

Concepts for the prevention and control of microbial threats – 2

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UC Berkeley School of Public Health
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1

[INSTRUCTIONS ARE IN CAPITAL LETTERS. Talking points are in normal type.]

This lecture covers Part 2 of the core epidemiologic concepts necessary for the investigation, prevention, and control of infectious diseases, including microbial threats.

The purpose of this talk is to provide you with the underlying principles on how to prevent and control infectious diseases. As public health professionals, this lecture reviews why you do what you do.

Learning objectives: Participants will be able to ...

- Describe the characteristics of infectious cases that promote microbial agent transmission to susceptible hosts;
- Describe the characteristics of susceptible hosts that promote microbial agent transmission to them;
- Describe six control strategies for interrupting transmission of a microbial agent;
- Design comprehensive control measures based on the the six control strategies



Infectious disease epidemiology concepts – Overview

- Mechanisms (Part 1)
 - Chain model of infectious diseases
 - Natural history of infection/infectiousness
 - Convergence model for human-microbe interaction
- Dynamics (Part 2)
 - Reproductive number (R)
 - Conditional infection rate (I)
 - Generation time (T)
- Control points and Control measures

3

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In Part 1, we covered the infectious disease transmission mechanisms.

In this lecture we turn our focus to understanding infectious disease transmission dynamics: how the occurrence of infectious cases appear at the population level and how this helps us control transmission.

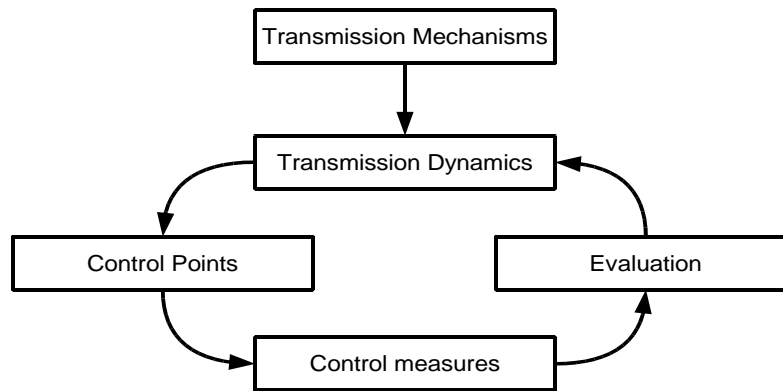
First, we cover the reproductive number (R). The reproductive number is the average of number of secondary infectious cases produced by an infectious cases during the infectious period. Understanding the components that go into the reproductive number is fundamental to understanding how to reduce it.

Second, we then turn our attention to understanding the components that determine the per-capita infection rate among susceptible persons.

Third, we introduce the generation or serial time: this is the average time between the onset of symptoms in a given infected individual and the onset of symptoms in individuals that person has infected (pmid=16222170).

NEXT SLIDE

Epidemiologic concepts for the control of microbial threats



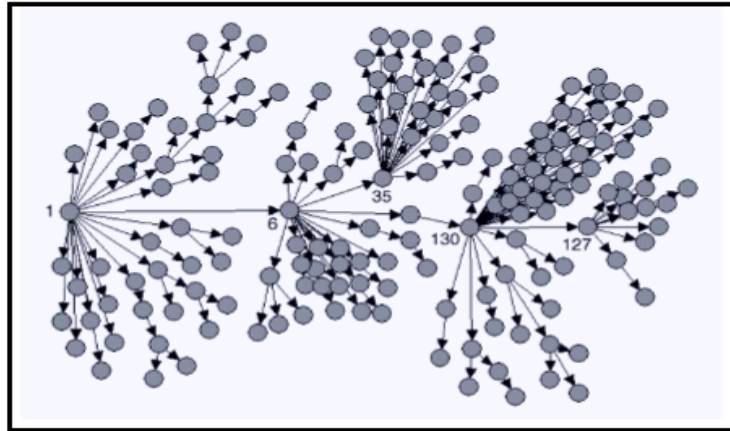
4

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Fourth, from transmission dynamics we will identify critical control points for understanding, preventing, and controlling infectious diseases. We will use these control points to systematically develop comprehensive disease control measures (strategies plus interventions).

Finally, this approach lays the foundation for evaluating our control measures.

Reproductive number & conditional infection rate



Probable cases of severe acute respiratory syndrome, by reported source of infection, Singapore, Feb 25-Apr 30, 2003 [CDC. MMWR 2003;52(18):405.]

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5

Here is a good visual display depicting the SARS outbreak in Singapore in 2003. We'll use this graphic to understand the concept of the reproductive number.

To understand the reproductive number we adopt the perspective of the microbial agent (represented by the infectious case). In order for a communicable microbe to survive, it must produce, on average, one other infectious case. This is the only way it can survive in the host population. Put another way, the reproductive number is the average number of secondary infectious cases produced by infectious cases during their infectious period.

To assess the inherent potential for a microbe to cause an outbreak/epidemic in a given population we pose the following question: If a single infectious case were introduced into a completely susceptible population with no control measures, how many secondary infectious cases would be produced, on average? This is called the basic reproductive number (R_0). For a given population, a communicable microbe has an expected R_0 . R_0 allows us to compare the potential for different microbes to cause outbreaks/epidemics in a population. More importantly, understanding the components that determine R_0 are necessary to design and implement control measures.

The reproductive number

- Basic reproductive number (R_0)
 - Average number of secondary infectious cases produced by an index case in a susceptible population in the absence of control measures
- Effective reproductive number (R)
 - Average number of secondary infectious cases produced by infectious cases
- Control reproductive number (R_c)
 - The effective reproductive number in the presence of control strategies

6

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In general, as an epidemic spreads, susceptibles are infected and either die, or recover with or without immunity. Even in the absence of control measures, the number of susceptibles generally decline and less are available to be infected. This is especially true when an infection results in lasting immunity, the population is “closed” (no/little migration), or an infection moves rapidly through the population. Therefore, as an epidemic evolves, the average number of secondary cases produced by infectious cases generally declines and this is called the effective reproductive number. The effective reproductive number is changing and may settle to about 1 (endemic) or less than 1 (extinction).

In the presence of control measures, the effective reproductive number is called the control reproductive number.

Our goal in communicable disease control is to get the control reproductive number less than 1 as fast as is feasible and cost-effective.

Basic reproductive number (R_0) (perspective of infectious case)

DEFINITION

The average number of secondary infectious cases that are produced by a single index case in a completely susceptible population in the absence of control strategies

$$R_0 = c p d$$

number of contacts per unit time

transmission probability per contact

duration of infectiousness

7

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More formally, here is the definition of the basic reproductive number [READ DEFINITION—DO NOT FOCUS ON EQUATIONS, BUT THE CONCEPTS!!!].

From the perspective of an infectious case, the basic reproductive number consist of three components:

1. How long I am infectious? (duration of infectiousness);
2. How often do I have contact with susceptible hosts? (contact rate); and
3. What is the chance (probability) of transmitting the microbial agent from this contact? (transmission probability)

GIVE EXAMPLES:

1. Sexual transmission of HIV in San Francisco in the early 1980s
2. IDU transmission of HCV before the availability of HCV testing.
3. Blood transfusion transmission of Non-A Non-B hepatitis before the availability of HCV testing and other screening tests.
4. SARS transmission early in outbreaks (e.g., Singapore)

Effective reproductive number

$$R(t) = R_0 x(t)$$

↑
Fraction of population
that is susceptible to
infection

8

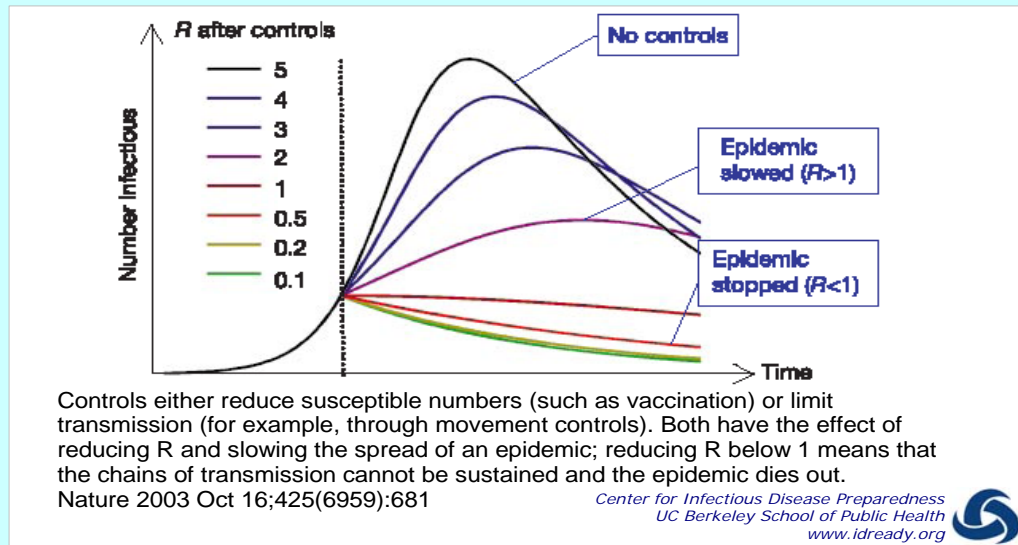
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Now we look more carefully at the effective reproductive number. The effective reproductive number is the basic reproductive number times the fraction of the population that is susceptible to infection (x). As an epidemic spreads uncontrolled, the fraction susceptible, x , decreases and eventually x becomes small enough so that the effective reproductive number drops below 1.

We can see this phenomenon in the top curve of graph on the NEXT SLIDE.

Planning for smallpox outbreaks



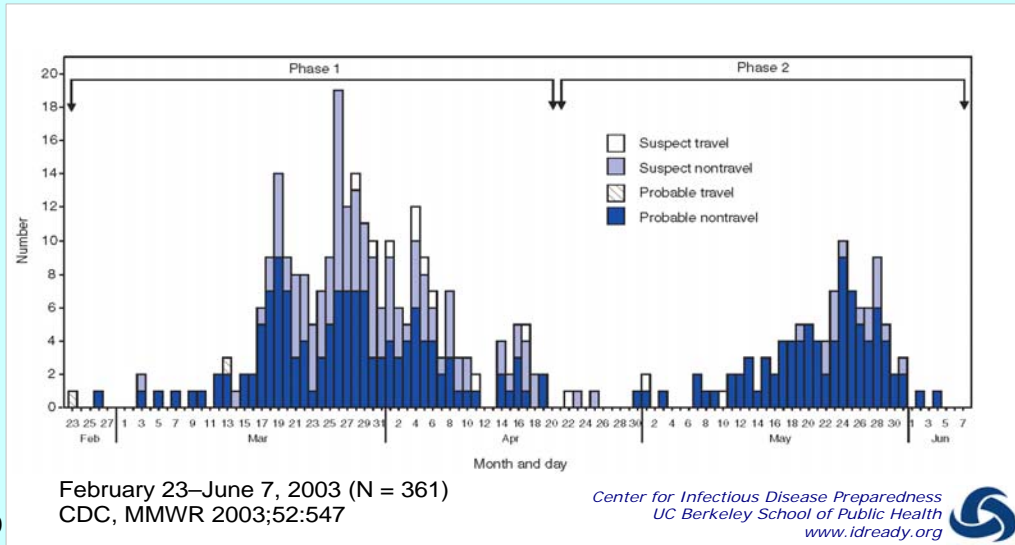
9

This graph displays the number of smallpox cases during an outbreak under different scenarios. The top curve is under the setting of no control measures. R_0 drives the initial exponential increase in the curve. Even with no control measures, the curve peaks and the number of cases decline (R). In a closed population, this happens because the supply of susceptible hosts is depleted. This also happens in an open population for an infection that moves rapidly through a community such as influenza.

The effect of control measures is to blunt this curve. In the presence of control measures the average number of secondary infectious cases per infectious case is called the control reproductive number (R_c). The primary goal of all communicable disease control interventions is to get the control reproductive number less than 1. When $R < 1$, the infection will become extinct in that population.

These phenomenon can be seen in real data on the NEXT SLIDE.

Number of reported cases of severe acute respiratory syndrome, by classification and date of illness onset — Ontario, 2003



10

Here is a real-world example of the concepts from the previous slide. This is the outbreak of SARS in Toronto, Canada.

This slide illustrates the “blunting of the curve.” In February 2003, the novel agent for SARS caused the initial outbreak. This epidemic curve shows a sharp upward increase in cases representing R_0 : the average number of secondary cases when an index case is introduced into a completely susceptible population with no control measures. Once the outbreak was recognized and control measures implemented, the curve peaked and returned to baseline.

Unfortunately, a second outbreak occurred, but notice the flatter initial rise and decreased height in the epidemic curve. This is because infection control measures were implemented immediately.

What we don't see is the natural curve in the absence of control measures because this outbreak, being deadly, was recognized and control measures implemented.

Can you think of a recent epidemic that spread for several years without any control measures? ANSWER: HIV in San Francisco in the late 1970s and early 1980s; HCV before HCV testing

Control reproductive number: Vaccination example

$$R_c(t) = R_0 [1 - hf]$$

Fraction of those vaccinated that have complete protection (vaccine efficacy)

Fraction of population that has been vaccinated (vaccine coverage)

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11

The control reproductive number is the average number of secondary infectious cases produced by infectious cases in the presence of control measures. Vaccination is one proven control strategy to get $R_c < 1$, so let's look at this in more detail.

If vaccination is our control measure, then x is equal to 1 minus the fraction of the population that has been vaccinated (f) times the fraction of those vaccinated that have completed protection (h). The fraction f is called vaccine coverage, and the fraction h is called vaccine efficacy. For a well studied vaccine-preventable disease we will know the basic reproductive number and the vaccine efficacy. Armed with this data we can estimate what fraction of the population would need to get vaccinated to bring $R_c < 1$.

NEXT SLIDE

Control reproductive number: Vaccination example (cont'd)

Goal: $R_c(t) < 1$

Fraction to
vaccinate: $f > \frac{1 - (1/R_0)}{h}$

12

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Therefore, using estimates of the basic reproductive number and vaccine efficacy, we can calculate what fraction of the population should be vaccinated to get the effective reproductive number less than 1.

This is also an example of the phenomenon of herd immunity. Herd immunity is the indirect protection non-vaccinated persons have because of less infectious cases caused by the direct protection of vaccinated persons.

NEXT SLIDE

Herd Immunity Thresholds for Selected Vaccine-Preventable Diseases

<http://www.bt.cdc.gov/agent/smallpox/training/overview/pdf/eradicationhistory.pdf>

Disease	R_0	Herd Immunity	Immunization Levels	
			1999 19-35 Months	1997-1998 Pre-School
Diphtheria	6-7	85%*	83%*	97%
Measles	12-18	83-94%	92%	96%
Mumps	4-7	75-86%	92%	97%
Pertussis	12-17	92-94%	83%*	97%
Polio	5-7	80-86%	90%	97%
Rubella	6-7	83-85%	92%	97%
Smallpox	5-7	80-85%	—	—

*4 doses

† Modified from Epid Rev 1993;15: 265-302,
Am J Prev Med 2001; 20 (4S): 88-153,
MMWR 2000; 49 (SS-9); 27-38

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13

Here is a slide from a CDC webpage for public health planners preparing for smallpox. We would not be able to interpret this slide if we did not understand the fundamental concept of the reproductive number.

Here we see a comparison of R_0 for several vaccine-preventable to diseases. Notice that the R_0 for smallpox is much smaller than the R_0 for, say, measles. Why do the R_0 s, or the potential to cause outbreaks or epidemics, differ so much between these two diseases?

The differences in R_0 are primarily explained by the transmission mechanisms covered in lecture 1. Smallpox was primarily transmitted by large respiratory droplets and patients were not infectious until they developed a rash (that is, no asymptomatic infectiousness). In contrast, measles in spread by the airborne route and an infected person is infectious before the onset of symptoms. Hence, measles is much more infectious than smallpox.

However, we still need to cover one more concept to complete the picture.

Per-capita infection rate among susceptible hosts

$$I(t) = \frac{\text{Number of new infections}}{\text{Person-time at risk}}$$

Components

$$I(t) = c p P(t)$$

Contact rate with a potentially infectious source

Probability of transmission given contact with infectious source

Probability that source is infectious

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14

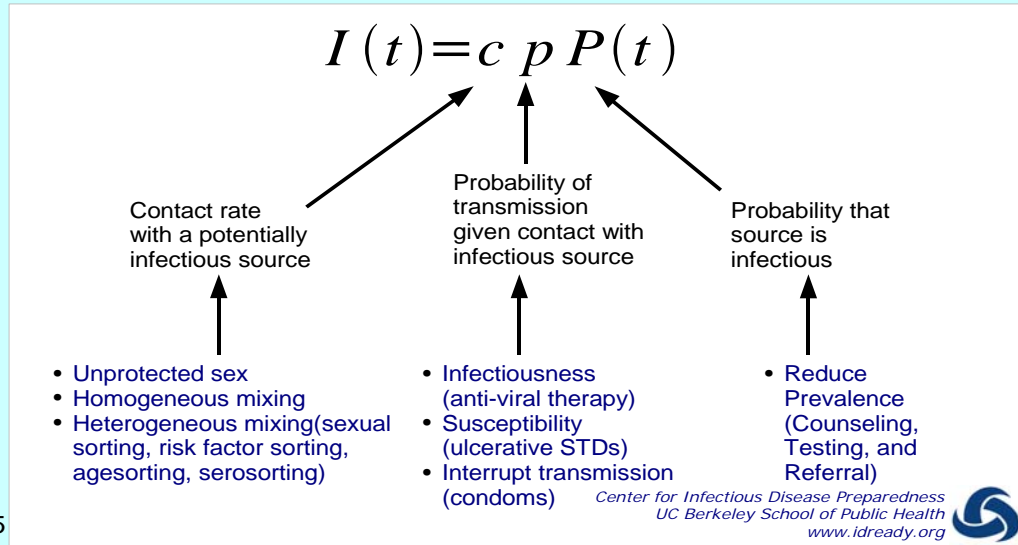
To complete the picture we need to take the perspective of the susceptible host (in contrast to the perspective of the infectious case). In epidemiology, we are taught that the infection rate among susceptibles is the number of new infections divided by the person-time at risk.

Now let's look at the components of the infection rate:

1. How often do I have contact with a potentially infectious source? (contact rate, c)
2. What is the probability that the source is infectious? (P)
3. What is the probability I am infected if I have contact with an infectious source? (transmission probability, p)

The probability that the source is infectious, P , is first estimated as the prevalence of infectious cases circulating in the community. For example, in San Francisco in the mid-1980s, a man who has sex with men (MSM) who selects a sexual partner from the MSM community had a ~50% chance of selecting an HIV-infected sexual partner. In this example, P is about 50%.

Per capita infection rate: HIV



15

This conceptual assumes that infectious cases are homogeneously mixing with susceptible hosts. In spite of this, this simple model helps one categorized new scientific knowledge or interventions as they become available. For example, HIV researchers know that sexual mixing in the MSM community is heterogeneous: for example, in “serological sorting” HIV-positives tend to seek HIV-positives for unprotected sex, and HIV-negatives tend to seek HIV-negatives for unprotected sex. This heterogenous mixing still operates through the parameter c (contact rate).

The transmission probability is affected by infectiousness of the case, the susceptibility of the infected host, and any interventions that may interrupt transmission. For example, an ulcerative STD in the uninfected host may increase the susceptibility to infection and, hence, modify the transmission probability.

The prevalence of circulating infectious cases can be modified by counseling and testing programs that identify infectious cases, thereby, potentially decreasing the number of circulating cases.

ASK ATTENDEES TO ESTIMATE THE PER-ACT TRANSMISSION PROBABILITY FOR AN HIV-DISCORDANT COUPLE HAVING SEX. ...NEXT SLIDE

Estimated per-act risk for acquisition of HIV, by exposure route to an infected source

Exposure route	Risk per 10,000 exposures
Blood transfusion (BT)	9,000
Needle-sharing injection-drug use (IDU)	67
Receptive anal intercourse (RAI)	50
Percutaneous needle stick (PNS)	30
Receptive penile-vaginal intercourse (RPVI)	10
Insertive anal intercourse (IAI)	6.5
Insertive penile-vaginal intercourse (IPVI)	5
Receptive oral intercourse on penis (ROI)	1
Insertive oral intercourse with penis (IOI)	0.5

CDC MMWR 2005;54(No. RR-2)

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16

Summarized here are the per-act or per-event transmission probabilities for HIV infection. For sexual transmission, these transmission risks are much lower than one would generally guess or intuit. Using the reproductive number concept, we can understand that with HIV transmission, the contact rate (between infectious and susceptible persons) and the duration of infectiousness have a bigger impact than the transmission risks.

In general, it's important to think of all of these components at the same time. For example, an HIV vaccine affects the transmission probability by reduce the susceptibility of the uninfected host. Suppose, however, one introduces an ineffective HIV vaccine. What can happen?

ANSWER: Although vaccinations decreases the fraction of susceptibles, it may also provide the vaccinee with a false sense of protection. Vaccinees may increase their high risk behavior (increase the contact rate) and actually worsen an epidemic. Therefore, it is very important to always consider these components at the same time, and to consider how changing one component may influence another.

Generation or serial time (T)

- Generation or serial time is the average time between the onset of symptoms in a given infectious individual and the onset of symptoms in individuals that person has infected
- Communicable diseases with shorter generation times require more rapid detection and implementation of control measures (for example, influenza vs smallpox)



THE SLIDE IS SELF-EXPLANATORY

Transmission dynamics and control points

Effective reproductive number

$$R(t) = c p d x(t)$$

Conditional infection rate

$$I(t) = c p P(t)$$

Control points	Prevention and control strategies
Contact rate (c)	1. Reduce contact rate
Prob. source infectious (P)	2. Reduce proportion infectious sources
Transmission prob. (p)	3. Reduce infectiousness 4. Reduce susceptibility 5. Interrupt transmission
Duration infectiousness (d)	(see #3)
Fraction susceptible (x)	6. Increase herd immunity

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18

Now let's put it all together. From these two basic equations we identify five critical control points. All infectious diseases act through these control points. Therefore, the success or failure of our disease control interventions are ultimately explained by the impact on these control points.

Now we can develop a comprehensive prevention and control strategy that always makes sense. Using this approach we derive the 6 control strategies (see Table). These 6 strategies all map back into the 5 critical control points.

To design an infectious disease control intervention, you gather an interdisciplinary group of people and select your interventions based on these 6 strategies. It is important to consider all of them at the same time. Failure to do so can result in unintended adverse effects.

Control measures (strategies + interventions)

1. Reduce contact rate
 - Behavior change (host and/or source)
 - Case finding for intervention (e.g., isolation)
 - Contact tracing for intervention (e.g., quarantine)
 - Isolation of cases
 - Quarantine of exposed (individual, community, geographic boundary [Cordon sanitaire])
 - “Reverse” isolation (isolation of non-exposed)
 - Reduce number of infectious sources
 - Social distancing (school closures, restrict mass gatherings, etc.)

19

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Now we are back to where we started. Use the 6 control strategies to select control interventions that make epidemiologic sense.

The transmission dynamics helped us identify the critical control points. The critical control points can be affected using the 6 control strategies. Using this approach guides the selection of infectious disease prevention and control interventions.

The transmission mechanisms helps us to tailor our interventions. For example, to develop the infection control component of your plan you need to understand the Chain Model of Infectious Diseases (reservoir, mode of transmission, etc.).

Finally, these concepts help to guide how you will evaluate your the implementation of your plan (program).

Notice that some of the interventions act at more than one level; for example, treatment can reduce magnitude and duration of infectiousness.

Control measures [cont'd] (strategies + interventions)

5. Reduce proportion of infectious sources
 - Case finding for intervention (e.g., isolation, treatment)
 - Identify and control infectious sources
 - Environmental measures
3. Reduce infectiousness
 - Treatment
 - Vaccination
4. Reduce susceptibility
 - Vaccination
 - Immune globulin
 - Treatment (e.g., ulcerative STD)

20

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CONTROL MEASURES CONTINUED

Control measures [cont'd] (strategies + interventions)

2. Interrupt transmission
 - Infectious control practices
 - Barrier methods (e.g., masks, condoms)
 - Insect repellent (e.g., reduce feeding time)
6. Increase herd immunity
 - Vaccination, consider the following
 - Naturally acquired immunity
 - Fraction vaccinated
 - Vaccine efficacy



CONTROL MEASURES CONTINUED

Translating control strategies into smallpox control program

Control strategies

1. Reduce contact rate
2. Reduce infectiousness
3. Reduce susceptibility
4. Interrupt transmission
5. Reduce proportion of infectious sources
6. Increase herd immunity

CDC Prevention and control program

- Smallpox pre-event strategies
 - Vaccination program
 - Enhanced surveillance & detection
- Smallpox post-event strategies
 - Epidemiologic investigation
 - Surveillance and case reporting
 - Contact identification, tracing, vaccination, and surveillance
 - Isolation and Quarantine
 - Infection control
 - Personal protective equipment

22

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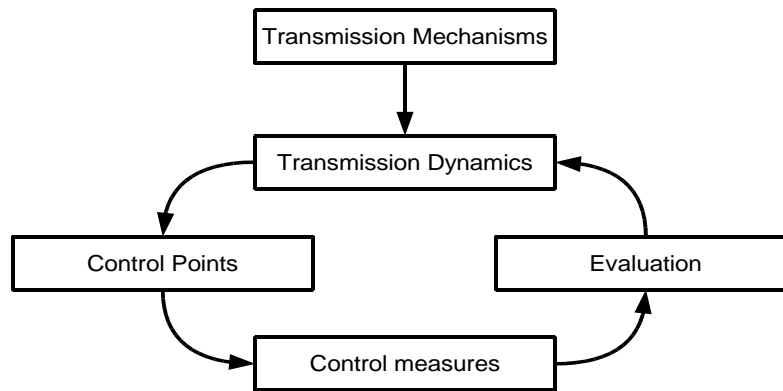


On the right box, we see the components of the CDC Smallpox Control Plan. All these interventions can be understood and justified by these epidemiologic concepts.

In fact, if there were an outbreak of smallpox from an intentional release, and you did not have access to the CDC website to download the control plan, you could gather a interdisciplinary group of public health and medical professionals, and design and implement a rationale control plan using only these concepts and the knowledge base of your group.

Having a systematic, comprehensive approach is even more important when facing an unknown microbial threat. We saw this with SARS, and we'll see this with pandemic influenza.

Epidemiologic concepts for the control of microbial threats



23

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We covered infectious disease transmission mechanisms, transmission dynamics, and control points.

We derived an 6-step control strategy to guide the selection of the control interventions (=control measures).

A control plan describes how these interventions will be implemented.

This epidemiologic approach guides the evaluation of your control program.

Infectious disease epidemiology concepts – Summary

- Mechanisms (Part 1)
 - Chain model of infectious diseases
 - Natural history of infection/infectiousness
 - Convergence model for human-microbe interaction
- Dynamics (Part 2)
 - Reproductive number (R)
 - Conditional infection rate (I)
 - Generation time (T)
- Control points and Control measures



This is what we covered today!