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ORIGINAL ARTICLES

The strategic need for the implementation of a technological platform for the microproduction of antidotes for the CBRN medical protection

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Abstract: *The "volatile" international context requires the strengthening of the national security measures, including in the field of CBRN and public health. The medical countermeasures for the defense are based ultimately on the prophylactic treatment (pre-exposure, intra-exposure and post-exposure) and on the curative treatment (of emergency, maintenance and recovery) of the contaminated and the sick. Depending on the rapid and correct etiological diagnosis, the appropriate treatment is immediately applied. Although in times of peace this scenario is almost non-existent, during war or terrorist attack it can be a mass pathology, like an explosive epidemic, that requires specific therapeutic means.*

Military medicine had and has the conceptual capacity to make antidotes for CBRN medical protection; some have been patented and/or produced as experimental models, but it has no manufacturing capacity anymore.

Keywords: *medical protection, antidote, microproduction, technological platform, medical countermeasures, pharmaceutical technique, orphan drug production*

INTRODUCTION

The international context following the conclusion of the "Cold War" paradoxically requires the strengthening of national security measures, including in the field of CBRN and public health. The international context shows that although the risk of biological warfare has been reduced following the Geneva Convention (Biological and Toxins Wapons Convention – BTWC 1972), signed and ratified by about 90% of the world's countries, the risk of bioterrorism is real, as is the risk of pandemics, zooanthroponosis etc.

The World Health Organization (WHO), the European Union (EU) and the North Atlantic Treaty Organization (NATO) recommend concrete measures to reduce these risks and to increase the responsiveness of each country, of the alliance and of the international community. Therefore, in this context, it is absolutely necessary to implement cutting edge technologies for diagnostic and prophylactic treatment, taking into account the mechanism of action in infectious diseases, the therapeutic means of counteracting the effects of biological agents and the epidemiological surveillance.

The existing international concerns force us to align ourselves with the situation existing worldwide. Designing and equipping such platforms according to international recommendations, determines the level of performance of such infrastructure to contribute to the worldwide effort of medical protection against biological agents. The present study was performed at the request of the Medical Directorate, following the request of the Control Body of the National Ministry of Defence.

MEDICAL COUNTERMEASURES

The medical countermeasures for CBRN defense are based ultimately on the prophylactic treatment (pre-exposure,

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intra-exposure and post-exposure to the attack with pathogens) and on the curative treatment (emergency, maintenance and recovery) of the contaminated and the sick. Depending on the rapid and correct etiological diagnosis, the appropriate treatment is applied immediately. In times of peace this case is almost non-existent; however, during war or terrorist attack it can be a mass pathology, like an explosive epidemic. that requires specific therapeutic means. Medical intervention requires the same strengths and the medical means all at the same time, so medical aid becomes inefficient in quantity. Moreover, the necessary drugs, in principle the specific antidotes, are orphan drugs, being little used because they are addressed to very rare diseases, and therefore they are manufactured in very small quantities and are not available when needed for urgent treatment for a large number of patients.

The medical protection against the effects of the weapons of mass destruction: chemical, biological, radiological and nuclear (CBRN WMD) is based on fundamental and applied scientific research (CDI) and later on its application in practice.

Critical situations caused by CBRN weapons/agencies are major medical emergencies and can be caused by CBRN WMD attacks, terrorism or criminal acts. The medical system must immediately have at its disposal the necessary force and means of special facilities and appropriate procedures, because "later it may be too late".

Antidotes are specific drugs for the emergency, prophylactic and curative treatment of diseases caused by physical, chemical or biological harmful factors, including CBRN agents, pollutants, etc. There is a risk of using a large variety of WMD agents: chemical warfare agents (CWAs), biological warfare agents (BWAs), radiological warfare agents (RWA), industrial toxicants, etc. which cause a wide range of diseases. As a result, many types of antidotes are needed, permanently available in stock. These must continuously exist, in appropriate forms and in reasonable quantities, for the emergency treatment of the contaminated, the suspected and the sick among the military and civilians, and possibly for the treatment of service animals, etc. In this category can be included decontaminants for internal and external use for humans and animals, in the form of solutions, powders, etc.

In medical practice, antidotes, in a broad sense, can be classified according to several criteria. WHO 20 list of essential medicines, 2017 edition, includes at chap. 4. Antidotes and orher substances used in poisonings, only 15 pharmaceuticals with antitoxic effect, but without taking into account the other CBRN agents. Antidotes can be classified pharmacologically, depending on the agent for which they are used, hence etiological. Antidotes can also be classified according to clinical use: preventive (eg protectors, vaccines), post-exposure prophylaxis (eg atropine, specific antibiotherapy, decontaminants for the skin, mucous membranes, eyes etc.), or therapeutic (e.g. decorporators, chelators, therapeutic sera). From a pharmaceutical point of view, there are antidotes for external use, including hygiene-cosmetics (solutions, lotions, pastes, ointments, powders, etc.), antidotes for internal use (buccal solutions, powders, granules, tablets, dredges, capsules etc.) used preventively, post-exposure or therapeutically, as the case may be. Injectable antidotes (specific vials and devices, self-injecting syringe, auto-injector) and infusions represent an important category in the medical-military arsenal of countermeasures against CBRN agents.

Like any other drug, antidotes can be prepared industrially, galenically or masterfully, from natural and/or artificial pharmaceuticals. These can be of mineral origin (eg sodium sulfate), vegetable (eg charcoal, atropine), animal (anti-venom), microorganisms (eg vaccines, immuno-modulators). Depending on the context, they can be used for prophylaxis (eg pyridostigmine bromide, vaccines), for post-exposure prophylaxis (eg decontaminants for skin and mucous membranes, atropine, anatoxins, antibiotics), curative (eg EDTA, therapeutic sera, antimicrobial chemotherapics).

Antidotes must meet a number of basic conditions required by the Medicines Law: proven therapeutic effect, undesirable side effects as less as possible, preparation in appropriate conditions, reasonable cost price, the possibility of being produced in the required quantities and to be stored for a certain time period, as well as being distributed in a timely manner for emergency treatment. However, an issue arises concerning the cost/efficiency: if within the antidote's validity period there are no cases or there are very few (desirable situation), the remaining antidote must be discarded at the expiration of the term of validity. These stocks cannot be refreshed by "being put in use" in the sanitary units, because under normal conditions they are of no use except to a very small extent. As European Medicines Law no longer allows re-endorsement after expiry, at most, the antidotes that correspond to the pharmaceutical and pharmacological control may be used only for possible veterinary use, if applicable. In the event the numbers of cases require a certain antidote exceeding the existing stock, the product will have to be prepared quickly, according to a product portfolio located at the manufacturer. If there is no authorized manufacturer, a call can be made for emergency imports or international aid. In fact, the EU Charter also

provides for a solidarity clause, whereby European countries are obliged to help each other in case of emergency, but it is obvious that this can be done only after covering their own needs.

In practice, it is difficult to find a pharmaceutical industry producer (one of the most profitable in the world) to manufacture the full range of antidotes, because the orders are small, the products are "niche", and the prices are monitored. This is because antidotes are orphan drugs, being used only for rare diseases, so the demand is so low that their manufacture would mean a lot of work for little money, and would not be cost effective. It turns out that a private producer could not be forced to manufacture them in normal circumstances.

The production of specific antidotes for CBRN medical protection can be achieved only in conjunction with:

1) the medical research's need to physically manufacture the newly designed products (medicines, diagnostic kits, kits and medical devices), at the level of experimental model (EM), functional experimental model (FEM), prototype and/or technological demonstrator, for endorsement, receipt and possibly patenting (as an invention or industrial model), with

2) the need of the industry to carry out the 0 series, the microproduction and the batch series production for clinical testing and for obtaining the marketing authorization (MA), so the principle of integration must apply: research, education and production.

This integrative principle promoting success in the development of specific antidotes, was introduced in Romanian medicine by Prof. Ioan Cantacuzino, since 1901, (Biography Cantacuzino, Ciuca) being applied at the Institute that bears his name, but was subsequently abandoned under unjustified circumstances. Obviously, nowadays, such a dedicated objective involves a pharmacological and pharmaceutical collaboration in the form of a technological platform for the production of antidotes for medical protection, whose components (facilities and utilities) include a Pharmaceutical Laboratory for CBRN antidotes and that must comply with the recommendations of the ANMDM (National Agency for Medicines and Medical Devices) and implicitly with those of the WHO.

State-of-the-art for the production of antidotes for CBRN medical protection is different from one country to another. Civil drug manufacturers (the pharmaceutical industry) generally avoid manufacturing antidotes, as these are "orphan drugs", meaning that they are rarely used under normal conditions, so it would be a difficult commodity to sell. State producers can be forced, through the Production Plan, to manufacture them, but in Romania there is no longer the case, as a result of privatization, and private producers risk financial losses or even bankruptcy, if they manufacture without and end profit.

The beneficiaries and the producers avoid ordering or storing antidotes, because they can remain unused until the expiration date and the prolongation of the duration is not allowed even if they maintain their therapeutic effect, so the medicines are canceled and financial problems arise. As a result, CBRN-specific antidotes do not appear as such in the List of Essential Medicines (WHO Model List of Essential Medicines, edition 21, WHO 2019).

The solution would consist in the specific pharmaceutical manufacture in military or militarized facilities, according to the needs of the national military forces, of the population exposed to specific risk and possibly for other allied armies or for the population in general.

PREVIOUS EXPERIENCE

In Romania there was the Pharmaceutical Production Laboratory of the Medical Directorate belonging to the Ministry of National Defence, which operated without interruption for almost a century, near the Sanitary Warehouse. It prepared specific usual medicines for the military staff, which were distributed free of charge to military hospitals and unit nurses. Different products were manufactured, depending on the needs, as solid forms (tablets, dragees, suppositories, spark plugs, powders), liquid forms (solutions, lotions), ointments, etc. But the injectable, infusable forms and the eye drops, which must be sterile, were prepared only in the pharmaceutical laboratories of the military hospitals. These drugs, along with others, manufactured in the country or imported, have been used to treat the military during peace and war: the Balkan Wars, the First World War, the Second World War, the Revolution, etc. After Romania's entry into NATO and the EU, this laboratory was closed by the pharmaceutical micro-production and moved to another headquarters because it did not comply with the new European norms for the pharmaceutical industry. At the entry into force of the Medicines Law, it was closed down and the machines, inventory objects and consumables (pharmaceuticals and chemicals) were redistributed, some of them ending up at CMMSR for scientific research. They no longer meet the conditions required for the pharmaceutical industry, can no longer be used for the initial purpose and cannot be exploited.

The laboratories of The Center for Military-Medical Scientific Research (CMMSR) have experimentally produced various

specific drugs, including antidotes, some of which have been used for the troops in peace or war time. These include: Dostirav (Pyridostigmine) and other CBRN protective equipment provided, including in the Iraq war, 1991; the cyanide antidote that, although patented, is not manufactured by the pharmaceutical industry and the tragic consequences could be seen in the tragic accident which took place at “Colectiv” etc.

The applied research, through the module "Scientific and technological research on the production of antidotes and products with special purpose", has completed technological researches on the manufacture of protective and decomposing antidotes under conditions of peace and in critical conditions (campaign, natural and technological disasters) and, since 2002, ended by:

- establishing the technologies for industrial production and by micro-production under critical conditions for oral preventive antidotes (eg Dostirav/30 mg);

- establishing technologies for industrial production and by micro-production under critical conditions for decontaminants for skin and the mucous membranes (eg DCPM);

- establishing the structure and operating conditions of certain microproduction lines under critical conditions for antidotes;

- research on the synthesis of some organic derivatives of obidoxime with improved pharmacokinetic properties, etc.

These research projects were approved and accepted, the microproduction was performed at galenic level, and the financing of a Pharmaceutical Micro-production Laboratory for antidotes was approved. However, the necessary funds were not allocated and the objective was not achieved. This problem must be resumed in the current political-military context and updated according to the legislation in force. We present below, as an example, some products resulting from the CMMSR’s activity, such as Patents of invention/innovation and/or experimental/galenic models (Table 1). To these can be added numerous sets and diagnostic and treatment kits for medical intervention in CBRN events, some of which have been presented at military exhibitions: ACTTM Clinceni, EXPOMIL Bucharest, BSDA, Inventions fairs, etc. and have been used in applications and theaters of operations (Saudi Arabia, Somalia, Angola, Iraq, etc.).

Regarding orphan drugs, which are very rarely needed, the cost of making and placing a medicinal product on the market for the diagnosis, prevention or treatment of the disease, cannot be recovered through the expected sales of the medicinal product, and the pharmaceutical industry would be refractory to its realization, under normal market conditions. The antidotes for medical protection in case of CBRN attack, terrorism, catastrophe or industrial accident are also considered orphan drugs.

Another aspect of these medicines is represented by the expired drugs. The supplier guarantees the efficacy of the drug only within the deadline, so an orphan drug may expire before it is needed. This can create a financial problem that is difficult to solve. The US Army is currently studying the possibility of extending the shelf life of medicines from stocks, if they have retained their pharmacological properties (internet).

The operating costs differ depending on the chosen variant, the assortments and the quantities of antidotes manufactured, being able to reach the order of millions of euros, depending on the spaces, equipment, personnel and portfolio of pharmaceutical products.

Implementation Opportunities. Providing antidotes is mandatory in medical practice and especially in military medicine. Antidote insurance is nationally deficient and globally they are considered "orphan drugs".

A compromise formula, adapted to the current context in Romania, could be the strategic cooperation regarding fundamental, applied, developmental, innovation scientific research integrated with the production and education of the profile. Thus, the Ministry of National Defence, through virtual reorganization can achieve an Integrated Technological Platform, by sharing the scientific basis and launching the production of antidotes for public health needs and for CBRN crisis situations.

To this would contribute first of all the Military Medical Research Center (CCSMM), the “Cantacuzino” National Military-Medical Institute for Research Development (INCDMM Cantacuzino), the CBRN Defense and Ecology Scientific Research Center (CCSACBRNE), as well as other competent military entities and civilians, from the academic, university, industrial health field, etc. In order to launch the specific antidote micro-production or production, it may be necessary to build or adapt an appropriate facility (pharmaceutical laboratory or drug factory). As a back-up formula, in case of force majeure, a virtual "ad hoc" structure can be created, which will integrate different structures and microstructures existing in Ministry of National Defence, to achieve this common purpose.

Table 1: Examples of CBRN medical protection products resulting from the activity conducted by the Military Medical Research Center

No	Product	
1	Medicinal product with effective action against organophosphorous compounds	Patent State Office for Inventions and Trademarks 79914/1974 V. A. Voicu, C. Miu, M. Jiquidi, C. Furnica, I. Elian
2	Dixidextracaine 70, a drug intended for subarachnoid hyperbaric anestesia	Patent State Office for Inventions and Trademarks 81100/1975 I. Curelaru, C. Furnica, V. A. Voicu, E. Ionescu-Visan, C. Miu, P. Nitescu, L. Ivanescu, I. Manolache
3	Pharmaceutical combinations with antiseptic effects	Patent State Office for Inventions and Trademarks 65237/1977 Al. Bors, V.A.Voicu, C. Rizescu
4	Dynamic repolarization solution	Patent State Office for Inventions and Trademarks 65235/1977 Al. Bors, V .A. Voicu
5	Anti-arrhythmic compound	Patent State Office for Inventions and Trademarks 65236/1977 Al. Bors, V .A. Voicu
6	Equipement for objectifying drug interactions	Patent State Office for Inventions and Trademarks 74803/1980 Al. Ionescu-Stoian, V. A. Voicu, M. Jiquidi
7	Anti-arrhythmic compound and synthesis process	Patent State Office for Inventions and Trademarks 69027/1978 Al. Bors, V. A. Voicu, V. Aldea, E. Olteanu
8	Radioprotective compound	Patent State Office for Inventions and Trademarks 3198/1970 Al. Bors, V. A. Voicu, C. Paun, Gh. Dumitrescu
9	New anti-hypertensive compund	Patent State Office for Inventions and Trademarks 76911/1980 V. A. Voicu, St. Muresan, Gh. Radu, M. Jiquidi
10	New anti-hypertensive compund	Patent State Office for Inventions and Trademarks 76912/1980 V. A. Voicu, St. Muresan, Gh. Radu, M. Jiquidi
11	New antiseptic compound	Patent State Office for Inventions and Trademarks 80051/ 1979 Al. Bors, V. A. Voicu, A. Karassi
12	Anticholinergic compound	Patent State Office for Inventions and Trademarks 87010/1985 V. A. Voicu, Al. Ionescu-Stoian, L. Antoniu, M. Jiquidi
13	Herbal compound with anti-inflammatory, analgesic and vasoprotective action	Patent State Office for Inventions and Trademarks 87147/1985 Al. Ionescu-Stoian, L. Antoniu, V. A. Voicu, V. Florea
14	Complex antidote for the absorption, neutralization and inactivation of ingested toxins	Patent State Office for Inventions and Trademarks 99921/1989 V. Mihaila, V. A. Voicu
15	Medicine with anti-inflammtory, analgesic and decongestant effect	Patent State Office for Inventions and Trademarks 102954/1991 V. A. Voicu, C. Mircioiu, Al. Ionescu-Stoian, M. Jiquidi, E. Rolea
16	Collagen bandage for the treatment of burns	Patent State Office for Inventions and Trademarks 103550/1991 V. A. Voicu, V. Trandafir, T. Giurgiu, T. Safta, D. Burlacu, A. Nica, L. Dragoescu
17	Medicine with anti-inflammtory, analgesic and decongestant effect	Patent State Office for Inventions and Trademarks 106333/1996 V. A. Voicu, M. Jiquidi, C. Mircioiu
18	Method and compounds for the simultaneous determination of acetyl-cholinesterase and pseudo-colinesterase in blood	Patent 67856/19.10.1976
19	Versatile antidote against chemical agents, with effect on skin lesions and mucous membranes	Patent 7959/23.06.1978
20	Device for measuring the caloric response	
21	Protective mixture for impregnating fabrics	
22	Device for measuring contamination with radioactive isotopes of the human body	
23	Device for rapid desiccation of biological or chemo-pharmaceutical compounds	
24	Medicinal product with specific anti-stress, anti-wear synergistics, polyvalent, neuropsycholobiological revitalization effects	Invention Patent No. 87905/2005
25	Immuno-enzymatic test for the detection of microorganisms	Patent 91566/1984/09.01.1987
26	Enzyme conjugation process	Patent 90105/1984
27	Herbal compound with anti-inflammatory, analgesic and vascular-protective effect	Patent 9992/30.10.1989
28	Collagen bandage for skin lessions	Patent 103550/20.02.1989

Military medicine has had and has the conceptual capacity to make antidotes for CBRN medical protection, some of which have been patented, but it does not have the production capacity. It is possible to arrange or build a self-production capacity for specific antidotes, as orphan drugs, on constructive variants, depending on complexity. The total costs are important, but the objective can be amortized in a short time if the supplier has a regional opening and the social benefit is very high.

The problem of self-injection syringes

We consider that the most important and stringent problem is to equip the active and the non-commissioned military staff and the risk group population, with self-injection syringes (over 1 million people in Romania), according to NATO norms (STANAG 2871 CBRN MED, 3-6 syringes per person, plus reserves); therefore, a total of over 3-6 million self-injection syringes.

The issue of providing CBRN antidotes in Romania is not solved by NATO standards. For example, the RDG model self-injection syringes, made of stainless steel, that were in the Romanian Army's endowment, were withdrawn in the 1980s and have not been replaced until now. The Romanian model made of plastics (made by the Center for Military-Medical Scientific Research as an experimental model, a functional experimental model, a prototype and a zero series) was no longer manufactured in series due to the privatization of the manufacturer (the Plastics Factory Bucharest). At present, the Center for Military-Medical Scientific Research has developed a prototype of self-injecting syringe for antidotes, with the intention to carry out a technological transfer through projects funded by the Ministry of Research and innovation.

THE PHARMACEUTICAL LABORATORY

The pharmaceutical laboratory for the production of antidotes for CBRN medical protection must be a basic component of CBRN medical protection. It must be complex, must have functional autonomy (space, equipment, staff and specific procedures) and must operate in compliance with national and international norms in the field. Its main activity shall consist in the pharmaceutical research, manufacture and pharmaceutical control of CBRN medical protection medicines (antidotes and decontaminants), as well as the storage (in pre-determined quantities) and must be in charge of their distribution (in effect of an order) to the military or the civilian health network, nationally or internationally.

The Romanian Army had 17 facilities authorized for the microproduction of military-specific drugs, including antidotes: 12 in the pharmaceutical laboratories of the Military Hospitals, one in the pharmaceutical laboratory at the Bucharest Garrison Health Center (led by chief pharmacist colonels (eg Col. Pharm. Dr. Oiţa from Iasi who prepared and patented over 100 innovative drugs), a laboratory for blood and derivatives at the Hematology Center (led by Col. Pharm. Dr. Coreni), a galenic laboratory for antidotes at Military Medical Research Center (CCSMM) (led by Col. Pharm. Prof. Dr. Mircioiu), one at the Pharmacology and Drug Control Laboratory (led by Col. Vatasescu), a microproduction laboratory for specific drugs for the military staff, at the Sanitary Warehouse (led by Col.Pharm. Rosnovschi), and a chemical synthesis laboratory for antidotes (led by Col. Pharm. Miu) was also operating at CCSMM. These had incorporated a department for injectable and infusible medicines and were able to prepare any master or galenic drugs recommended by clinicians or researchers. However, all were abolished at the restructuring of the army from the beginning of this century, and the current legislation no longer allows them to be re-instated.

We recall that the Medical Directorate had a Pharmaceutical Microproduction Laboratory, with an old tradition, that provided specific sanitary-pharmaceutical materials, but it was abolished, after almost a century of existence, at the entry into force of the Medicines Law, because it did not comply with the requirements imposed by the European Union, although strictly speaking, they refer only to the "marketing authorization" of the products.

It can also be exemplified based on the experience of CCSMM, that had a Galenic Laboratory, which implemented the products created by the researchers from the laboratories of the Center (under direction of General Prof. Victor A. Voicu, MD, PhD, SR, member of Romanian Academy) but which was renamed and reorganized, because the new Medicines Law no longer provides the "galenic" category. This laboratory, with pharmacists and chemists, had the task of pharmaceutical, pharmacological research and prepared the reagents and drugs resulting from scientific research activities of the center, in quantities of up to 50 doses per lot, in order to remain in the field of microproduction. The products were used for physico-chemical tests, animal experiments or cell cultures and some were distributed to units located in Operations Theaters (for example in Iraq, Somalia, Angola), in applications (for example Campulung, Brasov, Tulcea), in specific missions (for example, anthrax, cholera, BDA epidemics), have been presented at different thematic exhibitions (Clinceni, Central Army House, Expomil, Inventions, BSDA) and many have been patented as inventions or innovations. However, at the

present moment, the Romanian Army no longer has any facilities for drug production, so neither specific CBRN antidotes nor qualified personnel for pharmaceutical preparations.

REQUIREMENTS AND LEGISLATION IN FORCE FOR CERTIFICATION/ACCREDITATION/OPERATION

After designing, obtaining the necessary permits and financing, the platform can be built and the specific endowment can be started. From the moment it is put into operation, with the commissioning protocol, the sanitary-veterinary authorization of operation is requested from the Center for Preventive Medicine, then the RENAR and ANMDM approval for the manufacturing authorization. After completing these mandatory steps, it can be proceeded to micro-production, but for each particular product the marketing authorization must be obtained.

Corroborating the need of medical research to physically make the newly designed products (medicines, diagnostic kits, sets and medical devices), at the level of experimental model (EM), functional experimental model (FEM), prototype and/or technological demonstrator, in order to obtain the approval, commissioning protocol, authorisation and possibly patenting (as an invention or industrial model), with the need for the industry to carry out the microproduction and serial production of 0 series for clinical trials and obtaining the marketing authorization (MA), the integrative principle must apply: research, education and production.

The current legislative requirements can be found in: the Guide on good manufacturing practice for medicinal products for human use, the Guide on good practice in drug distribution, the Order 1807/2006 regarding the approval of the Norms for the application of some provisions of Regulation no. 141/2000/EC on orphan drugs, entered into force in 2007, GMP Regulations – Good Practice Regulations in production, consultancy-certification.ro, etc.

CONCLUSIONS

Medical countermeasures for CBRN defense are based on the prophylactic and curative treatment of the infected and the sick. Depending on the rapid and correct etiological diagnosis, the appropriate treatment is immediately implemented. However, in time of peace, this case is almost non-existent, and during the war or during a terrorist attack it can be a mass pathology, like an explosive epidemic, in which the forces and means involved for medical counter-measures become insufficient.

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