the program evolved to include additional medical and emergency supplies, on March 1, 2003, it was renamed the Strategic National Stockpile (SNS). e program is currently overseen by HHS/ASPR.

e SNS contains multiple products for preventing and treating anthrax; in fact, from scal years 2015 through 2021, HHS obligated nearly $2.3B (approximately 50% of the total allocated for the SNS) speci cally for anthrax MCM. (Smallpox MCM was second at $1.1B or 24% of the total.) In 2022 the US Government Accountability O ce conducted an assessment of the SNS and their reviews shows the SNS "contained most medical countermeasure types recommended, but o en not in the recommended quantities. HHS o cials noted that gaps in quantities are due to budget constraints and acknowledge these gaps present risks" [PUBLIC HEALTH PREPAREDNESS HHS Should Address Strategic National Stockpile Requirements and Inventory Risks. Accessed Oct 21, 2022. It was unclear from the report if anthrax-speci c MCM recommended quantities were de cient, although this seems unlikely.

Of note here is the Department of Health and Human Services Fiscal Year 2023 Public Health and Social Services Emergency Fund Justi cation of Estimates for Appropriations Committee, which references the SNS. Speci cally, the budget justi cation includes $975 million for the SNS to procure products transitioning from Project Bio Shield support and prioritizes funding for sustainment of current product lines and procurement of several products previously supported by BARDA that lack a signi cant commercial market. ese items include procurement of su cient quantities of a domestically manufactured, FDA approved, smallpox antiviral, procurement enough bandages to treat an estimated 14,000 people impacted by a radiological/nuclear incident, and limited quantities of anthrax therapeutics.

e National Emergency Strategic Stockpile in Canada is managed by the Public Health Agency of Canada. Among its assets are pharmaceuticals and vaccines for various infectious disease emergencies, including medicines for anthrax. As with the SNS in the US, details of speci c requirements are not publicly available, although as previously noted Obiltoxaximab has been purchased for the NESS.

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e European Health Emergency Preparedness and Response

In addition, as the COVID-19 pandemic demonstrated, disruptions

39. Pavia CS, Wormser GP (2021) Passive immunization and its rebirth in the era of the COVID-19 pandemic