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Long, thin transmission chains of Severe Acute Respiratory Syndrome Coronavirus 2 may go undetected for several weeks at low to moderate reproduction numbers: Implications for containment and elimination strategy

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1) infections almost always caused overt symptoms, so effective case and contact management enabled its effective eradication within months. However, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) usually causes only mild symptoms, so transmission chains may grow to include several individuals before at least one index case becomes ill enough to self-report for diagnosis and care. Here, simple mathematical models were developed to evaluate the implications of delayed index case detection for retrospective contact tracing and management responses. Specifically, these simulations illustrate how: (1) Contact tracing and management may effectively contain most but not all large SARS-CoV-2 clusters arising at foci with high reproduction numbers because rapidly expanding transmission chains ensure at least one overtly symptomatic index case occurs within two viral generations a week or less apart. (2) However, lower reproduction numbers give rise to thinner transmission chains extending through longer sequences of non-reporting asymptomatic and paucisymptomatic individuals, often spanning three or more viral generations ($\geq$2 weeks of transmission) before an overtly symptomatic index case occurs. (3) Consequently, it is not always possible to fully trace and contain such long, thin transmission chains, so the community transmission they give rise to is underrepresented in surveillance data. (4) Wherever surveillance systems are weak and/or transmission proceeds within population groups with lower rates of overt clinical symptoms and/or self-reporting, case and contact management effectiveness may be more severely limited, even at the higher reproduction numbers associated with larger outbreaks. (5) Because passive surveillance platforms may be especially slow to detect the thinner transmission chains that occur at low reproduction numbers, establishing satisfactory confidence of elimination may require that no confirmed cases are detected for two full months, throughout which presumptive preventative measures must be maintained to ensure complete collapse of undetected residual transmission. (6) Greater scope exists for overcoming these limitations by enhancing field surveillance for new suspected cases than by improving diagnostic test sensitivity. (7)

Abbreviations: SARS-CoV-2, Severe Acute Respiratory Syndrome Coronavirus 2.

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While population-wide active surveillance may enable complete traceability and containment, this goal may also be achievable through enhanced passive surveillance for paucisymptomatic infections, combining readily accessible decentralized testing with population hypersensitization to self-reporting with mild symptoms. Containment and elimination of SARS-CoV-2 will rely far more upon presumptive, population-wide prevention measures than was necessary for SARS-CoV-1, necessitating greater ambition, political will, investment, public support, persistence and patience. Nevertheless, case and contact management may be invaluable for at least partially containing SARS-CoV-2 transmission, especially larger outbreaks, but only if enabled by sufficiently sensitive surveillance. Furthermore, consistently complete transmission chain containment may be enabled by focally enhanced surveillance around manageably small numbers of outbreaks in the end stages of successful elimination campaigns, so that their endpoints may be accelerated and sustained.

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Introduction

As the world continues to struggle with the ongoing global pandemic of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) (Scudellari, 2020) it is essential to clearly understand the distinctive epidemiological characteristics that make it so difficult to contain. It is particularly useful to compare and contrast SARS-CoV-2 with Severe Acute Respiratory Syndrome Coronavirus 1 (SARS-CoV-1), so we can understand why these two pathogens have followed such dramatically different epidemic trajectories, despite being so closely related and sharing so many epidemiological characteristics (Wilder-Smith, Chiew, & Lee, 2020). SARS-CoV-1 was first identified as an emerging human pathogen in late 2002 and rapidly spread to 29 countries (R. Smith, 2019), for similar reasons to those underpinning the rapid spread of SARS-CoV-2 across the globe early last year:

> *The relatively prolonged incubation period allowed asymptomatic air travellers to spread the disease globally and resulted in more than 8000 cases in 2003* (Chan-Yeung & Xu, 2003).

Not only did SARS-CoV-1 spread internationally as rapidly as SARS-CoV-2 (R. Smith, 2019; Wilder-Smith et al., 2020), it was also similarly difficult to distinguish from other common causes of illness, especially early in the onset of infection:

> *No individual symptom or cluster of symptoms has proved to be specific for a diagnosis of SARS. Although fever is the most frequently reported symptom, it is sometimes absent on initial measurement* (World Health Organization, 2020).

In stark contrast with SARS-CoV-2, the epidemic curve of SARS-CoV-1 was rapidly crushed (Fineberg, 2020) and then terminated with only 774 deaths occurring before the main outbreak ended in July 2003 (R. Smith, 2019). While SARS-CoV-1 probably persists as a potential zoonotic threat in its original animal reservoir, human-to-human transmission of this virus may be considered eradicated because no human case has been documented since four minor, brief outbreaks in 2004 (R. Smith, 2019; Wilder-Smith et al., 2020).

So why is it that SARS-CoV-1 was so rapidly and decisively eliminated or even eradicated (R. Smith, 2019; Wilder-Smith et al., 2020), whereas the ongoing SARS-CoV-2 pandemic has spiralled out of control internationally? Also, why has SARS-CoV-2 proven so difficult to eliminate locally, even for countries that successfully shrank their national epidemics down to a handful of residual cases?

While the incubation periods and natural serial intervals of these two coronaviruses are similar, both are slightly shorter for SARS-CoV-2 (Bi et al., 2020; Cheng et al., 2020; He, Zhao, Li, et al., 2020; Rai, Shukla, & Dwivedi, 2021; Wilder-Smith et al., 2020; Zhao, 2020). More importantly, the viral shedding patterns of SARS-CoV-2 more closely resemble those of influenza than SARS-CoV-1 (He, Zhao, Li, et al., 2020), so it has a far shorter latent period that can be as brief as 3 days or less (Ali et al., 2020; Cheng et al., 2020; He, Zhao, Li, et al., 2020; Zhao, 2020). Crucially, the shorter latent period of SARS-CoV-2 facilitates a pre-symptomatic transmission period (Cheng et al., 2020; He, Zhao, Li, et al., 2020; Wilder-Smith et al., 2020; Zhao, 2020) that averages about two days in duration, during which time approximately one third of secondary infections may arise before any signs of illness are experienced (Zhao, 2020).

However, perhaps the most important difference between these two coronaviruses from a containment perspective seems to lie in their virulence patterns, the implications of which we explore in this article. While SARS-CoV-1 caused severe symptoms in almost all of those infected (Wilder-Smith et al., 2005), most SARS-CoV-2 infections cause only mild symptoms, if any (Wilder-Smith et al., 2020), so large fractions of community transmission evade detection with passive, facility-based surveillance of self-reporting individuals seeking testing and care (Chow, Chang, Gerkin, & Vattikuti, 2020; Hao et al., 2020; Killeen & Kiware, 2020; Li et al., 2020; Wilder-Smith et al., 2020).

Here we develop and apply a simple, deterministic mathematical model to outline how the generally mild symptoms associated with SARS-CoV-2 can constrain the effectiveness of retrospective contact tracing of transmission chains back to

branch points over a week into the past. Specifically, we explain how the lower mean clinical severity of SARS-CoV-2 infections allows long, thin transmission chains to extend for several weeks without being detected through conventional, passive surveillance of self-reporting symptomatic cases. We then outline the implications of this phenomenon for ongoing containment and elimination efforts.

Methods

Although the clinical manifestations of viral infections are distributed along a continuous spectrum of severity, for simplicity, new infections are assumed here to result in one of three symptomological category outcomes, each associated with a distinct probability of self-reporting to clinical facilities or otherwise seeking testing at disease-specific testing centres: (1) The proportion of people infected who experience severe symptoms at some stage over the full course of their infections (θ_s) and consequently all report for testing, (2) The proportion of infections that, sooner or later, result in some mild symptoms (θ_m), sometimes referred to as *paucisymptomatic* infections, of which only a fraction self-report for testing (ρ_m), and (3) the remaining proportion of infections that do not result in any obvious symptoms ($\theta_a = 1 - \theta_s - \theta_m$) and consequently do not self-report for testing. Based on the values assumed for these input parameters, the proportion of infected persons self-reporting for testing (θ_r) may be calculated as:

$$\theta_r = \theta_s + \rho_m \theta_m \tag{1}$$

Allowing for the imperfect sensitivity of currently available diagnostic tests for viral genetic material, only a proportion of all self-reported active infections will be successfully confirmed when tested (ρ_c), so the proportion of infections successfully tested and confirmed by routine symptom-based passive surveillance (θ_c) may be calculated thus:

$$\theta_c = \rho_c \theta_r \tag{2}$$

For SARS-CoV-1, these input parameters were set at $\theta_s = 0.9$, $\theta_m = 0.05$ and $\theta_a = 0.05$ based on previously reported low rates of mild or asymptomatic infections among a carefully monitored cohort of healthcare workers (Wilder-Smith et al., 2005). For SARS-CoV-2, these values were set at $\theta_s = 0.1$, $\theta_m = 0.4$ and $\theta_a = 0.5$, based on previous literature review of normal early-outbreak surveillance systems, in which so many mild paucisymptomatic cases went unnoticed and were either misclassified as asymptomatic or simply not distinguished from them (Killeen & Kiware, 2020). For both coronaviruses, approximately half of all mildly symptomatic infections were assumed to self-report for testing ($\rho_m = 0.5$) based on literature review relating to early-outbreak surveillance of SARS-CoV-2 under conditions where public awareness of paucisymtomic carriage was limited (Killeen & Kiware, 2020). Test sensitivity of 70% was assumed in both cases ($\rho_c = 0.7$), based on performance of current SARS-CoV-2 tests (Woloshin, Patel, & Kesselheim, 2020), so that the contrasting simulations for both viruses can be considered on an "all other things being equal" basis. Based on these assumed input parameters, the derived overall probabilities of infection confirmation through routine surveillance are calculated as approximately 65% for SARS-CoV-1 and 21% for SARS-CoV-2 ($\theta_c = 0.6475$ and 0.21, respectively).

The mean number of secondary cases arising from the primary cases that seed an epidemic in a given context, circumstance and intervention scenario, is commonly known as the effective reproduction number (R_e). Here, that baseline reproduction number specifies an intervention scenario lacking contact tracing and management for confirmed cases identified through routine, symptom-based passive surveillance at health facilities and testing centres. After a given number of complete but overlapping viral generation (g) durations of approximately two weeks, each separated by a mean serial interval of just under one week (Bi et al., 2020; Cheng et al., 2020; He, Zhao, Li, et al., 2020; Rai et al., 2021; Wilder-Smith et al., 2020; Zhao, 2020), the relative size of the F_g viral population in the absence of any contact tracing and management intervention (V_g), when compared to the original F_0 population that seeded the outbreak, may be calculated as follows:

$$V_g = R_e^g \tag{3}$$

The overall probability that a transmission chain seeded by a single primary case remains unconfirmed after a given number of descendant secondary generations ($P_{uc,g}$) may then be calculated as the same probability for the previous generation multiplied by the proportion of infections evading detection through routine surveillance (1 - θ_c) to the power of the expected number of active infections derived from the primary infection by that generation:

$$P_{uc,g} = P_{uc,g-1}(1 - \theta_c)^{V_g} \text{ starting with } P_{uc,0} = 1 \tag{4}$$

The probability that a single transmission chain can sustain itself, despite reproduction numbers too low to enable viral population expansion ($R_e \leq 1.0$), and remain unconfirmed ($P_{suc,g}$) by evading detection through passive surveillance may be calculated as:

$$P_{suc,g} = P_{uc,g} R_e^{\,g} \tag{5}$$

The implications of this key interaction between the length of unnoticed transmission chains and their width may be explored numerically, first by calculating the probable fraction of transmission chains that evade retrospective tracing and management for each secondary generation ($P_{uct,g}$):

$$P_{uct,g} = P_{uc,g} P_{ut,g} \tag{6}$$

$$\text{where } P_{ut,g} = (1-\theta_c)^{R_e} \text{ when g} > 1, \text{ otherwise } P_{ut,g} = 0 \tag{7}$$

The expected mean number of viral infections that cannot be contained by case and contact management because they branched off two generations, or approximately two weeks, ago ($V_{uct,g}$) may be calculated for each secondary generation as the product of the probability of infections being both unconfirmed and untraceable ($P_{uct,g}$) and the otherwise expected number of viral offspring descended from the primary seed infection (V_g):

$$V_{uct,g} = V_g P_{uct,g} \tag{8}$$

The expected mean number of infections arising from entire transmission chains over their full duration that are fundamentally untraceable, and will escape containment regardless of how effectively case and contact management is implemented because their nearest common ancestors with confirmed cases occurred two or more generations previously (E), can then be calculated by summing these probabilities per generation over the lifetimes of the transmission chains:

$$E = \sum_{g=1}^{\infty} V_{uct,g} \tag{9}$$

Similarly, the mean length of transmission chains, in generations, before they are detected through confirmed cases identified through routine passive surveillance (G), may be calculated by summing the per-generation probabilities for chains remaining unconfirmed ($P_{uc,g}$):

$$G = \sum_{g=1}^{\infty} P_{uc,g} \tag{10}$$

Results

Complete containment of SARS-CoV-1 through case and contact management

The predicted median lengths of SARS-CoV-1 transmission chains up to the point where they are identified, tested and confirmed through routine passive, symptom-based surveillance are consistently short (Fig. 1A). Even when effective reproduction numbers drop slightly below the threshold required to sustain them, SARS-CoV-1 transmission chains rarely extend beyond 2 secondary generations without being detected (Fig. 1A). At the lower end of this spectrum of reproduction numbers, where SARS-CoV-1 transmission chains may occasionally extend for two or more secondary generations before being detected, it is nevertheless feasible to fully contain them because they are consistently detected before they have branched too much to trace comprehensively back through a single generation (Fig. 2A and B).

At moderate effective reproductive numbers that are nevertheless comfortably above this minimal self-sustaining level and capable of seeding rapid exponential growth ($R_e = 1.5$), it may be expected that almost three quarters (72%) of all SARS-CoV-1 transmission chains will be identified either at the point of the seeding primary infection or within a single secondary generation and 96% within 2 secondary generations (Fig. 1A). At the higher effective reproductive numbers that drive explosive outbreaks ($R_e \geq 2.0$), the vast majority ($\geq$77%) of SARS-CoV-1 transmission chains should be detected and contained within a single secondary generation and essentially all ($\geq$99%) within two secondary generations, even though a substantial minority of infections (35%) are predicted to evade detection (Fig. 1A) because of either the absence of overt symptoms (<7.5%) or, more likely, false negative tests (27.5%). Overall, and regardless of effective reproductive number, essentially all SARS-CoV-1 transmission chains are expected to be identified and contained before any early branches have had the opportunity to extend beyond the traceability limit of one subsequent generation (Fig. 2A–D).

Obstacles to complete SARS-CoV-2 containment through case and contact management

However, SARS-CoV-2 transmission chains are predicted to extend far longer before being detected, simply because overtly symptomatic infections are the exception rather than the rule (Figs. 1B and 2E–H). The longest undetected SARS-CoV-

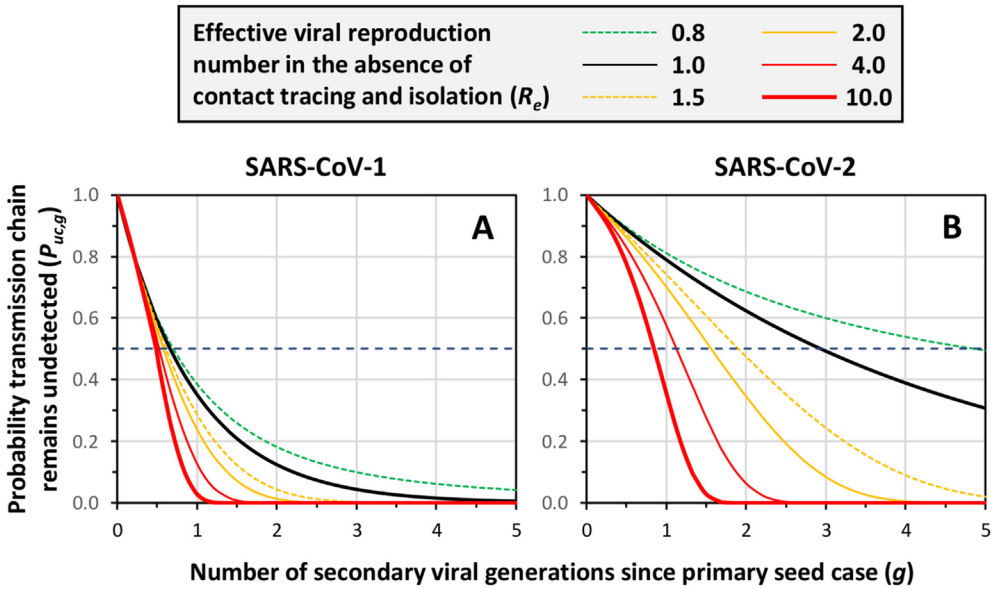


Fig. 1. The declining probabilities over time, expressed in terms of full viral generation durations (g) separated by a mean serial interval of just under one week for both SARS-CoV-1 and SARS-CoV-2 (Bi et al., 2020; Cheng et al., 2020; He, Zhao, Li, et al., 2020; Rai et al., 2021; Wilder-Smith et al., 2020; Zhao, 2020), that transmission chains seeded by single individual primary cases remain unconfirmed by routine passive surveillance of self-reporting symptomatic cases ($P_{uc,g}$). A range of values for the effective reproduction number in the absence of any case and contact management intervention (R_e) was assumed. Predicted values for $P_{uc,g}$ were calculated using equations (1)–(4). Horizontal dashed lines in both panels represents a probability of 50%, from which median chain length can be interpolated onto the horizontal axis.

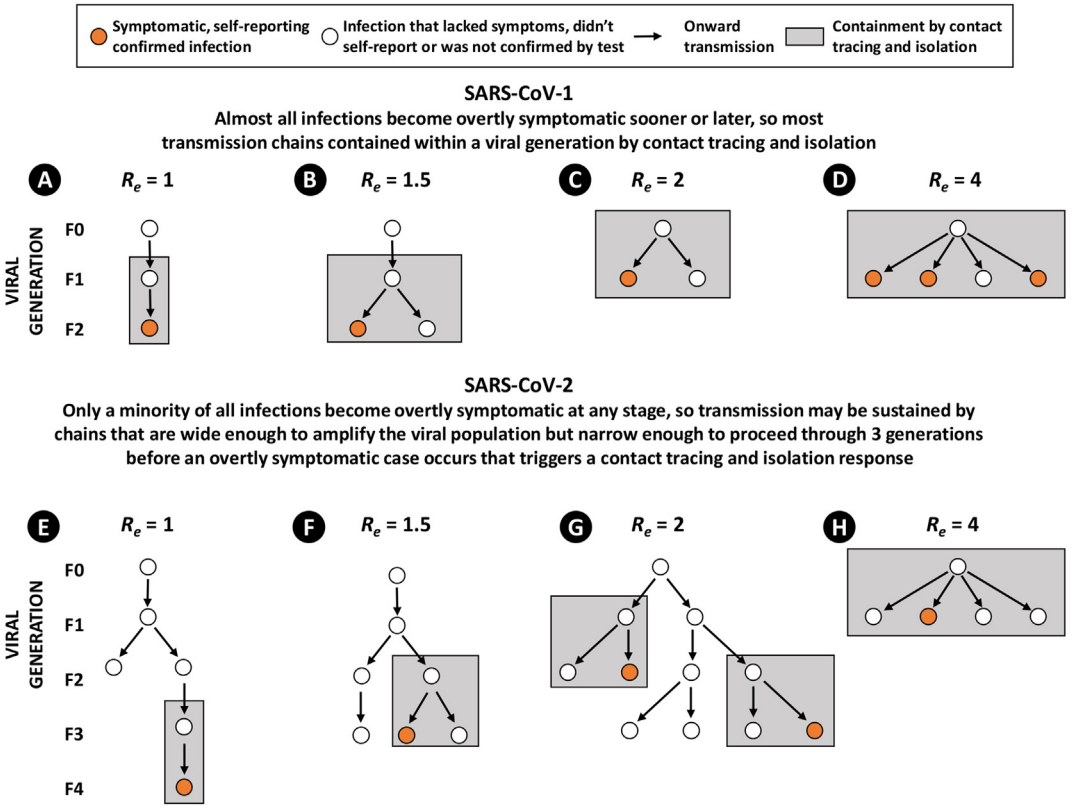


Fig. 2. A schematic illustration of how (**A to D**) SARS-CoV-1 transmission chains may be consistently contained through effective case and contact management because the vast majority of infections result in clinical symptoms overt enough to motivate self-reporting to health facilities or testing centres, whereas (**B to H**) for SARS-CoV-2 only a small minority of infections cause sufficiently overt symptoms to motivate self-reporting, so transmission chains often extend too long before being detected for retrospective case and contact management to completely contain them.

2 transmission chains occur in settings with the lowest transmission potential (Re $\leq$ 1.0), simply because these chains do not consistently expand and therefore remain thinner over time (Figs. 1B and 2E). Reproduction numbers that are only moderately higher, but nevertheless sufficient to drive strong, steadily branching outbreaks of SARS-CoV-2 (R_e = 1.5), can also generate remarkably extended transmission chains that go unnoticed for quite some time before an overtly symptomatic infection occurs, self-reports and is confirmed with laboratory diagnostics (Figs. 1B and 2F). Indeed, such epidemic growth of 50% per generation results in transmission chains that are expected to usually branch once in the first two secondary generations but also to extend for three secondary generations or more before being detected in 24% of cases (Fig. 1B). As a result, branch points may commonly occur too long ago to be realistically traced retrospectively, so containment may be only partially effective (Fig. 2F). While only 8.4% of transmission chains will span three secondary generations or more at a slightly higher R_e of 2.0 (Fig. 1B), this is counterbalanced by their faster rate of expansion and greater likelihood of branching too early to allow consistent tracing to single common ancestor infections by the time a confirmed index case is identified (Fig. 2G).

Explosive epidemic growth at $R_e \geq 4.0$ shortens the duration over which SARS-CoV-2 transmission chains may go undetected (Fig. 1B), because their greater width will usually yield an early confirmed index case in the first secondary generation (Fig. 2H). Nevertheless, it is notable that 6% of such rapidly widening transmission chains are expected to extend to the F2 secondary generation before any symptomatic case is confirmed, at which point it will often be too late to trace the initial branch point of the primary case (Fig. 3). While such untraceable early branch points in extended, unnoticed transmission chains are rarer at such high reproduction numbers, their consequences are obviously greater simply because those escapee lineages amplify themselves so quickly (Fig. 3).

At least some degree of viral population expansion is required to allow some SARS-CoV-2 infections to evade containment through contact tracing and management because that requires at least occasional sustained branching (Fig. 2F, G and H). This intuitive, descriptive rationale is reflected numerically in the lack of any predicted escapee infections in Fig. 4B despite the prediction that some of these essentially linear chains may extend for up to 10 generations before being detected through routine surveillance. However, while higher reproductive numbers obviously accelerate early branching and viral population expansion, this risk is counterbalanced by the fact that such wider chains will also be identified and confirmed earlier through routine surveillance (Fig. 4B, D, F, H and J). Overall, the probability that SARS-CoV-2 transmission chains will yield untraceable offspring therefore peaks consistently in the F2 secondary generation and tails off rapidly in subsequent generations, especially at higher reproductive numbers. At low to moderate reproduction numbers (1.0 < Re $\leq$ 2), modest rates of expansion may proceed through longer transmission chains with much higher overall probabilities of producing untraceable offspring infections (Fig. 4D, F and H).

However, these untraceability probabilities alone (Fig. 4) underrepresent the influence of reproduction numbers because later secondary generations arising from faster-expanding transmission chains represent larger viral populations, from which any given proportion of untraceable infections will amount to a greater number of escapees overall (Fig. 3). Fig. 5 illustrates how the distribution of probabilities of transmission chains remaining undetected and then yielding untraceable escapee infections is modified by accounting for the fact that they are rapidly widened by higher reproduction numbers. At the same default assumption as Figs. 1 and 4 for the proportion of infections detected and confirmed through passive surveillance (θ_c = 0.21), high reproduction numbers rapidly curtail the distribution of probabilities that transmission chains remain undetected (Dashed red line in Fig. 5A). Consequently, even the concomitantly greater population size of later generations is compensated for, because so few chains ever get the chance for offshoot lineages to go undetected for more than one generation beyond their common branch point (Dashed red line in Fig. 5B). The highest rates at which transmission chains result in untraceable escapees therefore occur at lower reproduction numbers that are just sufficient to sustain steady expansion of transmission chains and outbreaks in the absence of case and contact management. Crucially, the estimated mean number of untraceable escapees for SARS-CoV-2 approaches two per chain at reproductive numbers ranging up to about 2 and comfortably exceeds the threshold of 1 per transmission chain required for outbreak persistence up to effective reproduction numbers of 3 or more.

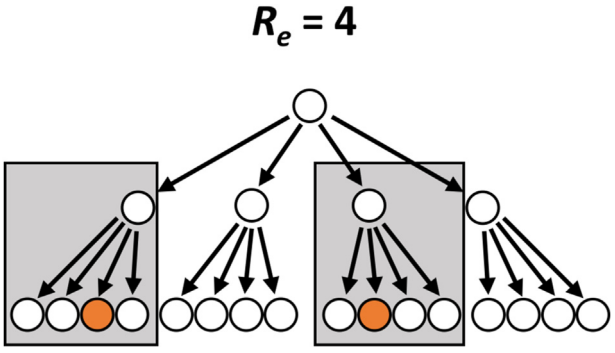


Fig. 3. A schematic illustration of how wide, rapidly expanding transmission chains for SARS-CoV-2 can sometimes extend over three generations before being detected, at which point they most probably branched far too early for case and contact management to completely contain them.

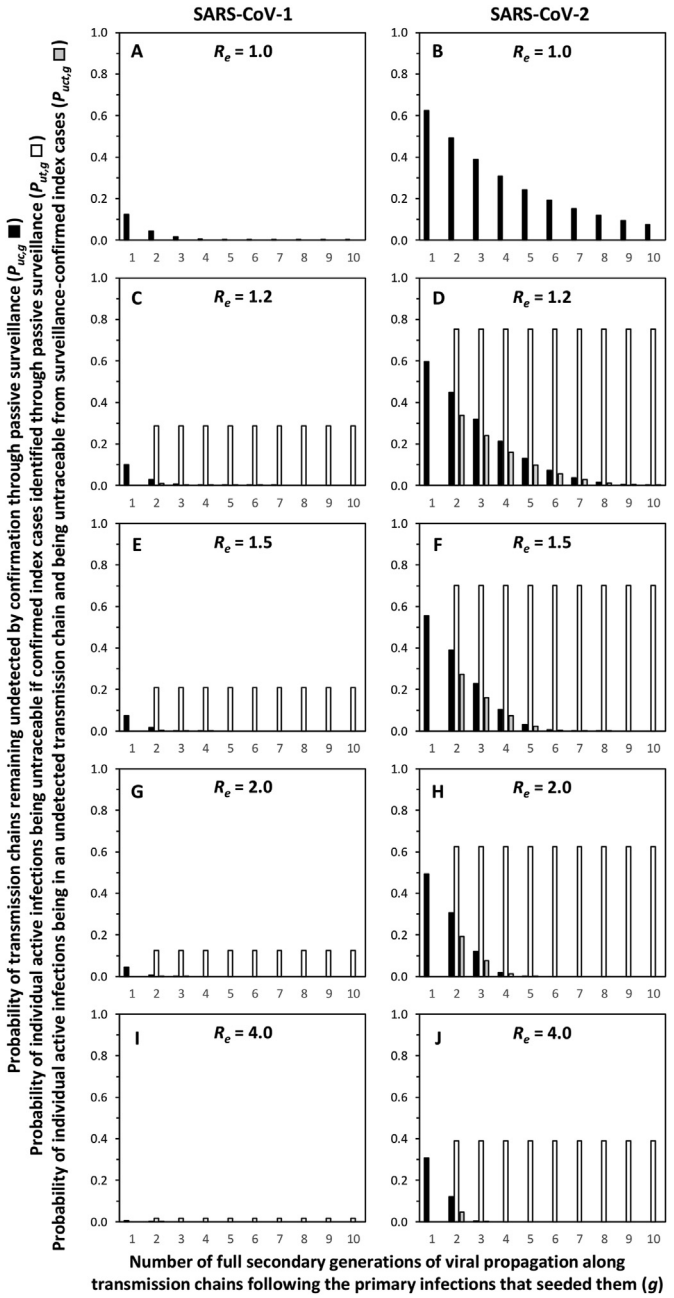


Fig. 4. Predicted probabilities for each secondary viral generation that transmission chains of SARS-CoV-1 (Left hand panels **A**, **C**, **E**, **G** and **I**) and SARS-CoV-2 (Right-hand panels **B**, **D**, **F**, **H**, **J**) remain undetected (Equations (1)–(4)), that individual infections are untraceable because they originate from a common ancestor branch point more than two generations ago (Equations (5) and (6)), and that untraceable infections arise from undetected transmission chains (Equations (7) and (8)) at reproductive numbers varying from 1.0 (Panels **A** and **B**) to 4.0 (Panels **I** and **J**).

The influence of local effective reproduction numbers upon the traceabilitv of SARS-CoV-2 infections (Fig. 5B) also has important implications for the interpretation of surveillance data. Moving from left to right across Fig. 2E to H, it is intuitive that much higher fractions of all infections will be detected in larger clusters arising where local transmission potential is elevated. While the attention of epidemiologists and the public alike are often captivated by large numbers of associated cases within explosive outbreaks (Fig. 2G and H), smaller numbers of isolated cases occurring at lower transmission rates are likely to be heavily under-represented (Fig. 2E and F).

For comparison, almost all SARS-CoV-1 infections may be retrospectively traced within one previous viral generation, regardless of reproduction number (Fig. 2E–H and Fig. 4A, C, G and I), so no such detection biases occur. This also means that

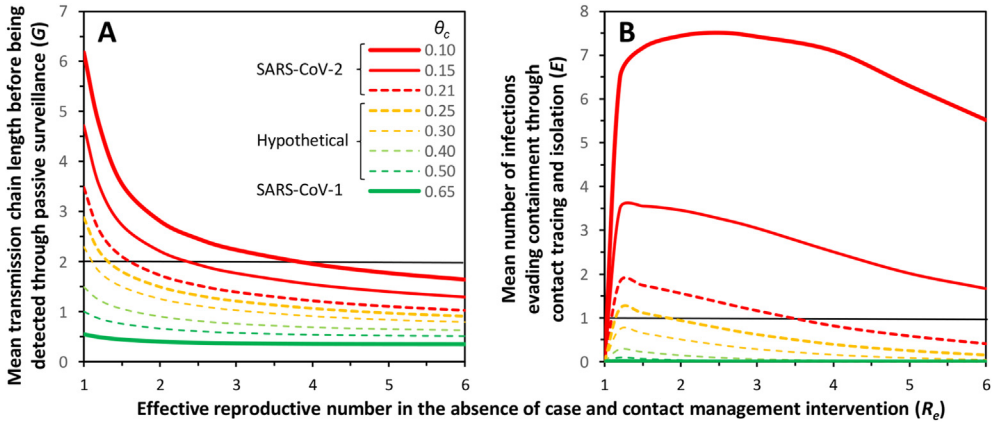


Fig. 5. A comparison of the simulated potential for SARS-CoV-1 and SARS-CoV-2 and a series of otherwise identical hypothetical viral pathogens with intermediate rates of infection confirmation through routine surveillance (θ_c) to evade containment through case and contact management. **A**: Predicted mean length of viral transmission chains up to the point at which they are detected through routine passive surveillance (Equation (10)). **B**: Predicted mean number of untraceable infections arising from individual transmission chains (Equation (9)). For SARS-CoV-2, a range of infection confirmation rates are assumed, to match either the default approximate rates assumed for Figs. 1, 4 and 6 based on previous literature review ($\theta_c = 0.21$ (Killeen & Kiware, 2020)), or similar to some even lower recent estimates ($\theta_c = 0.15$ (Chow et al., 2020; Hao et al., 2020; Li et al., 2020)) that may be further attenuated in settings where surveillance systems are weaker and/or ongoing transmission is dominated by other population groups who are less likely to become overtly symptomatic and self-report ($\theta_c = 0.10$). The horizontal line in panels **A** represents the minimum number of secondary generations, which approximates to weeks since the primary infection (Bi et al., 2020; Cheng et al., 2020; He, Zhao, Li, et al., 2020; Wilder-Smith et al., 2020; Zhao, 2020), that a transmission chain should extend without being detected for some of its earliest branch points from the primary generation to be considered untraceable. The horizontal line in panel **B** represents the minimum mean number of escapees per transmission chain required for those chains to robustly sustain themselves despite highly effective case and contact management because of early branch points that occurred too long ago to be traced once the first symptomatic case is tested and confirmed.

SARS-CoV-1 is grossly incapable of evading effective containment contact tracing and management over multiple generations (Solid green lines in Fig. 5), simply because overtly symptomatic index cases always occur before transmission chains become too extended (Fig. 2E–H and Fig. 4A, C, G and I).

Examining the influence of variable surveillance sensitivity upon containment effectiveness

Real surveillance systems, however, will of course deviate from these default input parameter value assumptions. Simulations for a range of otherwise identical hypothetical viral pathogens with intermediate rates of case confirmation (Orange and green dashed lines in Fig. 5) suggest that any substantive increase in detection rate above those typically expected for SARS-CoV-2 would close off this escape route for transmission chains with early branches. The infection confirmation rates assumed for SARS-CoV-2 in the simulations presented in Figs. 1 and 4 appear to be just low enough for it to robustly evade containment with case and contact management (Dashed red lines in Fig. 5). If passive, symptom-based surveillance can be enhanced and/or supplemented to push confirmation rates above the predicted tipping point of about 30% (Green lines in Fig. 5), this could enable complete containment through case and contact management by facilitating comprehensive detection of all transmission chains before they become too long and branched.

On the other hand, even the low SARS-CoV-2 confirmation rates assumed as the default for simulations in Figs. 1 and 4, as well as the dashed red lines in Fig. 5 ($\theta_c = 0.21$ (Killeen & Kiware, 2020)) may lean on the optimistic side, even in situations where transmission is broadly distributed across all age groups so that high detection rates may occur amongst the elderly (Chow et al., 2020; Hao et al., 2020; Li et al., 2020). Furthermore, even lower values may be more representative of contexts where surveillance systems are weaker and/or transmission is dominated by younger age groups, who are less likely to experience overt symptoms and/or less likely to self-report for diagnosis and care. Under such conditions, even very wide transmission chains may frequently escape prompt detection (Solid red lines in Fig. 5), so that incomplete tracing and containment of larger outbreaks (Fig. 3) becomes commonplace. It is therefore crucially important that passive surveillance systems achieve at least the same mean confirmations rates assumed here as default values. It is also vital that surveillance data interpretation is tempered by the likelihood that even small population groups with below average rates of overt illness and/or self-reporting may be heavily underrepresented.

Implications of covertly extended transmission chains for achieving elimination endpoints

Assuming a mean infection duration of two weeks, and a mean serial interval of approximately one week for both coronaviruses (Bi et al., 2020; Cheng et al., 2020; He, Zhao, Li, et al., 2020; Rai et al., 2021; Wilder-Smith et al., 2020; Zhao, 2020), one primary and four secondary generations could span up to one month. For SARS-CoV-1, it is highly unlikely that a single transmission chain would persist so long without confirmation of any overtly symptomatic index cases (Fig. 6A and

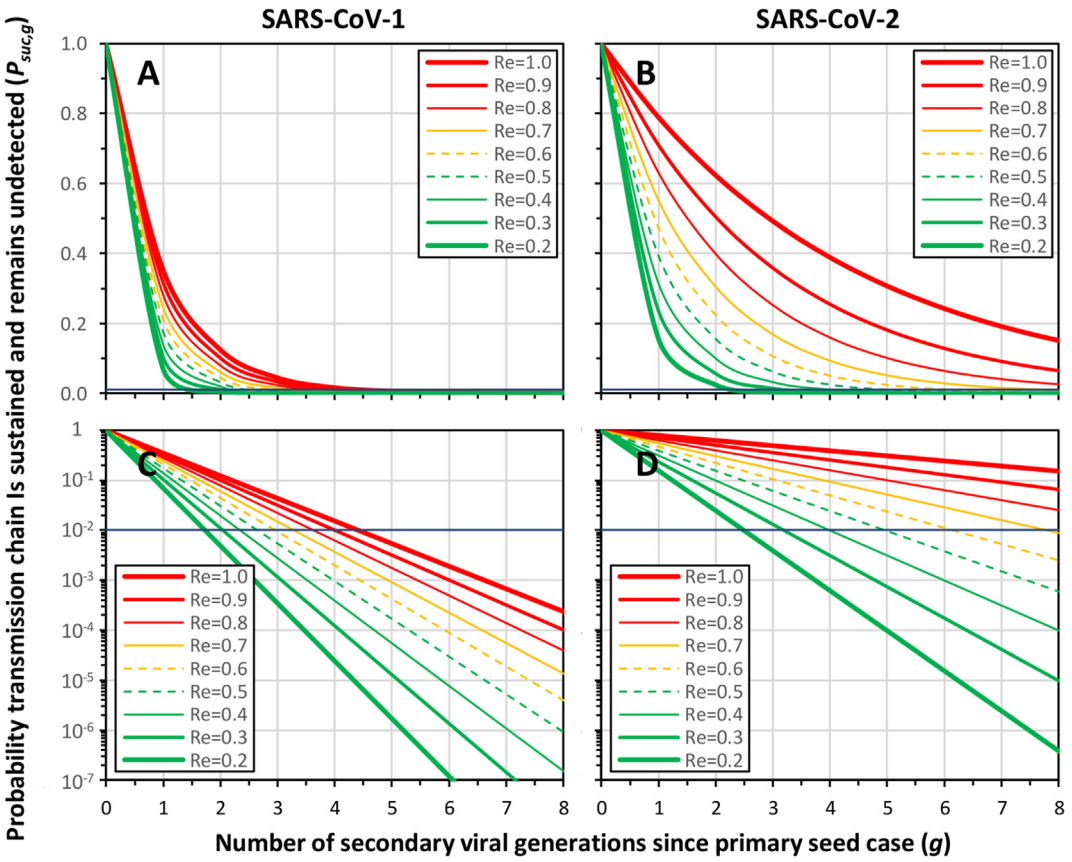


Fig. 6. Predicted probabilities that individual transmission chains of SARS-CoV-1 (**A** and **C**) or SARS-CoV-2 (**B** and **D**) will both persistently sustain themselves and remain undetected and unconfirmed ($P_{suc,g}$) after a given number of overlapping secondary generations (g) separated by mean overlapping serial intervals of just under one week (Bi et al., 2020; Cheng et al., 2020; He, Zhao, Li, et al., 2020; Rai et al., 2021; Wilder-Smith et al., 2020; Zhao, 2020) by routine passive surveillance at reproductive numbers low enough to facilitate virus elimination (Equation (5)). The horizontal lines in both panels represent a 1% probability threshold at which a period without any confirmed cases may be considered to reflect de facto elimination with a reasonably satisfactory degree of confidence ($P_{suc,g} = 0.01$). For all simulations, the same default input parameter values were assumed as for Figs. 1 and 4, as well as the dashed red lines in Fig. 5, corresponding to infection confirmation rates (θ_c) of 0.65 for SARS-CoV-1 and 0.21 for SARS-CoV-2.

C). Such a follow up period of one month without any confirmed cases at least approaches satisfactory confidence ($P \leq 0.01$) of elimination under any conditions that are compatible with elimination endpoints ($R_e < 1.0$). In fact, even at the maximum reproduction number low enough to prevent epidemic resurgence ($R_e = 1.0$), such stringent confidence levels may be closely approached after one month and surpassed only a week later.

For SARS-CoV-2, however, long, thin transmission chains may persist and go undetected for several viral generations, even at reproduction numbers too low for those chains to sustain themselves indefinitely (Fig. 6B). At a steady state reproduction number of 1.0, which yields essentially linear transmission chains on average (Figs. 2E), 39% of SARS-CoV-2 chains are expected to evade detection for up to 4 secondary generations or one month (Fig. 6B). At lower reproduction numbers ($R_e < 1.0$), while most SARS-CoV-2 transmission chains will collapse before extending for so many generations, a small but important minority that do survive longer than a month are likely to remain undetected (Fig. 6B and D) because they are so long and thin (Fig. 2E). Even at reproduction numbers as low as 0.7, it may take two months without any confirmed cases to achieve satisfactory certainty of elimination under the default assumptions for passive surveillance detection sensitivity used to generate Fig. 6.

Opportunities for enhancing passive surveillance sensitivity to enable complete traceability

Consistently robust containment is predicted for SARS-CoV-1 (Figs. 1 and 4–6), even though the same 30% rate of false negative test results was assumed as for SARS-CoV-2 (Woloshin et al., 2020). While this suggests that low reporting rates of those with only mildly symptomatic infections are the most more important cause of incomplete transmission chain traceability, improvements in diagnostic test sensitivity limitations may nevertheless contribute to earlier detection of transmission chains. In order to explore where the greatest scope for improving infections confirmation rates might lie, a sensitivity analysis was conducted within the plausible range of values for diagnostic test sensitivity, the proportion of

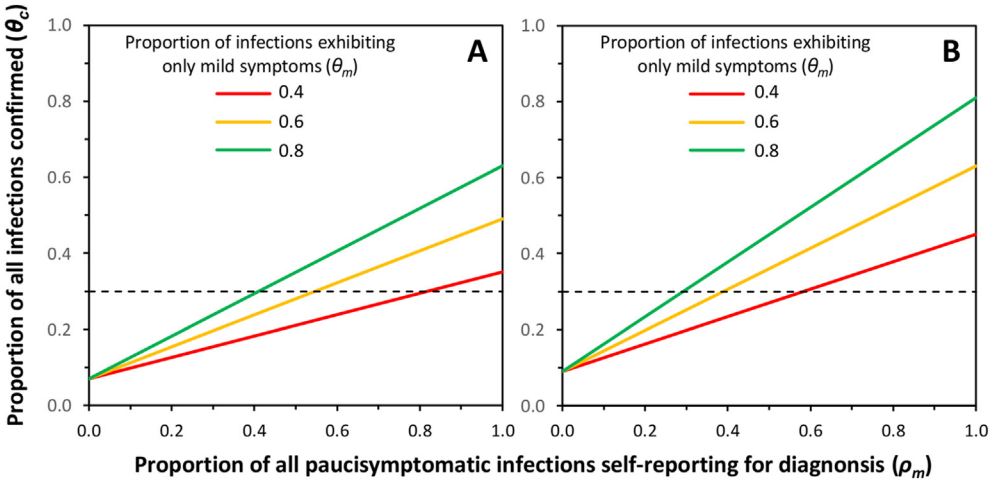


Fig. 7. Sensitivity analysis for the dependence of the proportion of all infections confirmed (θ_c) upon diagnostic test sensitivity ($\rho_c = 0.7$ (Panel **A**) or 0.9 (Panel **B**)), the proportion of infections that exhibit only mild symtoms (θ_m), and the proportion of such paucisymptomatic infections who self-report for testing (ρ_m), calculated with equations (1) and (2) and varying these input parameters within plausible ranges for their potential values (Buitrago-Garcia et al., 2020; Killeen & Kiware, 2020; Mizumoto, Kagaya, Zarebski, & Chowell, 2020; Nishiura et al., 2020; Park et al., 2020; Woloshin et al., 2020).

infections that exhibit only mild symptoms, and the proportion of such paucisymptomatic infections who self-report for testing (Fig. 7).

At the somewhat pessimistic default assumption that only 40% of infections exhibit some mild symptoms, the minimum 30% infection confirmation threshold required to ensure complete transmission chain traceability (Fig. 5) may only be reached if diagnostic test sensitivity is improved from the conservative default value of 70% to the much more optimistic level of 90% and at least two thirds all such paucisymptomatic carriers dutifully self-report for testing (Fig. 7). However, assuming the default test sensitivity of 70% but a higher paucisymptomatic carriage probability of 60%, this minimum infection confirmation threshold may be reached at self-reporting rates of 54%, while improved test sensitivity brings complete traceability within reach if 30% of such carriers or more self-report (Fig. 7). Assuming a paucisymptomatic carriage rate of 80%, which leans towards the higher but perhaps more justifiable end of the plausible range (Buitrago-Garcia et al., 2020; Mizumoto et al., 2020; Park et al., 2020), the same threshold for complete traceability may be reached at self-reporting rates of 41% and 29% for test sensitivities of 70% and 90%, respectively (Fig. 7).

Discussion

Incomplete containment of long-thin SARS-CoV-2 transmission chains at lower reproduction numbers

While these theoretical simulations are no more than that, they do provide several detailed insights that are consistent with early perspectives of investigators with in-depth practical experience of both SARS-CoV-1 (Wilder-Smith et al., 2005) and now SARS-CoV-2:

> … many more patients with COVID-19 rather than SARS have mild symptoms

that contribute to spread because these patients are often missed and not isolated (Wilder-Smith et al., 2020).

For SARS-CoV-1, these model predictions indicate that untraceable branches in transmission chains should almost never occur, regardless of transmission potential, simply because the overt and consistent symptomology associated with this coronavirus always draws attention to itself within a one or two viral generations. For SARS-CoV-2, however, much longer chains can occur before they are detected through routine passive surveillance, especially at lower reproductive numbers, and this allows sufficient time for early branches of chain expansion to become untraceable before the first index case is confirmed. The prediction that untraceability of SARS-CoV-2 peaks at low to moderate reproductive numbers may help rationalize widespread observations that case and contact management systems are highly effective when applied to large clusters but leave large fractions of untraceable community transmission of unexplained origin (He, Zhao, Li, et al., 2020; He, Zhao, Xu, et al., 2020).

Long, thin transmission chains occurring at lower reproductive numbers are underrepresented in routine surveillance data

Large outbreaks may occur rapidly in settings with high reproduction numbers (Cheng et al., 2020; Kucharski et al., 2020; Mizumoto & Chowell, 2020; Park et al., 2020; Steinbrook, 2020; Xu et al., 2020), but these should be easier to retrospectively

associate into complete clusters that can be fully contained (Fig. 2H). However, longer, narrower transmission chains that go unnoticed for several viral generations are probably typical of most community transmission events occurring at lower reproductive numbers, the collective importance of which is widely underappreciated (He, Zhao, Li, et al., 2020; He, Zhao, Xu, et al., 2020). Correspondingly, studies based exclusively on data from clusters of two or more associated cases (Ali et al., 2020; Qian et al., 2020; Xu et al., 2020) may particularly underrepresent the role of community transmission in sustaining epidemics. Any interpretation of routine surveillance data should therefore consider those inherent and potentially large biases, as well as the fact much larger factions of SARS-CoV-2 transmission occur through untraceable community transmission and small outbreaks than was the case for SARS-CoV-1 (He, Zhao, Li, et al., 2020; He et al., 2020).

The importance of covert transmission at lower reproductive numbers is underappreciated

SARS-CoV2 clearly follows the same 80-20 rule of thumb for transmission distribution (Adam et al., 2020; Bi et al., 2020; Endo, Centre for the Mathematical Modelling of Infectious Diseases, Covid Working Group, Abbott, Kucharski, & Funk, 2020; Laxminarayan et al., 2020) as every other known infectious disease (Woolhouse et al., 1997), but transmission distribution is nevertheless far less aggregated than was the case for SARS-CoV-1 (He, Zhao, Li, et al., 2020; He, Zhao, Xu, et al., 2020). Scattered pockets of community transmission and small outbreaks therefore play a much more important role in sustaining transmission of SARS-CoV-2 than SARS-CoV-1 and bolsters the ongoing pandemic against contact tracing and management interventions (He, Zhao, Li, et al., 2020; He, Zhao, Xu, et al., 2020), especially when the detection biases illustrated in the bottom half of Fig. 2 are considered. Such moderately aggregated transmission distributions for SARS-CoV-2 (He, Zhao, Li, et al., 2020; He, Zhao, Xu, et al., 2020) mean that most people probably lived in social networks with reproductive numbers substantially below the population mean of 3–4 typically reported for this virus (Killeen & Kiware, 2020), even before any pre-emptive, presumptive, population-wide suppression measures were rolled out. While covertly extended transmission chains may be rare among the small fraction of the population capable of mediating SARS-CoV-2 super-spreader events (Adam et al., 2020; Bi et al., 2020; Endo, Centre for the Mathematical Modelling of Infectious Diseases, Covid Working Group, Abbott, Kucharski, & Funk, 2020; Laxminarayan et al., 2020), they may be remarkably common among the majority of the general population who are unknowingly responsible for the community transmission events (He, Zhao, Li, et al., 2020; He, Zhao, Xu, et al., 2020) that silently seed new outbreaks.

While the majority of people in most countries live in households of several people, within which transmission potential is greater than between households, secondary attack rates within households are nevertheless remarkably modest (Bi et al., 2020; Koh et al., 2020; Madewell, Yang, Longini, Halloran, & Dean, 2020). Furthermore, every population includes a substantial minority who live alone. Indeed, single adults comprise over 20% of European households, and may even be the most common type of household in some countries, notably Sweden where 40% of the population lives alone (Eurostat:StatisticsExplained, 2020). So while such population groups might seem small, they may nevertheless be large enough to quietly seed ubiquitous community transmission across the population as a whole. In most countries, reported cases of community transmission may well represent the mere tip of a much larger iceberg that facilitates largely unnoticed, slower but more generalized spread.

Exacerbated covert transmission risks associated with insensitive surveillance and surveillance blind spots

Such containment limitations and observation biases are likely to be further exaggerated wherever surveillance systems are weak and/or transmission proceeds within population groups with lower rates of overt clinical symptoms and/or self-reporting. Specifically, if less than one fifth of infections are detected, case and contact management effectiveness may be more severely limited, even at the higher reproduction numbers associated with larger outbreaks (Fig. 5). Even if low confirmation rates are restricted to only small fractions of society, these nevertheless create dangerous *blind spots* in surveillance platforms that allow transmission chains to extend for several weeks before at least one index case becomes ill and report for medical care (Fig. 8).

While broadly inadequate surveillance platforms and/or inadequate societal participation in self-monitoring and self-reporting will obviously undermine containment effectiveness of case and contact management, natural biological variability in susceptibility to clinically overt illness may also create population surveillance gaps that merit careful consideration. For example, social interactions between small peer groups of young people with generally low probabilities of severe symptoms may act as covert transmission hubs that disperse infection untraceably across a community, into several other settings where transmission potential may be higher and more vulnerable individuals may be exposed (Fig. 8). While larger gatherings resulting in bigger clusters may be more obvious and easier to trace, covert community transmission through smaller pods of students in secondary schools, contact sports teams in their 20s, or modest social gatherings of youths may be just as important but underrepresented in surveillance data. Similarly, an apartment complex occupied by single thirty-somethings living in one-person households but meeting each other for coffee in the evenings, or a carefully controlled restaurant where young professionals meet, may also act as crossroads through which such long, thin transmission chains may pass without being detected . SARS-CoV-2 may quietly transit unnoticed through such a channel of low surveillance sensitivity, into several different households, workplaces or other settings before becoming identifiable as the focal transmission hub that connects them all (Fig. 8). Again, it is crucial to not only recognize that such inherent biases exist but also where, when and how they are most likely to arise:

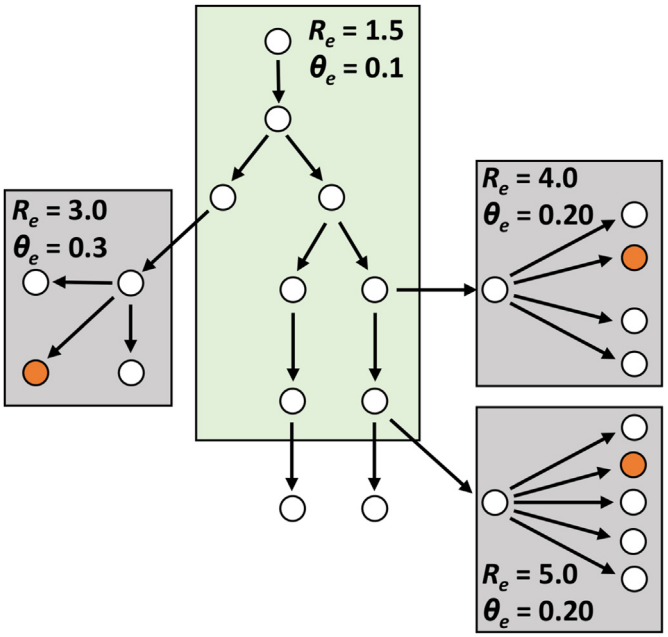


Fig. 8. A schematic representation of how community hub with low-to-moderate rates of transmission ($R_e = 1.5$) through modest-sized peer groups of exhibiting low rates of overt symptomatic manifestation and/or self-reporting with symtoms of illness ($\theta_c = 0.1$) may constitute *blind spots* in passive surveillance platforms that mediate covert dissemination of SARS-CoV-2 to several separate households and work places with higher reproduction numbers ($R_e \geq 3.0$) and rates of overt symptomatic manifestation ($\theta_c \geq 0.2$) before these are identified as clusters and contained through case and contact management.

> *We also cannot account for any potential selection bias in our results where small family clusters are more readily traceable than smaller social clusters, which might go unrecognized, thus biasing estimates of their frequency and size* (Adam et al., 2020).

Such blind spots also commonly arise among population groups who are less likely to self-report for testing and medical care, even when they become quite ill, because they have either been marginalized by society or have deliberately marginalized themselves. The former typically include vulnerable populations, such as the homeless and immigrants, while the latter may include criminal gangs, religious groups and peer groups of those unconvinced that SARS-CoV-2 is a major threat.

Implications of covert transmission chains for elimination end point certainty

The stark contrast between SARS-CoV-1 and SARS-CoV-2 in terms of covert transmission chain persistence under heavily suppressed conditions (Fig. 6) has two key implications. First, surveillance becomes less sensitive and reliable as an indicator of freedom from infection at the low reproductive numbers required to achieve elimination end points. Passive surveillance systems may therefore need to document zero new cases for two full months to establish certainty that elimination has been achieved and stringent restrictions may be confidently eased. Second, reproductive numbers should be kept as low as possible throughout such follow up periods with no apparent cases, to ensure such long, thin, undetected transmission chains all self-terminate before the necessary restrictions, which are too socially burdensome and economically damaging to sustain indefinitely (Jefferson et al., 2008; Nachega et al., 2020), are finally eased and reproduction numbers are allowed to rebound.

While a range of effective reproductive numbers have been simulated for both coronaviruses in Fig. 6, to ensure direct comparability on the basis that all other things are assumed equal, in reality the basic reproductive numbers of SARS-CoV-1 was substantially lower than for SARS-CoV-2 (Wilder-Smith et al., 2020). The remarkable difference between these two coronaviruses, in terms of requirements for achieving and establishing confidence in their elimination, are therefore likely to be even starker than the contrast in Fig. 6 suggests. It may therefore be easy to understand why so many counties that successfully applied social distancing, hygiene and mask wearing interventions to crush the curve of their initial SARS-CoV-2 epidemics then experienced resurgent transmission after attempting to transition to end-game strategies relying more heavily on the case and contact management approaches (Scudellari, 2020) that proved so successful against SARS-CoV-1 (Wilder-Smith et al., 2020).

Enhancing surveillance sensitivity to enable complete containment of SARS-CoV-2 transmission chains

While population-wide active surveillance strategies could enable complete traceability and containment by pushing case confirmation rates above the 30% threshold indicated in Fig. 5, such proactive screening for new infections may be very difficult to achieve. In our experience (Hamainza et al., 2014), they may also be even more difficult to sustain at adequate levels of regular population participation. Fortunately, the same confirmation rate targets may also be achievable through enhanced passive surveillance for paucisymptomatic infections, combining readily accessible decentralized testing with population hypersensitization to self-reporting with mild symptoms. While such voluntary self-reporting with even the mildest of symptoms may also not be possible to sustain for long periods, it may be possible to achieve such heightened active or passive surveillance sensitivity on limited geographic and temporal scales at the end stages of successful elimination campaigns (Ali et al., 2020). Under such conditions, with manageably small numbers of outbreaks ongoing at any given time, it becomes possible for rapid response teams to locally boost infection confirmation rates by targeting transmission foci with far more sensitive surveillance tactics over limited time periods than would otherwise be possible.

Probably the most advanced and well-characterized operational models for routinely sustained active, population-wide surveillance of pathogens causing similarly vague, non-specific symptoms have been developed for malaria, HIV and tuberculosis in Africa and much could be learned from ongoing African initiatives to adapt these community-based approaches to SARS-CoV-2 (Nachega et al., 2020). While it remains to be seen whether any sizeable jurisdiction can scale up, much less sustain, active surveillance across its entire population for long periods, it has proven feasible to achieve in a geographically targeted manner over limited periods in a wide diversity of contexts around the world. In our experience, presumptive testing of entire communities centred around focal outbreaks in hostels, apartment blocks, prisons, work places, small towns and urban neighbourhoods usually captures all local cases and associates them into single clusters, especially if serology is used to trace further back in time than the 2-week window assumed here (Yong et al., 2020). Note, however, that this is only practically feasible in situations where rigorous suppression with complementary hygiene, social distancing, mask wearing and quarantine measures have first driven incidence down to near-elimination conditions, so that only a handful of such small, focal outbreaks require attention at any given time.

We have also experienced that effective community engagement during such focal rapid response campaigns can hypersensitise local communities to self-report for testing, so that even passive surveillance can capture high proportions of infections. While numerous studies differ on exactly what proportion of all SARS-CoV-2 infections are paucisymptomatic, rather than truly asymptomatic, they do consistently indicate this fraction should be large enough to push confirmation rates above the 30% threshold required to adequately curtail the length of unnoticed transmission chains (Fig. 5). Experience with other diseases like endemic malaria, which also usually causes only mild, non-specific symptoms among semi-immune adults, also indicates that only a minority of infections are really asymptomatic in the strict sense and most carriers may be classified as paucisymptomatic instead (Chen et al., 2016). While quantitative studies differ on exactly what proportion of all SARS-CoV-2 infections may be classified as paucisymptomatic, many now indicate they constitute the majority of infections in practice when study participants are monitored carefully and heavily sensitized to the need to report any symptom of illness whatsoever [Park et al., 2020 #7707; Mizumoto et al., 2020 #7209; Buitrago-Garcia et al., 2020 #7733]. It should therefore be feasible to push passive surveillance confirmation rates high enough to enable complete traceability of transmission chains if most paucisymptomatic individuals can be motivated to self-report (Fig. 7). While improvements in diagnostic test sensitivity could clearly help enable complete transmission chain containment, it seems unlikely that this alone will be sufficient and greater scope exists for overcoming the limitations of SARS-CoV-2 case and contact management through focally-enhanced, time-limited passive surveillance for new suspected cases (Fig. 7). While it may not be realistic to expect such high rates of self-reporting with only mild, often non-specific symptoms from any population over the long term, it may be reasonable to occasionally ask of communities under short term outbreak response conditions they also perceive merit an emergency response. It is therefore feasible for SARS-CoV-2 elimination programmes to reach “sticky” (D. L. Smith et al., 2013) end points that are easier to sustain than achieve, because reactive case and contact management responses can be fully enabled by more intensified surveillance tactics than would be feasible under conditions of widespread community transmission. Beyond constructive and compelling engagement with as many nodes of such targeted communities as possible, such reactive and focal surveillance campaigns need to minimize barriers to testing and medical care through decentralized, freely available and ubiquitously publicized services. Efforts to optimize the accessibility, awareness and perceptions of such temporarily-heightened health services should especially target the most vulnerable and marginalized members of society who carry a disproportionate share of SARS-CoV-2 disease burden while also providing the virus with surveillance blind spots to hide in (Fig. 8).

Erring on the cautious side by allowing for blind spots in enhanced surveillance systems

Having said all that, even focally enhanced active and/or passive surveillance will always miss some infections due to false negative tests and, more importantly, incomplete population participation. In any society there will always be individuals and population subgroups who will be far less compliant than others and who often co-associate as households, peer groups or social networks. The concerns expressed above about the potential for long, thin transmission chains to extend covertly without being detected (Fig. 6) therefore stand even under such conditions of focally enhanced surveillance in response to a local outbreak. Even if the vast majority of the population participate enthusiastically in such campaigns, covert transmission

chains may be sustained by even a single, small resiliently non-compliant group, especially one living at the margins of society. The extended elimination confirmation surveillance periods indicated by Fig. 6, necessitating as long as two months without any confirmed case to pass before an outbreak can be confidently declared over, should therefore be applied consistently, regardless of how well the general population engages with such focally enhanced surveillance platforms.

Conclusions

Case and contact management is less effective against slow, steady, undetected community transmission of SARS-CoV-2 than against its more consistently virulent predecessor, SARS-CoV-1. Overall, the most important conclusion of this analysis is that case and contact management should be viewed as an invaluable supplement to all the difficult hygiene measures and behavioural restrictions that have proven so effective (Chu et al., 2020; Jefferson et al., 2008; Xiao, Lin, Hodges, Xu, & Chu, 2020) but never as a substitute for any of them (Cheng et al., 2020; Kucharski et al., 2020; Sanche et al., 2020; Steinbrook, 2020; Wilder-Smith et al., 2020; Xu et al., 2020) until a sustainable elimination state has been achieved or at least approached. Containment and elimination of SARS-CoV-2 will therefore have to rely far more upon the presumptive hygiene, distancing and mask-wearing prevention measures that have proven so effective thus far (Hao et al., 2020). Furthermore, these more burdensome population-wide measures will have to be sustained at far more stringent levels and for longer periods after the last detected case of community transmission than was necessary for SARS-CoV-1. Given the lack of alternatives at present, the most important missing ingredients now required for countries to progress towards elimination and exclusion of SARS-CoV-2 transmission are ambition, political will, public support, persistence and patience (Cutler & Summers, 2020; Editors, 2020; International Monetary Fund, 2020).

Despite the limitations imposed upon index case surveillance by low rates of overt illness, case and contact management remains an invaluable intervention, especially for at least partially containing onward transmission from large clusters that would otherwise be devastating (Adam et al., 2020; Bi et al., 2020; Endo, Centre for the Mathematical Modelling of Infectious Diseases, Covid Working Group, Abbott, Kucharski, & Funk, 2020; Laxminarayan et al., 2020). Having said that, the effectiveness of even that partial containment function is heavily dependent upon prompt detection of at least one out of every five infections as index cases to trigger contact tracing and management responses, so the importance of sufficiently sensitive surveillance cannot be overemphasized. Furthermore, consistently complete transmission chain containment may be feasibly enabled through focal enhancement of surveillance to capture at least one third of all infections around the manageably small numbers of outbreaks that occur towards the end of successful elimination campaigns, to accelerate and sustain their end points.

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CRediT authorship contribution statement

Gerry F. Killeen: Conceptualization, Methodology, Visualization, Investigation, Writing – original draft, preparation. **Patricia M. Kearney:** Writing – review & editing. **Ivan J. Perry:** Writing – review & editing. **Niall Conroy:** Conceptualization, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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