Presentation to the AMORS IX

Planning and Response Resources for Infectious Disease

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Good morning/afternoon, ladies and gentlemen. I am Norm Johnson from Referentia Systems. I want to share with you today my experience over the last 10 years in developing planning and response resources for addressing infectious diseases - mostly for the U.S. Government and public. While I was at Los Alamos National Laboratory I worked on the problem all the way from the pathogen (the bug that kills you) to developing the advanced epidemiological simulation resources to conducting comprehensive risk assessments to biological threats. At the end of this talk I include a list of references and contact information to help you learn more.

Because we live in a world of infectious disease in personal, public and military systems, there are many ways to begin. I will start by summarizing how the health community views infectious threats.

Infectious threats, unlike nuclear threats, are common and daily cause many deaths, and are becoming more so as our populations become denser and we travel and transfer goods worldwide. The potential for an outbreak to start is proportional to the number of people and the speed of spread is proportional to our travel.

Infectious disease is also a major source of instability in developing and underdeveloped countries, as we have seen after regional wars and disasters, largely due to the relative decline of healthcare in these countries.

Finally, developed countries are at great risk to new biothreats, just as we are to terrorism in general. Because our economies are sensitive to elective consumerism and because we operate our countries more optimally, we are more sensitive to disruption. We also are becoming more at risk because medical advances have "dual ``uses": biotechnology can be used for aiding public health, as well as developing, even unintentionally, the next biothreat.

Leading Infectious Causes of Death Worldwide

Cause	Rank	1993 rank	~Number of Deaths
Respiratory infections	1	1	3,871,000
HIV/AIDS	2	7	2,866,000
Diarrheal diseases	3	2	2,001,000
Tuberculosis	4	3	1,644,000
Malaria	5	4	1,124,000
Measles	6	5	745,000
Pertussis	7	7	285,000
Tetanus	8	12	282,000
Meningitis	9	8	173,000
Syphilis	10	11	167,000

Source: WHO, 2002

This slide illustrates many of these points. As you see in the table above of the yearly deaths from infectious disease in year 2002, many parts of the world are still very much fighting a battle of life and death - most of these deaths occur in developing countries. Three observations: First, the diseases in yellow are preventable - about 30% of the total deaths - illustrating that we are not addressing even curable problems due to poor public health resources. Secondly, the third killer, HIV/AIDS, wasn't even known 20 years ago and has grown by a factor of 10 in 7 years. Many of the biothreats that concern health officials in developed countries are new ones (such as Ebola) or old ones that have developed resistance to our treatments - a common approach to biological warfare - as in the case of tuberculosis. Finally, an influenza pandemic will happen and could increase the first number by 10 to 100 times.

Infrastructure Impact and Dependency

Dependency matrix - Critical Infrastructure Protection Task Force of Canada

		Energy & Utilities					Services		
Sector	Element	Electrical Power (Greatest Impact)	Water Purification	Sewage Treatment	Natural Gas	Oil Industry	Customs and Immigration	Hospital & Health Care Services	Food Industry
Energy & Utilities	Electrical Power		L			M			
	Water Purification	H				M			
	Sewage Treatment	M	H			H			
	Natural Gas	L				L			
	Oil Industry	H	L						
Services	Customs & Immigration	H	L	L	L	L		L	
	Hospital & Health Care Services	H	H	L	H	H	M		H	(Greatest Dependency)
	Food Industry	H	H	H	L	M	M	L	

KEY H High M Medium L Low

- Because workers are required to support all systems, high dependency of health care is a problem.
- Not evaluated is workforce impact - as might be drastically reduced by a failure of the health care system.

See Grenier, Jacques. "The Challenge of CIP Interdependencies". *Conference on the Future of European Crisis Management* (Uppsala, 19-21 March 2001). http://www.ntia.doc.gov/osmhome/cip/workshop/ciptf_files/frame.htm.

The greatest concern of a potential outbreak is the possibly of a failure of civilization. One could cite as proof the economic impact of the Severe Acute Respiratory Syndrome, or SARS, outbreak in Asia, which was devastating to some regions, particularly considering that the number of SARS deaths was well below those of a normal influenza season - this illustrates how we have become more vulnerable because consumer behavior dominates the economy in developed countries.

Another perspective is the growing dependencies of our infrastructures and is relevant to the rest of this talk. An important study was released in 2001 by Canada based on the input of about 60 experts - evaluating the dependency of one infrastructure on another. The above chart summarizes the results. You can read dependency by rows: the Food Industry has a low dependency on Health care, but health care has a high dependency on the food industry.

Not surprisingly, electrical power had the biggest impact on other infrastructures (reading down the chart). Maybe more surprising was that the public health services have the highest dependencies of all infrastructures. But because all infrastructures depend on a workforce, one can propose a rapid failure of many infrastructures if the public health system collapses. A study of the impact on the workforce by sector due to pandemic influenza strongly reinforced this conclusion.

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Operational Response to Infectious Disease

Approach:
- Capture primary impact - disease progression
- Capture secondary/tertiary effects - e.g, mission readiness

Goal:
- Avoid breakpoints - significant system transitions from relatively small changes - particularly, in the health system
- Breakpoints in one system can cause breakpoints in other systems.

Game Changer: Mitigations (preventative measures) can prevent breakpoints.

What resources are available?

How is the previous discussion applied to determining operational readiness to infectious diseases? We conclude that we must first capture the primary impact of an infectious disease on the population or subpopulation of interest. And then we need to evaluate how the change in the workforce impacts the mission readiness, both for the public, which may choose not to work if they are threatened, and for the military, which may have to supplement the public workforce, while at the same time also being impacted by illness.

A major lesson learned in risk assessment is that the first analysis is to determine if a small change results in a significant system transition - a tipping point or breakpoint. And as reflected in the prior dependency matrix, breakpoints in one system can cause breakpoints in other systems if there is a high dependency. Our goal then is to avoid breakpoints by applying preventative measures or mitigations where necessary.
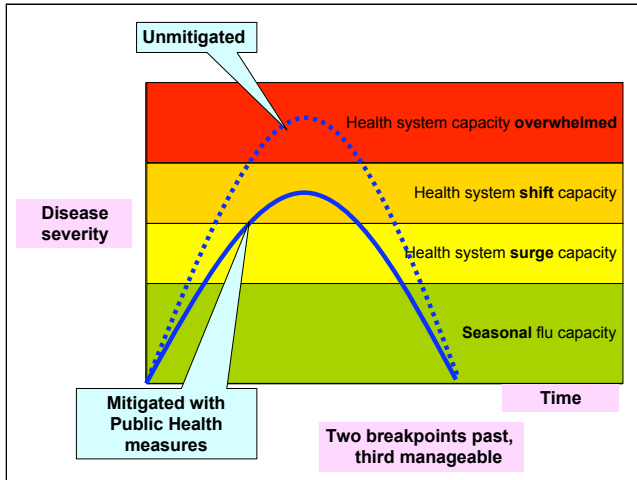
The rest of this talk discusses the resources available to help us in these goals.

Breakpoints in the public health systems (from AUS MoH)
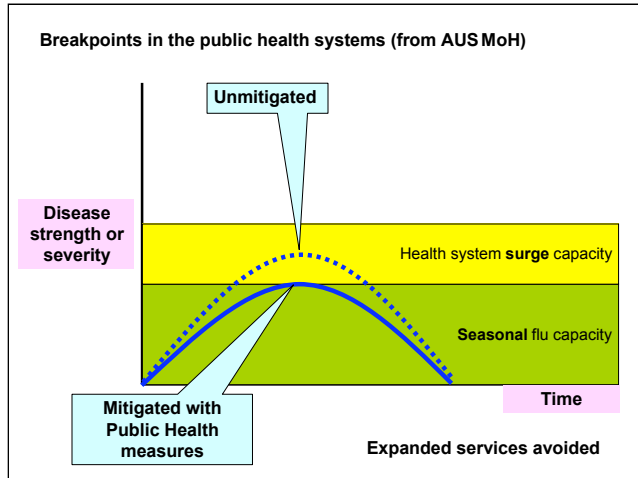
Let's first address what a breakpoint looks like in the public health system. The following sets of slides are from the Australian Ministry of Health and describe very well the different breakpoints in the health system and how mitigations can potentially avoid them. Take the response to pandemic flu. At a first level of response, if a pandemic is more severe than a normal flu season, then it may cause the health system to provide a surge capacity to address the extra cases. At this level of disease severity the system may not experience a breakpoint, but a normal expansion of services. Mitigation actions can keep an outbreak within the normal fluctuation of cases and the need to utilize the surge capacity is avoided.
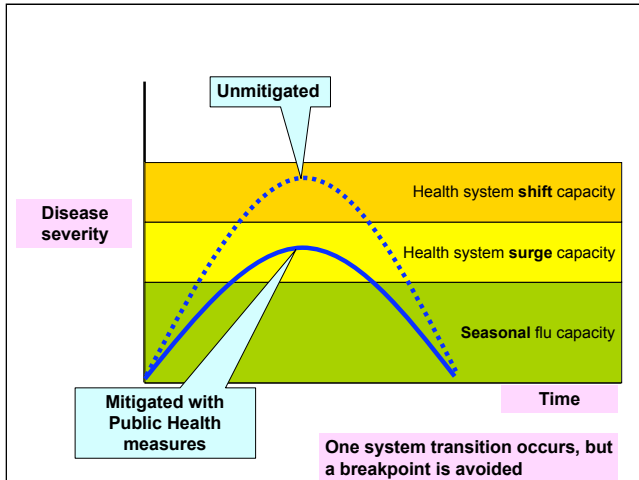
If the disease severity is greater, then the health system will have to respond with extreme shifts in resources, such as triage of patients, establishment of temporary treatment centers or large scale quarantine. Mitigation measures can avoid the this breakpoint.

If the disease severity is even greater, then mitigations can mean the difference between the health system in a extreme operational response or being overwhelmed and possibly failing - with the potential of extreme public reactions and societal impact. Again mitigations can avoid this breakpoint.
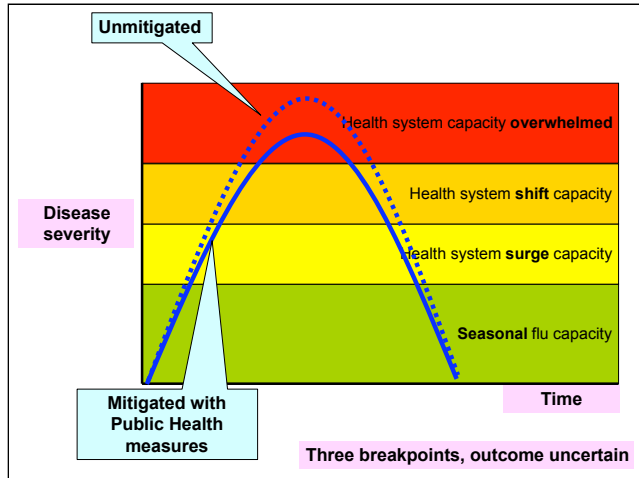
Finally in extreme disease severity, there may be no mitigation options that avoid breakpoints, as indicated in the figure.

How are these transitions determined and what do they depend upon? Not surprisingly, each infectious disease has different resource requirements, breakpoints and mitigations. For example, because of the limited supply of ventilators (medical devices for assisting breathing), diseases that require ventilators, such as a botulism toxin exposure or pandemic influenza, quickly overwhelm the health system, whereas other threats would not. Furthermore, different strains of an infectious disease may behave very differently. For example, pandemic influenza in the first years tends to attack healthy adults, but in later years attacks children and the elderly. Hence the early phase of a pandemic can have a significant impact on the workforce, including health care workers.

So what resources are available for the quick determination of breakpoints, which depend on response times and resources available and mitigation options?

Disease Progression in a diverse population
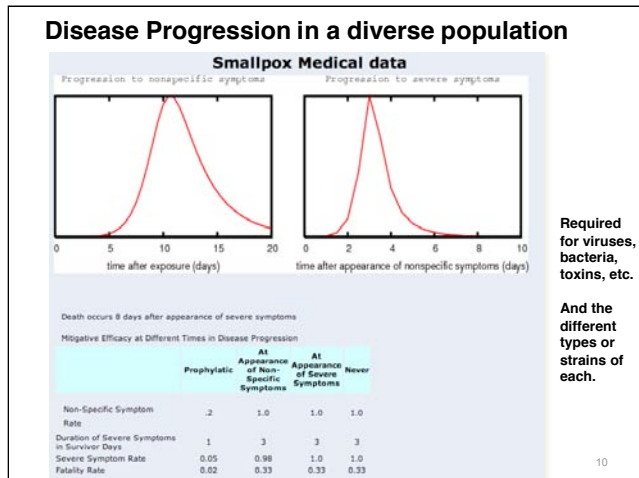
Before considering the first type of resource required, one point must be stressed: The greatest challenge to an operational response is planning and responding to an unknown threat. The faster the threat agent can be identified, the faster existing knowledge can be applied, such as how to avoid spreading the disease. Severe Acute Respiratory Syndrome (SARS) was an excellent example - until it was identified, there was great uncertainty how to limit its spread and how to develop a treatment. But once identified, response strategies were quickly implemented and public fears lessened. The health community is severely challenged at present to identify unknown threats, particularly engineered threats. Addressing this issue is beyond the scope of this talk, although I would be happy to talk with you about it. In the remainder of this talk, we assume the threat can be identified.
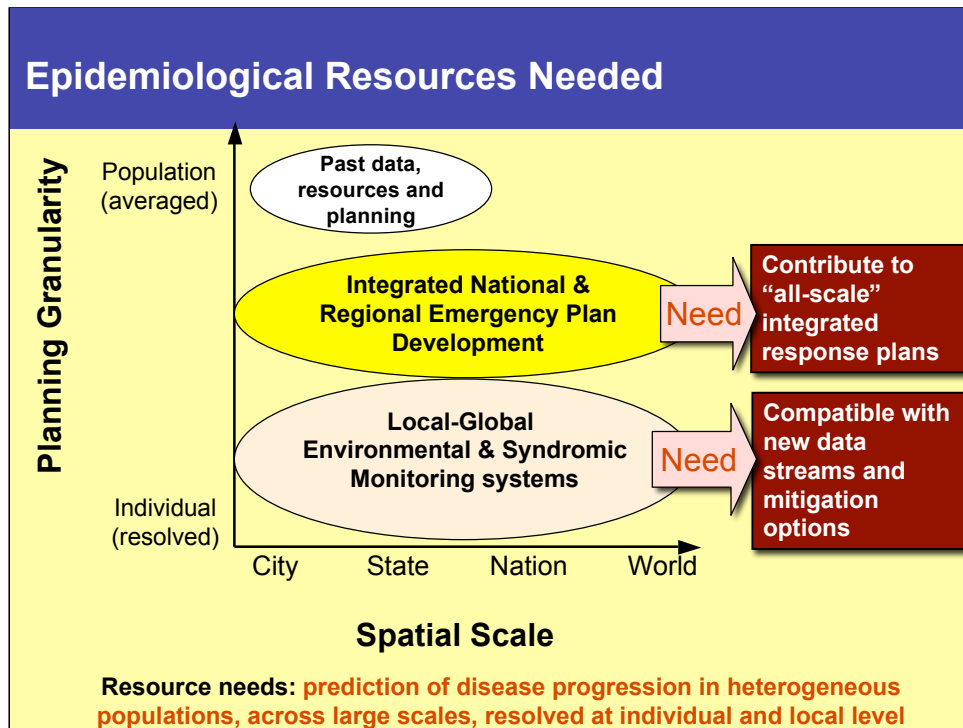
After determining the biothreat, a major consideration is the distribution of responses by the population exposed. Some individuals may never get sick, even though they are exposed. And some individuals may be the first to be sick, particularly immune-compromised individuals (such as children, elderly, or HIV patients). We need to understand the sensitivities and disease progression in a diverse population. This is particularly true if there is a widespread low-level dispersion of a threat, such as the anthrax mail attack in the United States, where many people are exposed and the extremes of the sensitivity of the population becomes important.

What we find is that analysis resources that can handle diverse responses (like agent-based models) are often computationally intensive and are not useful for quick analysis.

A unique approach to this problem is captured in the Bio-Agent Reference Tool (BART) resource. The inputs to BART are shown on this slide, and they begin with distributions of progression to different stages of a disease. For example, the curve for smallpox at the left represents the likelihood at different times that an individual will progress after being exposed to showing nonspecific symptoms (meaning they are difficult to diagnose). These distributions are based on progressions of known diseases in a general population, but exhibit a general shape as shown. They capture the sensitive individuals at the left edge of the distribution and the strong individuals at the right. And if the area under the distribution is less than one, some individuals will never become ill. The curve on the right shows the progression to the next stage of illness, severe symptoms, again reflecting the same general shape. These distributions when combined with fatality information capture the main disease stages recognized by health officials, providing the numbers of individuals in each stage of disease progression (incubating, non-specific, severe, dead, or recovered) over time, but unlike the SIRx models, it accurately captures the extremes of the response.

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Example: **Biological Agent Reference Tool (BART):**
a Web-based response information tool
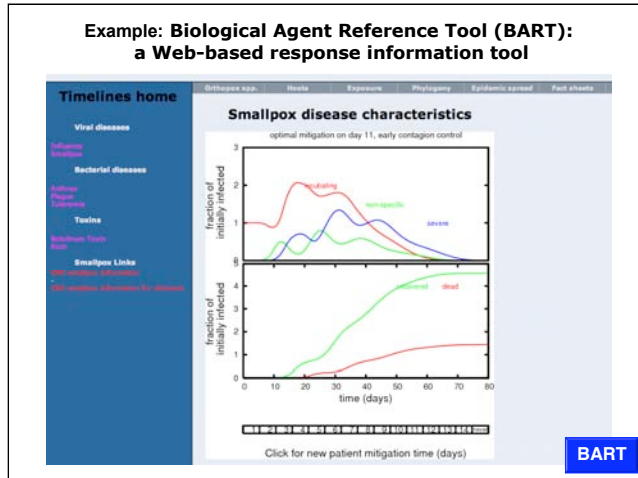
This is what the BART output looks like for smallpox. The tool is web-based so it can be quickly demonstrated as I will do now. In the figures the fraction of initially infected is given for each stage over time. For example the red curve in the upper figure is the fraction of incubating cases. By clicking at different times of mitigation, the impact on the stages can be quickly observed. This allows analysts to determine when actions must be taken to avoid breakpoints, all assuming that the threat agent is known. The results are given in fractions of the initial population exposed, so that the values of the curves can quickly be adjusted to different numbers of populations exposed. For example for an initial exposed population of 1000 people (using a mitigation of 11 days after first exposure) results in about 1300 people with severe symptoms at 30 days, the peak. Alternative mitigation times can be examined, quickly finding the breakpoints where actions must be taken. BART also allows for different severities of epidemics if appropriate. The resource provides valuable information on the symptoms and treatments of the disease, enabling the analyst to quickly become knowledgeable. I am happy to let you explore this resource yourself. In this prototype, 7 bioagents are available, with different severities and mitigation times.

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Epidemiological Resources Needed

Planning Granularity

Population (averaged)

Past data, resources and planning

Integrated National & Regional Emergency Plan Development

Need → Contribute to "all-scale" integrated response plans

Local-Global Environmental & Syndromic Monitoring systems

Need → Compatible with new data streams and mitigation options

Individual (resolved)

City   State   Nation   World

Spatial Scale

Resource needs: prediction of disease progression in heterogeneous populations, across large scales, resolved at individual and local level

Although the BART resource is good first option to answer "How quickly do I have to respond and with what resources?" there are additional resources required driven by two new requirements for planning and response:

1) Because of the appreciation of the vulnerability and dependency of our national systems on local outbreaks, we are developing integrated national, regional and local response plans; and

2) Because monitoring systems are being developed that provide resolution at an individual or local level and because we are developing response options that are deployed at a individual and local level (such as targeted antiviral prophylaxis - TAP), we require resources that are resolved at an individual level.

Therefore we need resources that can predict disease progression in diverse populations at an individual-to-global level, and resolved spatially at least at community level. This is a major challenge, unthinkable 10 years ago.

A Landscape of Epidemiological Options
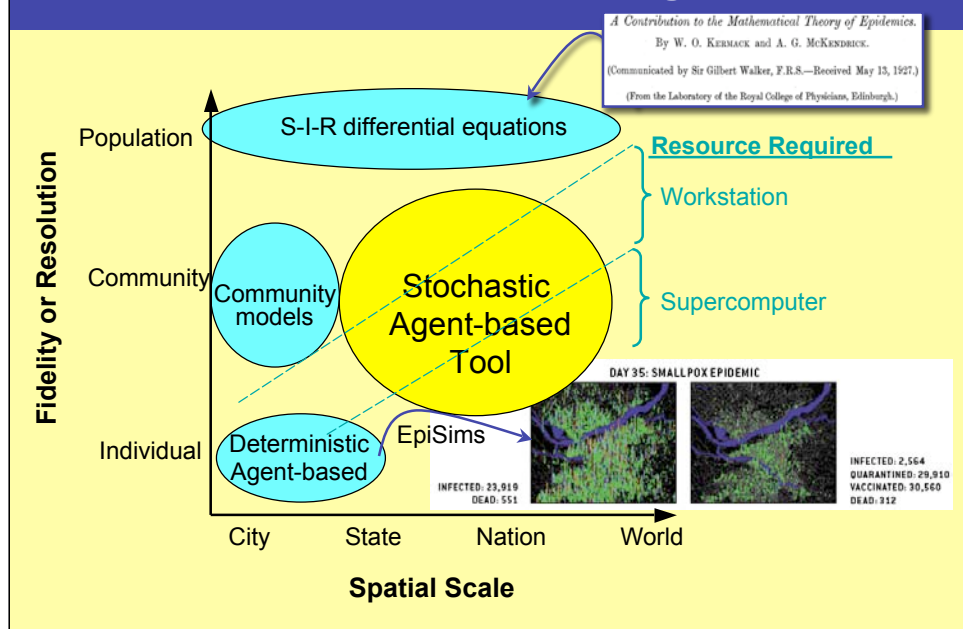
This diagram organizes the different approaches available based on population resolution and spatial scale. Math-based epidemiological models have been developed over the last 80 years, starting in 1927 with the populations level models: the so-called Susceptible-Infected-Recovered (SIR) model. These models have three or more differential equations that capture the movement of a disease progression within well-mixed populations. "Well-mixed" means that individuals are not modeled, but portions of a homogenous population. These models are still in use, because they can easily be modified, solved and analyzed for stability conditions. But they suffer because they cannot describe individuals or random aspects of an epidemic. Unless modified, they give the same answers each time they are solved, although we know that initial epidemics are quite variable.

At the other end of the resolution are deterministic agent-based models that capture each individual at every moment. The data requirements of these models are very detailed and costly. These models are consequentially very computationally demanding. One of the first resources of this type is EpiSims, a project I worked on at Los Alamos. Just as in other applications, these high-fidelity models are typically not useful for analysis of ongoing events, but can be valuable to support the development of faster-running resources.

The middle of the chart shows agent-based models that simplify the detailed contact networks of the deterministic models by using a community model to capture the likelihood that you'll encounter different groups within your community. We'll see an example of this shortly. Because these models are more computationally efficient, they can be extended to address the needs identified in the previous slide of connecting local to global response plans and the new local and individual monitoring and mitigation resources. I helped lead the team that developed the first large-scale stochastic agent model, called EpiCast, in 2002. EpiCast was developed to address the limitations of the EpiSims resource.

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EpiCast (Epidemiological Forecasting)

- A stochastic agent-based simulation model to predict the global/national/regional spread of infectious diseases and to assess mitigation strategies
- Capable of simulating billions of agents on supercomputers and millions on laptops

Four components:

1. An Individual disease progression model - varies by type of person: age, occupation, health status, but not location.
2. Demographics (where people live) and workerflow data (where they work) – at "community" resolution.
3. Community network: Contacts between people based on contact groups (family, work group, school, community…).
4. Irregular travel - travel between Community networks, usually long range.

Disease model is general. The rest are determined by data from area of operations

T. C. Germann, K. Kadau, I. M. Longini, and C. A. Macken, "Mitigation Strategies for Pandemic Influenza in the United States," *Proceedings of the National Academy of Sciences* **103**, 5935-40 (2006).

EpiCast stands for Epidemiological Forecasting - and was developed by applying a world-class atom modeling simulation resource (called SPASM) to epidemics. We have shown that it can be used to model all the people in the world if the right data is available to initiate the simulation. Four components of information are required:

1. A disease progression model within an individual: this describes how a person gets sick given their age, state of health, etc.
2. Demographics: this identifies where people live and work at an individual level and is usually taken from census data.
3. Community network: This specifies how people come into contact with each other in a "normal" day or night. Typically the community includes all aspects of life that are important to an infectious spread: family, work, schools, social gatherings, etc.
4. Irregular travel: this describes the contacts that are in addition to the community network model, and are typically long-range travel.

Of these four, the disease model is general for each threat type, but doesn't depend on location. The rest are determined by the activities of individuals in the area of application. Note that because infections can spread in different ways, a community model for aerosol transmission does not work for direct contact transmissions
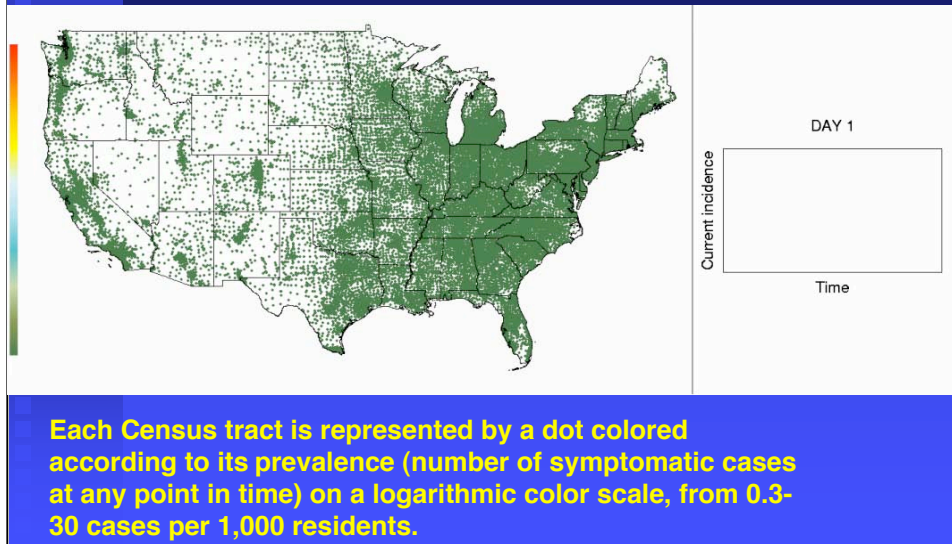
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Influenza in the US:
Planning for the next pandemic

To show you an application of EpiCast and how it is used in planning, we turn to pandemic influenza in the United States. These simulations of 280 million people were mostly done on a large computer cluster or in some cases on massively parallel supercomputers at Los Alamos. These were done to support the President's Pandemic Influenza Response Plan.

Data from the United States were used to set up the simulations: using demographics from the 2005 census, workflow data, and long-range travel statistics. For example, if you filled out a census form in the United States, you are represented in the simulation; your home is resolved at a community or "track" level, about 1000 to 5000 people. The community model used is a validated model of how an infection spreads in a community of 2000 people and captures the likelihood of transmission in your home, school, work and community. The community model is general enough that simulations can be quickly transferred to other countries. For example, Australia is using EpiCast for their pandemic flu planning. EpiCast can also be used on a laptop for regional simulations, as is being done in 3 U.S. cities in a Deptarrtment of Homeland Security program.

Baseline - Moderate Severity

Each Census tract is represented by a dot colored according to its prevalence (number of symptomatic cases at any point in time) on a logarithmic color scale, from 0.3-30 cases per 1,000 residents.

This is what a baseline pandemic flu outbreak looks like using EpiCast - where the flu is introduced by 40 infected travelers returning from abroad entering 14 airports in the United States and returning to their families. This is for a moderately severity pandemic with a reproductive number of 1.9 (meaning approximately 1.9 new cases for each infection).

The color represents the prevalence on a logarithmic color scale, shown at the left, from 0.3 to 30 cases per 1000 people at a given time. A baseline means that no additional mitigation is used besides what an individual normally does: when you are severely sick you stay at home: you don't travel, you don't infect people at work or your community, but you still can infect family or visitors. The details of the simulation are as realistic as possible, for example the disease progression allows for a person to be contagious when they are not aware they are sick, just as in the real influenza. All ages are resolved, so children and adults have different behaviors and rates of infection.
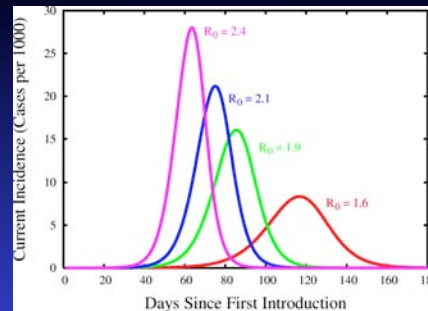
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Baseline simulated pandemics

Most of the epidemic activity is in a 2-3 month period, starting 1-2 months after introduction

Table 4. Characteristics of nationwide outbreaks of pandemic influenza, as given by baseline simulations without any interventions.

	0.12	0.15	0.17	0.20
Probability of transmission given contact, P_{Trans}	0.12	0.15	0.17	0.20
Basic reproductive number, R_0	1.6	1.9	2.1	2.4
1,000th ill person, days after initial introduction	14	13	12	11
10,000th ill person, days after initial introduction	29	24	22	19
100,000th ill person, days after initial introduction	48	37	34	29
1,000,000th ill person, days after initial introduction	70	52	46	39
Peak of epidemic, days after initial introduction	117	85	75	64
Peak of epidemic, number of new cases	2.3 M	4.5 M	6.0 M	7.9 M
Duration, number of days with >100,000 new cases	86	68	60	52
Cumulative number of ill persons	92 M	122 M	136 M	151 M

Different severities of the pandemic can be simulated by adjusting the disease progression parameters. Note that EpiCast does not have a parameter for the reproductive number, as in the SIR models, but the disease parameters have to be adjusted to reproduce a desired reproductive number. Generally for these unmitigated pandemics, the change in severity changes the location of the peak of the epidemic, but has less effect on the total number of infecteds (the area under the curve). For example in these runs the total number infected only varies by 50% where the peak varies by 2. Note how the epidemic is not really noticeable for 1-2 months and then peaks in 2 to 4 months, as is observed in a normal flu season.

Breakpoint ($R_0 \sim 1$) Behavior

$R_0 \sim 0.9$

$R_0 \sim 1.2$
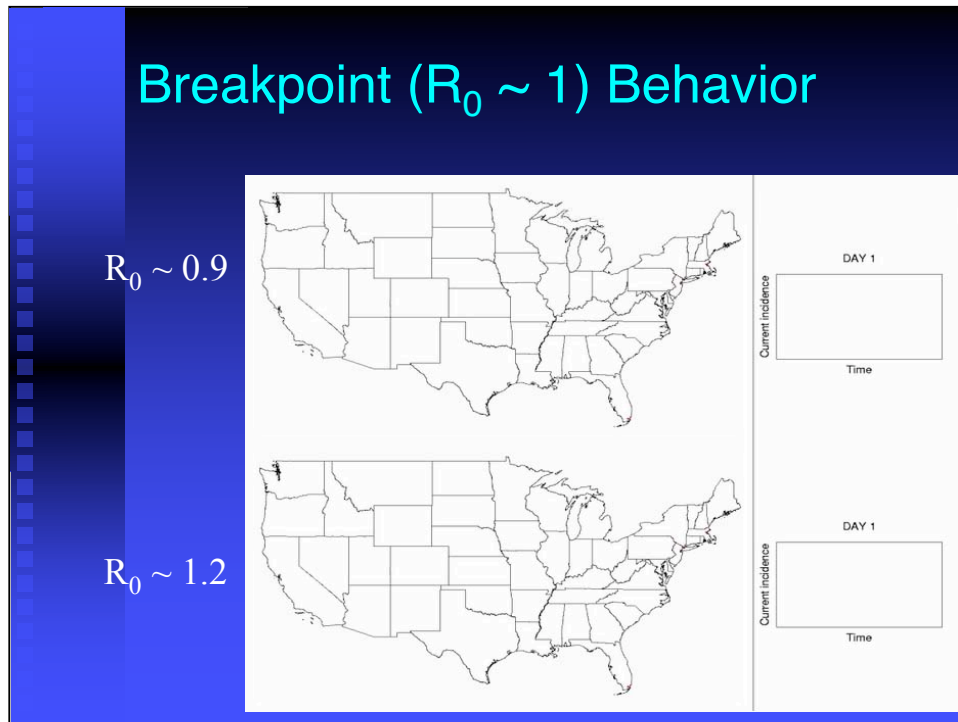
A very important point is illustrated by these two baseline simulations, which show two different severities of a pandemic. Note how different they are in intensity. The pandemic has a breakpoint around a reproductive number of one. Therefore if a mitigation strategy can consistently reduce the reproductive number to less than one, a significant reduction in the intensity of the pandemic occurs. This is the best outcome of an effective mitigation.

Introduction of 40 infecteds on day 0, either in NY or LA, with and without nationwide travel restrictions

Day 60

Day 80

Day 100

Day 120
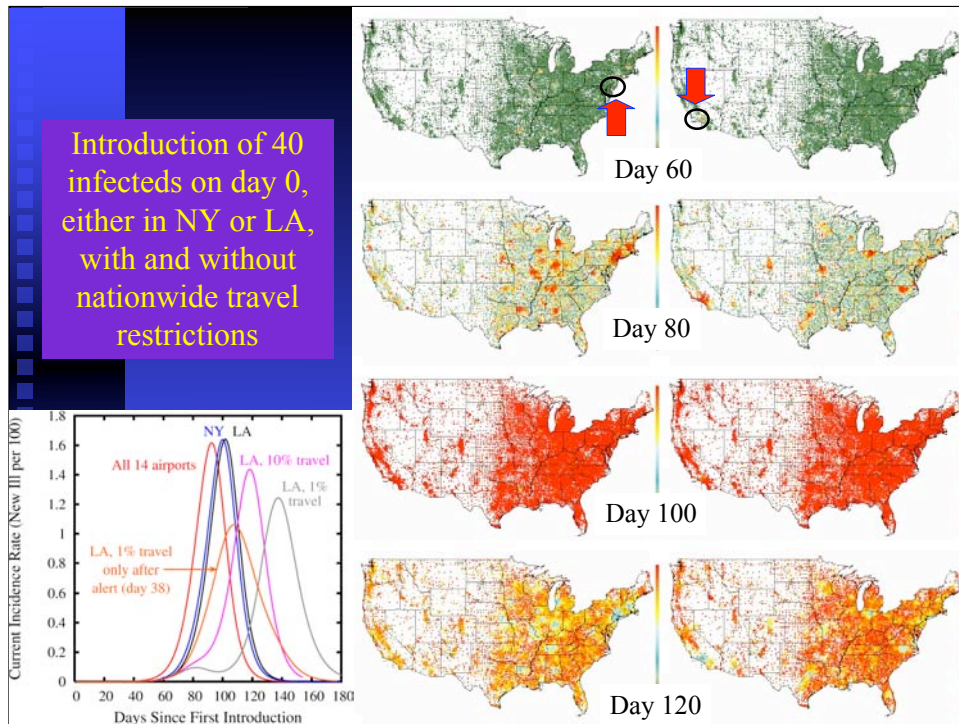
Because we don't know how the pandemic will start, we examined different introductions of the pandemic flu into the United States. Shown here is a comparison of an east and west coast introduction (40 infected individuals). In general, the initiation of the pandemic had little final impact on the pandemics. Also shown in the figure is how travel restrictions affect the pandemic: although they delay the pandemic, they have almost no impact on the total number of infected people, even for a 99% reduction in long-distance travel. Therefore, quarantine and stopping long-range travel only buys time for other mitigation strategies, such a development and distribution of a low-efficacy (effectiveness) vaccine.

Strategies for Pandemic Influenza Mitigation for R_0 = 1.8
(Simulations of 280 mill people in USA for "moderate" pandemic)

Successful Mitigations

- ☐ 60% TAP (182 M)
- ■ Vaccination – child-first
- ■ Vaccination (random) + school closure + social distancing + travel restrictions
- ■ Vaccination (child-first) + school closure + social distancing + travel restrictions
- ■ 80% TAP (0.7 M) + vaccination (random) + school closure + social distancing + travel restrictions

Number ill per 1000

0   10   20   30   40   50
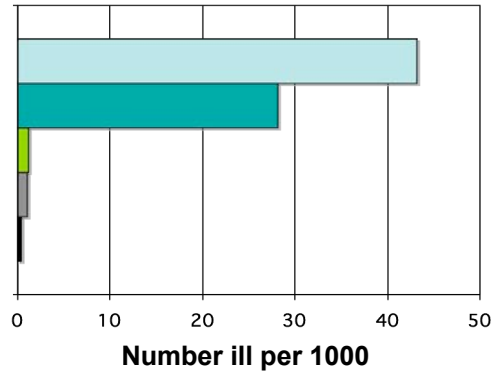
Failed Mitigations - Full Pandemic (>10%)	Uncertain Mitigations
• Social distancing alone • Travel restrictions alone • Social distancing + travel restrictions	• Vaccination - random • School closure alone

Hundreds of simulations were done. This is a summary of the most realistic mitigation strategies and was used into develop the U.S. Pandemic Response Plan. The upper half shows the successful mitigations - called successful even though many people still get sick - but less than 10% of the population. Note how that even the better mitigations still require multiple interventions for this moderate pandemic - this is largely due to the fact that influenza is difficult to stop spreading and that the entire population is susceptible to the pandemic, unlike a normal influenza season. Also note that the first one using Therapeutic Antiviral Prophylaxis (TAP) alone requires numbers of anti-viral doses that currently exceed those U.S. stockpiles.

At the bottom are the uncertain and failed mitigations. The uncertain ones sometimes work and sometimes don't. They have a reproductive number near one.

As the severity of the pandemic increases, some of the successful mitigations will fail (like TAP alone), leaving fewer options. At the most severe pandemic, only the mitigation that use all options prevents a full pandemic.

While I talk about the these EpiCast results with confidence, there are many uncertainties. For example, the effectiveness of TAP is unknown because anti-viral effectiveness will depend on the viral strain that causes the pandemic. Given the many uncertainties, simulation resources can always be improved and better tailored to the current problem. But in a system-of-systems viewpoint, there are other considerations that are of equal concern.

Resources like EpiCast tell you the impact of illness but do not tell you the how these illnesses impact the functioning of society or mission readiness. To end the presentation I'll review the resources that provide a system-of-systems analysis.

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Modeling Military Force Structure & Interactions

How "community network" (#2) is determined:
• Each individual solider belongs to a specific squad, platoon, …, army
• The squad … division levels comprise a hierarchy of "community networks: an individual's likelihood of becoming infected from these interactions is: $p_{sqd} \cdot n_{sqd} + p_{plt} \cdot n_{plt} + … + p_{div} \cdot n_{div}$
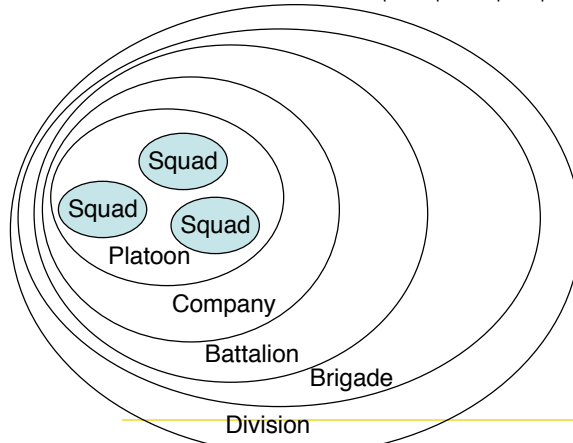
• where the p_X are contact rates from the unit interaction survey, and n_X are the number of infectious soldiers in that unit.
• A survey was done to determine p_X.

Squad
Squad
Squad
Platoon
Company
Battalion
Brigade
Division

To show how EpiCast can be applied to the military, the next slides show how EpiCast examined the spread of smallpox in the Korean peninsula. First a "community" network model is needed for the military. Each individual belongs to a specific squad, platoon, etc. This comprises a hierarchy of community networks as shown. The likelihood of an individual becoming infected depends on the interactions of an individual with infecteds in each of these "communities", as shown in the equation. Px is the probability of having contact with an infected person in that unit. And Nx is the number of infectious soldiers in that unit. A survey was done to determine Px. Please inquire about how how this was done and how you can duplicate the same process.

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Modeling military force structure & interactions

How "irregular travel", typically long-range travel, is modeled:
• Interactions with other divisions are captured in a manner analogous to the long-range travel in the civilian sector:
    • With a specified frequency, soldiers are randomly selected and sent for a period of 1-14 days to a unit outside their own division
    • The outside unit is randomly selected, but biased towards those in the same corps to approximate "upward" interaction rates

PLT
CO
BTN
BDE
DIV

PLT
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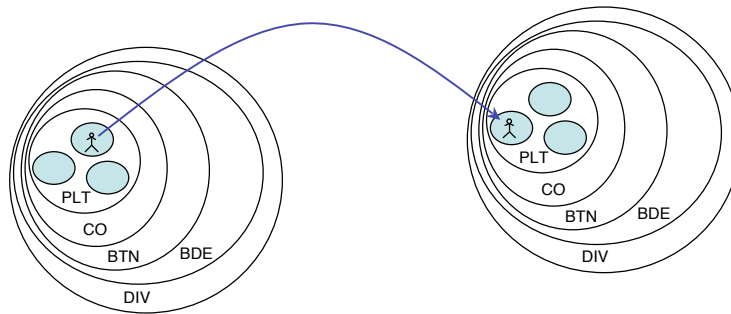
The next requirement is to capture "irregular travel". This was captured by moving a solider selected randomly and with a specified frequency to another unit for 1-14 days. Because one is more likely to interact within the same corps there is a bias in the frequency of unit selection to capture this.

Demographics and Workflow (#2) and Irregular travel (#4) for Public-military Model for South Korea

Public (#2 and #4):
- Census for 2000 for the 9 provinces and 6 special cities, ranging from 0.5 to 10 million people each (46 million total) - used in "public" community network.
- Worker-flow data estimated by geographic proximity (no USA census-like data available).
- Random long-range travel by public

Military demographics (#2):
- Republic of Korea forces down to battalion level
- U.S. forces in South Korea

Military-Civilian interaction (#4):
- Based upon the geographic position of each military unit; soldiers occasionally (very rarely) interact with a random community in the local province/special city.

The details of the public community model is similar to what was used for the earlier pandemic simulations. These were based on the 2000 Census of Korea for the 9 provinces and 6 cities; 46 million people total. The worker flow data for the public was estimated by geographic proximity (comparable data to what we used for the USA was not available). Finally random long-range travel was used for the public, as for the military. The Republic of Korea forces were modeled down to the battalion level. And the U.S. forces were modeled in the detail that was available. The military-civilian interaction was modeled by a relatively rare random interaction between a military and public individual.

Effect of US vaccination policy on public (smallpox)
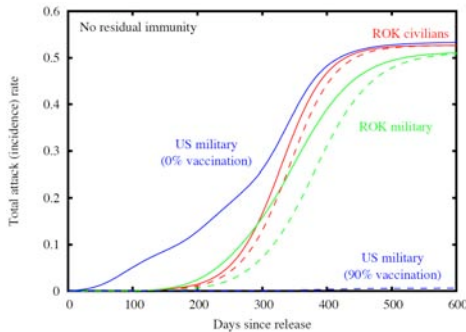
Final attack rates
(averaged over 10 realizations):

US military vaccination level	civilians	ROK forces	US forces
0%	52.7%	51.3%	53.4%
90%	52.7%	51.4%	0.6%

- No protection of public is observed for different rates of vaccination of US forces (as expected - military are not "spreaders").

- US forces remain at risk due to the widespread epidemic among the surrounding (unvaccinated) population.

This combined military and public model was then used to evaluate different mitigation strategies for a smallpox epidemic within South Korea. Representative results are shown. Attack rates are the percent of the total population infected. In examining the effect of vaccination rates of U.S. troops on the South Korean public, not unexpectedly no dependency on U.S. forces vaccination was observed - that is, the military don't act as spreaders. The opposite is not true: the U.S. force remains at risk due to the widespread epidemic in the surrounding population, even though their contact is rare. There is nothing surprising here. But this leads to looking at quarantine as an option.

Mitigation: Post-detection intervention of quarantine

- Assume 50% leakage from civilian quarantine, but perfect squad-level quarantine of military personnel
- Quarantine benefits non-quarantined civilians

Final attack rates
(averaged over 10 realizations):

US military vaccination level	civilians	ROK forces	US forces
0%	52.7%	51.3%	53.4%
90%	52.7%	51.4%	0.6%
90% + quarantine	0.04%	0.01%	0.04%
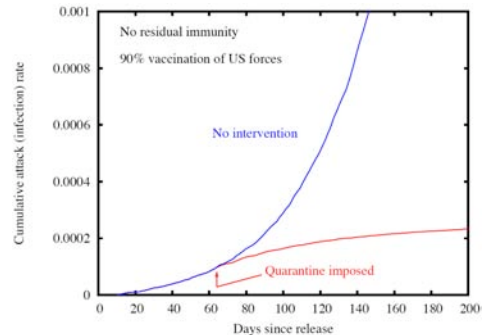
Conclusions: no surprises because of the long time of disease progression of small pox. The same conclusions are NOT true for pandemic influenza!

To simulate a real quarantine, we assume that 50% leakage would occur from civilian quarantine, but military quarantine would be perfect at a squad level. Not surprising, for smallpox, even a poor quarantine is a ver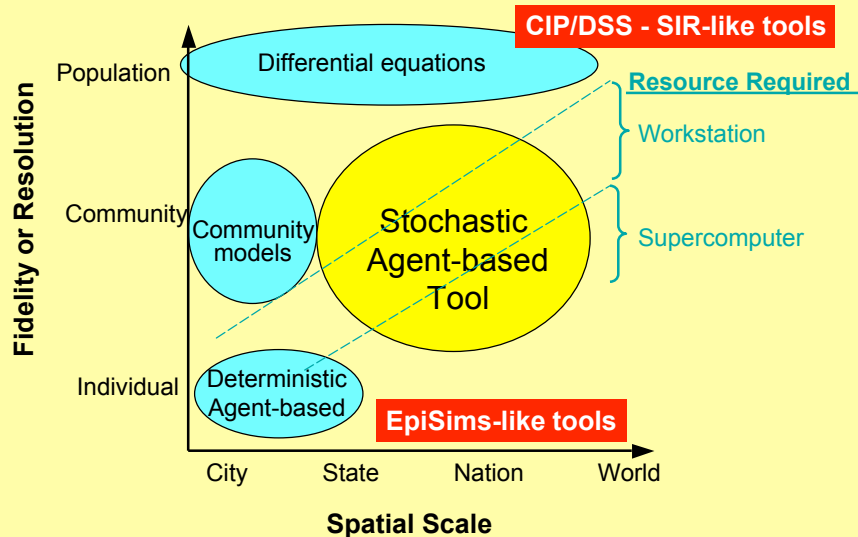y effective mitigation, for all populations. Largely this is due to what we saw earlier that smallpox takes many days to become infectious and you know when you are infectious, so quarantines are effective options. But the same is not true for pandemic influenza, where a person can become a spreader even before they show symptoms.

While I talk about the these EpiCast results with confidence, there are many uncertainties. For example, the effectiveness of vaccine is unknown because vaccine effectiveness will depend on the viral strain. Given the many uncertainties, simulation resources can always be improved and better tailored to the current problem. But in a system-of-systems viewpoint, there are other considerations that are of equal concern.

Resources like EpiCast tell you the impact of illness but does not tell you the how these illnesses impact the functioning of society or the readiness of a mission. To end the presentation I'll review the resources that provide a system-of-systems analysis.

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System-of-System Resources

Critical Infrastructure Protection (CIP) resources

CIP/DSS - SIR-like tools

Differential equations

Resource Required

Workstation

Community models

Stochastic Agent-based Tool

Supercomputer

Deterministic Agent-based

EpiSims-like tools

Population / Community / Individual — Fidelity or Resolution

City / State / Nation / World — Spatial Scale

System-of-systems analysis tools, often call Critical Infrastructure Protection (CIP) tools, are available using different approaches, from simple formulas to simulations, and covering different infrastructures. Just as we presented a landscape for epidemiological models in a previous slide, the same can be done for the CIP analysis resources. All the same observations made earlier apply here as well - what are their advantages and disadvantages, what are their different uses, what are their computational and data requirements, etc. Two are highlighted: CIP/DSS at the top and EpiSims-like tools at the bottom. These resources were developed by the National Infrastructure Simulation and Analysis Center (NISAC) Program and include the extremes of differential equation models (which include the SIRx models) at the top and deterministic agent-based models at the bottom (which include the previously described EpiSimS). Let's look at one of these.

Critical Infrastructure Interdependency Modeling: A Survey of U.S. and International Research (Aug 2006)

30 infrastructure simulations tools reviewed, based on infrastructure included, approach, coupling type, platform, software requirements, user skill, maturity.
·Tools: AIMS, Athena, CARVER+, CIMS, CIP-DSS, CIPMA, COMM-ASPEN, DEW, EMCAS, FAIT, FINSIM, IIM, MIN, NEMO, Net-Centric GIS, NISAC, NGTools,…

This slide presents results from a recently published document that reviewed 30 CIP tools. I don't expect you to read this, but the tools are listed in rows and the columns are modeled infrastructures, coupling method between infrastructures, software requirements, user skill required, and level of maturity. The more the checkmarks in a row, the more general the tool. The blue box is around the CIP/DSS tool and you see that it has more boxes checked than most.

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**CIP/DSS Resource: Coupled Infrastructures**

- **Critical Infrastructure Protection / Decision Support System (CIP/DSS) Toolset:**
    - Includes 14-17 infrastructures
    - Calibrated to detailed National Infrastructure Simulation and Analysis Center (NISAC) resources
    - Open-source approach - Implemented in a system simulation resource: VENSIM

- **Public Health component combines:**
    - A multi-binned SIRx infectious spread model (modifiable) capable of treating regional, public/military, age populations
    - Includes hospitals, staff, beds, etc.
    - Includes many medical mitigation options including use of therapeutic stockpiles and time required to distribute these

This slide summarizes CIP/DSS. It can be comprehensive because is uses an average, high-level differential equation approach. It includes 14-17 infrastructures and their many interdependencies. The public health component includes many aspects not previously mentioned - occupancy in hospitals, availability of staff and beds, medical supplies, etc.

CIP-DSS Combined Epi and Public Health
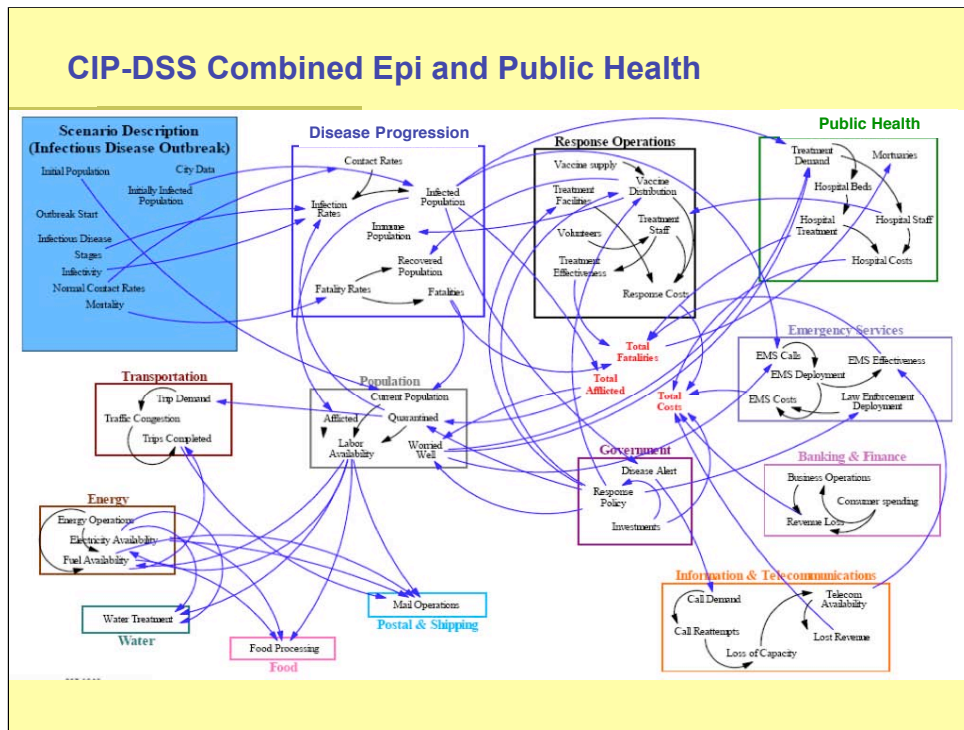
This busy figure shows the CIP/DSS infrastructures that are engaged during a large-scale outbreak. In addition to the public health system, it also includes emergency services (ambulances), workforce impacts, government functions, banking and finance, the transportation system, and postal and shipping as primary systems, and many others when secondary interdependencies are included. One can begin to see how much is missed in the prior epidemiological models and the many opportunities for breakpoints to arise for interdependencies. For example, the epidemiological models may show that you have an excellent mitigation option, but unless you can deploy it quickly using health services or postal systems, it may have no value.

Toolkit for Operational Medical Modeling (TOMM)

Disease Model

Personnel

Organization Model

Personnel Readiness Behavior Metrics

Personnel Readiness

Equipment

Equipment Maintenance Model

Equipment Readiness Behavior Metrics

Equipment Readiness

Determines impact on operational readiness and optimal course of action from automated scenario exploration
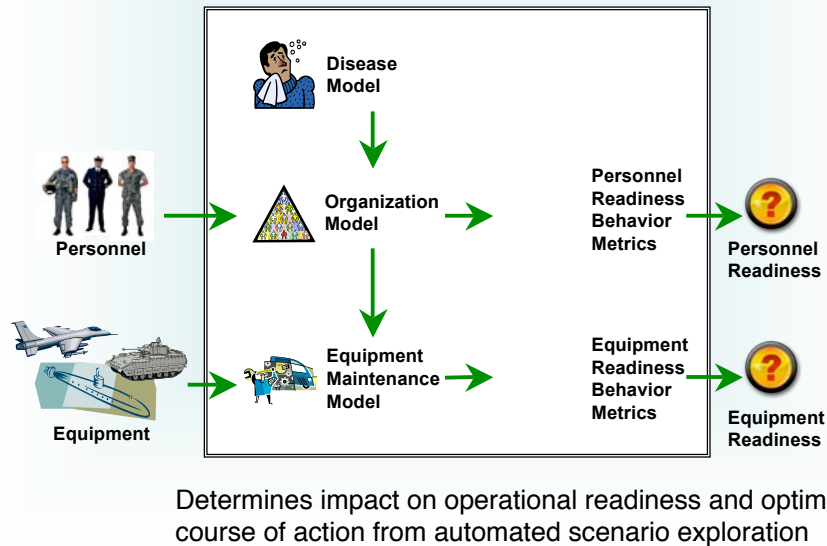
For completeness, there are tools being developed specifically as military operational planning support tools for infectious disease. One such tool is called the Toolkit for Operational Medical Modeling, or TOMM, developed by the Office of Naval Research in the U.S. Department of Defense. It combines the ability to use any of the previously discussed approaches for epidemiological modeling with readiness models that capture the impact on personnel and equipment from personnel changes. And because it can do automated scenario exploration, it can also suggest optimal courses of action from among a variety of options.

Summary of Disease Progression Resources and Their Uses

Resource	Method	Scope	Resolution	Typical Uses
BART Sponsor: DHS/S&T	Novel: distributions and disease stages	Diverse populations but well mixed	Spatial: none; Individuals: distributions; Time: minutes	**Population impact Tool:** · How quickly do I have to act? · What is the basic knowledge I need to address the threat?
CIP-DSS Source: DHS/NISAC	Couple differential equations (SIRx type)	Regional-Multisector	Spatial: regional; Individual: none; Time: minues	**Multisector Consequence Analysis:** · Sector impact? · Multiple breakpoints?
EpiCast Sponsor: DHS/S&T	Community based agent model, census data driven	World, nation, regional and local	Spatial: 2000 people tracks; Individual: yes; Time: 1/2 day	**Epidemic Forecasting Tool:** · National impact? · Individual-national options
EpiSimS Source: DHS/NISAC	Individual activity based agent model	Regional and local (to building and car level)	Spatial: buildings; Individual: detailed activity; Time: minutes	**High-fidelity geospatial epidemic progression:** · Validation of coarse models · Individual mitigation options
TOMM Sponsor: DoD/ONR	Use any epidemiolog-ical model, adds readiness evaluation	Theater of operations; public optional	Depends on epi model uses.	**Operational readiness:** · Personnel? · Mission/equipment? · Best coarse-of-action

To close, we present a chart to summarize the resources discussed and their scope, their spatial and time resolution, and typical uses. These are listed from the population-level resources at the top to the individual-based resources near the bottom. The TOMM resource is included for comparison. Basically the method that is used determines the scope and resolution possible, which in turn determines the typical uses. The method also determines the assumptions and the type of data required to initiate the simulation. This summary is good for understanding the differences between each resource, but not for selection of a resource for a specific purpose.

Selection of Resource by Application				
Application	**BART**	**CIP-DSS**	**EpiCast**	**EpiSimS**
Approach used	**Distribution functions**	**Differential SIRx models**	**Stochastic agent-based**	**Deterministic agent-based**
Predict disease progression in diverse populations for planning	Data driven for populations	Requires aggregate disease progression parameters 🟡	State of the art for national-regional epidemics 🟢	State of the art for regional epidemics 🟢
Utility of different medical mitigation options at local level	Single mitigation for each biothreat 🔴	Limited local and individual mitigations 🟡	Full spectrum, realistically implemented 🟢	Full spectrum, realistically implemented 🟢
Impact on civilian workforce	Inferred only 🔴	Explicitly captured in model 🟢	Limited workforce impact 🟡	Predictive workforce impact 🟢
Use in Operations Response	Coarse response resource only 🟡	Ideal option for CIP impact - but limited epi 🟢	Good for regional impact and detailed mitigations 🟢	Computer intensive, limited adaptability 🟡
green: go, yellow: caution - limited utility, red: not feasible				

A more useful way to summarize the information is to evaluate each resource based on the application. This summary is useful for selecting a resource to match an application.

The green dots indicate an appropriate resource for the application. The yellow dots indicate caution is required. And the red dots indicate strong limitations exist.

Of course these evaluations are my recommendations and will depend on the resource used and the user of the resource.

My experience has shown me that all resources can be used to interpolate between known results in the hands of an expert, but not all resources can be used to predict or extrapolate outside of known results or expertise.

We can conclude that because different types of analysis have different requirements, no one tool can meet all needs. That said, by looking at the green dots in the different columns, representing the utility of different approaches, the stochastic agent-based models are a good compromise, capturing both the needs for individual or local use in order to evaluate new surveillance and mitigation options and sufficient computational efficiency to address local to national planning. Finally, the CIP resources to understand the impact of infectious disease are just now becoming available.

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