



IMPROVING TESTS SPEED

WRITING A “CURRENT AFFAIRS” SCIENTIFIC PAPER AT SPEED

PERFECT COVID-19

NICK GRAHAM

UNIVERSITY OF LIVERPOOL

SRA STUDENT WEBINAR. 26TH FEBRUARY 2020

ANCIENT HISTORY

31st December 2019 - “Unexplained pneumonia” cases in Wuhan, China reported to WHO

10th January 2020 - Public Health England issues guidance on performing RT-PCR testing for Covid-19

20th January - US CDC created Covid testing kit (these kits were later found to be ineffective)

24th January - *The Lancet* medical journal publishes a paper that “stressed the need for testing for the virus”

ANCIENT HISTORY

5th February - Chinese experts say that PCR testing may have significant number of false negative results

24th February - A patient in Sichuan province tested positive only on her 9th test

14th March - I send an email to colleagues saying “I think we should write a blog post or something about the UK governments response to coronavirus”

16th March - Director of WHO says in a press conference “We have a simple message for all countries: test, test, test.”

ANCIENT HISTORY

20th March - Donald Trump says that Covid antibody tests will be a “game changer”

23rd March - UK enters national lockdown

25th March - Hold meeting with Risk Institute colleagues in which we discuss doing some research about Risk and Covid

- *Numberphile* YouTube channel releases a video called “The Coronavirus Curve” which explains SIR models

ANCIENT HISTORY

Before 31st March - “How does testing impact the spread of the virus?” *Someone in a meeting*

- Alex Wimbush, Dom Calleja and I (with the help of many others) begin to create an epidemiological model to answer this question

2nd April - Matt Hancock says in a press conference “No test is better than a bad test”

10th April - First draft of paper is written

ANCIENT HISTORY

12th April - Spend 8 hours on a zoom call finalising paper

14th April - Submit paper to The Lancet Journal and upload it

15th April - Paper is rejected by The Lancet

6th May - After a rewrite and reformatting paper is submitted

21st October - Paper published

PLOS ONE

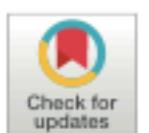
RESEARCH ARTICLE

Is “no test is better than a bad test”? Impact of diagnostic uncertainty in mass testing on the spread of COVID-19

Nicholas Gray^{1*}, Dominic Calleja^{1*}, Alexander Wimhurst¹, Enrique Miralles-Dolz¹, Ander Gray¹, Marco De Angelis¹, Elfridae Derrer-Merk¹, Bright Uchenna Oparaji¹, Vladimir Stepanov¹, Louis Clearkin¹, Scott Ferson¹

¹ Institute for Risk and Uncertainty, University of Liverpool, Liverpool, United Kingdom, ² Wirral & Liverpool University Teaching Hospitals, Birkenhead, United Kingdom

* These authors contributed equally to this work.
* nickgray@liverpool.ac.uk, COVID19@riskinstitute.uk



Abstract

Testing is viewed as a critical aspect of any strategy to tackle epidemics. Much of the dialogue around testing has concentrated on how countries can scale up capacity, but the uncertainty in testing has not received nearly as much attention beyond asking if a test is accurate enough to be used. Even for highly accurate tests, false positives and false negatives will accumulate as mass testing strategies are employed under pressure, and these misdiagnoses could have major implications on the ability of governments to suppress the virus. The present analysis uses a modified SIR model to understand the implication and magnitude of misdiagnosis in the context of ending lockdown measures. The results indicate that increased testing capacity alone will not provide a solution to lockdown measures. The progression of the epidemic and peak infections is shown to depend heavily on test characteristics, test targeting, and prevalence of the infection. Antibody based immunity passports are rejected as a solution to ending lockdown, as they can put the population at risk if poorly targeted. Similarly, mass screening for active viral infection may only be beneficial if it can be sufficiently well targeted, otherwise reliance on this approach for protection of the population can again put them at risk. A well targeted active viral test combined with a slow release rate is a viable strategy for continuous suppression of the virus.

OPEN ACCESS

Citation: Gray N, Calleja D, Wimhurst A, Miralles-Dolz E, Gray A, De Angelis M, et al. (2020) Is “no test is better than a bad test”? Impact of diagnostic uncertainty in mass testing on the spread of COVID-19. PLoS ONE 15(10): e0240775. <https://doi.org/10.1371/journal.pone.0240775>

Editor: Jishnu Das, University of Pittsburgh, UNITED STATES

Received: May 6, 2020

Accepted: October 4, 2020

Published: October 21, 2020

Peer Review History: PLOS recognizes the benefits of transparency in the peer review process; therefore, we enable the publication of all of the content of peer review and author responses alongside final, published articles. The editorial history of this article is available here: <https://doi.org/10.1371/journal.pone.0240775>

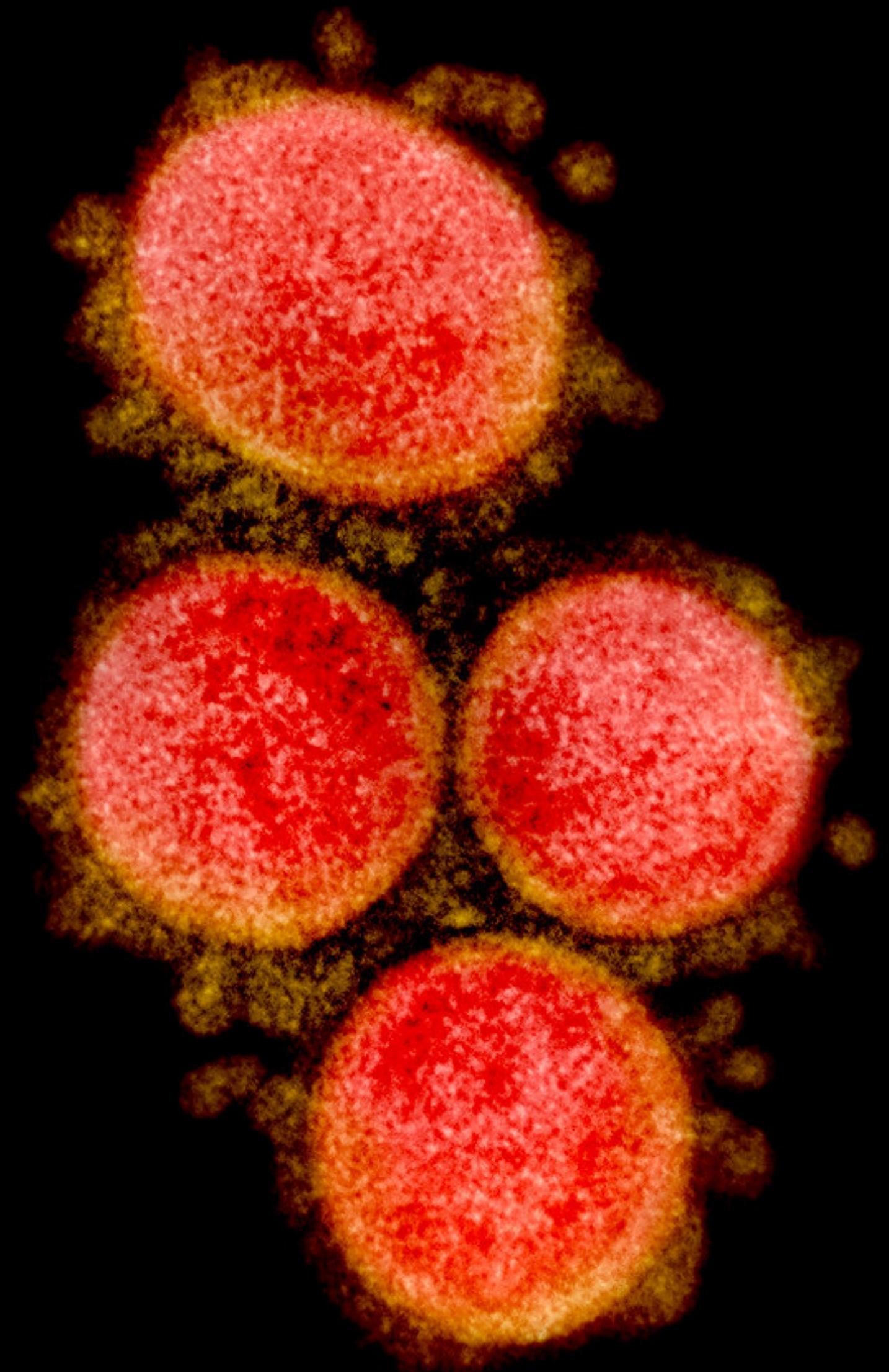
Copyright: This is an open access article, free of all copyright, and may be freely reproduced, distributed, transmitted, modified, built upon, or otherwise used by anyone for any lawful purpose. The work is made available under the Creative Commons CC0 public domain dedication.

Data Availability Statement: <https://github.com/Institute-for-Risk-and-Uncertainty/SIRQ-imperfect-testing>.

Introduction

During the early stages of the United Kingdom's SARS-CoV-2 epidemic, the British government's COVID-19 epidemic management strategy was influenced by epidemiological modelling conducted by a number of research groups [1, 2]. The analysis of the relative impact of different mitigation and suppression strategies concluded that the “only viable strategy at the current time” is to suppress the epidemic with all available measures, including the lockdown of the population with schools closed [3, 4]. Similar analysis in other countries lead to over half the world population being in some form of lockdown by April 2020 and over 90% of

EPIDEMIOLOGICAL MODELS



SIR MODELS

SIR MODELS

UNCERTAINTY IN TESTING



TESTING FOR COVID

3 DIFFERENT TESTS

RT-PCR

- Detects genetic material of the virus
- In theory can detect one virion in a sample

“Have you got it”

Active infection test

Lateral Flow

- Detects whether the virus is on a swab.
- Gives results in as little as 15 minutes

Antibody

- Detects whether a person has antibodies for the virus
- Can be used in order to see whether someone has immunity

“Have you had it?”

Past infection test

**ALL TESTS ARE
IMPERFECT**

BUT SOME ARE MORE IMPERFECT THAN OTHERS

IMPERFECT TESTING FOR COVID

Active infection tests

NO TEST IS ABLE TO DETECT WHETHER SOMEONE CURRENTLY HAS COVID-19 OR IF THEY ARE INFECTIOUS

Tests only detect whether there is virus present on the swap.

PCR is much more sensitive than Lateral Flow tests.

“False” Positives can occur if people have been infected in the past

False positives can occur if samples are cross-contaminated

False negatives can occur if test is incorrectly performed

Tests may give a positive result when they detected RNA from other coronaviruses

TESTING STATISTICS

4 KEY STATISTICS

Sensitivity - proportion of diseased people who are given a positive results

Specificity - proportion of well people who are given a negative result

Positive Predictive Value - How likely one is to have the disease given a positive result

Negative Predictive Value - How likely one is to not have the disease given a negative result

$$s = \frac{TP}{TP + FN} \quad t = \frac{TN}{TN + FP} \quad PPV = \frac{ps}{ps + (1-p)(1-s)} \quad NPV = \frac{t(1-p)}{t(1-p) + p(1-s)}$$

PREVALENCE MATTERS

IF 50% PREVALENCE, WITH 90% SENSITIVITY AND 90% SPECIFICITY

1000 people

500 sick people

500 well people

450 Test Positive

50 Test Negative

450 Test Negative

50 Test Positive

PPV = 90%, NPV = 90%

PREVALENCE MATTERS

IF 2% PREVALENCE, WITH 90% SENSITIVITY AND 90% SPECIFICITY

1000 people

20 sick people

980 well people

2 Test
Negative

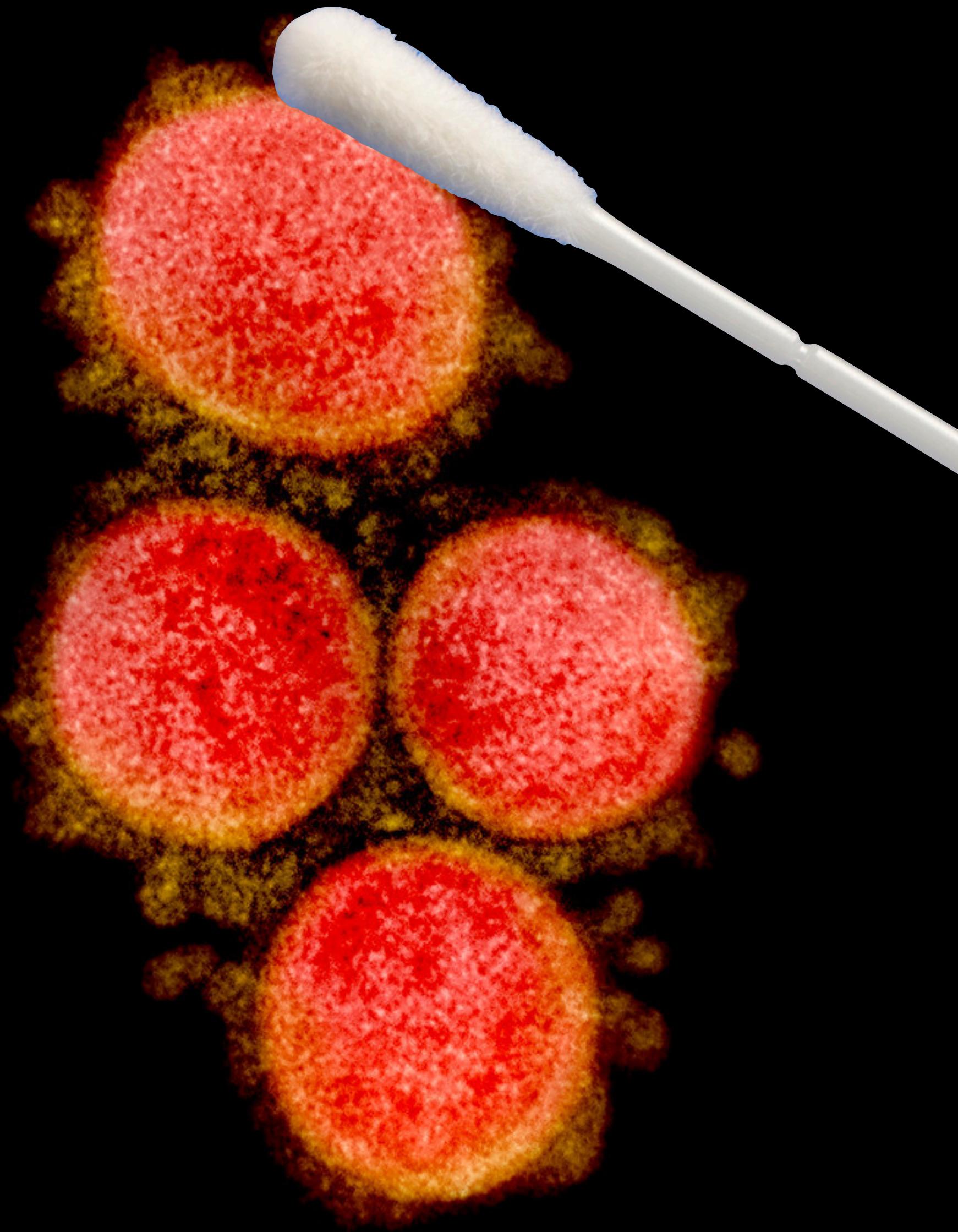
18 Test
Positive

98 Test Positive

882 Test Negative

PPV = 15.5%, NPV > 99%

SIR WITH TESTING



THE SIRQ MODEL

Rates depend on:

Sensitivity, s

Specificity, t

Testing Capacity, C

Test targeting, T

SOME ASSUMPTIONS

Immunity is permanent

Quarantined people do not infect or become infected

THE AIM OF THE MODEL IS TO DEMONSTRATE WHAT EFFECT IMPERFECT TESTING CAN HAVE ON THE SPREAD OF DISEASE.

IT IS TOO SIMPLE TO USED FOR PREDICTIVE REASONS

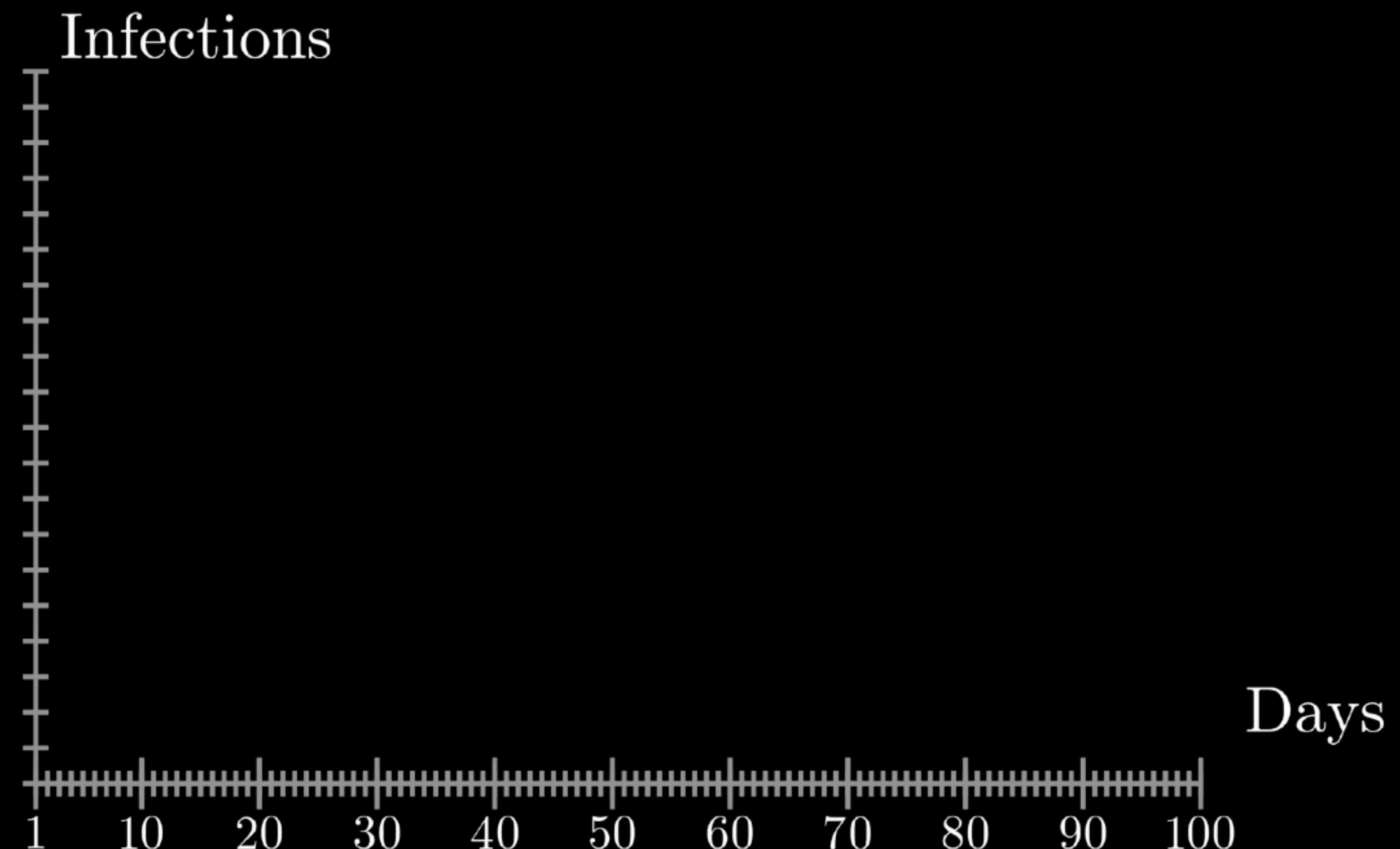
THE SIRQ MODEL

Start with most of the population in quarantine

Release everyone on day 1.

Try to control the virus using by detecting and isolating cases

Vary test sensitivity



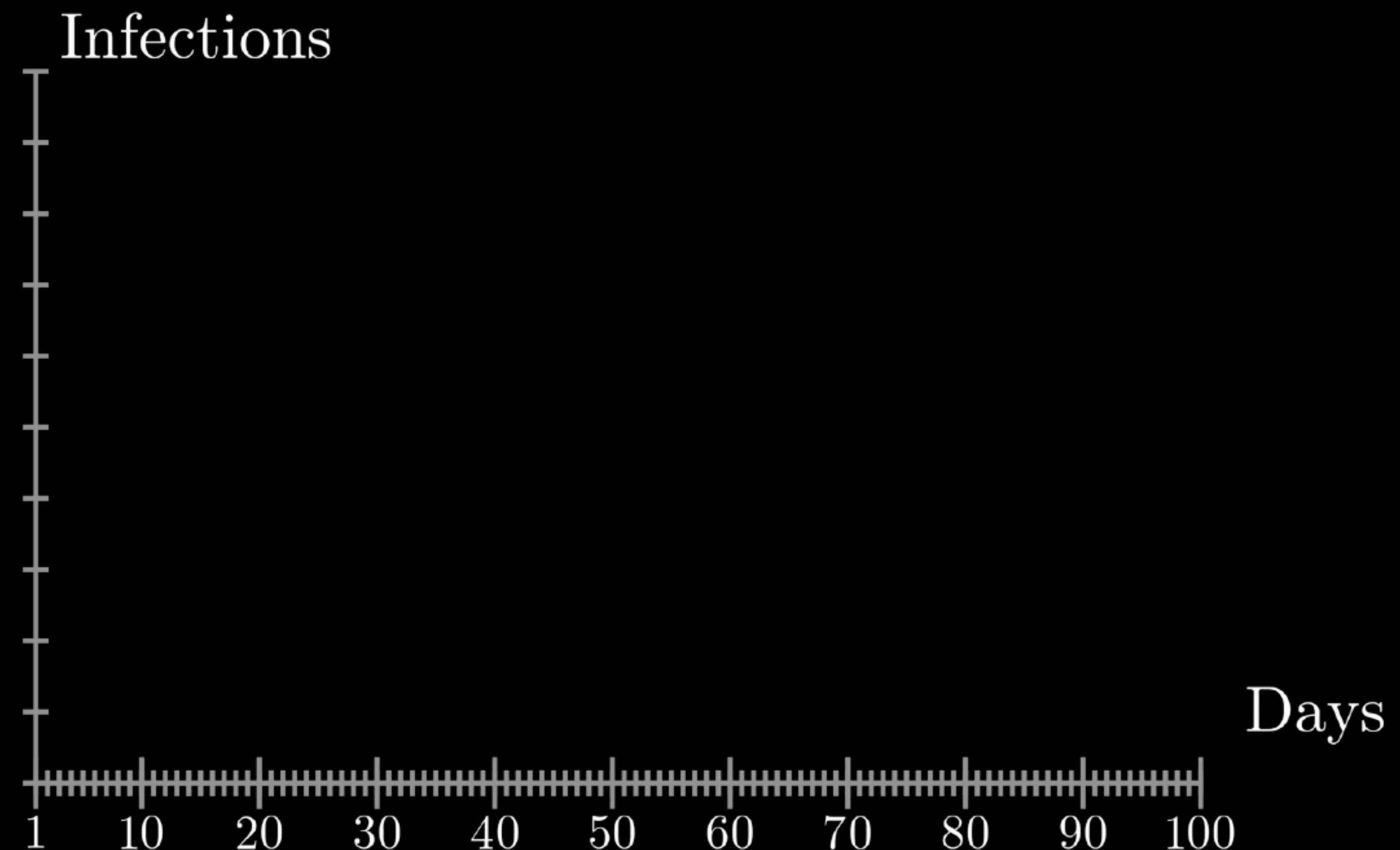
THE SIRQ MODEL

Start with most of the population in quarantine

Release everyone on day 1.

Try to control the virus using by detecting and isolating cases

Vary test targeting



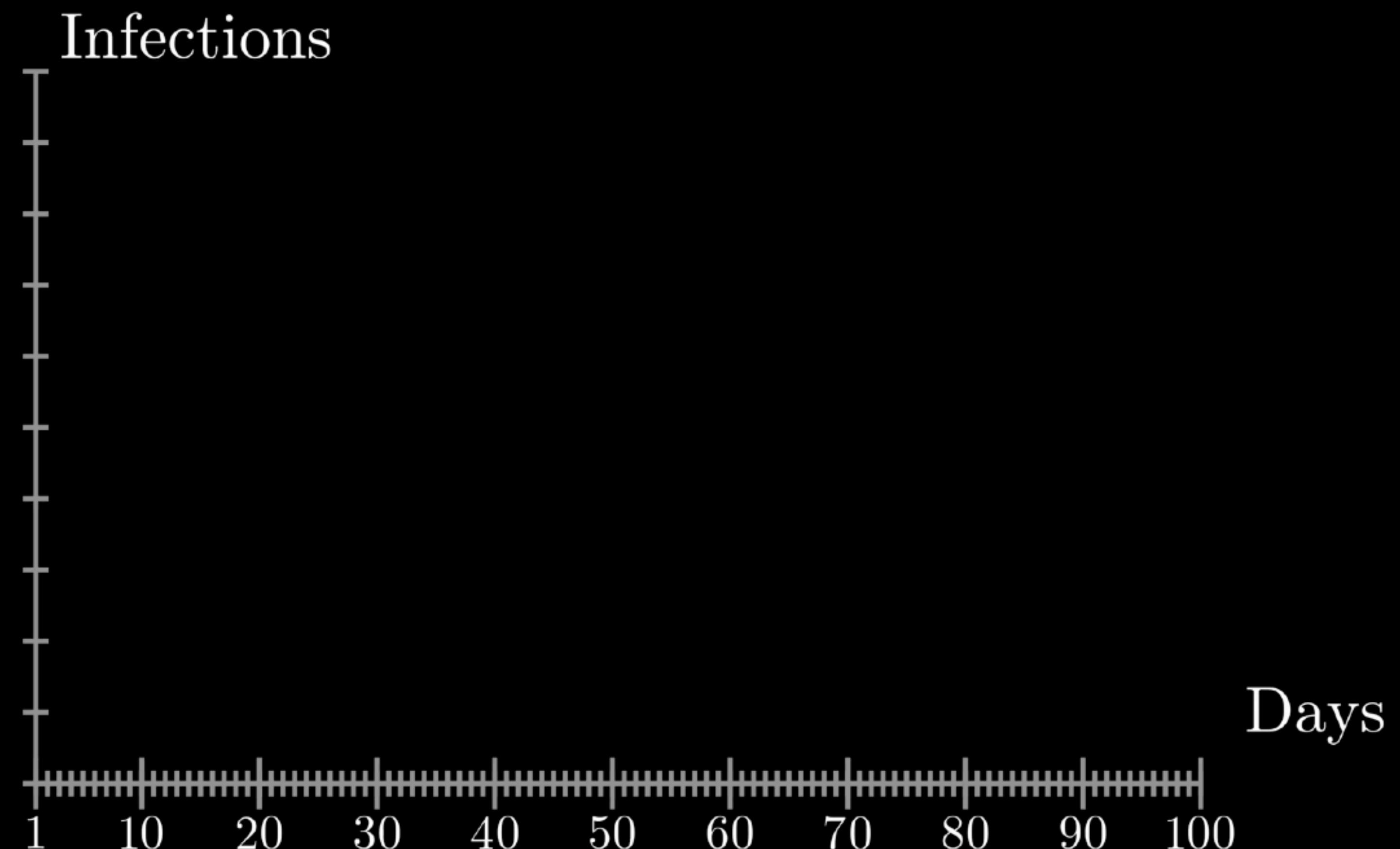
THE SIRQ MODEL

Start with most of the population in quarantine

Release everyone on day 1.

Try to control the virus using by detecting and isolating cases

Vary test capacity

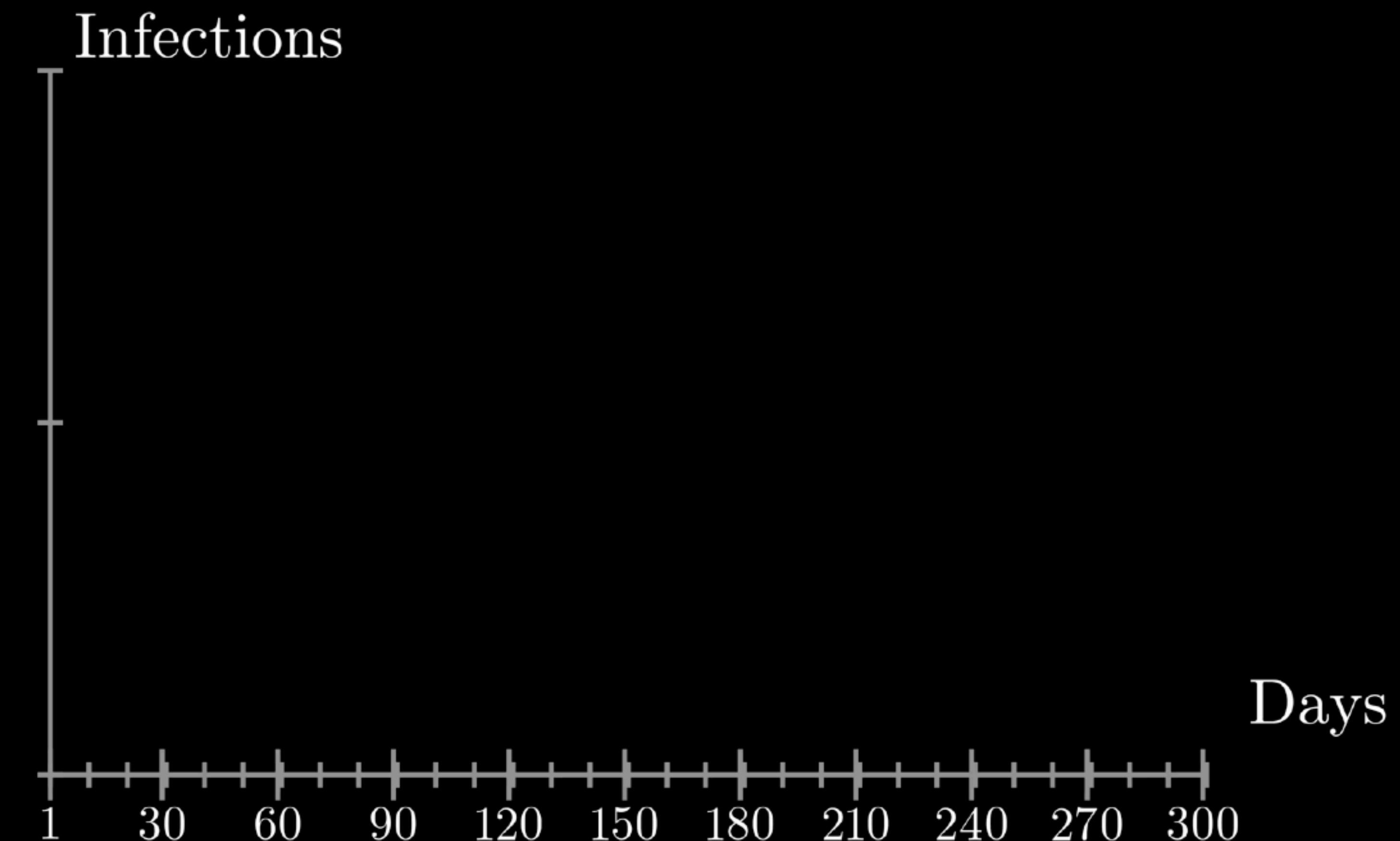


THE SIRQ MODEL

Start with most of the population in quarantine

Release people with positive antibody test

Vary prevalence of antibodies



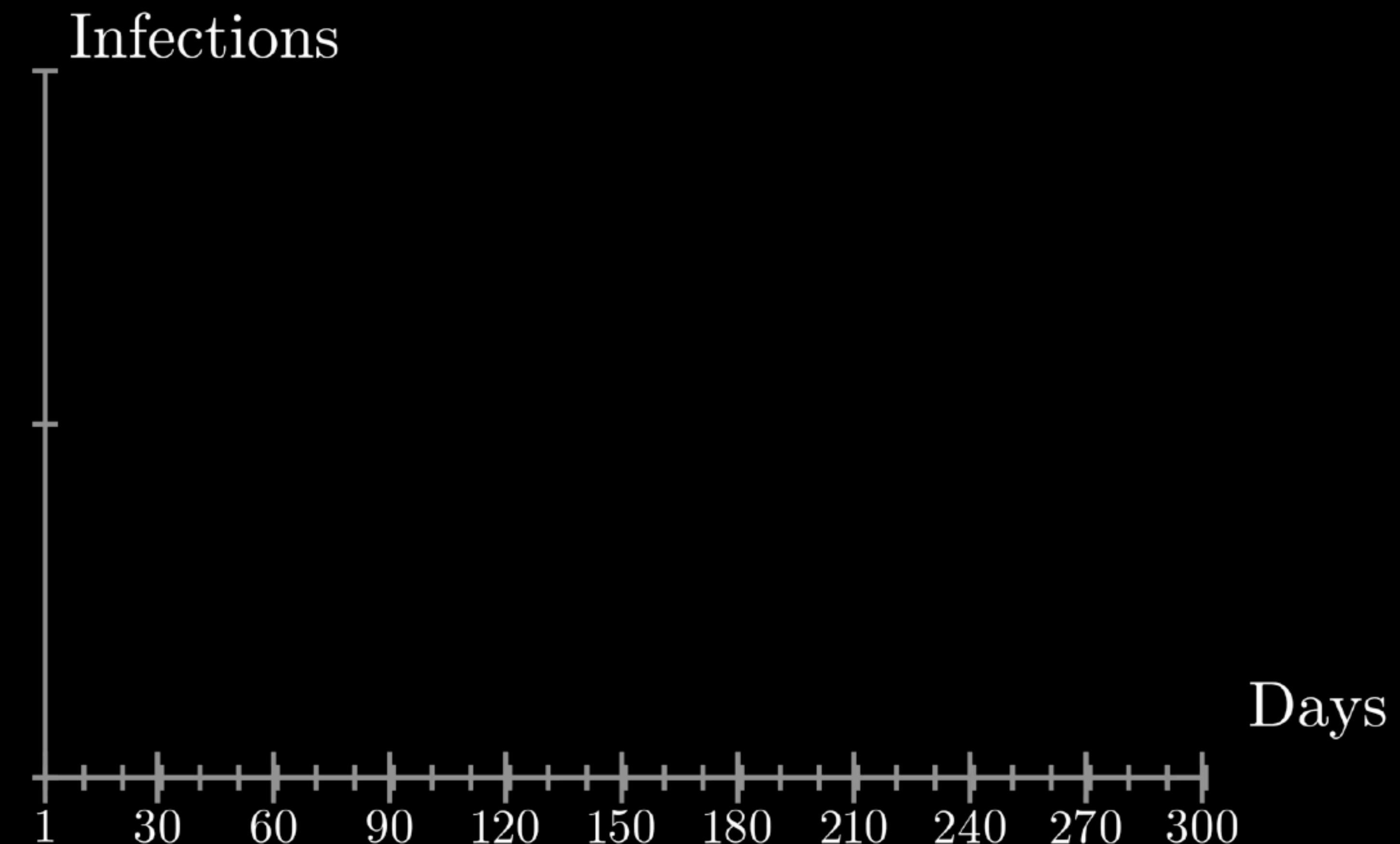
THE SIRQ MODEL

Start with most of the population in quarantine

Slowly relax restrictions

Try to control the virus using by detecting and isolating cases

Vary test targeting



CONCLUSIONS

Diagnostic uncertainty can have a large effect on the dynamics of an epidemic.

Therefore policy makers need to be aware the sensitivity and specificity of tests

Mass testing should be targeted to individuals who are likely to have the virus

Antibody testing doesn't work unless large numbers of people have already had the virus

If restrictions are relaxed slowly then high accuracy, targeted tests can help.

TESTING ALONE IS NOT A VIABLE STRATEGY TO PREVENT THE VIRUS SPREADING

WRITING A PAPER AT SPEED

We wanted to make a media splash and didn't

We didn't write the paper we should have written

Paper is too narrowly focused on the specifics of the UK in early April 2020

We were conscious of the fact that we aren't epidemiologists and kept the paper within the scope of our expertise

We weren't wrong

UGH, EVERYONE'S AN EPIDEMIOLOGIST.
IT'S LIKE WHEN THERE'S A MOUNTAINEERING DISASTER IN THE NEWS, AND SUDDENLY EVERYONE IS AN EXPERT ON MOUNTAIN CLIMBING SAFETY.



ANY QUESTIONS?

NICKGRAY@LIVERPOOL.AC.UK



Full Paper