Perfect as the Enemy of the Good: Using Low-Sensitivity Tests to Mitigate SARS-CoV-2 Outbreaks

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Perfect as the enemy of the good: Using low-sensitivity tests to mitigate SARS-CoV-2 outbreaks

Authors: Lee Kennedy-Shaffer[1,2], Michael Baym[3], William P. Hanage[1,2]*.

Affiliations:

[1]Center for Communicable Disease Dynamics, Harvard T.H. Chan School of Public Health, Boston, MA, USA.

[2]Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA.

[3]Department of Biomedical Informatics, Harvard Medical School, Boston, MA, USA.

*Correspondence to: whanage@hsph.harvard.edu.

Abstract: Preventing future infection waves of COVID-19 will depend on effective and efficient contact tracing. SARS-CoV-2 transmission appears to be characterized by high individual variation and a large role of superspreading events. Taking this into account can improve the cost-benefit tradeoffs of contact tracing. In particular, an individual who is known to have transmitted the infection once is more likely to have transmitted to other individuals. We propose a strategy of identifying transmission events, making use of the variability in secondary case numbers. A rapid, high-specificity test with only 50% sensitivity can still identify the vast majority of these transmission events. This strategy can lead to the isolation of a large proportion of infected individuals while drastically reducing the isolation of uninfected contacts.

One Sentence Summary: Tracing transmission events rather than infected individuals can efficiently and effectively prevent infection waves.

Main Text:

Recently, attention has focused on superspreading events (SSEs) as a key component in the transmission dynamics of SARS-CoV-2. Several articles have identified a large role for SSEs in understanding observed disease clusters (*1, 2*) and in reproducing observed transmission patterns (*3, 4*). Further, the low rate of within-household transmission, although higher than similar pandemic respiratory diseases, implies that the person-to-person variance in transmissibility is particularly high (*5*). This has led to suggestions that prevention and mitigation of SSEs, along with contact tracing that targets such events, can be particularly impactful in reducing transmission (*6–8*). This is even more true if, as has recently been suggested, biological mechanisms drive SSEs and lead to individuals infected in an SSE being more likely to cause a future SSE than individuals infected through smaller transmission events (*9*).

As the COVID-19 pandemic continues, growing and declining in various countries around the world, "test and trace" strategies are becoming an increasingly important part of the

response to the virus (*10–14*). These strategies can be highly effective in halting transmission chains (*14, 15*), but rely heavily on rapid availability of test results and/or presumptive isolation of many asymptomatic contacts (*10–12*). In fact, low cost and rapid results may be even more important than high test accuracy, especially sensitivity (*16, 17*). The success of these strategies also relies on the efficiency with which cases and contacts are identified (*18*). In order for testing strategies and contact tracing strategies to be most effective, they must account for SSEs and the latest evidence of their importance in the transmission of SARS-CoV-2.

A key implication of the high frequency of SSEs and, more generally, the overdispersion of infectivity is that once you know a person has transmitted SARS-CoV-2, the probability that they have transmitted to multiple people increases dramatically. Given that all current testing technologies have fairly high false-negative rates (*19–21*), the information that an index individual has infected a contact is a strong and useful predictor of infection and future disease among other contacts. A rapid, highly-specific but modestly-sensitive test for SARS-CoV-2 could improve the risk-benefit analysis and more appropriately balance the short-term costs of isolation with the long-term benefits of reducing the spread of the disease (*12, 16, 17*). We propose here a strategy for balancing these costs and halting transmission chains through use of such a test.

Traditionally, contact tracing focuses on identifying infected individuals and presumptively isolating all of their contacts (*10*). In a setting where SSEs are a major source of infections, identifying transmission events provides substantially more information about prospective cases than identifying infected individuals alone. Therefore, we propose the following strategy for transmission tracing of an identified index case:

1. Test all potential contacts of the index case using a rapid, high-specificity test.

2. If **any** contacts test positive, isolate **all** contacts and conduct more thorough epidemiological assessments of these individuals. This may include more accurate testing, active monitoring, presumptive quarantine or self-isolation (with appropriate support measures to ensure it can be followed), and tracing of their contacts, potentially using this same strategy. Peak et al. discuss the tradeoffs of different approaches to monitoring and quarantine (*18*).

3. If **no** contacts test positive, all contacts are presumptively treated as negative and self-isolation is not suggested.

Or, equivalently, if an individual tests positive and the source of infection can be identified, immediately isolate **all** contacts of the **source** and conduct more thorough testing. Note that we use the phrase "isolation" of contacts here even for those who test negative because this approach treats them as presumptive positives. Depending on the setting, other epidemiological control measures may be more appropriate for the presumptive positives and these may be used in step 2 above. Both formulations rely on the key point that identification of a transmission event is far more informative of the infection state of other individuals than a positive test result alone.

A schematic of this strategy is given in **Fig. 1**, denoted (A). This strategy can be compared to two alternative approaches to contact tracing: (B) quarantining all contacts and, potentially, their contacts until a high-accuracy test can be performed or the period of potential

asymptomatic transmissibility has passed; or (C) providing a rapid, moderate-accuracy test to all contacts and isolating only those who test positive.

This approach relies on the availability of a rapid, high-specificity test. The sensitivity of the test, however, need not be high. Under this strategy, if an index individual infects four other individuals, a test with sensitivity of 50% will identify that group over 90% of the time.

Models for SSEs generally consider the overdispersion of the number of secondary infections caused by an index infection as an individual-level random variable rather than a single value of the basic reproduction number, R_0 (*22*). This model, appropriately parameterized for a given disease, can provide an estimate of the distribution of secondary infections and thus the pattern of transmissions in a community. Estimated ranges for these parameters for SARS-CoV-2 have recently been proposed (*1, 23*).

To assess the effectiveness of this approach in reducing transmission, we can determine the expected number of secondary cases that are identified and isolated through this strategy compared to a strategy that quarantines all contacts. This number depends on both the sensitivity of the test, denoted *a*, and the distribution of the number of secondary cases infected by an index individual, denoted *Z*. We assume that *Z* follows a negative binomial distribution with mean R_0 and dispersion parameter *k* (*22*). Note that a lower value of *k* indicates more potential SSEs. For simplicity, we assume perfect specificity of the test.

Fig. 2 displays the proportion of secondary cases isolated using transmission tracing (strategy A) for a range of values of *a*. Several values of R_0 and *k* are considered, within estimated ranges for SARS-CoV-2; R_0 is taken to be between 1.5 and 3 and *k* between 0.1 and 1 (*1, 3, 23–25*). The diagonal line indicates the proportion of secondary cases isolated if only the individuals who test positive are isolated (strategy C).

When there is overdispersion of transmission, the proportion of cases who are isolated is drastically higher using the transmission tracing strategy than only isolating contacts who test positive. Even for a test with sensitivity of 50%, for all parameter values considered here, over 80% of cases are isolated using this strategy. There are also decreasing returns to increased sensitivity of the test, especially for lower values of *k*. If there are lower-sensitivity tests available that can be deployed more quickly and more cheaply, the logistical advantages of those tests may make up for the decreased accuracy in the context of this approach. This advantage of quicker, cheaper, lower-sensitivity tests has been identified for surveillance approaches as well (*16, 17*).

To assess the cost of this approach in terms of isolation and follow-up, we can determine the proportion of index cases whose contacts are isolated compared to a strategy that isolates all contacts. Again, this will depend on the sensitivity of the test and the distribution of the number of secondary cases infected by an index individual. **Fig. 3** displays the proportion of index cases whose contacts are isolated using this strategy for the scenarios shown in Fig. 2. This proportion is much lower than 100% for all parameters considered here, representing a significant decrease in the number of index cases whose contacts are quarantined compared to strategy B.

Note that this proportion is not necessarily equal to the proportion of identified contacts who are isolated. If the number of secondary cases infected by an index individual increases as the number of identified contacts increases, those index individuals whose contacts are isolated will, on average, have more contacts than those whose contacts are not isolated. In any case, only

isolating cases who test positive will result in a lower number of individuals isolated, but this difference is more pronounced if the number of secondary cases is highly correlated with the number of identified contacts. That is, if transmission variation occurs primarily because of "social" factors such as how many contacts an index individual has, this method has less of an impact on reducing the number of contacts isolated. If transmission variation occurs primarily because of "biological" factors such as the viral load, this method has a greater impact.

Transmission tracing provides a means to drastically reduce the burden of quarantine/isolation and successive contact tracing while still identifying the vast majority of transmission events and, especially, superspreading events. This can occur even using tests with sensitivity of 50% or less. It can be modified to focus on specific types of contacts or events. For example, this approach can be used to rapidly test all contacts in specific workplaces, campuses, residential facilities, or other locations where SSEs are likely to occur (*7, 26*). This provides another approach, like group testing, to identify SSEs in these locations without the expense and delay of individual contact tracing (*27, 28*). Using test results and these probabilistic properties can aid in the rapid identification of clusters and speed "cluster response" approaches like those used in Japan (*29*). Variations on this approach, such as isolating contacts whose contact date was within one day of the identified transmission pair, can allow for more focus on superspreading events rather than simply individual variation in infectiousness. As superspreading becomes better understood for SARS-CoV-2, this strategy can also be tailored to account for factors, such as age and social structure, that affect transmission probabilities (*24*). Gaining more information from a test with moderate accuracy can also reduce concerns of scarce testing resources (*30–32*). Combining these methods to more quickly and efficiently identify infected contacts with appropriate measures to prevent onward transmission from those contacts is key to mitigating the COVID-19 pandemic (*18*).

This method is necessarily limited by the availability and speed of deployment and reporting of such a test. Local, point-of-service tests would be most valuable for this approach. It is also limited by the ability to identify index cases and locate their contacts for testing quickly. The longer this process takes, the more burden there is on epidemiological work after testing to isolate those contacts and identify their contacts, in order to halt the entire transmission chain. These difficulties are common to more traditional contact tracing approaches, however, and can potentially be offset by using a more rapid and easily deployed test with lower sensitivity. This approach, along with recent research on the value of frequent testing, demonstrates the need for rapid virologic tests for COVID-19, even if they have lower sensitivity than current tests (*16, 17*). This method can help prioritize resources when the monitoring of contacts is the limiting factor, but is less valuable when identifying, locating, and testing contacts is the limiting factor. For that reason, it may be more practical in workplaces and campuses where the contacts may be more readily identified and accessed.

The analysis here may very well underestimate the efficacy of this approach in some settings. If, as has been suggested, superspreading events arise in part because of higher viral loads in the index individual (*4, 9*), individuals capable of initiating SSEs are less likely to be missed even by a low-sensitivity test. If their infected contacts also have a higher viral load, they will also be more likely to be detected. Thus, for a nucleic acid test, the effective sensitivity for identifying both index and secondary cases will be inflated. In addition, if individuals infected by a high viral load are more likely to have a high viral load and have higher infectiousness

themselves, this method best identifies the chains that cause the vast majority of new cases, increasing its effectiveness.

As municipalities, workplaces, and schools consider how best to resume activities in the wake of the COVID-19 pandemic, contact tracing and, in particular, cluster identification will be an integral part of measures to ensure that subsequent waves of outbreaks are avoided or lessened (*13, 29*). Designing test and trace strategies that can be enacted quickly and at lower cost yet efficiently isolate a large proportion of infected individuals will be crucial to the success of these reopening plans. Further research on the causes of SSEs of SARS-CoV-2 will provide valuable information on the relative benefits of various such strategies. By focusing on identifying transmission events and then isolating all other contacts of that index individual, transmission tracing with a low-sensitivity, high-specificity test has a high chance of identifying SSEs while reducing the likelihood of isolating uninfected contacts. Given the apparent importance of overdispersed transmission in this pandemic, transmission tracing may be a particularly valuable strategy.

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Supplementary Materials:

Materials and Methods

Effectiveness of Transmission Tracing

We assume the test has perfect specificity, sensitivity of $a \times 100\%$, and that the test results of any two individuals are independent conditional on their true infection status (that is, there are no strain effects that would cause two people infected by the same source to be more likely to both incorrectly test negative).

The value of the transmission tracing strategy depends on two key points: that an individual who has transmitted to at least one contact is more likely to have transmitted to more contacts than an individual not known to have transmitted at least once; and that a low-sensitivity test has a high probability of identifying a group of infected contacts who are all tested.

The first point relies on the negative binomial distribution of secondary cases. The expected number of infected contacts of an individual is $E[Z] = R_0$. We can reparameterize the negative binomial distribution by letting $p = \frac{R_0/k}{1 + R_0/k}$ (22). The expected number of infected contacts of an individual given that they have infected at least one individual is: $E[Z|Z \geq 1] = \frac{R_0}{1 - P[Z=0]} = \frac{R_0}{1 - (1-p)^k}$. When $E[Z|Z \geq 1] - R_0 > 1$, the probability of any other contact of an index individual known to have infected at least one contact is higher than the probability of any contact of an index individual not known to have infected any contacts.

The second point relies on the independence of test results among secondary cases. If this condition holds, then the probability of at least one positive test among *n* infected individuals is given by: $P[\geq 1 \text{ positive test among } n \text{ selected individuals}] = 1 - (1-a)^n$. Even for low sensitivity values, this probability increases quickly as *n* increases.

More concretely, we can calculate the expected number of secondary cases isolated/quarantined under strategies A, B, and C. The expected number of secondary cases per index case isolated by transmission tracing (strategy A) is:

$$E[Z_A] = \sum_{n=0}^{\infty} nP[Z = n]P[\geq 1 \text{ positive test among } n \text{ infected individuals}]$$

$$= \sum_{n=0}^{\infty} n \binom{n+k-1}{n} (1-p)^k p^n (1-(1-a)^n)$$

$$= E[Z] - \sum_{n=0}^{\infty} n \binom{n+k-1}{n} (1-p)^k (p(1-a))^n$$

$$= R_0 - \left(\frac{1-p}{1-p+ap}\right)^k \frac{p(1-a)k}{1-p+ap} = R_0 \left(1-(1-a)\left(1+\frac{aR_0}{k}\right)^{-(1+k)}\right).$$

The expected number of secondary cases per index case quarantined by quarantining all contacts (strategy B) is $E[Z_B] = R_0$. The expected number of secondary cases per index case who test positive (and are thus isolated under strategy C) is $E[Z_C] = R_0 P[\text{positive test} \mid \text{infected}] = aR_0$.

Cost of Transmission Tracing

We use the proportion of index cases whose contacts are isolated as a proxy for the cost (in terms of number of people isolated and resources spent on epidemiologic measures for isolated individuals) of the strategy. For strategy B, the proportion quarantined is 1. For strategy C, this proportion is less relevant as individuals are isolated based on their own test results rather than based on the source of their potential infection. For transmission tracing (strategy A), the probability that an index case's contacts will be isolated is given by:

$$P[\text{isolated}] = P[Z = n]P[\geq 1 \text{ positive test among } n \text{ infected individuals}]$$

$$= \sum_{n=0}^{\infty} \binom{n+k-1}{n} (1-p)^k p^n (1-(1-a)^n)$$

$$= 1 - \sum_{n=0}^{\infty} \binom{n+k-1}{n} (1-p)^k (p(1-a))^n = 1 - \left(\frac{1-p}{1-p+ap}\right)^k$$

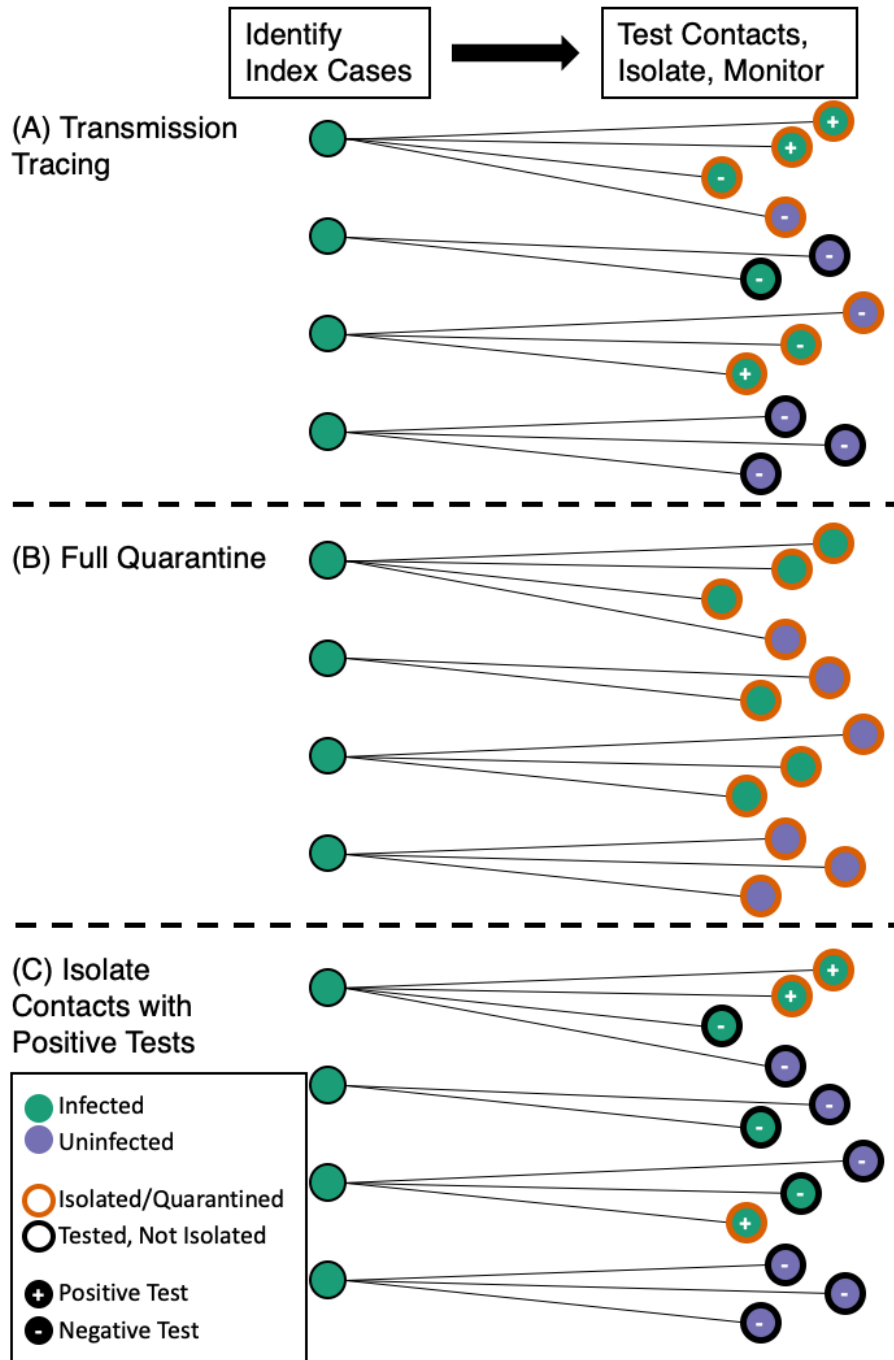$$= 1 - \left(1+\frac{aR_0}{k}\right)^{-k}.$$

Fig. 1. Schematic of three approaches to test and trace contacts of infected individuals: (A) transmission tracing; (B) full isolation of identified contacts; and (C) isolation of contacts who test positive. Infected individuals are green; uninfected individuals are purple. Individuals who test positive are denoted "+" and those who test negative are denoted "-". Isolated contacts have an orange border while contacts who are not isolated have a black border.
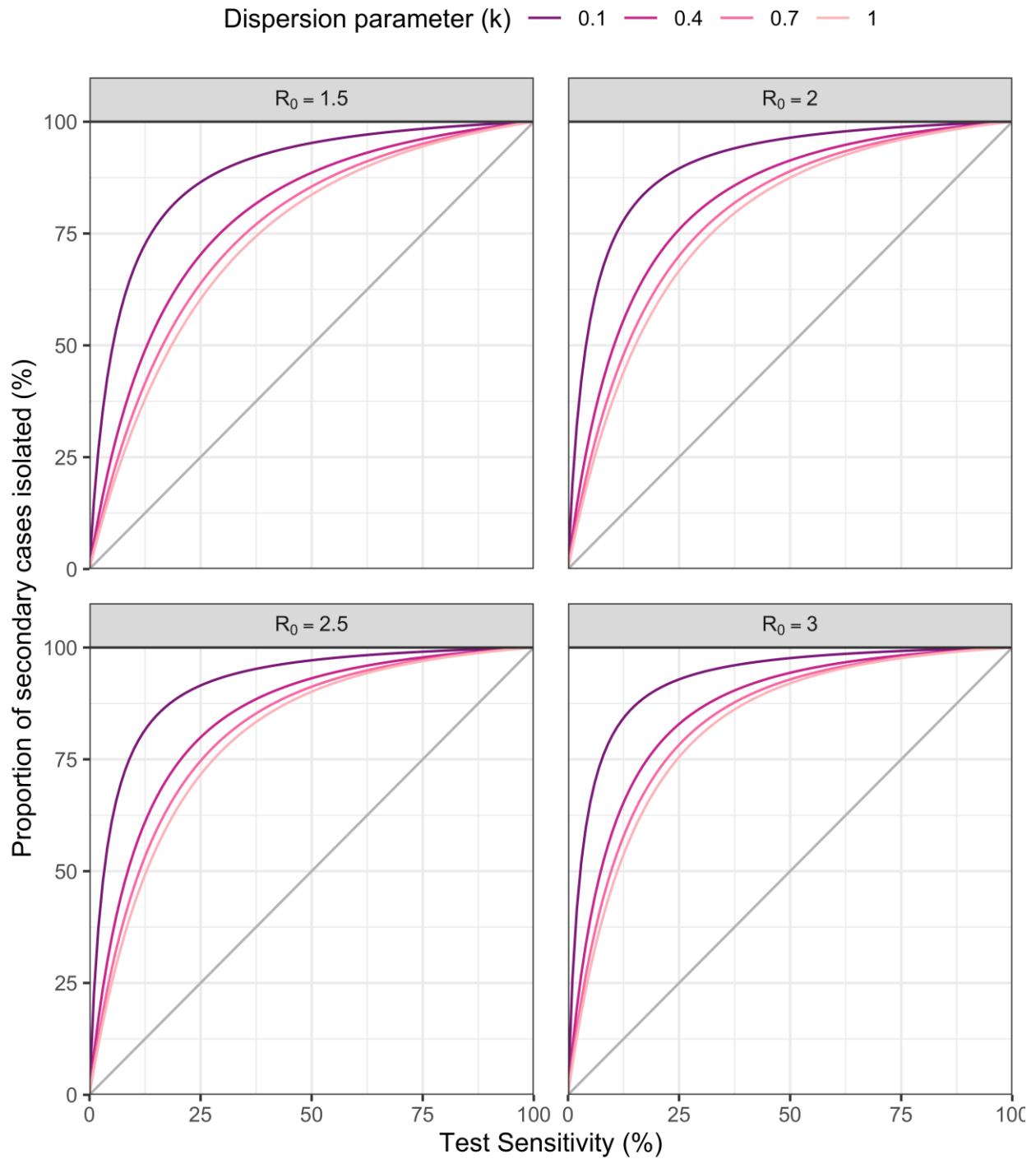
Fig. 2. Proportion of secondary cases isolated under the transmission tracing strategy vs. test sensitivity by R_0 and k. The diagonal line indicates the proportion of secondary cases who test positive and are isolated under strategy C.
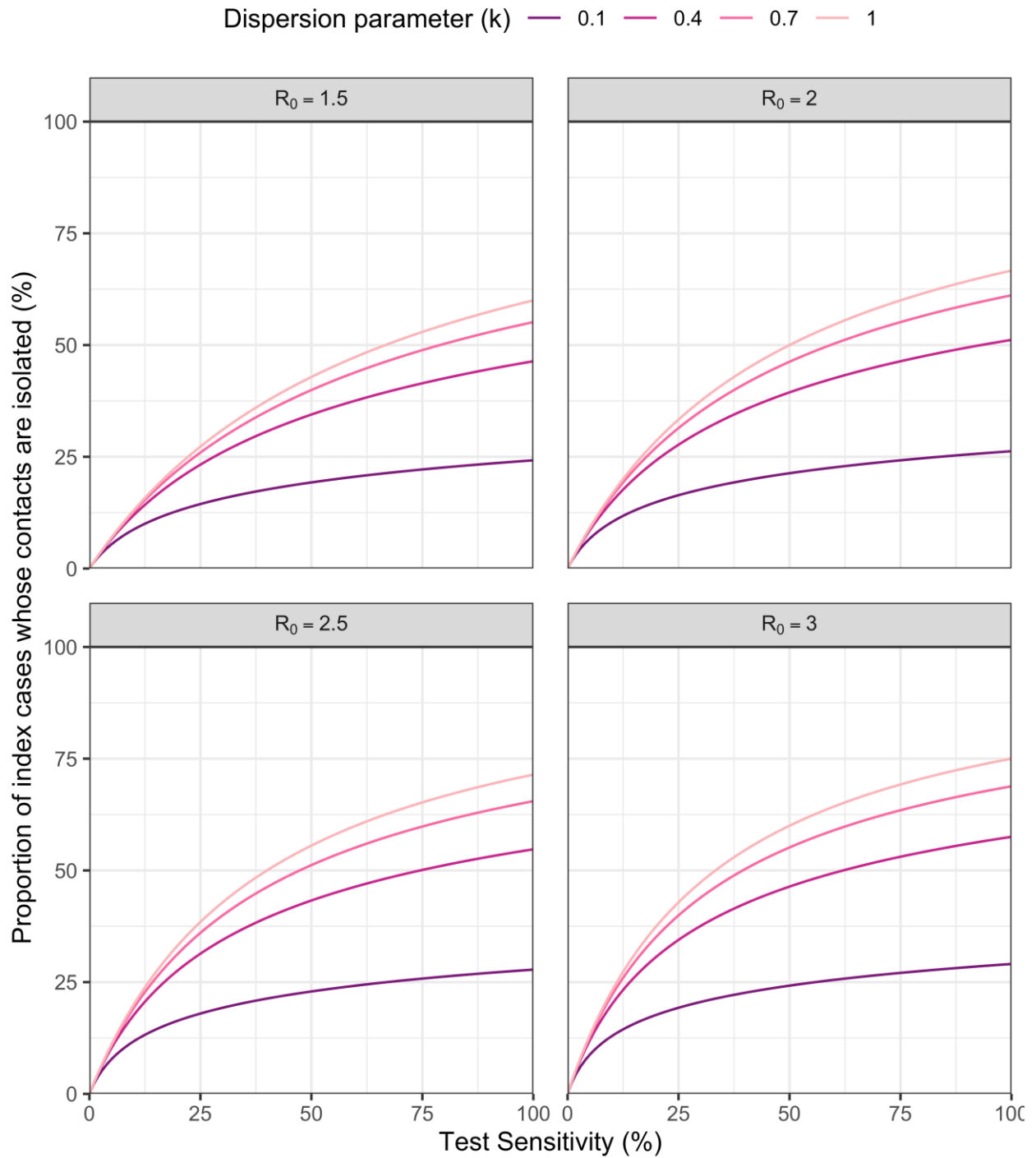
Fig. 3. Proportion of index cases whose contacts are isolated under the transmission tracing strategy vs. test sensitivity by R_0 and k.