

## Bestrijding van verspreiding

### Wat is het doel van de corona app?

In de eerste plaats is het bedoeld om te assisteren in het traceren van besmettingen om zo goed overzicht te houden op de verspreiding van het virus in Nederland. Tot op heden is het in kaart brengen van deze verspreiding gedaan door het zogeheten “contact tracing”. Dit is in essentie handmatig detective werk en vereist veel mankracht zoals uit een artikel van een halve maand geleden blijkt. [1]

“In South Korea, which had a head start on developing contact tracing plans through its response to Middle East Respiratory Syndrome (MERS) in 2015, contact tracers are combining patient interviews with cellphone GPS data, credit card transaction records and surveillance camera footage. Singapore has introduced a mobile app that uses Bluetooth to log when people are close together and then uses the data to identify contacts after new cases are confirmed. In China, around 9,000 contact tracers were employed in Wuhan alone. And closer to home, the Canadian government has launched a nationwide contact tracing program, which has brought on 27,000 volunteers.”

De volgende resultaten uit een onderzoek met simulatie van uitbraak van een epidemie toont de waarde aan van contact tracing en tot in welke mate dit mogelijk effectief verwacht kan worden voor verschillende scenario's (individuen hebben wel/niet een groot netwerk (“K”), tijd tot infectie na contact met geïnfecteerde (“latency”)).

“However, if K is too large or the latency period is too short, figure 4b shows that although the final size of the epidemic is similar to that in figure 4a,  $R(\infty)$  is much higher: many nodes that were not infected were removed. Hence tracing, even if aimed primarily at removing exposed and infectious nodes, targets and removes susceptible nodes at a higher rate.”

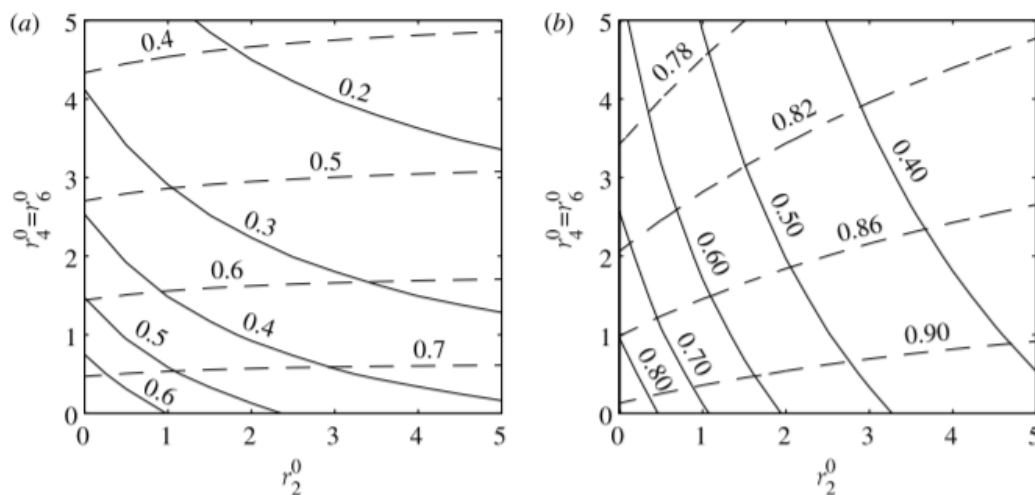


Figure 4. Contour plots of the final epidemic size, i.e. the proportion of all the nodes that eventually become infected during the epidemic (continuous lines) and  $R(\infty)$ , i.e. the proportion of all the nodes that were removed by the end of the epidemic (dashed lines). The two plots contrast the case of effective tracing (long latency period and few connections per node) with the case of less effective tracing (short latency periods and many connections per node). The other parameters used were:  $R_0^{MF} = 3.0$ ,  $Inf\_P = 3.5$ ,  $Tr\_P = 2.0$  and (a)  $K = 5$ ,  $Lat\_P = 10.0$  and (b)  $K = 20$ ,  $Lat\_P = 3.5$ .

“This does not occur for the parameters in figure 5b, and is explained by the early extinction of the epidemic in the case where the tracing levels are higher. This illustrates the efficacy of

contact tracing when  $K$  is small; in this case, even though  $R_0$  is above one, high levels of tracing stop the epidemic early and with fewer nodes removed by tracing.”

Dit is het geval in Nederland op het moment aangezien mensen een kleiner netwerk hebben door de intelligente lockdown. Wel is de latency heel erg laag, d.w.z. het virus verspreid zich relatief gemakkelijk/ er is weinig contact voor nodig. **Bovendien worden er stappen gezet om de maatregelen van de lockdown te versoepelen en dit kan dus mogelijk “K” drastisch vergroten en de effectiviteit van contact tracing via de app ondermijnen!**

De minimale eisen die hieraan te stellen zijn, komen dan ook vanuit een oogpunt van wens naar verbetering, zowel in effectiviteit als in efficiëntie.

#### Waarden om vast te stellen als maatstaf voor app

- Hoeveelheid getraceerde infecties zonder app -> moet op z'n allerm minst geëvenaard worden (anders heeft app geen toegevoegde waarde)
- “Critical tracing efficiency” [3] -> moet aan voldaan worden voor succesvolle bestrijding
- Hoeveelheid fout getraceerde (vermoedelijke) infecties -> moet niet meer zijn dan zonder app

“Applying the pairwise approximation to SIR-type infections results in a critical level of tracing with a much simpler form  $t_c = (rn(n - 2) - n) / (n - 1)$  .”

We hebben een SIR-type infection omdat mensen geacht worden immuniteit op te bouwen nadat ze geïnfecteerd zijn geweest en hersteld zijn. Hier is “ $t_c$ ” de zogenaamde “Critical tracing efficiency”, wat er minimaal nodig is aan tracing om het virus volledig uit te bannen. “ $r$ ” is de hoeveelheid transmissies van het virus per tijdseenheid vermenigvuldigd met de hoeveelheid tijdseenheden dat een geïnfecteerde het virus kan overdragen. “ $n$ ” is de gemiddelde hoeveelheid contacten/ associaties per persoon in de populatie.

“Hence, when the number of contacts,  $n$ , is large, equation (3.2) implies that critical tracing efficiency,  $t_c / (t_c - 1) \approx 1 - 1 / R_0$  , (3.3) although this is a slight underestimate (figure 1c). For example, if  $R_0 = 4$ , around 75% of contacts must be traced to control infection.”

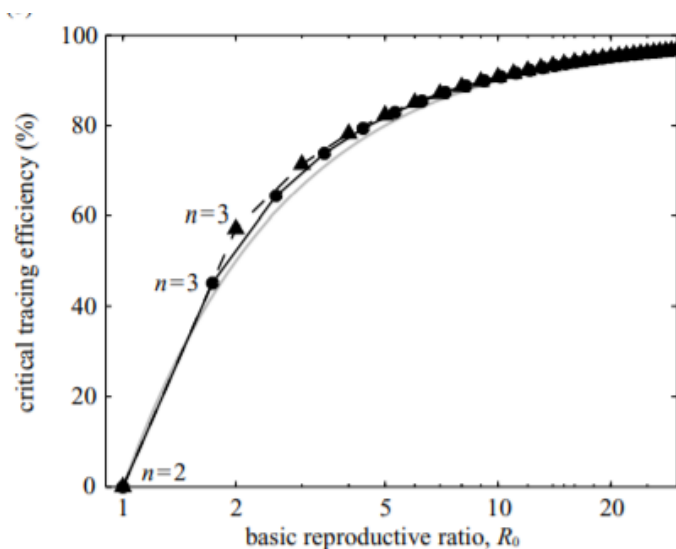
Hier is  $R_0$  de verwachte hoeveelheid nieuwe gevallen die ontstaan bij een “susceptible population” uit een enkele geïnfecteerde.

“It should be noted that we have implicitly assumed that all contacts are known and therefore theoretically traceable. However, if a proportion,  $p$ , of contacts are unknown (and therefore untraceable), then, to maintain the same average level of tracing, the tracing efficiency for the remaining known contacts must be increased to critical tracing efficiency  $(1 / (1 - p)) * (1 - 1 / R_0)$ . Thus, control of diseases with large reproductive ratios requires not only a high level of contact tracing but also comprehensive knowledge of the potential transmission routes.”

Belangrijk om te realiseren is dat deze critical tracing efficiency een absolute lowerbound is!

“Finally, we note that, once above the critical level of contact tracing, the number of cases decreases through time, as the effective reproductive ratio,  $R$ , is less than 1. However, when

this rate of decline is not sufficiently rapid ( $R$  is close to 1) the epidemic may be long-lived and many subsequent cases can arise. Hence, the theoretical threshold, which reduces the reproductive ratio to below 1, acts as a lower bound to the tracing efficiency that should be sought. In practice, much higher tracing efficiency may be needed to reduce the epidemic size quickly to a minimal level. Highly efficient contact tracing may place fewer demands on medical resources as a rapidly curtailed outbreak will involve fewer individuals needing to be traced and treated.”



Dit geeft ons duidelijke nieuwe subdoelen:

- $R_0$  bepalen
- De geschatte gemiddelde hoeveelheid unknown contacts bepalen ( $p$ )

Dit samen geeft ons een waarde voor de derde maatstaf, de critical tracing efficiency.

“Expert Arnold Bosman stelt dat je binnen 2 dagen alle risicocontacten kent. Zij moeten thuisblijven, zodat de rest van Nederland wel naar buiten kan. Nieuwsuur deed onderzoek bij 8 van de 25 GGD 's. Wat bleek: iedereen deed het anders: landelijke regels ontbreken. Een app is slechts een aanvulling op wat mensen van de GGD moeten doen. Bij 1 besmette patiënt is de GGD-medewerker 35 uur bezig (1e gesprek, gesprek met contacten, dagelijks nabellen of er klachten zijn). Volgens Bosman wordt er niet gewerkt aan uitbreiding capaciteit, zijn er onvoldoende werkinstructies, is er geen protocol wie er thuis moet blijven. Samengevat: “ik mis een plan op detailniveau”. Nieuwsuur journalist Siebe Sietsma zegt dat Duitsland het anders doet. Gisteren heeft Merkel gezegd dat de capaciteit voor bron- en contactonderzoek (BCO) moet worden opgevoerd naar “5 onderzoekers per 20.000 bewoners”. Het advies van het OMT richting VWS is het oprichten van een werkgroep om te bepalen hoe NL een BCO moet vormgeven.” [4]

“Het eerste en belangrijke telefoongesprek met een contact van een besmette patiënt duurt volgens Ziemons gemiddeld een uur. Duitsland heeft vijf onderzoekers voor elke twintigduizend inwoners.

Als Nederland dat zou aanhouden, zouden er 4250 contactonderzoekers aan het werk zijn. De GGD's hebben nu naar eigen schatting slechts beschikking over enkele honderden tot duizend onderzoekers.” [5]

Hier kunnen we uit concluderen dat er helaas weinig BCO op gang is om als maatstaf te gebruiken in Nederland. Daarom kunnen we critical tracing efficiency als leidraad houden.

“Recent onderzoek toont aan dat van een besmettelijke ziekte als corona het essentieel is dat tenminste 90 procent van de contacten moet worden opgespoord om de ziekte-overdracht naar beneden te krijgen.” [5]

Dit zou in onze formule  $p = 0.10$  opleveren.

Deze 90% wordt ondersteund door recent onderzoek dat op deze waarde uitkomt bij input van bepaalde  $R_0$  en andere parameters. De vraag blijft hoe accuraat deze zijn voor de daadwerkelijke situatie, ondanks dat het wel een redelijke indicatie lijkt van betrouwbaarheid.

“Outbreaks were deemed controlled if transmission ended within 12 weeks or before 5000 cases in total.

for an  $R_0$  of 3-5 more than 90% of contacts had to be traced. The delay between symptom onset and isolation had the largest role in determining whether an outbreak was controllable when  $R_0$  was 1-5. For  $R_0$  values of 2-5 or 3-5, if there were 40 initial cases, contact tracing and isolation were only potentially feasible when less than 1% of transmission occurred before symptom onset.” [6]

“Implications of all the available evidence

The effectiveness of isolation of cases and contacts to control outbreaks of COVID-19 depends on the precise characteristics of transmission, which remain unclear at the present time. Using the current best understanding, around 80% of symptomatic contacts must be traced and isolated to control over 80% of outbreaks in the model. Future research on the transmission characteristics could improve precision on control estimates.” [6]

Dit geeft ons duidelijke nieuwe subdoelen:

- $R_0$  bepalen
- De geschatte gemiddelde hoeveelheid unknown contacts bepalen ( $p$ )
- De geschatte hoeveelheid infecties voordat symptomen van het virus waarneembaar waren

Het volgende onderzoek bevat berekeningen op basis van gegevens uit de vroege stadia van uitbraak van covid-19 in de provincie Hubei, China.

[7]

“We performed a detailed analysis of the timing of events in defined transmission pairs, derived the generation time distribution, and attributed a probability for each pair that transmission was pre-symptomatic. We also fit a mathematical model of infectiousness through the four routes discussed above, over the course of infection. This allowed us to calculate  $R_0$ , estimate the proportion of transmission from different routes, and make predictions about whether contact tracing and isolation of known cases is enough to prevent spread of the epidemic.

We used the exponential growth rate of the epidemic,  $r$ , from the early stages of the epidemic in China [...] We used the value  $r = 0.14$  per day (20), corresponding to a doubling time of 5.0 days.

We used the incubation period distribution calculated by (21). The distribution is lognormal with mean 5.5 days, median 5.2 days and standard deviation 2.1 days.

The generation time is defined for source-recipient transmission pairs as the time between the infection of the source and the infection of the recipient. We combined dates of symptom onset with intervals of exposure for both source and recipient (when available) and the above distribution of incubation times and from these inferred the distribution of generation times. The distribution is best described by a Weibull distribution (AIC=148.4, versus 149.9 for gamma and 152.3 for lognormal distribution) with mean and median equal to 5.0 days and standard deviation of 1.9 days.

For each of the 40 transmission pairs we estimated the posterior probability that transmission was presymptomatic, i.e., occurred before the onset of symptoms in the infector. We used a Bayesian approach with an uninformative prior (transmission before or after symptoms equally likely). The 40 probabilities inferred are shown in the right panel of Fig. 1; the mean probability is 37% (95% CI: 27.5% - 45%).”

**Table 1. Parameters of the infectiousness model.**

Name	Symbol	Description	Central value	Uncertainty	Source
<i>Parameters directly calculated from data</i>					
Doubling time	$T_2$	The time taken for the epidemic to double in size during the early uncontrolled phase of expansion	5.0 days	95% CI 4.2 - 6.4	(20)
Incubation period (2 parameters)	$s(\tau)$	lognormal meanlog lognormal sdlog	1.644 0.363	95% CI 1.495 - 1.798 95% CI 0.201 - 0.521	(21)
Generation time (2 parameters)	$w(\tau)$	Weibull shape Weibull scale	2.826 5.665	95% CI 1.75 - 4.7 95% CI 4.7 - 6.9	This paper
<i>Parameters with Bayesian priors informed by anecdotal reports or indirect evidence</i>					
Proportion asymptomatic	$P_a$	The proportion of infected individuals who are asymptomatic	0.4	Prior = beta( $\alpha=1.5, \beta=1.75$ ) Mode = 0.4 Mean = 0.46	Media reports (Diamond Princess)
Relative infectiousness of asymptomatics	$\alpha_a$	The ratio of infectiousness of asymptomatic individuals to infectiousness of symptomatic individuals	0.1	Prior = beta( $\alpha=1.5, \beta=5.5$ ) Mode = 0.1 Mean = 0.21	Observation of few missing links in Singapore outbreak to date. Suggestion from (19)
Fraction of all transmission that is environmentally mediated	$R_e/R_0$	Self-explanatory	0.1	Prior = beta( $\alpha=1.5, \beta=5.5$ ) Mode = 0.1 Mean = 0.21	Anecdotal observation that many infections can be traced to close contacts once detailed tracing is completed.
Environmental infectiousness	$E(t)$	Rate at which a contaminated environment infects new people after a time lag $l$	3	Box function (0,n) days. Prior for $n = \text{Gamma}(\text{shape} = 4, \text{rate} = 1)$ Mode = 3 Mean = 4	(39) - variety of values for many different surfaces.

**Table 2.  $R_0$  and its components.**

	Pre-symptomatic	Symptomatic	Environmental	Asymptomatic	Total $R_0$
Absolute	Point estimate: 0.9 Uncertainty median: 0.7 CI: 0.2 - 1.1	Point estimate: 0.8 Uncertainty median: 0.6 CI: 0.2 - 1.1	Point estimate: 0.2 Uncertainty median: 0.4 CI: 0.0 - 1.3	Point estimate: 0.1 Uncertainty median: 0.2 CI: 0.0 - 1.2	Point estimate: 2.0 Uncertainty median: 2 CI: 1.7 - 2.5
Fraction of $R_0$	Point estimate: 0.47 Uncertainty median: 0.35 CI: 0.11 - 0.58	Point estimate: 0.38 Uncertainty median: 0.28 CI: 0.09 - 0.49	Point estimate: 0.1 by assumption Uncertainty median: 0.19 CI: 0.02 - 0.56	Point estimate: 0.06 Uncertainty median: 0.09 CI: 0.00 - 0.57	1 by definition

## IMPORTANT TO NOTE

“We calibrated our estimate of the overall amount of transmission based on the epidemic growth rate observed in China not long after the epidemic started. Growth in Western European countries so far appears to be faster, implying either shorter intervals between



individuals becoming infected and transmitting onwards, or a higher  $R_0$ . We illustrate the latter effect in figs. S18 and S19. If this is an accurate picture of viral spread in Europe and not an artefact of early growth, epidemic control with only case isolation and quarantining of traced contacts appears implausible in this case, requiring near-universal App usage and near-perfect compliance. The App should be one tool among many general preventative population measures such as physical distancing, enhanced hand and respiratory hygiene, and regular decontamination”

Results are very useful yet potentially not very accurate, challenge will be in corroboration of these values with regards to the spread of covid-19 in western Europe/ the Netherlands.

[1] <https://time.com/5825140/what-is-contact-tracing-coronavirus/>

[2] <https://royalsocietypublishing.org/doi/pdf/10.1098/rspb.2005.3092>

[3] <https://royalsocietypublishing.org/doi/pdf/10.1098/rspb.2003.2554>

[4] <http://zorgenstelsel.nl/het-bron-en-contactonderzoek-bij-covid-19-heeft-last-van-het-afwentelvirus/>

[5] <https://nos.nl/nieuwsuur/artikel/2331268-grootschalig-contactonderzoek-nodig-maar-wie-moet-dat-gaan-doen.html>

[6] <https://www.sciencedirect.com/science/article/pii/S2214109X20300747>

[7] <https://science.sciencemag.org/content/early/2020/04/09/science.abb6936/tab-pdf>

## Determining Contact

A essential requirement of the app is that it determines contact with others. It is essential in 2 ways:

- Once you have been tested positive, all people who have been in contact with you should be contacted about this.
- Once you have been in contact with a (later) positive tested person, you should receive a notification about this.

However, what do we mean with having contact? Is being 'a second' within 1.5 meters of each other already enough to establish this contact and to take measurements for both persons. Or should we set so time to this, the more time a user is within 1.5 meters of someone, the more risk this person has on getting infected. To set this requirement, we should take a look at the the number of new infections estimated to stem from a single case, and how this contamination takes place.

<https://www.nytimes.com/2020/04/23/world/europe/coronavirus-R0-explainer.html>