A Brookings Press Briefing

USING COMPUTER SIMULATIONS, EXPERTS DEVISE STRATEGY TO CONTAIN SMALLPOX

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MS. CAROL GRAHAM: Good morning and welcome to Brookings for a discussion of one of the more pressing policy problems on our agenda, bio-terror. I'm Carol Graham. I'm Director of our Governance Studies program and Co-Director of the Center on Social and Economic Dynamics here at Brookings.

Prior to turning the agenda over to our two speakers, Josh Epstein and Don Burke, I wanted to say a word about our Center on Social and Economic Dynamics which is a joint effort of the Brookings Institution and the Johns Hopkins University and it's key to this collaborative effort between Drs. Epstein and Burke, and also a word about the Bloomberg School of Public Health at Hopkins.

Our Center on Social and Economic Dynamics is a joint center between Hopkins and Brookings where a number of us are trying to change the way we think about social policy and public policy. We focus on dynamics. Most social science focuses on equilibrium. We actually focus on dynamics. Phenomenon such as tipping phenomenon in crime, sudden explosions of civil violence, the dynamics of the market reform process and many other policy problems where dynamics are really what we are worried about and not equilibrium phenomenon.

One of our major focuses is social interaction. This is going to be key to what you see today. But both social dynamics and social interactions are very difficult to measure and to do so we need new and better data, and more importantly we need new analytical approaches.

What you will see today hinges on an agent-based computer modeling approach to social science that's been pioneered here at Brookings by Joshua Epstein and his colleague Rob Axtell, and it allows us to capture social interactions and social dynamics. Today you'll see it applied to a key public policy issue, bio-terror.

Key to this model and this effort is our collaboration with Professor Burke who's at the Johns Hopkins School of Public Health in Baltimore, and I wanted to say a word about the Bloomberg School of Public Health. It's the oldest, largest, and most academically acclaimed school of public health in the country. Its faculty comprises one-quarter of all faulty of U.S. schools of public health -- in other words, one-sixth of all public health doctoral degrees.

Today the Bloomberg School of Public Health teaches almost 2,000 students per year from 80 different countries. The school is renowned worldwide for its expertise in disease control and prevention.

Dr. D.A. Henderson, the former Dean of the school led the global smallpox eradication effort, and the current Dean, Al Summer, proved that the vaccination as late as four to five days after exposure, provided protection against smallpox.

I'd also like to say a word about our two distinguished speakers. Professor Don Burke has been Professor of International Health and Epidemiology at Hopkins since 1997. He directs the Center for Immunization Research there and teaches courses on vaccine science and policy. He has a BA from

the Western Reserve University in Cleveland and an M.D. from Harvard Medical School. He's Board Certified in Internal Medicine and Infectious Diseases, and he served for 23 years on active duty in the U.S. Army where he conducted research on vaccine development against epidemic infectious diseases.

Josh Epstein is a Senior Fellow in both Economic Studies and Governance Studies here at Brookings and also a member of the external faculty at the Santa Fe Institute. He holds a PhD from the Massachusetts Institute of Technology and a BA from Amherst College.

Previously Josh has been a lecturer at the Woodrow Wilson School at Princeton University and an International Relations Fellow at the Rockefeller Foundation. He's the author of over five books including the most recent one called "Non-Linear Dynamics, Mathematical Biology and Social Science", and a number of articles on a range of topics pertaining to social science phenomenon. He's also the architect of the computer simulation approach that you'll see today.

With that, I'll turn this over to our two speakers.

DR. JOSHUA M. EPSTEIN: Thanks very much, Carol. Thank you all for being here.

We'd like to show you work we've been doing to develop a containment strategy for smallpox using this individual base or agent based computational approach that Carol just outlined.

First we want to talk a little bit about individually based or agent based models, then tell you specifically about the county level epidemic model we've built. Using that model we'll talk about smallpox vaccination strategies and particularly the phenomenon of quenched epidemics or epidemics that die out. The policy application is, of course, the vaccination strategy that we think is most promising to induce epidemics to die out, and then discuss some extensions of this work.

Agent based computational models differ from traditional mathematical models in a variety of ways. Mathematical epidemic models typically posit a few pools of homogenous, undifferentiated agent -- susceptible, infectives and the like. We dispense with this assumption of homogeneity and represent every single agent in the society. There are heterogeneous populations of agents that differ from one another by their disease state, by their immuno-competence, by their social network, by their family members and so on in a variety of ways, so this type of modeling, this computational style of modeling permits us to represent agent heterogeneity and that's important in discussing epidemics.

Agents behave autonomously in this model. There's no central direction of them. They move about an explicit space, in our case a two-town county. Going to work, going to school, going to the hospital, going home, and so on, without any central direction. Again, unlike traditional models they interact locally with members of their network, work group, school mates and so on. Most, again, mathematical models of epidemics assume a kind of perfect mixing in which all infectives interact with all

susceptible each period. This produces very fast epidemic dynamics and can lead away from the consideration of policies that actually deserve attention.

The model represents delays and lags in the progress of a disease and the social contact process itself, and as Carol mentioned, is focused on non-equilibrium dynamics and in the case of epidemics the most important issue here is whether epidemics take off or fizzle. This is a type of tipping phenomenon, a type of non-equilibrium issue. Whether the epidemic takes off or fizzle is the core question as far as we're concerned, and we're trying to engineer a policy that inclines the epidemic to fizzle. We'll come back to that and you'll see that this technique allows visualization and interactive pedagogy which is another important point.

There are a lot of applications. I won't go into these in any length except to say that there is a special issue of the proceedings of the National Academy of Sciences that reviews many of these -- civil violence, market phenomena, evolution of norms, one paper in which I participated reconstructs the entire history of a civilization using this technique, the Anastasi. And there's a nice review of that in Nature by Jared Diamond. I refer you to the proceedings volume for further work along these lines.

Turning now to this county level model, it involves two towns which you'll see very soon. Each town has 400 people, 100 households, each with two adults and two children. Non-commuting adults work in the town workplace, of which there is one per town. Ten percent of the adults commute to the other town's work place and a few adults work in the common hospital. Kids go to school in the town's school. There's no busing to the other town's school.

The idea of doing the model at this level of resolution was to build the simplest model that captures the main components reflected in the data on smallpox transmission. The data we will review in detail and we calibrated the model to agree with that data. It involves these same components -- hospitals, work places, households, and the like. That's why we chose to model at this level of resolution, although it's a highly idealized model as you'll see.

Here's a picture of this idealized two-town county. We've depicted a northern town that's comprised of squares which we will call Square Town, and a southern town, all of his members are circles which we will refer to as Circle Town. You see one green agent -- this agent here, the green agent. He's home with his family right now. This is the picture of this county at night. There are 400 people per town, 100 households. So you see, each of these squares has four individuals in it. There are four circles in each of the southern households, four squares in each of the northern households, and at night they're all home with other members of their household.

In the day they go to work and school. Some of them commute. This is the only point of having squares and circles, so that we can keep track of commuters.

For example here's our green agent, he's a Circle towner, but he works in the Square Town workplace, as you can see. Here he is in the Square Town workplace in the day time, along with other commuters, and you can see commuters from each town going to work in the other town. So it toggles

back and forth and this cycle simply repeat with each individual going to work and school and home and so on.

When they contract the disease they go to the hospital and you can see hospital workers from each town depicted in the hospital. And if they survive, they go back into circulation and if they die, they move on to the morgue. So you're going to see events transpire in this artificial two-town space with this cycle of day and night repeating, and we're going to color code agents for their disease state as they progress through the phases of smallpox in a typical individual, and Don will tell you about that.

DR. DONALD S. BURKE: For the natural history of the disease of smallpox we developed a color code system here that shows when an individual is healthy and well and susceptible, the square appears as blue as they do in the original Circle and Square Town. If an individual becomes infected they turn green. And then if they become symptomatic with fever and early rash they turn yellow. When they become seriously ill they are colored red. If they die, they are colored black. If they recover and are immune they're colored white and move back into the community.

Shown on the bottom is the time line of this process. If an individual becomes infected on day zero on the bottom of the line, they stay healthy and asymptomatic for 12 days, after which they may develop a fever, a prodromal state in which they'll have a high fever and feel very incapacitated, but don't yet have the diagnostic smallpox rash.

After an average of three days they'll develop the smallpox rash and become highly contagious.

Shown above the red bar there is the highly contagious period from day 16 to day 19. By day 23 the rash is finally resolved and the individuals go on to either recover or die. The individual can die any time during that red period.

Important on this is if you vaccinate an individual after exposure within the first four days of exposure, the vaccine is effective. You don't need to use smallpox vaccine before the onset of infection, but you can use the vaccine as late as four or five days after a person has been exposed to smallpox and that's the period of vaccine efficacy as shown.

In order to standardize our model we went back into the literature and reviewed 49 different epidemics that occurred between 1949 and 1971 in Europe. During this time in Europe smallpox was not naturally circulating. It had been eliminated from Europe but there were periodic and continual reintroductions into Europe during this time. In fact there were 49 episodes where the disease was imported into Europe from other countries.

Most of the cases occurred in persons either in hospitals or associated with hospitals. About a quarter of the cases in these 49 epidemics involving 650 people total, about a quarter of the cases were acquired at work or at school, but importantly a quarter were in the household. So collectively in the

experience in Europe of new introductions of smallpox, 75 percent of cases were either acquired at the hospital or at the home.

Similarly, if you look at the size of these introductions, most of the epidemics introduced into Europe at this time were small epidemics, zero to four cases. There were a few epidemics that were limited to only a dozen or so, five to 19. And some of the epidemics affected 20 or 49 individuals.

So what we did then was to standardize our epidemic in this model to reflect these two distributions. We standardized the rate of transmission, the amount of transmission per day and the contacts per day to make this distribution look like this, assuming that 80 percent of the population was immunized, which was what in fact happened, which was the state of Europe at that time. When we did that, then we proceeded with the model.

We then did a parameter search of these biologically plausible values of transmission, reactive, contact tracing, hospital contacts per day, and then did a statistical analysis to standardize and choose parameters.

There were a number of other variables that I won't go into in the model here. The transmission per day, the pathogenicity, the seasonality, the vaccine efficacy, and a wide variety of variables that we can choose by literally setting a knob on the model and choosing the variables.

The ones that are shown in red here are the ones we calibrated to make sure that the model fit to the European data.

Josh will now tell us about the base case runs.

DR. EPSTEIN: The base case run of this model is the epidemic beginning with a single infective. One commuter is the so-called index case. It assumes no policy interventions of any sort. No vaccine, no isolation, no policy interventions whatever, and no background of pre-existing immunity.

Here we begin the epidemic with our single index case, this green agent in Circle Town. He's a commuter, and you'll see him commute to the Square Town work place. There he's in the Square Town work place. Every day we re-randomize the positions at the work place that the agent goes, so he comes into contact with different agents on a random basis at work each day.

We're going to let it continue.

He goes home. Now he's turned yellow, as you can see, in this Circle Town household. He is now in this yellow contagious phase or early contagious phase. The other agent in his household, another member of his household, has turned green indicating that he or she has contracted the disease from our index.

If we continue, things simply transpire, as Don mentioned, through the color coding. Green,

yellow, red for the rash. Our agent has now developed the full smallpox rash and I'll stop it.

You see he's gone to the hospital where we assume he is diagnosed correctly. Things continue.

I'll speed it up in a minute, but you get the idea.

He went to the morgue because he died. Smallpox has a 30 percent case fatality rate, meaning that about 30 percent of the cases die and another 70 percent recover.

I'll speed this up.

All of these movies are posted on the Brookings web site and you can play them.

Here it is, farther along. One interesting point is that you can see that the epidemic is worse in Square Town than in
Circle Town, despite the fact that the index case was from Circle Town. So seemingly sensible strategies like vaccinate the entire town where the first case is detected will do poorly because by the time you've detected the first case, the disease may have spread far beyond the initial town.

I'll let it go a little further.

You begin to see white agents who have recovered. More black agents in the morgue. We'll just let this play out.

That is the base case.

In the base case with no interventions of any sort, everyone in this county eventually contracts smallpox. All 800 members of the county get smallpox and 30 percent of them die.

There are run-to-run differences in this model. It's a stochastic model with randomness, so over many many realizations there will be a distribution of outcomes, but those will be typical results as will these.

We believe this is a reasonably good representation of the situation where European smallpox was introduced into the Americas in the 1600s. No background immunity, no vaccine, no intervention.

Here's the typical curve for these runs of incidents on the top which has exactly the shape of observed smallpox data, these waves of outbreak. And the bottom is the cumulative curve for this run. The cumulative number of individuals infected over time.

That's the problem. The problem is an event in which a smallpox epidemic begins. What are the policies we'd like to implement in order to deal with that?

The main ones under discussion have been trace vaccinations and mass vaccinations. Both of those have problems that we'll discuss and we'd like to propose a hybrid strategy that involves aspects of those but departs from each of those.

Trace vaccination. This involves something called contact tracing. The idea is a very elegant idea. That is you find all the contacts of a confirmed case and vaccinate them. A contact is a person who had close proximity, contact with a confirmed or suspected smallpox patient after the patient developed fever and until all scabs have separated. This is CDC language and accepted language.

The problem with perfect and complete contact tracing is it's difficult to trace all your contacts if you were here in a modern metro system, or here in an airport. It's just very daunting to imagine tracking down and tracing everyone's contacts under these modern circumstances.

Mass vaccination has two problems. One is that the vaccine is a live virus and may be fatal if you are immune suppressed. So if you have AIDS, are undergoing chemotherapy or fall into a number of other categories, you may actually have a fatal reaction. Even if it is not fatal it can have very serious side effects if you have eczema, as in the case of this child on the right, or you can develop progressive vaccinia given other backgrounds.

Don, if you wanted to say more about that.

DR. BURKE: No.

DR. EPSTEIN: All right. So the challenge is this.

Design a policy that is more feasible than perfect trace vaccination, less risky than mass vaccination, and is highly effective in minimizing a smallpox epidemic.

The easy part is this. If there's a confirmed release then of course the U.S. government must provide vaccine and they are stockpiling enough vaccine to do that. But that's really the easy part.

The hard part is what do you do before any relief to contain the epidemic and ease the burden of further vaccination? We have one important piece of science leverage in designing such a policy and it is this. Epidemics are non-linear stochastic threshold phenomena. What that means is sometimes they fizzle out. That's really what it amounts to. The trick is what can we do before an attack to arrange that an epidemic fizzles out?

The place to begin in thinking about that is the data, as Don said. This is data that we calibrated the model to, collected by a scientist named Mack, in the '70s. It's about the question where do cases contract the disease? AS you can see, 50 percent of the cases for the Europe cases 1950 to 1971, 50 percent of the cases contracted smallpox in the hospital. Another 20 percent contracted it from family members.

So the data really does suggest that if you vaccinate hospital workers preemptively and set yourself up to immediately trace and vaccinate family, which is easier than the complete dendrite of all contacts, you should do well.

Is that what the model shows? Yes. You do very well. The red curve is the no intervention case again where 800 people get the disease. The black curve is the result if you preemptively vaccinate hospital workers in our model and immediately trace and vaccinate family members.

When you begin to add to those measures a background of large-scale immunization that we'll talk about, you begin to see a very very high frequency of epidemic die-out. We're going to come back to this but we want to talk a little bit more about these dynamics from a scientific standpoint and discuss the detailed analysis we've done of these die-out or quenching events for various levels of interventions, and then we'll come back and talk about the sort of policy package.

DR. BURKE: As Josh has said, one of the major objectives of any public health immunization strategy should be to limit the size of the epidemic as fast as possible. The traditional mathematical literature on epidemics doesn't deal with this issue very much or very well and so we've introduced a term called epidemic quenching. That is the idea, what can you do to put out the epidemic as quickly as can be, taking advantage of the dynamics in these highly stochastic events, these highly chance-driven events. And what are the strategies that we could do on a broader scale to increase the probabilities of this quenching of epidemics?

What this shows is a series of graphs of immunization of the population -- The epidemics on each of these curves here. This is the proportion of individuals who are vaccinated in the population, and shown on this axis are the number of individuals who become infected during the course of the epidemic.

So in the upper left curve there it's essentially a straight line that goes from the zero percent vaccinated on the far left with everybody becoming infected, each of those represents 100 runs of the epidemic. As we increase the percent coverage in the population, not surprisingly fewer and fewer individuals become infected to the point where in the power part of the curve over here, you begin to see that some of the epidemics have totally died out even when only 50 or 60 percent of the population is immunized. These epidemics are quenched.

Whereas here every vaccination that you get gives you one person protected so there's a one-to-one payoff, when you get to some of the higher levels of immunization you end up with some epidemics that never take off and are totally quenched. This is in a setting without any family contact tracing at all.

If you have 25 percent of your family contacts are traced you get the same curve, essentially what you vaccinate is what you get, except you start to see more of these quenched epidemics to the point if you had 50 percent family contact tracing and now here, by the time you're having 75 percent family contact tracing you've got a very strong series of quenching of epidemics here, where the

epidemics don't infect a large part of the population. And by the time you do 100 percent family contact tracing most of the epidemics are well contained, even when you have background immunization in the population of only 20 percent or so.

This is the case where I showed you of 75 percent of the epidemics having family contact tracing.

What this shows is that this is the percent of individuals who are vaccinated before the epidemic begins; this is the number of people that are infected during the epidemic; and this is a two-dimensional surface with a third dimension showing the probability of that size of an epidemic.

So here's one ridge, here's another ridge of probability, and here's where most of the epidemics occur.

These are quenched epidemics. Even though you've only got 50 percent of the population immunized, most of the epidemics are essentially zero cases.

Here's another view of this that shows the ridges of probability for different percent immunized. On the far right here going from zero percent immunized to 100 percent and the number infected, and the probability distribution shown here.

What's important about this is that these epidemics are being confined by the social structure.

Along this ridge what you find are epidemics in which the epidemic has been confined to Square Town and there is no epidemic in Circle Town at all.

Alternatively there are epidemics here where the epidemic is not only confined just to Square Town but just to the work place at Square Town.

DR. EPSTEIN: So we think there is an important advance there in the study of epidemics generally in the phenomenon of epidemic quenching that is not the same as confinement to a particular social network or confinement to a specific geographical region. It has more to do with confinement to specific social units and we believe we can exploit that in the design of vaccination strategies.

Now back to the policy issue. If we imagine the policy of 100 percent family contact tracing. We have hospitals, we imagine hospitals are preemptively vaccinated beforehand. That's number two here. We imagine 100 percent of the families are traded and vaccinated on confirmed diagnosis of a family member. And if you imagine adding to this 60 percent mass vaccination preemptively, you get this curve in our model that's shown.

The number of cases is the horizontal axis and the frequency with which that number of cases occurs in 100 runs is the vertical axis. You can see that in 100 percent of the cases, 100 percent of the runs, fewer than 70 cases occur. We'll come back to this.

I will tell you that in 50 percent of the cases fewer than 45 occur.

So this package is a very powerful set of measures to contain this epidemic and in fact this is what we're offering as a hybrid containment strategy. Preemptive measures and reactive measures are involved.

The preemptive ones are vaccination of all hospital workers. Voluntary re-vaccination of healthy vaccinees, individuals successfully vaccinated in the past. The mass vaccination risks are minimized in this case. People who successfully had the vaccine before are very unlikely to have a bad reaction now unless they developed risk factors in the intervening period. The reason we chose 60 percent preemptive mass vaccination is that is the proportion of the population represented by this group. So you could achieve 60 percent background immunization by re-vaccinating healthy vaccinees from before.

Reactive measures are vaccination of household members, again this family contact tracing. It's much easier to do that than the full perfect contact tracing we talked about before. And isolation of confirmed cases in the hospital. This set of measures has a very powerful result on these epidemics. Under this package in 100 percent of the simulated outbreaks, fewer than 70 cases occur. Twenty-one deaths, assuming a 30 percent case fatality rate. In 75 percent of the outbreaks fewer than 45 cases. In 50 percent of the outbreaks, fewer than 35. That's a very powerful containment compared to the base case where 800 are infected and roughly 240 die.

The package is more feasible than perfect trace vaccination; less risky than mass vaccination; and as Don and I have been saying, gives the public an excellent chance of epidemic die-out or quenching.

Given a credible bio-terror threat, we think this is a good basis for a national containment strategy.

It's important to emphasize that we do not make any valuation of the bio-terror threat and its credibility. We're not claiming that this set of measures should be implemented right now. But that given a credible threat it's a useful basis for a containment strategy.

There are a number of extensions that perhaps we should take up if people are interested, but perhaps that's a good place to open ourselves to questions.

QUESTION: How does this differ -- John Tidwell from the Associated Press.

How does your model differ, or your policy model differ from the Bush Administration's current policy plan? And does this imply that Americans would be in more danger under the Bush Administration plan?

DR. BURKE: As Josh said, our purpose here is to introduce a different way of looking at policy decisionmaking, not to make the policy itself.

So what we've said is that you can take advantage of the social structure to eliminate the epidemic. So again we're not saying this is the policy. We're saying this is a way of thinking about how to make policy. A subtle distinction.

What the President recommended was that health care providers and emergency workers, 500,000 approximately around the United States become immunized and that's similar to our part of the model where we immunize the hospital workers. So in that regard it's very similar and we agree that that's a very powerful step in containing an epidemic by itself.

The next question is can you add to that? The next step that's been proposed by some is mass immunization. We think there's a step short of mass immunization, to offer it broadly to the community, that we can get a lot of bang for the buck by immunizing only those individuals who have already been immunized, not by introducing immunization to persons who have never been immunized before. You can get a lot more mileage for the safety of the vaccine by that strategy.

So it's not a lot different than the President's recommendation it just extends it and gives a different idea of how to implement the next phase.

QUESTION: If part of the strategy is immunizing 100 percent of hospital workers, what happens if there are hospital workers that can't be immunized because they're immune compromised or whatever? What would be the implications of that?

DR. BURKE: Although we didn't show all of the data, you don't have to immunize 100 percent of hospital workers. But having immunized a substantial proportion of hospital workers goes a long way toward quenching the epidemic. So even though it's not a perfect immunization strategy, it still is a very powerful immunization strategy.

QUESTION: Rita Cummings from National Institutes of General Medical Sciences.

You considered only three compartments of nexogenation. How about including public transportation, children going to soccer classes, ballet and so forth? Increasing the number of compartments, how does this affect the model?

And also I would like you to comment on multiple introductions.

DR. EPSTEIN: The last point, on multiple introductions, we plan to look at that. Can easily look at it. Our sense, however, is that we introduced one agent in a population of 800. That's a very high density attack when you think about it. If you imagine a city of 12 million like Manhattan, one in 800 would be 15,000 attackers. So one in 800 we thought was, we certainly weren't making the

problem easy on ourselves in introducing one in 800.

In terms of adding compartments, it's certainly something we can do and it's something that other modelers have done. Again, the game here was to produce the simplest model that could be calibrated to the data and included things like commuters, hospitals, schools, work places and homes which are the units that loom largest in the actual historical records.

DR. BURKE: One of the things to keep in mind is that persons who are able to transmit smallpox are already very sick. The notion that someone can walk around and apparently be healthy and transmit smallpox just isn't true. Persons who are in the late yellow or red stage in our model by that time are very very sick and that's the reason that most cases are transmitted in the hospital is that by the time that you're able to transmit the infection to others, you're already so sick you can't walk.

So the notion that smallpox can be transmitted by someone sitting next to you in the subway who looks perfectly healthy and well is just not the case in the historical epidemic. And if you look at the epidemics in Europe during the 1950 to '71, all of those epidemics were transmitted by sick people. If you try to find cases where there are persons on a transportation, like a bus or an airplane like that, they're actually very very rare. So most of the transmission is by sick people. One way of phrasing this is that the contacts come to the cases, the cases don't come to the contacts.

QUESTION: David Eisenberg with the British-American Security Information Council.

To what extent is the usefulness of your strategy dependent on having prior warning or indication of an attack? I noticed one of the recent articles in the New England Journal of Medicine favored vaccination only if the likelihood of an attack is high. If it is dependent on prior warning, does that not then dictate devoting greater resources to public health surveillance systems?

DR. EPSTEIN: I don't know what resources exactly, but I think in principle, yes. It makes surveillance crucial. Surveillance is a way you decide whether we are in a state that would trigger this strategy or not.

DR. BURKE: The paper you're referring to by the Rand Group balanced the potential negative impact of vaccination ahead of time versus the benefit based on what you perceived the risk to be. I agree, that's a very rational way of optimization for this.

What our strategy does is a little different than what they said. By introducing a strategy where you immunize only people who have already been immunized once, the complication rate is only one-tenth of what it is when you immunize persons for the first time. And yet you still provide those individuals with substantial protection. So it changes the cost/benefit ratio somewhat. The optimization curve moves a little more toward the idea of intervening with a somewhat lower expectation or lower perception of risk. Again, it doesn't say that we're not taking a stand. What that perception of risk is right now, but this is one way of moving the odds in your favor.

QUESTION: Chad Henry from WTOP Radio.

Do I take it then that you don't suggest vaccinating police officers, ambulance crews, firemen, in this group that you call hospital workers?

DR. BURKE: There are two kinds of risk groups that we're talking about. The hospital workers historically have been people who have been exposed to patients who are already ill. Persons who were exposed say 15 days ago who got exposed from anther case and then came to the hospital already sick. In that case firemen and emergency responders and the like aren't really at risk.

But times are different now. The other concern is that there may be an event, a release of an aerosol where firemen and police and the like might become exposed. So this is different than the European situation in 1950 to 1971.

Adding immunization of those individuals I think is reasonable at this point.

QUESTION: Christy Fine from CNN.

After September 11th we got a lot of phone calls from mothers who were saying where can I get the smallpox vaccination, my kids haven't been vaccinated?

What are you going to tell them whenever they're not a re-vaccination candidate but they want their kids to get the vaccine?

DR. BURKE: One way to think about this re-vaccination strategy is the reason to be re-vaccinated isn't necessarily to protect yourself, but to protect the entire population. And there are other times where we as a society have used this general strategy to immunize one group to protect another group.

A good example is German measles. We immunize all boys in the United States against German measles today even though the reason you use the vaccine is to prevent birth defects in women who are pregnant who become exposed to German measles.

Obviously the boys aren't going to get pregnant and they're not going to have children who have -- But we immunize them anyway because it provides the protection to the entire group.

You can think about re-immunizing adults the same way. The more we raise the probability that we can stop an epidemic, the more we increase our chances of quenching an introduction, the better the chances that the children won't get infected at all in the first place.

So as you consider your strategies you want to put together this notion of how much can we do to quench an epidemic without having to put kids at risk of immunization. That's one of the rationale behind it, and that's what I'd tell them.

QUESTION: This is sort of a two-pronged question. One of them being, this being a computer model, how accurate is it really or applicable to a real-life kind of model where there are a lot of variations?

A second aspect of the question is, you've based in on smallpox which has a very particular pathology and behavior. What if other agents were used? What if Dengue Fever or anthrax or other kinds of biologicals or a cocktail of biologicals that behaved in different ways?

DR. EPSTEIN: On the first question, yes it's a computer model and like all models it's an idealization. I don't think the issue in this connection is exactly whether it's realistic or not, but whether we have unduly simplified the problem for ourselves or distorted its representation in such a way as to be misleadingly optimistic, for example. And I don't think we've erred in any of those directions.

We've also made sure to calibrate it to the actual data on smallpox so that what realism is possible is ensured. Of course it can be made more sophisticated. And there are a variety of extensions we have in mind.

For example, we know smallpox transmits very differently in winter than in summer. So we're working on seasonality.

There are isolation strategies. True, it's an 800-person model. It is not clear that it's scales up with complete fidelity to the 300 million agent cases of the United States and we don't claim that it does. The idea is to point policymakers in the direction of promising avenues, offer insights that they might not otherwise have, and we think it's successful in doing that.

But yeah, there's an issue of whether it scales up.

On the question of pathogens, we have been doing, let me just say, the software's design in such a way to accommodate any pathogen you like. We could do Dengue, we could do measles, we could do West Nile, lots of other things, and in fact our whole idea is to build a laboratory for computational epidemiology in which we can study a huge array of public health questions and pathogens. And in another connection for one of the working groups of the Academy of Sciences, we've been modeling novel pathogens, genetically modified smallpox.

So we're at work on other topics but today's topic is really the smallpox vaccination issue.

QUESTION: I just wanted to make sure I understand how you're differentiating your model from the Rand study, especially when it come to the math vaccinations.

They also assumed a 60 percent vaccination rate under a mass vaccination and they estimate nearly 500 deaths. Is what you're saying under your model, your 60 percent comes from these people that are specifically previously vaccinated, and so --

DR. EPSTEIN: So the risk is vastly lower for that group.

QUESTION: Do you know how much lower?

DR. BURKE: The best data we have from this are from a couple of studies from 1968 toward the end of the real smallpox epidemics that we used to have. And the serious complication rates from vaccinia in persons not previously immunized is around 10 to 30 per million. These are life-threatening, serious, events. With a death rate of may be one or two or three per million among persons who again, have not been immunized previously.

About ten times that number get severe reactions but not life threatening, so that may be 100 to 300 maybe even more than that. For persons not previously immunized.

For persons who have already been immunized for all of these categories, the risks are about one-tenth of that.

So if you take -- across the board. The serious but not life threatening, 300,000 to 1,000 it drops down, but about a tenth. The life threatening of around ten to 30 dropped down to about a tenth. And the risk of death of one or two or three per million drops down to about a tenth, too.

That's one of the reasons for putting forward this as the strategy.

QUESTION: Laura MacIness from Reuters.

I just wanted to refer back to the discussion of close proximity, measuring that and the problems of the subway systems and the airports. I'm just wondering if there's any way to minimize the spread from town to town, city to city, state to state, country to country? Would you recommend sort of treating workers at an airport or in the subway the same way as in a hospital?

DR. BURKE: Contact tracing is very important. That is a bedrock of our national strategy and it's an important bedrock of the strategy. You can get a lot of mileage just by hospital and family contacts. But where there are other contacts, where there's a known contact, finding that individual and immunizing an individual and then the contact of that contact is also a very cost-effective way of stopping the spread of the epidemic. So we're all in favor of contact tracing. That's an important strategy.

What we're trying to say is that prior immunization of a percentage of the population strengthens that. The two are more than additive together. You get this synergy, this extra non-linear complementarity between prior immunization and contact tracing. And the better your contact tracing and the more background immunization you have, the more complementary, the more synergy you have.

QUESTION: Do you recommend preemptive vaccinations for people working in those major

hobs?

DR. EPSTEIN: No, because -- Again, what we keep trying to say is we're presenting here ways of thinking about the problem, not presenting the decision itself. And right now the persons working those hubs are not seen as a major, my understanding of the risk as it's been presented publicly, is that that's not a major issue right now.

QUESTION: Al Millikan, Washington Independent Writers.

Are there ways each of us can be prepared or be able to spot an outbreak of smallpox? And is there anything we can learn from other nations? In your biographical information I see you do have experience in collaboration with other nations on health concerns. Is there anything they can do to help us?

And specifically, at a recent press conference there was a Russian political leader who implied that the United States needed Russia and their help in combating biological and chemical warfare. Are other nations prepared in a way we are not?

DR. BURKE: Yes, my specialty is international health and I do a lot of my time on the road in other countries in Africa and Asia so I think about this a lot.

One other way of phrasing the question if I could is to say if there were to be a reintroduction of smallpox today anywhere in the world, should that be seen as a threat to the United States, should we respond, and should we make every effort to quench or re-eradicate smallpox? I'll use the word re-eradicate. It's been eradicated once. It gets introduced again. Should our goal be to re-eradicate it?

Certainly that's the policy in the United States. If we have smallpox in the United States we want to stop every case in the United States. But then you ask what about the rest of the world? If there's an epidemic that occurs somewhere else is it in our interest, our national interest, to see that the epidemic -- and I think strongly the answer is yes. If there's smallpox going around anywhere in the world, it's going to be a threat to the United States.

So I would echo those sentiments, that we want to work internationally on this. And already the United States has quietly made a number of preparations to deal with an epidemic anywhere on the face of the earth, and I think that's a very sound strategy.

QUESTION: Beth Sauer from Johns Hopkins University.

I'm sort of curious about the tactical implications or the counter-tactical implications of this. Sitting here if I were a terrorist, and if the work place were an airport, it seems like it's one thing to go to work in an office where you can sort of trace office contacts. It's another, if I were an airport workers, for example, of a bus driver, subway driver. My contact in the work place would be very different.

So on the one hand have you considered those kinds of contacts? And the second is, how could this model be used sort of counter to the policy implications as a tactical strategy for terrorism, and have you thought about that?

DR. EPSTEIN: We haven't thought about it a great deal although I suppose it's a possibility that people could use this for other purposes. But regarding other tactics for vaccinations, again I just want to come back to this point, that by vaccinating a large body of the population you protect yourself against the introduction wherever it might be. The evolution of the epidemic is not particularly sensitive.

We gave it to a commuter, for example, to make it the worst case. Someone who is circulating well. And he is a worker. He goes to the other towns' work place and comes back. He doesn't work in the hospital.

But I don't think, I'd be surprised if varying the index case or even playing with a number of index cases moderately would vastly change our conclusions regarding those directions that seem most promising.

I guess this is it. Thank you very much for coming.

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