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A Brief History of Biocontainment

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Opinion statement

The concept of clinical biocontainment, otherwise known as high-level containment care (HLCC), had its birth among a confluence of near-simultaneous events in 1969. The U.S. Army's Medical Research Institute of Infectious Diseases (USAMRIID) began construction of the first modern biocontainment unit that year, and opened the two-bed facility, often referred to as "the Slammer" in 1971. Over its 41-year existence, 21 persons exposed to highly hazardous infectious diseases were admitted to the Slammer, but none ever contracted the disease to which they had been exposed. Owing, in part, to this underutilization, some questioned the utility of HLCC units. This concern notwithstanding, Emory University and the University of Nebraska opened HLCC units in civilian academic medical centers in 2004 and 2005, respectively. These units, distinct from conventional infectious disease isolation wards found in most major medical centers, proved their worth during the West African Ebola Virus Disease (EVD) outbreak of 2014–2015. It is our opinion that such units, as well as the parallel high-level containment transport systems necessary to move patients to them, will continue to play an important role in the global response to emerging and highly hazardous contagious pathogens. Moreover, we feel that the lessons derived from their successful operation will lead to improvements in infection control procedures and practices throughout the healthcare system.

Introduction

The successful management, in a few specialized biocontainment (or high-level containment care [HLCC]) units, of a small number of patients transported from West Africa during the 2014–2015 outbreak of Ebola Virus Disease there, has generated newfound interest in these highly-specialized facilities. Although based on very small numbers of patients, the mortality among EVD patients managed in these units was 18 % during

the West African outbreak [1••], compared to a case-fatality rate of 70 % among all patients and 64 % among patients managed in conventional hospitals (albeit in resource-poor African nations) [2]. In this paper, we discuss briefly the history of infection control and laboratory biosafety before chronicling the fascinating history of these HLCC units, as well as the high-level containment transport systems utilized to deliver patients to these units.

Rudimentary efforts aimed at infection control date back thousands of years, as evidenced by the isolation of lepers noted in the Old Testament book of Numbers [3]. While banishment in those days was more likely carried out as punishment for perceived sins rather than out of hygienic concerns, it was well understood by the thirteenth century that persons with leprosy posed a risk to others and leprosaria were widely established throughout Europe [4••]. These facilities, often known as "pest houses," were also employed in the management of bubonic plague victims, as was the incineration of bedding and clothing.

While Girolamo Fracastoro, in 1546, first suggested that epidemics might actually be caused by such fomites, it was not until the widespread acceptance of germ theory in the mid-to-late nineteenth century that more effective and evidence-based infection control measures were developed and broadly employed. In 1847, Ignaz Semmelweis, a Hungarian obstetrician, postulated a link between the contaminated hands of physicians and the development of puerperal fever among their patients. By imposing mandatory hand washing, he reduced peri-partum maternal mortality from 18 to 2 %. In the 1860s, Louis Pasteur began to advocate for the use of boric acid as an antiseptic and hospital disinfectant, and in the 1870s, Joseph Lister employed carbolic acid in a similar manner. In 1897, Paul Berger, a French surgeon, was credited with first donning a surgical mask, and in 1943, Barnes Hospital in St. Louis opened the first dedicated isolation ward [5]. Detailed histories of the growth and maturation of the science of infection control [2, 6] are published elsewhere.

Biocontainment, as the term is widely understood today, and as it is used in this review, refers to a broad array of infection control measures and engineering refinements that go beyond those found in conventional hospital isolation wards and in standard clinical laboratories. These measures and refinements serve multiple purposes: (1) they protect the patient by offering care in a unique, self-contained unit typically staffed by selected individuals with expertise in critical care and infectious diseases; (2) they protect families by removing difficult decisions about visitation (which is typically not permitted in biocontainment units); (3) they protect other patients from the potential threat of contagion; (4) they protect the laboratory worker who may be required to handle specimens containing some of the world's most dangerous pathogens; (5) they protect the community by offering an additional level of assurance; and, finally, (6) they protect the healthcare worker. Such protection is critical in view of nosocomial risk during the 2014–2015 West African Ebola Virus Disease (EVD) outbreak, during which at least 815 healthcare workers acquired the disease [7]. Similarly, the World Health Organization reports that, during that same outbreak, healthcare workers were 21–32 times more likely to acquire Ebola infection than the general population [8].

In this paper, we will briefly discuss laboratory biocontainment before focusing on clinical biocontainment, or HLCC, the latter consisting of two components: definitive care and transport to that care. In 1951, Pike and Sulkin published one of the first surveys of laboratory-acquired infection [9], and in 1955, at Camp Detrick (now Fort Detrick), Maryland, the first meeting of what would later become the American Biological Safety Association (ABSA) was held [10]. In 1964, Arnold Wedum, Director of Health and Safety at the Fort Detrick-based Army Biological Laboratory (ABL), drawing upon ABSA discussions, published some of the earliest comprehensive guidance on microbiologic safety, offering recommendations on protocols and procedures, laboratory construction and equipping, the employment of biosafety cabinets, animal handling and caging, and other facility and personnel safeguards [11]. Over the next two decades, growing CDC, NIH, and OSHA participation in ABSA annual meetings further solidified biosafety guidelines, culminating in the 1984 publication of the first edition of the text, Biosafety in Microbiological and Biomedical Laboratories (BMBL). The BMBL guidelines laid out four levels of increasingly intensive safety practices, equipment, facilities, and engineering controls to be employed in the safe handling of microbial agents: Biosafety Levels 1, 2, 3, and 4 (BSL-1, -2, -3, and -4), with BSL-4 being the highest (or "maximum") containment. At this level, the person is physically separated from the agent using either a glove box (class III biosafety cabinet) or by wearing a fully encapsulating ("space") suit. At that time, the CDC and USAMRIID possessed the only BSL-4 laboratories in the USA but, with an increased emphasis on (and funding for) counter-bioterror research following the terror attacks of 2001, these facilities have proliferated in recent years; as many as 13 are currently in operation

or under construction. Similarly, as many as 200 BSL-3 laboratories operate within the USA, with most located at universities and State Health Departments.

Biocontainment, as the term is widely understood today, is most often applied to the clinical care setting, where the concept of HLCC derived in large part from four separate events which took place in 1969:

a) In May, Michael Crichton published his novel, *The Andromeda Strain*. While the work was clearly fictional, it captivated the public and thus caught the attention of political and media leaders. Moreover, it was followed by at least three important real-world events which heightened this attention:

b) In July, Neal Armstrong and "Buzz" Aldrin first set foot on the lunar surface, carried there aboard Apollo 11. In order to protect against the remote possibility of these astronauts introducing extraterrestrial pathogens to the earth upon their return, a new facility, the Lunar Receiving Laboratory (LRL), was designed in consultation with experts from Fort Detrick's ABL and constructed at the Johnson Manned Spaceflight Center in Houston, Texas. This facility would receive spacecraft, equipment, and lunar samples from Apollo 11 (as well as future Apollo missions) and would also serve as a quarantine facility, housing astronauts for 21 days following their return. The LRL employed myriad novel engineering controls, including protective isolation garments with high-level respirators, chemical treatment of waste and shower effluent, submersible "transfer-lock" pass-boxes, and serial negative pressure gradation.

c) In November, following many months of discussion and internal negotiation, amidst significant media attention occurring in conjunction with renewed interest in the ratification of the 1925 Geneva Protocol, and despite the continued existence of a massive extant, though unrecognized, Soviet weapons program, President Richard Nixon unilaterally renounced the use of offensive biological weapons. He noted that they "have massive, unpredictable, and potentially uncontrollable consequences [12]." Nixon went on to state that "the United States has decided to destroy its entire stockpile of biological agents and confine its future biological research program to defensive measures." This newfound defensive posture would include an emphasis on the management of patients potentially infected with highly hazardous human pathogens to minimize secondary cases.

d) Finally, Dr. Jordi Casals-Ariet, a professor at Yale University, discovered a new arenavirus in 1969 that he named Lassa after the town in Nigeria from which his index patient originated [13]. Dr. Casals contracted Lassa fever himself while studying the virus and fell critically ill. He ended up receiving convalescent serum from one of his patients. Unfortunately, one of his technicians succumbed to laboratory-acquired Lassa fever in December. As a result, Dr. Casals moved his research activities to a new maximum-security laboratory at the Communicable Disease Center in Atlanta (the predecessor of the Centers of Disease Control and Prevention (CDC)). A new era of laboratory safety had thus begun.

During these activities, a new ABL was already under construction since 1967 at Fort Detrick, Maryland. After Nixon's 1969 pronouncement, the building was repurposed as a medical institute, and its name was changed to the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID). Inside the facility, a two-bed state-of-the-art HLCC unit was outfitted. This unit, often referred to as "the Slammer," presumably owing to the ominous sound (and, perhaps, the sense of forboding) produced by the closure of its heavy steel air-lock doors, opened in 1971. This facility included engineering controls analogous to those employed in BSL-4 laboratories. Not only would the Slammer provide a facility in which to treat infected patients, it would also a lend a sense of security to scientists studying some of the world's most dangerous pathogens, and to the surrounding community of Frederick, Maryland (where Fort Detrick is located). Scientists potentially exposed in the field or through a laboratory mishap were promised monitoring in the modern facility while the community was assured that infected individuals would not intermingle with the citizenry.

As it turns out, this latter observational role was the only one for which the Slammer was ultimately utilized. Between 1972 and 1985, 20 individuals were admitted to the Slammer following exposure to a variety of BSL-4 pathogens [14]. Although the majority of exposures had occurred in the laboratory involving Lassa, Machupo, or Junin virus, two of these exposures occurred in the field. Following a 19-year hiatus, an additional patient [15] (exposed to Ebola in the laboratory) was admitted in 2004. Remarkably, none of the 21 patients became ill or otherwise demonstrated evidence of infection and all were discharged from the facility after periods of observation extending to the upper limits of the relevant pathogens' incubation periods.

Ultimately, a number of factors led to a reconsideration of the Slammer's utility: (1) cost; (2) accreditation issues, because the facility existed in what was otherwise a basic science research institute with no proximate medical support (the Slammer's parent institute was Walter Reed Army Medical Center, 35 miles distant); (3) the absence of any infected patients over a 40+ year existence; (4) an inability to procure replacement parts for isolation equipment owing to the demise of the sole company manufacturing these parts; (5) an increasing understanding of infection control science and the evolving opinion that even patients infected with BSL-4 pathogens could be safely managed in conventional settings; and (6) the construction of civilian HLCC facilities in Bethesda, Atlanta, and Omaha. In 2012, the Slammer was decommissioned; a new USAMRIID building, with an estimated opening in 2017, will not house a containment care unit.

The "Amerithrax" attacks of October 2001, occurring on the heels of the World Trade Center assault and, ironically, attributed to a USAMRIID scientist, convinced some experts to move in the opposite direction and examine the need for civilian HLCC facilities. The emergence, in the spring of 2003, of Severe Acute Respiratory Syndrome (SARS), a novel, highly lethal, and apparently very contagious disease caused by a newly discovered Coronavirus and transmitted via the airborne route added impetus to those discussions, as did a near-simultaneous outbreak of Monkeypox in the upper Midwest. The latter was ultimately linked to the importation of Gambian giant rats and was particularly problematic in that some physicians, fearful of becoming infected, refused to treat infected patients [16]. In response to these developments, civilian and academic leaders at Emory University in Atlanta and at the University of Nebraska Medical Center in Omaha embarked upon a program to create HLCC units at their institutions. Emory's two-bed unit, intended, in part, to house infected scientists from the adjacent CDC, and Nebraska's ten-bed unit, opened in 2004 and 2005, respectively. The facilities employed some (but not all) of the engineering controls contained within the USAMRIID facility (Fig. 1). In 2006, leaders from the three facilities published the first consensus guidelines for the employment of these units [17••].

In that same year, Saint Patrick Hospital in Missoula MT constructed the first HLCC unit housed outside of a large university-based medical center in order to care for scientists exposed to BSL-3 and -4 pathogens at the NIAID's Rocky Mountain Laboratories in nearby Hamilton [18]. As of this writing, no patients have been cared for in this facility and its future remains uncertain. In 2010, the National Institutes of Health outfitted its seven-bed special clinical studies unit with the capability to provide HLCC. This facility cared for two of the 11 EVD patients transported to the USA for care during the 2014–2015 West African outbreak. The HLCC units at Emory and Nebraska, meanwhile, cared for four and three patients, respectively; a tenth patient was managed under HLCC conditions at Bellevue Hospital in New York.

The utility of HLCC controls and practices was validated by the fact that nine of the ten HLCC patients survived (the tenth was in extremis upon arrival in the USA) and no caregivers became secondarily infected. One other patient, who had a delay in care, was cared for outside an HLCC and resulted in two caregivers also being infected. Similar results have been achieved utilizing HLCC in other nations. Germany presently has seven HLCC facilities, and four of these cared for EVD victims during the 2014–2015 West African outbreak. Moreover, the German units have also treated patients infected with Marburg and Lassa viruses. Biocontainment units in Britain, France, Spain, the Netherlands [19], Norway, Switzerland, and Italy also successfully cared for expatriate patients during the recent EVD outbreak; the mortality rate among patients treated under HLCC conditions in western nations was 18 %, comparing favorably to historical mortality rates of 50–90 % [1••]. In addition, other European nations possess HLCC capacity [20], and Europe has been a pioneer in the development of HLCC doctrine [21, 22]. China, during the Severe Acute Respiratory Syndrome (SARS) outbreak in 2003, constructed a 1000-bed infectious disease treatment facility equipped with engineering controls designed to ameliorate the risk of airborne transmission of the SARS-coronavirus [23]. Singapore and South Korea are currently constructing HLCC facilities, and several Middle Eastern states are exploring this possibility.

In light of the success of HLCC in managing Ebola victims, the CDC and Department of Health and Human Services (DHHS) developed a three-tiered system to screen and manage potential Ebola victims. Under this system, HLCC capability would be developed by tertiary care facilities, which would then be designated as "Ebola Treatment Centers" (ETC). As of this writing, approximately 55 such centers have applied for designation and funding [24]; among them are ten designated as regional referral centers by DHHS (one in each of its 10 geographic regions) [25]. In addition, other hospitals would be designated as "Ebola Assessment Hospitals" (EAH), able to manage and isolate persons under investigation (PUI) until a diagnosis of Ebola Virus Disease (EVD) can be confirmed or refuted. Finally, remaining hospitals ("Frontline Facilities") would receive training in order to improve their ability to isolate

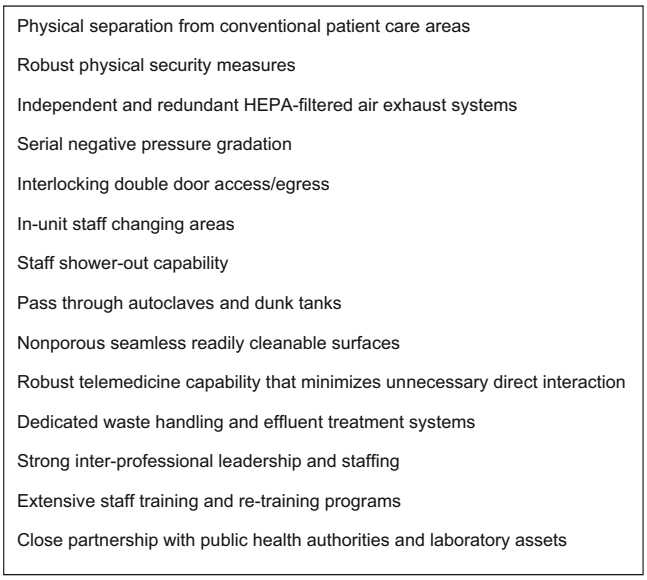

Fig. 1. Select features of a high-level containment care unit.

potential Ebola victims until they could be transferred to an EAH or ETC.

While the four biosafety levels discussed earlier pertain to microbiology laboratories, and were not intended to apply to clinical care facilities, it is nonetheless instructive to consider these latter facilities under an analogous classification scheme. With such a scheme, a conventional hospital room employs methods similar to those used in a BSL-2 laboratory while a negative pressure isolation room employs controls closer to a BSL-3 facility. Although USAMRIID's shuttered Slammer was the nation's only BSL-4-like facility, the current HLCC units at Nebraska, Emory, Bellevue, and the NIH, as well as the majority of European units, can be viewed as BSL-3+ entities.

Containment can be viewed as a two-component process: definitive care, as described above, and transport to that definitive care. Given that most of the Slammer's patients were USAMRIID scientists and that none of the 21 were symptomatic at the time of their admission, transport under containment conditions was not required. This is fortunate in that no specialized capability existed in the early years of HLCC and plans at the time called for improvisation using conventional precautions, equipment, and airframes.

As was the case with HLCC, high-level containment transport (HLCT) had its origins in the US space program when NASA commissioned the construction of four Mobile Quarantine Facilities (MQF) from converted Airstream trailers (Fig. 2). Three of these were utilized for the Apollo 11, 12, and 14 missions. In the case of Apollo 11, the MQF, positioned aboard the space capsule recovery ship USS Hornet, housed the three astronauts, along with a physician and cook, for a period of 88 h until they could be transferred to the Lunar Receiving Laboratory. Following the first three successful lunar landings and amidst growing confidence that no organisms existed on the moon, it was decided that isolation was no longer necessary and the MQF program was abandoned.

In 1975, Phillip Trexler, building upon technology developed for the creation of gnotobiotic research animals [26], described a positively pressurized plastic isolator for use in the treatment of leukemia patients [27]. Two years later, he reported on his experience with a negatively pressurized version designed to isolate patients with dangerous infectious diseases [28].

In preparation for the 1976 Montreal Olympic Games, the Canadian government procured three of Trexler's isolators, to be utilized in the event that foreign visitors to the Olympics brought with them smallpox, pneumonic plague, or a filoviral or arenaviral hemorrhagic fever [29]. Shortly thereafter, they commissioned Vickers Medical Limited of England to develop isolators based on Trexler's technology that could be transported aboard a Boeing 707 aircraft and utilized for intra- or international patient transport. The Canadians had an opportunity to employ their air-transportable isolator (ATI) in 1977, when they moved a 6-year-old boy suspected of having Lassa fever from Toronto to their National Defense Medical Center in Ottawa [28]. Meanwhile, there are reports that an ill US Peace Corps worker assumed to have been infected with Ebola virus while working in Zaire was transported from

Fig. 2. President Nixon greets the returned Apollo XI astronauts, shown here in the Mobile Quarantine Facility.

Kinshasa to Johannesburg in 1976 in an ATI provided by the CDC (and presumably procured from Vickers) [30, 31]. Interestingly, the Royal Free Hospital in London (which successfully managed three patients with EVD in 2014–15) also envelopes patients in a Trexler isolator designed to fit around their standard hospital bed [32].

In the 1980s, USAMRIID also began to use the Vickers ATI to move patients from the site of exposure to definitive care within the Slammer. Moreover, they developed a second, smaller "stretcher transport isolator" (STI; Fig. 3) which could be used to move exposed persons from austere settings to the more robust ATI parked on the tarmac. The two isolators could be "docked" together and the patient passed from the STI to the ATI without contacting the outside environment. The ATI could then be wheeled aboard an aircraft, moved to USAMRIID, and similarly "docked" to a port on USAMRIID's external wall, passing directly into the Slammer (alternatively, the STI could be directly docked, as depicted in Fig. 4). Ultimately, the same problems which led to the decommissioning of the Slammer led to the demise of USAMRIID's HLCT system.

Over the past few years, new encapsulating transport systems have been fielded, including the Air Force's Patient Isolation Unit, developed by Gentex, and AirBoss Defense's ISO-POD. Current plans call for patients placed into one of these transport isolators to be moved to definitive care via

Fig. 3. The stretcher transport isolator (STI). Used with permission.

Fig. 4. Docking the stretcher transport isolator at USAMRIID's slammer. Used with permission.

specialized aircraft operated by the Phoenix Air Group. Phoenix, in conjunction with the CDC, has developed a system which, instead of encapsulating the patient, envelops the aircraft interior. This system was utilized in transporting EVD patients from West Africa to the USA in 2014–15.

With their utility proven during the recent West African Ebola outbreak, a sustained emphasis on HLCC and HLCT appears likely. Along with this emphasis will come funding for research and development, as well as capability procurement. In the near-term, we can expect to see improved containment and transport systems such as US Transportation Command's Transport Isolation System (TIS) and the State Department-sponsored Containerized Biocontainment System (CBCS) [33]. The TIS is a plastic envelope-based system capable of encapsulating as many as four patients at a time and provides an anteroom for caregivers. Two such modules can be loaded aboard military evacuation airframes. The CBCS is a rigid, fully-containerized system which can contain four patients and four caregivers during lengthy transport missions. In the longer term, developments in vaccinology, detection, diagnostics, and therapeutics will undoubtedly assist in mitigating the threats that now prompt us to resort to HLCC. Conversely, history tells us that new threats will continue to emerge. We maintain that properly trained and equipped HLCT assets, as well as HLCC facilities and care teams, will continue to serve as a valuable part of our armamentarium against such threats.

Compliance with Ethical Standards

Conflict of Interest

Dr. Theodore J. Cieslak declares that he has no conflict of interest. Dr. Mark G. Kortepeter declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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