COVID-19 Evidence Update

COVID-19 Update from SAHMRI, Health Translation SA
and the Commission on Excellence and Innovation in Health

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End to an epidemic / 2 x incubation time rule

Executive Summary

The end to an epidemic is often linked to a 2 x incubation period rule. The objective of this rule is to create a time span sufficiently long to ensure the interruption of human-to-human transmission of a virus.

Origins: This 'rule' came from the World Health Organization and the Ebola Virus epidemic [1], where 2 x 21 days (twice the empirical maximum incubation period) = 42 days of **no new cases**, was adopted as the end of the epidemic. This was supplemented with 90 days of heightened surveillance.

Definitions: The 2 x incubation time rule has been reported slightly differently. Usually it is reported as 2 x the maximum incubation time [i.e. 2 x the time frame for onset of infection] from the **last detected case**. It has also been reported as 2 x the time since the **last known case either recovered** (with 2 negative tests) **or died**.

Scientific bases: The WHO 'rule' appears to have been generated without extensive scientific justification.

Benefits: It is transparent and easy to follow. It may have intuitive merit for the public.

Limitations: The rule was not perfect in the case of Ebola. 42 days failed to capture a limited number of outlier cases, partly due to then unrecognised chains of transmission (e.g. a case report of sexual transmission). It has been reported as being too conservative in other settings (e.g. MERS South Korea [2]).

Advances: There have been attempts to refine the end of epidemic criteria using mathematical modelling. The instantaneous reproduction number, the case reporting rate, and the delay between symptom onset and recovery/death of the last detected case, are the most important inputs. Modelling of Ebola indicates **surveillance sensitivity** (i.e. case reporting rate) of **79%** is necessary for 95% confidence that an outbreak is over after 42 days without symptomatic cases [3].

Multiple methods, used in combination, may be needed to declare an end to an epidemic; surveillance and mathematical modelling are complementary instruments that can be combined to overcome their respective limitations [4].

COVID-19 specific context:

- The most commonly accepted **incubation time is 14 days**, which can be expected to detect 97-99% of cases. (Mean incubation time is 5-6 days; range 0-27 days) [5].
- Cases are potentially **infectious** from 1-3 days prior to becoming symptomatic. Evidence indicates that people may be more infectious around the time of symptom onset, compared to later in the disease [6].
- **Undetected cases and transmission**: The majority of cases of COVID-19 are known to be mild or moderate. While reports of asymptomatic cases vary enormously (5-80% [7]), the WHO reports that there are in fact **few confirmed reports of truly asymptomatic cases** of SARS-COV-2 [8]. Therefore, most cases are symptomatic, albeit often very mildly. Significantly, the WHO also reports that "to date [2/4/2020], there has been **no documented asymptomatic transmission**." This is different to pre-symptomatic cases where transmission may occur.

  While this does not preclude future evidence emerging of asymptomatic transmission, or unknown transmission mechanisms, the longer the passage of time, and the higher the number of cases (currently >3 million) without such evidence makes this increasingly unlikely.

  The implication is that **thorough symptom identification remains critical** to the detection of SARS-COV-2, and control of potentially transmissible disease.

Other considerations, and the SA context:

- This 'rule' relies on the effectiveness of **case detection**. South Australia and Australia are in a strong position with regard to case detection. Contact tracing of cases is comprehensive. Furthermore, SA has very few and no recent cases of community (unknown source) transmission.
- This 'rule' does not make a distinction between cases of known and unknown transmission source. Arguably, cases of known source are less significant for this purpose than cases of unknown source. The timeframe could be justifiably shortened, and/or the rule could be adapted to exclude cases that emerge within supervised quarantine.
- A heightened surveillance period of indefinite length will be required.
  The SARS-COV-19 might be (virtually) eradicated in South Australia, Australia and New Zealand but will continue to be imported at low levels as trade borders are open and while other countries have not eradicated SARS-COV-19. This will remain the case until a vaccine or effective treatment is discovered, or the virus is otherwise contained or eradicated.
- **Heightened surveillance period strategies** can include:
  - Continued quarantining of known cases and their close contacts
  - Controlling the importing of new cases (current strategies: international border control with 14-day supervised quarantine, with exceptions for trade, essential services and on compassionate grounds)
  - Continued active contact tracing (SA Health CDCB plus COVIDsafe app)
  - Continuing active testing of suspected cases and close contacts, passive testing (symptomatic people self-presenting for testing), and sentinel testing (currently under consideration [9])
  - Maintenance of some social distancing provisions and personal hygiene recommendations
  - Potential 'return to normal' permits/status for those with immune status. Note: at the time of writing the evidence about immunity and antibody testing are not yet sufficiently advanced to support this strategy [10, 11].
- There is discussion of "trigger points" for reintroduction of controls including: numbers of deaths; cases in ICU; hospital capacity compared to demand; testing capacity and contact tracing all confirmed cases [12].

Conclusion

- While conservative, a **2 x 14 day = 28 days of no new cases rule**, can reasonably be applied.
- It would also be reasonable to exclude any cases emerging among people while in supervised quarantine (as very low risk).
- Other cases of known source, emerging while in self-quarantine, with complete contact tracing are also of much lower risk than cases of unknown source.

SUMMARY OF KEY EVIDENCE

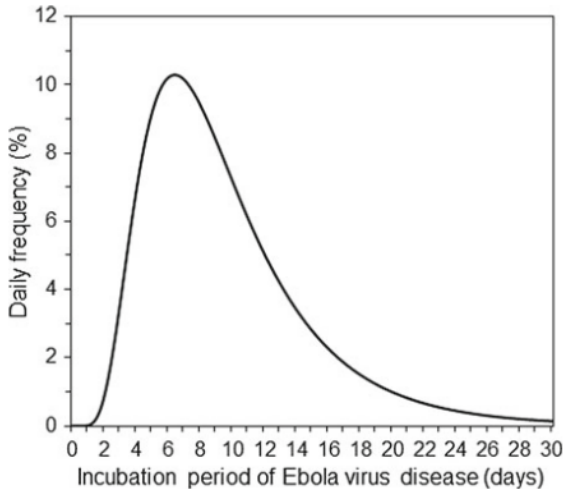
WHO criteria - explanation of the '42-day' or '2 x incubation' criterion [1]

Forty-two days is double the maximum observed incubation period for Ebola of 21 days, with timing starting from the day the last case has tested negative twice to the virus. The WHO also advised maintaining heightened surveillance for an additional 90 days due to transmission occurring through undetected cases, migration, sexual transmission, and the possibility of new emergence from an animal reservoir.

Reviews

A short review was conducted to identify what methods are available to determine the end of an infectious disease epidemic [4]. Key points from the review included:

- There are limited methodological options to explicitly judge the end of an epidemic; most published studies are limited to a setting with single and brief exposure
- The WHO guidelines based on its definition of zero Ebola cases (i.e. 42 days since the last confirmed case had tested negative twice for the virus on blood samples) is derived from doubling the empirically observed maximum incubation period of 21 days. The choice of 42 days stems from the right tail of the incubation period, as shown in the figure below.
- Figure 1. Probability density function of the incubation period of Ebola virus disease:



- The authors state: "As long as the time of potential exposure among traced contacts is known, the incubation period could indicate the length of time to be waited to ensure that no more symptomatic case exists. Even provided that the time of potential exposure is not directly observed, the use of the latest time at which an exposure could have occurred (e.g. the last date of PCR positive outcome in the last confirmed case) as "clock zero" point would offer a conservative suggestion to ascertain the absence of additional symptomatic infections".
- While there has been no additional justification for the formula, the fixed length criteria has made it transparent and easy to follow. Nevertheless, issues arise from using the formula due to sample size (larger maximum incubation period observed in a larger sample), managing asymptomatic cases and unrecognised chains of transmission, and post-symptomatic infections are not accounted for in the incubation phase.

    - Several erroneous declarations of the end of Ebola epidemic were observed in West Africa (see more below under Narrative reviews)
- Single exposure approach (e.g. food-bourne outbreak): modelling is statistically very robust but the application is very limited and is justified only when all of infected individuals develop symptoms and all cases are reported.
- Laboratory testing to ensure the absence of cases (often used in animal disease outbreaks): statistical modelling is simple but relies heavily on laboratory testing performance and sampling effort. This method can overcome the problem of asymptomatic infections.
- Epidemiological methods to determine the end of an epidemic with multiple exposures are very scarce, possibly due to the complex dynamics involved in human-to-human transmissions that cannot be captured using simple equations. It has been attempted with tracking polio cases, but results were limited due to truncated data and complexity in model fitting.
    - The authors noted that a heuristic approach was used for MERS in the Republic of Korea [2].
- Multiple methods, used in combination, may be needed to declare an end to an epidemic; surveillance and mathematical modelling are complementary instruments that can be combined to overcome their respective limitations. It should also be acknowledged that the decision for declaring the end of an epidemic is highly politicised and discussions should involve modellers and policy makers.

Narrative reviews have also been published on why further Ebola outbreaks occurred following the declaration of end-of-epidemic.

- Five erroneous declarations were made in West Africa during 2014-16; suspected cases of recrudescence were due to sexual contact (3 cases), international migration (1 case), and a potentially immunocompromised mother (1 case) [13].
- Cases arose in Conakry towards the end of the Guinea epidemic due to: not following safe burial requirements (1 case), negative Polymerase Chain Reaction (PCR) results were interpreted as no infection but sample was either not taken properly or disease was at its early stage (2 cases), migration (1 case), delay of 3 weeks in identifying a case despite characteristic symptomatology [14].

Advancements on and critiques of the WHO approach

Modelling

There have been attempts to refine the end of epidemic criteria using mathematical modelling. It has been noted that the benefits of a quick end-of-outbreak declaration, involving reductions in travel restrictions, must be balanced against the flare-ups from undetected residual cases [3].

- One study developed a simulation-based model based on Ebola data to provide an objective estimation of the probability of cases arising post-end of epidemic declaration [15]. Probability was most sensitive to the instantaneous **reproduction number**, the r**eporting rate**, and the **delay between symptom onset and recovery/death** of the last detected case.
    - Results showed that 63 days from the symptom onset day of the last detected case was more suitable than the WHO criterion of 42 days. Enhanced surveillance for 90 days was also recommended. This corresponded **to less than 5%** probability of flare ups in most scenarios examined.
    - The authors noted that the WHO criterion of 42 days for EVD was too short and very sensitive to underreporting.
    - The authors also noted that a range of end-of-outbreak criteria have been used in relation to other infectious disease outbreaks e.g. **no new case reported** for:
        - **6 months for Yellow fever** (DRC and Angola 2015-2017); and
        - **seven weeks for Cholera** (South Sudan 2017-2018)

- Nishiura et al. [2] objectively calculated the probability of observing additional cases of **MERS in South Korea** compared to the probability based on WHO criteria. They found that the end-of-epidemic declaration **could have occurred 10 days earlier** than the date calculated based on the **WHO criteria**. However, the method did not account for missing undiagnosed or mild cases, and **all possible contact with diagnosed case patients had been traced**. Modelling was based on a maximum incubation period being 14 days for MERS.

- Thompson et al. [3] used simple epidemiological modelling of an **Ebola** outbreak to show that **surveillance sensitivity** (i.e. case reporting percentage) of **79%** is necessary for 95% confidence that an outbreak is over after 42 days without symptomatic cases. If surveillance is only 40%, then 62 days are needed for 95% certainty.

- The concept of **outbreak threshold (T0)** of an epidemic has been proposed [16]. It is defined as the number of infected hosts above which there is very likely to be a major outbreak, and can be estimated using simple formulae. However, modifications are needed to set a specific cutoff value or to capture host heterogeneity in transmission or incomplete sampling. Examples of how the outbreak threshold works are shown in the figure below:

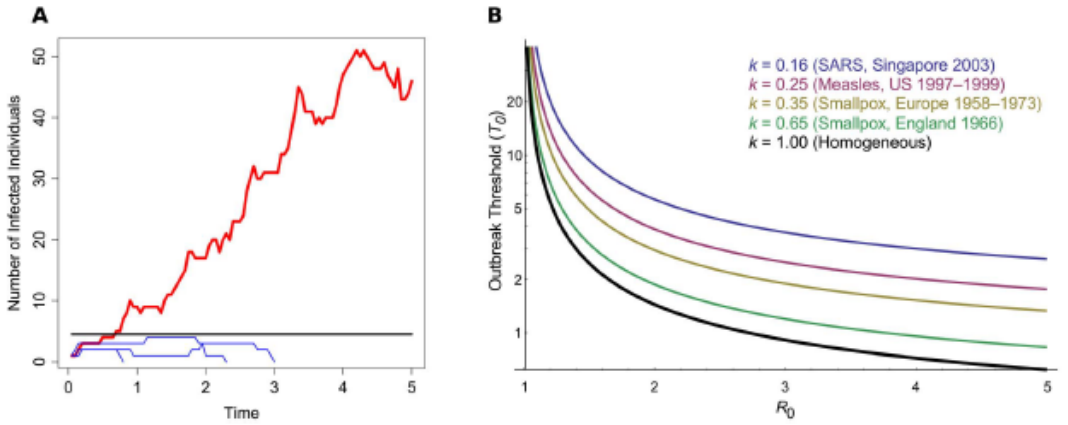


Figure 1. The outbreak threshold in homogeneous and heterogeneous populations. (**A**) A schematic of pathogen emergence. This graph shows the early stages of several strains of an epidemic, where $R_0 = 1.25$. The black line denotes the outbreak threshold ($T_0 = 1/\text{Log}(R_0) = 4.48$). Blue thin lines show cases in which the pathogen goes extinct and does not exceed the threshold; the red thick line shows an epidemic that exceeds the threshold and persists for a long period of time. Simulations were based on the Gillespie algorithm [22]. (**B**) Outbreak threshold in a homogeneous (black thick line) or in a heterogeneous population, for increasing R_0. The threshold was calculated following the method described by Lloyd-Smith et al. [11] and is shown for different values of k, the dispersion parameter of the offspring distribution, as obtained from data on previous epidemics [11]. If the threshold lies below one, this means that around only one infected individual is needed to give a high outbreak probability.
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    - The authors applied the concept to a case study: **SARS, Singapore 2003:** “outbreak with known super-spreaders, with an estimated initial R0 of 1.63 and a low k of 0.16 (k is the dispersion parameter which determines the level of variation in the number of secondary infections; k=1 is homogenous outbreak, heterogeneity [e.g. number of ‘super-spreaders’ that are present] increases as k drops below 1). T0 is estimated to be around 27 infections. The first cases were observed in late February, with patients being admitted for pneumonia. Strict control measures were invoked from March 22nd onwards, including home quarantining of those exposed to SARS patients and closing down of a market where a SARS outbreak was observed. By this date, 57 cases were detected, although it is unclear how many of those cases were still ongoing on the date. This point is important, as it is the infected population size that determines T0. Quick containment of the outbreak was difficult to achieve since SARS was not immediately recognised, as well as the fact that the incubation period is around 5 days, by which point it had easily caused more secondary cases. However, in subsequent outbreaks super-spreaders might not be infected early on, allowing more time to contain the spread.”

Modelling and expert opinion of Containment strategies (avoid rebound in transmission):

- There is a lot of commentary on widespread serological testing to identify people who have already contracted the virus based on antibody detection. This is based on the hypothesis that those who have already contracted the virus are immune from contracting it again (e.g. [17, 18]). The state of evidence is mixed and the evidence about immunity and antibody testing are not yet sufficiently advanced to support a "**immunity status passport**" style strategy [11].

- A commentary in the Lancet [10] made the following points:
    - The only selective pressure on SARS-CoV-2 is transmission; stop transmission and you stop the virus
    - Strategies for moving out of lockdown proposed in the literature include:
        - **Increased testing and contact tracing**
        - Removal of social distancing based on immune status
        - Repurposed or new therapeutics
        - Vaccination
    - The strategy relating to immune status is the most contentious because there is no certainty that detecting SAR-CoV-2 antibodies corresponds with immunity, or what proportion of the population must attain immunity to mitigate subsequent waves of infection.

- Modelling of containment strategies to reduce COVID-19 mortality and healthcare demand in the UK [12] suggested that **adaptive hospital surveillance-based triggers** for switching on and off population-wide social distancing measures offer greater robustness to uncertainty than fixed duration interventions, and can be adapted for regional use. The results suggested that social distancing would need to be in force for at least ⅔ of the time given a R0 of 2.4 until a vaccine was found. The figure below illustrates adaptive triggering over time, which can be adjusted for proportion of time social distancing is in place, on and off triggers and R0:

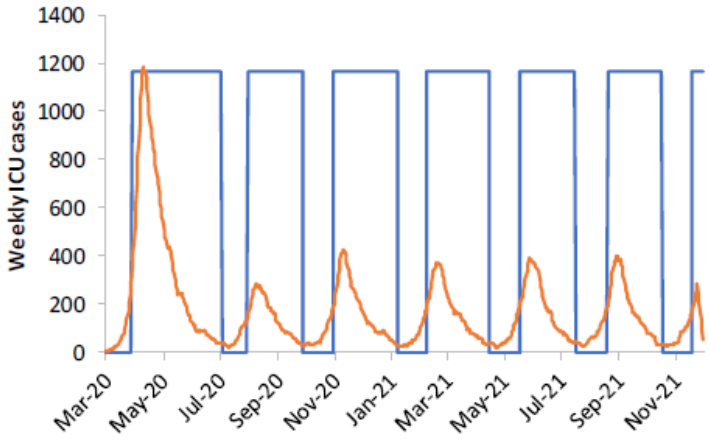

Figure 4: Illustration of adaptive triggering of suppression strategies in GB, for R_0=2.2, a policy of all four interventions considered, an "on" trigger of 100 ICU cases in a week and an "off" trigger of 50 ICU cases. The policy is in force approximate 2/3 of the time. Only social distancing and school/university closure are triggered; other policies remain in force throughout. Weekly ICU incidence is shown in orange, policy triggering in blue.

- A report describing how the US could navigate its reopening outlined several steps that could be taken as the COVID-19 epidemic transmission is brought under control [19]. The trigger to move to phase 2 (gradual reopening) was a **sustained reduction in cases for at least 14 days** (i.e. one incubation period), **local hospitals being able to cope** without resorting to crisis standards of care, and **capacity to test all symptomatic people** and **contact trace** all confirmed cases.
    - Reverting to phase 1 (slow the spread) should occur if a substantial number of cases cannot be traced back to known cases, if there is a sustained rise in new cases for five days, and if hospitals reach capacity to safely treat all patients.
    - Progressing to phase 3 can occur when safe and effective tools for mitigating the risk of COVID-19 are available (e.g. broad surveillance, therapeutics to treat severe disease or prevent serious illness in those most at risk, or a safe and effective vaccine).
- Australian expert opinion [20]: Bringing epidemic under control using a short, sharp lockdown buys time to scale up required testing, capacity for rapid case identification and isolation, and for thorough tracking and quarantine of contacts, which may be aided by technology (e.g. **smart phone app**).
- Australia's Group of Eight (Go8) universities have also published a report for Australia's roadmap to recovery citing two options: elimination (longer lockdown, fewer total infections, hospitalisations and deaths, but risk of re-introduction of cases will remain) or controlled adaptation (shorter lockdown, accepts higher number of cases, hospitalisations and deaths) [21].
- Two epidemiological models were developed to study the disease dynamics of the COVID-19 pandemic and exit strategies from lockdowns [22]. The authors concluded adaptive triggering, or repetitive short term contact reductions when relevant figures (e.g. deaths, need for ICU) exceed a threshold, could be used to manage the virus until a vaccine was available. Antibody tests would also add benefit if they allowed people with antibodies to be excluded from contact reductions.

Evidence from other countries

- News report that China eased restrictions in Hubei province following reports of zero new local COVID-19 infections for five days in a row.

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