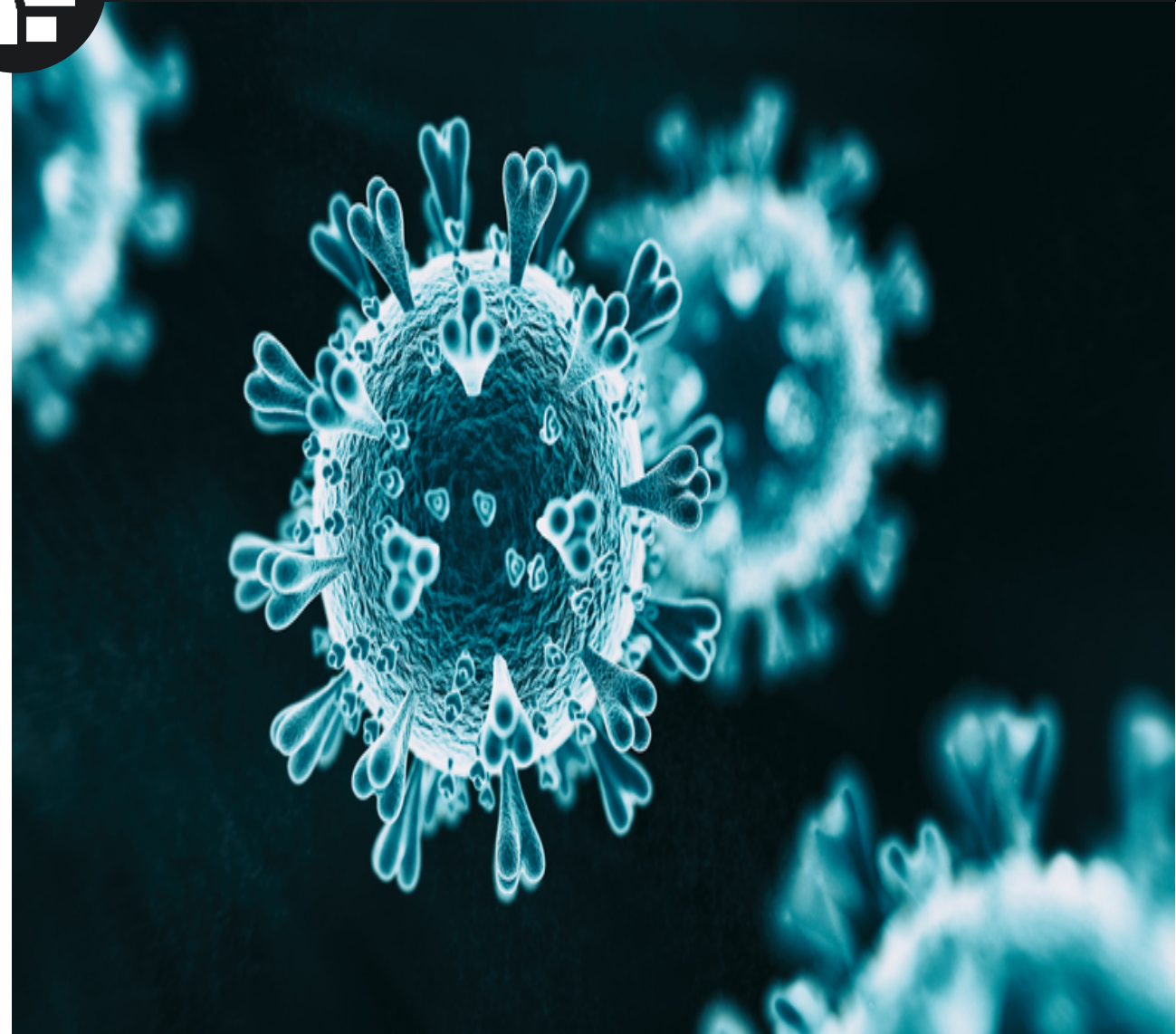




# COVID-19: MARCH 26 UPDATE



March 26, 2020

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## OUTLINE

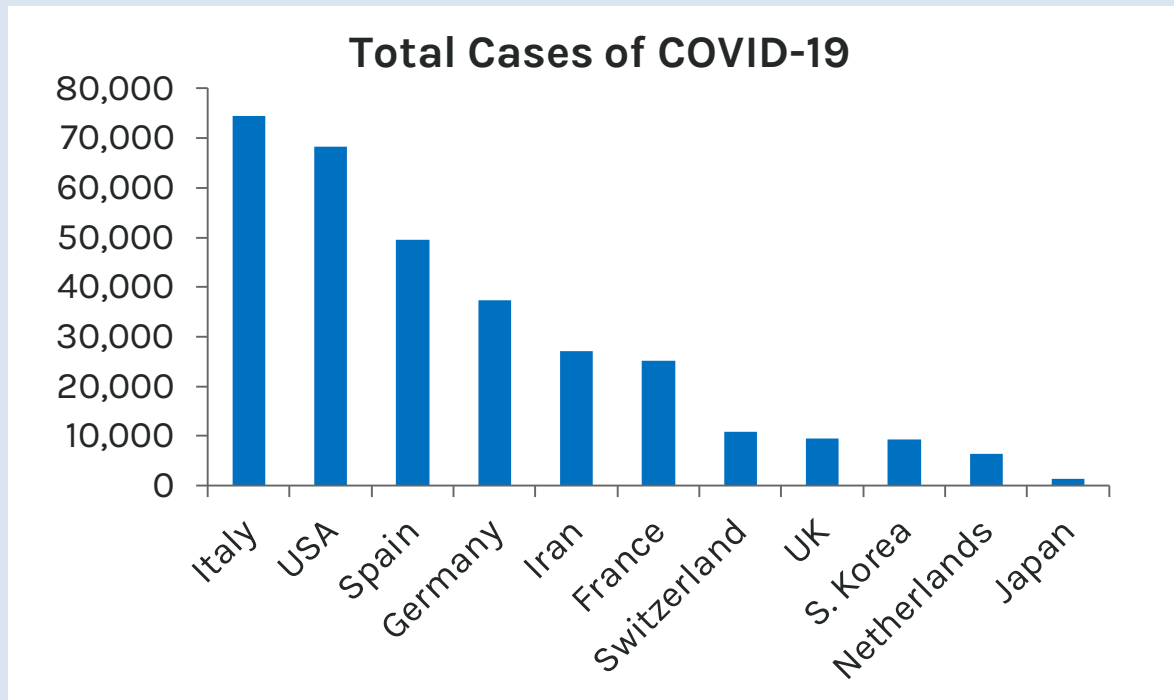
- Overall Observations
- Importance of Cases-to-Deaths Ratio (higher is better)
- Effects of Policy Come With a 3-4 Week Lag (Beware the “Second Wave”)
- Global Case and Death Count Update Plus China Indicators
- The Case for “Smart Suppression”
- The Biology of Antiviral Drug Candidates

## OVERALL OBSERVATIONS

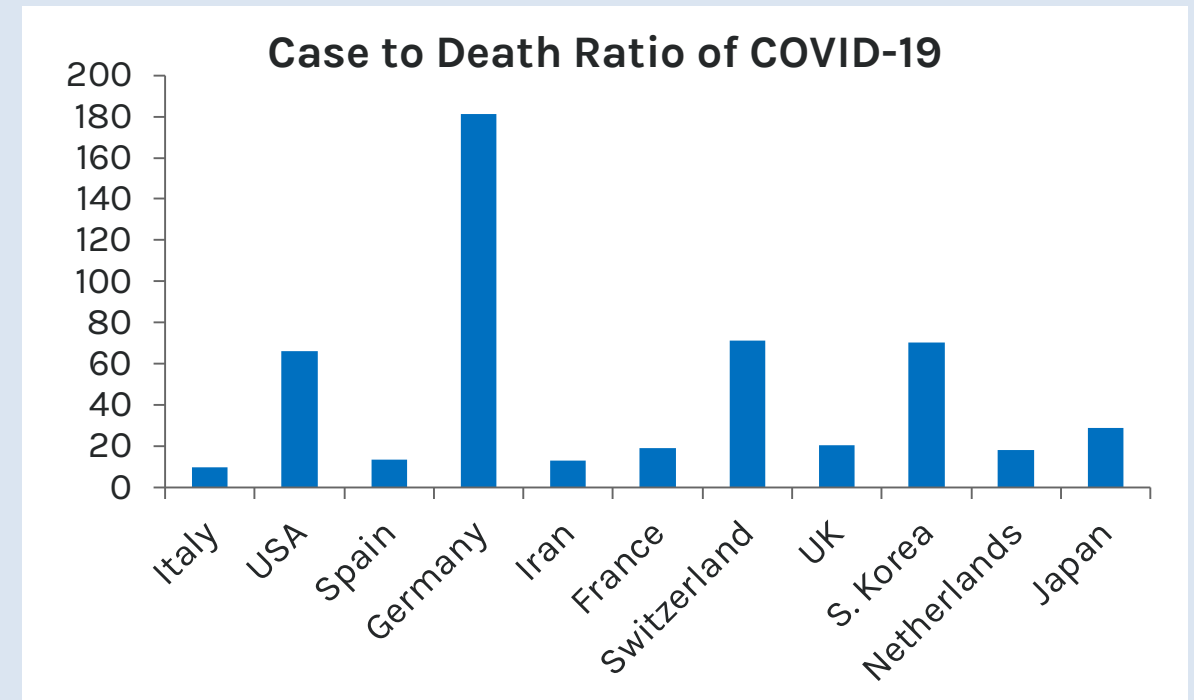
- Size and speed of hit to our economy is without historical precedent:
  - Already: 2- & 3-handle PMIs; 3M+ jobless claims; 10-20% production declines (China).
  - Ahead: GDP declines and unemployment rates in the double digits.
- Ditto for the scope of monetary/fiscal mobilization:
  - For first time, Fed buying corporate debt and lending directly to firms & munis.
  - Federal deficit in CY2020 may reach 15% of GDP; only higher years were 1943, 44, & 45.
- Millennial moment? Victory after all for Bernie's total-system makeover movement?
- Pandemic caution #1: Don't look at number of cases; look at ratio of cases-to-deaths.
  - High ratio is good; low ratio is dangerous and may indicate rampant unseen growth.
- Pandemic caution #2: Wait 3-4 weeks before assessing consequences of either IMPOSING or LIFTING regional shutdown and containment measures; i.e., beware "second wave."

# CASES DON'T TELL THE WHOLE STORY...

## COVID-19 Cases and Case to Death Ratio Updated March 26, 2020



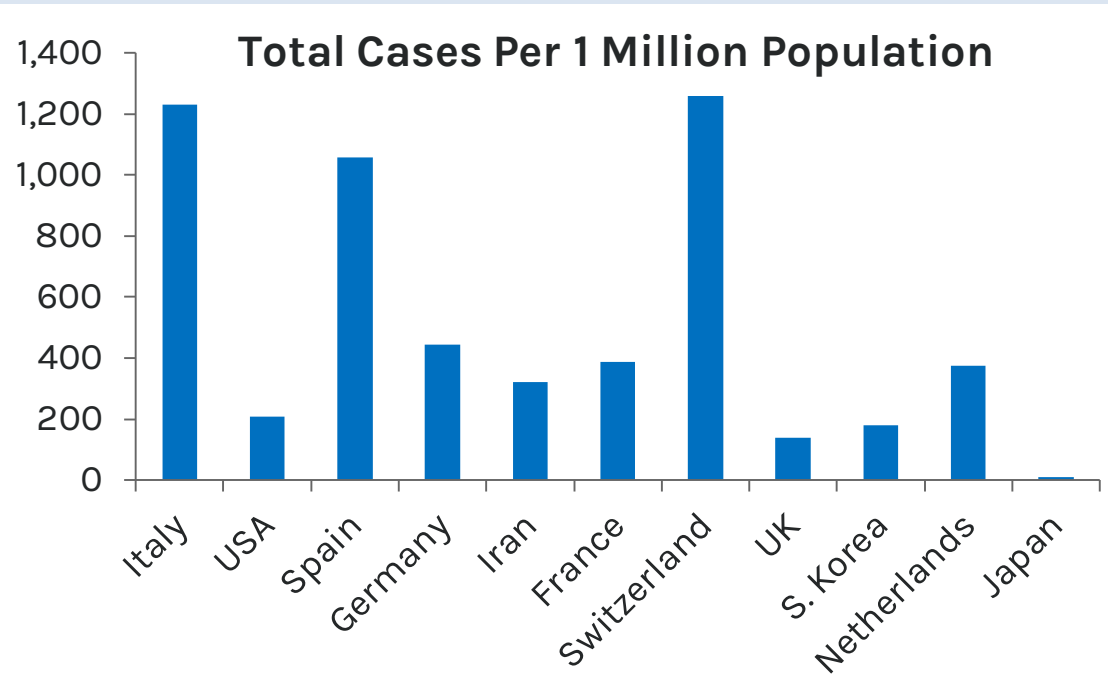
Countries are aligned from greatest number of cases to least, left to right.



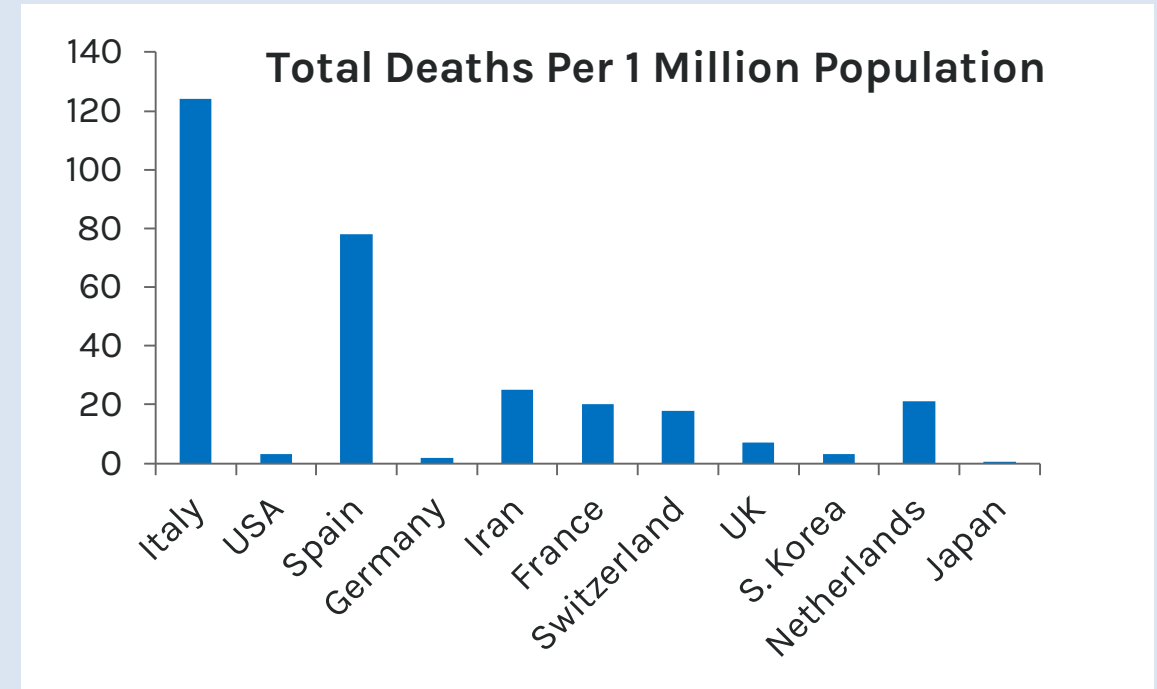
Countries are aligned from greatest number of cases to least, left to right.

# ANOTHER WAY OF LOOKING AT THE SITUATION...

## Total Cases and Total Death of COVID-19 Per 1 Million Population Updated March 26, 2020



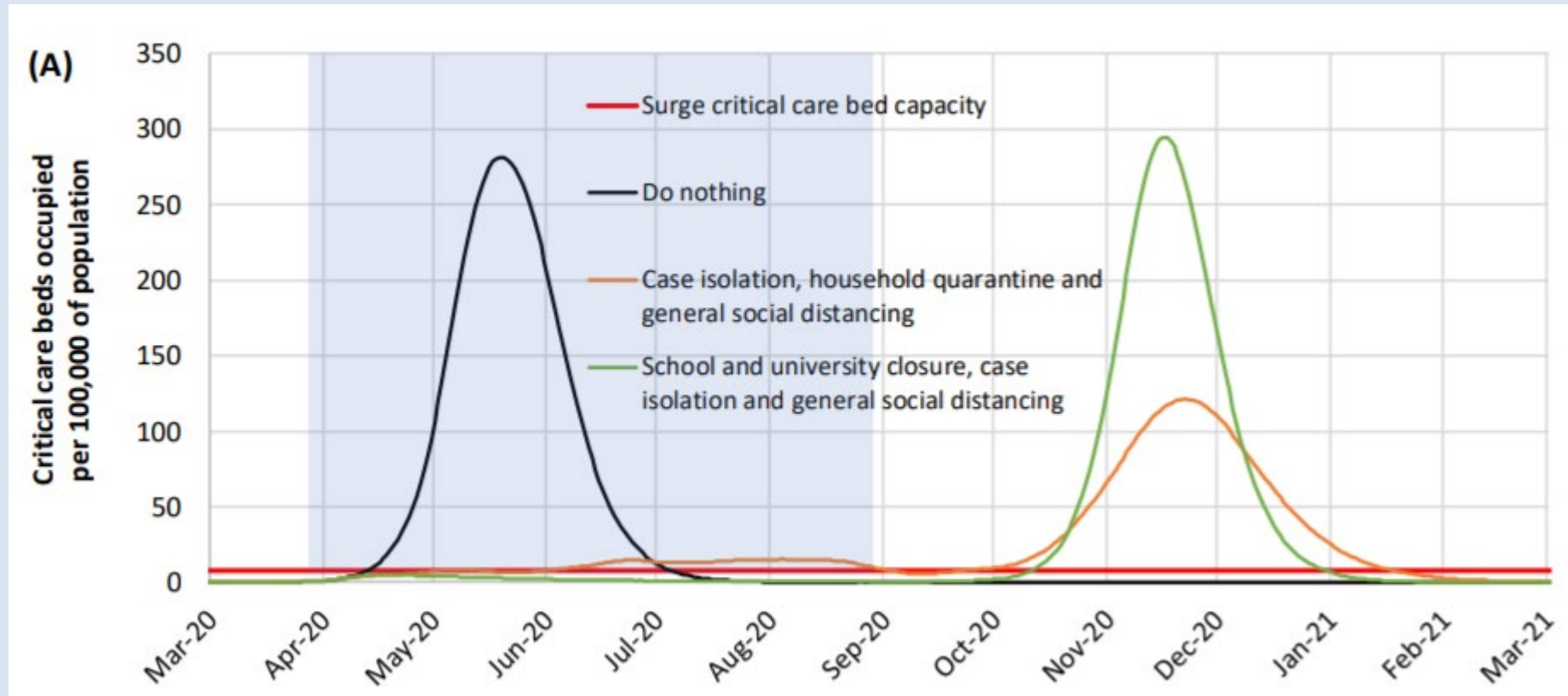
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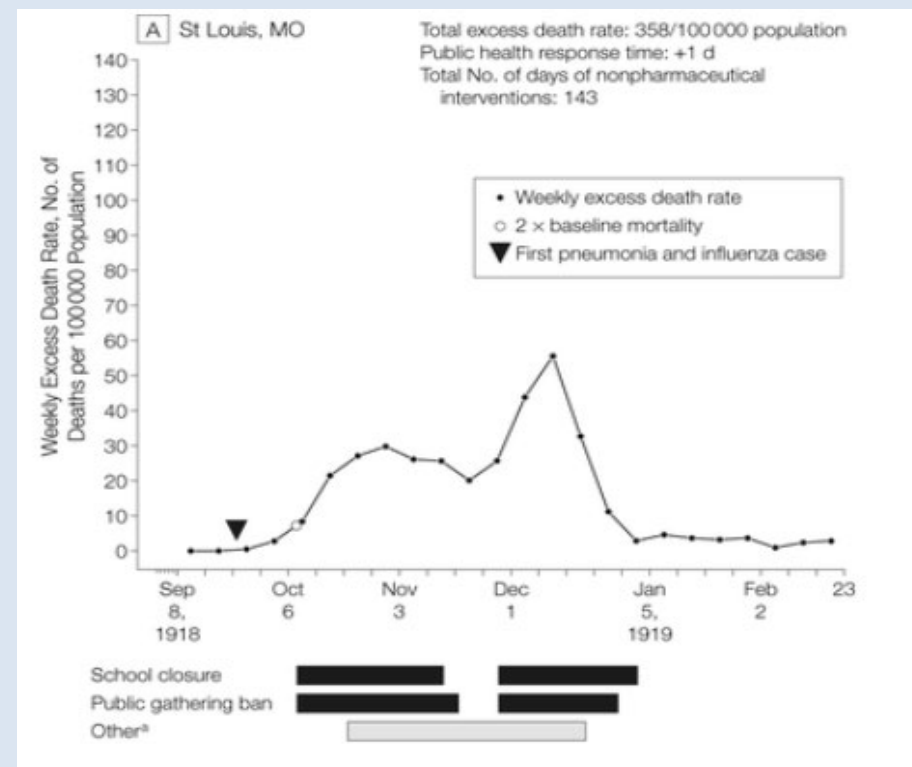
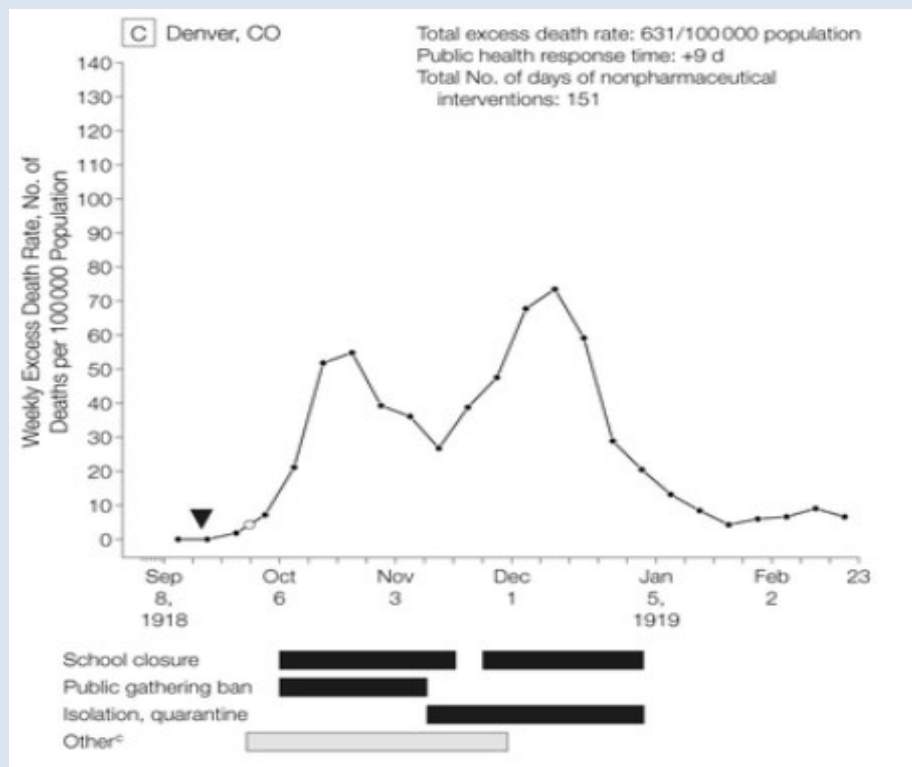
# SUPPRESSION PUSHES THE PEAK FORWARD

## Suppression Strategy Scenarios for Great Britain Showing ICU Bed Requirements



# BEWARE THE 2ND WAVE: LESSONS FROM HISTORY

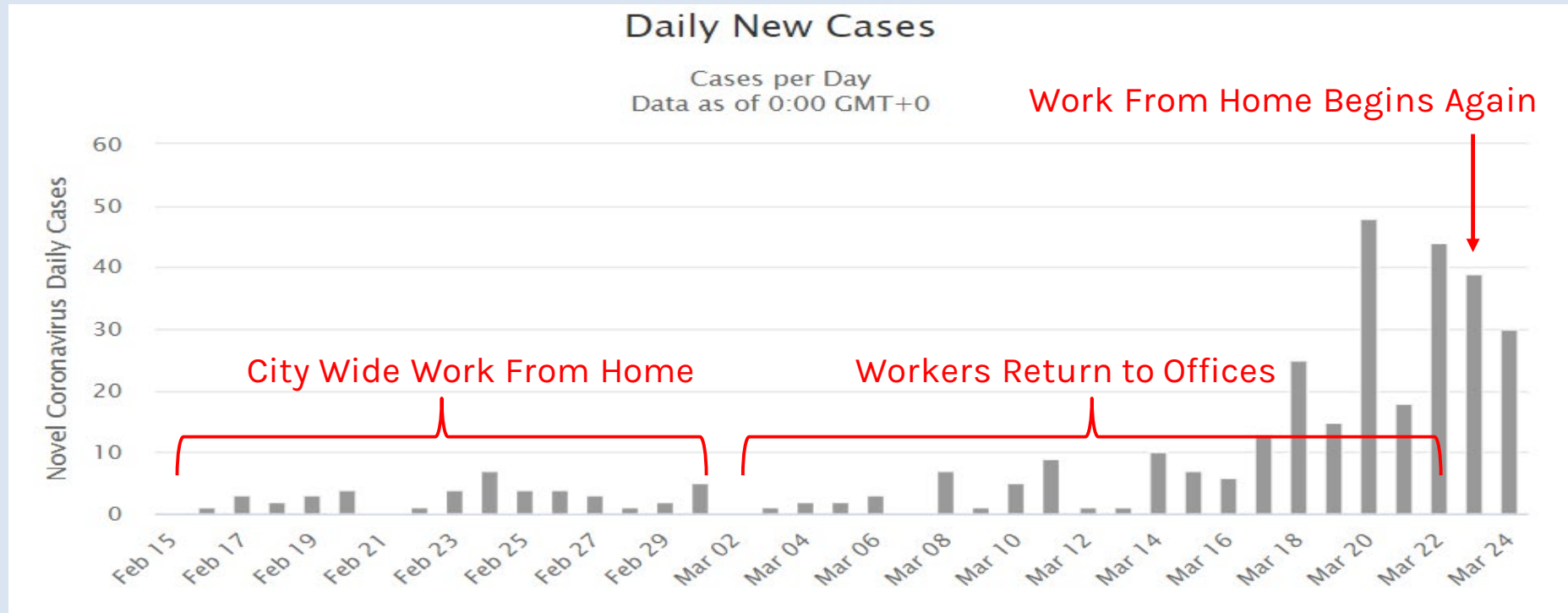
## Weekly Excess Death Rate in Denver and St. Louis With Differing Methods of Suppression, 1918-1919





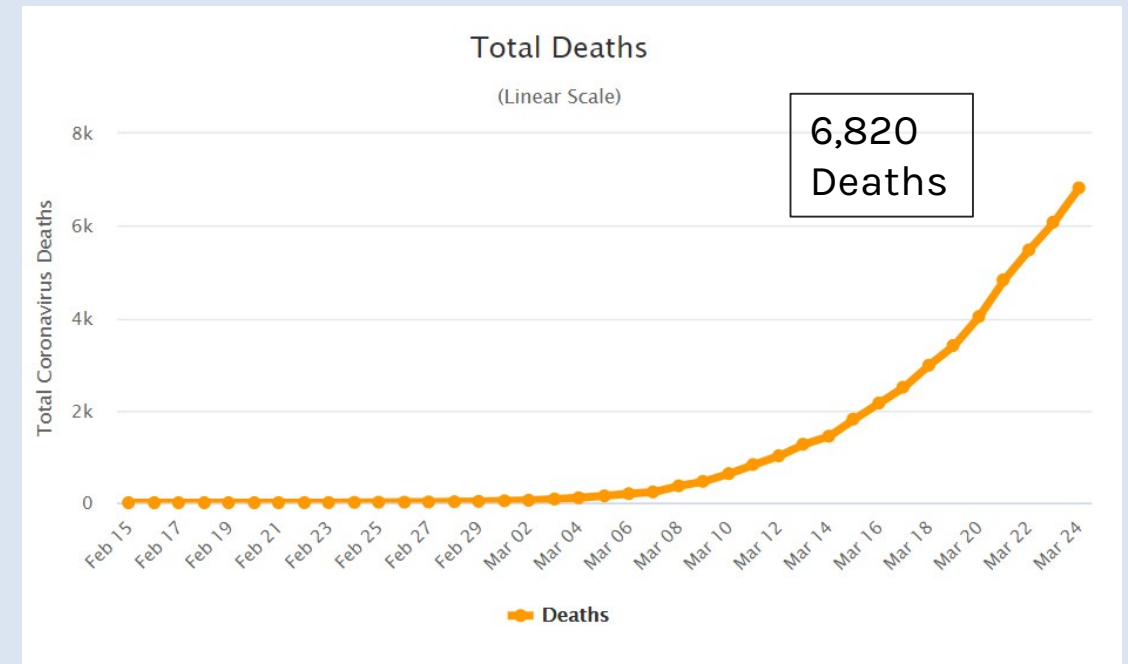
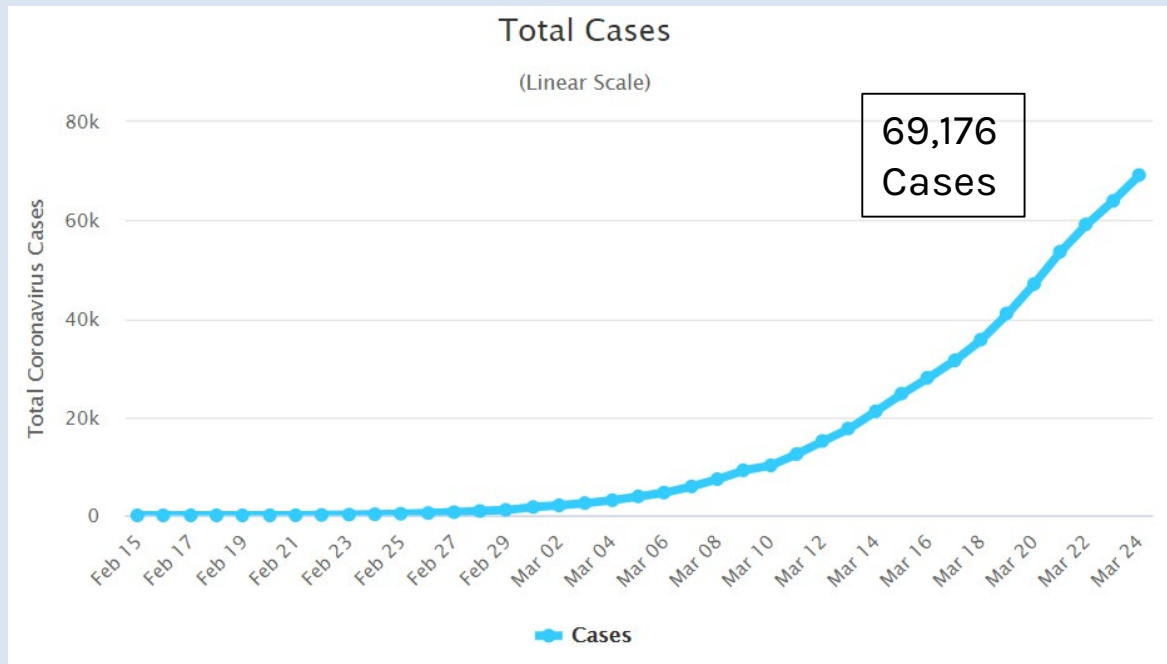
# BEWARE THE 2ND WAVE: EXAMPLE FROM HONG KONG

## Daily New Cases of COVID-19, Hong Kong Updated March 25, 2020



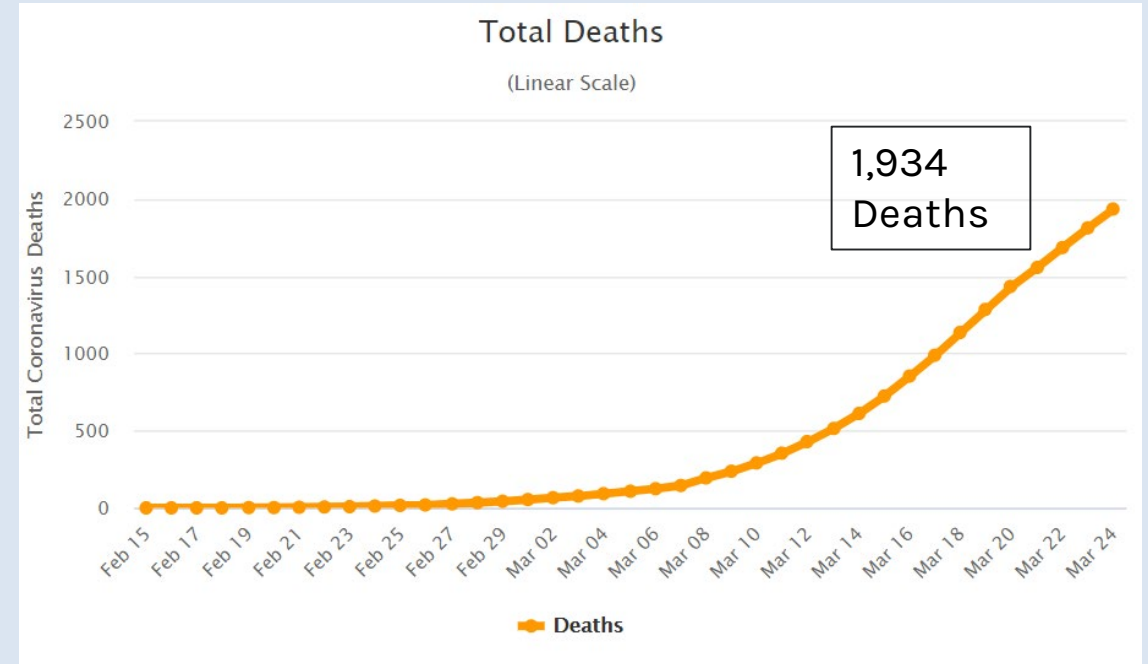
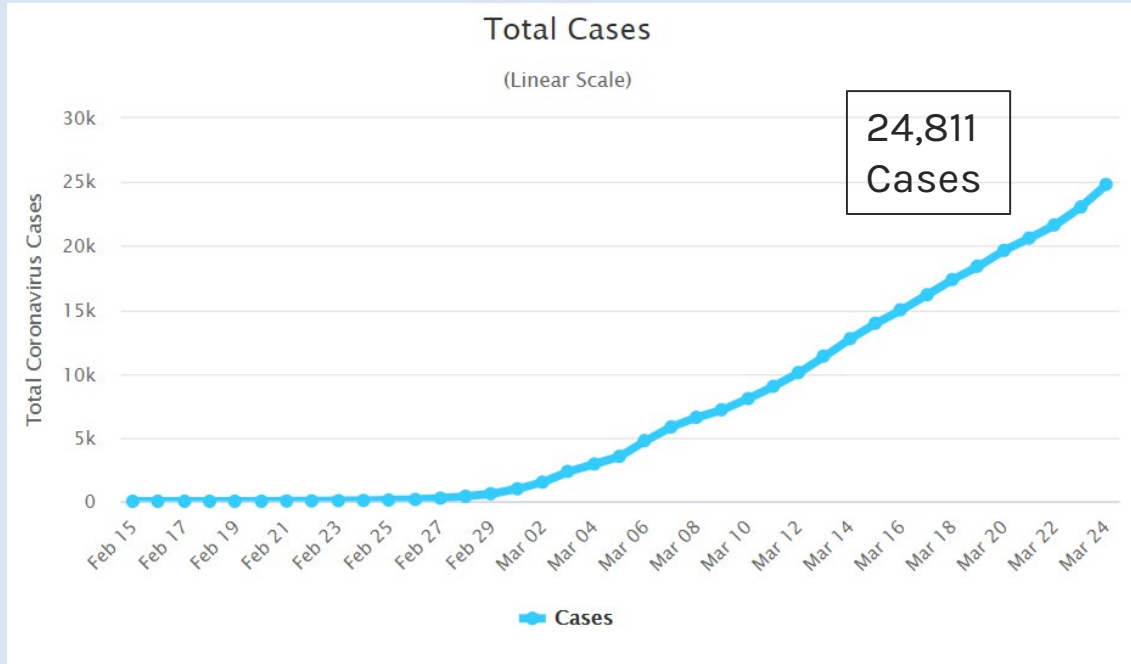
# THE SITUATION IN... ITALY

## COVID-19 Cases and Deaths in Italy Updated March 25, 2020



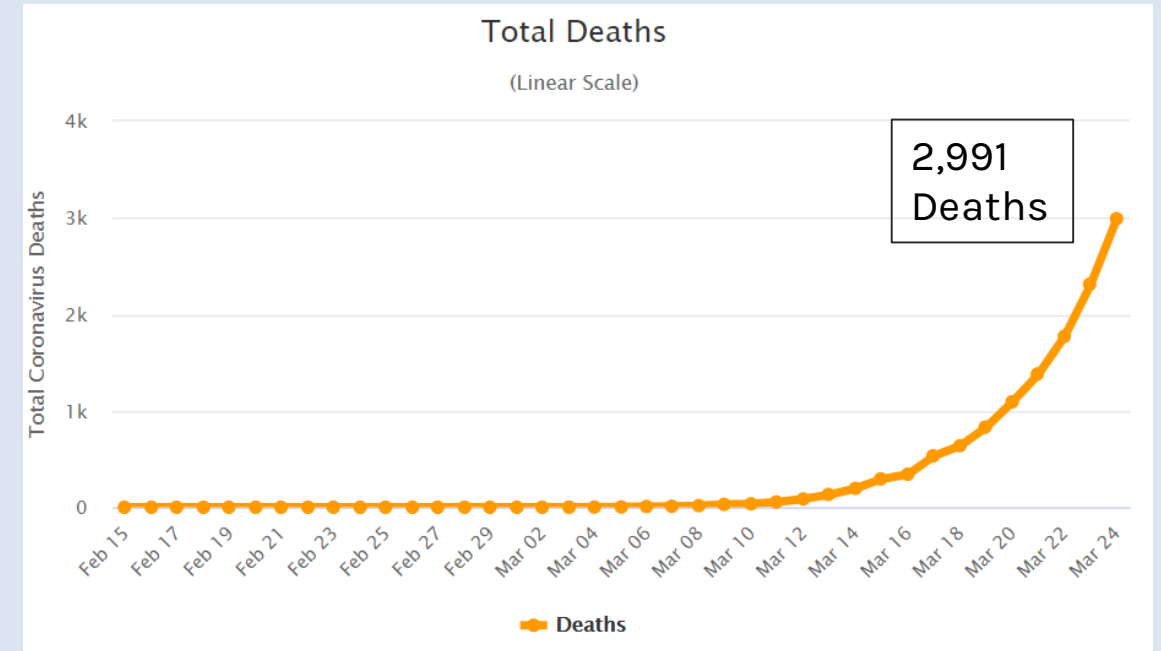
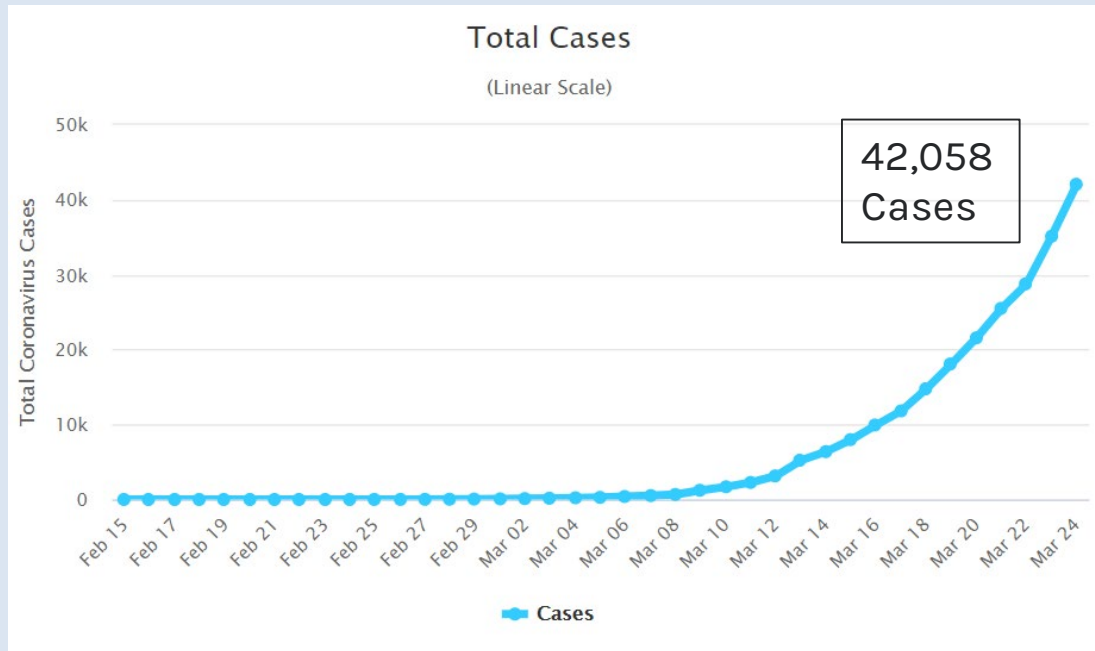
# THE SITUATION IN... IRAN

## COVID-19 Cases and Deaths in Iran Updated March 25, 2020



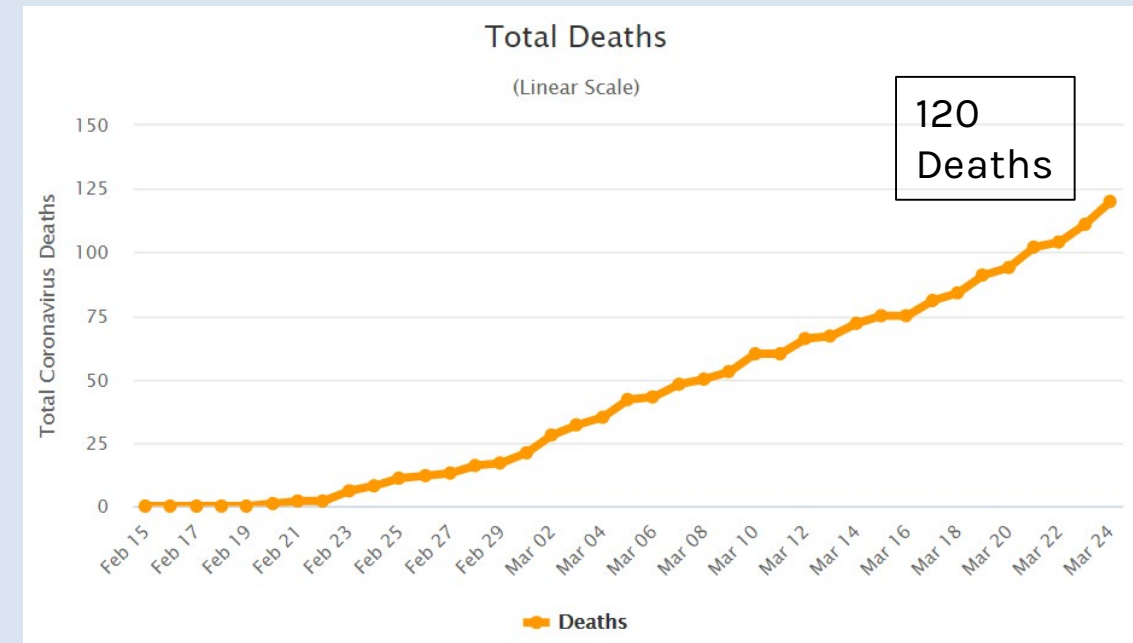
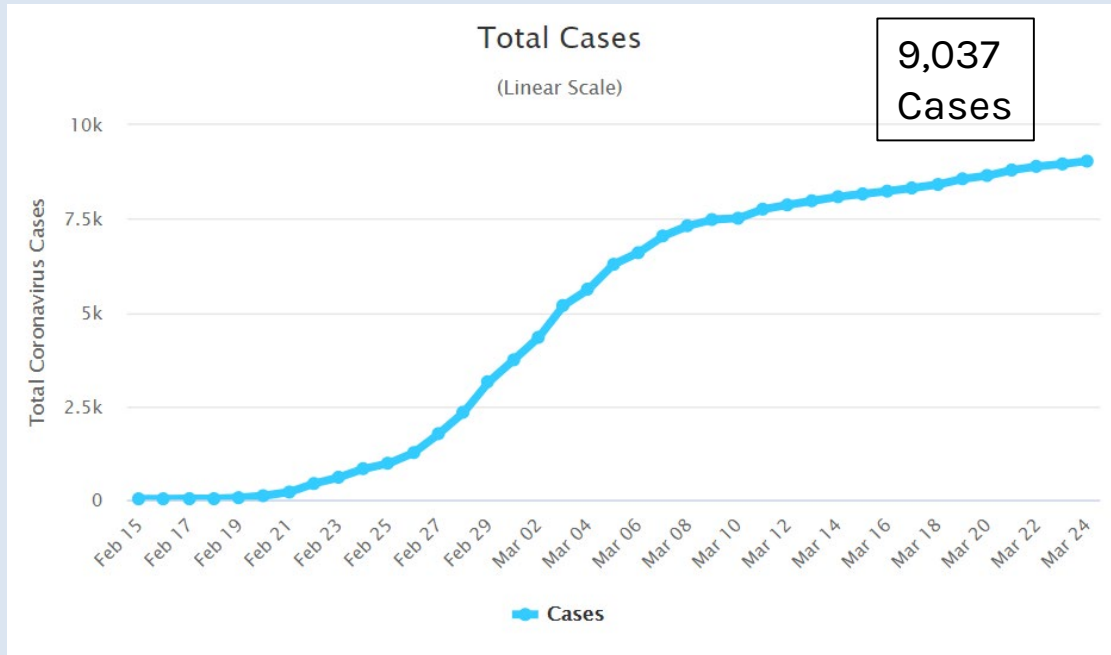
# THE SITUATION IN... SPAIN

## COVID-19 Cases and Deaths in Spain Updated March 25, 2020



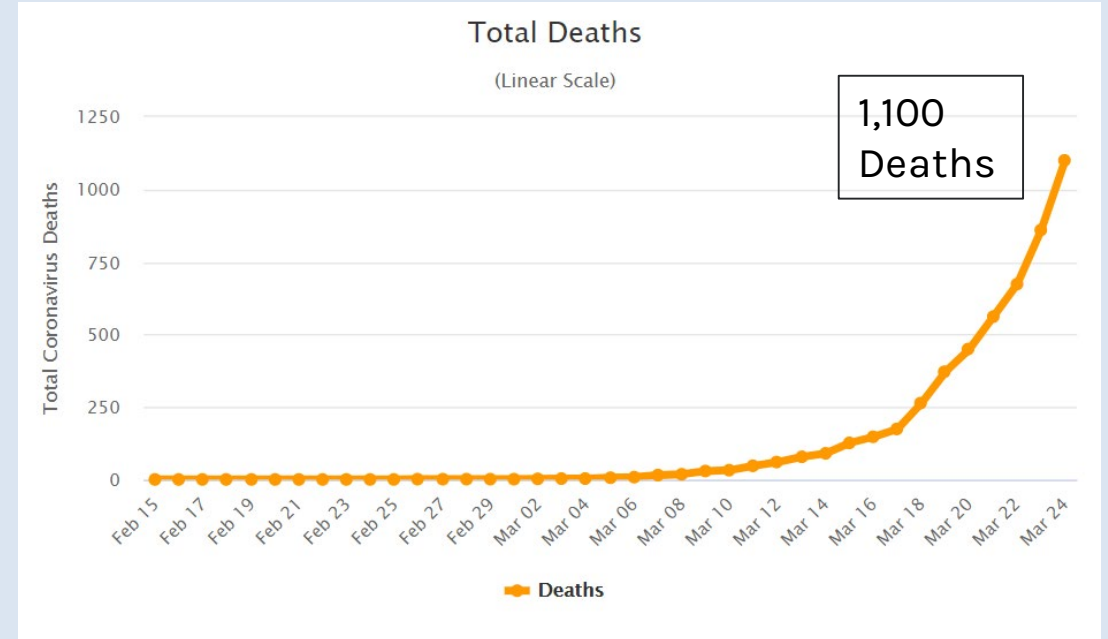
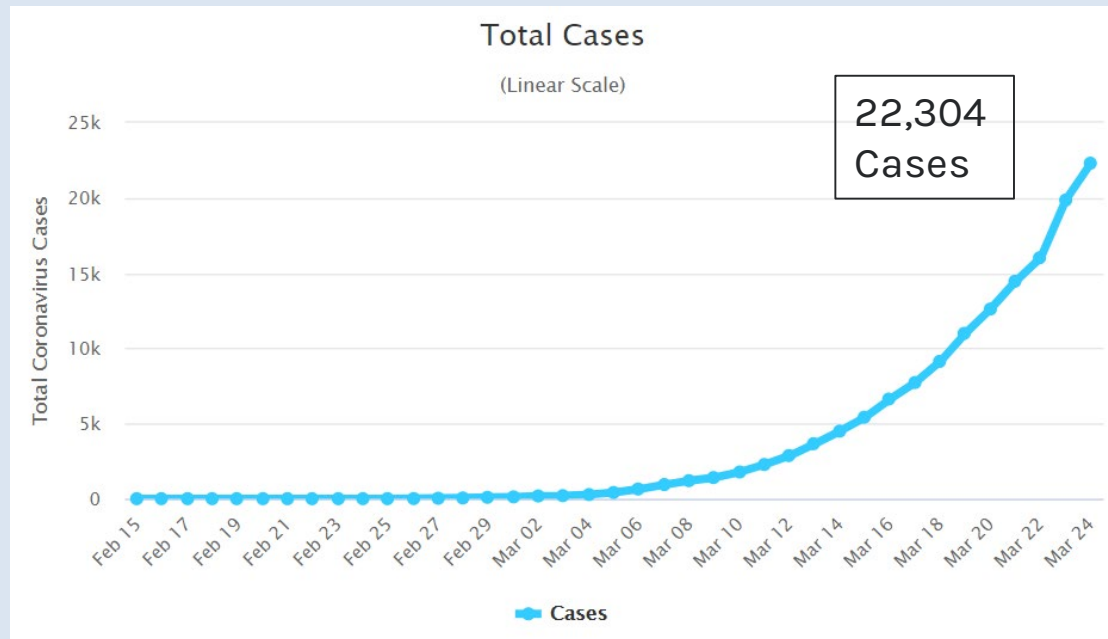
# THE SITUATION IN... SOUTH KOREA

## COVID-19 Cases and Deaths in South Korea Updated March 25, 2020



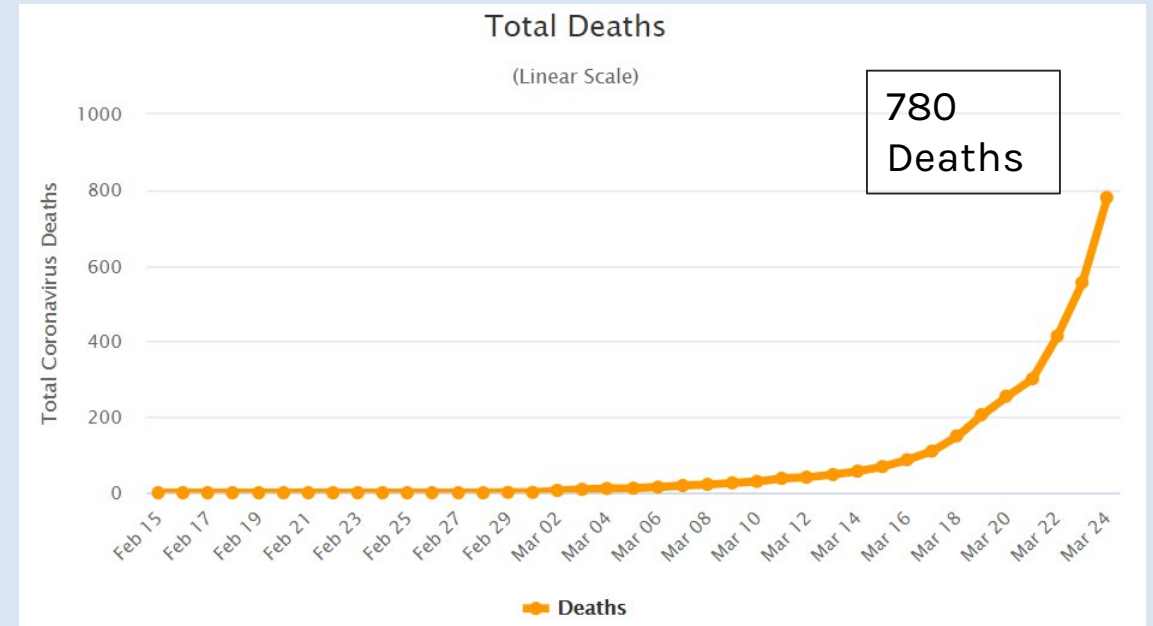
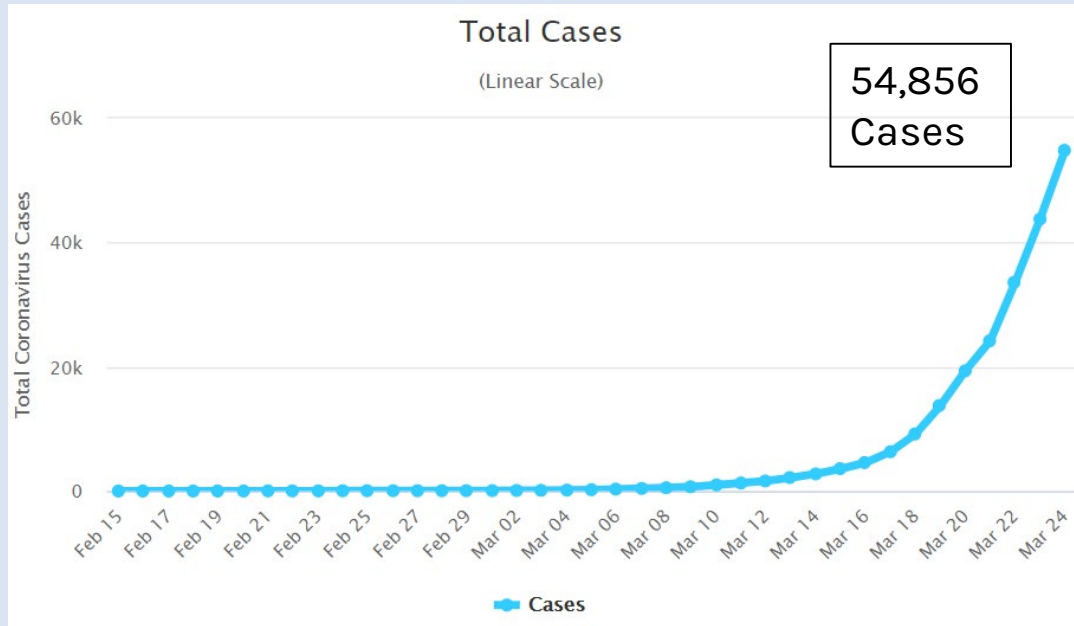
# THE SITUATION IN... FRANCE

## COVID-19 Cases and Deaths in France Updated March 18, 2020



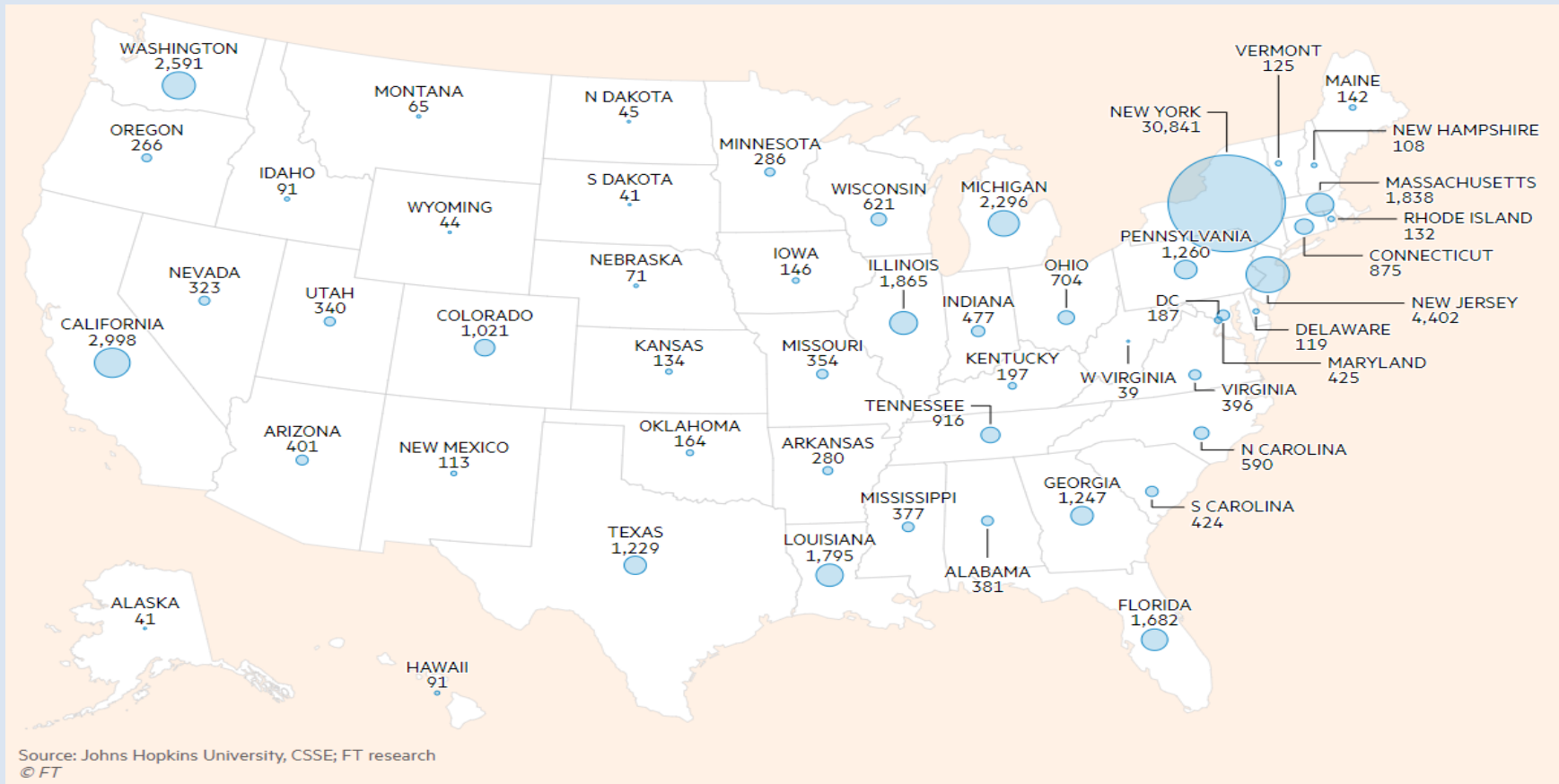
# THE SITUATION IN... USA

## COVID-19 Cases and Deaths in USA Updated March 25, 2020



# NEW YORK IS NOW THE EPICENTER

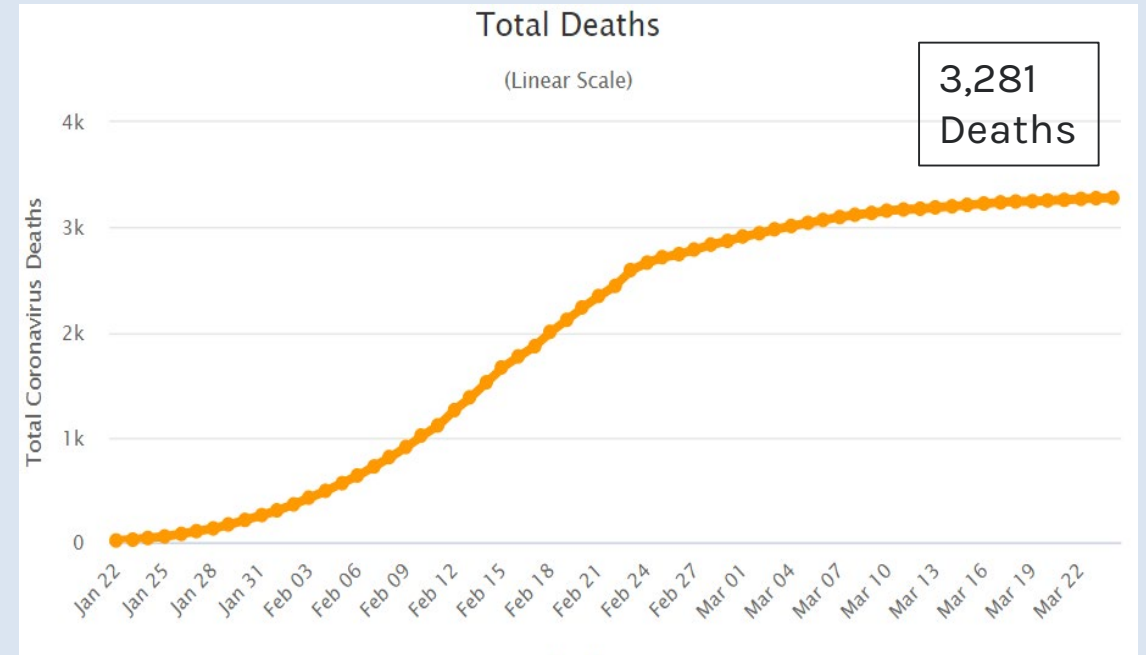
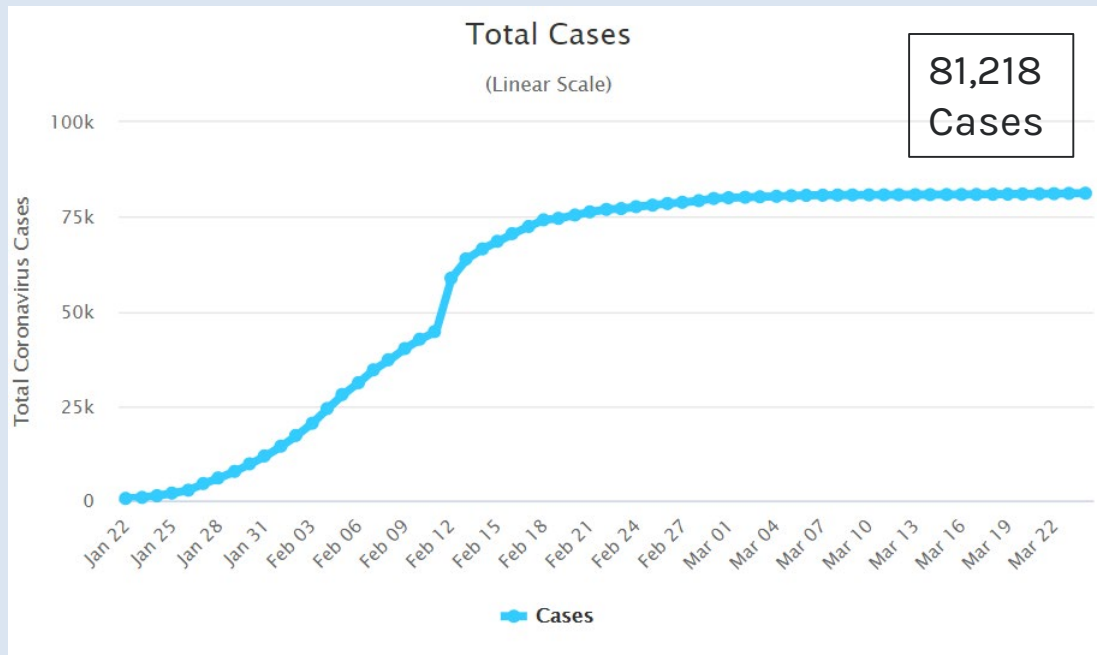
## Total COVID-19 Cases Confirmed in Each State, Updated March 26





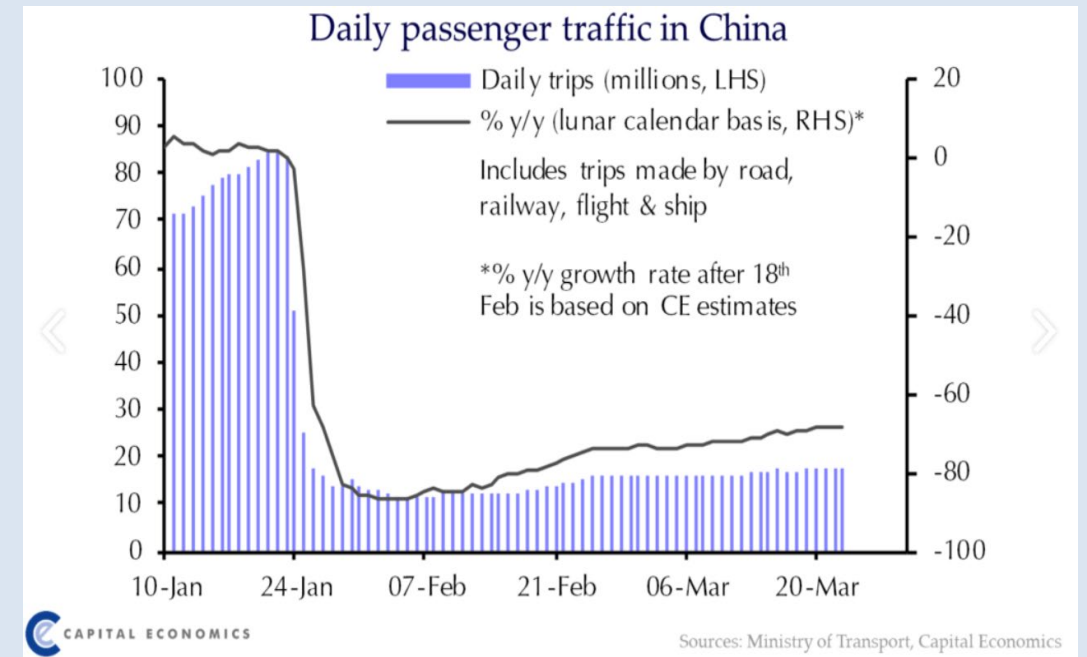
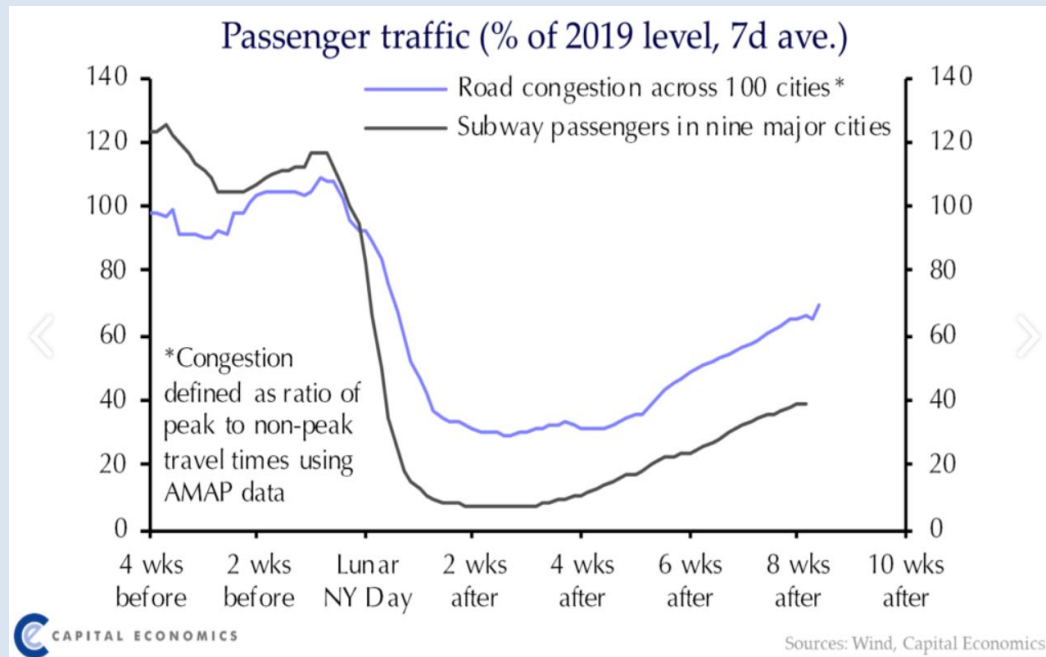
# THE SITUATION IN... CHINA

## COVID-19 Cases and Deaths in China Updated March 25, 2020



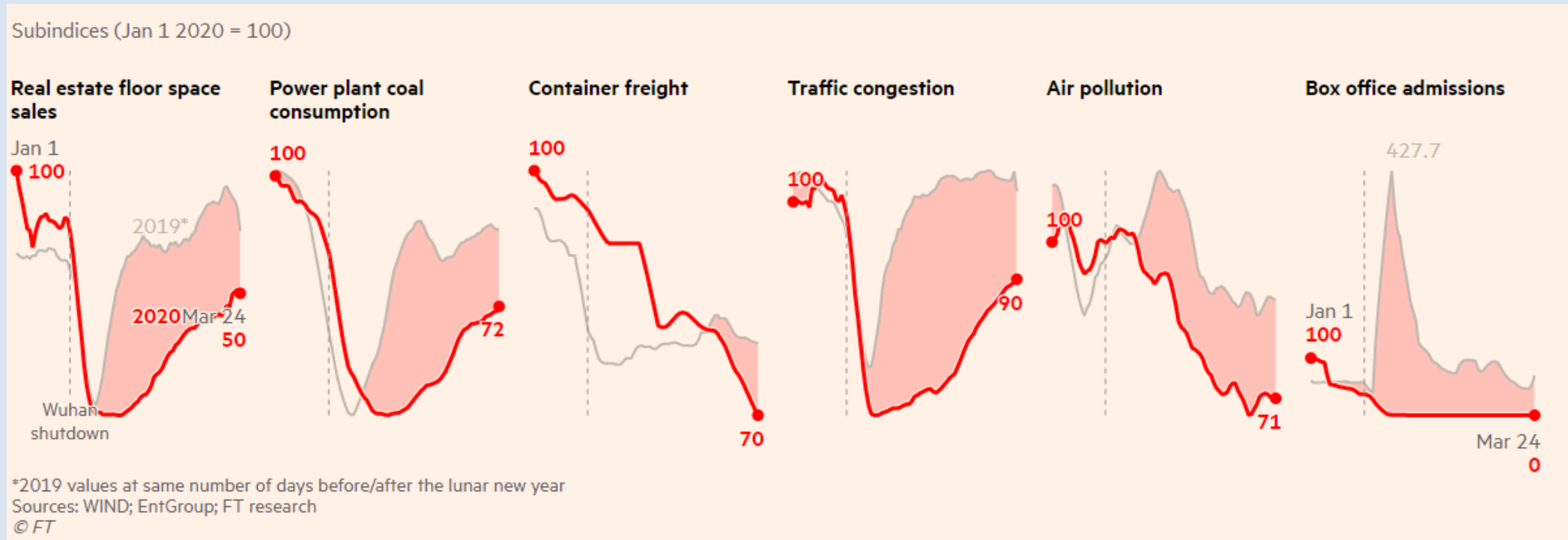
# CHINA... COMING OUT OF DEEP FREEZE?

## Road Congestion, Subway Passengers, and Daily Passenger Traffic in China Updated March 25, 2020



# CHINA... COMING OUT OF DEEP FREEZE?

## Store Floor Space, Coal Consumption, Container Freights, Traffic, Pollution, and Box Office Sales in China Updated March 25, 2020



# “SMART SUPPRESSION” MAY BE OUR BEST ENDGAME

## SMART SUPPRESSION: THE THIRD POLICY OPTION

Current Policy Dilemma: Choosing between rising death rates that overwhelm our health system and universal shutdowns that crush economic activity

“Smart Suppression” May Be a Third Option: “Smart Suppression” suppresses death rates to tolerable levels while minimizing economic damage

Basic Premise of Any Suppression Strategy: Maximize Healthcare Capacity and Limit Duration

- Maximize capacity by speeding expansion of adequate clinics, beds, personnel, and equipment (masks, ventilators, ECMOs, etc.)
- Limit duration by speeding testing and manufacture of anti-viral drugs and (ultimately) an effective vaccine

Basic Premise of Smart Suppression Strategy: Eradicate, Test, Follow Up, Enforce, and Inform

- (1) Eradicate: Initially, maximal shutdown for at least 4 weeks
- (2) Test: Extensive random testing everywhere plus intensive testing in hotspots
- (3) Follow Up: Register all “infected” and locate and register all “contacts”
- (4) Enforce: Self isolations and quarantines must be monitored and enforced
- (5) Inform: Population must be informed and mobilized to support effort

# HOW “SMART SUPPRESSION” WOULD WORK

## SMART SUPPRESSION: THE PLAN

### Who Is Succeeding With Smart Suppression:

- Certainly: Singapore, Taiwan, South Korea, and Hong Kong
- Possibly: China, Japan, and Germany

(1) Initial Eradication: Every successful plan either began w/ small number of identified infecteds or opted for initial regional shutdowns & containment (China, S. Korea)

### (2) Testing:

- No smart suppression will work without widespread testing, period.
- Adding serum antibody test to PCR (swab) test would be huge gain.

### (3) Follow up:

- Requires mobilizing personnel to track down and register all contacts.
- Method: interviews, electronic trails, cellphone GPS; in China, universal cellphone app.

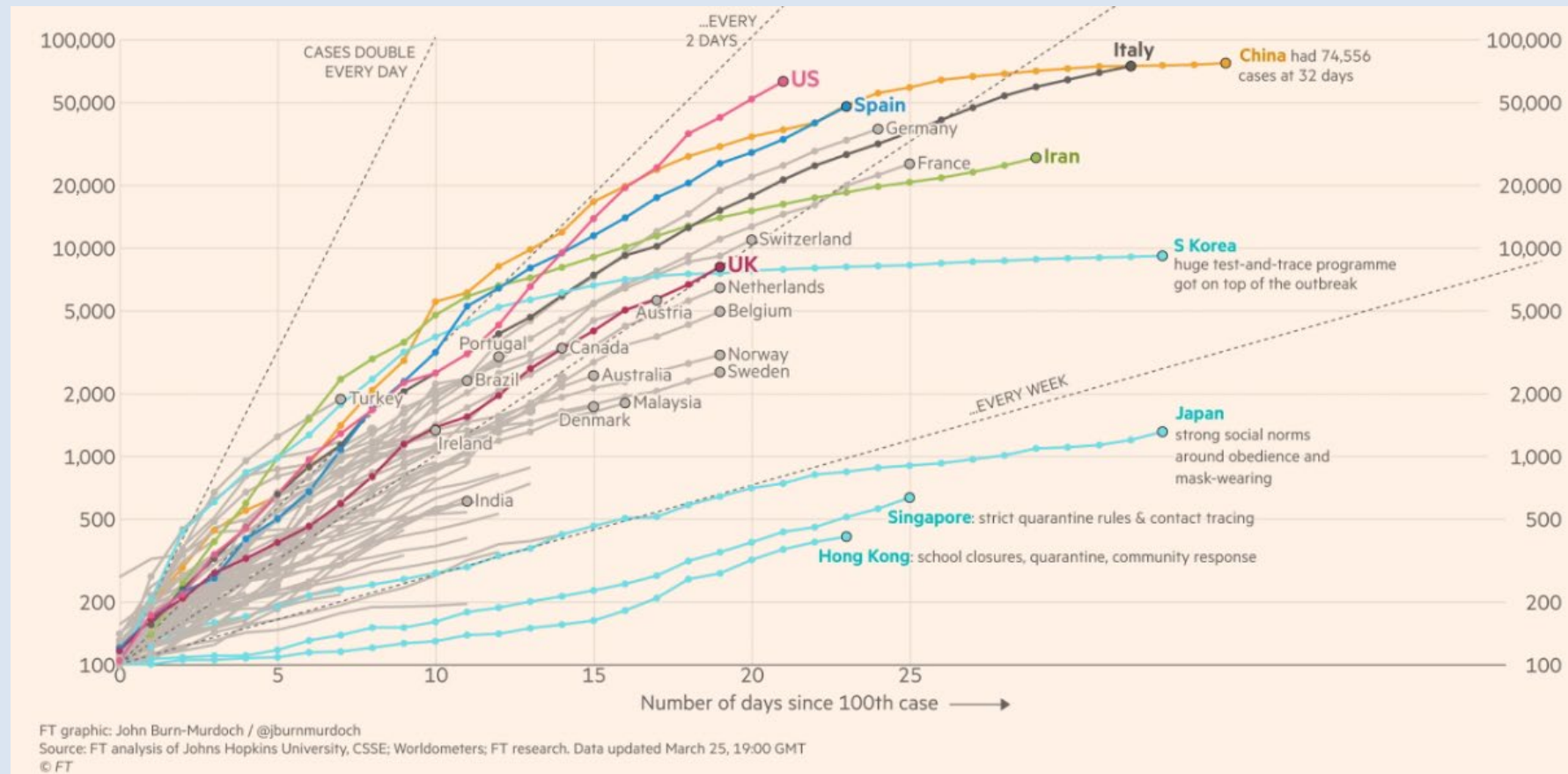
### (4) Enforcement (of Self Isolation or Quarantine):

- Mandatory cellphone app + 2x daily call; door cam; wrist band; honor system
- Color codes for everyone (China); earmarked cellphone shows up on map (S. Korea)

(5) Inform: Every successful plan includes accurate & real-time reporting to public of exact location of outbreaks; and recruits public help in tracking contacts.

# WHICH COUNTRIES SUCCEEDING AT SMART SUPPRESSION?

## Country By Country COVID-19 Case Trajectories, March 25



# THE PROMISE OF ANTI-VIRALS...

## ANTI-VIRAL DRUG CANDIDATES:

### 69 Possible Drugs Now Listed As Anti-SARS-CoV-2 Agents

- Updated list (03/23/2020) published in study by UCSF Quantitative Bioscience Institute
- 69 total drugs; 24 are already FDA approved; rest are in various preclinical stages

### Pro-Immune Interventions: Boosts body's own acquired immunity defense against virus

- Identify and destroy infected cells
- Shut down protein production in infected cells
- Speeds up RNA destruction in all cells
- Example: Interferon alfa-2b and (possibly) metformin and resveratrol

### Anti-Inflammatory Interventions: Suppresses dysfunctional inflammation response

- Prevents systemic inflammatory response (“cytokine storm”)
- Retards acute respiratory distress syndrom (ARDS)
- Example: tocilizumab (Actemra) and vitamin D (supplement, not drug)

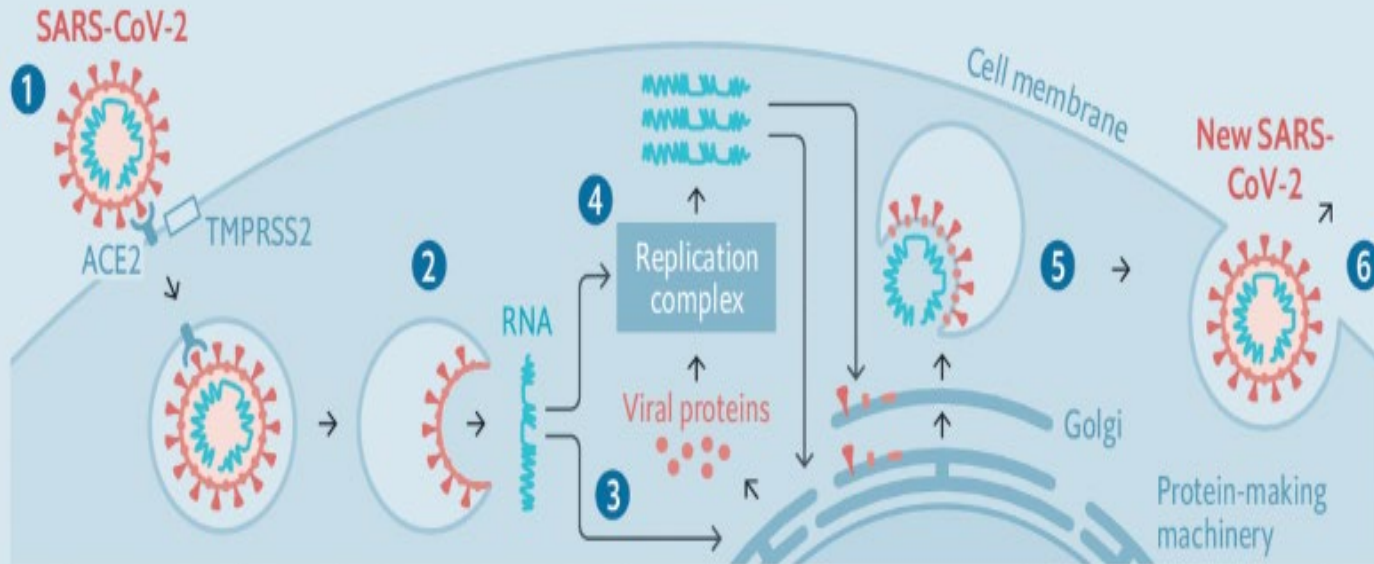
### Viral Entry or Replication Interventions: Works on the virus itself

- Foils some process needed for virus to enter host cell or to assemble new copies
- Three basic modes of intervention (that we know of); see next chart.

# HOW COVID-19 INFECTS...

## Hijack

How SARS-CoV-2 replicates itself in the cells of those infected



1 Spike protein on the virion binds to ACE2, a cell-surface protein. TMPRSS2, an enzyme, helps the virion enter 2 The virion releases its RNA 3 Some RNA is translated into proteins by the cell's machinery 4 Some of these proteins form a replication complex to make more RNA 5 Proteins and RNA are assembled into a new virion in the Golgi and 6 released

Sources: Song et al., *Viruses*, 2019; Jiang et al., *Emerging Microbes and Infections*, 2012; *The Economist*

## HOW ANTI-VIRAL DRUGS MAY WORK

### Protease Inhibitors

- Prevents splitting of enzymes necessary for virus to enter cell (stage 1) or build proteins (stages 3).
- Examples: Kelatra (ritonavir+lopinavir); chloroquine; lisinopril.

### RNA>RNA Polymerase Chain Reaction Inhibitors

- Prevents catalyzing replication of RNA to RNA: process essential to virus but one that normal cell does not perform (stage 4). Examples: favipiravir.

### Nucleoside Analogues

- Introduces phony nucleotides that prevent viral RNA from completing the production of proteins (Stages 4 & 5).
- Examples: remdesivir.