In what situations do modeling studies suggest quarantine is more versus less effective to control infectious disease outbreaks?

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Description and Main Findings

This report to the National Academy of Medicine committee synthesizes findings from modeling studies selected from a larger systematic review conducted by the committee. The goal of the report is to describe what computer modeling studies say about the effectiveness of quarantine in outbreak situations across a range of diseases and assumptions. *The report synthesizes what computer modeling studies identify as situations where quarantine is expected/likely to be relatively more or less effective.*

The modeling studies selected for synthesis in this report have broad coverage of pathogens, geographic settings, and modeling techniques employed. The modeling analyses consider a range of infectious diseases (**Table 1**) including: Ebola, Hepatitis A, Influenza A, MERS, Pertussis, SARS, Smallpox, Measles. Likewise, the modeling studies consider these pathogens in settings/locations that range from abstract/non-specified to specific countries/subnational regions in areas of North America, Europe, Asia, and Africa. Finally, the modeling studies use a variety of methods that almost always include numerical simulation techniques. These include the majority of studies using systems of differential equations that are sometimes age-stratified or established as linked systems of equations to reflect spatial heterogeneity and one model using a highly detailed agent-based network model, enabling the possibility of that susceptible pools of individuals can be depleted and/or immune individuals can disrupt chains of transmission relevant in scenarios allowing for widespread epidemics. Other models use branching processes or exponential growth processes that are also stratified in various ways and comment directly on early phases of outbreaks and epidemic spread where depletion of susceptible individuals and the fraction of individuals who are recovered and immune is small. *The synthesis demonstrates that coverage across the papers is reasonably good and that overall findings, regarding the cases in which quarantine is expected to be more or less effective and the explanation of the reasons for these differences, are unlikely to be overly influenced by focus on one pathogen, population, or modeling approach.*

Table 1. Studies Focused on Each Disease

Study	Year	Ebola	Hepatitis A	Influenza A/H1N1	MERS	Pertussis	SARS	Smallpox	Measles
Peak	**2017**	X	X	X	X	X	X	X	
D'Silva	**2017**	X							
an der Heiden	**2009**			X					
Ahn	**2018**				X				
Podder	**2007**						X		
Day	**2006**						X		
Mubayi	**2010**						X		
Hsieh	**2007**						X		
Gupta	**2005**						X		
Feng	**2009**						X		
Meltzer	**2001**							X	
Enanoira	**2016**								X

In order to compare findings from the modeling studies, a definition of effectiveness is required which can be challenging because the modeling studies are undertaken for a variety of reasons and hence report a variety of outcomes. However, it is generally possible to extract or infer a common notion of effectiveness from them. Theoretically, the assumed goal of quarantine is to reduce the level of transmission in an outbreak so that the outbreak is extinguished or at least so that prevalence of infection does not grow into an epidemic but returns to low endemic levels. The corresponding infectious disease epidemiological concepts related to this effectiveness goal are: 1) that the effective reproductive number with intervention is below one so that the incidence (and hence the prevalence) declines; 2) that the rate of decline of prevalence is faster with quarantine than without quarantine, or equivalently that the duration of measurable prevalence is shorter. *While some of the modeling studies report a variety of outcomes including important resource-related outcomes like the total number of people who need to be intervened upon and costs of interventions, they all include reports of outcomes that can be mapped to these underlying infectious disease epidemiological concepts of control effectiveness and hence are comparable.*

While the modeling studies contain a variety of assumptions that may influence the specific numerical conclusions that they reach, the studies differ in the assumptions that they make, and hence synthesizing their findings is likely to reduce any strong biases due to assumptions made in any particular study. In "Details of Reviewed Studies and Their Assumptions" below, further discussion is provided. *In general, risk of bias from such assumptions in terms of overall conclusions of this synthesis is deemed low.*

In summary, across the modeling studies considered, quarantine is seen as being more likely to be effective for pathogens and environments/settings with certain characteristics because those characteristics are important for determining quarantine effectiveness (**Table 2**). In other words, the drivers for when quarantine is found to be more or less likely to be effective are systematic and consistently relate both to characteristics of the pathogen and to the population/setting. Understanding these systematic relationships is aided specifically by one of the included modeling study (Peak et al. 2017) which contains analyses for a range of diseases and attempts to provide answers to this question within a common modeling framework. *Consistent with the findings of Peak et al. and including the other modeling studies and the drivers of effectiveness they identify or imply, the following situations make quarantine more effective:*

1. *Moderate R_0*: When the basic reproductive number (R_0) of a given pathogen is in a range in which quarantine can be expected to importantly reduce transmission. Quarantine may be more effective for a pathogen with a moderate R_0, or for a pathogen with a higher R_0 that has previously produced durable immunity in a population (i.e., the population in question has been previously exposed) such that the effective reproductive number (R_e)[1] in the population even without intervention is relatively lower. If a pathogen has a high R_0, more transmission may occur before quarantine can be implemented, reducing quarantine's effectiveness at limiting the final size of the outbreak. As a practical matter, for pathogens with a very low R_0 (i.e., <1), disease transmission will not be sustained, making quarantine theoretically effective but perhaps practically unnecessary.
2. *Shorter incubation period:* When quarantine can reliably separate identified individuals from the general population for durations commensurate with the expected duration of asymptomatic infectiousness. Quarantine may become infeasible or less effective as a result of reduced adherence if its duration must be very long, because of a prolonged incubation period (the period between exposure and when infection becomes detectable).
3. *Relatively short asymptomatic infectiousness period*—when the asymptomatic infectious period is short or there is no asymptomatic infectious period. When there is a long period of asymptomatic infectiousness, then quarantine of recently infected people must be extremely rapid and comprehensive to prevent transmission by asymptomatic individuals, which may be so logistically challenging as to be practically infeasible. In addition, if the asymptomatic infectious

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[1] Effective reproductive number (R_e): Note that the pathogen's R_0 changes over time due to interventions and as the infection establishes immunity. The R_e (in this case in the presence of quarantine) which conceptually is related to the ability of an infection to have persistent or growing prevalence in a population (when the effective reproductive number is above 1 the disease will have growing prevalence; below 1 it will decline)

period is long in absolute terms, quarantine may become infeasible or less effective because of reduced adherence (see the previous bullet).

4. *Rapid identification:* When exposed individuals can reliably and quickly be identified.
5. *To aid isolation*: When isolation of individuals once they become symptomatic is slow or unreliable without quarantine, then quarantine may reduce transmission via its effects on facilitating more rapid isolation of ill and contagious individuals.

Table 2. Summary of Quarantine Effectiveness Findings*

Disease	**Quarantine Likely Effective?**	**Notes**
Ebola	Yes	<u>2 studies</u> find quarantine can drive R_e<1 (D'Silva et al., 2017; Peak et al., 2017)
Hepatitis A	Yes based on 1 study	<u>1 study</u> finds quarantine can drive R_e<1 (Peak et al., 2017)
Influenza A/H1N1	Maybe	<u>2 studies</u>. One study finds quarantine can drive R_e<1 (Peak et al., 2017). Another study focuses on delaying the epidemic peak and suggests that quarantine possibly can be effective depending on the specific features of the pathogen in the population and the level of intervention (An der Heiden et al., 2009).
MERS	Yes	<u>2 studies</u> find quarantine can drive R_e<1 (Ahn et al., 2018; Peak et al., 207)
Pertussis	No based on 1 study	<u>1 study</u> finds quarantine unlikely to drive R_e<1 (Peak et al., 2017)
SARS	Maybe	<u>7 studies</u>. Three studies identify situations where quarantine may not be effective in driving R_e<1, with effectiveness of quarantine depending on the pathogen's basic reproductive number in a given population (less likely with higher R_0), likely effectiveness of isolation of symptomatic individuals as an alternate strategy, the likelihood and fraction of there being individuals who are asymptomatic but infectious, and the ability to quickly identify a large fraction of exposed individuals for quarantine (Day et al., 2006; Hsieh et al., 2007; Peak et al., 2017. Four studies find (or in essence assume [models of past limited outbreaks]) that sufficiently effective, properly scaled and targeted, or potentially dynamic quarantine polices can drive R_e<1 (Feng et al., 2009; Gupta et al., 2005; Mubayi et al., 2010; Podder et al., 2007).
Smallpox	Maybe	<u>2 studies</u>. One study finds quarantine unlikely to drive R_e<1. Another study finds that with quarantine initiated early that removes a large fraction of exposed cases can likely avoid an epidemic set off by a smallpox bioterrorism attack(Meltzer et al., 2001; Peak et al., 2017).
Measles	Yes/Maybe based on 1 study	<u>1 study</u> finds that despite measles high basic reproductive number, if there is a sufficient level of background immunity, it may be possible to use quarantine to end an outbreak quickly. However, with lower levels of background immunity, quarantine is unlikely to drive R_e<1 or to do so quickly (Enanoira et al., 2016).

* R_e: The effective reproductive number (in this case in the presence of quarantine) which conceptually is related to the ability of an infection to have persistent or growing prevalence in a population (when the effective reproductive number is above 1 the disease will have growing prevalence; below 1 it will decline)

The modeling studies make a number of other important points when considering quarantine not directly related to effectiveness but still worthy of consideration:

1. Importance of Pre-Outbreak Surveillance: Modeling studies that explore the timing of initiating quarantine tend to emphasize that it is more effective if implemented closer to when the first case occurs or else is equivalently effective but involves quarantining substantially fewer exposed individuals. To initiate rapid quarantine requires accurate and granular pre-outbreak surveillance as well as linkages to rapid decision making and implementation efforts.
2. Quarantine at Local, Regional, and National Levels: Modeling studies that explore quarantine efforts at various localities or focus differential quarantine efforts on locally exposed individuals and travelers entering an area suggest that the relative value of these control efforts depends on the fraction of an epidemic/outbreak driven by local transmission versus imported cases. More generally, there can be direct and indirect spillover effects of local quarantine efforts as they can reduce transmission in other areas – namely, by using quarantine to better control an outbreak in one area, other areas can face fewer imported cases and hence the quarantine levels and speed with which they must be developed can potentially be lower (an example of direct spill-over); more generally, chains of such spillovers to areas not directly connected to the original area can occur which may alter the required level and speed of quarantine in these areas as well (indirect spill-overs). However, if uncoordinated and implemented at a very intense level in multiple geographies there is the potential of redundancy and hence excess effort and resource expenditure.
3. Invasiveness of Quarantine: Modeling studies that compare quarantine with other less invasive/intensive interventions like symptom monitoring or voluntary reporting note that it may be possible to achieve similar levels of effectiveness/control for less transmissible infections that do not have asymptomatic infectious periods using these alternatives without the potential social stigma of quarantine, its potential for social/economic disruption, and/or its potentially large scale use of resources. Some studies also note that quarantine can help to accelerate isolation in some circumstances, while others note that there may be greater compliance with less strict quarantine procedures leading higher effectiveness despite being less strict.

Details of Reviewed Studies and Their Assumptions

Definitions of quarantine

Modeling studies vary somewhat in terms of what they mean when they report modeling “quarantine”. The most common definition of quarantine used in the studies in individual quarantine – separation from contact with others for those exposed (or suspected of being exposed to infection) but who do not yet have symptoms or other confirmation of infection/infectiousness. Frequently, such studies use the term quarantine separately from isolation – removing symptomatic/proven infections from contact with others. Sometimes studies use quarantine to refer to both individual quarantine and isolation, though even studies who use quarantine separately from isolation typically assume isolation will occur at some level even without quarantine. Several studies consider both quarantine for the local population and for travelers and others coming into the local population (e.g., Hsieh and also D’Silva). Somewhat differently, D’Silva notes that the way it models quarantine can be considered a combination of individual quarantine and “lock-down” or community quarantine.

Static versus dynamic quarantine policies

The terms “Static” versus “Dynamic” with respect to quarantine policies, refers to whether or not a quarantine policy is changed in some way in response to the course of the epidemic. Static policies are implemented at a given level of coverage, intensity, etc. and do not change in response to the course of the epidemic. Dynamic policies are those that do change; for example, a dynamic policy might be that the intensity of tracing to identify contacts for quarantine may be more intensive and rapid when the incidence of the epidemic is rising and be somewhat less rapid when the epidemic is falling. A number of studies consider static levels of quarantine potentially initiated at various amounts of delay after the outbreak begins. Other studies (e.g., Mubayi and also Feng) consider dynamic quarantine programs that seek to reduce or increase the intensity of quarantine efforts in response to the growth patterns of the epidemic in order to achieve comparable results while using fewer resources or needing to intervene on fewer people.

Consideration of other interventions

The pre-specified goal of this synthesis was to examine which situations quarantine is expected to be more or less effective compared to not implementing quarantine. While the synthesis included quarantine in combination with isolation of symptomatic cases in its definition of quarantine (see above), it did not examine the potential effectiveness of other intervention alternatives to quarantine or the use of quarantine in combination with other interventions. Examples of these other interventions include: symptom monitoring or raising awareness to prompt rapid health seeking behavior. A symptom monitoring intervention might involve having exposed individuals continue to live in the community and periodically be contacted regarding any (potentially minor) occurrence of (early) symptoms which would then lead to rapid medical contact and isolation as required. An intervention focused on prompting rapid health seeking behavior might provide information on what to look for in terms of early signs or symptoms of infection so that individuals were more likely to (more rapidly) contact healthcare providers in such situations. Likewise, it might involve increased linkage to providers to ensure that such individuals were transitioned to isolation as required. These interventions are typically thought of as less invasive and/or resource intensive than quarantine though also potentially less effective. Likewise, examples of interventions that might be used in combination with quarantine when available include vaccination or prophylactic treatment.

Other study assumptions

Studies vary in terms of a variety of other assumptions they make, especially with regard to implementation and human behavior.

- Some studies do not consider that quarantine efforts (and isolation efforts) may be incomplete in terms of the fraction of exposed/infected individuals they identify. In this case, they may overestimate the effectiveness of quarantine at a given intensity level.
- Some studies do not consider delays in implementing quarantine efforts, assuming that they can be implemented very early in an outbreak. This assumption can overestimate the real-world effectiveness of quarantine and even if it does not lead to an overestimate of effectiveness will tend to underestimate the number of people who would require quarantine to achieve a given level of control.
- Some studies assume high/perfect levels of compliance with quarantine (that all individuals quarantined remain separated until after they are either definitively shown to be not infected or until they infections have definitely ended). This assumption likely overestimates the effectiveness of quarantine for some pathogens/situations; realistic assumptions about compliance are likely pathogen/setting-specific and therefore it may be prudent for modeling studies to consider a variety of plausible assumptions.
- Some studies assume that contact patterns in the absence of intervention do not change over the course of an outbreak/epidemic. This tends to overestimate the size that an outbreak/epidemic can reach and the speed at which it reaches that size, as other processes like social distancing or increased use of relevant personal hygiene measures will reduce/slow transmission. While for lower levels of quarantine/quarantine effectiveness this may underestimate the potential of

quarantine to reduce the effective reproductive number below 1 (overemphasizing the need for more intense/high coverage/rapid quarantine), it also tends to overstate gains made by sufficiently intense quarantine – the cases averted from stopping a large outbreak are greater than stopping a small outbreak.

Not all models make the same assumptions, and despite variation in assumptions, different studies of the same pathogens/settings (or pathogens/settings with similar characteristics) tend to reach similar conclusions. Given that a number of assumptions tend to overestimate the potential effectiveness of quarantine as well as the ease of implementation at high levels fidelity, it is probably prudent to assume that quarantine's effectiveness is somewhat lower than the estimates/predictions from the model studies, though likely qualitatively similar.

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Table 3. Specific Aspects of Studies Synthesized

Study	Year	Pathogen(s)	Reproductive Number before Intervention*	Quarantine Effective? (Y/N)	Key Assumptions	Geography	Model Type
Peak	**2017**	Ebola,	1.83 (1.72-1.94)	Y	• Uses branching process relevant to early stages of outbreaks when depletion of susceptibles and contact with immune individuals not relevant • Explicitly explores alternate assumptions about asymptomatic infectious individuals	Abstract	Stochastic branching process
		Hepatitis A,	2.25 (2.00-2.50)	Y			
		Influenza A/H1N1,	1.54 (1.28-1.80)	Y			
		MERS,	0.95 (0.60-1.30)	Y			
		Pertussis,	4.75 (4.50-5.00)	N			
		SARS,	2.90 (2.20-3.60)	Maybe			
		Smallpox	4.75 (4.50-5.00)	Maybe			
D'Silva	**2017**	Ebola	"widespread intense transmission"	Y	• Intervention timing not considered as its implementation level begins immediately and is held fixed for the duration	Guinea, Sierra Leone, and Liberia	Linked Ordinary Differential Equations for Spatiotemporal Heterogeneity
an der Heiden	**2009**	Influenza A/H1N1	(1.34-2.04)	Y (early quarantine with limited prophylactic treatment can delay the epidemic)	• Contact patterns do not change over time in the absence of quarantine	Germany	Age-Structured Ordinary Differential Equations
Ahn	**2018**	MERS	"human-to-human transmission occurs in healthcare settings"	Y	• Contacts decline over time so that outbreak dies out even without quarantine	Korea	Ordinary Differential Equations

Podder	**2007**	SARS	(2.00-5.00)	Y (But depends on basic reproductive number. When the number low (~ <2.2) isolation alone may be sufficient especially with low levels of asymptomatic infectiousness)	• Quarantine and isolation identify all contacts and are not “leaky” and hence all necessary individuals cannot transmit • Explicitly explores alternate assumptions about asymptomatic infectious individuals	Canada(?)	Ordinary Differential Equations
Day	**2006**	SARS	None reported/directly implied	N (However for quarantine to be substantially more effective than isolation alone: 1) isolation cannot be “too effective”; 2) quarantine can prevent cases (asymptomatic infections substantial or acceleration of cases into isolation; and/or 3) quarantine rapid to avoid asymptomatic infection transmission)	• Assumes that we are examining cases where isolation alone could reduce the reproductive number to 1 or below so that they can ask how much more rapidly quarantine can cause the outbreak to die out (and hence how many fewer total infections)	Canada(?)	Multiple techniques including Stochastic branching process and Compartmental Models
Mubayi	**2010**	SARS	3.50 (0.86-4.23)	Y	• Considers both dynamic and non-dynamic control strategies that use combinations of	Hong Kong	Ordinary Differential Equations

					isolation and quantine at various levels - Contact patterns do not change over time in the absence of quarantine		
Hsieh	**2007**	SARS	(8-25)	N (quarantine may have reduced cases but without quarantine, modeled SARS in Taiwan was not expected to become epidemic)	- Assume no super-spreaders (no person-level variation in distribution of the number of susceptible people infected by an infectious individual)	Taiwan	Ordinary Differential Equations then approximated by linear equations
Gupta	**2005**	SARS	None reported/directly implied	Y	- R_0 (basic reproductive number) for SARS assumed to be much higher than other models because of the hospital setting - Assume complete perfect quarantine which is the maximum potential effect - Growth model with 4 infection generations assumed so most relevant to early stages of outbreak but may bias total effect downwards if subsequent generations possible - Explore effects of having super-spreaders	Toronto (hospital setting)	Exponential growth model truncated at 4 infection generations

Feng	**2009**	SARS	3.16 early 0.86 late	Y	• Assumes gamma distributed dwell times in states instead of the typical exponential assumption made by most Ordinary Differential Equation models • Contacts decline over time so that outbreak dies out even without quarantine (use 2 stages: early higher; late lower) • They consider dynamic quarantine strategies	Hong Kong/Singapore	Ordinary Differential Equations
Meltzer	**2001**	Smallpox	(1.50-3.00)	Y	• Uses epidemic growth model relevant to early stages of outbreaks when depletion of susceptibles and contact with immune individuals not relevant • Not clear that term quarantine used in this paper refers to removal of exposed individuals prior to developing systems or only isolation of symptomatic individuals • Intervention effect is defined as fraction of people isolated each day of their	US(?)	Markov-chain model of disease stages with an epidemic growth model (i.e., “assumed an unlimited supply of susceptible persons”)

					symptomatic period (50% per day for even 4 days is very high cumulative removal fraction) with no individual differences in the likelihood of removal • Assumes possibility of very rapid symptom identification and removal • Contact patterns do not change over time in the absence of quarantine despite large epidemic growth		
Enanoira	**2016**	Measles	Lower than measles normally due to prior immunity levels of 85-95%	Y (If high background immunity [~95%] is present, quarantine can be effective but not if background immunity is lower [~85%])	• Contacts patterns of individuals who are infected and feel sick are lower even without quarantine	California	Stochastic network simulation of highly heterogeneous agents across specific geographies and daily timings

* This is often equivalent to the basic reproductive number of the pathogen in a completely susceptible population (R_0), but for infections that generate durable immunity and for which there is prior vaccination or prior outbreaks of infection, the pool of immune individuals reduces the reproductive number in the population. Likewise, populations that are in less frequent/dense contact have fewer cases produced for each infectious individual so that even in novel outbreak situations there can be variation in this quantity. Also, for many of the studies ranges of values are used sometimes as confidence intervals and sometimes as simple ranges.