Therapeutic challenges posed by bacterial bioterrorism threats
Peter H Gilligan

The events of the autumn of 2001 in the United States made it clear that the spectre of the use of microorganisms to intentionally harm humans is a reality. The current strategy to control disease outbreaks caused by the intentional release of bacteria is to use antimicrobial agents, both therapeutically and prophylactically. However, multidrug-resistant strains of bacterial bioterrorism agents occur naturally or have been bio-engineered, indicating how vulnerable this strategy is.

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Abbreviations
BT bioterrorism
CDC Centers for Disease Control and Prevention
MIC minimum inhibitory concentration
TMP/SMX trimethoprim/sulfamethoxazole

Introduction
In April 2000, the Centers for Disease Control (CDC) in the United States released a strategic plan for responding to a bioterrorism (BT) attack [1]. In that report, they categorized several infectious agents, including three bacteria, *Bacillus anthracis*, *Yersinia pestis*, and *Francisella tularensis*, that were likely to be used as BT agents for three reasons. First, these agents are either easily transmitted (*B. anthracis* and *F. tularensis*) or they can be spread from person to person (*Y. pestis*); second, they have the potential to cause high mortality; and third, their release might result in public panic and disorder. They designated these organisms as ‘category A’.

A second group, designated as category B, were judged to be less dangerous but still a cause for concern. Three additional bacteria, *Brucella* spp., *Burkholderia pseudomallei*, and *Burkholderia mallei*, were listed. Both *Brucella* and *B. mallei* also have the potential for being used in agro-terrorism, since both are primarily animal pathogens, whereas *B. pseudomallei* is a human pathogen.

In October 2001, the hypothetical concerns surrounding the use of microbes as BT agents became reality with the recognition of a fatal case of anthrax in a Florida man [2**]. Over the next few months, another ten individuals developed inhalational anthrax, four of whom died. Eight confirmed cutaneous cases of anthrax also occurred but with no fatalities [3**,4]. It is now clear that a series of letters containing anthrax spores, sent through the US mail, were responsible for this outbreak. Because large numbers of individuals were potentially exposed to these spores via handling tainted letters or being present when such letters were opened, thousands of individuals received antimicrobial prophylaxis, with most taking ciprofloxacin and a small minority receiving doxycycline or amoxicillin [5].

Because infections with the category-A and -B organisms listed above are so uncommon in the industrialized world, there is limited knowledge on the frequency of and how best to detect in vitro drug resistance of these organisms. The understanding of the effectiveness of various antimicrobial regimens in treating infections with these organisms or their prophylactic use is limited. In this review, these issues will be examined for the six bacterial agents listed in Table 1.

*Bacillus anthracis*
Of the six agents to be discussed here, *B. anthracis* is the only organism that has been used during the antibiotic era as a BT agent. There is relatively little known about the mechanisms of drug resistance in this organism and the correlation of in vitro susceptibility to in vivo efficacy. Susceptibility studies done at the CDC [6**] by broth microdilution using *Staphylococcus aureus* breakpoints [7] showed all strains tested to be susceptible to the recommended antimicrobials, ciprofloxacin and tetracycline (doxycycline), as well as to chloramphenicol, rifampin and vancomycin. Antimicrobials that were less active against *B. anthracis* were erythromycin, clindamycin and ceftriaxone. The *B. anthracis* isolates tended to have reduced susceptibility to these three agents rather than being resistant, however. One of 65 isolates studied was highly resistant to penicillin. This finding is in keeping with the reports of infections caused by penicillin-resistant *B. anthracis* isolates [8,9]. This is an important observation, since penicillin is still frequently cited in textbooks and antibiotic pocket-guides as a treatment of choice for anthrax infections [10,11].

A French group determined the antimicrobial susceptibility of a fairly large number (\(n=95\)) of environmental and animal isolates of *B. anthracis*. The susceptibility of these isolates was similar to those of the human isolates tested by the CDC [12**]. Penicillin resistance was more common in this group of isolates (observed in 11.5%). All isolates had reduced susceptibility to ceftriaxone. Interestingly, all 96 produced \(\beta\)-lactamase, as measured by nitrocefin hydrolysis. It has been reported that this \(\beta\)-lactamase is a constitutive cephalosporinase [13]. These data indicate that cephalosporins should not be used therapeutically for anthrax. This is an important observation because ceftriaxone and cefotaxime are used frequently as empiric therapy in immunocompetent hosts who present with a clinical syndrome consistent with septic shock, a clinical presentation also consistent with fulminant anthrax [2**].

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**Table 1.** Bacterial agents categorized by the CDC as potential BT agents

<table>
<thead>
<tr>
<th>Category</th>
<th>Organism</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td><em>B. anthracis</em></td>
<td>High potency, high mortality</td>
</tr>
<tr>
<td>A</td>
<td><em>Y. pestis</em></td>
<td>High potency treponematosis, bubonic plague</td>
</tr>
<tr>
<td>A</td>
<td><em>F. tularensis</em></td>
<td>High potency tularemia</td>
</tr>
<tr>
<td>B</td>
<td><em>B. anthracis</em></td>
<td>Low potency, low mortality</td>
</tr>
<tr>
<td>B</td>
<td><em>B. mallei</em></td>
<td>Low potency, low mortality</td>
</tr>
<tr>
<td>B</td>
<td><em>B. pseudomallei</em></td>
<td>Low potency, low mortality</td>
</tr>
</tbody>
</table>

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An additional question that must be resolved is whether the presence of β-lactamase production, as measured by nitrocefin hydrolysis, predicts the likelihood of therapeutic failure by penicillin. All isolates were doxycycline- and ciprofloxacin-susceptible. Although these data are encouraging, reports exist in the literature concerning the development of B. anthracis strains resistant to a variety of antimicrobial agents. Strains have been developed by repeated passage on antibiotic-containing medium to the primary therapeutic and prophylactic agents — doxycycline and the fluoroquinolones, as well as rifampin [14,15]. Rifampin was used frequently with other antimicrobials to treat patients with inhalational anthrax during the recent US outbreak [2••]. Most disturbing was the development by recombinant technology of a multidrug-resistant strain of B. anthracis by Russian scientists [16]. This bio-engineered strain was resistant to penicillin, rifampin, tetracycline, chloramphenicol, erythromycin and clindamycin. Although the scientists suggested that such a genetic construct could be used as a vaccine strain in conjunction with antimicrobial therapy during a large-scale bioterrorism event, Ken Alibek, the former first deputy chief of the Biopreparat in the Soviet Union, argues in his book Biohazard [17] that multidrug-resistant strains of a variety of organisms were being developed as offensive weapons.

Two well-documented outbreaks of inhalational anthrax caused by weapon-grade organisms have been reported in the medical literature. In a 1979 outbreak in Sverdlovsk, Russia, where anthrax spores were released accidentally from a bioweapons manufacturing facility, mortality occurred in 66/77 (86%) patients with inhalational anthrax. These patients were treated with penicillin, chloramphenicol and cephalosporins, as well as with anti-anthrax serum; but no details concerning the antibiotic regimens or the antimicrobial susceptibility of the isolates were reported [18]. In the recent US outbreak, only 5/11 (45%) with inhalational anthrax died [2••,3••]. These patients typically received multiple antimicrobials to which the organism was susceptible. Frequently used antimicrobials include fluoroquinolones, rifampin, doxycycline, clindamycin, penicillin and cephalosporins. Patients who survived presented in what was judged to be the initial stages of the illness and received multiple antimicrobials to which the organism was susceptible in vitro. Of the five patients who died, all had fulminant disease at presentation and received treatment with at least one antimicrobial active against B. anthracis in vitro. This would suggest appropriate antimicrobial therapy given early in the disease course is essential for survival.

The programme of prophylactic antimicrobial therapy proved to be highly effective in preventing inhalational anthrax in a large number of at-risk individuals. The total number of individuals who received prophylaxis has not yet been reported. Among over 8000 postal workers who received prophylaxis primarily with ciprofloxacin, only 8% discontinued prophylaxis and only 3% discontinued because of adverse events. No individual receiving prophylaxis developed a B. anthracis infection [5]. There is some controversy on the exact length of prophylaxis, but current recommendations and clinical experience suggest 60 days is adequate for both ciprofloxacin and tetracycline [3••,13].

One of the keys to success in managing future BT attacks with B. anthracis is to be able to detect antimicrobial resistance in these isolates. Currently, there is only very limited data on the accuracy of susceptibility testing methods for B. anthracis. Only two studies in the past 10 years have tested a large number of B. anthracis isolates [6••,12••]. One used agar dilution, a technique that would be difficult to use outside a research setting or with individual patient isolates [12••]. The other used broth microdilution and compared those results with those obtained by using the E-test, an agar gradient diffusion technique. The E-test is easy to use and is widely available, making it an ideal test system in the event of such an emergency. Unfortunately, E-test did not compare well with broth microdilution.

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**Table 1**

Therapeutic and prophylactic recommendations for category A and B bacterial agents of bioterrorism.†

<table>
<thead>
<tr>
<th>Agent</th>
<th>Disease</th>
<th>Therapeutic</th>
<th>Prophylactic</th>
</tr>
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<tbody>
<tr>
<td>Bacillus anthracis</td>
<td>Anthrax</td>
<td>Ciprofloxacin or doxycycline, and one or two additional antimicrobials</td>
<td>1° ciprofloxacin or amoxicillin</td>
</tr>
<tr>
<td>Yersinia pestis</td>
<td>Plague</td>
<td>1° streptomycin or gentamicin</td>
<td>1° doxycycline or ciprofloxacin</td>
</tr>
<tr>
<td>Francisella tularensis</td>
<td>Tularemia</td>
<td>2° doxycycline, ciprofloxacin or chloramphenicol</td>
<td>2° chloramphenicol</td>
</tr>
<tr>
<td>Burkholderia pseudomallei</td>
<td>Melioidosis</td>
<td>1° ceftazidime or imipenem</td>
<td>None available</td>
</tr>
<tr>
<td>Burkholderia mallei</td>
<td>Glanders</td>
<td>None available</td>
<td>None available</td>
</tr>
<tr>
<td>Brucella spp.</td>
<td>Brucellosis</td>
<td>1° streptomycin/doxycycline or gentamicin/doxycycline</td>
<td>None available</td>
</tr>
</tbody>
</table>

†Recommendations are based on either JAMA consensus documents [3••,19•,28] or from a widely used antibiotic pocket guide [10] and infectious disease textbook [11].
Specifically, the E-test gave much lower minimum inhibitory concentrations (MICs) for penicillin, calling to question whether this technique could detect accurately penicillin resistance [6••]. This is an issue of central importance, since penicillin is an important alternative antimicrobial for treatment of anthrax provided that the isolate is susceptible to penicillin [3,13]. No data currently exist on the accuracy of disk diffusion or commercial susceptibility systems to detect drug resistance in B. anthracis.

**Yersinia pestis**

*Yersina pestis* is the etiological agent of both bubonic and pneumonic plague. *Y. pestis* is an endemic zoonotic disease in the south-western United States and primarily causes bubonic plague in humans [19••]. Plague is also an endemic disease in Africa, Asia and South America [19••].

The drug of choice for treating plague is streptomycin, with gentamicin recommended as an alternative agent because of the limited availability of streptomycin. Chloramphenicol, doxycycline and ciprofloxacin are recommended as alternative therapeutic agents as well as prophylactic ones. These recommendations are supported by excellent *in vitro* activity of these agents [20–23], clinical experience [19••,23], and superior efficacy in animal models of pneumonic plague [24]. Although studies have shown that β-lactams have good activity *in vitro* [20–22], animal-model studies indicate that they are not as effective *in vivo* [24].

Although several surveys have found *Y. pestis* strains to be highly susceptible to all the antimicrobials recommended for treatment or prophylaxis [20–23], reports of drug resistant strains of *Y. pestis* in Madagascar are cause for concern [25,26••]. Over 500 confirmed cases of the bubonic form of this disease were detected there in the late 1990s. Two different drug-resistant strains were recovered from adolescent boys with bubonic plague. The first strain carried a plasmid that encoded for resistance to ampicillin, streptomycin, chloramphenicol and tetracycline [25]. The organism produced TEM-1 β-lactamase, chloramphenicol acetyltransferase, and a streptomycin-modifying enzyme. The second strain carried a plasmid that encoded for the streptomycin-modifying phosphotransferase gene that resulted in high-level streptomycin resistance [26••]. Both organisms contained a plasmid that could be transferred to other *Y. pestis* strains as well as to *Escherichia coli*. It is important to remember that *Y. pestis* is a member of the Enterobacteriaceae and as such is likely to be able to exchange genetic material with multiple genera within this family of organisms. This means that multidrug-resistant plague bacilli can be selected for naturally or could be easily bioengineered.

Little is known about the accuracy and reproducibility of antimicrobial susceptibility testing of *Y. pestis* isolates. Because *Y. pestis* is a member of the Enterobacteriaceae, there are National Committee on Clinical Laboratory Standards (NCCLS)-approved methods for testing these isolates [7]. However, no formal studies comparing commercial susceptibility testing systems frequently used in clinical laboratories with broth microdilution reference methods are available. Therefore, the accuracy of the commercial systems in predicting drug resistance in *Y. pestis* is unknown. A real-time PCR assay for detection of ciprofloxacin-resistant *Y. pestis* has been developed by the US Army in anticipation of the use of *Y. pestis* as a BT agent bioengineered to be resistant to ciprofloxacin [27].

**Francisella tularensis**

*F. tularensis*, a fastidious Gram-negative bacillus, is the etiological agent of tularemia. Although *F. tularensis* can be spread by both water and ticks, its greatest potential as a BT agent would be release as an aerosol [28••]. Such a release would result in a large number of non-specific febrile illnesses, with some developing a pleuropneumonitis over the intervening days and weeks. Morbidity and mortality is not anticipated to be as high as that seen with plague or anthrax, but it would still be significant [28••].

The recommended therapeutic and prophylactic agents for tularemia are the same as those for plague (see Table 1). *In vitro* susceptibility testing is problematic for *Francisella* because the organism is slow-growing and requires enriched medium. There also is concern about transmission of this agent in the laboratory [29]. There are limited data on the *in vitro* activity of antimicrobials against *F. tularensis*. It is well recognized that *F. tularensis* is a β-lactamase producer and as such β-lactam antimicrobials lack activity against this organism [30]. The *in vivo* correlate of patients infected with tularemia failing ceftriaxone therapy has been documented in the literature [31]. *In vitro* susceptibility data support the use of the aminoglycosides, chloramphenicol, tetracycline and fluoroquinolones [32,33]. Currently, fluoroquinolones appear to be the most active agents, both *in vitro* and *in vivo* against *F. tularensis*, with relapse less likely following therapy with this antimicrobial than with streptomycin and doxycycline [34,35••,36,37], although there is not universal agreement in the literature on this point [38].

One of the challenges that exists in evaluating the activity of antimicrobials against *F. tularensis* responsible for outbreaks is having clinical isolates to test. In a recent outbreak in Martha’s Vineyard, MA, USA, only one of 15 patients judged to be infected had a micro-organism recovered from clinical specimens [39••]. The laboratory diagnosis of tularemia is much more likely to be made using PCR or serology [39••,40••]. Although PCR is a very attractive diagnostic tool because of its superior sensitivity and speed compared with culture, the ability to detect antimicrobial resistance by this method is currently not available. Isolation of organisms continues to be essential for the detection of drug resistance.

**Brucella, Burkholderia mallei and pseudomallei**

Of these category-B organisms, *B. pseudomallei* is the most likely organism to harm humans, while *Brucella* and
B. mallei are more likely to target animals and to be used as agents of agro-terrorism. Currently, there are no consensus recommendations for treatment of these agents although there is extensive medical literature on the treatment of human infections caused by both B. pseudomallei and Brucella. There are also no well-standardized susceptibility-testing methods for these organisms. Over the past 50 years, only one human case of B. mallei has occurred in the industrialized world, seen in a laboratory scientist who was working with this organism in a biodefence laboratory in the United States [41].

B. pseudomallei is the etiological agent of melioidosis, which can have several different manifestations. These include acute, septic episodes with mortality of 40%, or a more chronic pulmonary process that can mimic tuberculosis [42,43**]. Melioidosis is associated with environmental exposure to B. pseudomallei [42]. It is likely that this organism could be spread by aerosolization. Treatment of serious infections typically involves parenteral therapy usually with ceftazidime or, if available, imipenem, for two to four weeks followed by three to six months of oral eradication therapy, typically with either trimethoprim/sulfamethoxazole (TMP/SMX) or doxycycline [42,43**]. Relapse following appropriate antimicrobial therapy is a common problem [42,43**]. In patients who relapse, the development of resistance to the both TMP/SMX and doxycycline has been documented [43**.44]. No data exist as to what antimicrobial agents would be effective prophylactically. Antimicrobials used for oral eradication therapy would likely be appropriate for prophylaxis if in vitro susceptibility results indicate that the antimicrobials are active against the particular isolate that has been released.

The in vitro susceptibility of B. pseudomallei is based on NCCLS breakpoints for Pseudomonas aeruginosa. Most data generated for in vitro susceptibility have been done either by agar dilution or broth microdilution [43**.45,46]. Disk diffusion is not recommended for determining the susceptibility of B. pseudomallei [43**.47], although reports in the literature are based on this method [44,48]. E-tests have been found to be a reasonable method for determining susceptibility of this organism [43**]. The in vitro susceptibility of B. pseudomallei is similar to that of other Brucella species [46]. It usually is resistant to aminoglycosides and penicillin and to first-, second- and some third-generation cephalosporins owing to its ability to produce a β-lactamase [43**.45,46]. Isolates are frequently resistant to fluoroquinolones in vitro, so it is unlikely that this agent could be used either therapeutically or prophylactically [46,48]. Greater than 90% of isolates are susceptible to carbapenems, ceftazidime, amoxicillin/clavulanic acid, piperacillin, doxycycline, chloramphenicol and trimethoprim/sulfamethoxazole. It should be emphasized that susceptibility testing would be needed in a BT incident, since isolates resistant to many of these active antimicrobials occur naturally. Engineering of isolates resistant to many of these agents is clearly feasible since strains of the closely related organism Burkholderia cepacia resistant to all the antimicrobials listed here have been selected in patients on long-term antimicrobial therapy [49].

There is limited information in the modern medical literature concerning B. mallei. This is the etiological agent of glanders, a febrile illness that primarily attacks equine populations. Human infections are exceedingly rare. Because B. mallei has been developed as a biological weapon [1,41], there has been interest in learning more about the effectiveness of various antimicrobials in vitro and in animal models.

In vitro susceptibility data are available on only a limited number of isolates. By broth microdilution, B. mallei and B. pseudomallei have similar antimicrobial susceptibilities profiles, with the exception that B. mallei isolates were generally resistant to TMP/SMX and susceptible to aminoglycosides [46,50]. Large discrepancies were seen between microbroth MIC values and E-test MIC values for TMP/SMX, with E-test giving MIC values 100- to 1000-fold lower than broth microdilution values [50]. This suggests that MIC values for TMP/SMX obtained by E-test for this organism should be viewed cautiously. Animal-model data are very limited but suggest that both ciprofloxacin or doxycycline could be used prophylactically [51]; however much more data are needed before solid recommendations could be made. The one case of glanders seen in humans in the United States in the past 50 years was successfully treated with parenteral imipenem and doxycycline, followed by oral therapy with azithromycin and doxycycline [41].

The species of Brucella most frequently associated with human disease are B. suis (from pigs), B. melitensis (from sheep and goats) and B. abortus (from cattle and camels). Although animal populations are probably more likely targets of a BT attack with this organism, secondary infection in individuals working with the infected animals would be a clear danger. Brucella has the potential to be spread by aerosol, so it to could be used as a BT agent against human populations. Human disease is typically a chronic febrile illness that can mimic military tuberculosis [52]. Because this organism is a facultative intracellular pathogen, effective antimicrobial therapy should include an antimicrobial agent that can penetrate into phagocytic cells [53]. As with B. pseudomallei, relapse following antimicrobial therapy is a common clinical problem [54].

In a large, multicenter open-label trial done in Spain, the combination of streptomycin and doxycycline was found to be more efficacious than rifampin and doxycycline. Both therapeutic failure and relapse were more common in the rifampin/doxycycline arm of the study.

There are limited in vitro susceptibility data on the different Brucella species. There are three reasons for this: first, the diagnosis of Brucella infection is more likely to be made serologically than by culture isolation [54]. Second, the
organism is fastidious and slow-growing, making agar dilution susceptibility testing the method of choice [53,55,56]. Third, like Francisella, Brucella is dangerous to work with in the laboratory [57]. Fluoroquinolones, rifampin, doxycycline, TMP/SMX and streptomycin all have good in vitro activity against this genera [53,55,56]. Azithromycin is the most active of the macrolides against Brucella [53,56] and with its high penetration into phagocytic cells might warrant further study in animal models.

Currently, there are no recommendations for prophylaxis for brucellosis. On the basis of in vitro data and clinical experience with treating infection, a combination of doxycycline and rifampin is likely to be effective prophylactically. A reasonable alternative may be TMP/SMX in combination with either doxycycline or rifampin. Animal model data would be required before other prophylactic regimens could be recommended.

The future
There are several issues that will need to be addressed to meet the threat of the six organisms reviewed here. First, improved culture methods and biosafety facilities are needed to recover these agents from naturally occurring disease. For both F. tularensis and Brucella, either serology or PCR are frequently used to diagnose infection with these organisms [40••,54]. As a result, pathogenic strains are not available to assess the in vitro activity of current therapeutic agents or those under development. It also would not be possible to detect strains that have been bio-engineered to be resistant to antimicrobials recommended for treatment or prophylaxis. In addition, little is currently known about the mechanisms of drug resistance in several of these organisms. Studies are needed to delineate these resistance mechanisms and to identify novel antimicrobial targets.

The second issue that needs to be addressed is that currently of the six organisms discussed in this review, there are NCCLS-approved techniques for performing susceptibility testing on only Y. pestis [7]. It has been suggested in a JAMA consensus statement on plague [19•••] that there is not a standardized method for susceptibility of this organism, so even among experts there is disagreement on susceptibility testing. Most data generated for these organisms have been done using either agar dilution or microbroth dilution [6••,12••,33,43••,45,46,50,53,55,56]. Attempts to use the more user-friendly and versatile E-test technique have been problematic for some of these organisms [6••,50] and has not been attempted for others. Clearly, guidelines on what susceptibility techniques should be applied to screen for resistance to key antimicrobial agents need to be developed in the event of a widespread BT attack. These may include guidelines that state that susceptibility testing should only be performed in reference laboratories for certain agents such as Francisella because of the danger and technical difficulty of working with these agents. Others, such as B. anthracis and Y. pestis, may be able to be tested in most clinical laboratories.

It will be important that these guidelines include the agents for which each isolate should be tested, because of the well-documented discrepancy between in vitro susceptibility testing and in vivo efficacy [24]. For example, ceftazidime has been shown to be highly active in vitro against Y. pestis [21], but to lack efficacy when compared with recommended therapeutic agents in treating experimental pneumonic plague in animals [24]. It will also be important to understand whether commercial susceptibility systems will be accurate and safe enough to be useful in assessing the in vitro resistance of these organisms.

Third, as new therapeutic agents are sought, carefully designed animal studies will be needed early in the discovery process to insure that compounds that show promise in vitro are active in animal disease models. Because infections in humans are so rare for F. tularensis, Y. pestis, B. mallei and B. anthracis, surrogate clinical trials in animal models will be needed to judge efficacy [58]. For Brucella and B. pseudomallei found primarily in poor, rural populations frequently far from Western-style medical care facilities, clinical trials of new agents will need to be supported both economically and ethically [42]. Safety studies of new compounds will be particularly important so that an understanding will be gained of the potential adverse events that may occur with wide-scale prophylactic use of these agents. Companies planning on assessing the activity of new antimicrobials against bioterrorism agents will have the added problem of obtaining and securing these pathogens in their facility or finding partners who will perform the necessary in vitro compound screening and animal studies. The National Institutes of Health, as part of its biodefence response, is currently planning on building and making available to interested parties biosafety level 3 and 4 space, which can be used in drug and vaccine development against BT agents.

The fourth issue to address is the spectre of bioengineered organisms, a grave concern. It is highly feasible to construct highly virulent organisms resistant to antimicrobials that are used for both treatment and prophylaxis. Imagine the difficulties that would have existed if the B. anthracis event that occurred in the autumn of 2001 was caused by a strain engineered to be resistant to ciprofloxacin and tetracycline. Current JAMA consensus statements [3••,19••,28••] make clear the recommended strategies for combating BT organisms. It is apparent that a defence plan built on prophylactic antimicrobials is highly vulnerable, given that multidrug-resistant plague bacilli have occurred naturally and multidrug-resistant agents can be constructed using recombination technology [16,25]. Vaccines have been a highly effective means of preventing infectious diseases and play a central role in our strategy to combat a smallpox attack [59]. It is clear that our national biodefence strategy must include the development of vaccines against multidrug-resistant strains of anthrax and plague to protect the population.
A perhaps less likely threat, but one that must be taken seriously, is the possibility of the creation of genetic constructs through recombination technology which combine the traits of several pathogens to create a highly transmissible, virulent and drug-resistant organism. Such an organism is called a chimera. Alibek and Handleman [17] describe work on chimeras being carried out by Soviet scientists. Such organisms would be a true test of our ability to respond to a public health emergency. However, the HIV epidemic has taught us that we can quickly respond to global public health emergencies and develop diagnostics, therapies, and hopefully soon vaccines, that can control a newly recognized infectious agent. Let us hope that we will not have to face such a challenge caused by the construction by humans of a deadly pathogenic organism to harm other humans.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:
• of special interest
•• of outstanding interest


8. Bradaric 7. NCCLS: that the E-test may not detect resistance to penicillin accurately. Comparison of the standard broth dilution methods with the E-test indicates that the E-test may not detect resistance to penicillin accurately.


B. pseudomallei is not uniformly susceptible to cefazidime, imipenem, doxycycline, and trimethoprim/sulfamethoxazole (TMP/SMX), making drug-susceptibility testing critical to the management of this disease. The drug resistance can develop during oral therapy with both doxycycline and TMP/SMX.


