Health Technology II
Measures against large-scale epidemics：

(4th of 4 lectures)
"Future steps"

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Goal of the class

To <u>discuss</u> the options of policies and health (and information) technologies needed to tackle the ongoing COVID-19

→ Please prepare to (be forced to) discuss whether you agree/disagree with each option with your own reasoning

Road Map

I) Review of past classes w/ some updates

II) How to detect silent spreaders?

III) General goals of the COVID-19 measures
- Proposals from Japan's leading economists
  from The Tokyo Foundation for Policy Research

IV) "Testing for COVID19: A way to lift confinement restrictions" proposed by OECD

(2nd of 4 lectures)
Individual behavior changes that affect epidemic levels
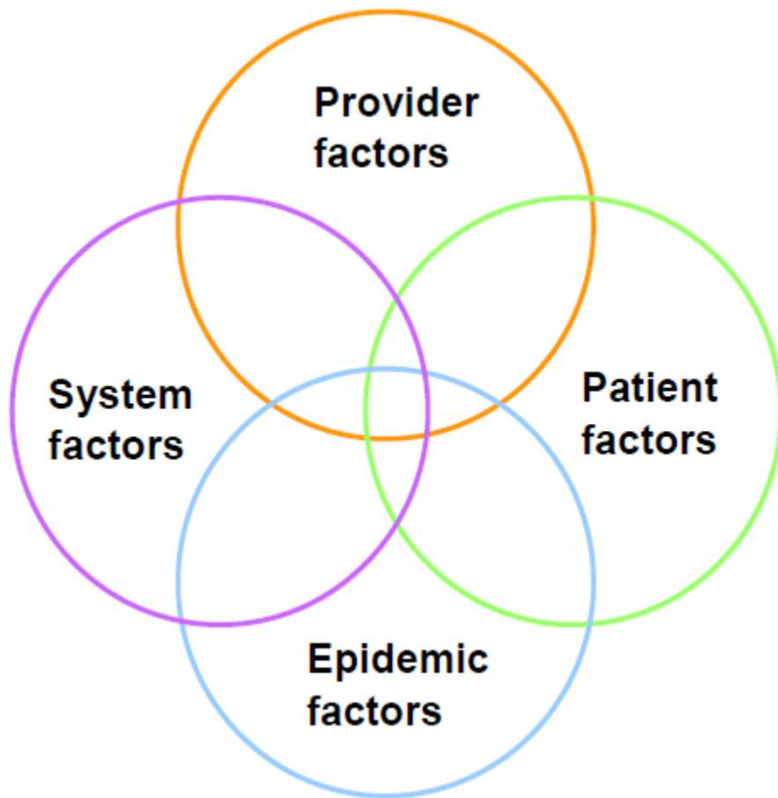
Class 2 Take-home messages

- Behavior change
  - Why Difficult? (Sensible reason?)
  - How to quantify?
  - Big or small? Compared to what?
    - Big enough to pandemic impacts?
    - (Hard to measure, Class 1)

- Theory is important
  - To read a paper
  - To analyze issues
  - To write your original paper

Why Theory is Important?

	Disciplines	Goal
Theory	Economics, Sociology, Political Science, Psychology, Pathology	Generate hypothesis (causality underlying phenomenon)
Method	Econometrics, Statistics, Epidemiology, CEA/CBA, Risk adjustment	Test hypothesis (i.e., theory) - empirically analyzing "real-world" data, e.x. dY/dX=(+)
Topic	Obesity, mental health, long term care, patient/provider/ organization behavior	Interpretation for policy implication

Discussion
A) How to replicate Yoo's influenza studies
for the ongoing COVID-19?

Provider
factors

System
factors

Patient
factors

Epidemic
factors

- Which factor(s)?
- What hypothesis?
- Which theory used to justify your hypo.?
- Which data sets?
- How will the hypothesized results change the related policy?

(3rd of 4 lectures)
Health disparity

Class 3: Take home messages

- Systematic analyses of health disparity
    - 1/2/3 prevention
    - Donabedian's model for quality care
- "Paradox in disparity"

    Disparity could be worsened by
    - Technological advancement
    - New information on disease/prevention/treatment
    - Insurance (and other?)

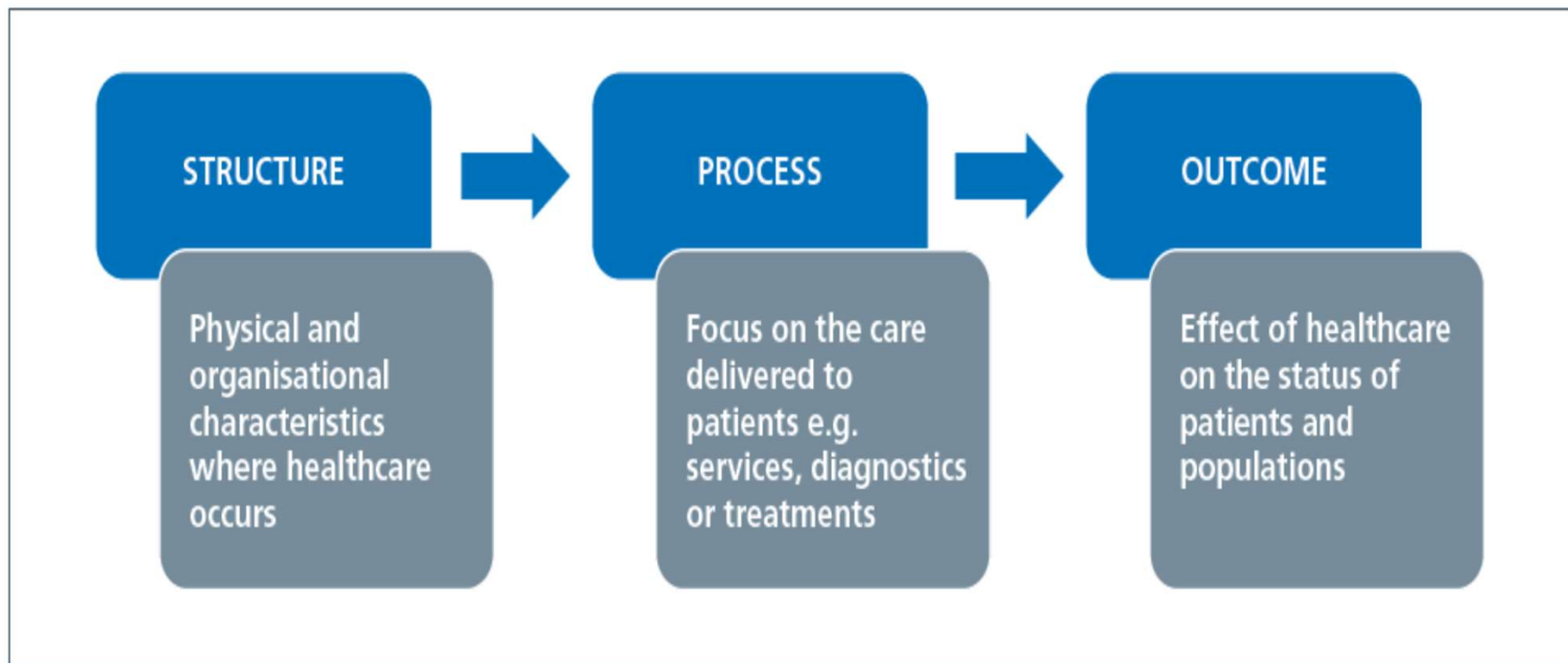   → Because highest SES can gain the full benefits

    → For lower SES, a sensible choice is to miss/delay COVID-19 tests in order to avoid loss of $/job/friends/housing

    → How to mitigate/prevent the potential exacerbation of disparity?

Donabedian's model for measuring quality care (Donabedian 2005)

Table source: UK NHS: https://improvement.nhs.uk/documents/2135/measuring-quality-care-model.pdf

Figure 1: The Donabedian model for quality of care

STRUCTURE → **PROCESS** → **OUTCOME**

- STRUCTURE: Physical and organisational characteristics where healthcare occurs
- PROCESS: Focus on the care delivered to patients e.g. services, diagnostics or treatments
- OUTCOME: Effect of healthcare on the status of patients and populations

(1st of 4 lectures)
Mathematical modeling of pandemics

Goals of Mathematical Modeling 1 of 2

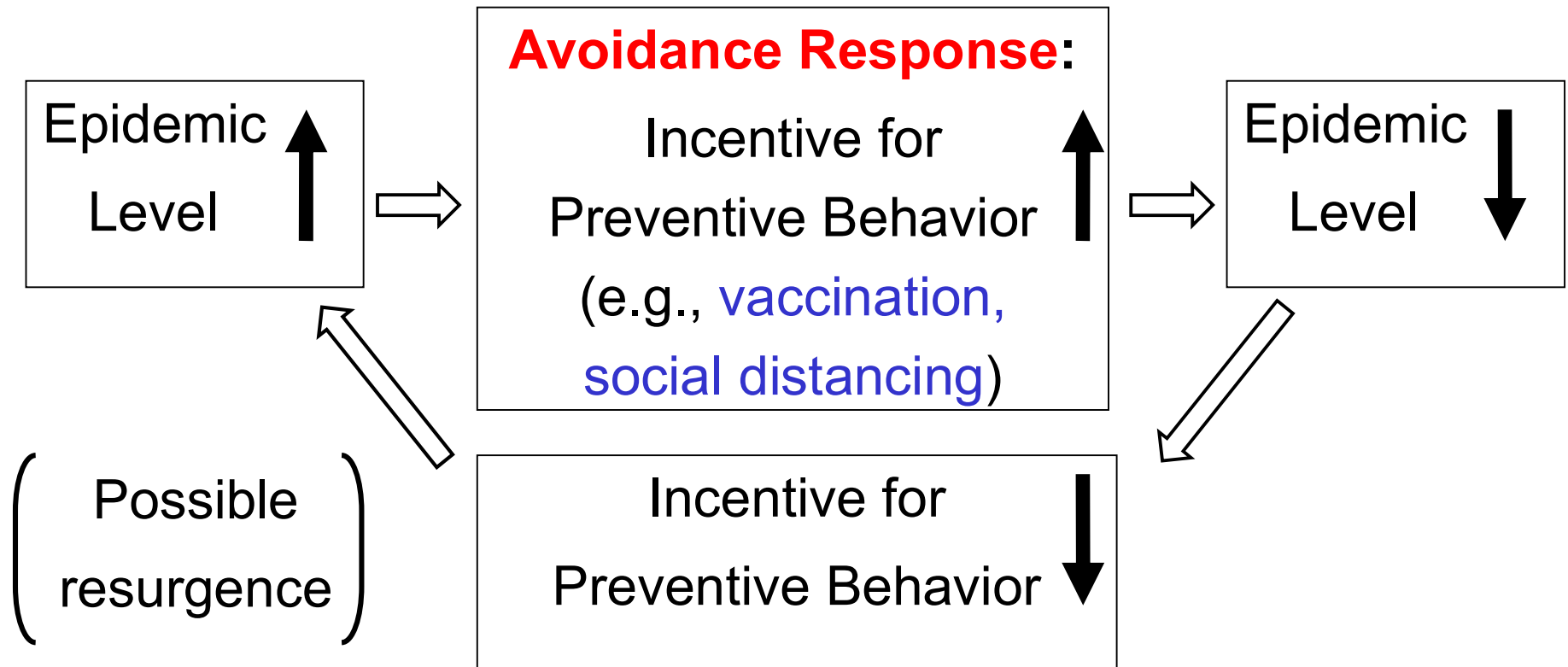|	Epidemic path/impacts	Specific measures
Evaluation	Past/Current Severity Ex. Reproduction number/rate	• Vaccination • Social distancing (Quarantine facilities; lock-down office, school, etc.) • Treatments (?) • Other measures (?) • (NOTE) In general, very difficult to evaluate specific measure's effectiveness.
Prediction	Future Severity [absolute # of cases, % population] and Timing/Period [when] Ex. Infected, Clinic visits, Hospitalized, ICU use, Death -> Will help prepare resources	

Very difficult to evaluate specific measure's effectiveness even w/ math modeling/econometrics

You must be careful to accept the policy with uncertain effectiveness with known high-risks

- Does cell-phone works for COVID-19?
    - Ogasawara, PhD (Sociology)
    - https://globe.asahi.com/article/13331044
    - Eda, PhD (Economics)
    - https://ascii.jp/elem/000/004/016/4016494/

- Detailed measures RE lock-down

Mutual (cyclic) Interaction between Epidemic Level and Incentive for Preventive Behavior
(Philipson 1996)

Epidemic Level ⬆ ⇨ **Avoidance Response**: Incentive for Preventive Behavior (e.g., vaccination, social distancing) ⬆ ⇨ Epidemic Level ⬇
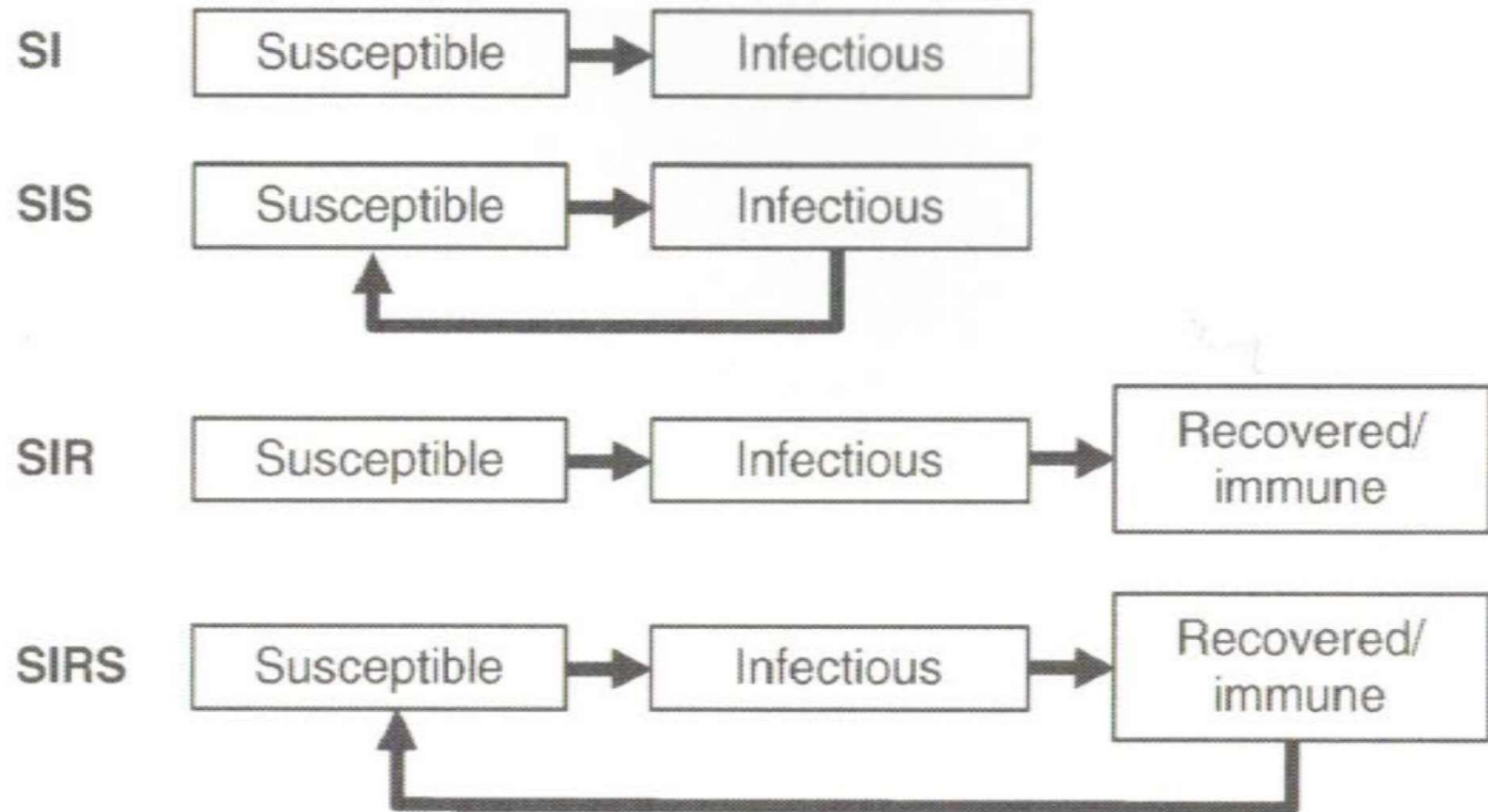
(Possible resurgence) ⬆ Incentive for Preventive Behavior ⬇

Test Validity of Avoidance Response Model:
novel H1N1 influenza epidemic path in the U.S.
from April 23 to August 31, 2009 (day 86)
[Cumulative laboratory confirmed cases]

15
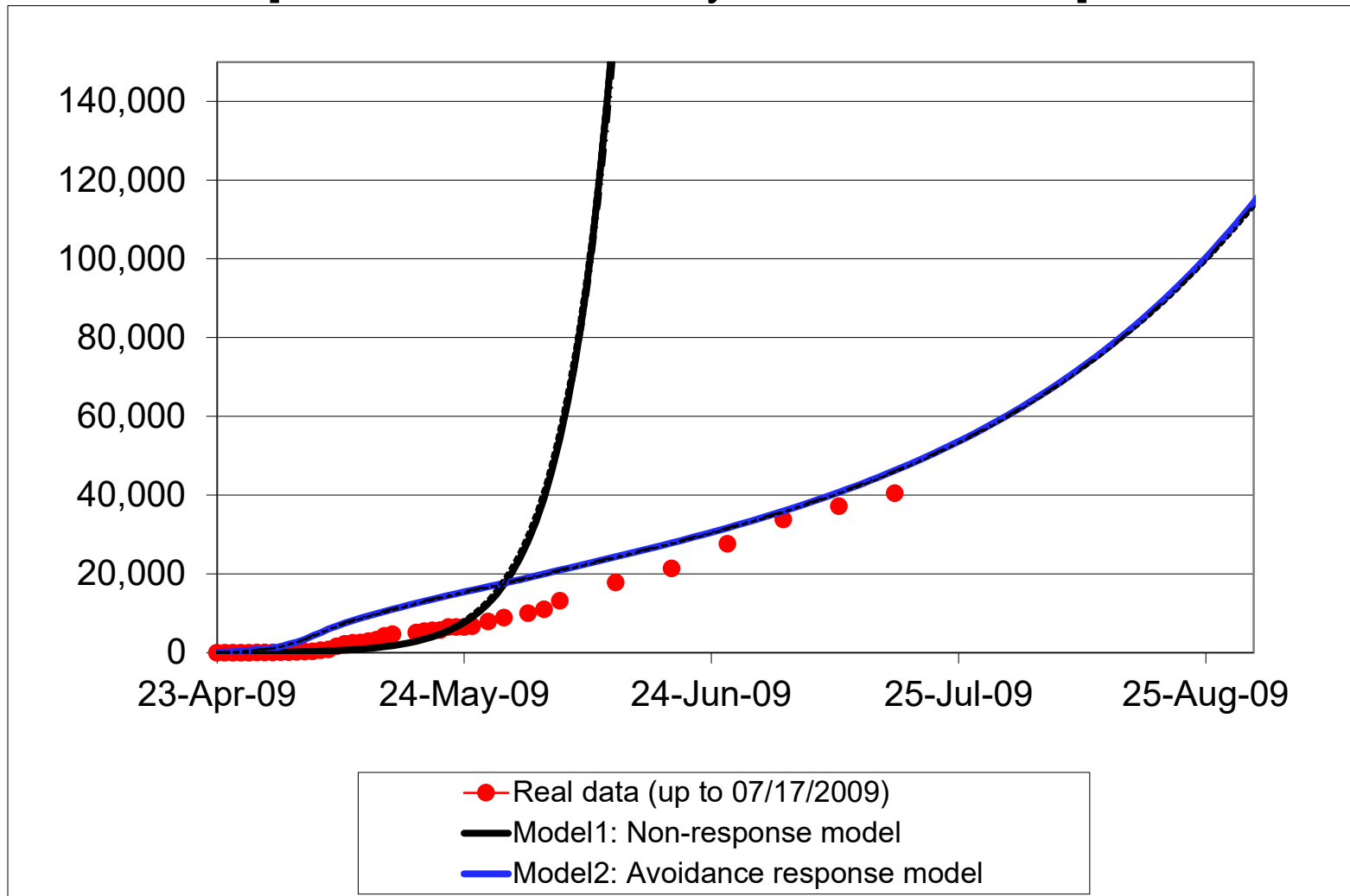
Common structures for models used to describe the transmission of infections. (source: Vyunncyky 2020, p.16) (same as slide #27)

Discussion Points
(Note: (?) indicates limited evidence as of today)

A) How applicable is the basic SIR model for the COVID19?

- Poor antibody response (?, how much % of infected?)
  - → Multiple infections (SIR or SIRS models with new (IR)s)
  - → Due to the rapid antigen change
  - → Potential risk of vaccination (Antibody Dependent Enhancement(ADE))

  (Ref: Kodama et al., 2020,
  https://www.youtube.com/watch?v=y6W83Y85zJs)

  - → "Better not to be vaccined" if ADE occurs
  - → Herd Immunity more difficult, i.e., longer time to reach herd immunity ?

- Infection w/out symptoms
- → Spread speed↑, Hard to trace infected
- → II. How to find How to detect silent spreaders?
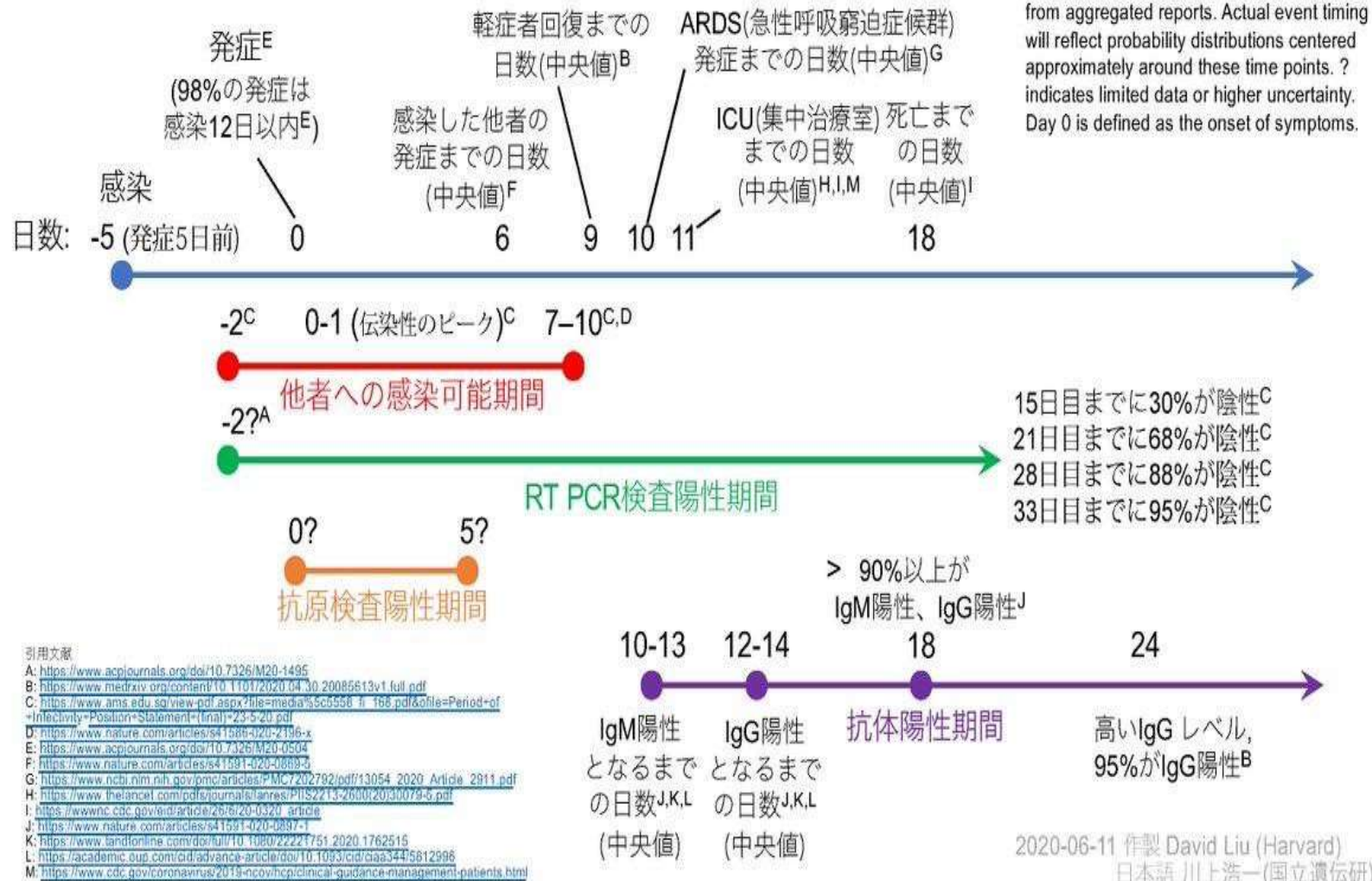
Road Map

I) Review of past classes w/ some updates

II) How to detect silent spreaders?
- Who are silent spreaders?
- How many?
- What conditions are needed for screenings?

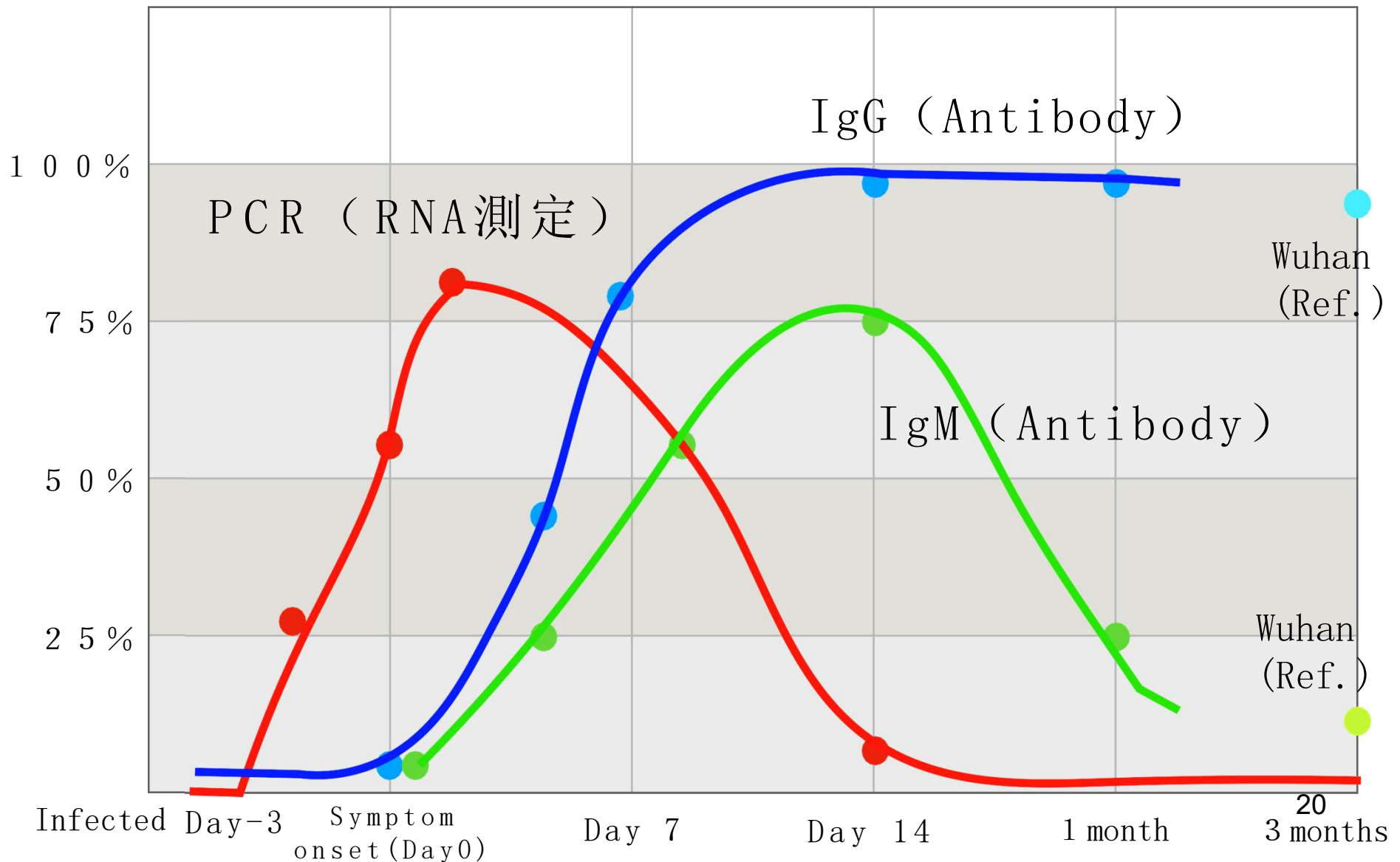III) General goals of the COVID-19 measures

IV) "Testing for COVID19: A way to lift confinement restrictions" proposed by OECD

COVID-19 症状の時間経過

Time points represent typical cases drawn from aggregated reports. Actual event timing will reflect probability distributions centered approximately around these time points. ? indicates limited data or higher uncertainty. Day 0 is defined as the onset of symptoms.

発症[E]
(98%の発症は感染12日以内[E])

軽症者回復までの日数(中央値)[B]

ARDS(急性呼吸窮迫症候群)発症までの日数(中央値)[G]

感染した他者の発症までの日数(中央値)[F]

ICU(集中治療室)までの日数(中央値)[H,I,M]

死亡までの日数(中央値)[I]

感染

日数: -5 (発症5日前)　0　6　9　10　11　18

-2[C]　0-1 (伝染性のピーク)[C]　7–10[C,D]

他者への感染可能期間

-2?[A]

RT PCR検査陽性期間

15日目までに30%が陰性[C]
21日目までに68%が陰性[C]
28日目までに88%が陰性[C]
33日目までに95%が陰性[C]

0?　5?

抗原検査陽性期間

> 90%以上が IgM陽性、IgG陽性[J]

10-13　12-14　18　24

IgM陽性となるまでの日数[J,K,L] (中央値)

IgG陽性となるまでの日数[J,K,L] (中央値)

抗体陽性期間

高いIgG レベル, 95%がIgG陽性[B]

引用文献
A: https://www.acpjournals.org/doi/10.7326/M20-1495
B: https://www.medrxiv.org/content/10.1101/2020.04.30.20085613v1.full.pdf
C: https://www.ams.edu.sg/view-pdf.aspx?file=media%5c5558_fi_168.pdf&ofile=Period+of+Infectivity+Position+Statement+(final)+23-5-20.pdf
D: https://www.nature.com/articles/s41586-020-2196-x
E: https://www.acpjournals.org/doi/10.7326/M20-0504
F: https://www.nature.com/articles/s41591-020-0869-5
G: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7202782/pdf/13054_2020_Article_2911.pdf
H: https://www.thelancet.com/pdfs/journals/lanres/PIIS2213-2600(20)30079-5.pdf
I: https://wwwnc.cdc.gov/eid/article/26/6/20-0320_article
J: https://www.nature.com/articles/s41591-020-0897-1
K: https://www.tandfonline.com/doi/full/10.1080/22221751.2020.1762515
L: https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa344/5812996
M: https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html

2020-06-11 作製 David Liu (Harvard)
日本語 川上浩一(国立遺伝研)

Time trend of COVID-19 tests by Kodama et al.

新型コロナウィルス抗体協議会（発症日は自主申告）現在検討中の経過中、PCR陽性、IgG,IgM陰性の特異１例を含まない (https://www.ric.u-tokyo.ac.jp/topics/2020/ig-20200611.pdf)

How many silent spreaders?

More basic question

- How many were infected so far?
  - Antibody tests are far more accurate than PCR(antigen) tests
  - MHLW conducted large antibody tests in June in 3 metropolitan areas
    - Positive defined by 2 different tests (+)
    - → Is the next slide method correct?

抗体保有調査結果

概要

■ 6月1日～7日にかけて、東京都・大阪府・宮城県において、各都府県により無作為抽出し、本調査への参加に同意をいただいた一般住民の方（東京都1,971名、大阪府2,970名、宮城県3,009名、計7,950名）を対象に抗体検査を実施しました。
■ 本調査では、陽性の判定をより正確に行うため、２種の検査試薬の両方で陽性が確認されたものを「陽性」としています。

測定結果

東京都

	アボット（+）	アボット（-）	計	モコバイオ（参考値）	累積感染者数（感染率）5/31時点
ロシュ（+）	2 (0.10%)	4 (0.20%)	6 (0.30%)		
ロシュ（-）	2 (0.10%)	1,963 (99.59%)	1,965 (99.70%)	21 (1.07%)	5,236人 (0.038%)
計	4 (0.20%)	1,967 (99.80%)	1,971		

大阪府

	アボット（+）	アボット（-）	計	モコバイオ（参考値）	累積感染者数（感染率）5/31時点
ロシュ（+）	5 (0.17%)	5 (0.17%)	10 (0.34%)		
ロシュ（-）	11 (0.37%)	2949 (99.29%)	2960 (99.66%)	37 (1.25%)	1,783人 (0.02%)
計	16 (0.54%)	2954 (99.46%)	2,970		

宮城県

	アボット（+）	アボット（-）	計	モコバイオ（参考値）	累積感染者数（感染率）5/31時点
ロシュ（+）	1 (0.03%)	6 (0.20%)	7 (0.23%)		
ロシュ（-）	2 (0.07%)	3000 (99.7%)	3002 (99.77%)	36 (1.20%)	88人 (0.004%)
計	3 (0.10%)	3006 (99.9%)	3,009		

■ 各自治体の抗体保有率は、**東京都0.10%、大阪府0.17%、宮城県は0.03%**でした。
■ 各自治体の抗体保有者は、累積感染者数と比較すると多いものの、依然として**大半の人が抗体を保有していない**という結果でした。
■ 本事業は国全体として過去に新型コロナウイルスに感染した人の割合を推定するものであり、**個別に現在の感染を診断するための調査ではありません。**
■ 現時点でこれらの**抗体の性質（体内での持続期間や、2回目の感染から守る機能があるかどうか）は確定していません。**

Road Map

I)   Review of past classes w/ some updates

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- Who are silent spreaders?

- How many?

- What conditions are needed for screenings?
    - Criteria
    - Specific examples for criteria

III) General goals of the COVID-19 measures

IV) "Testing for COVID19: A way to lift confinement restrictions" proposed by OECD

What conditions are needed for screenings?

Criteria: Numerical thresholds should be clarified

- Sensitivity
- Specificity
- Predicted prevalence of spreaders among a target population
- Cost of a screening per person
- Social cost after test (+) affects "sensible choice"
  - Medical treatment
  - Loss of income/job/housing
  - Cost to clean & shut/down office etc.

→ Who showed them so far as criteria?

→ Large/small -- *compared to what*??

COVID-19 mortality rates per million (far right column) are much lower in East Asia as of May 15,2020
(Source: Kodama et al, Accessed on June 8, 2020
https://www.youtube.com/watch?v=8crwEQN_DbA)

	感染者	昨日の感染者	死亡者	昨日の死亡者	人口百万人当り死亡者
USA	1,430,348	+21,712	85,197	+1,772	257
Spain	271,095	+1,575	27,104	+184	580
Russia	242,271	+10,028	2,212	+96	15
UK	229,705	+3,242	33,186	+494	489

China	82,926	+7	4,633		3
Japan	16,049	+81	678	+21	5
S. Korea	10,962	+26	259	+1	5
Taiwan	440		7		0.3

COVID-19 mortality per million population in 4 East Asian Countries
(from 2020/01/19 – 2020/06/07): Japan (blue curve)

https://web.sapmed.ac.jp/canmol/coronavirus/death.html?kw=China%2CJapan%2CSouth%20Korea%2CTaiwan
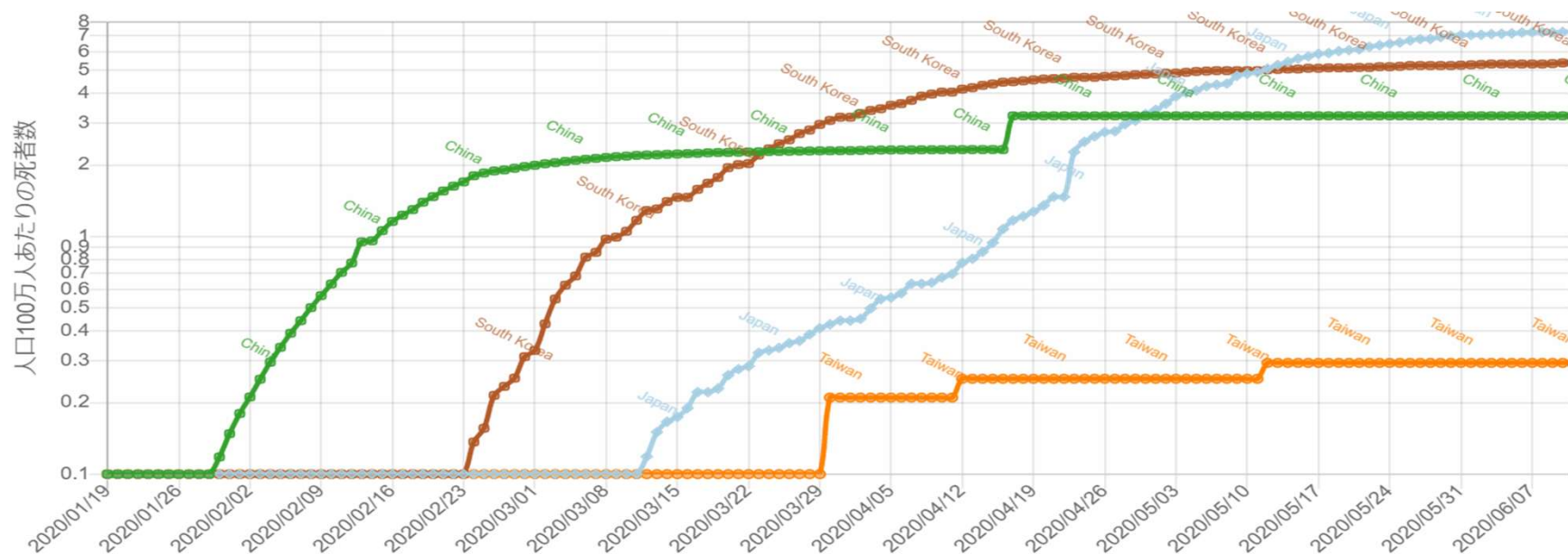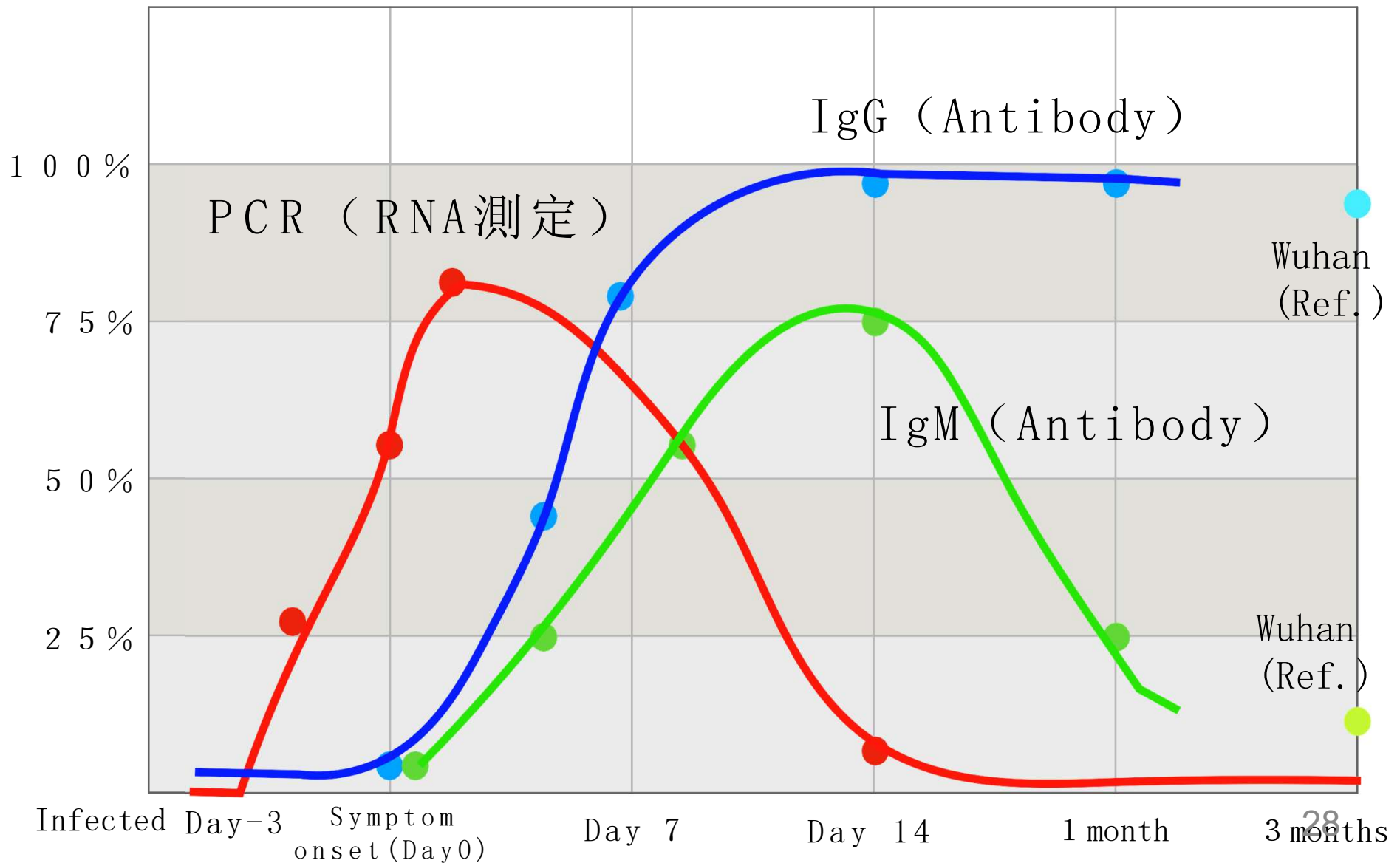
Antigen test for SARS-CoV-2

On the membrane in the reaction cassette, there is a SARS-CoV-2 antigen detection section as a detection line. The SARS-CoV-2 antigen determinant is equipped with an mouse anti-SARS-CoV-2 monoclonal antibody are solidified.
Figure source (Viruses 2020, 12(6), 582; https://doi.org/10.3390/v12060582)
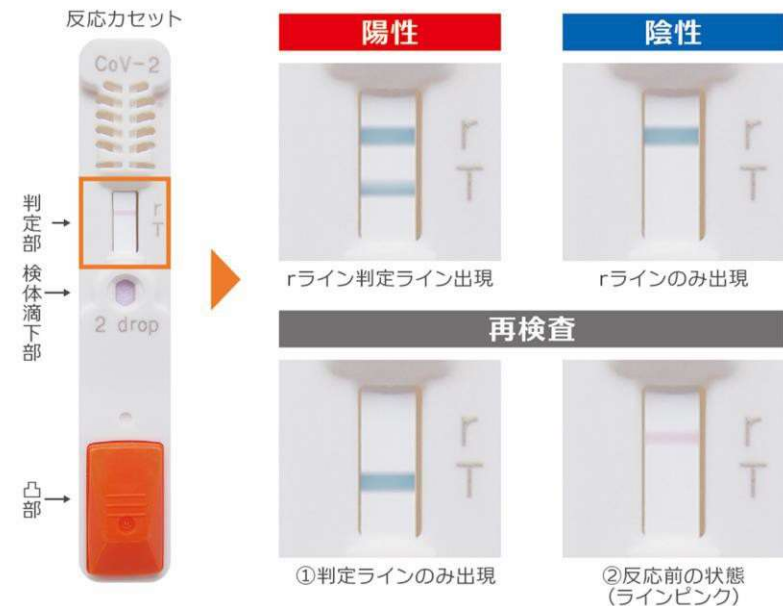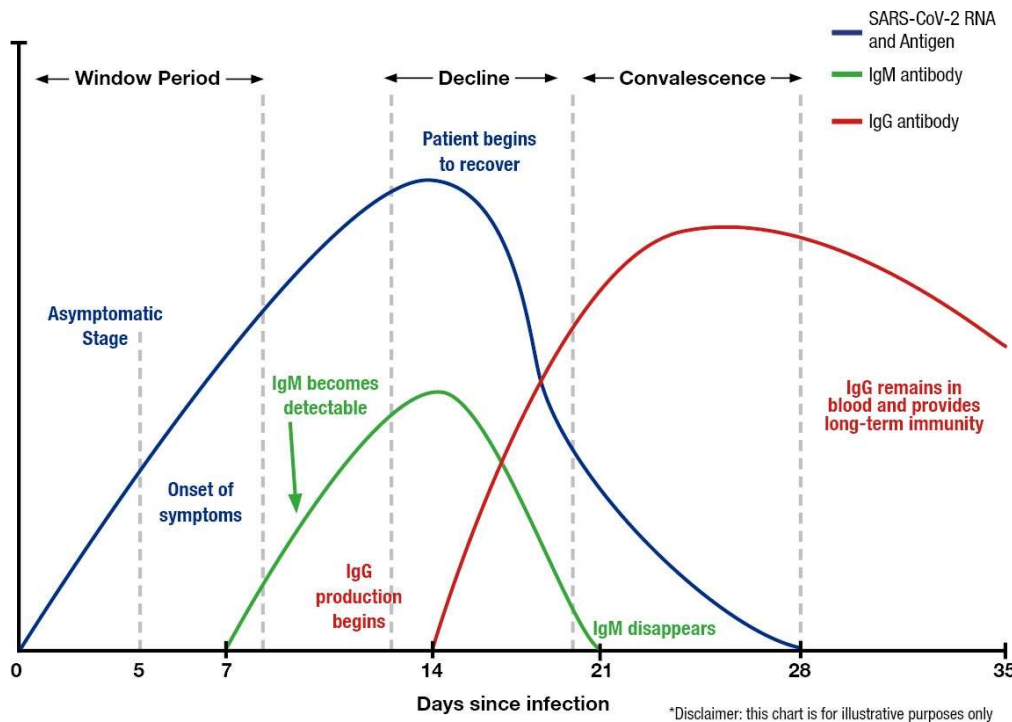
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IgG,IgM陰性の特異１例を含まない （https://www.ric.u-tokyo.ac.jp/topics/2020/ig-20200611.pdf）

IgG（Antibody）

PCR（RNA測定）

IgM（Antibody）

Wuhan
(Ref.)

Wuhan
(Ref.)

100%

75%

50%

25%

Infected   Day-3   Symptom   Day 7   Day 14   1 month   3 months
                      onset(Day0)

28

How 2 Types of Serology (Antibody) tests differ?

(source: Kodama et al. https://www.ric.u-tokyo.ac.jp/topics/2020/ig-20200531v04.pdf)

Simple-Kit
(Qualitative result only; High sensitivity but low in specificity; i.e., many false+)
簡易検査 イムノクロマト法

一人1個

感度はいいが定性的

ノイズ（偽陽性が多い）

Globally standardized
(Quantitative result to ↓false+; High sensitivity & specificity)
500 samples per day per machine. Can aggregate 20 samples into 1.
化学発光自動化血液検査機

１日最大５００件
（検診の残余血清でも可能）
感度がよく定量的
ノイズが少ない
偽陽性を判定できる

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Clinical criteria recommended by Kodama et al. from
新型コロナウィルス抗体測定協議会　2020年5月31日
https://www.ric.u-tokyo.ac.jp/topics/2020/ig-20200531v04.pdf

IgG Test to diagnose a past infection history

- Positive (+) if >= 10

- Follow-up observation needed if >= 5 & < 10

- Negative (-) if < 5

To estimate the infection condition based on the combined results of IgG and IgM

- Past infection: if IgG(+) & IgM<10 & No-symptom in the past 2 weeks

- Potential risk of active case: if IgG(+) & IgM>=10

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- Who are silent spreaders?

- How many?

- What conditions are needed for screenings?

  – Criteria

  – **Specific examples for criteria**

III) General goals of the COVID-19 measures

IV) "Testing for COVID19: A way to lift confinement restrictions" proposed by OECD

(To be updated)

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2 types of economics

- **Positive economics:**

  concerns the description and explanation of economic phenomena

  e.g., 10%↑ in copay → X%↓ in utilization

- **Normative economics**

  expresses value or normative judgments about economic fairness or what the outcome of the economy or goals of public policy *ought to be*

  e.g., universal health insurance (or access to healthcare) should be guaranteed by a government

Road Map

I) General goals of the COVID-19 measures

- Proposals from Japan's leading economists (March 17)

    from The Tokyo Foundation for Policy Research

    https://www.tkfd.or.jp/research/detail.php?id=3361

II) "Testing for COVID19: A way to lift confinement restrictions" proposed by OECD

III) A new testing strategy proposed by Prof. Kodama at the University of Tokyo

Proposals from Japan's leading economists (March 17)

Report title:

[Emergency proposals by economists] How to proceed with measures against the new coronavirus? — Stock price measures, life support cash benefit and loans, and infection control through online society —

＜発起人＞

　　　　小林慶一郎

佐藤主光

＜賛同者（五十音順・2020年4月12日現在）＞

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*1　提言1を除く
*3　提言3を除く
*4　提言4を除く
*5　提言5を除く
*8　提言8を除く
*9　序文を除く

Economic policy principles

1. Controlling the spread of infection

 2. Mitigating short-term economic impact (w/r/t decrease in income and lack of liquidity)

3. Promoting long-term industrial structural change

→ Agree/Disagree with why?

2 purposes

- Primary purpose is to create a society that is highly resistant to the spread of new coronavirus infections.
  - Deterring the spread of infection is the highest priority

- Secondary purpose is economic stabilization
  - To avoid a situation where consumption or investment that does not promote the spread of the infection becomes impossible (an unnecessary contraction of the economy to prevent the infection).

→ Agree/Disagree with why?

Details of 3 economic policy principles:
1. Controlling the spread of infection (1 of 4)

First, digitization of medical care is a challenge for short-term infection control (Proposal 1).

There is an urgent need to establish a system to reduce the number of face-to-face medical treatments at risk of infection and increase the number of online remote medical treatments.

→ Agree/Disagree with why?

Details of 3 economic policy principles:
1. Controlling the spread of infection (2 of 4)
https://www.tkfd.or.jp/research/detail.php?id=3361

The new Corona is likely to continue to threaten human society for the next few years or permanently.

It is necessary to structurally change the economic society to create a society that can prevent infection in the long run.

To that end, it is necessary to advance digitalization in all aspects of human social activity, including economic activity (Proposal 2).

→ Agree/Disagree with why?

Details of 3 economic policy principles:
1. Controlling the spread of infection (3 of 4)

https://www.tkfd.or.jp/research/detail.php?id=3361

Furthermore, it is necessary to enhance the test system so that the epidemic situation of new corona infectious diseases can be continuously monitored and measures can be taken based on the evidence in the long term (Proposal 3).

→ Agree/Disagree with why?

Details of 3 economic policy principles:
1. Controlling the spread of infection (4 of 4)
https://www.tkfd.or.jp/research/detail.php?id=3361

Inefficiencies that permanently increase the number of beds due to temporary needs should be avoided when expanding the healthcare provision system.

Since 80% of infected persons are mild and asymptomatic persons do not need advanced treatment, their hospitalization facilities do not have to be fully equipped hospitals. If the government temporarily rents inns and hotels all over the country and makes them hospitalized facilities for the isolation of mild and asymptomatic people, it will be a powerful support measure for the inn and hotel industry, and it will be "two birds with one stone" (proposal 4).

→ Agree/Disagree with why?

Details of 3 economic policy principles:
3. Controlling the spread of infection (3 of 4)

Furthermore, it is necessary to enhance the test system so that the epidemic situation of new corona infectious diseases can be continuously monitored and measures can be taken based on the evidence in the long term (Proposal 3).

→ Agree/Disagree with why?

Details of 3 economic policy principles:
3. Promoting long-term industrial structural change
https://www.tkfd.or.jp/research/detail.php?id=3361

Large and rapid changes in the industrial structure are expected to occur, but the exit of companies (closed business, bankruptcy) and the new entrants are essential for this.

Needless to say, it is necessary to support small and medium-sized enterprises that are suffering from a sudden deterioration in business performance due to the new corona problem, but it is also necessary to combine policies that promote corporate exits & new entrants at a proper speed (Proposal 8).

→ Agree/Disagree with why?

Road Map

I) Review of past classes w/ some updates

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-A) Introduction (Main strategy and 3 Goals)

-B) 6 Key messages

Q for students: Who (backgrounds) works for OECD?

Introduction (Main strategy)

Crucially, quick suppression of infections requires testing more people to identify who is infected;

tracking them to make sure they do not spread the disease further;

and tracing with whom they have been in contact.

→ Agree/Disagree with why?

Introduction (3 Main Goals)

1) suppressing the resurgence of local outbreaks;

2) identifying people who have developed some form of immunity and can safely return to work; and

3) gaining intelligence on the evolution of the epidemic, including on when a threshold for herd immunity has been reached.

→ Agree/Disagree with why?

Key Message 1

A key question behind any strategy to ease confinement restrictions and reopen economic activities is how to avoid a new spread of the SARS-CoV-2 virus that would necessitate further lockdowns.

Once the number of infected people has successfully been brought sufficiently down, quick suppression of new waves of viral infections will be key. Testing strategies are central to achieve this.

→ Agree/Disagree with why?

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Key Message 2

- There are two types of tests. First, molecular diagnostic testing (RT-PCR) helps to identify those individuals who are infected at the time of the test.

- An effective strategy that tests, tracks people infected and traces their contacts (TTT), helps to reduce the spread of the virus and thus bring its reproduction number below one.

→ Agree/Disagree with why?

Key Message 3-1

- Given the characteristics of this coronavirus– including the large number of asymptomatic cases and high reproduction number

- To be effective at suppressing the spread of the virus, the TTT strategy should be used very widely, requiring a very large proportion of all cases (between 70 and 90%) to be traced to prevent a new outbreak of the virus.

→ Agree/Disagree with why?

Key Message 3-2

(Continued from the previous slide)

This would require increasing capacity for testing enormously;

putting in place strict measures to prevent people who may be infectious from breaking quarantine;

as well as identifying ways to trace contacts,

which may push the limits of privacy concerns,

unless new approaches to digital tracing, currently under development, are put in place.

→ Agree/Disagree with why?

Key Message 4-1

Significant logistics and capacity constraints

– ranging from the availability of trained personnel to take accurate specimen,

to the time required for laboratory analysis

and the availability of reagents

– have impeded more widespread diagnostic testing in many countries so far.

→ Agree/Disagree with why?

Key Message 4-2

Recent development of faster RT-PCR molecular diagnostic testing,

which can be deployed at the point of care,

should help scale-up capacity for effective TTT in countries.

Digital enabled contact- tracing can help improve the speed and effectiveness of TTT strategies, as seen in some countries.

→ Agree/Disagree with why?

Key Message 5

A <u>second type of test</u> – so-called serologic test – detects people who have had a prior infection and thus developed antibodies.

Such tests can be used for **2 purposes**,

1. to allow people who have acquired immunity to return to work safely,

2. to provide intelligence on the evolution of the epidemic across the population.

Rapid serology test kits need to be developed

and their clinical performance needs to be demonstrated before deployment at scale can happen.

→ Agree/Disagree with why?

Key Message 6-1

Despite the fact that a relatively low number of people have so far been infected

and thus we are still far from herd immunity,

the successful implementation of serologic testing strategies at large scale can help reduce the spread of the virus and complement the TTT strategy.

→ Agree/Disagree with why?

Key Message 6-2

(Continued from the previous slide)

This will also require major efforts, including:

1) verifying the clinical performance of tests, particularly for rapid serologic tests;

2) preparing procurement and logistics arrangements to scale up production and deployment of the tests, and train and deploy human resources, particularly for diagnostic RT-PCR tests; and

3) providing adequate safeguards to protect civil right and privacy of populations while deploying or apps-enabled tracking strategies.

→ Agree/Disagree with why?

Question for all students

What are the differences between key messages of the leading economists in Japan and those of the OECD report?

2 types of economics

- **Positive economics:**

  concerns the description and explanation of economic phenomena

  e.g., 10%↑ in copay → X%↓ in utilization

- **Normative economics**

  expresses value or normative judgments about economic fairness or what the outcome of the economy or goals of public policy *ought to be*

  e.g., universal health insurance (or access to healthcare) should be guaranteed by a government

As of 4 May 2020, Diagnostic tests per 1000 population in OECD countries, varied from (<1) to (100+) tests per 1000 population

Tests per 1 000 population
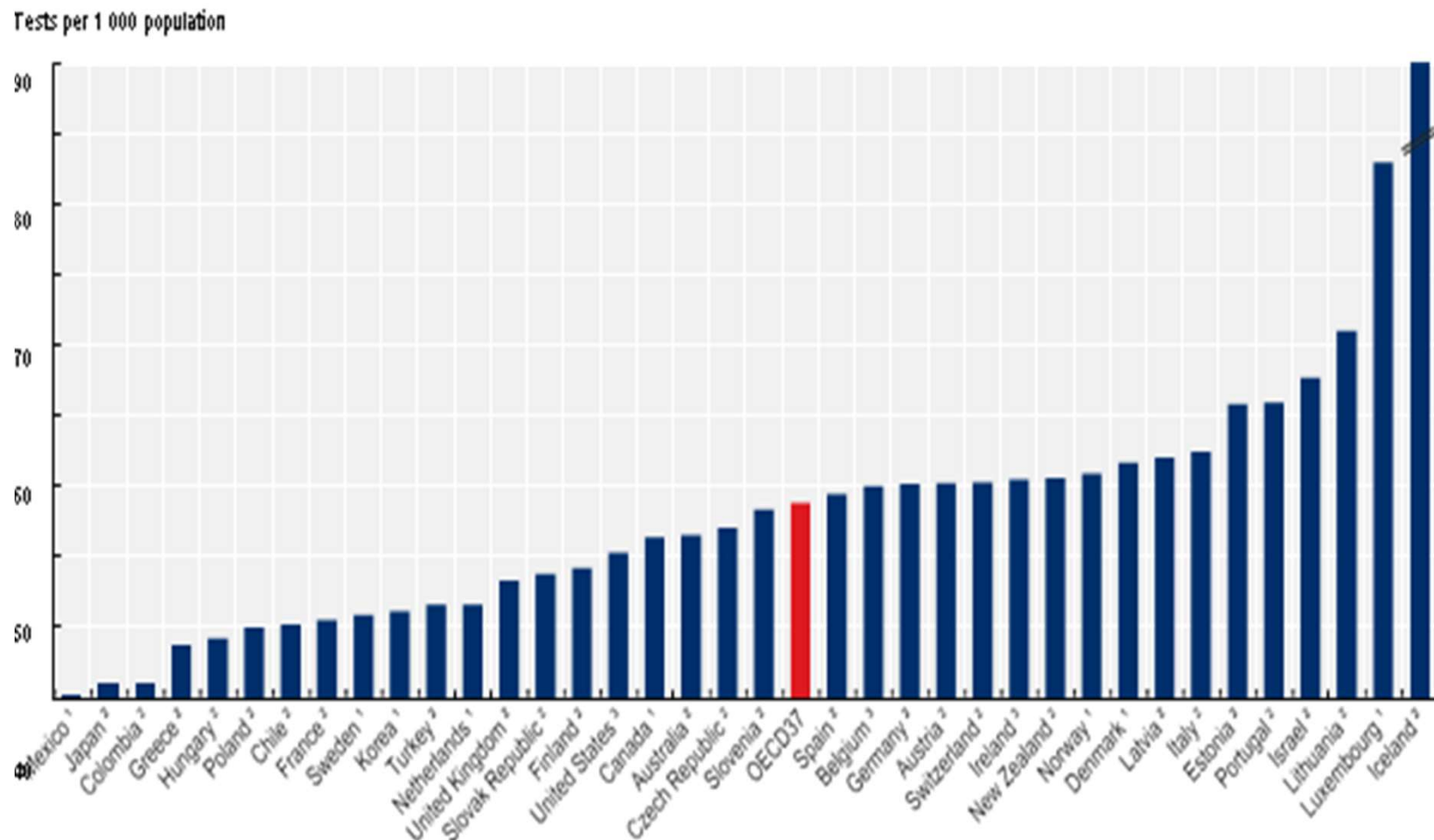
2 examples in the OECD report

- South Korea's widespread and digital TTT
  - Innovative solutions were developed
    - 600+ drive-through COVID-19 testing centres,
    - transparent "phone booths"

- Singapore's universal TTT strategy
  - 2,200 tests (RT-PCR) a day for a population of 5.7 million