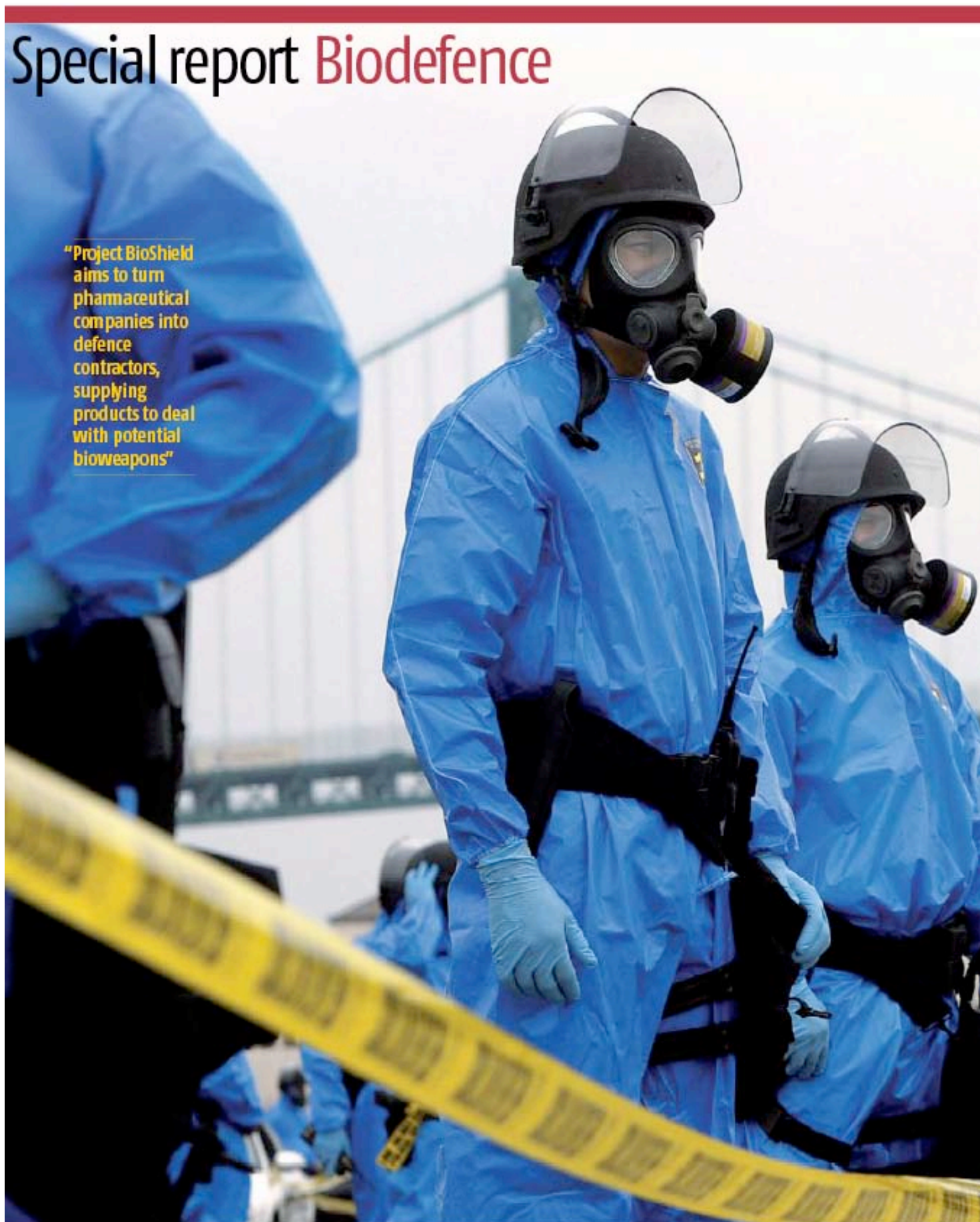


Special report **Biodefence**

“Project BioShield aims to turn pharmaceutical companies into defence contractors, supplying products to deal with potential bioweapons”



FORTRESS AMERICA?

Despite spending a fortune on biodefence, the US appears as vulnerable as ever to a concerted terrorist attack. More effective defences could be developed and deployed, but not without a change of strategy by the federal government

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IT WAS the nightmare many had been expecting. Five years ago, hard on the heels of 9/11, someone sent anthrax spores through the US mail to journalists and politicians. Five people died, and at least 17 more got sick. The culprit was never caught.

This relatively unsophisticated attack confirmed fears, already growing in the US, that with a bit more effort a determined bioterrorist could spread disease and mayhem across the nation. To combat the threat, the Bush administration launched an unprecedented biodefence effort. To

date it has spent \$44 billion – three-quarters of it aimed at protecting civilians – on new organisations, training, and buying existing remedies such as the classic smallpox vaccine.

Has this massive spending made Americans any safer? According to experts at the Center for Biosecurity at the University of Pittsburgh, the answer is no. Last month, they announced that the US remains unable to defend itself against any anthrax attack involving more than a few envelopes. So what has gone wrong?

The centrepiece of the administration's biodefence effort is Project BioShield. Launched in



How will preparations stand up in a real emergency?

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2004, it is designed to turn drug companies into defence contractors, delivering products to counter potential bioweapons. Project BioShield has \$5.6 billion to spend by 2014 on drugs to be stored in what is known as the Strategic National Stockpile. Yet, contrary to expectations, the pharmaceutical industry has not beaten a path to Project BioShield's door. The sluggish response has prompted a bill in Congress, expected to pass this year, that attempts to make BioShield more industry friendly (see "Into the valley of death", opposite).

Missing the point

Yet many biosecurity specialists say these adjustments do nothing to alter the fact that Project BioShield may be missing the point. They see problems in two crucial areas: the limited range of pathogens that BioShield is targeting, and inadequate plans for deploying the countermeasures it does have.

On the face of it, BioShield's underlying strategy seems sensible. Normally companies don't make remedies for the rare diseases thought most likely to be used as weapons, as there is no profit in it. So BioShield promises companies that it will buy particular drugs and vaccines for the threats it fears most, in theory giving the companies an incentive to do the rest.

Why, then, has the response so far been so unimpressive? Project BioShield has awarded contracts for seven products, worth \$2 billion. Two are for antibody-based therapies for botulism and anthrax. One is for 10 million doses of the military's existing anthrax vaccine – a concoction of bacterial debris whose alleged side effects have led some soldiers to prefer court-martial to vaccination. The single biggest slice of funding, \$878 million, has been pledged to VaxGen of Brisbane, California, for 75 million doses of a purer, new-generation anthrax vaccine. An order is also expected for 20 million doses of an improved smallpox vaccine from the Danish firm Bavarian Nordic, while Project BioShield has provided \$4 million to universities to fund basic pathogen research.

This is new territory for a government agency, which may explain the slow start. "The government has never done anything



like this before," says Brad Smith of the Center for Biosecurity. The Department of Homeland Security must first decide what "designated threats" to target – and then the Department of Health commissions drugs or vaccines designed to protect against them. So far the diseases it has picked extend to anthrax, botulism and smallpox.

This targeted "one bug, one drug" approach is, however, seen by some biodefence specialists as fundamentally misguided. Ken Alibek, head of the Soviet and then Russian bacterial weapons programme until 1992, says it allows attackers to create pathogens that evade or resist each remedy as fast as it is developed. "Based on the former Soviet model, it takes three to four years to engineer a drug-resistant or more virulent pathogen," he says. "It takes 10 to 15 years to develop a vaccine and have it approved." Jonathan Tucker of the Center for Nonproliferation Studies, a think tank in Washington DC, agrees. "It is myopic to focus on the designated threat organisms," he says, "especially when the bigger threat is probably from natural disease."

A better approach, these critics say, would be to aim for broad-spectrum remedies that work against many different bacteria or viruses. That would be more cost-effective, offer a blanket defence against terrorists whatever their choice of bioweapon,

Hospitals will face a surge of patients following any attack

"Broad-spectrum remedies would come with the enormous extra benefit of protecting against natural diseases too"

and come with the huge additional benefit of protecting against natural diseases too. "If something works for flu and for bioweapons as well, why not do that?" says Tucker.

BioShield has not pursued broad-spectrum remedies, partly because it is not allowed to fund anything that might be profitable in its own right. But according to Tucker, drug firms aren't making broad-spectrum antivirals precisely because they don't see them as profitable. "This is the sort of market failure that governments are supposed to step in and remedy if it is in the public interest," he says.

The Department of Defense, which provides biodefence for soldiers rather than civilians, seems less inhibited. This year it started awarding research grants under the new Transformational Medical Technologies Initiative, which aims to attack the common structures and functions of pathogens. That should lead to remedies effective against many organisms, including emerging diseases or genetically modified bioweapons.

James Joyce of Aethlon Medical in San Diego, California, which makes a device that removes viruses from blood, hopes this signals a new direction for Project BioShield. "The DoD's recent shift to broad-spectrum post-exposure therapeutics will set the tone for changes in BioShield, or perhaps new legislation," he says. Some companies already involved in BioShield seem to agree. PharmAthene is merging with Siga Technologies, based in New York City, which is developing broad-spectrum antibacterials as well as a promising smallpox drug.

Whatever countermeasures are developed, they will be pointless unless they can be delivered in a timely and effective way. This is the second area where critics say Project BioShield falls short. While the federal government buys and stockpiles biodefence remedies, more than 3,000 separate state, city and tribal administrations are expected to deliver them to the US population in an emergency, and the public health agencies they rely on to do the job have been underfunded for decades. The chaotic response to hurricane Katrina last year showed how easily state and local resources can be overwhelmed in the absence of help from Washington.

The Center for Biosecurity estimates that state public health departments have received an extra \$4 billion since 2001 to equip labs and hire epidemiologists and "bioterrorism coordinators". Similar amounts have gone to hospitals and local governments for bioterrorism "preparedness". Despite this, it says hospitals' capacity to absorb an unexpected surge of patients from an attack – or an epidemic – has not improved, because relatively little money has been spent on that aspect.

Research by Tucker and Andrew Grotto of the Center for American Progress, another Washington DC think tank, shows far more effort is required. "Only seven states and four cities have the capability to administer stockpiled vaccines on a large scale," Tucker says. More than half of all Americans live in states that have no plans for dealing with large numbers of casualties from any cause, he adds, and only two states

"Only seven states and four cities have the capability to administer stockpiled vaccines on a large scale"

have plans for encouraging medical personnel to report for work during an outbreak of contagious disease.

The bill now before Congress attempts to address some of these problems. It creates a new assistant health secretary for public health, improves planning and equipment for medical emergencies, and provides \$1 billion a year funding. But this may not be enough to solve the delivery problem, or give hospitals the capacity to deal with a surge in patients.

An additional problem is that most vaccines have to be given well before any outbreak or bio-attack. Yet vaccinating the general population against every likely bioterror agent is a prohibitively expensive non-starter, Alibek says. So vaccines developed under BioShield – one for Ebola is likely – would probably only be used after an attack, to keep the disease from spreading to uninfected people. That

means planning in advance where to go and who to vaccinate, and having enough people on the ground to do it – preferably people who are themselves vaccinated. None of these conditions is met by any of the US's overburdened public health agencies, for any of the diseases considered the most likely to be exploited in a bio-attack. An effort to create such a corps of responders by vaccinating healthcare workers against smallpox failed in 2003 (*New Scientist*, 23 August 2003, p. 6).

Any vaccine also carries some risk, however small, of side effects. If a vaccination drive were to be launched against a threat that failed to materialise, people who suffered side effects might feel they had been damaged needlessly, and sue the vaccine maker. That happened after 1976 when thousands of Americans were vaccinated against a swine flu epidemic that never occurred.

With this in mind, at the end of last year Congress made a last-minute addition to a big defence bill that would require anyone filing a lawsuit against manufacturers of biodefence medications to prove deliberate negligence – a more stringent test than for most such suits. To make up for this, the law also introduced an entitlement to compensation for people damaged by such products. What it has not done, however, is set aside money for the compensation fund, and that, Tucker says, could discourage people from accepting BioShield treatments.

All is not lost. The bill now before Congress mandates research into new tools and methods for developing drugs and vaccines, not just the drugs and vaccines themselves. That may go some way to moving Project BioShield's focus away from the "one bug, one drug" strategy and on to a broader spectrum of remedies. But it does little to solve the problems of how to get any remedies out to the potential victims of a bioweapons attack. Nor does it mandate stronger safety trials that might help identify side effects of any new therapies, and so give the public a better idea of the risks and benefits of the drugs and vaccines on offer. For now, the authorities appear bent on building a stockpile of silver bullets against imagined enemies that may not work or may never be needed. ●

Into the valley of death

Though underpinned by government contracts, Project BioShield was conceived as a model of free-market economics. The financial risk is borne by commercial contractors, while the government pays only when it gets the goods. That model now looks to be failing.

For the big pharmaceutical companies, funding ought not be a problem. They have the financial resources to back long, expensive drug development, especially if they know there's a buyer at the end of it. Yet the big guns have been ignoring BioShield.

The reason, say industry analysts, is that even with a promise of government purchase, biodefence drugs are only ever a one-time sale into a stockpile, or at most a few sales of replacement drugs to keep it topped up. That's small potatoes compared with an asthma or impotence drug that can be sold at a high price to millions.

Small firms, by contrast, are happy for any business they can get, and so far all BioShield's contractors have been small, innovative biotech firms. The \$878 million contract for anthrax vaccine, BioShield's biggest so far, went to VaxGen, a company that has

never sold a product. From a technical standpoint, this is not a problem, as start-ups are often where the real innovation is. Financially, it can be a different matter.

It can take years and hundreds of millions of dollars to bridge the gap between early blue-sky research, funded by research agencies, and the pay-off from sales – a gap dubbed the "valley of death" by the industry. "I can assure you, the valley of death is real, and it is long and treacherous," Lance Ignon, vice-president of VaxGen, told *New Scientist*. The company ran into difficulties with its anthrax vaccine formulation, and solving the problem pushed back its delivery date a year. Then BioShield hit it with new requirements for testing, Ignon says. All this has made finding finance for the tests ahead harder, and the company is now seeking a higher product payment to compensate for the extra work.

Bridging the gap

Not all companies have had the same searing experience. "We have never experienced a valley of death," says John Langstaff, chief executive of Cangene, based in Winnipeg, Canada.

His firm has already sold US authorities antibody-based treatments for side effects from the smallpox vaccine, and in May won a BioShield contract to supply 200,000 doses of an antibody that combats botulinum toxin. The company got late-stage development funding from the US Centers for Disease Control and other sources.

A provision of the new BioShield bill aims to help others in a similar way, via a new Biodefence Advanced Research and Development Agency (BARDA). This will bring the Department of Health closer to the way the Department of Defense does business through its DARPA research agency, which famously gave birth to the internet. BARDA will be a council of experts that will coordinate the development of biodefence measures. It will help contractors through the valley of death by paying them for reaching certain milestones, such as getting the product to clinical trials. BioShield has already begun to embrace that approach: in its contract with Maryland-based PharmAthene it has promised an initial \$35 million for the first clinical trials of its anti-nerve gas drug, as well as the eventual purchase of 90,000 doses.