A smallpox attack is widely seen as the ultimate nightmare scenario. But many scientists—including some who know the disease firsthand—say it wouldn't be as horrific as everybody thinks

How Devastating Would a Smallpox Attack Really Be?

It was 3 days before Christmas, but the National Security Council was not in a festive mood. Some 16,000 people across 25 U.S. states had come down with smallpox; 1000 had already died. Frightened citizens were fighting over the dwindling vaccine supply. Canada and Mexico had closed their borders, food shortages were looming, and people were fleeing the cities. When desperate council members asked experts what the future would hold, the answer was unfathomable: By early February, as many as 3 million U.S. residents might be struck by smallpox—and a million might be dead.

That stark picture was painted by "Dark Winter," an exercise designed by top U.S. bioterror experts and held last summer. Still the most widely publicized scenario, the exercise enlisted senior U.S. policy-makers and confronted them with an imaginary smallpox attack. An equally stark image—an apocalyptic event that could bring the nation to its knees—jumps out from many press stories and from *Smallpox 2002: Silent Weapon*, a chilling BBC docudrama in which a "suicide patient" strolling around New York City triggers a worldwide pandemic that leaves 60 million dead. (President George W. Bush has reportedly ordered a copy of the tape, which aired in Britain in February.)

Scary scenario. Stills from *Smallpox 2002: Silent Weapon*, a BBC docudrama in which a "suicide patient" in New York City sparks a smallpox pandemic.

Yet some experts—including several veterans of the eradication effort—are pushing a much less alarmist message: A smallpox outbreak needn't be dire. They don't dispute that even a single case would be an emergency, or that it would be horrific for the patients. But they argue that the disease would spread much more slowly than Dark Winter and other scenarios suggest and could, in many cases, be contained quite easily. "Smallpox is a barely contagious and very slow-spreading infection," says James Koopman of the University of Michigan, Ann Arbor, who helped fight the disease in India in the early 1970s. Indeed, the way it spread in Dark Winter was "silly," says Michael Lane, a former director of the smallpox eradication unit at the Centers for Disease Control and Prevention (CDC) in Atlanta. "There's no way that's going to happen."

Koopman, Lane, and others say it is especially important to tone down the hype now, as the government is reviewing its policy on smallpox vaccination and holding public hearings on the issue. Because the vaccine can have serious and sometimes deadly side effects, CDC's current plan is to use it only during an outbreak and give it just to those who have been close to a patient—a strategy called ring vaccination. But others question that approach. In a recent paper in The New England Journal of Medicine, William Bicknell, former commissioner of the Massachusetts Department of Public Health and now at the Boston University School of Public Health, instead called for the government to make the vaccine available now to those who want it. So did a policy analysis published last month by the Cato Institute, a conservative think tank.

Modeling the unfathomable

So what would a smallpox outbreak look like? That question has spawned a new growth industry since 11 September. At least six U.S. research groups are building computer models of an epidemic, enabling them not only to project its possible course under different scenarios but also to test the effect of vaccination and quarantine strategies. Many of these models are still in development, and their results are sometimes contradictory. But the outcomes—none of which are as gloomy as Dark Winter—are eagerly awaited by public health officials hoping for guidance. Already, in briefings for state and local officials, CDC's senior adviser for smallpox preparedness and response, Harold Margolis, is trying to "demystify" smallpox. "We know this disease," says Margolis. "We have eradicated it once, and we can do it again."

One reason Dark Winter, organized by the Johns Hopkins University Center for Civilian Biodefense Strategies and the Analytic Services Institute for Homeland Security, made such a big impression is that it was one of the first exercises of its kind. The underlying mathematical model was simple, says Tara O'Toole, director of the Hopkins center and one of the three authors of the scenario. The primary goal was not to accurately predict the course of an outbreak but to show gaps in the country's biodefense system and jolt policymakers into action.

That it did. In the exercise, conducted on 22 and 23 June 2001, former Senator Sam Nunn (D–GA) played the U.S. president. Republican Governor Frank Keating of Oklahoma—no stranger to dealing with terrorism—played himself, as did a handful of TV and print reporters covering the outbreak. The scenario assumed that three large aerosol clouds infected 1000 people each in

CREDITS: STILLS FROM *SMALLPOX 2002: SILENT WEAPON*/BBC

shopping malls in Oklahoma City, Atlanta, and Philadelphia. With the fictional policymakers woefully unprepared, the situation got "worse and worse and worse and worse and worse," as "President" Nunn put it.

"We have to take some of the responsibility" for giving smallpox an extremely scary reputation, concedes O'Toole. Indeed, she worries that because of the current fixation on smallpox, four dozen or so other potential biowarfare agents are being ignored: "That wasn't the intended message."

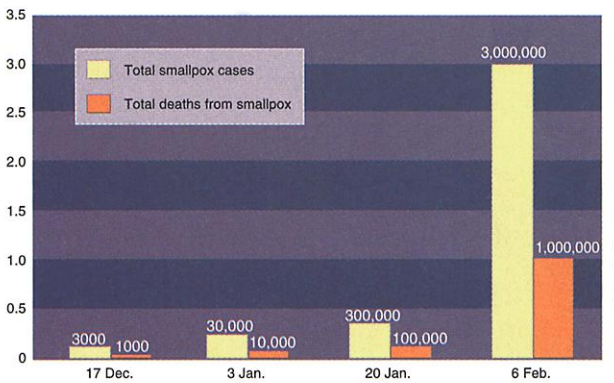
But O'Toole also blames the media. At the end of the exercise, she points out, there were still fewer dead than at Pearl Harbor; the 3 million number was a worst case prediction. And O'Toole stands by every assumption used in Dark Winter. One reason it was so bleak, she points out, is that the scenario provided only 15.4 million doses of vaccine—the actual U.S. stockpile at that time. The stockpile has since grown, and there will soon be enough to cover the entire U.S. population (*Science*, 5 April, p. 25).

Others question the assumption that terrorists could actually spread enough smallpox particles to infect 3000 people. In a model he has developed, for instance, Ira Longini, a biostatistician at Emory University in Atlanta, sets an Al Qaeda–style group of up to five infected terrorists loose and, not, surprisingly, the resulting outbreak is much smaller than the Dark Winter simulation. The most likely introduction scenario is still hotly debated, however, and most researchers say it's a question that the CIA, not epidemiologists, will have to answer.

The most contested assumption in Dark Winter, however, is the transmission speed for smallpox. A crucial factor in most disease models is what epidemiologists call the basic reproductive number, or R_0, which is defined as the number of secondary cases caused by each primary case, absent any control measures. When R_0 is high—say 10 to 13, as for measles—a disease will spread exponentially; when it's between 1 and 2, it will just keep going, and below 1, it will peter out. For most modern-day diseases, careful epidemiologic studies have determined R_0 in various populations.

But for smallpox, researchers can't agree on the right value. Past outbreaks yielded varying results, and the number can differ from population to population. Most people in the United States today lack immunity, which could make matters much worse than in the past. On the other hand, they don't live in crowded and squalid conditions, like many of the disease's erstwhile victims, which could reduce transmission rates.

O'Toole and her co-authors selected six smallpox importations into Europe after World War II that they thought might be typical for a 21st century attack. For instance, these outbreaks took place in winter, the season terrorists would choose because it's peak transmission time for smallpox; infected people had lots of interaction with others; and doctors were slow to recognize the disease, as they would likely be today. They settled on an R_0 of 10—although they think that may be on the low side. In one famous and "particularly instructive" case, they wrote in a paper, a patient who returned to Yugoslavia from a trip to Iraq in 1972 infected 11 others, who in turn caused 140 "second generation" cases. The same number—10—had also been suggested in several papers (including one in *Science*, 26 February 1999, p. 1279) by the former head of the smallpox eradication effort, Donald A. Henderson, who served as a consultant to Dark Winter.



Too gloomy? Sam Nunn, playing the president, scrambled to deal with a smallpox attack in Dark Winter. But some say the scenario exaggerated the spread of the disease.

But a team led by CDC's Martin Meltzer, which published a smallpox outbreak model in Emerging Infectious Diseases last fall, concluded after a similar analysis of many more past outbreaks that the average rate of transmission was lower than 2. The CDC group recognized that today's citizens might be more vulnerable but not all that much more, so they ran scenarios in which R_0 was 2, 3, or 5, resulting in outbreaks that were easier to contain than the one in Dark Winter. Raymond Gani and Steve Leach of the Centre for Applied Microbiology and Research in Porton Down, U.K., reached a conclusion somewhere in the middle after analyzing historic outbreaks. R_0 was usually somewhere between 3.5 and 6, they wrote in Nature last December. In reality, says Koopman, the transmission rate may be much lower than past publications suggest. The published literature contains a skewed record, he says, tending to register significant outbreaks, whereas small ones were never written up. Koopman puts smallpox's R_0 at "barely above 1." If true, a small attack may well fizzle after a handful of additional cases.

How fast would it spread?

Other researchers are using more sophisticated models that avoid the problem of choosing the right R_0. Instead of relying on a single transmission rate, these modelers estimate the chance that any given encounter—say, a colleague with smallpox sitting in the cubicle next to you for 4 hours—will result in an infection. They then plug these numbers into a model that simulates the behavior of all the individuals in a given community.

In his computer at Los Alamos National Laboratory in New Mexico, for instance, Stephen Eubank has data on each of the 1.6 million people in Portland, Oregon. Not the real citizens, he hastens to add, but a "synthetic population" based on census, transportation, and other data about real Portlanders. Eubank's people go to work, take their children to soccer practice, and go to movies.

To estimate the risk of infection from different types of encounters, Eubank and Longini, who has developed a similar model with his Emory colleagues Elizabeth Halloran and Azhar Nizam, have quizzed smallpox experts. Again, past experience suggests that the risks are much smaller than most people would think. Most smallpox infections were the result of several hours spent in close contact—usually 2 meters or less—to a patient, says Lane. Indeed, Koopman says some patients did not infect anybody at all. "In India, we got very worried sometimes, because a patient had gone into a big crowd, or boarded a bus—and yet there was no secondary transmission," he says. To Meltzer, the notion that an infected terrorist could condemn people to death by patting children on the head or bumping into Manhattan office workers, as happened in the BBC docudrama, is "absolutely preposterous."

Eubank has incorporated risk estimates from these experiences into his model. Now, when he releases a smallpox cloud in, say, a shopping mall, he sits back to watch the drama unfold; the model calculates the transmission rate. Depending on the model "run," the value can vary, but it usually turns out to be 3

CREDIT: JOHNS HOPKINS CENTER FOR CIVILIAN BIODEFENSE STRATEGIES, CENTER FOR STRATEGIC AND INTERNATIONAL STUDIES, ANSER, AND MEMORIAL INSTITUTE FOR THE PREVENTION OF TERRORISM

In Search of a Kinder, Gentler Vaccine

James Koopman saw the last 16 cases of smallpox in the Indian district of Azhagar in the early 1970s, but by now they blur together. Crystal clear, however, is the memory of a child, about 1 year old, who suffered from an uncontrollable infection called progressive vaccinia after receiving a smallpox vaccination in 1973. "It completely destroyed her arm, right down to the bone," says Koopman, now a researcher at the University of Michigan, Ann Arbor.

To Koopman, that girl is a grim reminder that the traditional smallpox vaccine, a virus called vaccinia that's harvested from the pustules on the skin of infected calves, is very effective—and also quite dangerous. So current talk of vaccinating thousands or millions makes him rather nervous. But it's not yet clear what the alternatives are.

Vaccinia—known in the United States as a Wyeth product called Dryvax—works by producing a local infection on the arm, a so-called take, which normally heals in 2 to 3 weeks. But in progressive vaccinia, it grows out of control. Other serious side effects include eczema vaccinatum, a localized or systemic infection in people with a history of eczema, and encephalitis, a brain inflammation. During the smallpox eradication era, about 1250 in every million vaccinees—many of them children under 2 years of age—suffered one of these side effects, and about one in a million died. Researchers expect that those numbers would be significantly higher today, as millions of people have compromised immune systems as a result of HIV or immunosuppressive drugs. Eczema rates have also shot up, for unknown reasons.

Waiting for a shot. In February 1947, New Yorkers lined up for smallpox vaccines after an outbreak hit the city. The vaccine can cause serious and fatal side effects.

A huge new batch of vaccine scheduled for delivery to the government before the end of the year is not expected to be much safer. Produced by a company called Acambis and its subcontractor Baxter, the vaccine is a single, clonal strain of vaccinia, rather than the mélange in Dryvax, and it's produced by cleaner techniques. But it was chosen to resemble the old vaccine as closely as possible, says Thomas Monath, chief scientific officer at Acambis, because that's known to work. Animal tests suggest that the new version has a slightly lower risk of causing encephalitis, but other side effects will probably be the same, Monath says. Clinical trials are under way.

The National Institutes of Health is pushing both academic and commercial researchers to develop a safer alternative. Such a vaccine could be used in the more than 20% of Americans who either belong to one of various risk groups or are in close contact with those in them—and perhaps in the long run, the general population. Prime candidates are vaccinia strains that are much more weakened, so that they're powerless to set up an infection but still elicit an immune response.

Such highly attenuated vaccinia viruses are already used as backbones for several other vaccines. Aventis Pasteur, for instance, is developing an HIV vaccine based on a highly weakened vaccinia strain called NYVAC; now, it plans to test whether NYVAC by itself might make a smallpox vaccine.

But the candidate with the best prospects, experts say—simply because it has the longest track record—is a vaccine called modified vaccinia Ankara (MVA). Produced by passaging vaccinia 574 times in chicken embryo fibroblasts, MVA was given to more than 150,000 Germans in the 1970s, most of them at high risk of side effects. The vaccine was used as a primer to establish a baseline immunity, thus preparing the body for the traditional smallpox shot given several months later. MVA was shown to be safe, and it helped people tolerate the real vaccine. One of the two companies developing it, Copenhagen-based Bavarian Nordic, has recently given its version of MVA to small groups of healthy and immunocompromised volunteers; they, too, didn't suffer serious side effects, the company recently reported.

But does the combination of MVA and a traditional vaccine work? Unlike Dryvax and other old-style vaccines, it has not proven its mettle in endemic areas, and there was no smallpox around in Germany when it was used. It doesn't produce the telltale take—and the subsequent scar—that researchers have always relied on to indicate protection. Because it's unethical to do tests in which human vaccinees are exposed to smallpox, the Food and Drug Administration will have to rely on animal tests, as well as measurements of the immune response it generates in humans. Researchers at the Centers for Disease Control and Prevention and the U.S. Army Medical Research Institute of Infectious Diseases have developed a monkey model of smallpox, which they hope to perfect this year (*Science*, 15 March, p. 2001); MVA is one of the first products they plan to test.

Because MVA protects against several other members of the orthopoxvirus family, Bavarian Nordic president Peter Wulff is confident that it will pass those remaining tests. He predicts that the combination will eventually replace Dryvax and other traditional vaccines—not just for high-risk groups but for the general population as well. The objection that it doesn't produce a take, Wulff adds, "is a little beside the point from a scientific viewpoint. What counts is the immune response."

But others are not so sure. Donald A. Henderson, former head of the World Health Organization's eradication effort and now a top bioterrorism adviser to the Department of Health and Human Services, for instance, says he'd be leery of relying on anything less than the tried and true to protect the population. "I don't know how you could ever be completely sure of [MVA's] efficacy," Henderson says.

The dilemma seems certain to crop up more frequently as scientists shore up the world's defenses against bioterrorist threats. Most of the diseases that would appeal to terrorists are extremely rare in nature, so doing efficacy tests of new drugs and vaccines in humans will usually be impossible—unless, of course, the worst scenario materializes. **–M.E.**

CREDIT: BETTMANN/CORBIS

or 4, he says. Longini and his colleagues found the mean to be about 2, although in some runs there were no secondary cases.

No simple answers

Earlier this month, a group of smallpox modelers met behind closed doors with officials from the Department of Health and Human Services at the John E. Fogarty International Center, part of the National Institutes of Health in Bethesda, Maryland, to compare and discuss their work. Some of those who attended say that there were great differences among the models. Not surprisingly, their gloominess had a major effect on the chances of success for the ring vaccination strategy. Longini, for instance, says his model shows that ring vaccination, even when it's started only after the 25th case of smallpox, can contain an epidemic almost as well as mass vaccination, provided that at least 80% of those exposed can be found and vaccinated. But a model by Edward Kaplan and colleagues at Yale University comes out more in favor of mass vaccination, others say.

"There are serious disagreements, and they're well founded," says Fogarty's Ellis McKenzie, who organized the meeting. But such differences can help clarify the debate, he asserts. "One of the important things modeling forces you to do is put all your assumptions on the table, which is extremely helpful." Until now, he adds, U.S. epidemiologists and public health officials have not been very interested in how mathematical models could aid disease control—in contrast to their counterparts in the United Kingdom, where the field has been thriving. Now, that attitude has changed, as has almost everything since 11 September.

–MARTIN ENSERINK

ASTROPHYSICS

For Whom the Stars Toll

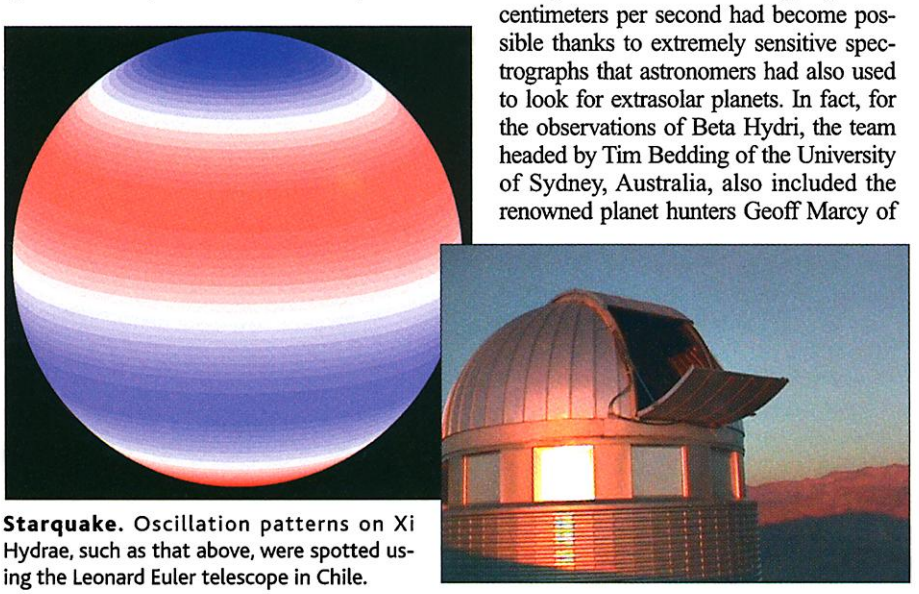
In the new field of asteroseismology, researchers are hoping to peer into stars by studying tiny oscillations of their gaseous surfaces

It is said that a blind musician can recognize a Stradivarius from its sound and even sense the occasional crack in its top plate. Similarly, astronomers hope that they will soon be able to detect the provenance and health of stars by listening to their sound.

For decades, solar physicists have extracted huge amounts of data about the interior of the sun by studying vibrations of its surface, a field that has become known as helioseismology. Over the past few years, astronomers have detected, across vast distances, similar vibrations in a few other stars. Earlier this month, a team reported for the first time the existence of vibrations in a giant star, 10 times the size of our sun. The new field of asteroseismology is taking off, and researchers hope it will provide a wealth of data on the size, density, temperature, age, structure, and chemical composition of stars. "Asteroseismology will become an extremely important tool in astrophysics," says Douglas Gough of Cambridge University.

The complicated oscillations of the sun's surface that physicists first spotted in the 1960s have periods of about 5 minutes. They are now known to be caused by turbulence and convection of hot gas in the outer mantle of the sun. The surface responds to these motions by ringing like a bell, at frequencies determined by the sun's physical properties and internal structure. These movements of the sun's surface are now tracked daily by satellites such as the U.S.-European Solar and Heliospheric Observatory (SOHO).

Astrophysicists are eager to know if their model of how the sun works also applies to other stars, but detecting similar oscillations at such distances has proved extremely difficult. It's little wonder: The quivering undulations of the solar surface have an amplitude of less than 25 meters and move at velocities well below 1 meter per second. And for distant stars, which appear as mere points of light from Earth, motions of different parts of the star tend to cancel each other out, giving an overall impression of a motionless surface. As a result, 10 years ago asteroseismology seemed like wishful thinking.



Starquake. Oscillation patterns on Xi Hydrae, such as that above, were spotted using the Leonard Euler telescope in Chile.

CREDIT: (LEFT) ESO

But in spring 1994, a team led by Hans Kjeldsen of the University of Aarhus in Denmark succeeded in detecting oscillations in the star Eta Bootis, 38 light-years from Earth. This star is larger and more massive than the sun and so should oscillate more slowly. By measuring subtle changes in the relative intensities of spectral lines, Kjeldsen and his colleagues deduced temperature changes of a few hundredths of a degree with periods of about 20 minutes. Other astronomers looked for corresponding Doppler shifts in the light from the star's heaving surface but were unable to confirm the findings, mainly because the star rotates quickly, making Doppler measurements more difficult. "Not everyone believed our results," says Kjeldsen.

The breakthrough came in 1999 and 2000, when astronomers finally measured minute variable Doppler shifts in the light from nearby stars Procyon and Beta Hydri. Detecting a star's surface moving at just 50 centimeters per second had become possible thanks to extremely sensitive spectrographs that astronomers had also used to look for extrasolar planets. In fact, for the observations of Beta Hydri, the team headed by Tim Bedding of the University of Sydney, Australia, also included the renowned planet hunters Geoff Marcy of the University of California, Berkeley, and Paul Butler, now at the Carnegie Institution of Washington in Washington, D.C.

Soon afterward, astronomers at the University of Geneva, Switzerland, detected vibrations on Alpha Centauri A, our sun's nearest stellar neighbor. They used the CORALIE spectrograph on the Swiss 1.2-meter Leonard Euler telescope at La Silla, Chile, which is also used for planet hunting. "It's a fantastic instrument," says Kjeldsen. "The results are just amazing." The surface of Alpha Centauri A was