Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

Opinion TRENDS in Microbiology Vol.12 No.6 June 2004

Full text provided by www.sciencedirect.com
SCIENCE DIRECT

The weapon potential of a microbe

Arturo Casadevall and Liise-anne Pirofski

Division of Infectious Diseases, Department of Medicine and the Department of Microbiology and Immunology, Albert Einstein College of Medicine, 1300 Morris Park Ave, Bronx, NY 10461, USA

The designation of a microbe as a potential biological weapon poses the vexing question of how such a decision is made given the many pathogenic microbes that cause disease. Analysis of the properties of microbes that are currently considered biological weapons against humans revealed no obvious relationship to virulence, except that all are pathogenic for humans. Notably, the weapon potential of a microbe rather than its pathogenic properties or virulence appeared to be the major consideration when categorizing certain agents as biological weapons. In an effort to standardize the assessment of the risk that is posed by microbes as biological warfare agents using the basic principles of microbial communicability (defined here as a parameter of transmission) and virulence, a simple formula is proposed for estimating the weapon potential of a microbe.

The potential use of microbes as weapons and agents of terrorism is greatly feared. The ability of such agents, or biological weapons, to cause mayhem was demonstrated in 2001 when five envelopes containing *Bacillus anthracis* spores resulted in eleven cases of inhalational anthrax, disrupted the functioning of the United States government and caused widespread fear and anxiety. Agents with a high potential for use as biological weapons have been included in a 'Select Agents List' that categorizes them as A, B or C, depending on the assessed threat posed by the agent (Table 1). Agents included in the list fall into two categories: toxins and live microbes. The inclusion of various toxins as select agents is based on their toxicities, ability to damage human tissues and/or normal human homeostatic mechanisms, potential availability and capacity for delivery to humans. Although the selection of toxins as potential biological weapons is based on their inherent toxicities and availability, the selection of live microbes for the select agents list is more complicated.

A biological weapon can be used against an individual, a group of individuals, a society, a civilization or a species. Humans have practiced biological warfare against other species by introducing into the environment predators or diseases that are intended to reduce the numbers of a target species. One famous example was the use of myxoma virus to control the rabbit population in Australia through the extermination of susceptible hosts [1]. Biological weapons have the potential to cause incalculable pain and suffering, and understanding them in the context of the larger problems of virulence and pathogenicity could translate into better preparedness and the development of preventative and therapeutic measures.

Live microbes considered to be potential biological weapons are classified on the basis of a variety of considerations, for example, prior use as a biological weapon, a history of causing pandemics with high mortality, and estimation of their potential for causing death, disease and terror if introduced into certain populations [2]. Consequently, the most common characteristics shared by microbes on the select agent list is that they are thought to be capable of causing great harm to human populations and that their management would

Table 1. Classification system for agents of bioterrorism

Category	Definition	Examples
A	Agents that can be easily disseminated or transmitted person-to-person; cause high mortality with potential for major public health impact; might cause public panic and social disruption; and require special action for public health preparedness	*Bacillus anthracis* (anthrax) *Clostridium botulinum* toxin (botulism) *Yersinia pestis* (plague) Variola major (smallpox) *Francisella tularensis* (tularemia) Viral hemorrhagic fevers *Coxiella burnetti* (Q fever)
B	Agents that are moderately easy to disseminate; cause moderate morbidity and low mortality; and require specific enhancements of the CDC's diagnostic capacity and enhanced disease surveillance.	*Brucella* species (brucellosis) *Burkholderia mallei* (glanders) Ricin toxin from *Ricinus communis* Epsilon toxin of *Clostridium perfringens* *Staphylococcus* enterotoxin B Nipah virus
C	Emerging pathogens that could be engineered for mass dissemination in the future because of their availability, ease of production and dissemination, and potential for high morbidity and mortality	Hantavirus Tickborne encephalitis viruses Yellow fever Multidrug-resistant tuberculosis

Corresponding author: Arturo Casadevall (casadeva@aecom.yu.edu).

www.sciencedirect.com 0966-842X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved. doi:10.1016/j.tim.2004.04.007

require massive public health efforts and preparedness. However, from a microbiological vantage point, there is no common denominator that ties the microbes on the select agent list together on the basis of their virulence or pathogenicity.

In this review, the relationship between microbial virulence and the classification of a microbe as a potential biological weapon is analyzed. Because the classical concepts of virulence appear to be insufficient to predict the suitability of a microbe as a biological weapon, we define the weapon potential of a microbe using a formula that is a function of various measurable and/or definable parameters. It is our goal to illustrate that the weapon potential of a microbe can be estimated using systematic methodology, which might be useful for prioritizing the relative threat posed by different microbes.

Virulence and microbe-based biological weapons

Biological weapons might constitute live microbes or microbial components or products (e.g. toxins). Microbial component or product weapons are preformed compounds that are intended to incapacitate or kill as a result of deleterious effects on host homeostasis. By contrast, live microbe-based biological weapons incapacitate or kill the host by inducing sufficient damage to produce disease. Microbial component or product weapons might differ in toxicity, but the concept of virulence is applicable only to microbe-based weapons.

Virulence has been variously defined over the years and even today there is no universally used definition for this term [3]. We recently defined virulence as the relative capacity of a microbe to cause damage in a susceptible host [3]. Therefore, rather than being a singular microbial property, virulence is dependent on microbial and host variables, and as such is a readout of the amount of damage a susceptible host sustains from a host–microbe relationship [4]. Virulence is defined as a relative term because we have no absolute measures of damage and consequently virulence is generally measured relative to another organism or to the historical experience with the disease [5].

When assessing the relationship between virulence and the suitability of a microbe to serve as a biological weapon, it is important to consider the goal and the intent of the user. For example, if the goal is to injure or kill individuals or groups of individuals, or to rapidly spread terror, the aggressor might select a microbe that causes disease and death soon after infection with a low inoculum. Such a weapon would have a high degree of virulence on the basis of its capacity to induce damage and/or disease in a short time and because only a few organisms would be needed for this outcome. By contrast, if the goal of a weapon is to undermine a society, civilization or species, the element of time and the inoculum that is needed to cause damage might be less important. For example, the inadvertent introduction of measles, smallpox and influenza into America by Europeans played havoc among indigenous societies and greatly facilitated their conquest, which in some cases occurred years after the initial contact [6,7]. Similarly, the Black Death epidemic might have originated from an act of biological warfare during a Black Sea siege, however, it took years to ravage Europe [8]. Both the smallpox and Black Death epidemics were caused by organisms currently grouped as class A select agents. However, analysis of other microbes not on the class A list suggests that they have similar potential to cause harm. This can be exemplified by human immunodeficiency virus (HIV), which has not been ranked high among biological warfare agents, presumably because of the difficulty in delivering this virus to a susceptible host and because the disease occurs many years after the initial infection. Nevertheless, there have been documented cases of deliberate HIV infection, indicating it has potential as a biological weapon [9]. Interestingly, the experience with HIV in certain countries bears similarities to those that have suffered from smallpox and bubonic plague epidemics, which has led some scientists to characterize HIV as a 'plague'. If the goal of an attack is to destabilize a society, then HIV has great weapon potential, as evidenced by the scourge and devastation that has visited numerous African societies. Such societal devastation poses a risk to the security and future of other nations around the globe, which cannot go forth without their youth. Given that the outcome of epidemics of bubonic plague, smallpox and HIV in susceptible populations is similar, then the assignment of plague and smallpox to class A status and not HIV must reflect considerations other than virulence. In the case of HIV, the outcome of infection is probably less relevant when assigning certain microbes to the select class than the process by which the outcome is achieved, the timing between infection and disease, and the preventative and therapeutic options that are available. In addition, other factors such as the deliverability of the agent to targeted populations will also probably influence the level of threat that is assigned to a particular microbe.

Although all successful microbe-based biological weapons are virulent in susceptible hosts, not all virulent microbes are considered candidates for use as biological weapons. Notably, some microbes notorious for causing epidemics of fulminant disease, such as *Neisseria meningitidis* and *Streptococcus pyogenes*, are not included in the select agents list. By contrast, other microbes that cause only sporadic cases of human illness, such as *Bacillus anthracis* and *Francisella tularensis*, are considered highly dangerous category A biological agents. These examples suggest a complex relationship between the virulence of a microbe and its potential use in warfare and terrorism, and imply the importance of additional variables in determining the suitability of a microbe as a weapon.

One reason that the weapon potential of a microbe is not directly related to virulence is that none of the proposed definitions of virulence includes the parameter of time in their formulation. Time is an important variable in the 'damage-response framework' because it is used to define the outcomes or states of microbial pathogenesis that follow infection [10]. The damage-response framework defines the outcomes of microbial infection (colonization, commensalism, latency and disease) as functions of host damage over time [10]. The weaponization of *B. anthracis* can be envisioned as a modification of anthrax pathogenesis, whereby the relative proportion of individuals

progressing to disease is increased and the route of infection is changed from gastrointestinal to pulmonary. Time is a significant variable because the effectiveness of biological agents as weapons is often a function of the rapidity with which they cause disease in a susceptible host.

The weapon potential of a microbe

We begin with the assertion that each microbe has some weapon potential, which can range from high to nil. Looking over the select list for common denominators we are struck by the paucity of commonalities that would allow classification within the generally accepted parameters of microbial virulence and pathogenicity. Because virulence is a necessary but not sufficient condition for classification of a microbe as a select agent, there must be other considerations that are involved in making such choices. Hence, we propose the parameter termed weapon potential (WP) to be used to denote the suitability of a microbe as a biological weapon. The WP of a microbe is a function that includes such variables as its virulence, time to disease and susceptibility of possible target populations. For a microbe, the WP can be thought of as WP $\propto$ virulence/time to disease.

The definition of virulence as the relative capacity of a microbe to cause damage in a host [3] is suitable as an operational concept in microbial pathogenesis, but computation of the WP of a microbe requires a more definable and/or quantifiable parameter. For biological weapons, a more suitable relevant parameter might be the ratio of symptomatic to asymptomatic infections. This narrower and more specialized definition of virulence includes the principle of host damage because a symptomatic infection is by definition one whereby the host suffers sufficient damage to manifest symptoms. In this regard, the WP incorporates the degree of host susceptibility, because damage that translates into disease can only occur in a susceptible host.

To determine the virulence of a biological weapon (V_{BW}) the following could be used: $V_{BW} = F_{SI}/I$, where F_{SI} is the fraction of symptomatic infections for a given inoculum (I). V_{BW} is not a fixed characteristic and is based on the degree of immunity in an individual or population. Hence, a vaccination program would reduce V_{BW} by reducing the fraction of symptomatic infections. For example, in a study of intrafamilial transmission of smallpox there were 73 cases of smallpox among 96 unvaccinated contacts ($F_{SI} = 0.760$) that presumably led to the infection, whereas among vaccinated individuals there were only 16 cases of smallpox among 331 contacts ($F_{SI} = 0.048$) [6]. Furthermore, a higher state of immunity would require a significantly higher inoculum, further diminishing V_{BW}.

The WP of a microbe is also a function of other characteristics that include communicability and stability. Communicability is a measure of transmissibility and contagiousness. Host-to-host communicability (C) is not a required quality of a biological weapon, as evidenced by the example of *B. anthracis* spores, but the potential for communicability can significantly influence the selection of an agent and its impact on the targeted population. Although communicability functions as a threat amplifier, it is not always a desirable quality in a biological weapon because the aggressor cannot control the agent once it is released and there is always the potential that person-to-person communicability would affect friendly, non-targeted populations. For a particular pathogen, the parameter C is ≥ 1.0. Microbes that are not transmissible have a C value of 1.0, such that this parameter does not influence the WP. For the purposes of this exercise we have arbitrarily set the value $1.0 \leq C \leq 100$. Stability (S) is a required parameter for biological weapons because one can anticipate that some baseline stability is needed for a microbe to be developed into a biological weapon. We arbitrarily set the parameter S to range from 0 (unstable) to 1 (eternally stable). For simplicity we assume that time (T), C and S modify WP in a linear fashion and that the above relation can be combined to obtain a relation for WP, such that $WP = V_{BW}SC/T$.

The element of time contributes in at least two ways. First, the shorter the time between use of a microbe and its effect reduces the likelihood that a targeted population can adapt to the threat, and as a consequence the potential effect of the microbe increases. Second, microbes that act rapidly are more likely to cause terror. Therefore, it is no surprise that the time between infection and disease is relatively short for all the microbes that are currently listed in the select agents list (Table 1). However, the relationship between the time to disease and the weapon potential of a microbe is more complex. If the devastation brought to Africa by the HIV epidemic is considered, it is clear that even microbes that take a long time to cause disease can cause tremendous havoc. Consequently, they have tremendous weapon potential and it might be appropriate to consider them separately by disregarding the parameter of time (e.g. assign $T = 1.0$).

This formulation can then be used to compare the WP of various agents in the select agents list for which there is sufficient information available in the literature to estimate the various parameters (Box 1). The formula yields significantly larger values for the WP of *B. anthracis* and variola virus than for *C. albicans*, a fungal commensal that is not considered a potential biological weapon. Our calculation suggests that the WP for variola virus is several orders of magnitude greater than *B. anthracis* because the infective inoculum is believed to be smaller, and its high communicability provides a strong multiplier effect. Interestingly, HIV yields a higher weapon potential than *B. anthracis* when certain assumptions are made (Box 1). However, if one disregards the parameter of time by assigning $T = 1.0$ then the formula estimates a WP for HIV that is comparable to variola in a susceptible population (Box 1).

Clearly, the WP formalism proposed here is the first approximation for a very complex relationship and we do not claim to have found the optimal formulation. In fact, the basic formula can be modified further to consider other variables. For example, one can add a terror modifier (X) based on the judgment that the agent would cause panic and social disruption: $WP = [V_{BW}SC/T]X$.

The X parameter can be large for conditions where there is high mortality, contagion and no prophylactic or therapeutic measures. An example of such an agent

Box 1. Calculation of the weapon potential for *Bacillus anthracis,* variola virus, human immunodeficiency virus (HIV) and *Candida albicans*

For *Bacillus anthracis* (Table I) the fraction of symptomatic infections (F_{SI}) of 0.008 was estimated from the Sverdlovsk anthrax outbreak where there were several hundred cases (we assumed 500) from a population of 59 000 that was selected for vaccination by the Soviet authorities following the accident [13]. Similarly, the time to disease was the mean incubation period for fatal cases in the Sverdlovsk incident [14]. In the second calculation the F_{SI} of 0.0008 was estimated from the *B. anthracis* mail attacks where two cases of inhalational anthrax occurred among the 2446 persons that were potentially exposed in the Brentwood Mail Processing and Distribution Center in the District of Columbia [14]. The inoculum values of 8000, 50 and 1 spores correspond to LD_{50}, LD_{10} and LD_1, respectively, in monkeys [2,11], and are used here with the caveat that we do not know the number of spores in the above incidents or the applicability of monkey susceptibility data to humans. The values for LD_{10} and LD_1 were taken from Ref. [11]. Communicability was arbitrarily assigned a value of 1.0 (not communicable) because person-to-person spread of anthrax does not occur. Stability was assigned a value of 1.0 because spores can remain viable for decades.

For variola virus (Table I) we have used the value of 0.76 for the F_{SI} based on a study where there were 73 cases of secondary smallpox among 95 unvaccinated contacts of individuals with smallpox in a study of intrafamilial transmission [6]. The inoculum used was taken from studies by Franz *et al.* [2]. The communicability value was arbitrarily set at 90 as there is widespread consensus that smallpox is a highly contagious disease [2]. The time to disease varies between 7–17 days [2], therefore we used the value of 10. Relative stability is unknown and we arbitrarily used 0.25 because it is a virus transmitted in aerosols.

For HIV (Table I) the inoculum for 50% infectivity was estimated to be 1000 from blood transfusion and needle stick studies [15]. The F_{SI} was set at 0.99 because the overwhelming majority of infected individuals progress to AIDS given sufficient time. Communicability was arbitrarily set relatively low, at 5, because it requires exchange of fluids. Stability was arbitrarily set a 0.25 and the time to disease was based on eight years between infection and development of AIDS. In the second calculation the parameter of time was disregarded by setting it at 1.0.

For *Candida albicans* (Table I) the values used are based on rough estimates from data on human vaginal candidiasis. The F_{SI} was calculated from the study of Levison *et al.* [16] based on estimates from vaginal candidiases, where 5 out of a total 17 women with *Candida* in vaginal fluids had symptoms. The infective dose for *Candida* spp. is unknown; a value of 10^6 organisms is used based on the observation that women with candidal vaginitis had fungal burden in the range of Log_{10} 7.9–11 colony forming units per milliliter [16]. The communicability of *Candida* spp. is unknown but it must be contagious because it is acquired shortly after birth and there is some evidence that it can be transmitted between sexual partners [17]. Hence, we have arbitrarily set communicability at the low value of 5. Because *Candida* spp. are free-living organisms that can survive in the environment we have arbitrarily set the stability value at 0.75. The time to disease in humans is unknown and we have arbitrarily used five days.

Table I. Calculation of weapon potentials assuming the microbe is deliverable[a]

Pathogen	Agent class	V_{BW}		C	S	T	WP
		Fraction symptomatic	Inoculum				
Bacillus anthracis	A	0.008	8000	1.0	1.0	14.2	7.0×10^{-8}
	A	0.0008	50	1.0	1.0	14.2	1.1×10^{-6}
	A	0.0008	1	1.0	1.0	14.2	5.6×10^{-5}
Variola virus	A	0.76	100	90	0.25	10	1.7×10^{-2}
HIV	Not on list	0.99	1000	5	0.25	2920	4.2×10^{-7}
	Not on list	0.99	1000	5	0.25	1.0	1.2×10^{-3}
Candida albicans	Not on list	0.29	7.9×10^8	5	0.75	5	2.7×10^{-10}

[a]Abbreviations: C, communicability; S, stability; T, time to disease in days; V_{BW}, virulence of a biological weapon; WP, weapon potential.

could be Ebola virus, where the X parameter would enhance the WP values calculated. Conversely, for organisms that have low mortality and for which prophylactic and therapeutic measures are available, the X parameter would reduce the value of the calculated WP. Another variable that influences the weapon potential of a microbe is the deliverability (D) of the agent, which is a function of the technical capabilities of the user and the biological characteristics of the microbe. Although this parameter is not fully independent of stability and communicability we have treated it differently, because deliverability is a major consideration in assessing the threat potential of microbes. We have arbitrarily set the value $0 \leq D \leq 1$, such that 0 denotes a situation where the microbe cannot be delivered and 1 describes a condition where microbial delivery is highly efficient and technological hurdles do not exist. Therefore, the WP formula can be modified to be $WP = [V_{BW}SC/T]XD$.

B. anthracis spores are regarded to have high potential as a biological weapon largely because these can be weaponized to enhance their ability to be deliverable to susceptible populations. By contrast, HIV might not be considered to have high weapon potential because infection would require parenteral inoculation or sexual contact. However, given sufficient time HIV can spread in a susceptible population as evidenced by the experience in sub-Saharan Africa where a significant proportion of the population is infected. In contrast to other parameters, the value of D is highly dependent on the technological prowess of the user. Technological advancements can significantly increase the value of D as shown by the relative ease with which weaponized *B. anthracis* spores can be disseminated.

It is immediately apparent that even for this simple relationship we lack the information to accurately calculate the WP for the overwhelming majority of pathogenic microbes. Even for well-studied agents, such as *B. anthracis*, variola virus and HIV, the calculation of WP must rely on a series of assumptions, which raise uncertainty on the calculated WP (Box 1). For example, the inoculum necessary to cause infection or disease for any of these agents in humans is not known and the best we can do is to provide an educated guess on that number. However, it is clear that the size of the inoculum is a critical parameter in determining the WP of a microbe and how one defines this variable will have a great impact on

Box 2. Uses of the weapon potential formula

- Defines the parameters that need to be known to adequately assess the weapon potential (WP) of a microbe.
- Provides a quantitative approach to classifying the potential of a microbe as a biological warfare agent.
- Can be applied to newly discovered microbial pathogens to assess their potential as biological warfare agents relative to known agents. Consider the case of severe acute respiratory syndrome (SARS)-associated coronavirus [12]. Estimates of the virulence of a biological weapon (V_{BW}) can be made from literature sources. The report of 22 cases of SARS among 119 individuals traveling in an airplane carrying a symptomatic patient with SARS yields a fraction symptomatic (F_{SI}) of 0.18 assuming that every individual in the plane was exposed to virus-contaminated air [18]. This value is consistent with the attack rates of 10.3–60% that were recorded among intensive care nurses during the outbreak in Toronto, Canada [19]. The inoculum needed for human infection is unknown but for the purposes of the calculation we will assume a value of 1000 viral particles. This estimate is inferred from the dose of coronavirus needed to induce an immunological response in cats infected lintratracheally [20]. However, this inoculum might be an over-estimate, given that for another coronavirus a dose of 112 plaque forming units is $10LD_{50}$ [21]. The communicability (C) of SARS was considered high and a value of 50 was used, which might be also an underestimate. Because the SARS agent is a virus we use a stability factor of 0.25 to be consistent with the other viruses that are mentioned in Table I in Box 1 within the main text, although this value might also be an underestimate because the survival ability of SARS coronavirus has been described as strong [22]. The time between exposure and disease for SARS ranges from 1 to 20 days with a mean duration of 5.9 days [23]. From these numbers one can calculate a WP as follows: $WP = (0.18/1000)(50)(0.25)(1/5.9) = 3.5 \times 10^{-4}$. On the basis of this estimate one could conclude that SARS coronavirus has a weapon potential that is intermediate between variola and *Bacillus anthracis*. When one reviews the numbers, it is clear that the data for F_{SI} and the time to disease are robust from the intensive epidemiological investigation that followed the SARS outbreak, whereas data for inoculum, stability and communicability are lacking and necessitate extrapolation and estimation. Therefore, the formula also serves to identify areas that need to be studied to properly assess the WP of certain microbes.
- Suggests direction for future research for developing treatments and preventative measures for agents of bioterror.
- Provides an educational tool by delineating the parameters that contribute to making some microbes biological weapons.

the final assessment of microbial capabilities. For example, although the LD_{50} for anthrax is between 4100 and 8000 *B. anthracis* spores, and extrapolation from monkey studies indicates that the LD_{10} is 50–98 spores and the LD_1 is 1–3 spores [11], the use of an LD_1 is justifiable when considering the weapon potential of a microbe. Therefore, for *B. anthracis* the WP is more than 1000-fold larger using LD_1 than LD_{50} (Box 1).

We believe that the formula proposed here provides a first step toward designing a rigorous system for evaluating extant and yet undiscovered microbes for their weapon potential, and that such use of a method could allow modifications to the select list that might lead to a more realistic identification of the threats we face now and that humanity might confront in the future. As shown in Box 2, this approach can be used to gauge the weapon potential of new agents, such as the coronavirus associated with severe acute respiratory syndrome (SARS) [12]. Furthermore, this approach suggests areas for investigation when assessing the threat posed by pathogenic microbes and when making policies for vaccination and other interventions.

Acknowledgements

We thank Dr. Matthew D. Scharff for critical reading of this manuscript. AC is supported by AI057158, AI033142, AI033774 and 5U54AI057158, and LP is supported by AI035370, AI044374 and AI045459.

References

1 Hayes, R.A. and Richardson, B.J. (2001) Biological control of the rabbit in Australia: lessons not learned? *Trends Microbiol.* 9, 459–460
2 Franz, D.R. *et al.* (1997) Clinical recognition and management of patients exposed to biological warfare agents. *J.A.M.A.* 278, 399–411
3 Casadevall, A. and Pirofski, L. (1999) Host–pathogen interactions: redefining the basic concepts of virulence and pathogenicity. *Infect. Immun.* 67, 3703–3713
4 Casadevall, A. and Pirofski, L. (2001) Host–pathogen interactions: the attributes of virulence. *J. Infect. Dis.* 184, 337–344
5 Casadevall, A. and Pirofski, L. (2003) On the definition of virulence. *ASM News* 69, 217
6 Heiner, G.G. *et al.* (1971) A study of intrafamilial transmission of smallpox. *Am. J. Epidemiol.* 94, 316–326
7 Guerra, F. (1993) The European-American exchange. *Hist. Philos. Life Sci.* 15, 313–327
8 Wheelis, M. (2002) Biological warfare at the 1346 siege of Caffa. *Emerg. Infect. Dis.* 8, 971–975
9 Anonymous, (1996) Zimbabwe to criminalise the deliberate spreading of HIV. *Pac. AIDS Alert Bull.* 15
10 Casadevall, A. and Pirofski, L. (2000) Host–Pathogen Interactions: The basic concepts of microbial commensalism, colonization, infection, and disease. *Infect. Immun.* 68, 6511–6518
11 Peters, C.J. and Hartley, D.M. (2002) Anthrax inhalation and lethal human infection. *Lancet* 359, 710–711
12 Holmes, K.V. (2003) SARS coronavirus: a new challenge for prevention and therapy. *J. Clin. Invest.* 111, 1605–1609
13 Brookmeyer, R. *et al.* (2001) The statistical analysis of truncated data: application to the Sverdlovsk anthrax outbreak. *Biostatistics.* 2, 233–247
14 Anonymous, (2003) Follow-up of deaths among U.S. Postal Service workers potentially exposed to *Bacillus anthracis*–District of Columbia, 2001-2002. *MMWR Morb. Mortal. Wkly. Rep.* 52, 937–938
15 Weusten, J.J. *et al.* (2002) Mathematic modeling of the risk of HBV, HCV, and HIV transmission by window-phase donations not detected by NAT. *Transfusion* 42, 537–548
16 Levison, M.E. *et al.* (1979) Quantitative bacteriology of the vaginal flora in vaginitis. *Am. J. Obstet. Gynecol.* 133, 139–144
17 Dromer, F. *et al.* (1997) Oral transmission of *Candida albicans* between partners in HIV-infected couples could contribute to dissemination of fluconazole-resistant isolates. *AIDS* 11, 1095–1101
18 Olsen, S.J. *et al.* (2003) Transmission of the severe acute respiratory syndrome on aircraft. *N. Engl. J. Med.* 349, 2416–2422
19 Varia, M. *et al.* (2003) Investigation of a nosocomial outbreak of severe acute respiratory syndrome (SARS) in Toronto, Canada. *CMAJ* 169, 285–292
20 Baldwin, C.W. and Scott, F.W. (1997) Attempted immunization of cats with feline infectious peritonitis virus propagated at reduced temperatures. *Am. J. Vet. Res.* 58, 251–256
21 Koo, M. *et al.* (1999) Protective immunity against murine hepatitis virus (MHV) induced by intranasal or subcutaneous administration of hybrids of tobacco mosaic virus that carries an MHV epitope. *Proc. Natl. Acad. Sci. U. S. A.* 96, 7774–7779
22 Duan, S.M. *et al.* (2003) Stability of SARS coronavirus in human specimens and environment and its sensitivity to heating and UV irradiation. *Biomed. Environ. Sci.* 16, 246–255
23 Wu, W. *et al.* (2003) A hospital outbreak of severe acute respiratory syndrome in Guangzhou, China. *Chin Med. J. (Engl)* 116, 811–818