

# Infectious disease modelling and the dynamics of the active cases



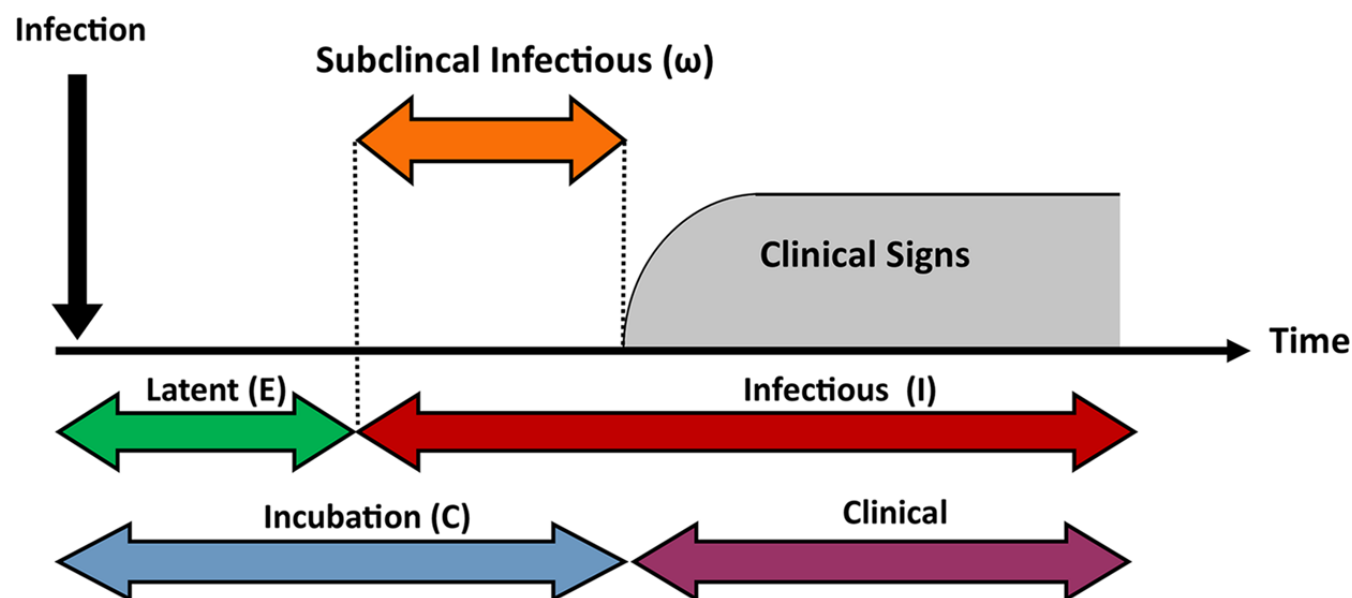
*Mauro Emanuele Dinardo*  
Università degli Studi di  
Milano Bicocca and INFN



**Goal:** we want to describe the dynamics of the spread of a disease among a population, in particular we are interested in the development of infected active cases

**Basic assumptions:**

- the disease can spread to other individuals from the infected ones
- the infected individuals can recover (either survive or die)
- recovered individuals can not become re-infected
- both symptomatic and asymptomatic cases are considered
- the system is closed (no “natural” demographic change)



**Definitions used to characterise distinct periods of infectious diseases.** The latent period (**E; green arrow**) begins at the time of infection and ends at the onset of the infectious period. (**I; red arrow**). The incubation period (**C; blue arrow**) starts at the time of infection and ends at the appearance of clinical signs of disease (**purple arrow**). The difference between incubation and latency is denoted by  $\omega$  (omega), and can have either a positive or negative value depending on whether transition to the infectious period occurs before or after appearance of clinical signs. The ratio of transmission occurring during incubation, and transmission occurring through the total infectious period is denoted by  $\theta$  (theta; not shown)



The model describe the dynamics of the number of infected active cases, i.e. the total number of currently infected individuals as a function of time

Finite difference model of infected population growth:

$$N_{n+1} = N_n + \underbrace{N_n K p q}_{\text{Increment}} - \underbrace{N_n r}_{\text{Decrement}}$$

Definition of the different terms:

- $N_n$ : number of active cases at time  $n$
- $K$ : average number of encountered people by one infected individual. Another way to interpret  $K$  is:  $K = (1 - Q) \times k$ , where  $Q$  is the fraction of active cases which are in quarantine and  $k$  is the average number of encountered people by one infected individual
- $p$ : probability to spread the disease from one individual to another



- **q**: probability that the new individual doesn't have already the antibodies. This probability is equal to 1 minus the probability of being infected, which can be derived from  $N_n$  and it's equal to:

$$\frac{N_n + r \sum_{i=0}^{n-1} N_i}{C}, \text{ where } \mathbf{c} \text{ is the carrying capacity}$$

- **r**: recovery rate (either to survive or die)  $\rightarrow$  related to the average recovery time through the relation  $\mathbf{\tau} = 1/\mathbf{r}$

### Final formulation of the model:

$$N_{n+1} = N_n + N_n K p \left( 1 - \frac{N_n + r \sum_{i=0}^{n-1} N_i}{C} \right) - N_n r$$

The basic reproduction number,  $\mathbf{R}_0$ , and the effective reproduction number,  $\mathbf{R}_n$  at time

$n$ , as referred in epidemiology, are  $R_0 = Kp/r$  and  $R_n = Kp \left( 1 - \frac{N_n + r \sum_{i=0}^{n-1} N_i}{C} \right) / r$ ,

respectively





From the finite difference equation we can construct the differential equation:

$$\frac{dN(t)}{dt} = N(t)Kp \left( 1 - \frac{N(t) + r \int_0^t N(t')dt'}{C} \right) - N(t)r$$

The integral-differential equation can not be solved in a closed form → it has to be treated numerically ( $Kp$ , i.e. the growth rate will be denoted  $g$ )

### Refining the carrying capacity

The carrying capacity,  $C$ , does not correspond to the total population of the system,  $T$ , but it's rather a subset that should evolve together with the number of infected people. In fact if the disease spreads out from a certain region, the probability that the individual encountered by an infected one doesn't have already the antibodies,  $q$ , can not be computed as the ratio of the total number of non infected individuals over  $T$ , because the encountered individual is not extracted uniformly from  $T$ , but rather from a subset which is "close" to the subset of infected individuals



Final system of equations:

$$\begin{cases} N_{n+1} = N_n + N_n K p \left( 1 - \frac{N_n + r \sum_{i=0}^{n-1} N_i}{C_n} \right) - N_n r \\ C_{n+1} = C_n + (N_{n+1} - N_n(1 - r)) K \left( 1 - \frac{C_n}{T} \right) \end{cases}$$

Differential form:

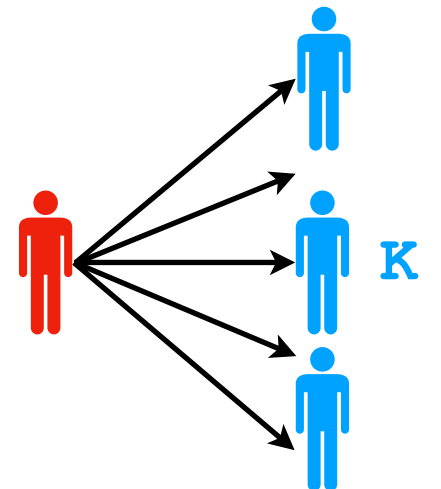
$$\begin{cases} \frac{dN(t)}{dt} = N(t) K p \left( 1 - \frac{N(t) + r \int_0^t N(t') dt'}{C(t)} \right) - N(t) r \\ \frac{dC(t)}{dt} = \left( \frac{dN(t)}{dt} + N(t) r \right) K \left( 1 - \frac{C(t)}{T} \right) \end{cases}$$

Which derives from:

$$C_{n+1} = C_n + N_n K p \left( 1 - \frac{N_n + r \sum_{i=0}^{n-1} N_i}{C_n} \right) K \left( 1 - \frac{C_n}{T} \right), \text{ in turns the carrying capacity}$$

is the total number of encountered individuals by the infected ones, in fact the increment of the carrying capacity depends upon the new infected cases,  $N_n K p q$ , each of which encounter  $K$  number of individuals, times the probability of not being already accounted for

**N.B.** the term  $Kp$  is estimated from a fit to the data, while  $p$  is estimated by scanning the  $\chi^2/\text{d.o.f.}$  and choosing the average best over multiple periods

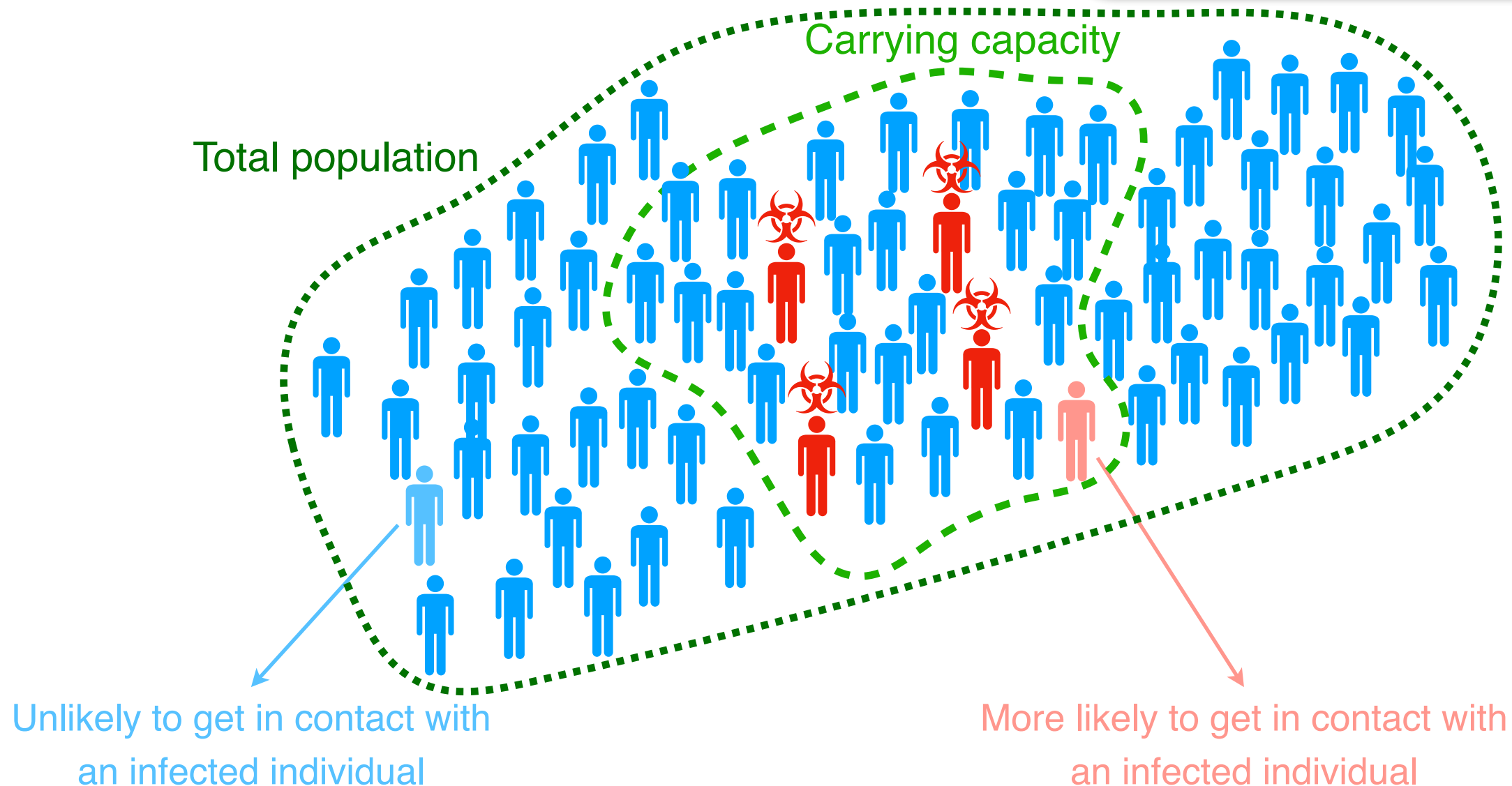


Final system of equations:

$$\begin{cases} N_{n+1} = N_n + N_n K p \left( 1 - \frac{N_n + r \sum_{i=0}^{n-1} N_i}{C_n} \right) - N_n r \\ C_{n+1} = C_n + (N_{n+1} - N_n (1 - r)) K \left( 1 - \frac{C_n}{T} \right) \end{cases}$$

**Herd immunity** established at  $R = 1$ :

- $K p q / r = 1 \rightarrow q = r / (K p)$
- $\% \text{infected} = 100 \cdot (1 - q) \rightarrow 100 \cdot (1 - r / (K p))$

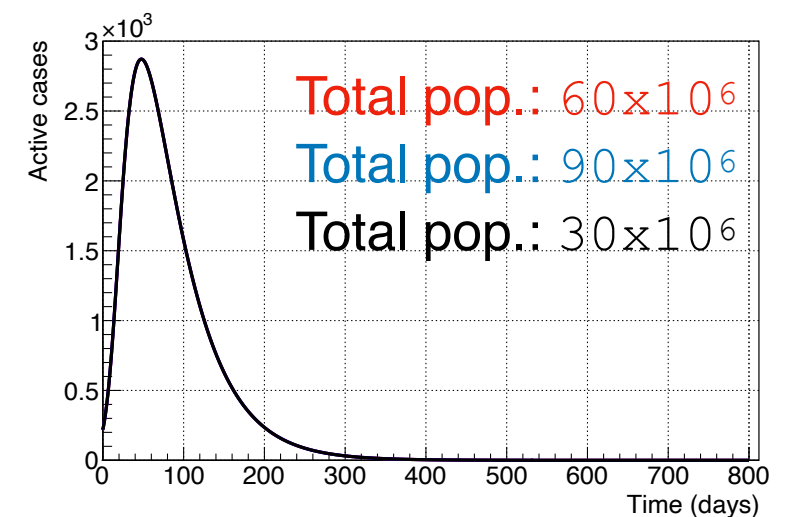
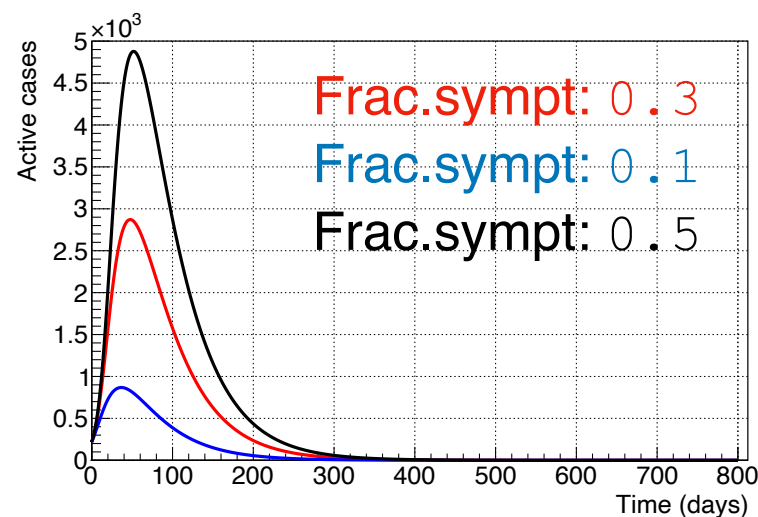
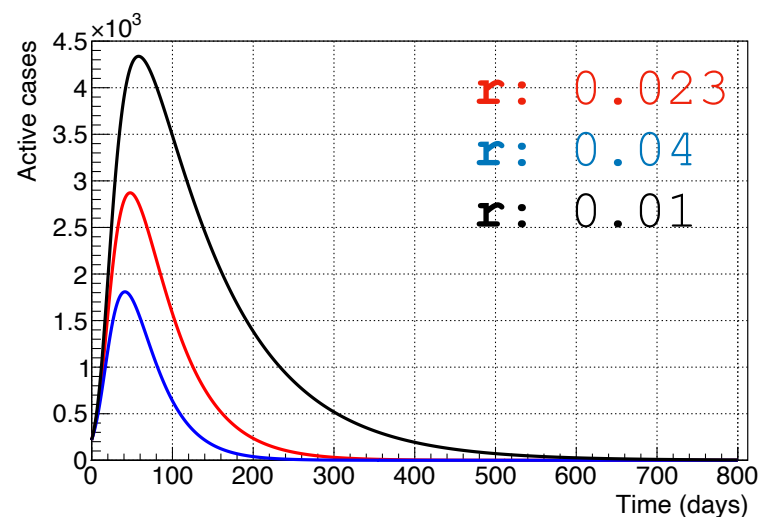
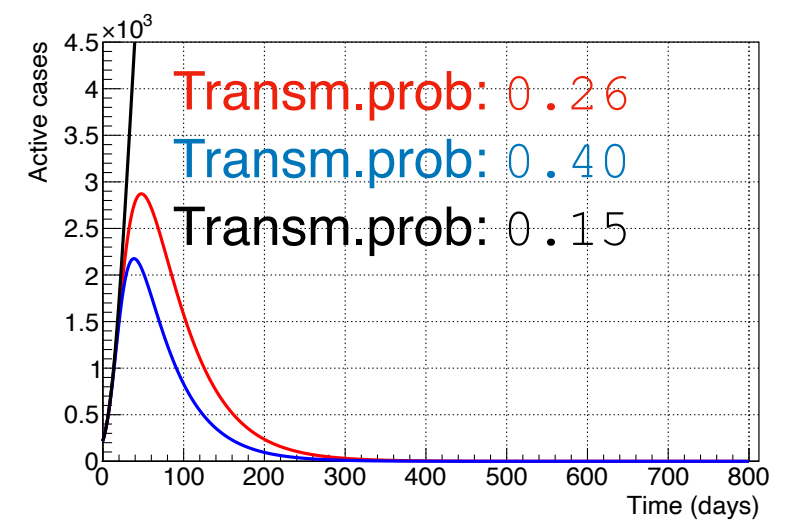
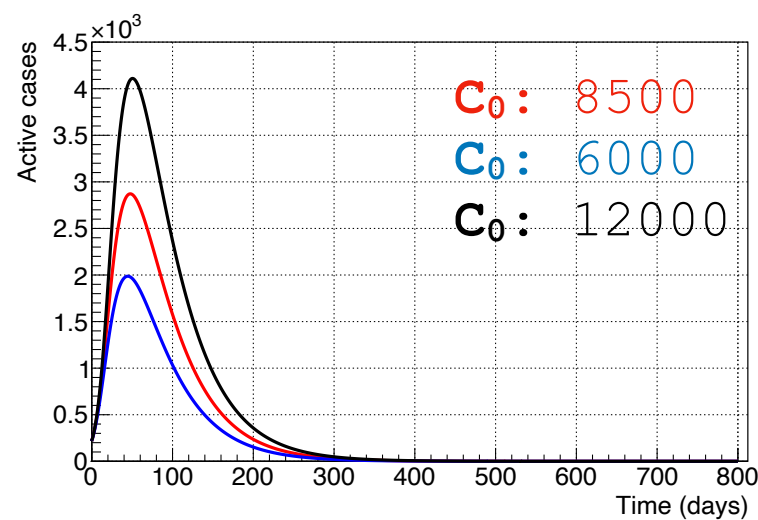
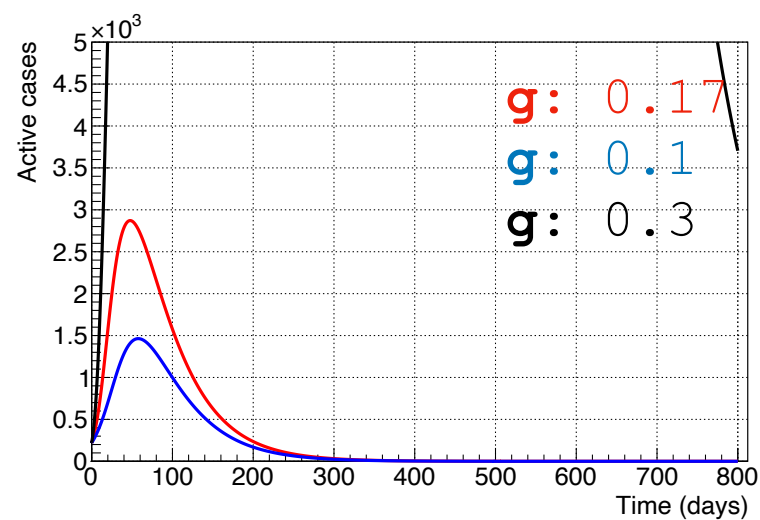




## Impact of the different parameters on the model

## Default model parameter values:

- $N_0$  (initial population): 220
- $C_0$ : 8500
- $g$ : 0.17
- $r$ : 0.023
- **Total population:**  $60 \times 10^6$
- **Frac.sympt:** 0.3
- **Transmission prob.:** 0.26



The model is very similar to the S.I.R. model (**S**usceptible, **I**nfected, **R**ecovered from Kermack and McKendrick, 1927), in fact:

$$\begin{cases} \frac{dS}{dt} = -\beta \frac{IS}{N} \\ \frac{dI}{dt} = \beta \frac{IS}{N} - \gamma I \\ \frac{dR}{dt} = \gamma I \end{cases}$$

We can identify  $\beta$  with  $Kp$ ,  $\gamma$  with  $r$ ,  $N$  with  $C$ ,  $I(t)$  with  $N(t)$ , and  $S(t)$  with

$$C - \left( N(t) + r \int_0^t N(t') dt' \right)$$

The key difference is that the model takes into account the non uniform spread of the disease with the equation:

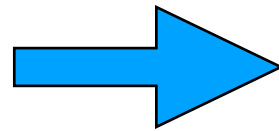
$$C_{n+1} = C_n + (N_{n+1} - N_n(1 - r))K \left( 1 - \frac{C_n}{T} \right)$$



Derivation of the coefficient  $q$  for the model of infected active cases

- The term  $q$  is equal to 1 minus the probability of being infected
- The probability of being infected can be derived from  $N_n$  and it's equal to the sum of the terms  $N_i \tilde{K}$  divided by  $C$  ( $\kappa$ -tilde is just a short writing for the product  $\kappa \cdot p \cdot q$ )

$$\begin{aligned}
 N_0 & \\
 N_1 &= N_0 + N_0 \tilde{K} - rN_0 \\
 N_2 &= N_1 + N_1 \tilde{K} - rN_1 \\
 N_3 &= N_2 + N_2 \tilde{K} - rN_2 \\
 &\dots
 \end{aligned}$$



$$\begin{aligned}
 N_0 & \\
 N_0 \tilde{K} &= N_1 - N_0 + rN_0 \\
 N_1 \tilde{K} &= N_2 - N_1 + rN_1 \\
 N_2 \tilde{K} &= N_3 - N_2 + rN_2 \\
 &\dots
 \end{aligned}$$

Summing up all the terms and simplifying, we obtain:

$$q = 1 - \frac{N_n + r \sum_{i=0}^{n-1} N_i}{C}$$



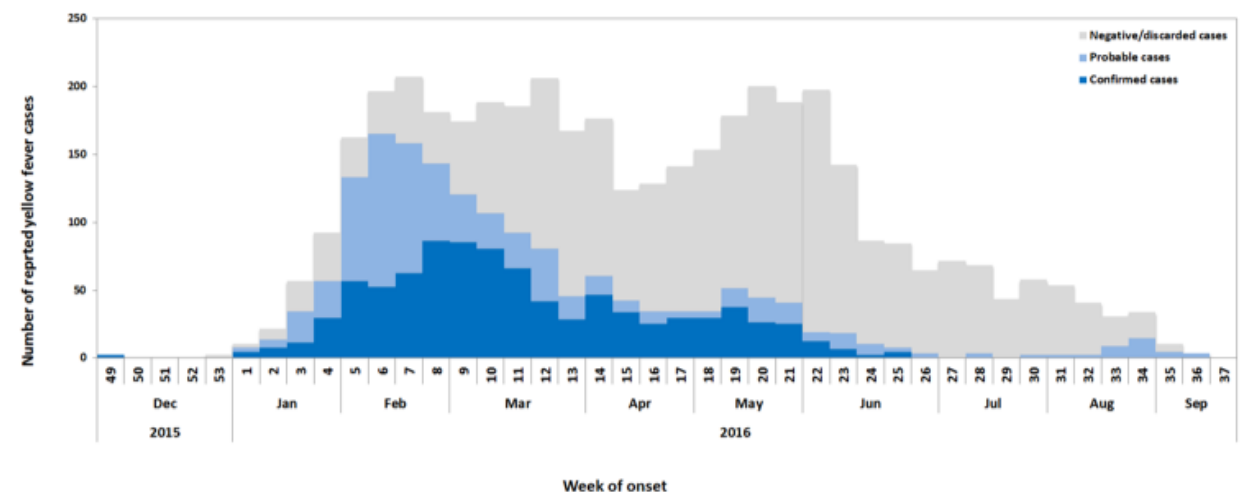
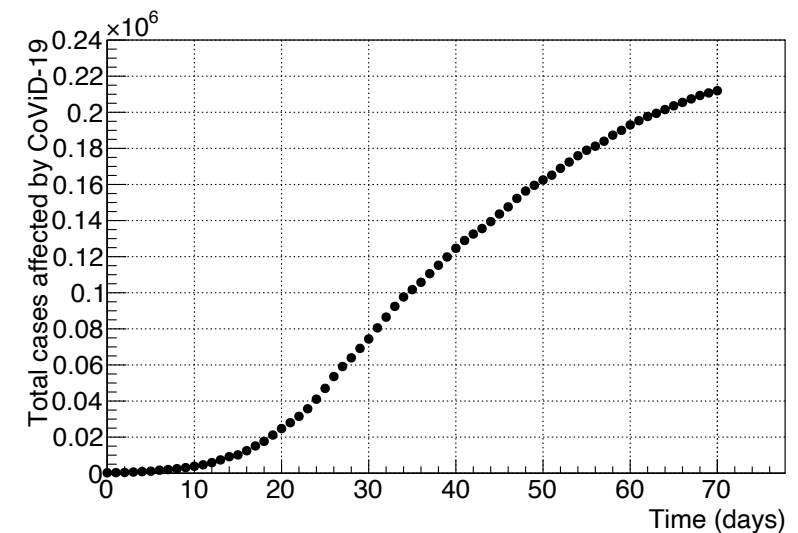


Just for completeness we would like to relate the equation to typical plots shown in epidemiology

$$N_{n+1} = N_n + N_n K p q - N_n r$$

- The sum  $\sum_n N_n K p q$  represent the total cases, i.e. the cumulated number of infected case as a function of time
- The derivative of the total cases, i.e. the term  $N_n K p q$ , represents the so called epidemic curve, i.e. the curve that shows the number of cases at the time of disease onset
- The term  $N_n$  itself instead represent the so called active cases, i.e. the total number of currently infected individuals as a function of time

Italy - Total cases CoViD-19 outbreak



Data source: Data as of 15 September 2016. Data for the past four weeks are subject to revision pending ongoing investigation and reclassification.



Parameter name	Symbol	Derivation
Recovery rate	$r$	Data plot $\Delta\text{recovered}/\text{active cases}$
Growth rate	$g$ , i.e. $KP$	Fit to the data
Transmission probability	$p$	Average best $\chi^2/\text{d.o.f.}$ on multiple periods
Fraction of symptomatic	N.A.	Obtained from literature
Total population	$T$	Demography
Initial conditions	$N_0$ and $C_0$	Fit to the data

## Summary

- Three free floating parameters during the fit ( $g$ ,  $N_0$ ,  $C_0$ )
- One parameter is determined by  $\chi^2/\text{d.o.f.}$  scan over multiple periods ( $p$ )
- One parameter determined from data plot ( $r$ )
- Two parameters determined from literature ( $T$ , fraction of symptomatic)



## Application to data: **Italy** - 3/5/2020

We will present results obtained from different refinements of the analysis:

1. Fit to single, self-consistent, time periods
2. Fit to multiple time-periods simultaneously
3. Fit to multiple time-periods, considering also data smearing



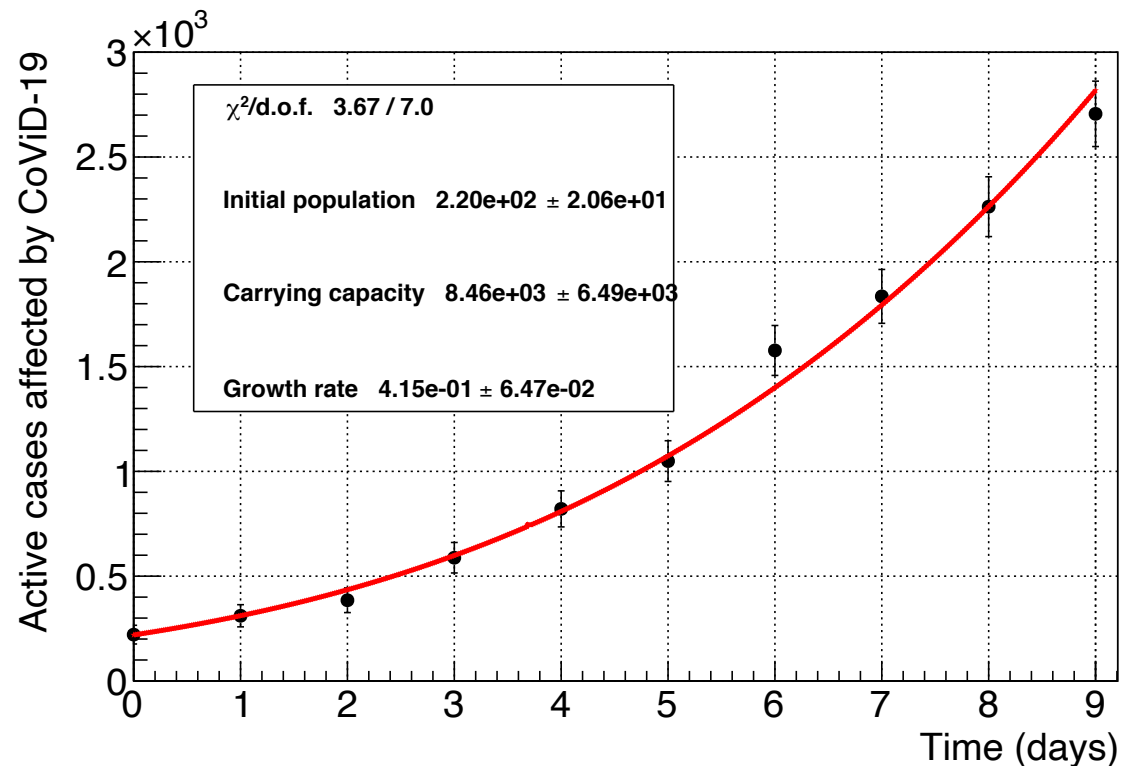


- Friday 21<sup>st</sup> February → Codogno become red zone
  - Monday 24<sup>th</sup> February → Data recording starts •
  - Wednesday 4<sup>th</sup> March → Lock down schools and universities •
  - Sunday 8<sup>th</sup> March → Lombardy isolated
  - Tuesday 10<sup>th</sup> March → Restrictions on movements •
  - Monday 23<sup>rd</sup> March → Total lock down •
  - Monday 4<sup>th</sup> May → Release lock down and entering in the so called phase-2
  - Monday 15<sup>th</sup> June → Start of the so called phase-3 (free movements with masks)
- 
- Start period 1
  - Start period 2
  - Start period 3
  - Start period 4

### Some references:

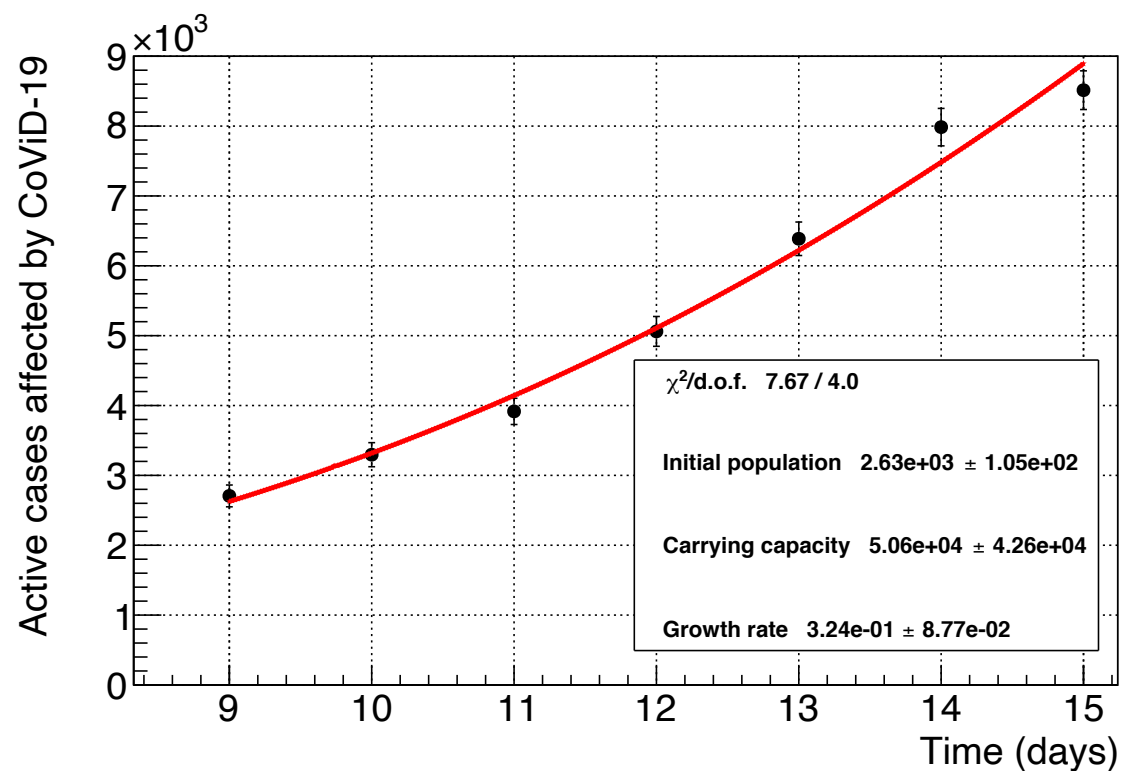
- Fraction of asymptomatic:
  - ★ [https://www.repubblica.it/salute/medicina-e-ricerca/2020/03/16/news/coronavirus\\_studio\\_il\\_50-75\\_dei\\_casi\\_a\\_vo\\_sono\\_asintomatici\\_e\\_molto\\_contagiosi-251474302/](https://www.repubblica.it/salute/medicina-e-ricerca/2020/03/16/news/coronavirus_studio_il_50-75_dei_casi_a_vo_sono_asintomatici_e_molto_contagiosi-251474302/)
- Latent/incubation period:
  - ★ <https://www.internazionale.it/notizie/graham-lawton/2020/03/26/sintomatici-diffondono-virus>
  - ★ [https://www.thelancet.com/journals/lancet/article/PIIS0140-6736\(20\)30746-7/fulltext](https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30746-7/fulltext)





Number of active cases, fit data from 0<sup>th</sup> to 8<sup>th</sup> day (period 1):

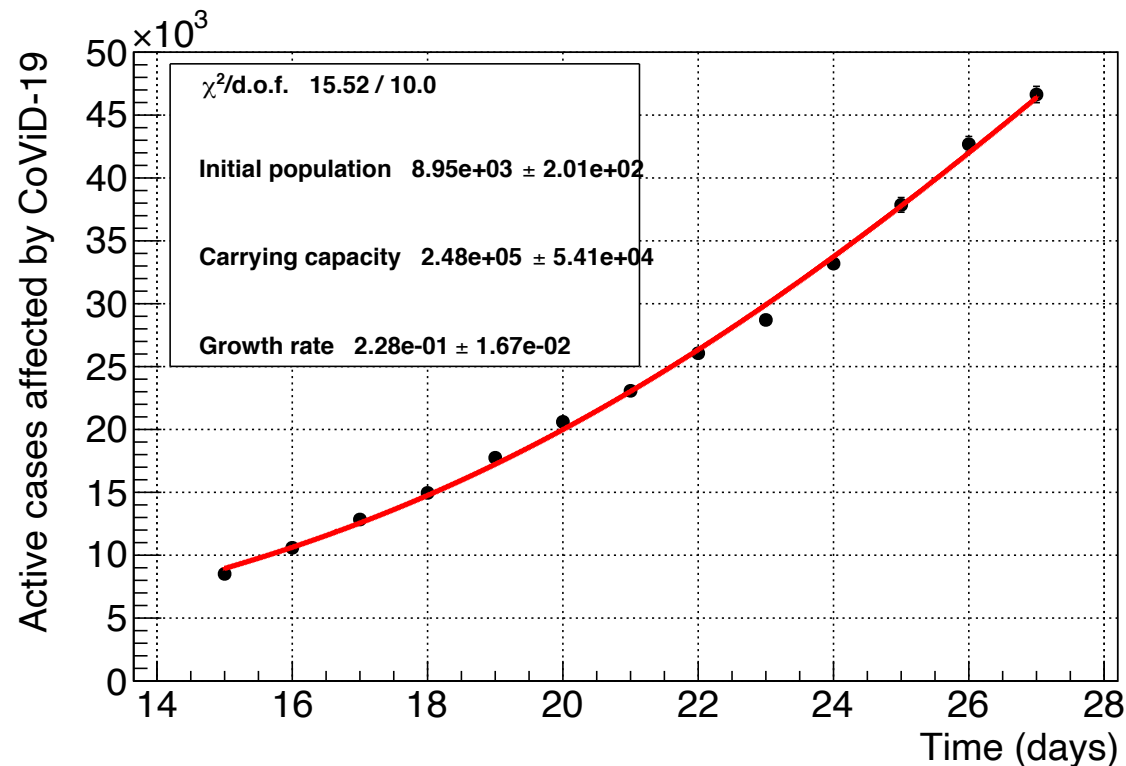
- $N_0: 220$
- $g: 0.415$
- $C_0: 8460 \pm 6490$
- $N_9: 2817$
- $C_9: 23538 \pm 18057$



Number of active cases, fit data from 9<sup>th</sup> to 14<sup>th</sup> day (period 2):

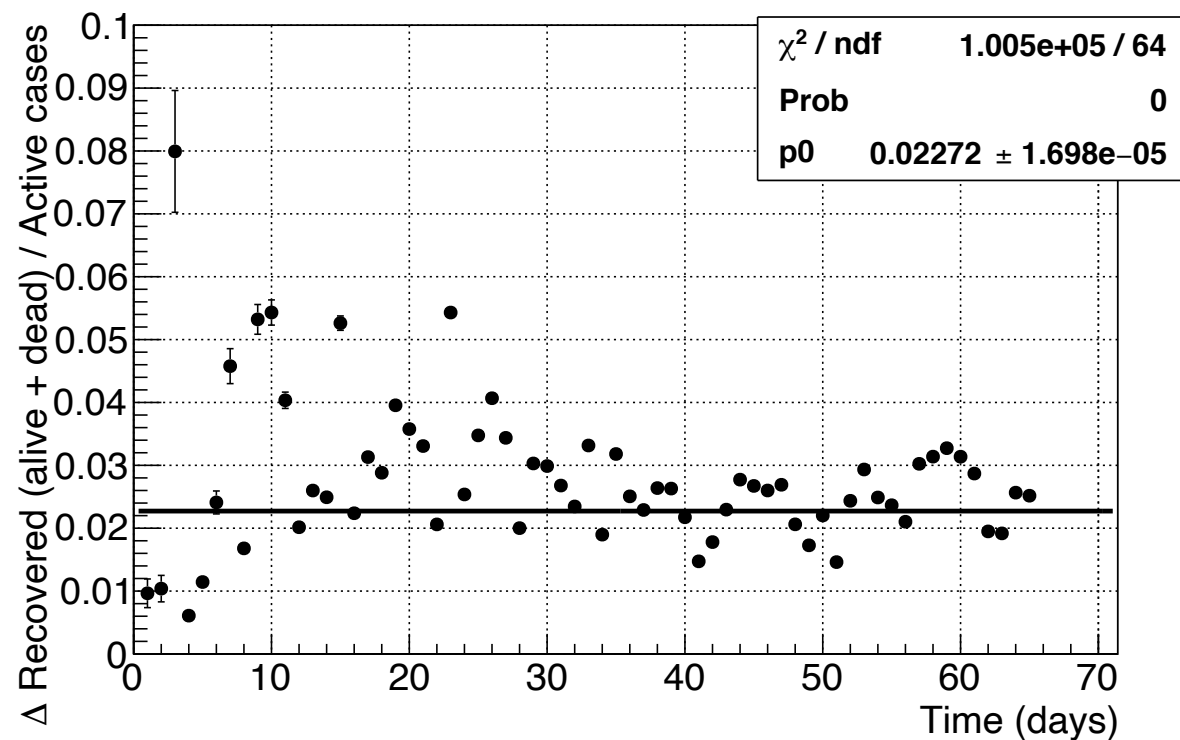
- $N_0: 2630$
- $g: 0.324$
- $C_0: 50600 \pm 42600$
- $N_{15}: 8895$
- $C_{15}: 79587 \pm 67004$





Number of active cases, fit data from 15<sup>th</sup> to 26<sup>th</sup> day (period 3):

- $N_0$ : 8950
- $g$ : 0.228
- $C_0$ :  $248000 \pm 54100$
- $N_{27}$ : 46390
- $C_{27}$ :  $376923 \pm 82224$

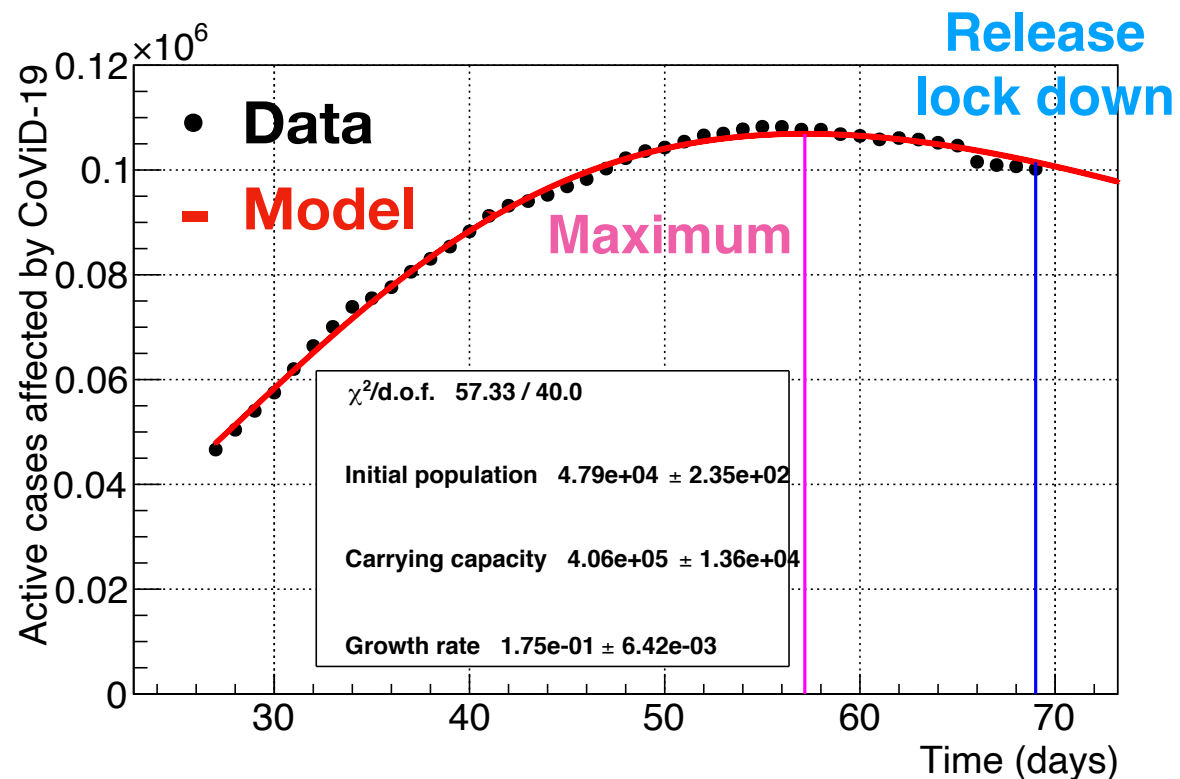


Recovery rate ( $r$ ) is derived from data:

- $r \sim 0.023 \rightarrow \tau \sim 44$  days







Number of active cases, fit data from 27<sup>th</sup> day till release (period 4)

For all fit:

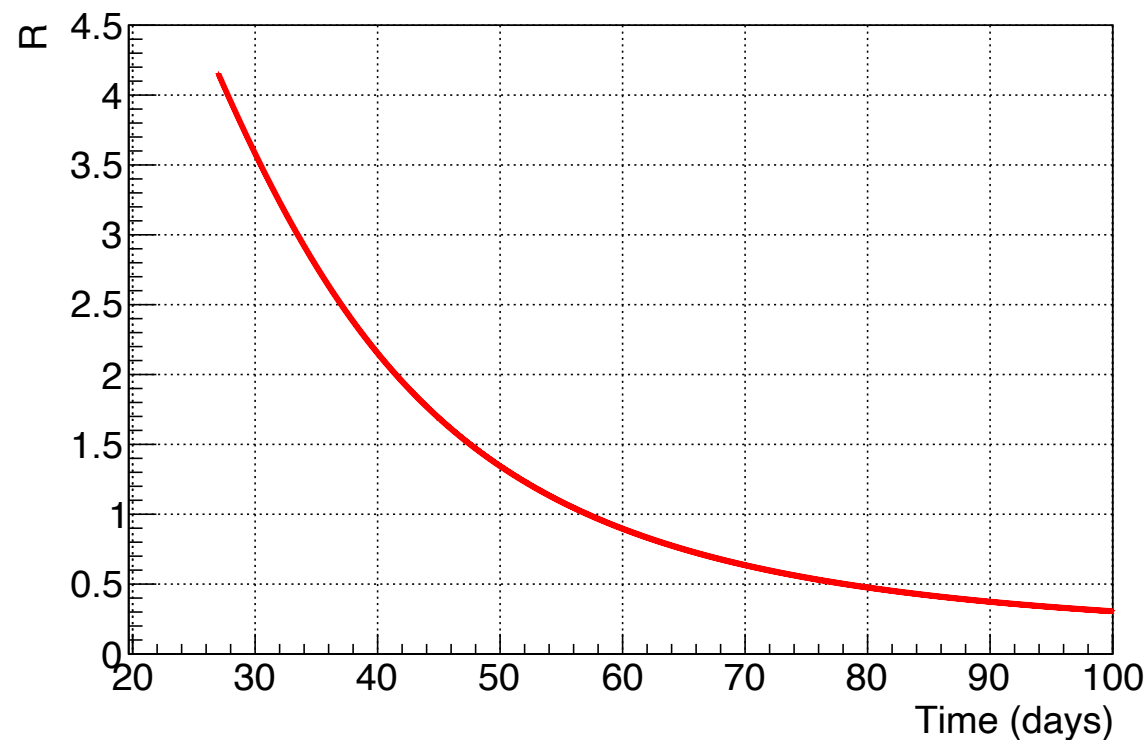
- Errors rescaled by  $\times 3$

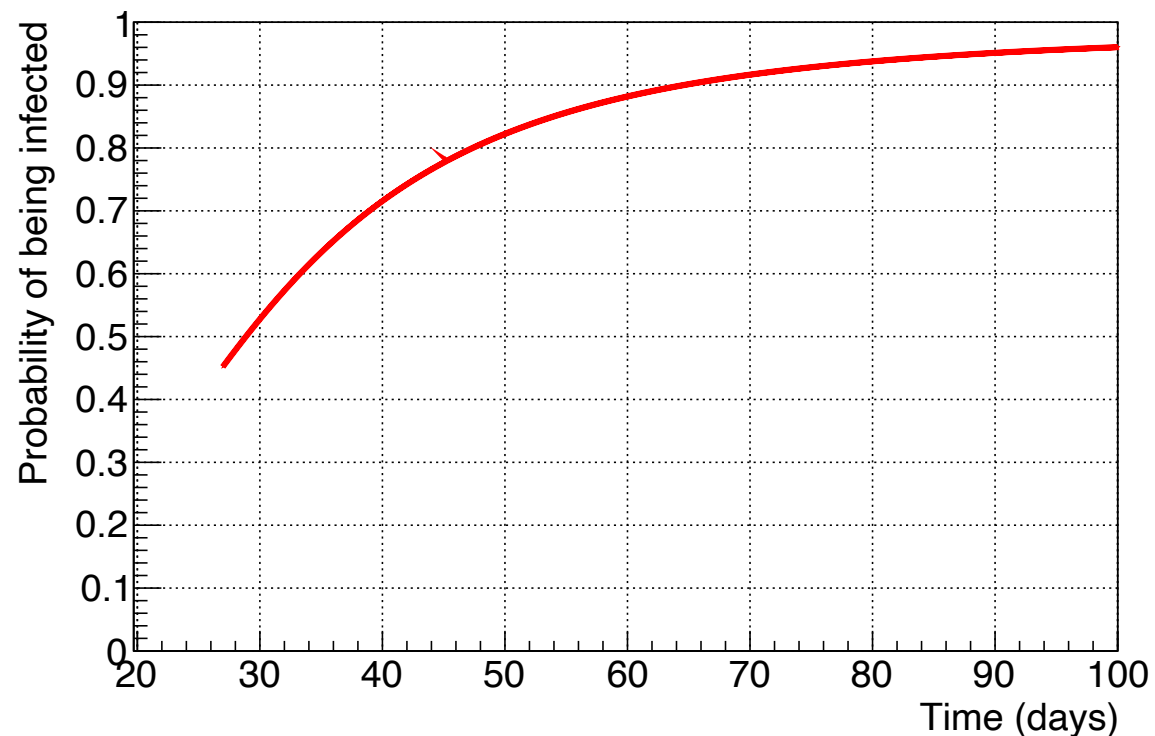
Fitted parameters:

- Initial population ( $\mathbf{N}_0$ )
- Growth rate ( $\mathbf{g}$ )
- Carrying capacity ( $\mathbf{C}_0$ )

Fixed parameters:

- Recovery rate ( $\mathbf{r} = 0.023$ )
- Fraction of symptomatic ( $\mathbf{0.3}$ )
- Transmission probability ( $\mathbf{p} = 0.26$  - see control plots)
- Total population ( $\mathbf{T} = 60 \times 10^6$ )





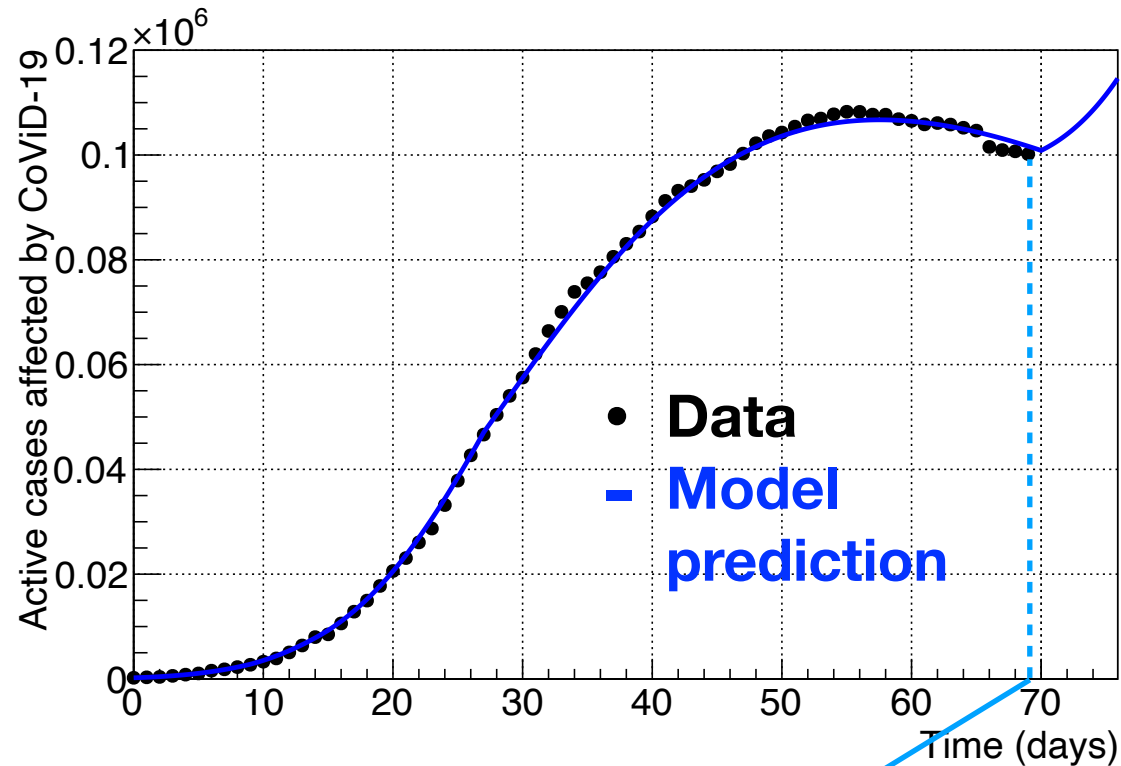
Probability of being infected, i.e.  $1-q$

### Parameter summary last period:

- $r = 0.023 \rightarrow$  plot  $\Delta\text{recovered}/\text{active}$
- $g = 0.175 \rightarrow$  fit
- $p = 0.26 \rightarrow \chi^2/\text{d.o.f. scan}$
- Symptomatic fraction =  $0.3 \rightarrow$  literature
- $T = 60 \times 10^6 \rightarrow$  demography

Nuisance parameters:  $N_0$  and  $C_0$





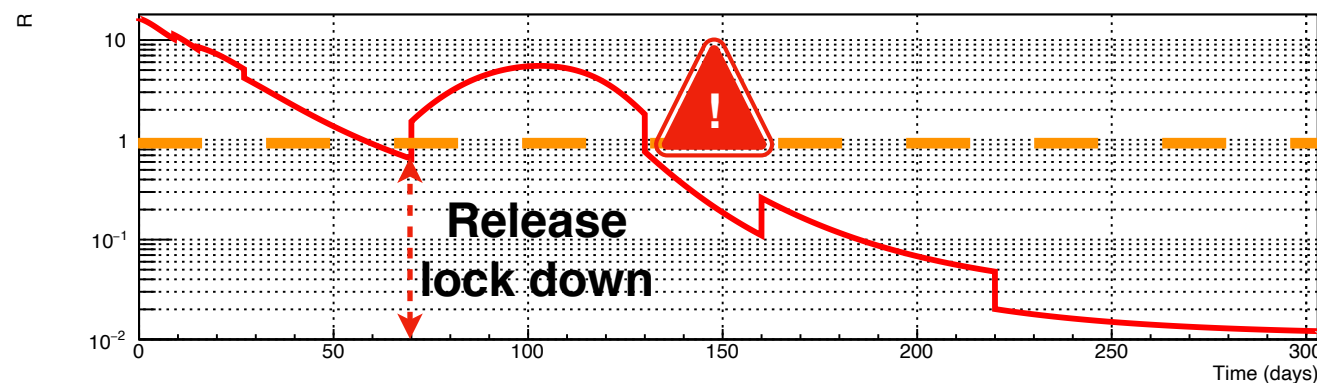
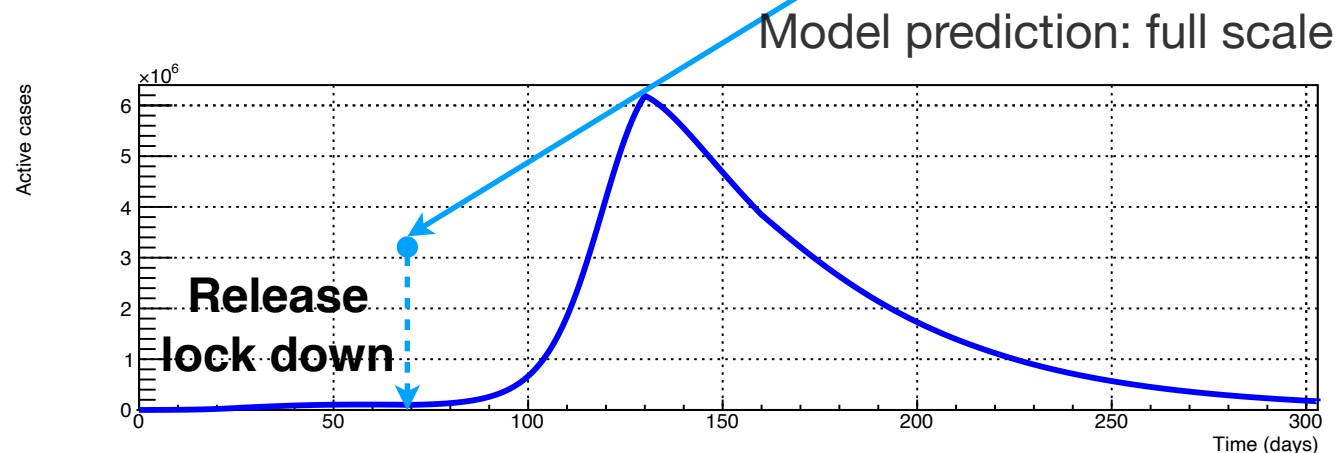
- Normal life style ( $g = 0.415$ ) for 9 days
- Mild soc.distance ( $g = 0.324$ ) for 6 days
- Medium soc.distance ( $g = 0.228$ ) for 12 days
- Hard soc.distance ( $g = 0.175$ ) for **42** days

☞ Past ☞ Future

- Normal life style ( $g = 0.415$ ) for 60 days
- Hard soc.distance ( $g = 0.175$ ) for 30 days
- Normal life style ( $g = 0.415$ ) for 60 days
- Hard soc.distance ( $g = 0.175$ ) for 120 days

### Other parameters:

- $N_0$ : 220
- $r$ : 0.023
- Symptomatic fraction: 0.3
- Transmission probability: 0.26

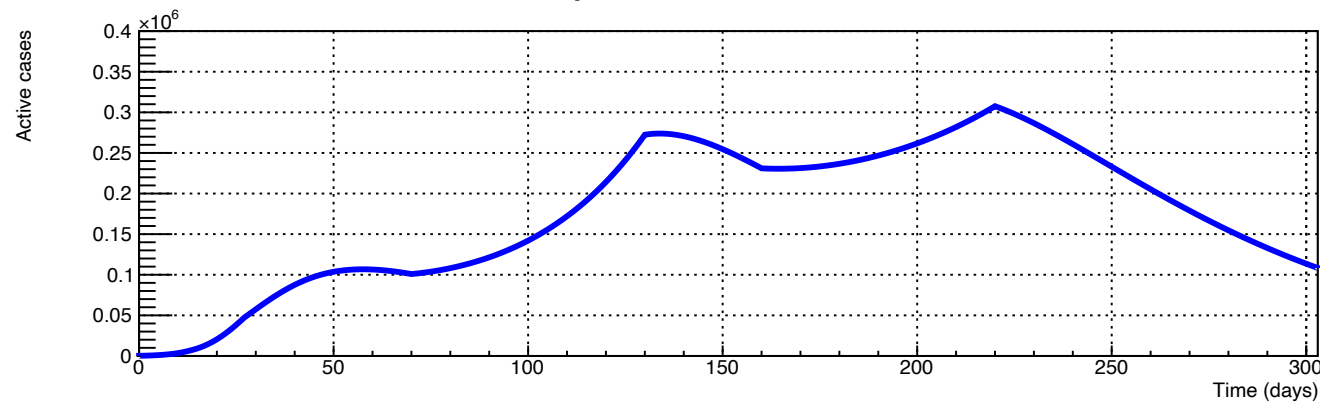


### Herd immunity:

- Normal life style ( $g = 0.415$ ): **94%**
- Mild soc.distance ( $g = 0.324$ ): **93%**
- Medium soc.distance ( $g = 0.228$ ): **90%**
- Hard soc.distance ( $g = 0.175$ ): **87%**

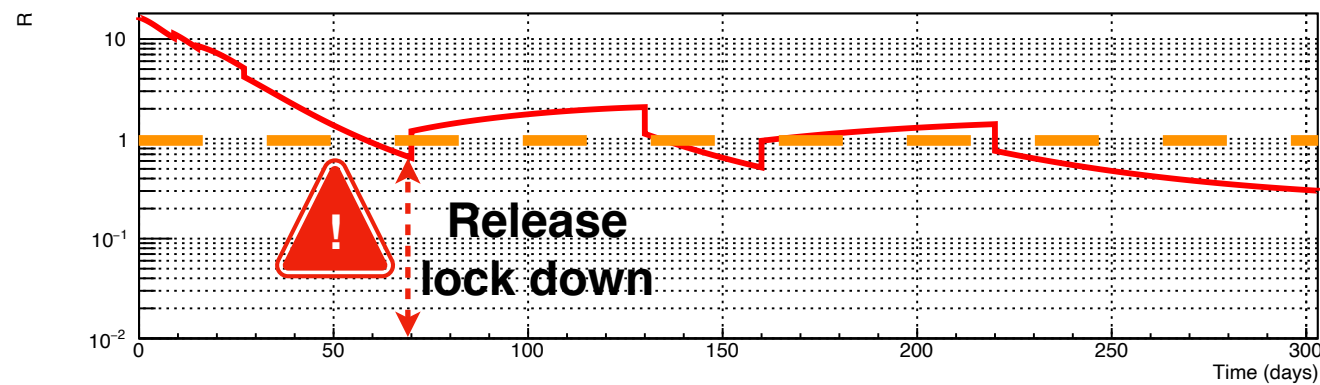


Model prediction: full scale



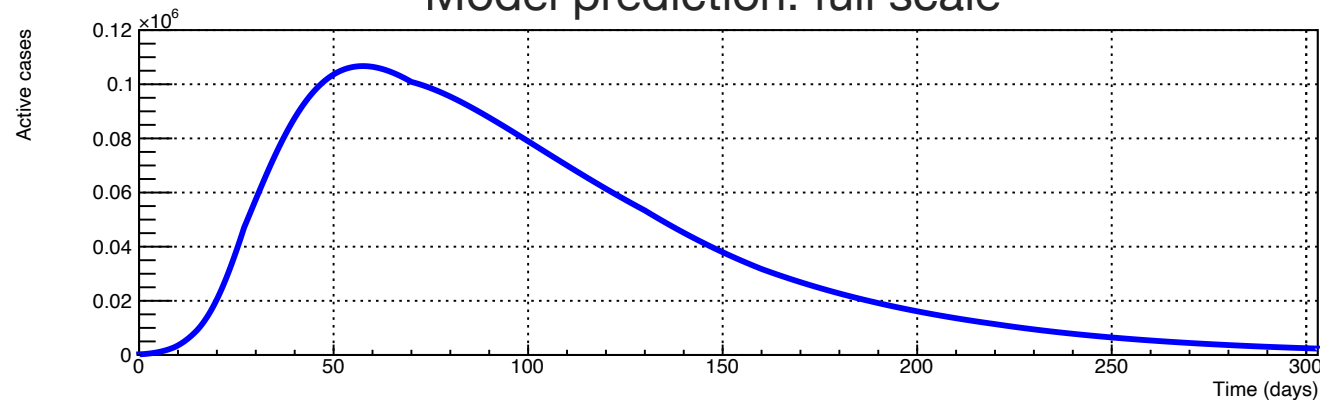
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👉 Past 👈 Future



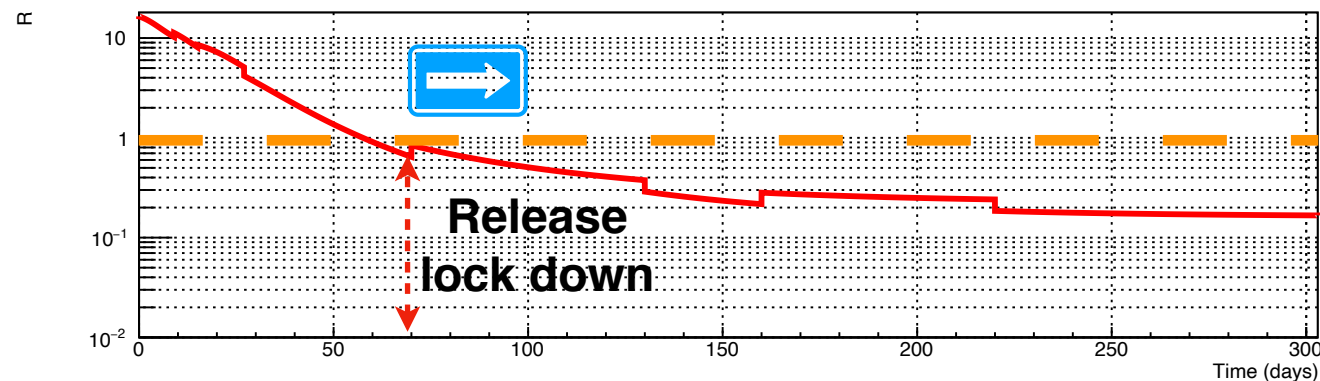
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Model prediction: full scale



- Normal life style ( $g = 0.415$ ) for 9 days
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👉 Past 👈 Future



- Medium soc.distance ( $g = 0.228$ ) for 60 days
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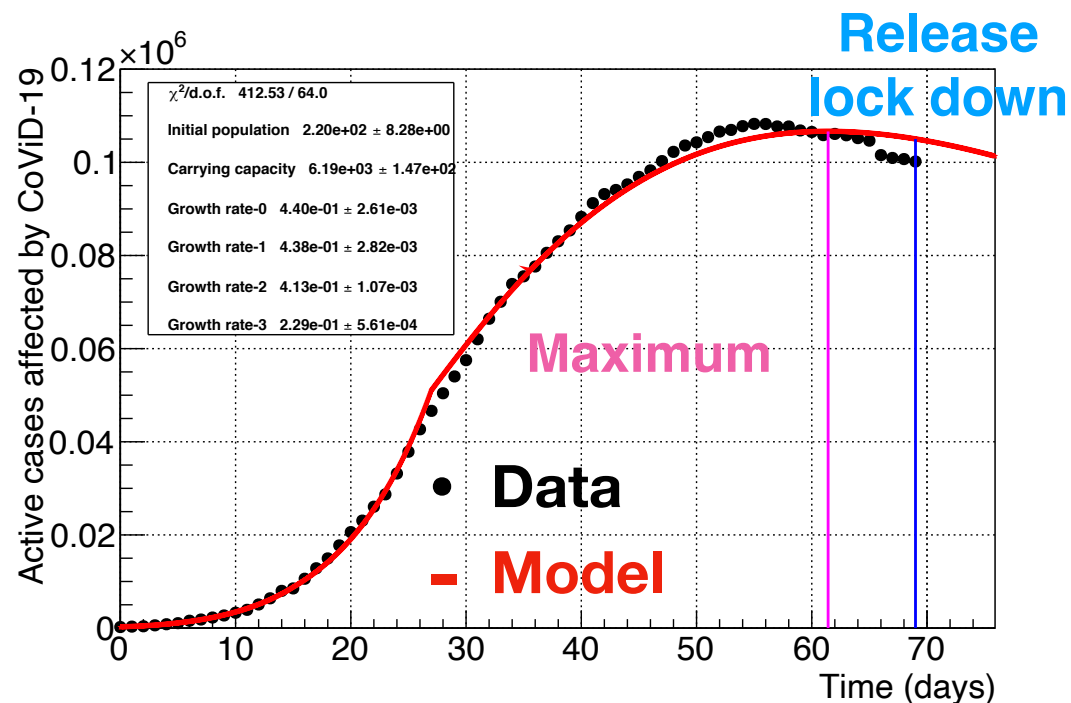
The model was first tested on different periods, independently, as shown in the previous slides. Then the analysis was further improved by performing:

1. a global fit, i.e. a joint fit, to multiple periods simultaneously, imposing continuity on the number of active cases ( $N_n$ ) and on the carrying capacity ( $C_n$ ) across periods, i.e.  $N_n$  and  $C_n$  at the end of period  $m$  must be equal to  $N_n$  and  $C_n$  at the beginning of period  $m+1$
2. a global fit with `logNormal` smearing to take into account effects such as latent/incubation periods or in general delays in data reporting, law enforcement, or social behaviour





# Application to data: fit to multiple time-periods



Number of active cases, **joint fit** periods 1 + 2 + 3 + 4

For all fit:

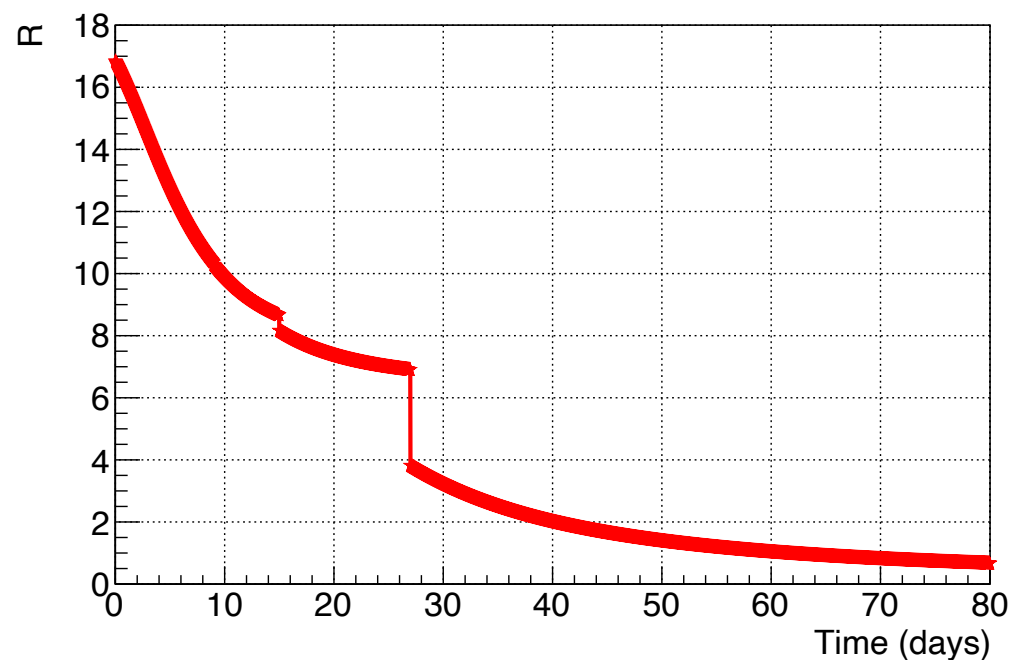
- Errors rescaled by  $\times 3$

Fitted parameters:

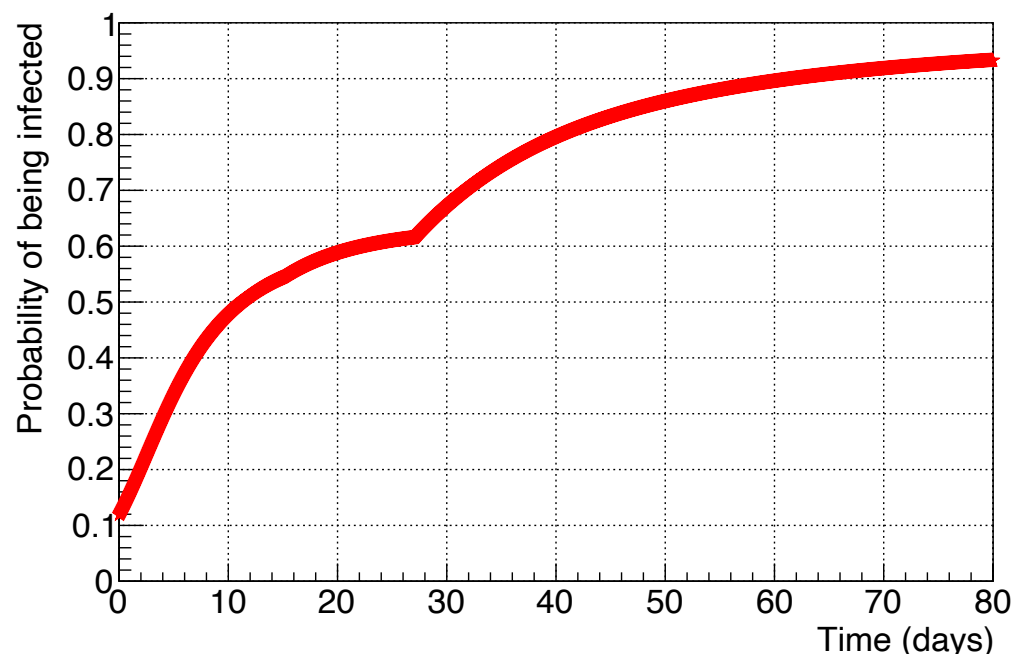
- Initial population ( $\mathbf{N}_0$ )
- Growth rates periods 1, 2, 3, 4 ( $\mathbf{g}$ )
- Carrying capacity ( $\mathbf{C}_0$ )

Fixed parameters:

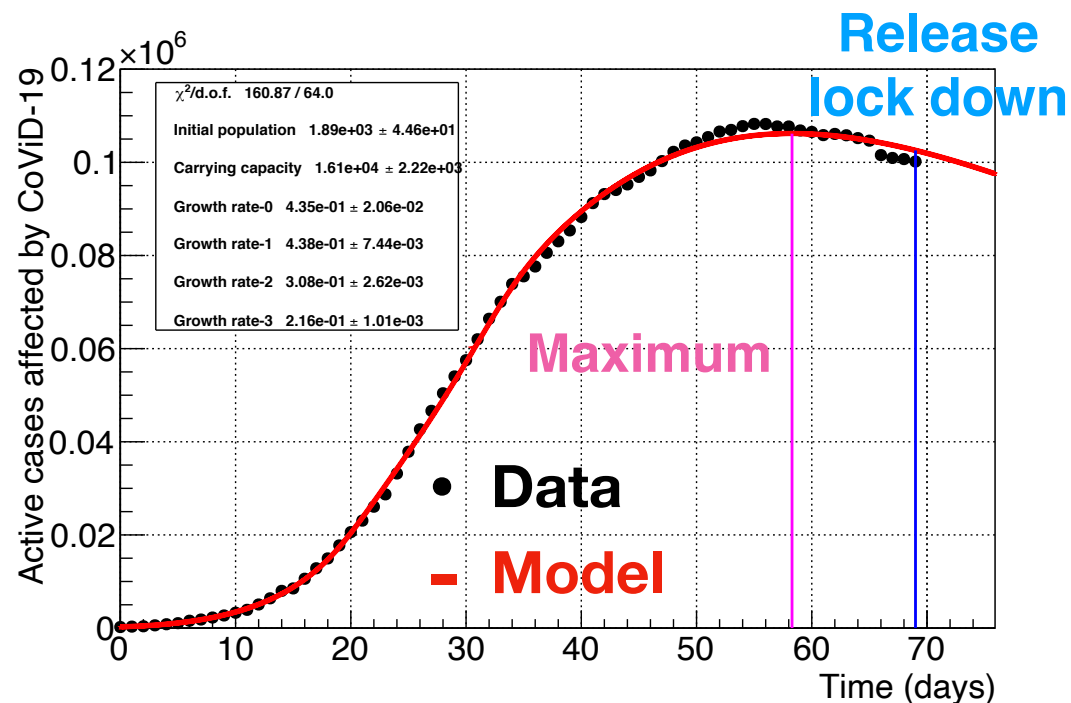
- Recovery rate ( $\mathbf{r} = 0.023$ )
- Fraction of symptomatic ( $\mathbf{0.3}$ )
- Transmission probability  
( $\mathbf{p} = 0.26$  - see control plots)
- Total population ( $\mathbf{T} = 60 \times 10^6$ )



Probability of being infected, i.e.  $\mathbf{1-q}$



# Application to data: fit to multiple time-periods



Number of active cases, **joint fit** periods 1 + 2 + 3 + 4 with `logNormal( $\mu=2, \sigma=0.3$ )` smearing, i.e. convolution, to mimic effects such as latent/incubation periods (`logNormal` is used to preserve causality)

For all fit:

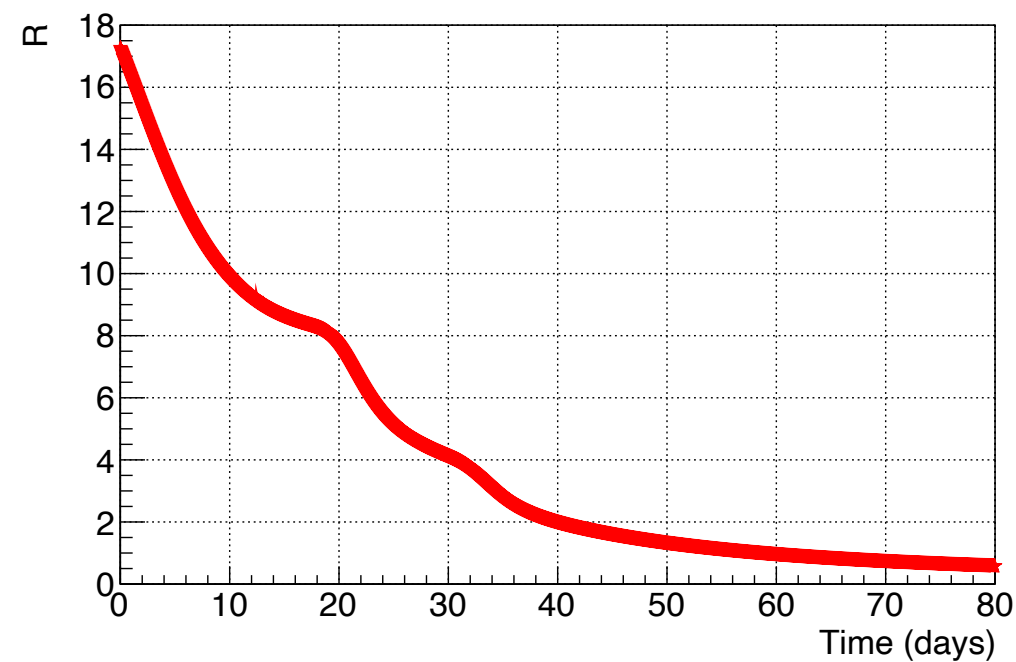
- Errors rescaled by  $\times 3$

Fitted parameters:

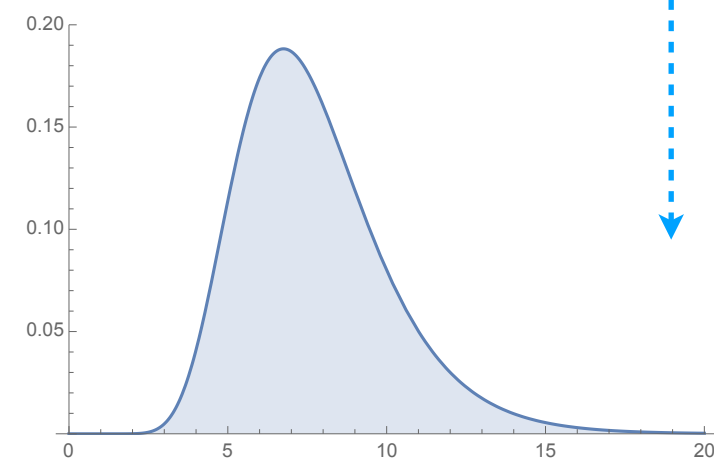
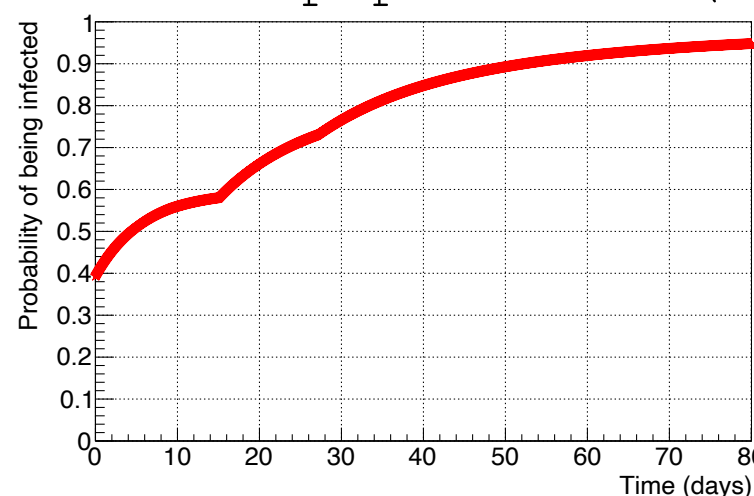
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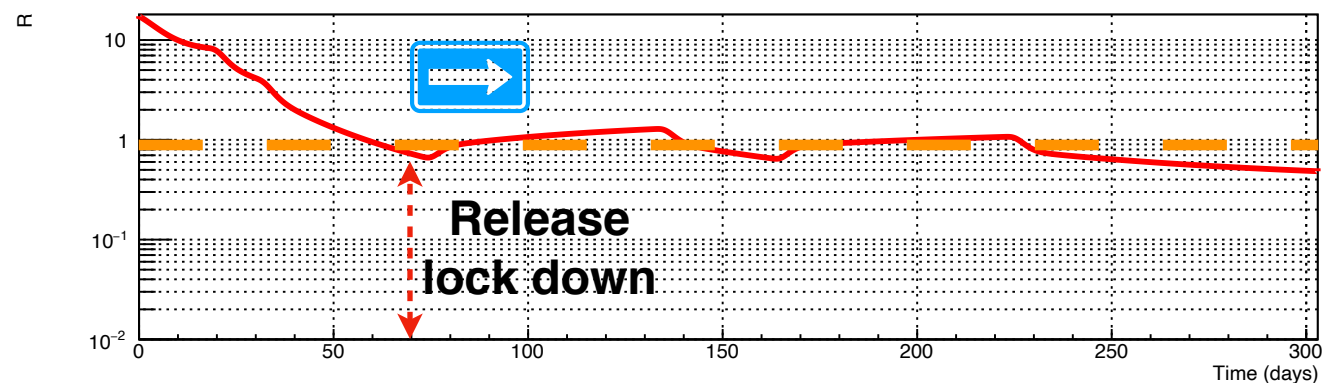
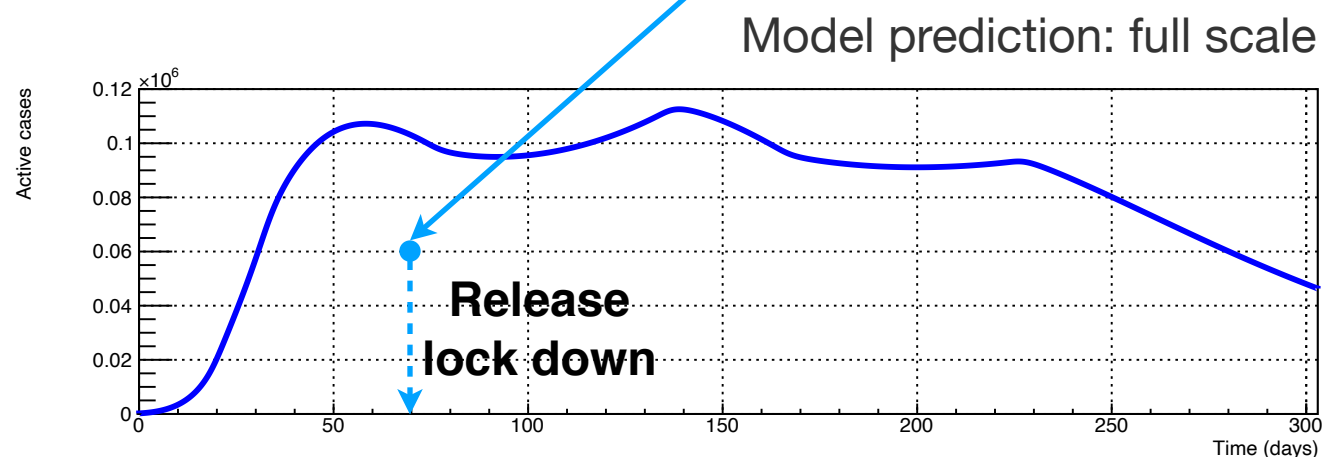
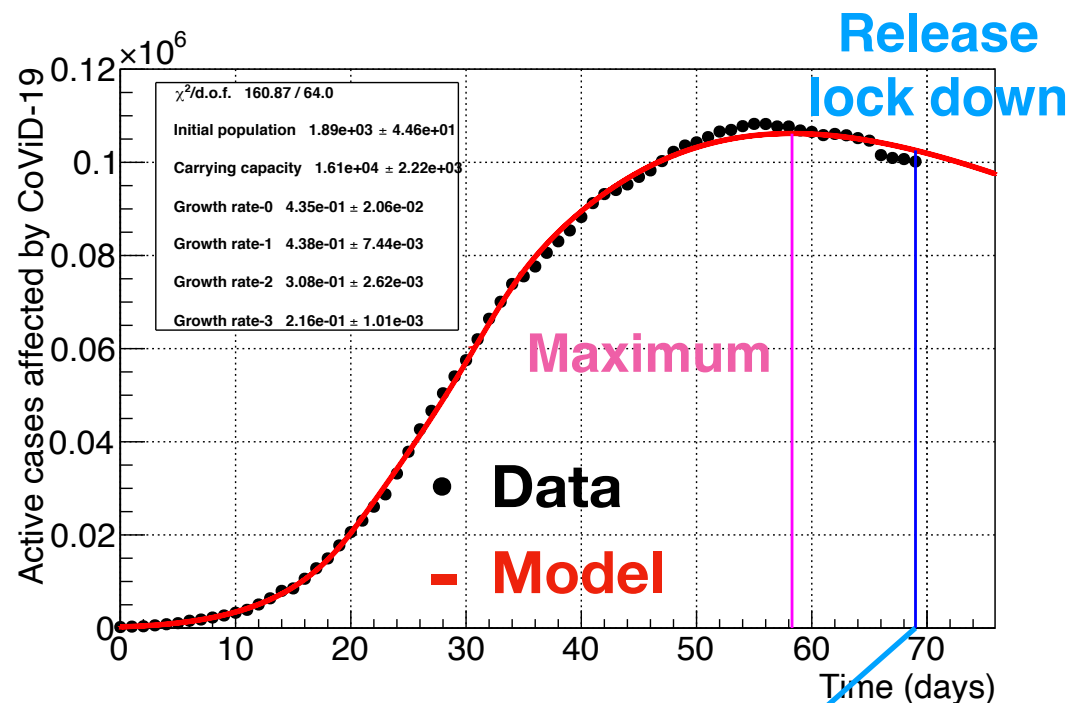
Fixed parameters:

- Recovery rate ( $\mathbf{r} = 0.023$ )
- Fraction of symptomatic ( $\mathbf{0.3}$ )
- Transmission probability ( $\mathbf{p} = 0.26$  - see control plots)
- Total population ( $\mathbf{T} = 60 \times 10^6$ )



Probability of being infected, i.e.  $\mathbf{1-q}$





- Normal life style ( $g = 0.435$ ) for 9 days
- Mild soc.distance ( $g = 0.438$ ) for 6 days
- Medium soc.distance ( $g = 0.308$ ) for 12 days
- Hard soc.distance ( $g = 0.216$ ) for **42** days

☞ Past ☞ Future

- Normal life style ( $g = 0.308$ ) for 60 days
- Hard soc.distance ( $g = 0.216$ ) for 30 days
- Normal life style ( $g = 0.308$ ) for 60 days
- Hard soc.distance ( $g = 0.216$ ) for 120 days

### Other parameters:

- $N_0$ : 1890,  $C_0$ : 16100
- $r$ : 0.023
- Symptomatic fraction: 0.3
- Transmission probability: 0.26

### Herd immunity:

- Normal life style ( $g = 0.435$ ): **95%**
- Mild soc.distance ( $g = 0.438$ ): **95%**
- Medium soc.distance ( $g = 0.308$ ): **93%**
- Hard soc.distance ( $g = 0.216$ ): **89%**



The model has in total 7 parameters:

- recovery rate  $r$   $\rightarrow$  obtained from data plot  $\Delta\text{recovered}/\text{active}$
- growth rate  $g$   $\rightarrow$  obtained from fit to the data
- transmission probability  $p$   $\rightarrow$  obtained from  $\chi^2/\text{d.o.f.}$  scan over multiple periods
- fraction of symptomatic  $\rightarrow$  obtained from literature
- total population  $T$   $\rightarrow$  demography
- initial conditions  $N_0$  and  $C_0$   $\rightarrow$  obtained from fit to the data

We extracted as much information as possible from the available data and we tried to avoid any a priori assumption, though the model unavoidably rely on a couple of tacit assumptions:

- the different periods are well defined, this of course might not be entirely realistic especially for those practices, e.g. wearing a mask, which were not dictated by law, and because the model doesn't take into account the latent/incubation periods, though the smearing with `logNormal` does not show significative effects
- possible differences/variations, region-by-region, double/under counting, etc..., in the criteria of measuring the data, are averaged out



Even so the model seems to reasonably describe the data and therefore we tried to project possible evolutions of the disease in the future by exploring three different scenarios:

1. normal life style
  2. lock down schools and universities: “mild soc.distance”
  3. mild soc.distance + restrictions on movements: “medium soc.distance”
- only the third scenario is capable of keeping the effective reproduction number below 1
- All other scenarios will unavoidably bring  $R > 1$  with the consequence of clogging the hospitals, even though  $R$  will no longer reach values as high as at the beginning of the contagion (~20)
  - Most likely we will get back to normal life thanks to the herd immunity, which will sets off at ~90% of infected population

*By any means this work pretend to describe the true dynamic of the infection spread, though it's interesting to notice that with just few parameters, and reasonable assumptions, the model is able to follow the evolution of the active cases*



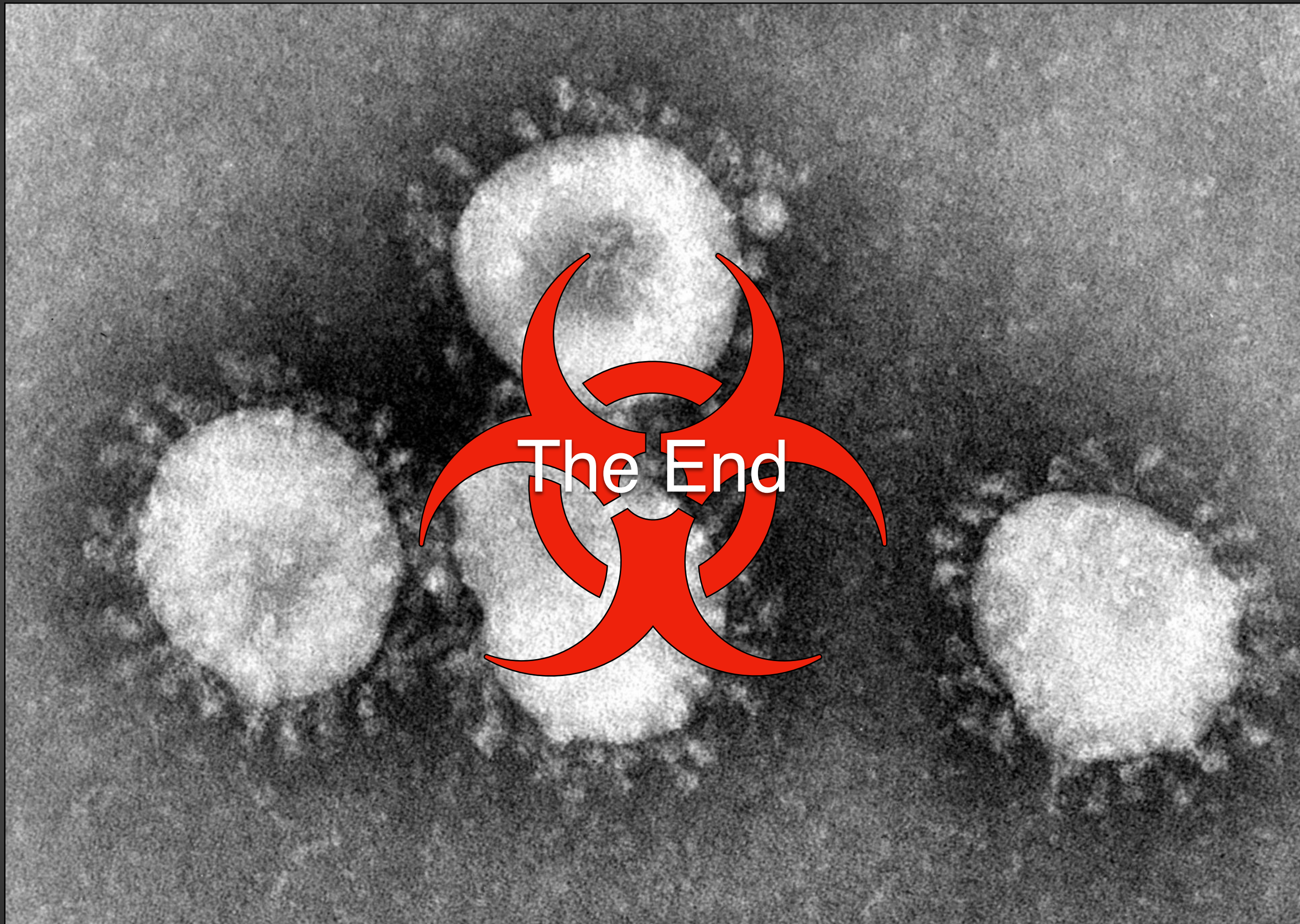


## How to act in order to dump the spread of the disease:

1. Decrease the factor  $p$  (*probability to spread the disease from one individual to another*): adopt masks, gloves, disinfections, etc... Mutations of the pathogen can also change  $p$
2. Decrease factor  $k$  (*average number of encountered people by one individual*): enforce social distancing
3. Increase factor  $Q$  (*fraction of active cases which are in quarantine*): quickly discover the new infected cases and put them in quarantine
4. Increase factor  $r$  (*recovery rate*): develop a vaccine ( $r$  is likely to be age-dependent). Mutations of the pathogen can also change  $r$







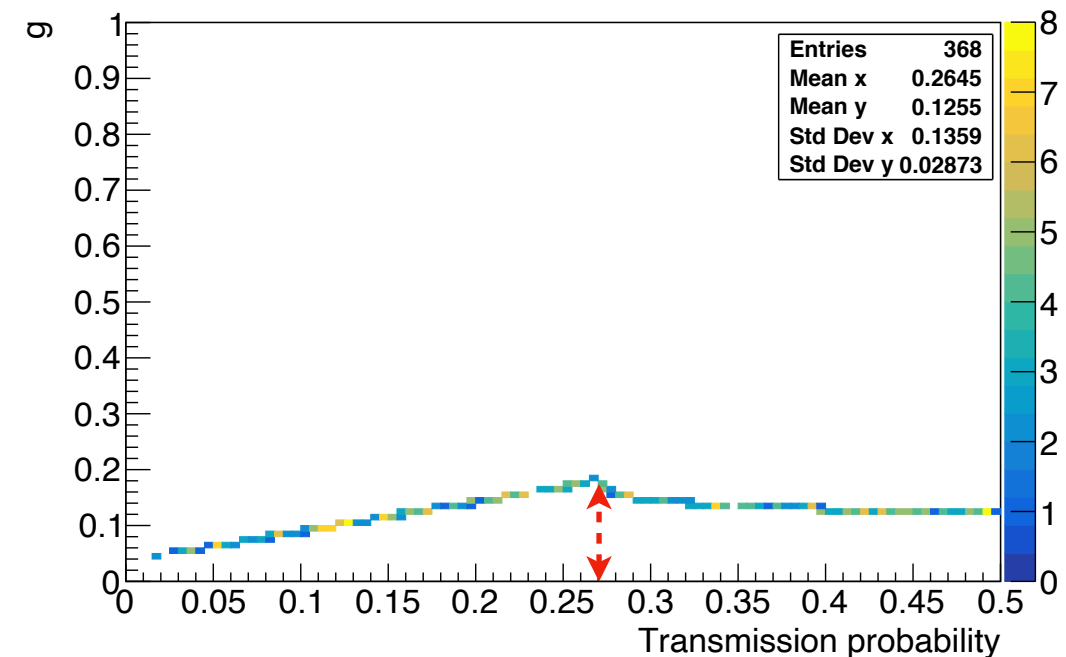
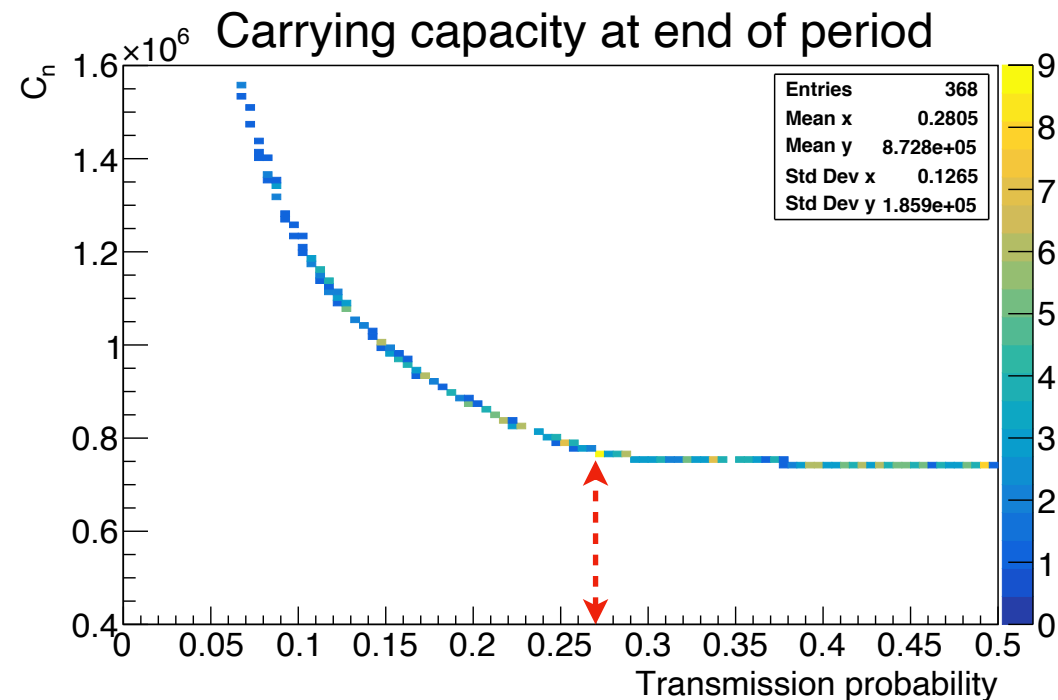
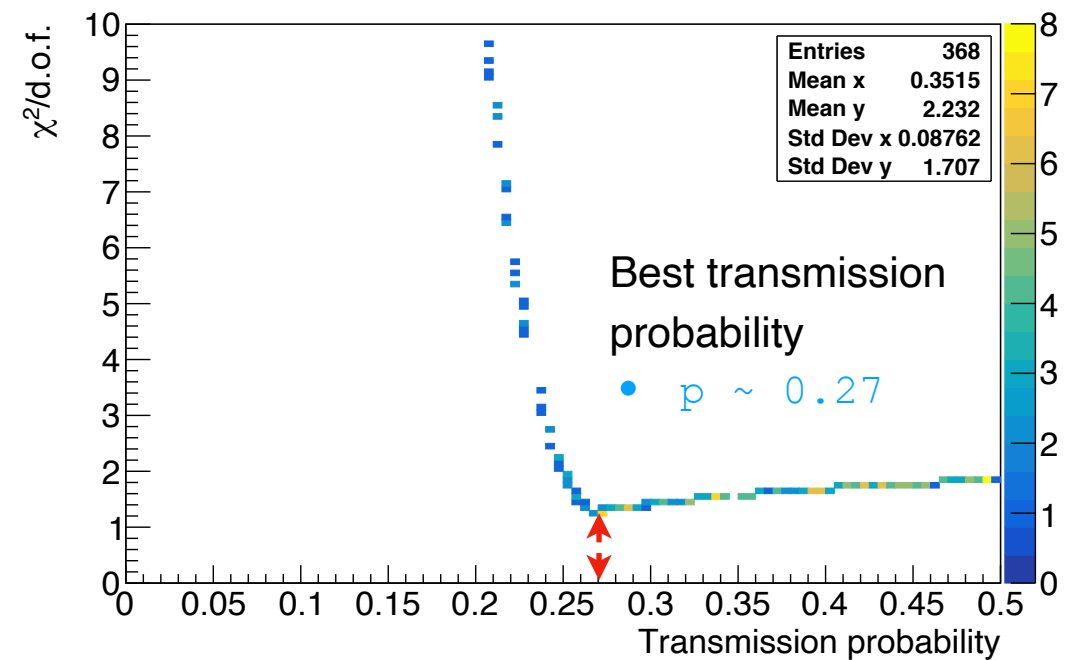
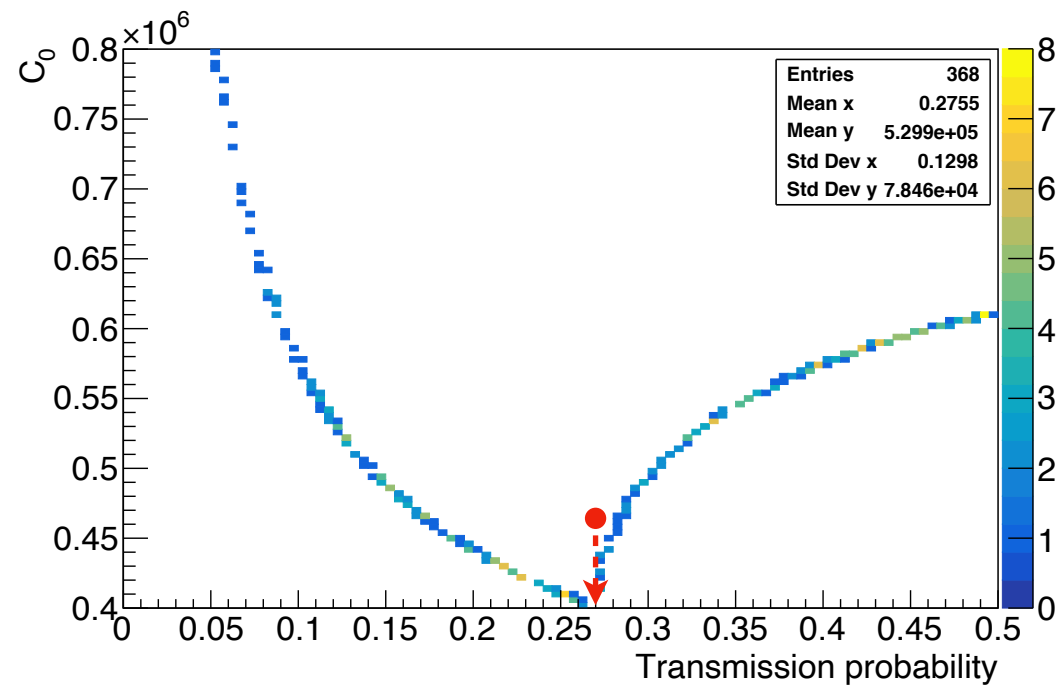


## Control plots

### Possible model ameliorations/extensions:

- Take into account natural demographic change





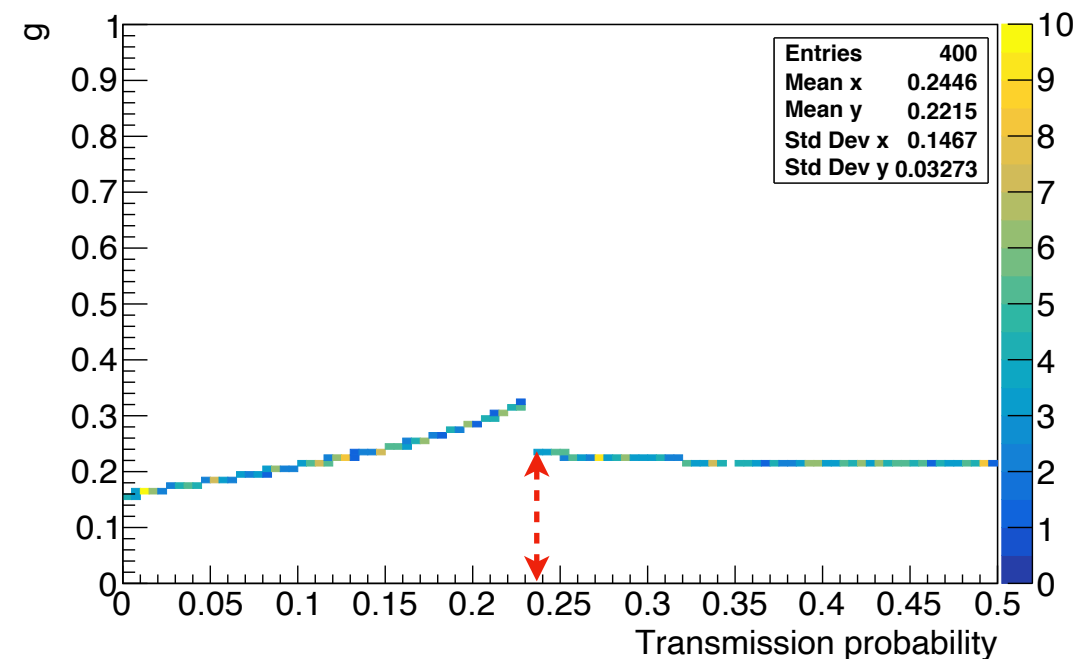
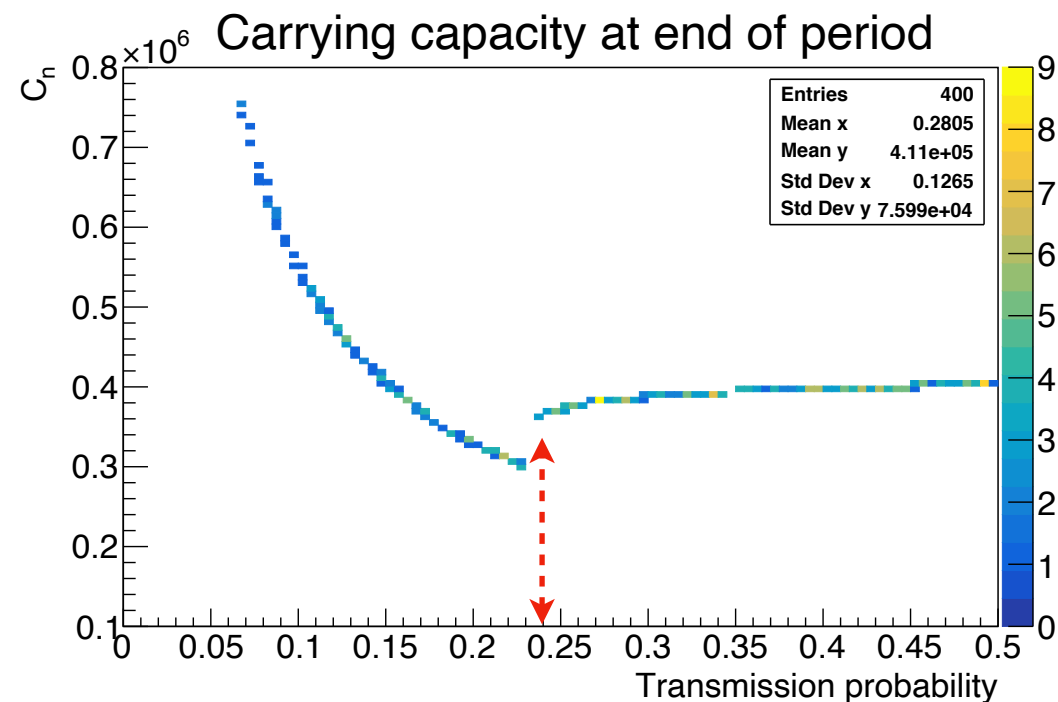
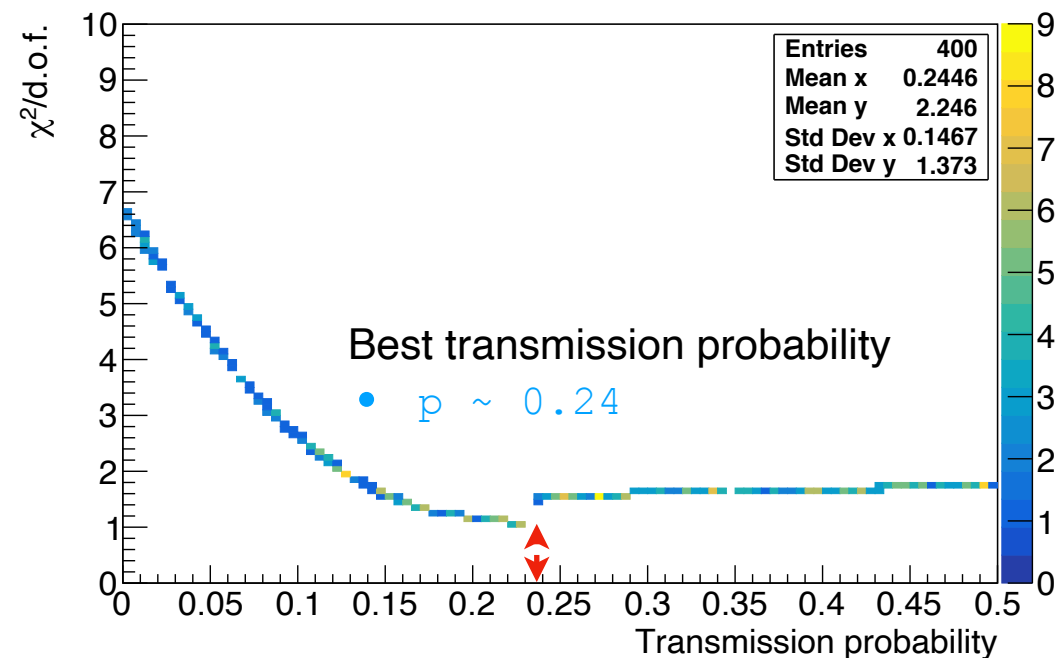
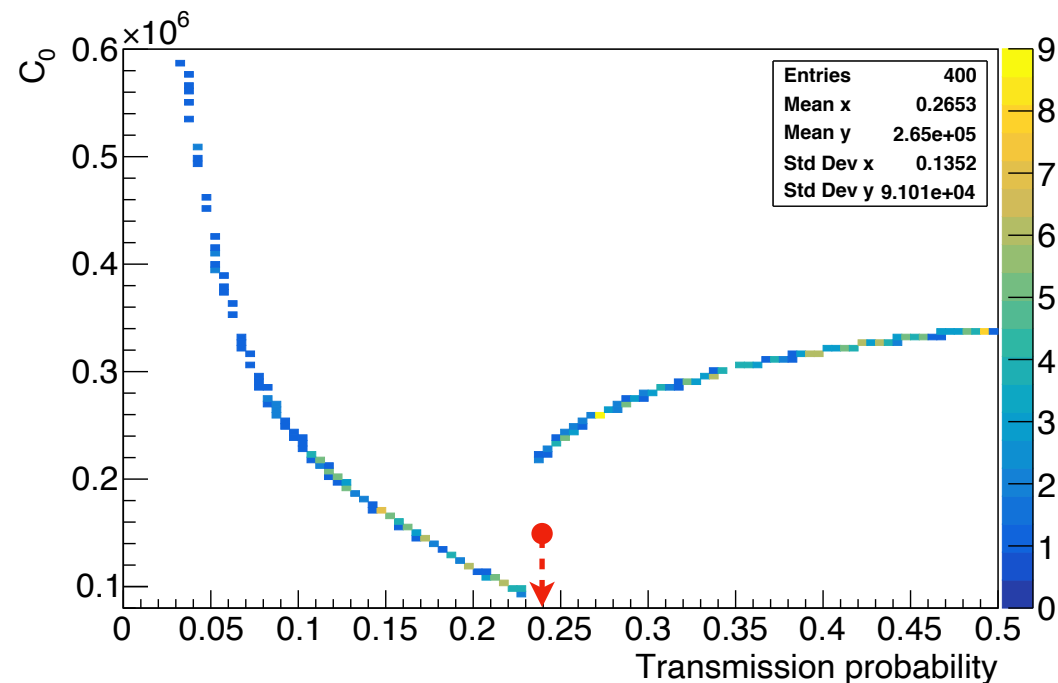
Fit data from 27<sup>th</sup> day till release (period 4)

- 400 extractions of transmission probability,  $p$

**Fixed parameters:**

- $r = 0.023 \rightarrow$  plot  $\Delta\text{recovered}/\text{active}$
- Symptomatic fraction =  $0.3 \rightarrow$  literature
- $T = 60 \times 10^6 \rightarrow$  demography





Fit data from 15<sup>th</sup> to 26<sup>th</sup> day (period 3)

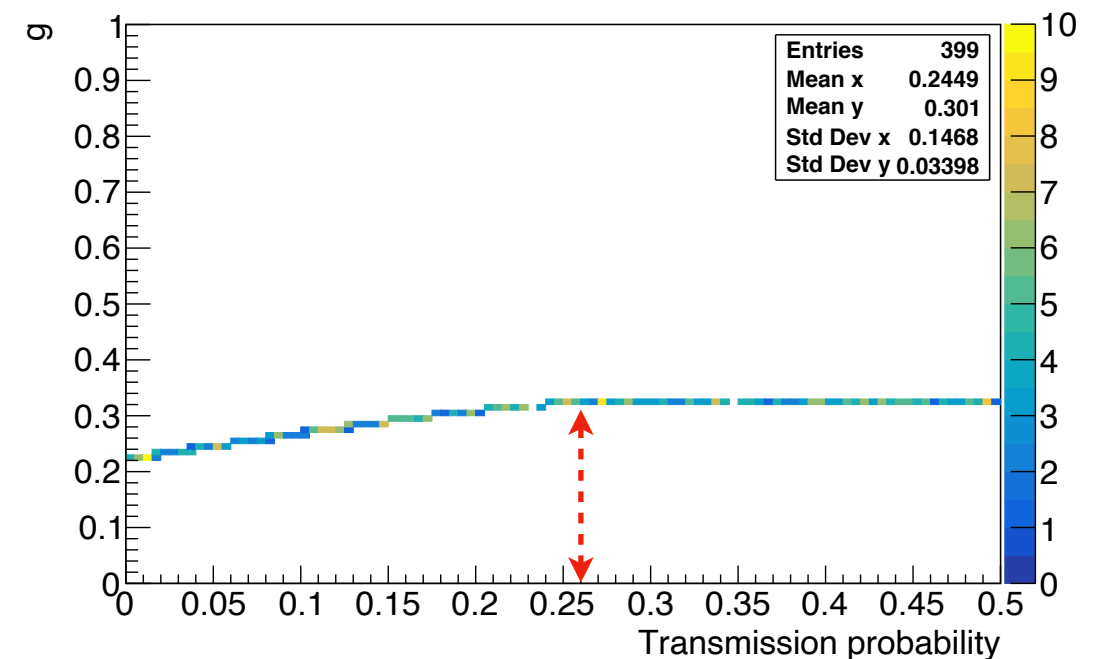
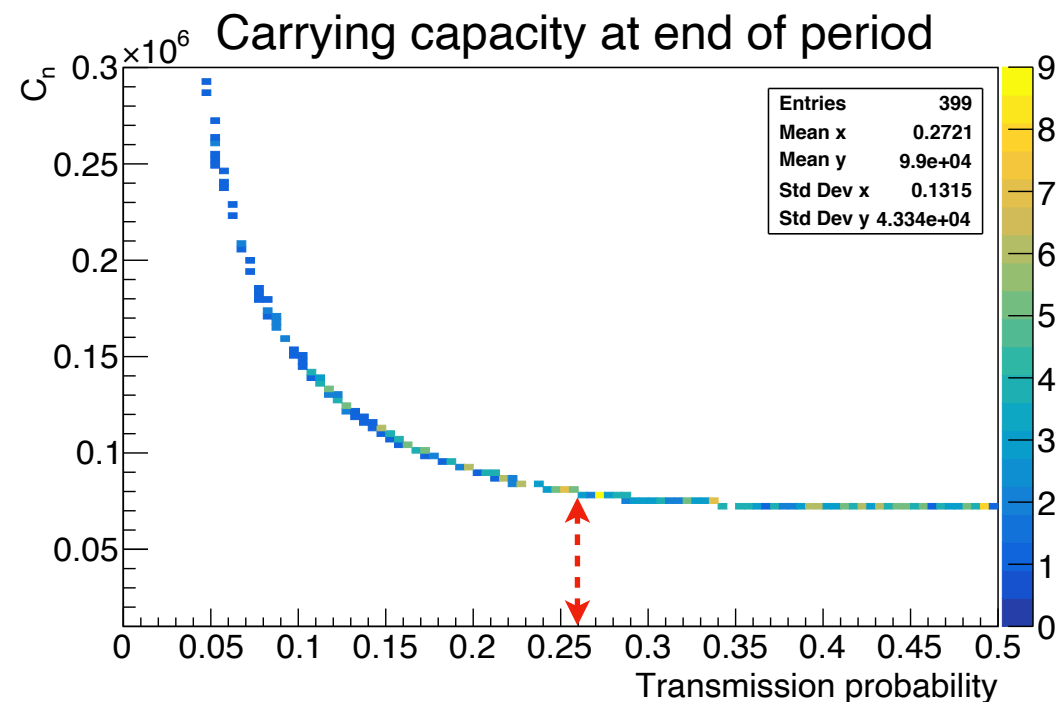
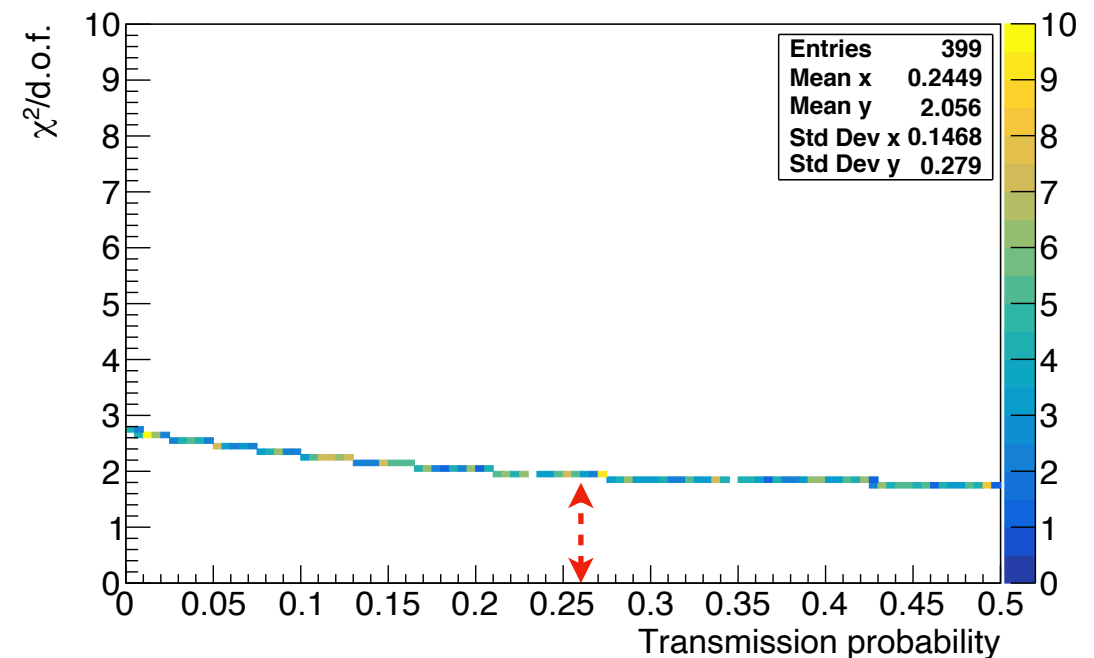
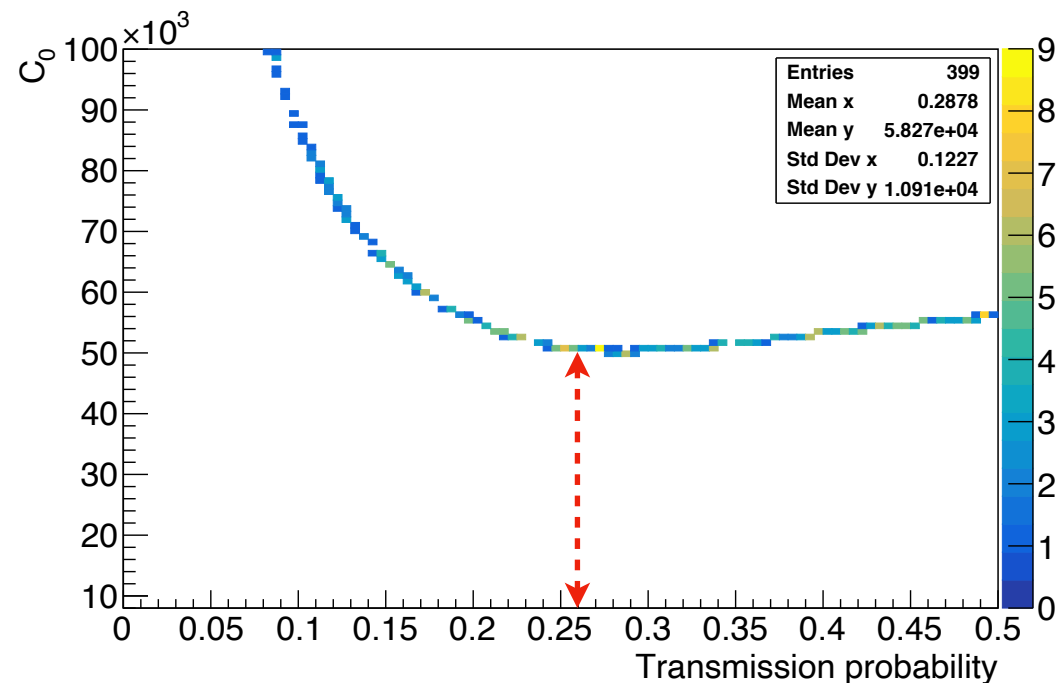
- 400 extractions of transmission probability,  $p$

**Fixed parameters:**

- $r = 0.023 \rightarrow$  plot  $\Delta\text{recovered}/\text{active}$
- Symptomatic fraction =  $0.3 \rightarrow$  literature
- $T = 60 \times 10^6 \rightarrow$  demography







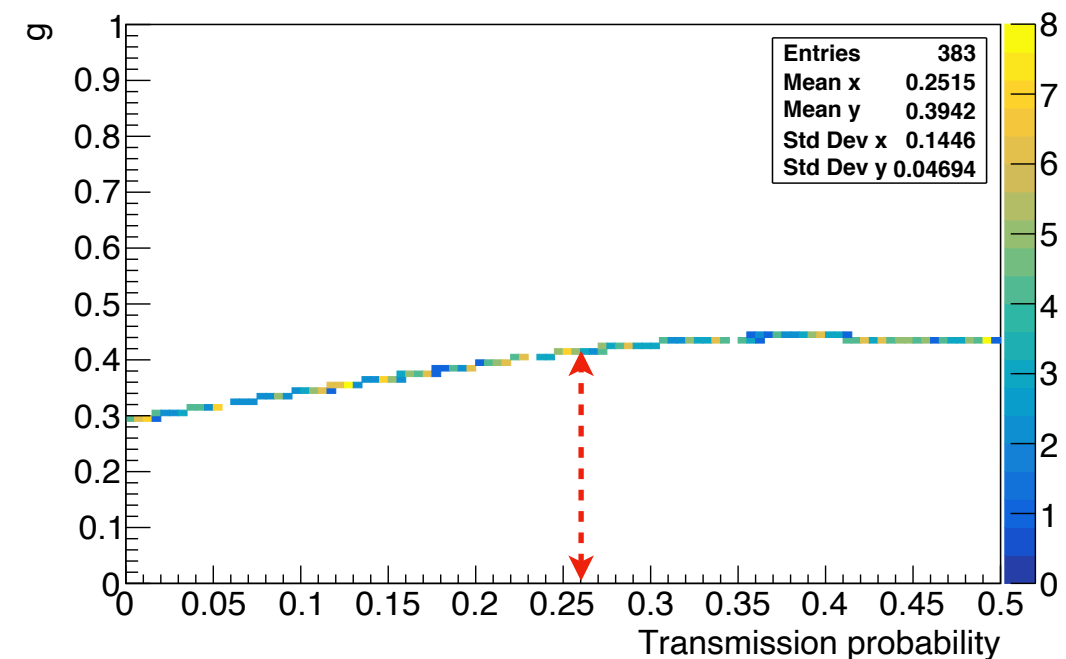
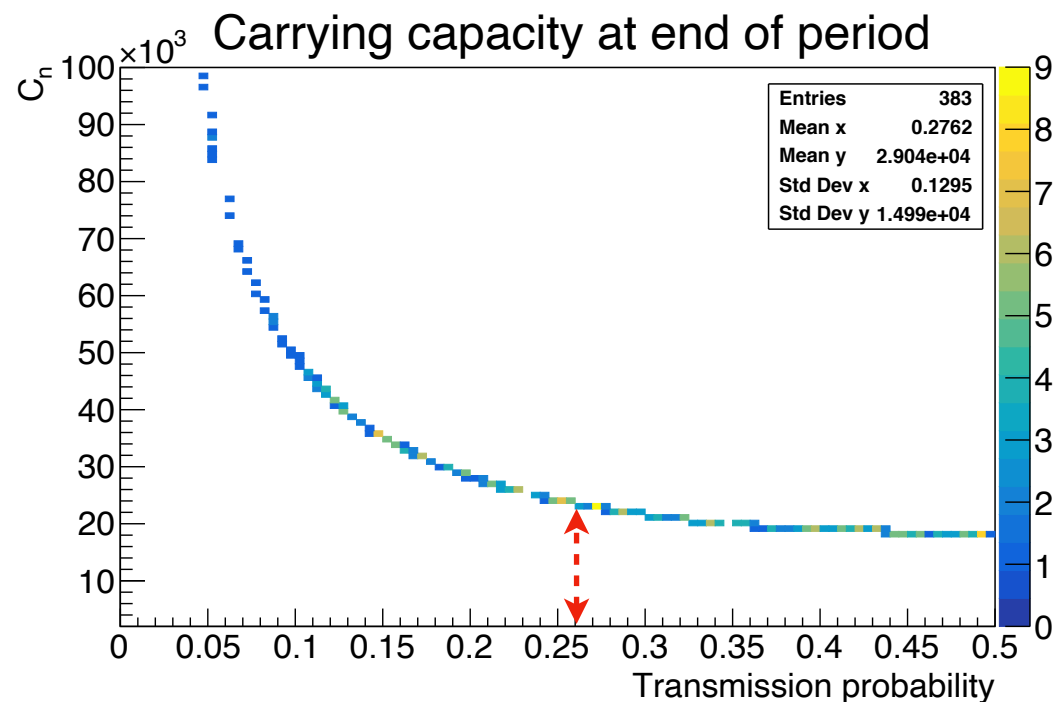
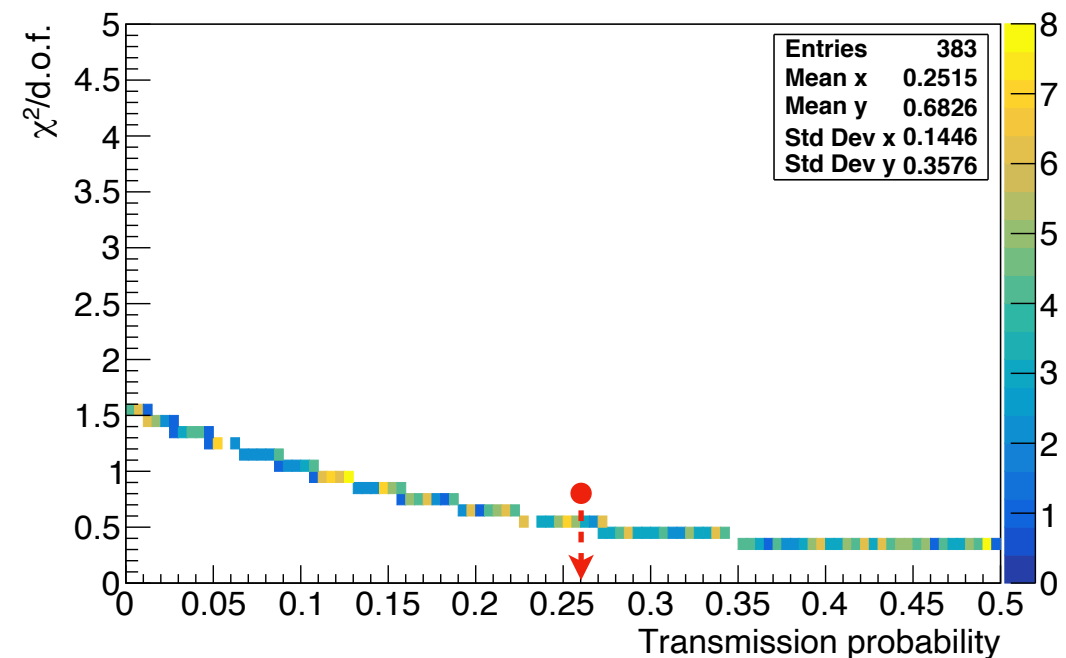
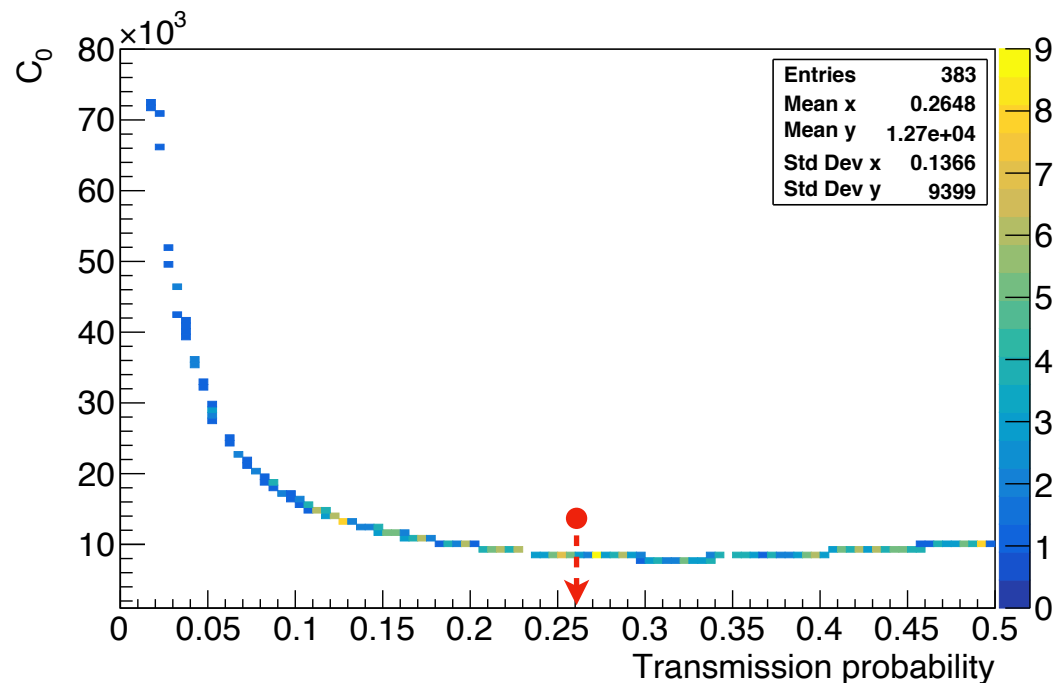
Fit data from 9<sup>th</sup> to 14<sup>th</sup> day (period 2)

- 400 extractions of transmission probability,  $p$

**Fixed parameters:**

- $r = 0.023 \rightarrow$  plot  $\Delta\text{recovered}/\text{active}$
- Symptomatic fraction =  $0.3 \rightarrow$  literature
- $T = 60 \times 10^6 \rightarrow$  demography





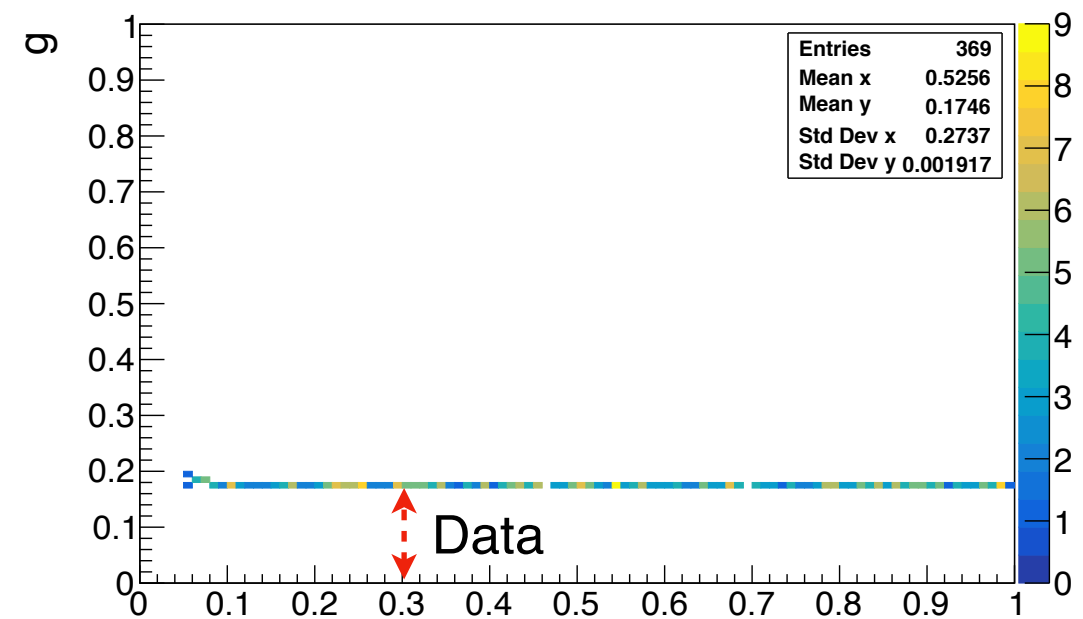
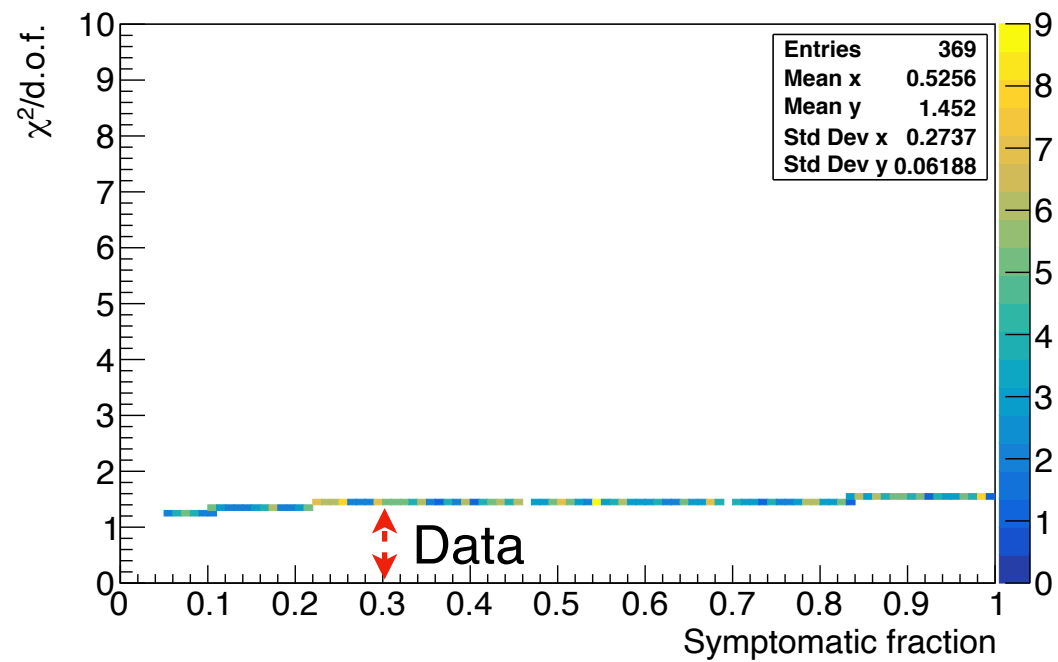
Fit data from 0<sup>th</sup> to 8<sup>th</sup> day (period 1)

- 400 extractions of transmission probability,  $p$

**Period 3 and 4 have slightly different transmission probability → averaging:**

- $p \sim 0.26$





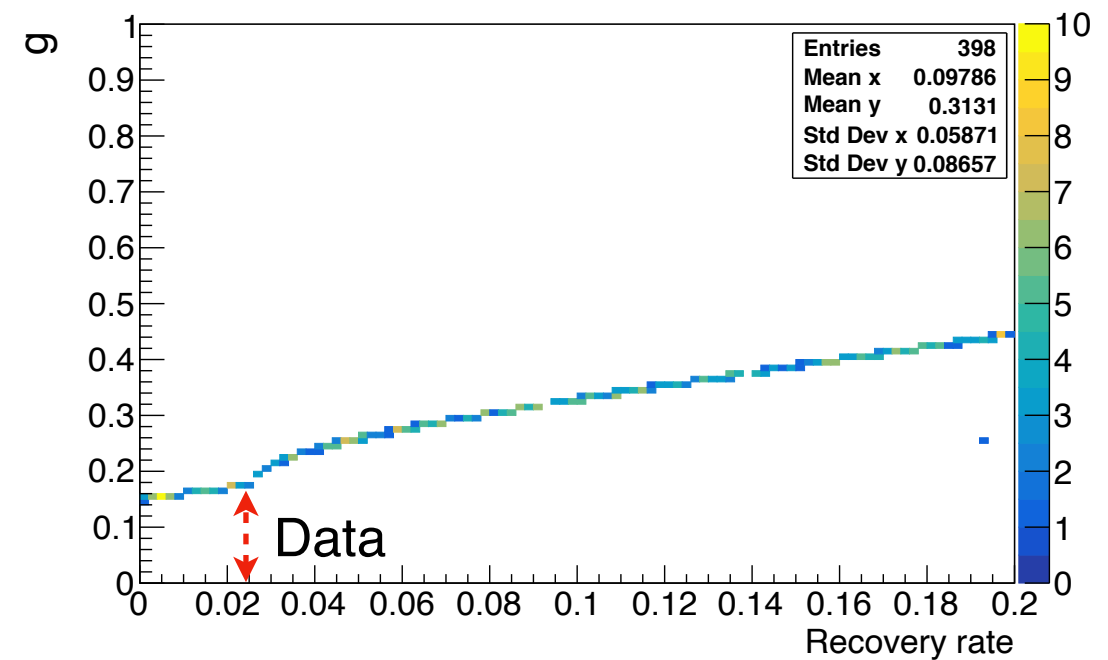
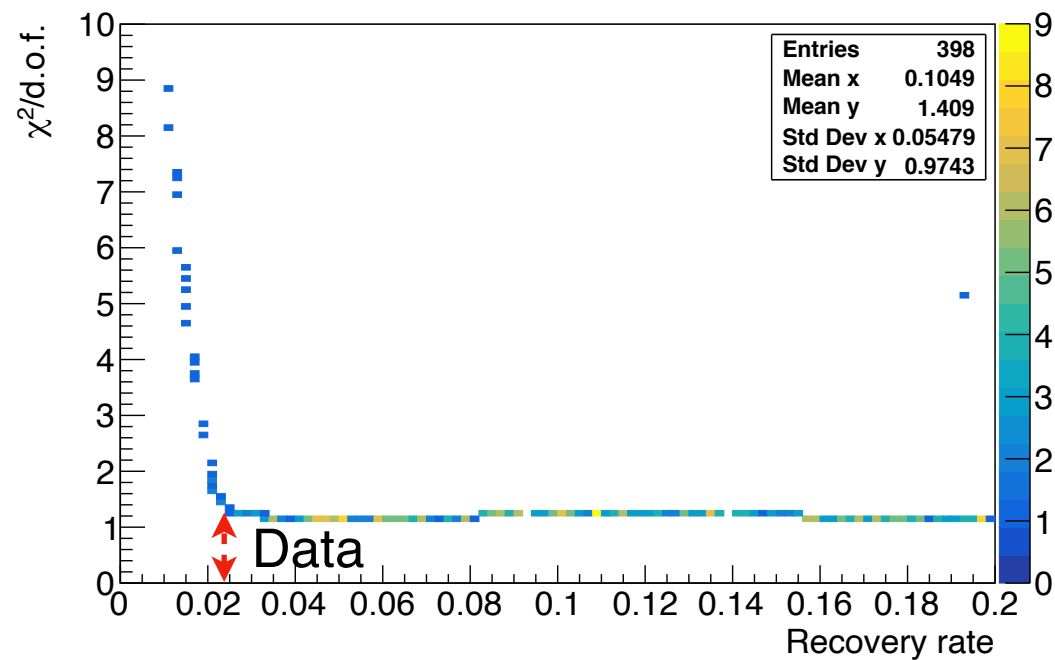
Fit data from 27<sup>th</sup> day till release (period 4)

- 400 extractions of symptomatic fraction

**Fixed parameters:**

- $r = 0.023 \rightarrow$  plot  $\Delta\text{recovered}/\text{active}$
- $p = 0.26$
- $T = 60 \times 10^6 \rightarrow$  demography





Fit data from 27<sup>th</sup> day till release (period 4)

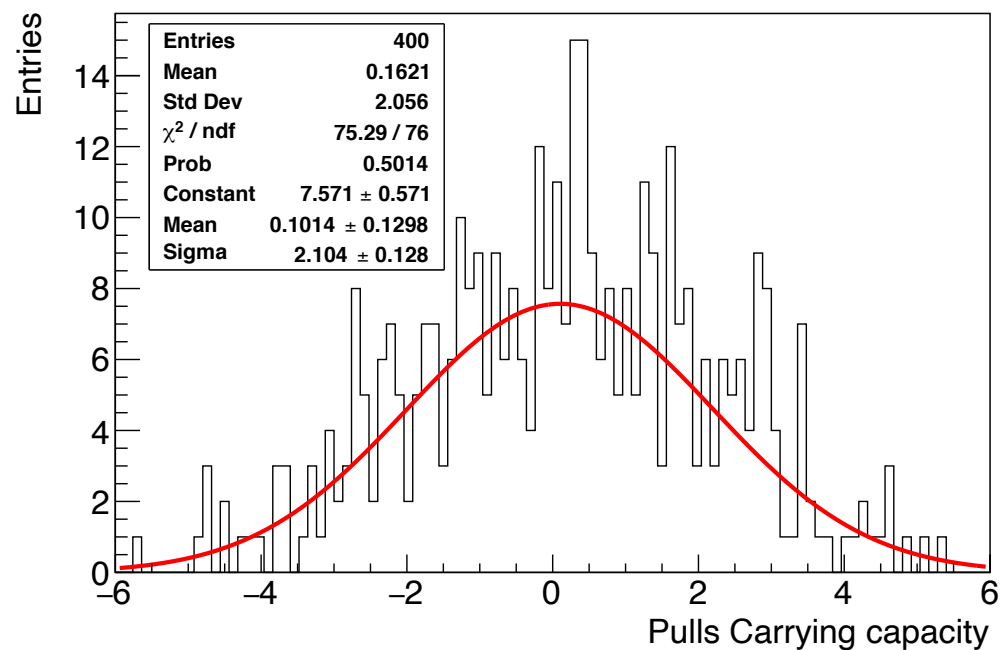
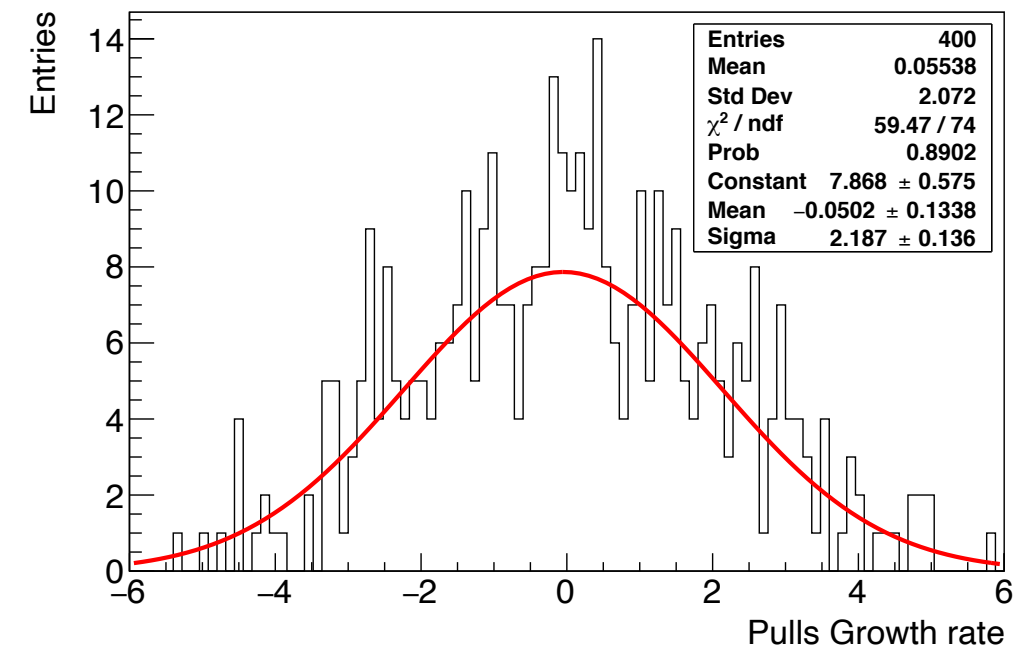
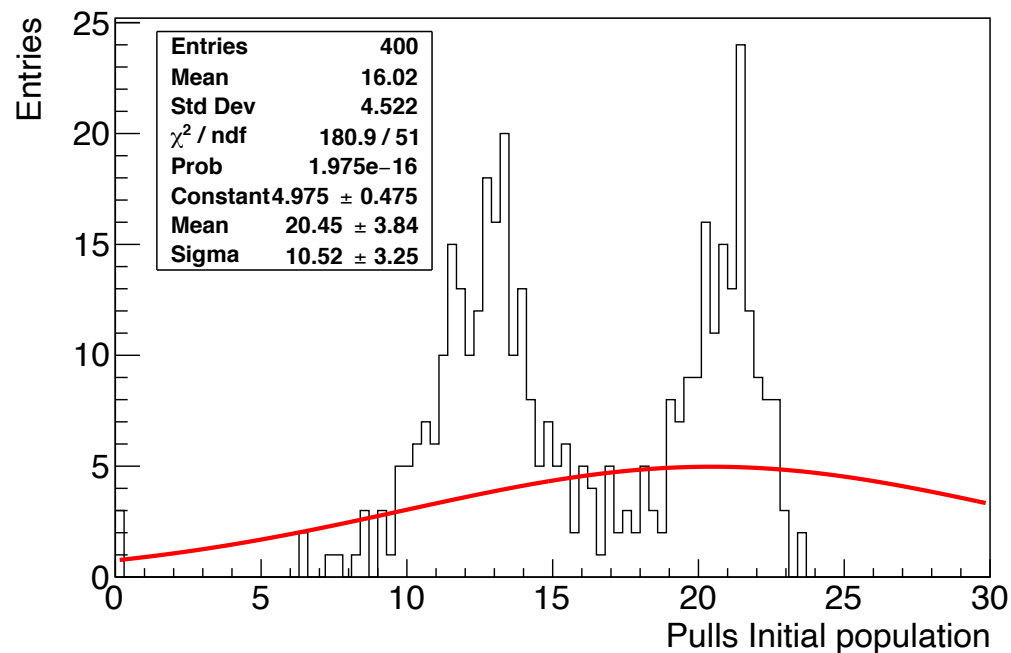
- 400 extractions of  $r$

**Fixed parameters:**

- $p = 0.26$
- Symptomatic fraction =  $0.3 \rightarrow$  literature
- $T = 60 \times 10^6 \rightarrow$  demography



Generated 400 pseudo experiments of period 4, and re-fit them in order to check stability of the fit procedure

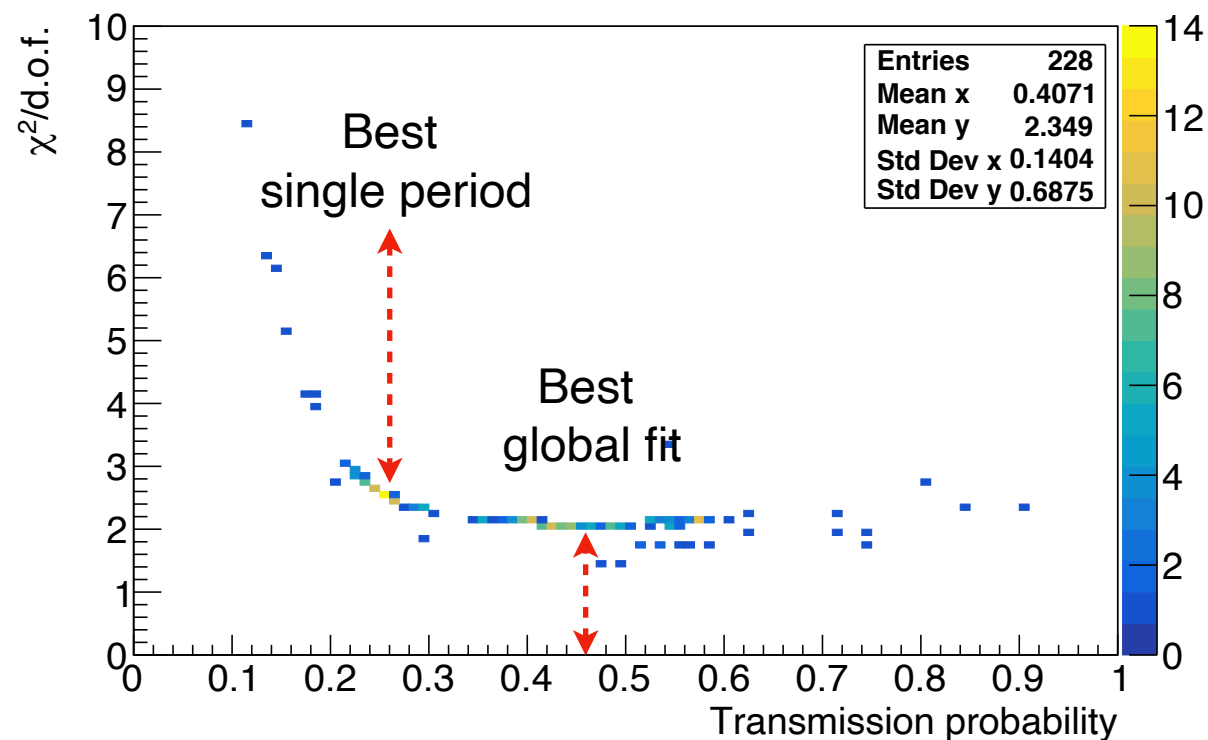


Uncertainties seems to be underestimated by a factor of 2





# Application to data: fit to multiple time-periods



Joint fit periods 1 + 2 + 3 + 4, with smearing

- 1000 extractions of transmission probability,  $p$

**Fixed parameters:**

- $r = 0.023 \rightarrow$  plot  $\Delta\text{recovered}/\text{active}$
- Symptomatic fraction =  $0.3 \rightarrow$  literature
- $T = 60 \times 10^6 \rightarrow$  demography

**Best transmission probability**

- $p \sim 0.46$

