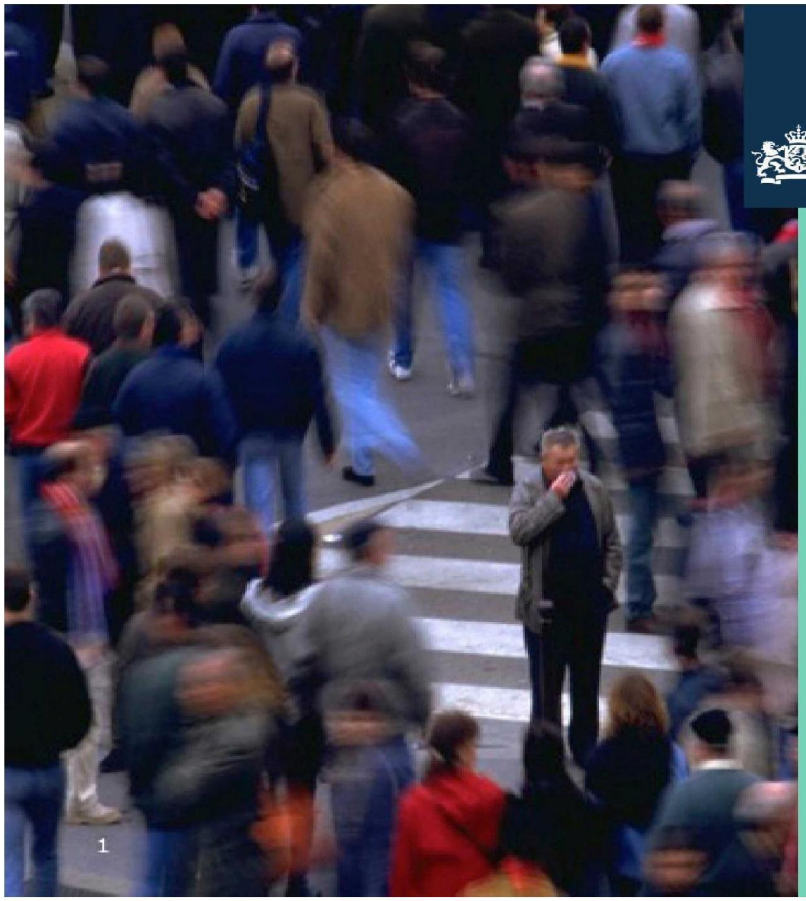

Rijksinstituut voor Volksgezondheid en Milieu
Ministerie van Volksgezondheid, Welzijn en Sport

Curbing the spread: observations, interventions, models and predictions

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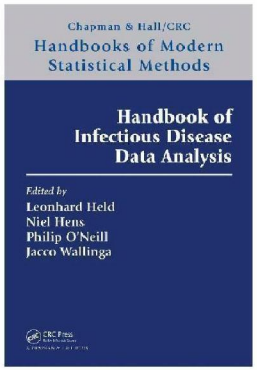
RIVM
Modelling Infectious Diseases

Leiden University Medical Center
Biomedical Data Sciences

Modelling spread and control of infectious diseases, before 2020

Infectious disease Modelling Unit at RIVM

- Developing methods to assist in controlling emerging epidemics and outbreaks
- Assessing costs and effects of infectious disease control
- Evaluation of vaccination programmes



Infectious disease modelling during the COVID-19 pandemic

Science Contents News Careers Journals

SHARE

Dutch models of COVID-19 are designed to help prevent overloading of hospitals and the need to transfer patients. THOMAS ANSELS/IMPERIAL COLLEGE LONDON

Mathematics of life and death: How disease models shape national shutdowns and other pandemic policies

By Martin Enserink, Kai Kupferschmidt | Mar. 25, 2020 , 6:40 PM

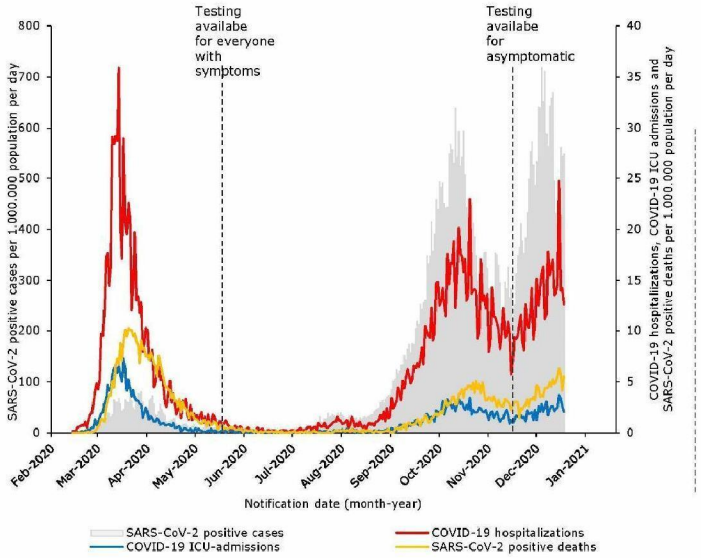
Jacco Wallinga's computer simulations are about to face a high-stakes reality check. Wallinga is a mathematician and the chief epidemic modeler at the National Institute for Public Health and the Environment (RIVM), which is advising the Dutch government on what actions, such as closing schools and businesses, will help control the spread of the novel coronavirus in the country.

- Statistical learning from incoming data
- Conducting scenario analyses, making projections
- Informing relevant platforms for decision making
- Explaining our work to media, public
- Unprecedented level of attention and pressure

- Our role in the decision process:

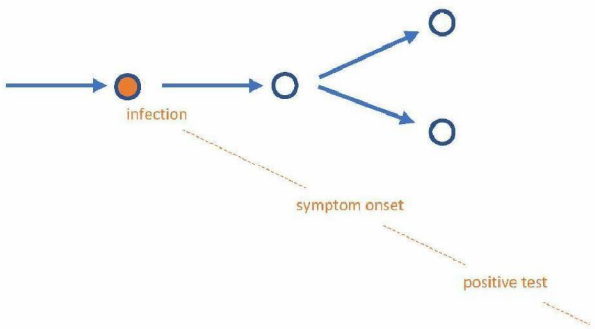
- We work in close collaboration with partners
  - Public health Institutes
  - Academic institutions
  - Within EU projects
  - WHO modelling network
  - WHO-Europe
  - ECDC

COVID-19 in the Netherlands: infectious disease epidemiology



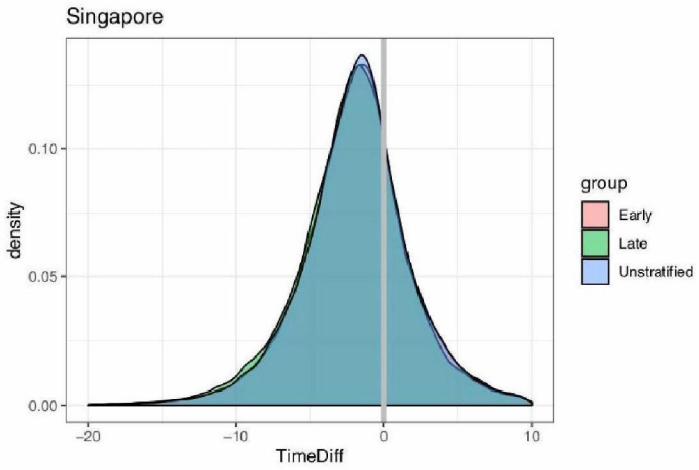
- We record the number and timing of events
  - Symptom onset
  - Positive test
  - Hospital admission
  - ICU admission
  - Death

Infectious disease modelling



- We model the relation between the events
- The causal relations in an epidemic are shaped by:
  - Transmission of infection from one individual to another
    - each infection implies one infector
  - Time order of events for the same individual
    - infection
    - symptom onset
    - positive test
    - hospital admission
    - ICU admission
    - death

Time scales of SARS-CoV-2 infections



- Incubation period, time from infection to symptom onset
  - about 5 days on average
- Serial interval, time from symptom onset of infector to symptom onset of infectee
  - about 4 days on average
- Generation interval, time from infection of infector to infection of infectee
  - about 4 days on average
- Proportion pre-symptomatic transmission, proportion of individuals where difference serial interval - incubation period is negative
  - more than half

- Using data available in January, February 2020
  - Backer et al. Eurosurveillance 2020
  - Tindale et al. Elife 2020
  - Ganyani et al. Eurosurveillance 2020

Transmissibility of SARS-CoV-2 infections

Case identifier	Symptom onset date	Infector identifier	Serial interval
1	20-2-2020	NA	NA
2	24-2-2020	1	4
3	25-2-2020	-	-
4	27-2-2020	-	-
5	25-2-2020	1	5
6	27-2-2020	2	3
6	27-2-2020	-	-

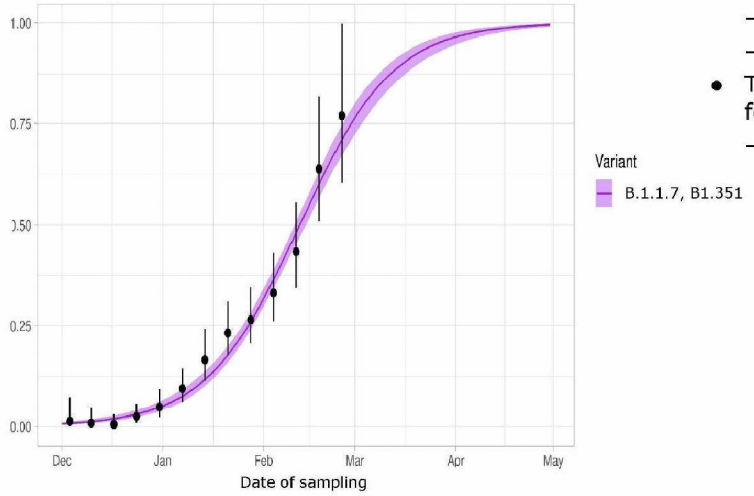
$$R_u = \int_{t=u}^{\infty} g(t-u)R_t \mathrm{d}t = \int_{t=u}^{\infty} \frac{\hat{b}(t)g(t-u)}{\int_{a=0}^{\infty} \hat{b}(t-a)g(a)\mathrm{d}a} \mathrm{d}t$$

$$R = \frac{1}{M(-r)}$$

- Reproduction number R, average number of secondary infections per primary infective
- Estimation procedure for R_t amounts to counting the average number of times that cases with symptom onset day t are listed as infector, while accounting for missing data
- Earlier, we developed estimators for the reproduction number, using the time series of case counts $b(t)$ and the distribution of generation interval $g()$
- When the epidemic grows exponentially, this estimator transforms exponential growth rate in calendar time r to geometric growth rate in generations of infection R, using moment generating function of the generation interval distribution $M()$

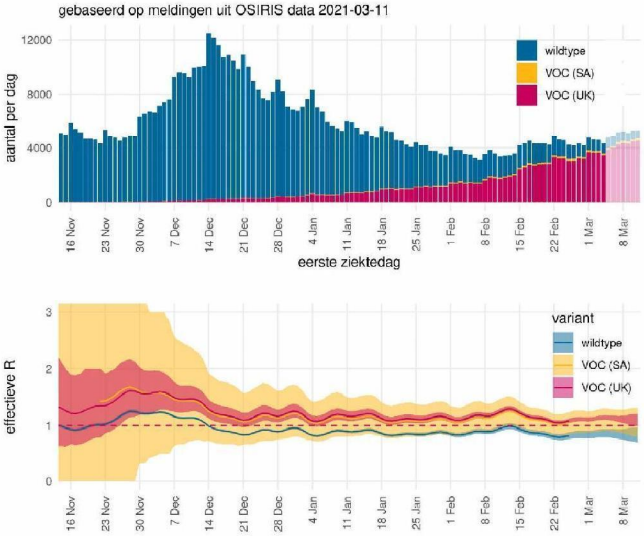
- Wallinga & Teunis American Journal of Epidemiology 2004
- Wallinga & Lipsitch Proc Roy Soc B 2007
- Gostic et al. PLoS Comp Biol 2020

SARS-CoV-2 variants of concern in the Netherlands



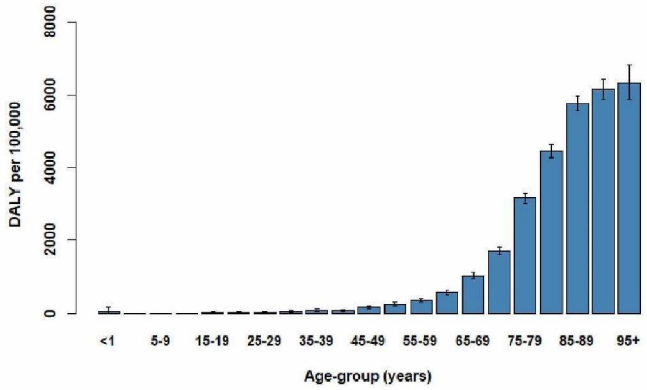
- Proportion of variants of concern in a representative sample of SARS-CoV-2 infections
  - B.1.1.7 the "British" variant
  - B.1.351 the "South African" variant
- The replacement of the old variants by new variants follows a logistic growth curve
  - data as of March 11th 2021

Reproduction number by variant of concern in the Netherlands



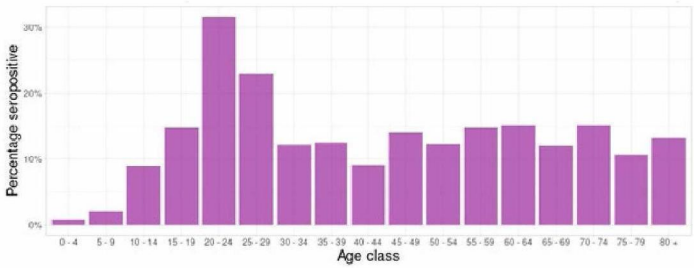
- The numbers of infections with the "British" variant B.1.1.1.7 and "South African" variant B1.351 continue to grow whereas the number of infections with old variants decline
- The new variants are more transmissible and harder to control than the old variants
  - data as of March 11th 2021

The disease burden of COVID-19



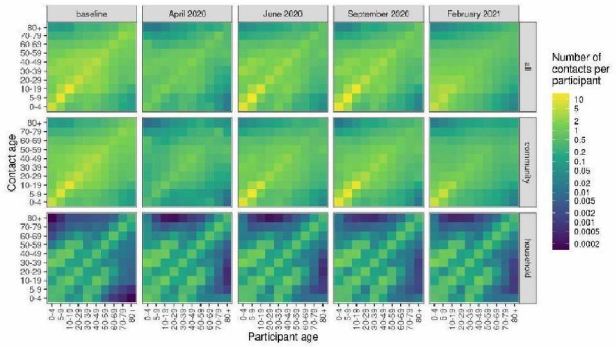
- Disease burden is measured in Disability-Adjusted Life Years (DALY) up to December 2020
- We provide an underestimate, since long-term effects are unknown
- Very high burden of disease among the elderly
- Despite stringent control measures the total disease burden in the first pandemic wave was approximately five times higher than an average influenza season
- https://www.rivm.nl/publicaties/staat-van-infectieziekten-in-nederland-2019#abstract_en

The cumulative number of infections with SARS-CoV-2 by age



- Based on the Pienter-Corona study
  - Representative sample of the Dutch population
  - Blood samples are collected and tested for presence of antibodies specific to SARS-CoV-2
  - Successive rounds: baseline in 2017, May 2020, July 2020, October 2020, February 2021
  - https://www.rivm.nl/pienter-corona-studie/resultaten
  - Here we took the results from October 2020 and added the expected number of infections since then
  - data as of February 9th 2021
- Most infections occurred among the 20-24 year olds

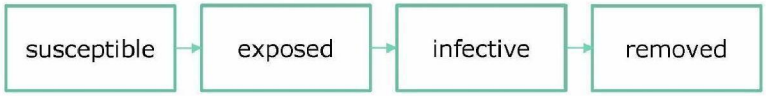
Age-specific patterns of contact



- As part of the Pienter-Corona study, a representative sample of the Dutch population is asked about their social contacts in their household, and in the community
- Successive rounds: baseline in 2017, May 2020, July 2020, October 2020, February 2021
- Most contacts occur with others of the same age, and between generations about 30 years apart
- The 0-15 year age groups have by far most contacts, but a smaller risk of getting infected during contact
  - data as of March 5th 2021

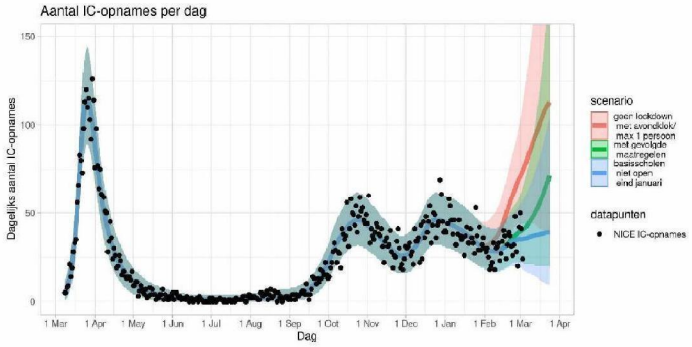
- Van de Kasteele et al. Ann Appl Stat 2017
- Backer et al. Eurosurveillance 2021

Transmission models



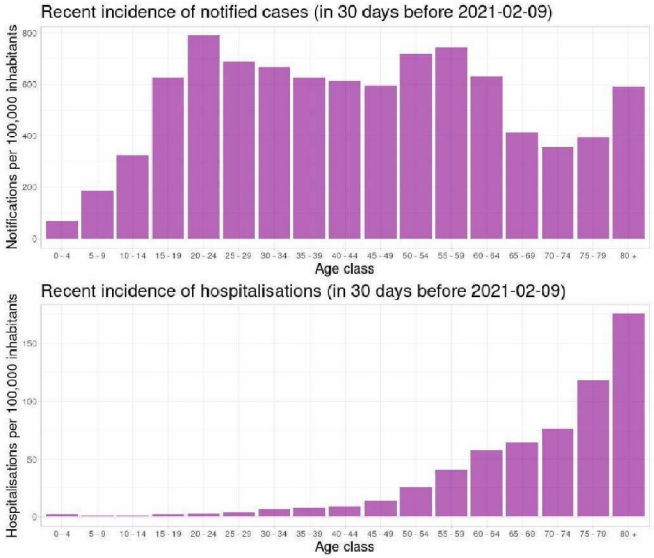
- We use these contact matrices to inform contact rates in a transmission model
- We use a compartmental SEIR-type epidemic model
- https://en.wikipedia.org/wiki/Compartmental_models_in_epidemiology
- Population is partitioned into age groups
- Time scales of infection chosen such as to match observed serial interval distribution
- We use age-specific probabilities of hospital admission, ICU admission
- We estimate the transmissibility parameter between change points such that the outcome fits the observed number of ICU admissions per day

Scenario's, projections, counterfactuals



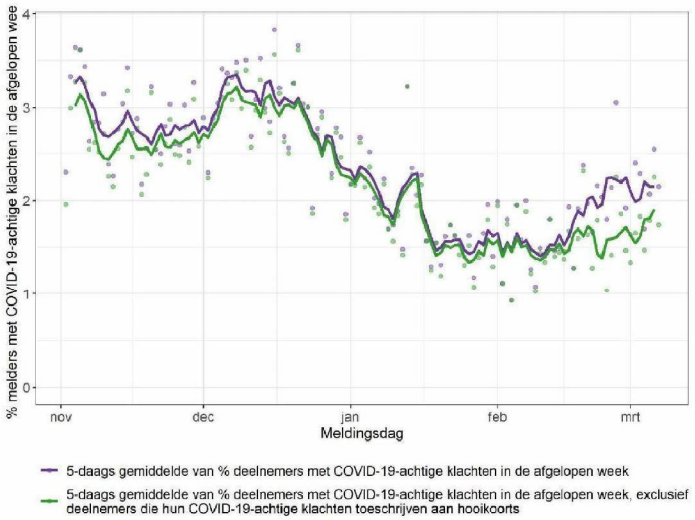
- Green line represents the fit, the intervals reflects uncertainty in parameter values, conditional on fit to observed number of ICU admissions per day
- https://www.rivm.nl/en/novel-coronavirus-covid-19/modelling
  - simulations as of March 5th 2021
- Projections into the future:
  - What if the contact matrix would remain the same?
- Counterfactuals (red and blue lines):
  - What if the contact matrix would have been different?
- Scenario analyses:
  - What if the contact matrix would change in the future?
- Anderson et al. Lancet 2020

Evaluating vaccination strategies



- If the objective is to minimize the number of infections, it is best to start with the age group with the highest hazard rate of infection (if the vaccine prevents against transmission)
- If the objective is to minimize the number of hospitalizations, ICU admissions, or death, the best to start with the age group with the highest risk of hospitalization or death
  - data as of February 9th 2021

Future directions



- Monitoring the epidemic will become more difficult, as positive tests at home will not be reported, and as hospital admissions will decline due to vaccination
- Self-reporting of COVID-19 symptoms provides a way forward
- https://www.infectieradar.nl
  - data as of March 12th 2021
- Many more topics:
  - COVID-19 on the Caribbean islands
  - Large scale testing
  - Contact tracing

Communicating system dynamics, risk and uncertainty

- To policy makers, via the WHO or the Outbreak Management Team
  - **confidentiality** statements are common
- To the public
  - **privacy** of personal data
- To colleagues
  - **open science** is a norm for publications
- In a crisis
  - **timeliness** is essential

- Regular public updates with snapshots of ongoing work
  - uncharted territory
  - unrealistic expectation that this should satisfy criteria for timeliness, confidentiality, privacy regulations, open science all at once and is achieved in a few hours

Acknowledgements

- Thanks to all colleagues who have taken over many of my tasks for a much longer period of time than we could previously imagine
- Thanks to colleagues at Leiden University Medical Center, for allowing me to focus on this pandemic
- For those of you who send me a message and heard nothing back: my apologies for not getting back to you in time. The number of messages has been too large, it has become impossible to respond to all reasonable requests, good suggestions and ideas

- The work presented here is a team effort
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- 5.1.2e 5.1.2e,
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- 5.1.2e 5.1.2e
- All colleagues of the EPI-COVID-19 team at RIVM