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Development of a matrix to evaluate the threat of biological agents used for bioterrorism

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Abstract. Adequate public health preparedness for bioterrorism includes the elaboration of an agreed list of biological and chemical agents that might be used in an attack or as threats of deliberate release. In the absence of counterterrorism intelligence information, public health authorities can also base their preparedness on the agents for which the national health structures would be most vulnerable. This article aims to describe a logical method and the characteristics of the variables to be brought in a weighing process to reach a priority list for preparedness. The European Union, in the aftermath of the anthrax events of October 2001 in the United States, set up a task force of experts from multiple member states to elaborate and implement a health security programme. One of the first tasks of this task force was to come up with a list of priority threats. The model, presented here, allows Web-based updates for newly identified agents and for the changes occurring in preventive measures for agents already listed. The same model also allows the identification of priority protection action areas.

Keywords. Bioterrorism, disaster planning, public health, Europe, needs assessment.

Background

In the aftermath of the September 11, 2001, attacks in the United States and the following deliberate release of anthrax through contaminated letters, bioterrorism has become a public health concern of high political priority [1, 2]. Public health authorities realised that preparedness for the deliberate release of biological agents was not an exclusively military concern anymore, but that it was urgent that it be addressed in the civil public health arena too. Among other things, this meant that public health authorities also needed to be ready to manage large numbers of cases of normally very unusual or even unknown diseases [3].

In the course of work for bioterrorism preparedness, elaboration of an agreed list of biological and chemical agents that are expected to be used in attacks or threats of attack has been seen as an essential starting point [4]. This list would then be used to evaluate the type and amount of resources needed [5]. The various lists available in the literature often also contain the characteristics and associated symptoms and diseases of these agents as well as some kind of indication that permits their timely detection and identification/diagnosis with agreed levels of certainty. The lists to be used by public health authorities for the purposes of preparedness planning should preferably be updatable both for new agents (e.g. SARS) and for developments regarding agents already listed (e.g. new diagnostic tests, new vaccines etc.). Many countries and organisations have developed lists of the most relevant agents from their perspective and expertise.

Identification of the diseases which need to be taken into account has been discussed extensively both in military circles dealing with biological weapons and in the public health world, which has become more concerned with bioterrorism. To a great extent, the military has, based its estimates on agents for which military research and intelligence indicated a potential use as a biological weapon. Military planning and preparedness in the area of chemical, biological, radiological or nuclear (CBRN) threats has been directed towards agents either already weaponised in the past or towards agents for which intelligence sources have revealed the existence or knowledge of their development as bioweapons.

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Lacking specific intelligence on weaponisable biological agents, public health authorities in many countries, tended to consider almost the same agents as their military counterparts. This is clearly not always relevant, and the Centers for Disease Control and Prevention (CDC) followed an alternative concept when they developed their list of priority agents for bioterrorism in the late 1990s. This CDC priority list focused on the public health impact that various agents would have if released in a civilian setting. Experts examined multiple agents according to the criteria listed in Table 1, which were then developed in categories of agents A, B and C [6].

The CDC has described the consensus process they used to develop their list: experts in different relevant fields were asked to rate the agents, and their ratings were then used for a comprehensive agent rating. They were able to include experts who could give information whether the agents, had been weaponised or not. The end result is a list with many similarities to the lists coming from military sources, with some new additions. The list was then divided into three sections depending on the public health measures needed, to improve the preparedness for the agents [6].

In work surrounding the Biological Weapons Convention [7], no formal list was developed, but a number of biological agents were discussed, and a list of 10 of them are cited as being the most dangerous threats in biological warfare (Table 2) [8]. The identified 10 agents and diseases have a long tradition in military bioweapons development and have without any doubt the potential to have an enormous impact on public health when deliberately released.

Table 1. CDC applied criteria and subsequent 'Category A' pathogens [1].

- Public health impact based on illness and death
- Delivery potential to large populations based on stability of the agent, ability to mass-produce and distribute a virulent agent, and potential for person-to-person transmission of the agent
- Public perception as related to public fear and potential civil disruption
- Special public health preparedness needs based on stockpile requirements, enhanced surveillance or diagnostic needs.

The CDC Category A pathogens.

Biological agent(s)	disease
Variola major	smallpox
Bacillus anthracis	anthrax
Yersinia pestis	plague
Clostridium botulinum (botulinum toxins)	botulism
Francisella tularensis	tularemia
Filoviruses and arenaviruses (e.g. Ebola virus, Lassa virus)	viral hemorrhagic fevers

Table 2. List of agents considered as the major threats during the work with Biological Weapons Convention.

Anthrax (*Bacillus anthracis*)
Botulism (*Clostridium botulinum* toxin)
Plague (*Yersinia pestis*)
Smallpox (*Variola major*)
Tularemia (*Francisella tularensis*)
Viral haemorrhagic fevers
Brucellosis (*Brucella species*)
Glanders (*Burkholderia mallei*)
Q-fever (*Coxiella burnetti*)
Ricin toxin from *Ricinus communis* (castor beans)
Staphylococcus enterotoxin B
Viral encephalitides (alphaviruses [e.g. Venezuelan equine encephalitis, eastern equine encephalitis, western equine encephalitis]).

The Australia Group is an informal initiative whose aim is to prevent the spread of the capacity to develop, among other things, biological and chemical weapons. Its tool is the restriction of export of items essential to the production of bio- or chemical weapons when there is no explanation for their legal use (dual use). The participating countries have consented to follow the agreements reached in this group and to transfer them into the relevant national and European Community legislation on non-proliferation. The Australia Group has published lists of agents that should be restricted (http://www.australiagroup.net/control_list/bio_agents.htm), but there is no clear statement or indication about the process followed to create those lists.

Besides these more official lists, there are also a number of similar threat lists mentioned in the quickly expanding literature on bioterrorism, such as the 'Salisbury list', which sought to identify those substances that might be applicable in a terrorist context and was based on a pragmatic hazard ranking.

Materials and methods

In response to the new challenges of bioterrorism and on demand from the European Union member states, the European Commission formed a task force on bioterrorism (BICHAT) [9,10] which became operational in May 2002. Through a committee with members nominated by the health ministers (Health Security Committee, HSC), the task force was asked to develop a 25-action point health security programme to improve the co-ordination and collaboration of bioterrorism preparedness activities

in the EU. One of the action points was to develop lists of agents for which activities should specifically be undertaken to improve the preparedness in the EU. To achieve this task, the task force developed a matrix to evaluate a long list of possible agents.

A matrix is defined as a rectangular array of mathematical elements (as the coefficients of simultaneous linear equations) that can be combined to form sums and products, with similar arrays having an appropriate number of rows and columns but also as something from which something else originates, develops or takes form.

We have used the word 'matrix' to signify a tool that can assist us to evaluate the impact of the release of an agent on the population and health systems of the EU member states. Furthermore, it should help us in prioritising public health needs to prevent and manage the impact of the agent used in a bioterror setting. Originally developed as a Microsoft Excel sheet, the tool is currently in practise as a Web-based application with a visual interface where, for each agent that needs to be assessed, a fixed number of variables must be filled in. The data for each agent is saved on a 'per country' basis and can allow customisation for each national authority. The agent and its relation to present public health activities are then described by variables identified under a number of headings. The Web applications were developed with Macromedia ColdFusion (http://www.macromedia.com/software/coldfusion/) and Oracle 9i (http://www.oracle.com/index.html).

The first group of variables defines the basic properties of the agent with emphasis on the epidemiological situation in the EU population today. Examples of variables that are given a value are the current incidence of the relevant disease in the EU MS member states and the percentage of the population that is expected to be susceptible, if exposed. The next set of variables looks at the present knowledge of the transmission routes of each pathogen, which gives an indication of the size of the expected epidemic, if released. The task force used the CDC criteria as published [6] but also expanded them to include other pathogens when possible. The potential for manufacturing an agent has been described with few variables, using, among others, the experiences from vaccine manufacturing. How the agent is managed from a public health perspective leads to management variables from the perspective of public health actions.

The members of the task force, with their various expertise, supplied the information for each column, and agreement was reached by consensus in the task force. The group included expertise in the areas of bacteriology, virology, epidemiology, vaccinology, clinical infectious diseases and disaster medicine. In areas of disagreement, reference literature was consulted and if necessary additional experts. Some of the more complex and difficult columns where reviewed by the whole team. For very unusual pathogens in Europe, (e.g. *Burkholderia*) a specialist in the field was consulted. In general, we have evaluated agents where data is missing as more of a threat than the ones where past experience could guide us in their management.

The descriptions and definitions of the contents of the variables have been collected in a separate explanatory document. This will make it possible to keep the assignment of values to the different variables reproducible and not person-dependent.

The information collected in the Excel sheet was then used to evaluate the agents. The first steps are based on a numeric appreciation of the impact that deliberate release of a particular agent would have on public health. The following formula was used:

$$\bar{T} = (B * M * A * D) - Tr + C$$

where T is threat, B is baseline score, M is mortality, A is aerosol spread, D is dissemination potential, Tr is availability of pharmaceutical countermeasures and C is creation potential.

Calculation of the baseline score is based on disease burden, deaths, dissemination potential from a point source, dissemination potential from person to person and public perception of the agent, in a similar manner to the CDC [6]. This baseline score is multiplied by the public health impact on mortality (diseases with high mortality are weight much more) and by the ability to be spread by aerosol. Since a disease that can easily propagate in the human population should weight more, the baseline score is multiplied by a 'dissemination score'. This score has been defined by estimating the likelihood of propagation calculated by the proportion of the population in the EU which is susceptible to the disease, since to a great extent this factor will determine how the disease will spread. We also included the possibility of spread from person to person, which will increase the spread of the disease. Finally, the incidence of the disease in the EU counties is subtracted, since a common disease is more likely to be identified at an early stage, thus diminishing the likelihood of propagation of the agent.

The baseline score is decreased with the availability of an effective pharmaceutical countermeasure (availability of post-exposure antibiotic or anti-viral treatment, or pre-exposure vaccination), taking into account the type of intervention: if any etiologic treatment is available, this treatment is given greater weight, which further decreases the score.

To the total baseline score a 'creation score' is added, a score which reflects the potential to acquire the pathogen, its stability and the potential to produce sufficient quantities of the agent to cause harm.

Table 3. List of pathogens and agents resulting from the evaluation of agents using the matrix developed by the EU task force on Bioterrorism.

List of diseases	Agents with very high threat
Anthrax	*Bacillus anthracis*
Botulism	*Clostridium botulinum toxin*
Glanders	*Burkholderia mallei*
Haemorrhagic fever	Congo-Crimean haemorrhagic fever virus, Ebola virus, Guanarito Junin virus, Lassa fever virus, Machupo virus, Marburg virus, Omsk, Haemorrhagic fever virus, Sabia
Plague	*Yersinia pestis*
Smallpox	Variola major
Toxic syndromes	Ricin, tetrodotoxin
Tularaemia	*Francisella tularensis*
List of diseases	**Agents with high threat**
Brucellosis	*Brucella abortus, Brucella melitensis, Brucella* spp*., Brucella suis*
Cholera	*Vibrio cholerae*
Coccidoidomycosis	*Coccidioides immitis*
Diphtheria	*Corynebacterium diphtheriae*
Dysentery	*Shigella dysenteriae*
Fever	Chikungunya virus
Hantavirus pulmonary syndrome	Hantaan virus
Heamorrhagic fever	Nipah, Rift Valley fever virus
Histoplasmosis	*Histoplasma capsulatum*
Haemolytic uremic syndrome	*Escherichia coli 0157:H7*
Influenza	Influenza virus (new strain)
Legionellosis	*Legionella pneumophila*
Melioidosis	*Burkholderia pseudomallei*
Meningitis	*Neisseria meningitidis*
Monkey pox fever	monkey pox
Neurological syndrome	palytoxin
Paratyphoid fever	*Salmonella paratyphi*
Psittacosis	*Chlamydia psittaci*
Q fever	*Coxiella burnetii*
Rocky mountain spotted fever	*Rickettsia rickettsii*
Scrub typhus	*Orienta tsutsugamushi*
Toxic syndrome	conotoxin, microcystin (cyanginosin), saxitoxin
Tuberculosis	*Mycobacterium tuberculosis*
Typhoid fever	*Salmonella typhi*
Typhus fever (Epidemic louseborne typhus)	*Rickettsia prowazekii*
Viral encephalitis	Eastern equine encephalitis virus, Getah virus, Hendra, (formely: Equine Morbilli virus), Herpesvirus simiae (B virus), Japanese encephalitis virus, Kyasanur Forest virus, LaCrosse, Louping III virus, Lymphocytic choriomeningitis virus, Murray Valley encephalitis virus, Powassan virus, Rocio virus, St. Louis encephalitis virus, tick-borne encephalitis virus, Toscana, Venezuelan equine encephalitis virus, West Nile, western equine encephalitis virus
Yellow fever	yellow fever virus

Results

The matrix has been primarily used to examine the threat to public health by different agents in the EU, and the need for intervention in the following areas:

1. Agents of high or very high threat
2. Agents for which laboratory monitoring is recommended
3. List of agents for which disease-specific plans are needed
4. Agents where the laboratory capacity in EU needs to be evaluated
5. Agents where surveillance needs to be further developed
6. Agents where sharing of expertise between EU countries is needed

To develop the lists mentioned above, the task force reviewed the information in the matrix, chose the important criteria for an agent to have a high public health impact and subsequently used these criteria in the formula as described above. Each variable could then be assigned different weights in the formula developed, in a group consensus process.

The algorithm used gave each agent a baseline score which could be up to 20,000 points. Some of the well-known threats and some of the diseases considered relatively harmless were used to calibrate the system. With the weight we gave to the variables, well-known threats consistently scored high, while harmless diseases scored very low. The evaluated agents were then divided in five different groups, and the two groups assessed to have the highest threat are presented in Table 3. Within these two groups, the diseases are listed in alphabetical order to compensate somewhat for the uncertainties that exist with this kind of calculation.

Using this list as a basis, the lists for specific activities could then be developed. The basis of these lists would be that in order for an agent to be included, it would have to appear in one of the two high-threat groups. Furthermore, another set of criteria needed to be fulfilled, each depending on the specific task that was being evaluated. The above-mentioned lists were then developed (they are not presented in detail in this article).

To further evaluate the usefulness of the matrix, we entered the known data regarding SARS or a new influenza strain. The results are shown in Table 4. With the information available at the initial stages of the outbreak, SARS starts at a threat level similar to some of the haemorrhagic fever viruses. If or when countermeasures are developed (such as specific antiviral agent or protective vaccine), it will still be a threat, but at the level of diseases such as cholera and seasonal influenza.

We also looked at the effect of introducing a new countermeasure for an agent or the effect of a change in the epidemiology of the disease in the EU. Table 4 presents some results of these calculations using our formula for smallpox and plague.

Table 4. Results from the matrix when used to evaluate new or changed agents.

Specification of agent	Points	Level of threat
SARS with information (June 2003)	7068	5
SARS if a protective vaccine would be available	6549	4
SARS if a protective vaccine and treatment would be available	5717	4
SARS as a disease common in the EU	3110	4
Smallpox today	16000	5
Smallpox as in 1950	7344	4
Smallpox with a new vaccine and effective treatment	7200	4
Smallpox with a new vaccine	9920	5
Plague	19451	5
Plague with a new vaccine	12675	5
Plague endemic in the EU with effective countermeasures	5652	4

Discussion

Setting priorities for which activities to pursue is an important aspect of public health. When the threat of bioterrorism took on heightened importance after the events of 2001, there was potentially a wide range of activities that needed to be considered. Since resources are always limited, only the most important of these activities can be implemented. This, in turn, requires proper priority setting. This process was mostly accomplished in the area of public health by trying to identify the diseases that were the most likely threats. In many instances, this meant consulting the experts in the field, meaning the military, and using their knowledge and their lists of high threat agents. The most widely published exercise for creating something more focused on the impact of a bioterror incident on public health is the CDC list. Using a structured consensus process, the CDC created a list that, although very similar to the ones prepared by the military, was developed using a process that seriously takes public health aspects into account.

In the European Commission task force there was also a need to set priorities, and identifying high-threat agents that should be included was included in the work programme (http://europa.eu.int/comm/health/ph_threats/Bioterrorisme/bioterrorism01_en.pdf). A matrix was developed that can function as a tool for epidemiologists, microbiologists and public health policy makers to estab-

lish the need for further interventions or other activities to improve preparedness for bioterror events. The tool can also be used in the wider context of general threats to public health from infectious diseases. To plan any given activity, an algorithm can be created that takes into account the relevant information entered in the matrix.

Some examples of potential use of the matrix approach:

- When considering a new activity: to establish which pathogens the activity should take into account.
- When considering the possible threat level of a new agent: to establish the level of threat to public health and the resulting preparedness activities that need to be undertaken to limit the threat.
- When considering changes in availability of vaccines or possibility of treatment: to establish the consequences to the threat level and resulting preparedness actions in other areas.

Initially, the matrix was set up as a tool to be used to assist the EU to prepare for deliberate release. Today, the approach has evolved into a tool that could serve public health authorities in identifying priorities for activities to limit infectious disease threats, including deliberate release, taking into account the specific national environment for which they are planning. For example, there are differences between the EU member states and the United States in the epidemiology of some diseases and the health sector infrastructure that would warrant different priorities. For example, preparations for tularaemia in an endemic area such as northern Europe would give priorities to different activities than in most parts of United States, where the disease is uncommon.

The extensive information of the matrix on many biological agents has been collected and reviewed by a group with a wide area of expertise. We have used the matrix with the information it contains to develop two lists of Very High Threat and High Threat pathogens (Table 3). Lacking the adequate information to judge from a military perspective the likelihood of release of agents in a bioterror attack, the EU task force concentrated its effort on generating a list which could be seen as an evaluation of the vulnerability of our public health system to certain diseases.

The matrix has enabled us to develop the presented list of public health threats in a way that is to a certain extent transparent and open for comments. The choice and relative weight of the variables that we have included can, of course, be debated and might very well change over time. But the process allows the same evaluation of all agents that need to be considered. The process allows for a quick evaluation of alternative agents and can also be used to identify weaknesses in our present systems for preparedness against major public health threats.

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