Pediatric Preparedness for Bioterrorism: A New Horizon in Developing Countries

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Bioterrorism Overview

Bioterrorism is the threat of deliberate release of viruses, bacteria, or other germs (agents) used to cause illness or death in people, animals, or plants. These agents are typically found in nature, but it is possible that they could be intentionally changed to increase their virulence, ability to cause disease, resistance to current medicines and dissemination into the environment. These noxious biological agents can be spread through the air, through water, or in food [1].

Bioterrorism Agents/Diseases

Bioterrorism agents can be classified either according to the severity of agents or according to the systems affected.

Classification according to severity of agents

The concept of categories: The biological disease agents are classified into three categories, based on the likelihood of the agent being used according to the degree of danger each agent is felt to pose. Determining the category of the anticipated attacking organism/disease would enable the health authority to take the necessary suitable measures against it.

Category A: The universal awareness of the importance of being prepared to address various biological agents, including rare pathogens became of high priority. The risky agents include organisms that pose a risk to national security because they rapid disseminate from person to person; resulting in high mortality rates affecting public health impact. This might cause public panic and social disruption; and therefore require special action for public health preparedness.

These agents/diseases include: Anthrax (Bacillus anthracis), Botulism (Clostridium botulinum toxin), Plague (Yersinia pestis), Smallpox (Variola major), Tularemia (Francisella tularensis), Viral Hemorrhagic FEVERs (VHF) as filoviruses (e.g., Ebola, Marburg) and Arealvirus (e.g., Lassa, Machupo) [2].

Special concerns of category A: Category A agents would have the greatest adverse public health, medical and social impact if used as a bioterrorist for the following reasons [2]:

- They are infectious and stable in aerosol form.
- The world population is highly susceptible to the infections they cause.
- They cause high morbidity and mortality.
- Some can be transmitted from person to person (smallpox, plague, VHF).
- The illnesses they cause can be difficult to diagnose and treat.
- They have been previously developed for biowarfare.

Common sources of exposure to an agent may include the following:

- Food and water that has been deliberately contaminated.
- Respiratory illness due to proximity to a ventilation source.

Category B: Second highest priority agents include those that are moderately easy to disseminate; result in moderate morbidity rates and low mortality rates; and require specific enhancements of CDC’s diagnostic capacity and enhanced disease surveillance.

Agents/Diseases include the following organisms: Brucellosis (Brucella species), epsilon toxin of Clostridium perfringens, food safety threats (e.g., Salmonella species, Escherichia coli O157:H7, Shigella), glanders (Burkholderia mallei), Melioidosis (Burkholderia pseudomallei), psittacosis (Chlamydia psittaci), Q fever (Coxiella burnetii), ricin toxin from Ricinus communis (castor beans), staphylococcal enterotoxin B, Typhus fever (Rickettsia prowazekii), viral encephalitis (alphaviruses [e.g., Venezuelan, eastern and western equine encephalitis], water safety threats [e.g., Vibrio cholerae and Cryptosporidium parvum]) [1].

Category C

Third highest priority agents include emerging pathogens that could be engineered for mass dissemination in the future because of availability; ease of production and dissemination; and potential for high morbidity and mortality rates and major health impact.

Agents: Emerging infectious diseases such as Nipah virus and Hantavirus [1].

Alphabetical Classification of Bioterrorism Agents by Their Names

The agents are alphabetically classified in table 1 according to the CDC guidelines

Availability of agents: agents are either isolated from sources in nature: The threat agents in (Table 1) are either biotoxins or agents that cause zoonotic diseases (that occur in wildlife and are transmissible to humans) except for smallpox, which is solely a human disease and has been eradicated from nature.

Acquired from laboratories or bioweapons stockpile: Smallpox virus is officially studied in only two WHO designated laboratories in the United States and the Russian Federation: the Centers for Disease Control and Prevention (CDC) in Atlanta, Georgia, and the State Research Center of Virology and Biotechnology in Koltsovo, Russia
A Bioterrorism: Infectious Diseases

B Aerosols:

- Buccivirus (Bacillus anthracis), Arenaviruses
- Bacillus anthracis (anthrax), Botulism (Clostridium botulinum toxin), Brucella species (brucellosis), Burkholderia mallei (glanders), Burkholderia pseudomallei (meliodosis)
- Chlamydia psittaci (psittacosis), Cholera (Vibrio cholerae), Clostridium botulinum toxin (botulism), Clostridium perfringens (Epsilon toxin), Coxieila burneti (Q fever)
- Ebola virus hemorrhagic fever, Escherichia coli (E, coli) O157:H7, Emerging infectious diseases such as Nipah virus and hantavirus, Epsilon toxin of Clostridium perfringens
- Food safety threats (e.g., Salmonella species, E. coli O157:H7, Shigella, Francisella tularensis (tularemia))
- Glanders (Burkholderia mallei)
- Lassa fever
- Marburg virus hemorrhagic fever, Melioidosis (Burkholderia pseudomallei)
- Plague (Yersinia pestis), Psittacosis (Chlamydia psittaci)
- Q fever (Coxiella burnetii)
- Ricin toxin from Ricinus communis (castorbeans), Rickeletia powsakeki (typhus fever)
- Salmonella species (salmonellosis), Salmonella Typhii (typhoid fever), Salmonellosis (Salmonella species), Shigellosis (shigellosis), Smallpox (variola major), Staphylococcal enterotoxin B
- Tularemia (Francisella tularensis), Typhoid fever (Salmonella Typhi)
- Variola major (smallpox), Vibrio cholerae (cholera), Viral encephalitis (alpha-viruses [e.g., Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis]), Viral hemorrhagic fevers (floviruses [e.g., Ebola, Marburg] and arenaviruses [e.g., Lassa, Machupo])
- Water safety threats (e.g., Vibrio cholerae, Cryptosporidium parvum)
- Yersinia pestis (plague)

Table 1: A-Z List of Bioterrorism Agents/Diseases.

[3]. Anthrax is widely studied in labs. Hemorrhagic fever viruses are studied only in limited high-security locations.

Synthesized or genetically manipulated in a laboratory: This would require expertise and access to advanced technology.

Delivery methods include:

- Aerosols: Biological agents are dispersed into the air, forming a fine mist that may drift for miles. Inhaling the agent may cause disease in people or animals.
- Animals: Some diseases are spread by insects and animals, such as fleas, mice, flies, mosquitoes and livestock.
- Food and water contamination: Some pathogenic organisms and toxins may persist in food and water supplies. Most microbes can be killed, and toxins deactivated, by cooking food and boiling water. Most microbes are killed by boiling water for one minute, but some require longer. Follow official instructions.
- Person-to-person: Spread of a few infectious agents is also possible. Humans have been the source of infection for smallpox, plague and the Lassa viruses.

Agents Categorized by System Predominantly Affected

Respiratory System

Anthrax, plague, and tularemia are all caused by infections with Category A agents and may present as respiratory illnesses [2].

Anthrax: The incubation period of inhalational anthrax: Usually less than 1 week, however it may be prolonged up to 8 weeks compared with 1–12 days for cutaneous anthrax, 1–7 days for gastrointestinal anthrax, and 1–7 days for oropharyngeal anthrax [4].

Symptoms: Inhalational anthrax typically progresses through two distinct stages [5]. The first, lasting from several hours to several days, involves influenza-like symptoms such as low grade fever, non-productive cough, malaise, fatigue and chest discomfort. The second stage involves abrupt onset of high fever, severe respiratory distress (dyspnea and hypoxia), and shock. A widened mediastinum is the classic chest X-ray finding [3].

Despite ventilatory support and antibiotic therapy, shock and death. Patients with inhalational anthrax are not contagious, so the only infection control measure necessary is standard precautions.

Case-fatality estimates for inhalation anthrax are based on incomplete information, the rate is extremely high, approximately 75%, even with all possible supportive care including appropriate antibiotics. Estimates of the impact of the delay in post exposure prophylaxis or treatment on survival are not known. This fatality rate is extremely high compared with Patients with cutaneous anthrax for whom the reported case fatality rates of 20% without antibiotic treatment and less than 1% with it. For Gastrointestinal (GI) anthrax, the case-fatality rate is estimated to be 25%-60% and the effect of early antibiotic treatment on that case-fatality rate is not defined [1].

Plague: Plague presents in many forms; (septicemic, bubonic, and pneumonic), with aerosolization of Yersinia pestis causing pneumatic plague would be the most effective mode for a bioterrorist attack.

Incubation period: 2 to 4 days.

Symptoms: Fever, headache, malaise, cough, dyspnea, and cyanosis. The cough is productive and may be watery, purulent, or bloody. Chest radiographs often reveal bilateral infiltrates and lobar consolidation. Sometimes, GI symptoms accompany pneumatic plague and include nausea, vomiting, diarrhea, and abdominal pain. The disease is rapidly progressive, often leading to disseminated intravascular coagulation. The plague case-fatality rate depends on the clinical presentation (i.e., bubonic, septicemic, or pneumonic) and timing of antibiotic therapy initiation; if untreated, the case-fatality rate is >50% for bubonic plague and approaches 100% for pneumonic plague [5].

Different diagnoses include community-acquired pneumonias and hantavirus respiratory distress syndrome. The time from exposure to death may be as short as 2 days and is often between 2 and 6 days. Pneumonic plague is spread by respiratory droplet, so droplet precautions should be strictly enforced.

Tularemia: Tularemia presents as glandular, ocuol glandular, oropharyngeal, septicemic, typhoidal, and pneumonic forms. Similar to plague, the most effective bioterrorist release would be aerosolization, causing the pneumonic form, although the typhoidal form is possible [6].

Incubation period: 1 to 14 days.

Symptoms: resemble influenza, beginning 3 to 5 days later. Clinical findings include sudden onset of fever (38–40°C), headache, malaise, coryza, sore throat, and chills and rigors. A dry, nonproductive cough may progress to bronchilitis, pneumonia, pleuritis, pleural effusions, and hilar lymphadenitis and may not be accompanied by objective signs of pneumonia (dyspnea, tachypnea, pleuritic pain, purulent sputum, or hemoptysis). The earliest findings on chest radiograph are peribronchial infiltrates that progress to bronchopneumonia. Primary tularemia pneumonia is uncommon and occurs after inhalation of the F. tularensis Only 25 to 50% of patients have radiological evidence of pneumonia in the disease’s early stages, and some patients show only minimal, discrete infiltrates. Other cases progress rapidly to respiratory
failure and death. Mortality from tularemia pneumonia is 30% if untreated but drops to less than 10% with prompt antibiotic treatment [6].

Nervous System

Botulism is the category A disease that most likely to present with CNS findings. An aerosolized or foodborne botulinum toxin weapon would cause acute symmetric, descending flaccid paralysis with prominent bulbar palsies such as diplopia, dysarthria, dysphonia, and dysphagia that would typically present 12 to 72 hours after exposure. Effective response to a deliberate release of botulinum toxin will depend on timely clinical diagnosis, case reporting, and epidemiological investigation. Persons potentially exposed to botulinum toxin should be closely observed and those with signs of botulism require prompt treatment with antitoxin and supportive care that may include assisted ventilation for weeks or months. Treatment with antitoxin should not be delayed for microbiological testing [7]. Symptoms of botulinum toxin ingestion are GI symptoms including abdominal cramping, nausea, vomiting and diarrhea. Inhalational botulism does not cause a pneumatic process. Both ingestion and inhalation of the toxin lead to nervous system findings, i.e., an acute, afebrile, symmetrical, descending flaccid paralysis. The first signs may appear as quickly as 2 to 72 hours; however, the rate of progression is dose dependent. In natural exposure, the symptoms may be insidious and unapparent for months. In a bioterrorist event, doses may be high, with prompt onset of symptoms. The first manifestation is a cranial nerve palsy, which may present as double or blurred vision, dysphagia, dysarthria, dysphonia, dry mouth, ptosis, gaze paralysis, enlarged or sluggishly reacting pupils, and nystagmus. Sensory changes do not occur. The paralysis eventually progresses to loss of head control, hypoesthesia, limb weakness, and respiratory muscle paralysis. Constipation often develops. Patients may appear comatose because of extreme weakness, but sensorium is intact. Deep tendon reflexes may be intact initially but eventually diminish. Without treatment, antitoxin, and ventilatory assistance, patients die of airway obstruction and inadequate ventilation due to respiratory muscle paralysis. Secondary respiratory infections due to aspiration pneumonia may also develop. Differential diagnoses for botulism include Guillain-Barré syndrome, myasthenia gravis, stroke, other ingestions/intoxications, tick paralysis, viral syndromes, and hypothyroidism. Bioterrorism should be considered when a botulism outbreak occurs within a common geographic area, yet no common source of ingestion can be identified. Botulism is not transmissible from person to person, so standard precautions are sufficient infection control measures.

GI System

A number of infections caused by Category A agents present primarily as syndromes other than GI, although they may be accompanied by some GI complaints. Those that present as respiratory syndromes after aerosol exposure (anthrax, plague, and tularemia) may also present with GI symptoms caused by respiratory distress, especially in children. Botulism, in any of its forms, is primarily a nervous system illness manifested by paralysis. Paralysis may cause some GI manifestations such as poor feeding and constipation.

GI anthrax: can occur when food is purposefully contaminated with anthrax spores.

Incubation period: few hours to a week.

Symptoms: Upper GI illness may result in an oral or esophageal ulcer, which may present with fever, drooling, dysphagia, regional lymphadenopathy, edema, and sepsis.

Lower GI illness often affects the terminal ileum or cecum, and presents with fever, loss of appetite, vomiting, and malaise and progresses to vomiting, hematemesis, severe bloody diarrhea, an acute abdomen, or sepsis. Sometimes, massive ascites develops. This form of anthrax is not transmissible from person-to-person, and standard precautions suffice.

Dermatologic Manifestations

Almost all of the diseases caused by Category A agents (anthrax, smallpox, plague, tularemia, VHF) can cause skin lesions, although dermatologic findings may not be the primary finding in a bioterrorist attack using aerosol dispersion.

Anthrax

Anthrax spores mixed with a fine powder substrate can be used as a weapon to cause respiratory and cutaneous disease.

Cutaneous anthrax: Incubation period: few hours to 12 days.

Symptoms: A small pruritic papule, often mistaken for an insect bite, forms at the inoculation site and rapidly progresses to an ulcer (1–3 cm in diameter) over the course of 1–2 days and may be surrounded by small vesicles (1–3 mm). The organism may be isolated from the serosanguineous fluid in these vesicles. A painless, depressed eschar of dark necrotic tissue forms at the site, and toxin production causes surrounding edema adjacent lymph glands may become enlarged and painful. The eschar separates from the skin in 1 to 2 weeks, often leaving no scar. The untreated case fatality rate is 5–20%; death is rare with appropriate therapy [3].

Smallpox

Rash is the key feature of smallpox, whether the disease is contracted via mechanical aerosolization or from person-to-person transmission [3].

Incubation period: 7 to 17 days (mean 12 to 14 days).

Symptoms: The prodromal phase, lasting 2 to 4 days, begins with acute onset of high fever, malaise, head and body aches and sometimes vomiting. The fever usually ranges from 101°F to 104°F and patients are usually too ill to carry on their normal activities. The patient is not contagious during this period.

Tularemia

Although airborne Francisella tularensis would most likely cause pneumonic or typhoidal disease, ulceroglandular and oculoglandular forms may occur that have cutaneous manifestations [5]. There is also a glandular form of the disease, which does not result in skin lesions. The rash of ulceroglandular tularemia begins with a papule at the inoculation site, accompanied by systemic symptoms (fever, chills, rigors, sore throat). The lesion forms a pustule that becomes a tender ulcer and may form an eschar. Regional lymph nodes become inflamed and fluctuant. The oculoglandular form of tularemia leads to conjunctival ulceration, blepharitis, chemosis, vasculitis, and regional lymphadenopathy.

Viral hemorrhagic fevers

VHFs are caused by a variety of organisms, with a variety of presentations, making clinical diagnosis difficult [8].

After an incubation period of 2 to 21 days, a rash develops that may range from a subtle cutaneous flushing to a nonpruritic maculopapular rash, similar to that seen in measles. The condition progresses to a bleeding diathesis of petechiae, mucosal and conjunctival hemorrhages, hematuria, hematemesis, and melena.

**Pediatric Practices and Preparedness Measures**

During a bioterrorist event, local pediatricians and their staffs in the hospitals and clinics should maximize their ability to keep the office running smoothly and to provide care.

1. The first step is for every staff member to have a personal family emergency plan. Once staff members are assured that they and their family members are safe, they are better able to focus on their professional duties.

2. Second, every office needs an emergency plan. This plan should include details for handling an emergency both in-office and in the community.

**Items that should be included in an in-office emergency plan include the following**

- Isolation guidelines for selected cases. A useful easily applied guide lines are encouraged to be used as that designed by Suzanne E., et al. [10].
- Contact information for local public health authorities.
- Phone numbers for emergency patient transport.

**Items that should be included in a plan for an emergency in the community include the following**

- Information sheets and telephone hotline numbers.
- Telephone triage protocols.
- Back-up staffing schedules.

Depending on the situation, dedicated and trained staff may be needed just to handle anxious or worried parents. A special attention should be present for the community people who want to volunteer in the health and humanitarian efforts to help the victims. A special plan should be present to organize and facilitate their participation in order to have a proper and effective management. A very good example for this is the Arizona Emergency System for the Advance Registration of Volunteer Health Professionals (AZ-ESAR-VHP) is a secure, Web-based system used to register, qualify and credential Arizona health care professionals before a major public health or medical emergency. The advance registration of volunteer health professionals enables the Arizona Department of Health Services (ADHS), local health departments and emergency management to rapidly identify and mobilize health care volunteers. Moreover, the system enables hospitals and other medical entities to meet crisis and surge capacity and mobilize health care volunteers. The community-based pediatrician should have the following items readily available to evaluate children suspected of having an illness related to bioterrorism:

- An examining room with a door that closes, in which to isolate a patient and accompanying family members.
- **Surgical masks**: tight-fitting, disposable surgical masks are recommended for any of those who come in close contact with patients with pneumonic plague, smallpox and VHF [11].
- Clean, non sterile gowns.

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**Recommended Therapeutic Countermeasures**

**Anthrax**

Selection of the antimicrobial agent for post exposure prophylaxis (PEP) should involve consideration of antimicrobial resistance. Variable β-lactam resistance, particularly to the cephalosporins, has been reported among naturally occurring *B. anthracis* isolates [8,12]. Additionally, resistance can be readily induced in vitro in *B. anthracis* to a variety of antimicrobial classes including fluoroquinolones, tetracyclines, macrolides, penicillins, and other β-lactams [13]. Ciprofloxacin and doxycycline as equivalent first-line antimicrobial agents for PEP, as they are equally efficacious for PEP and have similar susceptibility profiles among naturally occurring isolates. Both have similar safety profiles, with a low rate of anaphylactic reactions [14]. Levofloxacin is recommended as a second-line PEP antimicrobial agent, to be reserved for instances where medical issues may call for its use. Penicillins should not be initially used for PEP of anthrax, due to concern for penicillin resistance, which has been found in naturally occurring isolates, and because of the low concentrations achieved with oral penicillins in pulmonary secretions, tissue, and within alveolar macrophages [15-17]. Amoxicillin can be used for PEP once the *B. anthracis* strain has been proven penicillin susceptible, when other antimicrobial agents are not considered safe to use, such as for pediatric patients and for nursing or pregnant women. However, amoxicillin is not FDA-approved for this indication, and this use is considered “off-label.” Therefore, amoxicillin use for PEP in an mass-exposure event might be provided under an IND or under an Emergency Use Authorization in a declared emergency. Amoxicillin use for PEP is discussed further in the section below on special populations. Other antimicrobial agents, including clindamycin, chloramphenicol, rifampin, vancomycin, and other fluoroquinolones, may be considered for off-label use in patients unable to tolerate FDA-approved antimicrobial agents for PEP. We have to keep all the above mentioned agents in appropriate dosages and forms for children in all bioterrorism medication provision plans. This would include the Strategic National Stockpile (Push Packs, Vendor Managed Inventory), state and local health department stocking and deployment of these agents, and local responder and chemical terrorism treatment provisions [18]. The standard treatment for anthrax is a 60-day course of an antibiotic, such as ciprofloxacin or doxycycline. Which single antibiotic or combination of antibiotics will be most effective for you depends on the type of anthrax you have, your age, overall health and other factors. Treatment is most effective when started as soon as possible. Although some cases of anthrax respond to antibiotics, advanced inhalation anthrax may not. By the later stages of the disease, the bacteria have often produced more toxins than drugs can eliminate [19]. The use of anthrax vaccine adsorbed (AVA) in children is not contraindicated in a postevent setting that poses a high risk for exposure to aerosolized *B. anthracis* spores. During such an event, public health authorities will determine whether, under the existing IND protocol, to offer vaccine to children aged 0–17 years. Under this IND protocol, 3 doses of vaccine would be administered in conjunction with 60 days of appropriate antimicrobial therapy [20].

**Smallpox**

No antiviral treatment has been approved by the US Food and Drug Administration (FDA) for smallpox, and the only prevention is vaccination. Medical management of smallpox is mainly supportive [21]. However, certain medications, including topical idoxuridine and cidofovir, can be used under investigational new drug (IND) protocol for the management of smallpox. Cidofovir analogs CMX001 and...
the extracellular virus inhibitor ST-246 are in human safety trials for orthopoxvirus treatment. Although the effectiveness of this treatment has not been proven in humans [22].

The smallpox vaccine is the only known way to prevent smallpox in an exposed person CDC has begun distribution of a new-generation smallpox vaccine, ACAM2000™ (Acambis, Inc., Cambridge, Massachusetts), to civilian laboratory personnel, the military, and state public health preparedness programs. FDA licensed Smallpox (Vaccine) Vaccine, Live, with the proprietary name ACAM2000, for active immunization against smallpox disease for persons determined to be at high risk for smallpox infection. The vaccine is manufactured by Sanofi Pasteur Biologics Co. Advisory Committee on Immunization Practices (ACIP) does not recommend smallpox vaccination for children and adolescents aged < 18 years during the pre-event vaccination program [23].

Botulism

Early botulinum antitoxin administration and supportive care is very important. Rigorous and supportive care is essential in patients with botulism. Meticulous airway management is paramount, as respiratory failure is the most important threat to survival in patients with botulism. Patients with symptoms of botulism or known exposure should be hospitalized and closely observed [24].

Plague

No licensed plague vaccine is currently in production, despite the potential threat of *Yersinia pestis* (YP) being employed in bioterrorism and remaining prevalent in endemic regions of the world where rodent populations are high (including the four corner regions of the USA), an efficacious vaccine that confers immunoprotection has yet to be developed [25]. Depending on the stage of presentation, supportive care varies. Early presentation may require only crystalloid administration with monitoring of vital signs, clinical state, and urine output [26].

Use strict isolation precautions. If respiratory symptoms are present, institute universal precautions with strict respiratory isolation for the first 96 hours of therapy. Specific antibiotics used for plague treatment can include Streptomycin Gentamycin. Other antibiotics, including tetracyclines and chloramphenicol, can also be effective [27].

Physical Protection

There is little role for physical protection against bioterrorist agents in a civilian population. Although some companies are marketing devices such as gas masks for children, we think the risks of using these are likely to outweigh the benefits. For example, some media reports exist of Israeli children suffocating after donning gas masks during Operation Desert Storm. So research into future means of physical protection must consider the needs of children [18].

Children vulnerability to biochemical risks

Dealing with children before and after the possible bioterrorism attacks need a special planning and preparedness that may be even more important than those required for adults for the following reasons: first of all Children’s mental and physical abilities may affect their capabilities to escape danger.

Also, Children are different from adults so to have a special plans designed to deal with children is very important. Children have certain requirements; therefore, it is essential to define the needs of children and to plan for their care. These measures must include children who are at or outside their homes, Children with special medical needs; the handicapped ones are more vulnerable.

Children are more vulnerable to dehydration and shock due to exposure to biological agents. The drug dosages for children have to be recalculated. Those drugs may be either antibiotics or certain agents’ antidote. They are also more susceptible to the adverse effects of exposure to radiation and require different treatment approach than adults. Psychological stress constitutes a major challenge for dealing with the exposed children and requires a prior planning program.

Special training programs must be particularly designed for all the possible groups that may deal with the endangered children such as the first aid responders, paramedics and other medical professionals in order to ensure optimal care of those exposed to chemical, biological, or nuclear agents.

How bioterrorism agents may affect children

Children are physically different than adults, and not just in stature [28]. They have higher metabolic rates, immature immune systems, faster respiration rates, thinner skin and lower fluid reserves. If caught in a bioterrorism event they may not possess the fully developed motor skills necessary to flee a scene rapidly (if they are old enough to walk). Mentally, depending on their age, they may not possess the cognitive skills to comprehend when they are in danger and how to escape it. Curious children often touch unknown objects, then put their hands to their mouths, or touch their eyes and nose. If that happens, the child could easily introduce a pathogenic organism directly into their system. These normal childhood characteristics can put them at a greater risk to be infected, or affected by a biological attack.

Other problems children face in an attack

- Children take more breaths per minute than adults and in an aerosolized biological attack this would increase the amount of infectious particles taken in, or in the case of a chemical attack, increase the amount of gas taken in.
- Children’s thinner skin absorbs chemical agents more readily than adult skin.
- Their vulnerability extends to agents that may promote vomiting or diarrhea, as children’s low fluid reserves put them at risk for dehydration very quickly, and that can be deadly in itself.
- A child’s typically short stature is a disadvantage - many chemical agents are heavier than air and will sink towards the ground, directly into a child’s breathing space.
- Their immature immune systems are also defenseless to many bioweapon agents, and children are more susceptible to complications that don’t concern adults.
- Biological weapons may also induce an entirely different illness in children (e.g. hemolytic-uremic syndrome in an *E. coli* 0157:H7 infection).

Recommendations for Management of Biological Terrorism

The following recommendations were previously suggested and adoption of these measures in the Middle East region is warranted.

- Require that all new pharmaceutical and therapeutic testing include evaluation of applicability and dosing for children.
• Require that all existing antibiotics and antidotes be tested for their applicability to children and determine dosing.

• Develop delivery methods for these agents that are pediatric-specific, including liquid preparations and mechanisms for weight-based dosing.

• Develop improved drug administration techniques for mass casualty incidents involving children.

• Include children in future studies of new vaccines for anthrax and smallpox and of a multivalent botulism immunoglobulin; in all new antibiotic, vaccine, and immunotherapy development; and in licensure of new nerve agent and other chemical agent antidote kits. These should include use during terrorist incidents, development of optimal dosing schedules for currently available drugs, and pursing WMD indications for currently licensed medications.

• Include pediatric-specific models in research into optimal preventive and antidotal treatment and supportive care for all cases of WMD.

• Fund research to address the differences in effects of biological, chemical, and radiological agents on children based on their unique anatomy and physiology.

• Advocate for long-term epidemiologic research, including addressing the needs of children, in WMD.

• Further evaluate optimal decontamination strategies for children.

• Assess responder safety during different types of WMD and disaster events by federal and state environmental, health, and occupational safety agencies.

• Assess true efficacy of field treatment of children in response to actual biological, chemical, or radiological events

Dual potential of biotechnology

Biotechnology is a potential means to counteract the danger of bioterrorism, through the production of diagnostics, drugs and vaccines against bioweapons and/or their source organisms [29]. However, it can also be a source of bioweapons. Weaponised agents produced by biotechnology, not yet realized, are a potential threat. New pathogenic organisms can be created using genetic tools that are programmed to trigger replication or toxin production in response to an environmental chemical, such as an antibiotic in drinking water. The research that is now trying to understand what makes an organism pathogenic is aimed at designing more efficient drugs. Such knowledge can also be used to create pathogenicity in hitherto non-pathogenic organisms or to increase the existing pathogenic potential of an organism, posing enhanced threats, from bioterrorism. Nevertheless, research into these aspects should be adequately funded, in spite of the risks involved, for the outweighing advantages.

Race between the pathogen and the pathologist

Unfortunately, the efficacy of a drug against an organism is short lived, as pathogens acquire resistance, sooner or later, against the once effective drug. Recurrence of malaria and tuberculosis, thought to have been contained, is the case in point. There are very serious fears of recurrence of smallpox, believed to have been eliminated over two decades ago. The technical advancement failed to provide defence against the compelling evolutionary component of acquired resistance. It is an eternal race between the pathogen and the pathologist, the former being a little ahead of the latter, most of the time. Some aspects of preparedness against bioterrorism are similar to those needed to face natural disasters like floods and earthquakes, as epidemics often follow such disasters. We should act in advance and not after the disaster strikes, as we usually do.

Some urgent measures in this regard are

Public awareness: It is reasonable to expect that the bioterrorist would choose a particular disease for use in a particular country, and may even target a particular segment of the population of that country. For example, a human pathogen can be transmitted through susceptible or carrier bovine hosts to affect beef eaters. People can be affected by the New Variant of Creutzfeldt-Jacob’s Disease (nvCJD), a prion disease, on consumption of food contaminated with the mad cow disease (Bovine Spongiform Encephalopathy) that was a threat in Egypt in 2003-2005. Egyptian Public health and medical authorities identified those diseases and the means of its spread, and made the public aware of the evolving risks. Facts about different diseases of bioterrorist import should be publicized, the way Centers for Disease Control and Prevention in US do. All this is not a small task in countries with large illiterate populations but an infrastructure to achieve this must be built up, without loss of time.

Swine and Avian flu was a universal threat in the past 5 years. Preventive and therapeutic measures succeeded to limit the transmission and progression of the H1N1, H5N1 strains. The differences in the flu strains in various regions of the world made the screening, diagnosis and the treatment difficult. However the spreading of vaccination programs in the schools, universities and complex compounds added to the Governmental preventive measures lead to the limitation of the disease. After being unsettled by years of battling deadly avian flu, the Egyptian government has decided to slaughter the nation’s 300,000 pigs to prevent the spread of swine flu. The Egyptian health ministry has reportedly put all hospitals and quarantine center on alert to slow the spread of the virus in Egypt. The World Health Organization raised its alert level as the number of confirmed cases increased. Mexico has reported at least 150 deaths that may be due to swine flu. Schools there have been closed in an effort to stem the outbreak. Egypt is the country most affected by bird flu outside Asia; 65 cases, including 26 deaths, have been reported since 2006.

Research and development: Adequate numbers of well equipped labs are needed with facilities for microbiologists to develop quick and certain means to identify the pathogen and the disease, for biochemists to develop diagnostic kits, for pharmacologists to develop drugs and for immunologists to produce vaccines. In every country there is some activity of this nature but it is not adequate.

Stockpiling vaccines and drugs: Very large stocks of vaccines and drugs are needed for different diseases in times of disaster. Authorities should identify the vaccines and drugs that would be required to meet the eventuality and advice the manufacturing units to produce the required quantities. Care should be taken that the drug manufacturers do not exploit the situation by hiking the prices, as seems to have happened with anti-anthrax drugs recently.

Contingency plan of action: Authorities should draw contingency plans of action, separately for each vulnerable area, to meet with the situation when it develops, and identify the hospitals, health care units, doctors and para-medical personnel and prepare them to face the situation [29]. The Contingency Planning Policy Statement should be
developed to be effective and to ensure that personnel fully understand the organization’s contingency planning requirements; the contingency plan must be based on a clearly defined policy. The contingency planning policy statement should define the organization’s overall contingency objectives and establish the organizational framework and responsibilities for system contingency planning [30].

Problems of logistics: Practical difficulties will be faced. Stockpiling antibiotics and other drugs, against all the potential weapons of bioterrorism, in quantities adequate to protect the susceptible human populations and livestock, is an unimaginably immense and nearly impossible task, not to speak of the expenditure involved, even in the developed countries. ‘How much and of what?’ is a question that cannot be answered with confidence.

Biodefence Research and Preparedness

In our efforts of building measures of defence against bioterrorism we can never anticipate all possibilities. It would be naïve to think that any amount of investment in biodefence research will protect us in the long term against bioterrorism, which is almost always a random act of calculated savagery, often from a hidden insidious enemy, as is the case with any form of terrorism. Preparedness, more so advertised preparedness, minimizes the risks, particularly because a bioterrorist attack is futile in the face of defense.

Biodefence research must continue both to provide improved drugs and protective measures to deal with normal illness, as well as to prepare us to face a bioterrorist attack. One may argue that we should expect the unexpected, but that is not always possible, and certainly not all the time, and not forever. We should not forget that the degree of success of a terrorist attack lies in the element of surprise, in terms of the place, manner and the time of the attack. Almost certainly, there will be no bioterrorist attack where and when we are prepared.

Potential Role of Indigenous Systems of Medicine

In countries like India, China and Egypt, the indigenous systems of medicine have a number of herbal drugs effective against several infectious diseases that can be a means of bioterrorism, albeit there are clinical data in support of their efficacy [29]. A lot of damage can be contained if the probable diseases are identified and the precautionary and remedial measures from the indigenous systems of medicine are publicized. For example, the yellow sheets in the pomegranate fruit contain an active ingredient that is effective against a broad range of gastrointestinal pathogens, including the cholera bacterium. The dry powder of this material is traditionally administered in buttermilk or even water, to control diarrheal infections. In Korea the primary approach to contagious diseases like typhoid and malaria involved spiritual exorcisms. Poor countries that cannot afford the expenses of modern approaches, seek solutions from the traditional healing systems. Furthermore, the models of research and defense measures of modern approaches, seek solutions from the traditional healing systems. Almost certainly, there will be no bioterrorist attack where and when we are prepared.

problems involved, are all different. Even in the developed countries and in spite of their impressive public health achievements, people still turn today to natural products, hoping they will help mitigate infections. Among the most popular of these products for the American consumer is Echinacea, a widely used herbal medicine. Small studies suggest that it might lessen the severity of colds and the flu. Nonetheless, even if Echinacea proves to mitigate simple viral respiratory infections that almost always resolve on their own, it would be a far stretch to believe

that it could prevent or ameliorate highly virulent and disseminated bacterial or viral diseases with high mortality rates. It should be discouraged that products like Echinacea may serve in lieu of proven drugs like ciprofloxacin or doxycycline for people exposed to anthrax bacilli [31].

It may not even be prudent to combine such natural products with antibiotics because of the possibility that they would interfere with the proper metabolism and action of the drugs. An instructive example in this regard is the effect of the herb St. John’s wort on the metabolism of indinavir, a drug that has helped extend the lives of countless patients with HIV/AIDS. St. John’s wort accelerates removal of indinavir from the body, leaving drug levels that no longer are adequate to block the replication of the HIV virus.

The prophylactic benefits of exceedingly dilute substances are more in doubt than those of conventional vaccines. Starting with the use of ultra-high dilutions of belladonna to prevent scarlet fever in the late 18th century, there have been numerous claims that homeopathic medicine can prevent or treat infectious diseases. In the 19th century, practitioners of homeopathic medicine proposed that minuscule concentrations of killed anthrax or smallpox microbes could confer immunity to these infections. Although there have been studies of homeopathy’s potential against infections, it would be unethical and dangerous to withhold proven drugs and vaccines in order to see whether homeopathic remedies protect people who become exposed.

Another example of products being marketed on the Internet to a frightened public involves colloidal silver. Silver, like many substances, does possess antibacterial properties in vitro, rendering it a topical disinfectant. Its systemic use in humans, though, is limited by its toxicity. Even more serious illnesses and death were associated with exposure to heavy metals such as arsenic that was long included in popular remedies.

In the instance of bioterrorism, however, the best approach is to manifest an unwavering trust in the currently approved drugs and vaccines, and to not dissipate our energies or to distract the public by pursuing unproven remedies [31].

Recommendation

Exploration of such approaches should first involve careful studies in animals using contemporary methodologies to discern whether they hold any promise against diseases associated with biological weapons. In Egypt these studies should be funded by the Ministry of Health and executed in the National Research Center in collaboration with experts from the Faculties of Medicine and Pharmacy and the results of these studies should be publicized.

Should Biodefence Preparedness be a Public Knowledge?

A Transparency Issue

A question that is raised often is, whether it is wise to make the biodefence strategy and state of preparedness public knowledge? It is felt that the bioterrorist also gets to know of the detailed plans and defenses built up and would act bypassing them. There are at least three considerations in favor of transparency. Firstly, biodefence is aimed at facing a bioterrorist attack, but preventing this is the better choice. Well-advertised preparedness against the best arsenal of a bioterrorist would be a deterrent. We are fighting bioterrorism and not the bioterrorist. Secondly, if the public come to know of what the governments and other agencies have been doing for their safety, their confidence in our public institutions, which is a very important psychological
factor, would grow. Thirdly, awareness of the governmental efforts may inspire private organizations and individuals to add their own bit to the national effort. Upon these considerations, it is not wise to keep biodefence strategy under the warp, on the grounds that military strategy, which is an entirely different issue, is a closely guarded secret.

**Evaluating the preparedness of pediatricians for Bioterrorism**

Preparedness for bioterrorism is not only a challenge for the pediatricians in the developing countries but in the developed ones as well: In a recent survey [32] done in Michigan-USA by Stankovic C, and his colleagues, the investigators found that there is a perceived need for a coordinated educational program to improve level of preparedness. They conducted a survey that was mailed to 1,000 pediatricians practicing in Michigan to design a survey questions to evaluate the overall level of preparedness, as defined by the American Academy of Pediatrics, in dealing with a possible biological event and to describe key demographic variables. Sixty percent of responders believe terrorism is a threat, with biological agents as the most likely cause of an event. Half of the pediatricians who responded had a workplace disaster plan, but only 12% feel their preparedness for a biological attack/event was good.

**Preparedness and Public Health Systems in the Developed World**

The 2001 terrorist attacks on the World Trade Center and the subsequent release of anthrax shocked the U.S. into taking stock of the emergency response capacity of its public health systems [33]. Significant additional funding to strengthen this capacity followed [7]. In the U.S., the biodefence preparedness budget increased from $294 million to $5.2 billion. Of the funds committed since 2001, $3.6 billion was spent on state, local and hospital preparedness, representing a substantial infusion of new money into public health systems that had seen little new funding in the preceding decade [34]. At the same time, the European Union (EU) established the Health Security Committee to develop a health information system, EU-wide surveillance, a database of the medicines stock, a facility to disseminate medicines and specialists, and health-specific protocols for a coordinated EU response to an attack [9]. By 2006 a growing concern about the possibility of pandemic influenza of avian origin in the U.S. led to an infusion of another $3.8 billion into preparedness activities [10]. The bulk of preparedness budgets in the U.S. were allocated to a range of related health activities intended to respond to acts of bioterrorism, emerging infectious diseases, and later pandemic influenza. Bioterrorism and pandemic preparedness investments included the upgrading of disease surveillance, hospital capacity to handle mass casualties, patient isolation systems, laboratory diagnostics for new biologic agents, and the enhancement of command and control structures as well as communication among health and emergency services agencies [35]. Public health officials became concerned that the singular focus on new threats might overshadow the traditional activities of public health departments and hospitals and weaken their ability to tackle existing challenges [36-38]. Among the negative effects observed was the diversion of staff in hospitals and public health departments from routine activities to meetings and training sessions on preparedness, and reduced attention to non-bioterrorism-related concerns [36-39]. For example, the program to vaccinate health workers against smallpox—one of the most prominent bioterror-preparedness activities—caused many health departments to defer or cancel other core public health activities, because of the burden of program work and the required monitoring for adverse effects [35-41]. While infectious disease response may have received a boost from preparedness funding, chronic disease programs lost ground because of the diversion of managers’ attention [36-38]

**Implications for Public Health Systems in Developing Countries**

This experience with health system preparedness in the U.S. and Europe may offer insight into which investments may be particularly useful in improving the capacity of developing countries to respond to emergencies while strengthening their basic public health systems in developing countries to respond to emergencies while strengthening their basic public health systems [33].

**Infrastructure**

- **Laboratories**: Functional laboratories—well-equipped, -supplied, and -staffed—are essential to delivering quality routine health services and to responding to public health emergencies. Yet in the developing world, even basic laboratory facilities that, according to the WHO, should be able to perform malaria microscopic evaluation and hemoglobin, HIV, and glucose testing are scarce. This is compounded by a lack of diagnostic equipment and trained technicians, weak monitoring and inconsistent or absent standards for laboratory testing [42,43]. Ministries of Health are often unaware of the actual (as opposed to “on paper”) functionality of a given laboratory or hospital, making response planning difficult [44,45]. Laboratory-medicine experts have called for major investment in African laboratories, exhorting donors to build within, rather than circumvent the existing laboratory infrastructure to avoid the creation of redundant parallel systems [46]. While governments recognize the need for investments in laboratories in principle—74% of African countries have a national laboratory policy—these plans have not materialized in many countries, due in part to shortages of financial and human resources [47].

A promising example of the development of laboratory infrastructure is the Pasteur Institutes, a network of research laboratories in 30 developing countries, including some of the poorest countries in Africa: Central African Republic, Senegal, Côte d’Ivoire, Niger, Cameroon, and Madagascar. The Institutes conduct research on locally prevalent infectious diseases, train local scientists, and facilitate technology transfer in laboratory medicine [48-51]. The international community’s focus on AIDS has brought substantial new resources to developing countries, particularly in Africa, and this has also translated into better laboratory capacity. Thus, 90% of African countries responding to a WHO survey reported that they now have the capacity to screen for HIV antibodies at the district level [52]. New investments could expand these laboratories’ capacity to diagnose other infectious diseases.

**Health information systems**: Effective surveillance systems are essential to identifying potential outbreaks. While establishing real-time virologic or syndromic surveillance should not be a priority in developing countries, investing in well-functioning health information systems that can be used to communicate epidemiologic as well as administrative data in a timely manner—from the lowest level of the health system to the central ministry of health—is a shared priority area for health system development and emergency preparedness. The need for better health data is great: The WHO estimates that it receives accurate cause-of-death statistics from only 31 of its 193 member states [53]. As a result, the WHO has launched a global partnership for improved health information systems, the Health Metrics Network. This network supports developing countries in assessing their health information systems and improving their coverage of vital registration.

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as well as providing training on international health information standards (e.g. ICD classification). Cambodia, for example, is working with the Health Metrics Network and the Japanese International Cooperation Agency to scan and analyze 11 million birth and death records and to conduct a national census that will, for the first time, include information about mortality and causes of death [54]. Countries such as Sierra Leone are undertaking the assessment of health information systems and making 10-year strategic plans for improvement [55]. Health information systems could also be used to gather information on the actual (rather than planned) functionality of health posts, centers, and hospitals that would be valuable for a wide range of health planning activities. Linking community-level clinics with the health information system would dramatically expand the usefulness of the system for both routine and outbreak epidemiology. As experience has shown with the Demographic Surveillance Systems (DSS) in Bangladesh and in several African countries, with adequate investment it is possible to obtain near real-time information on a community’s burden of disease and causes of death in low-income settings [56-58]. Such systems can provide important information on the prevalence and seasonality of diarrheal illness and on the routine causes of death [59,60]. Finally, basic information systems need not be expensive. Experience from Tanzania suggests that collecting data on 38 sociodemographic and health indicators (via the census and DSS) costs approximately $0.53 per capita, per year [61].

**Human resources:** Human resource shortages are of the most pressing problems in the health systems of the developing world today [62,63]. While shortages of clinical staff have received the most attention, there are similar or worse shortfalls in public health personnel [63,64]. The shortages are exacerbated by low health worker motivation, due to poor working conditions [65-67]. All of these areas are targets for investment. An example of a successful approach is the Malawi emergency human resources program, a 6-year training and salary improvement program financed by the UK’s Department for International Development (DFID). The program aims not only to increase the number of front-line health workers (Malawi has one doctor per 62,000 people) but also to build capacity within the Ministry of Health for better health system management and planning as well as analysis of health data [68]. Trained and paid community health workers who are linked to and supported by the health system can also play a vital role in surveillance, communication, and outbreak-control activities [69,70]. Training higher-level public health personnel is also important. The same people can also perform a wide variety of essential public health tasks, such as monitoring the incidence of priority infectious diseases (e.g., HIV/AIDS) and estimating the impact of seasonal epidemics (e.g., malaria). Health economists can assist countries in estimating the resources required to respond to an emergency and to expand the health system to tackle existing morbidity.

Health policymakers need training and support to undertake comprehensive human-resource planning, which is critical to both targets. Health human resource planning relies on the sound assessment of current health worker numbers by category as well as the assessment of future inflows, attrition, and geographic distribution [66-70]. Gaps in different health worker categories can be identified and strategies for closing these elaborated.

**Communication:** Communicating with the public is a core part of emergency response, and increasing communication channels can be used to convey routine health information [60]. Investing in health communication would thus benefit broader health goals. The WHO influenza pandemic planning checklist suggests developing websites, leaflets, and fact sheets on topics related to pandemics [71]. The same communication tools could be used for a broad range of health priorities.

In many developing countries, health education materials for existing diseases, whether for the public or for health workers, are often of low quality, may not be in local languages, and are often outdated. The Internet can be used as an alternative effective tool to deliver the information an example for this approach was concluded by Ybarra ML et al.[72] concluded that the Internet may be a promising strategy to deliver low-cost HIV/AIDS risk reduction interventions in resource-limited settings with expanding Internet access.

Nominating spokespersons to address potential threats, as recommended by the WHO, has been an effective strategy to energize national efforts on HIV, and could be expanded to other diseases [73,74]. Prominent people, whether politicians or actors and other celebrities, can be an important catalyst to inform and motivate the public. Investing in improved mass-media campaigns may also be of benefit to both aims. For example, evidence is emerging that focused and locally specific media campaigns can result in the increased use of modern contraceptives [75,76]. Other promising avenues to communicate health information include the use of soap operas, radio broadcasts, plays, and village informal communication networks, particularly in countries where literacy and access to technology are low [77,78].

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