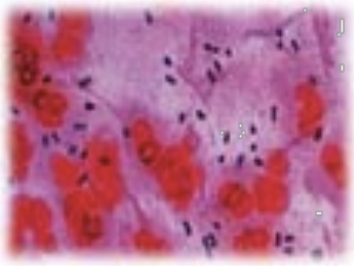





5 November 2020

Health Economics: Economic Evaluation in Practice: Case Studies in Health Economics

COVID-19 as a Case Study



Andrew Farlow
University of Oxford
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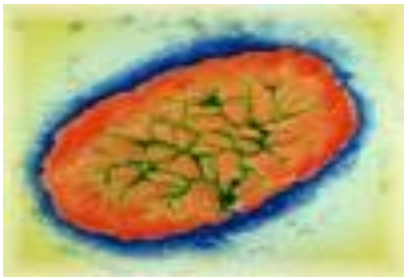
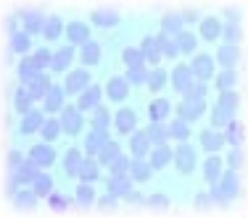
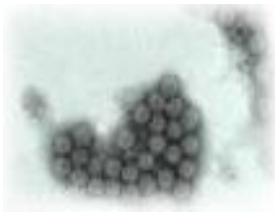









Overview

- 1) Antivirals
  - Systematic Review of cost-effectiveness of antivirals
  - A worked example, Remdesivir
  - A reworked example… Group Breakout
- 2) Personal Protective Equipment: Cost effectiveness of protecting public health workers
- 3) Pandemic Control
  - Systematic Review of interventions
  - Cost-effectiveness of strategies for COVID-19 epidemic control: A Case study for KwaZulu-Natal
- 4) Vaccine: Cost effectiveness case study of a hypothetical COVID-19 vaccine

By the end of this session, students will:

- Be able to critically evaluate health economic studies, their strengths and weaknesses, and possible ways to improve.
- We are less interested in memorizing techniques and more in creating a literate, nuanced, analytical understanding of what is going on in such studies…tthe flow of their creation (e.g. long lists of ingredients) and execution.
- Value the role of health economic tools in decision making, even during a pandemic, but be especially aware of the impact of uncertainty and how to handle it (COVID-19 being extreme example of this);
- Understand the role and value of randomized controlled trials (e.g. for antivirals and vaccines) but the challenge when they can't be done (e.g. of lock-down measures);
- Be able to critically evaluate and use literature reviews.

Questions as you go…

- How does the group interpret the evidence presented?
- Will it lead to good advice?
- What are the real-world limitations?
- How in particular is uncertainty handled?
- What new tasks might you set the modelers (or yourselves) to do so that you can make an informed decision in your own setting?
- How does a pandemic complicate things!

1) ANTIVIRALS

Antivirals…A Review of published Economic Evaluations

ScienceDirect

Contents lists available at **sciencedirect.com**
Journal homepage: **www.elsevier.com/locate/jval**

Themed Section: COVID-19

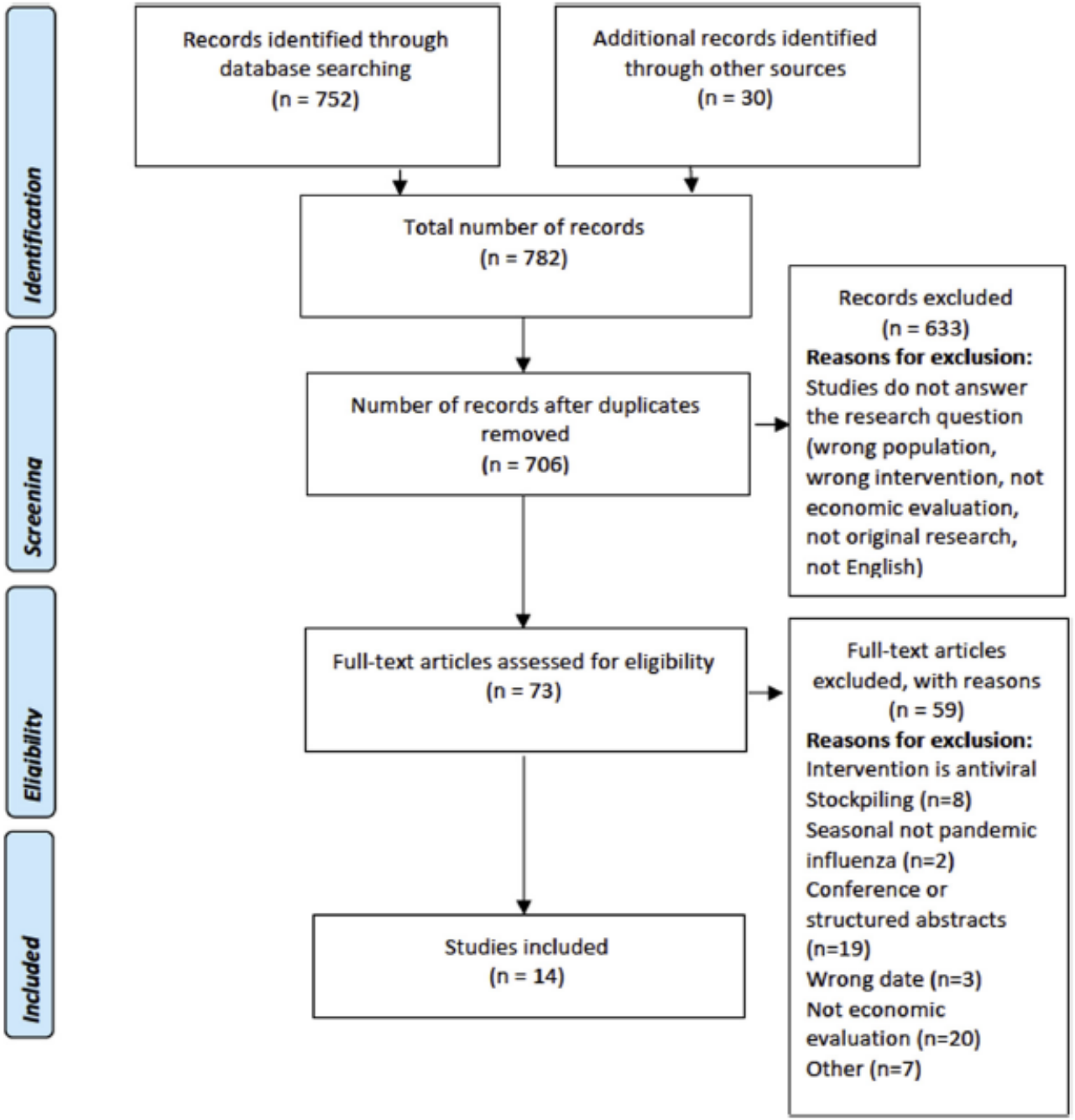
Cost-Effectiveness of Antiviral Treatments for Pandemics and Outbreaks of Respiratory Illnesses, Including COVID-19: A Systematic Review of Published Economic Evaluations

Dalia M. Dawoud, PhD,* Khaled Y. Soliman, MSc

Studies used

- Full economic evaluations of antivirals as a treatment in pandemics and outbreaks of respiratory illnesses (MERS, SARS, H1N1, and COVID-19).
- Databases: Medline (EBSCOhost), EMBASE (Ovid),
- EconLit (Ovid), National Health Service Economic Evaluation Database (Ovid), and Health Technology Assessment (Ovid).
- Published in the last 10 years (2010 onward)

Figure 1. Review flowchart.



Those studies that made the final cut (for reference, not detail)

- **Did you see how few made it?**
- United States (6/14, 42.9%)
- Australia (3/14, 21.4%)
- (1/14, 7.1%) each in United Kingdom, The Netherlands, China, Canada.
- Most societal perspective (10/14, 71.4%)
- (9/14, 64.3%)reported the antiviral agent used
- (7/14, **50%) cost-utility analyses, using quality-adjusted life-years (QALYs) as the main health outcome measure.**
- (4/14, **28.6%) cost-effectiveness analyses,**
- (2/14, 14.3%) cost-consequence analyses,
- (1/14, **7.1%) was a cost-benefit analysi**s
- 6 months to lifetime.
- **All used simulation models** to assess cost-effectiveness of interventions
- data on **effectiveness** of the antivirals based **from published studies**
- Antiviral treatment compared to **either doing nothing or to strategies that do not include antivirals**
- In the included cost-utility analyses, the ICER of the strategies including antivirals ranged from $68/QALY-gained to $39 674/QALY-gained from a societal perspective

Quality Assessment criteria:

(A template: I will just pick a few to highlight and skip most now)

- Does the model structure adequately reflect the nature of the topic under evaluation?
- Is **the time horizon sufficiently long to reflect all important differences in costs and outcomes**?
- Are **all important and relevant outcomes** included?
- Are the estimates of baseline outcomes from the best available source?
- Are the estimates of relative intervention effects from the best available source?
- Are all **important and relevant costs** included?
- Are the estimates of resource use from the best available source?
- Are the **unit costs of resources from the best available source**?
- Is an **appropriate incremental analysis** presented or can it be calculated from the data?
- Are all important parameters whose values are uncertain subjected to **appropriate sensitivity analysis**?
- Has **no potential financial conflict of interest** been declared?

SHORT CLASS DISCUSSION

- All are focused on H1N1 pandemic. So, how is that useful for COVID-19?
- Only 14?
- All rather rich-world focused.
- Can you base advice on specific antivirals for your own countries on this?

Some (interesting) results of search… first few of each only, just for the feel of what such studies do

Table 1. Study characteristics.

Study	Country and Currency	Population	Intervention(s) and Comparator	Type of Evaluation	Analysis Approach
Lee et al 2010[22]	United States US dollars	Adult patients presenting to the clinic or emergency room with influenza-like illness symptoms. 2 separate cohorts: younger adults (ages 20 to 64 years) and older adults (ages 65 to 85 years) Under both seasonal (not presented here) and pandemic influenza scenarios	7 strategies of testing and treating: (1) using clinical judgment alone to guide antiviral use, (2) using PCR to determine whether to initiate antivirals, (3) using a rapid (point-of-care) test to determine antiviral use, (4) using combination of a point-of-care test and clinical judgment, (5) using clinical judgment and confirming the diagnosis with PCR testing, (6) treating all with antivirals, and (7) not treating anyone with antivirals (comparator) Antiviral regimen: 75 mg of oseltamivir twice a day for 5 days	CUA	Monte Carlo decision analytic computer simulation
Lugner et al 2010[16]	The Netherlands Euros	Population of The Netherlands in 2007 High-risk groups include immunocompromised individuals, people with chronic respiratory diseases, and all people older than 65 years in nursing homes.	No antiviral treatment Antiviral treatment within the first 48 hours of symptoms Antiviral used: oseltamivir	CEA	Static (decision tree) and dynamic (SEIR [Susceptible-Exposed-Infectious-Removed]) models
Perlroth et al 2010[19]	United States US dollars	Demographically typical US community under pandemic influenza conditions	48 possible combinations of 4 social distancing strategies (child social distancing, adult social distancing, school closures, and household quarantine) and 2 antiviral medication treatments (antiviral treatment and antiviral household prophylaxis) and a "do nothing" strategy Antiviral treatment: A strategy in which patients with diagnosed cases (80% of symptomatic individuals) are given an antiviral within 48 hours of symptom onset at a probability of 30%, 60%, or 90%, depending on the compliance scenario, for 5 days. Antiviral used: oseltamivir (zanamivir in sensitivity analysis)	CUA	Networked individual-level computational model

First few results…

Table 1. Continued

Perspective	Time Horizon	Cost Categories	Cost Year	Discounting	Health Outcome(s)	Source of Antiviral Efficacy Data
Societal Third-party payer	Lifetime	Medications Hospitalization Clinic visits Staff time Tests Adverse events	2009	Costs: 3% Outcomes: 3%	Primary: QALYs Other: Mortality Hospitalization Side effects	Published systematic reviews and meta-analysis
Societal	NR	Over the counter drugs Visits to general practitioner (GP) Antibiotic prescriptions owing to influenza-related complication Hospitalizations Therapeutic intervention with AV drugs Productivity loss	2005	Costs: Not discounted Health outcomes: 1.5%	Primary outcome: Life years Other outcomes: hospitalization	Published literature
Societal	NR	Outpatient visits-Hospitalization Antiviral medication-Dispensing costs Daily wages Lost school days	2009	Costs: 3% Outcomes: 3%	Primary outcome: QALYs Other outcomes: clinical cases averted, deaths averted	Published literature

Table 2. Results of included studies.

Study	ICER/net benefit of antiviral based strategies (vs comparator)	Cost-effectiveness threshold (if applicable)	Sensitivity and scenario analysis	Author's conclusion regarding antivirals
Lee et al 2010[22]	(Under pandemic influenza and 30% probability of influenza scenario) (A) Societal perspective: All adults: Clinical judgment dominant Younger adults (20-65 years): Clinical judgment, followed by PCR then PoC testing (all dominant) Older adults (65-85 years): PCR, then clinical judgment then PoC testing (all dominant) (B) Third-party payer perspective: All adults: Do nothing strategy (comparator), followed by clinical judgment ($47 841/QALY), and PoC testing ($202 124/QALY compared to clinical judgment) Younger adults (20-65 years): Clinical judgment ($30 098-$35 000) followed by PCR testing ($38 109-$46 432) Older adults (65-85 years): PCR testing dominated, followed by clinical judgment, and PoC testing ($287 530/QALY compared to clinical judgment)	$50 000 per QALY gained	-Deterministic sensitivity analysis -Probabilistic sensitivity analysis -Scenario analyses explored the decision for higher-risk adults (ie, double the risk of hospitalization and mortality), older adults, and higher-risk older adults	"When hospitalization risk and mortality were doubled, using clinical judgment (>/= 50% sensitive) to guide antiviral initiation emerged as the most cost-effective option with PCR testing being the closest competitor but only when at least 20% of cases were influenza. Among older adults (65+ years old), employing PCR to guide antiviral initiation emerged as the most cost-effective option with the closest competitor being clinical judgment when judgment sensitivity was at least 50%. Treating all patients with antivirals appeared to be cost-effective only in older adults."
Lugner et al 2010[16]	Direct healthcare costs only: ICER: €1695 (static model) and €1637 (dynamic model) per life-year gained Societal perspective: intervention becomes cost-saving when including productivity loss	NA	Deterministic sensitivity analysis	Therapeutic use of antiviral drugs is cost-effective compared with non-intervention, irrespective of which model approach is chosen.
Perlroth et al 2010[19]	A strategy combining adult and child social distancing, school closure, antiviral treatment, and prophylaxis most cost-effective ICER: $31 300/QALY-gained All other strategies: dominated or extendedly dominated	$100 000 per QALY gained	Deterministic and probabilistic sensitivity analysis	Multilayered mitigation strategies that include adult and child social distancing, use of antivirals, and school closure are cost-effective for a moderate to severe pandemic. If antivirals are not available or are not effective, a strategy of adult and child social distancing and school closure is most effective, resulting in a cost per QALY-gained of $40 800, relative to a strategy of adult and child social distancing.

ANTIVIRAL COST EFFECTIVENESS CASE STUDY: REMDESIVIR

One study that had a go at COVID-19

Alternative Pricing Models for Remdesivir and Other Potential Treatments for COVID-19

Initially Published: May 1, 2020

Last Updated: June 24, 2020

ICER-COVID Model 1: Remdesivir Cost Recovery

- Two cost recovery pricing estimates
  - a price per treatment course that covers the minimal costs of production of the treatment
  - a price per treatment course that covers the cost of production plus the projected short-term spending by the manufacturer for clinical research directly related to the use of Remdesivir for COVID-19.
  - What is the logic of this?

Bits of ICER used:

- Marginal cost of producing Remdesivir (Hill et al. 2020)
- R&D costs of manufacturer
- R&D costs provided by government
- (Cost recovery not include admin-related costs)

Marginal cost of drugs

Table 1. Summary of costs of production and lowest/highest prices

Drug	Dose	Highest list price	Lowest list price	Estimated cost price (course)	Estimated cost price (day)
Remdesivir (10 Days)	100 mg IV BD (Day 1) 100 mg IV OD (Days 2–9)	___	___	$9	$0.93
Favipiravir (14 Days)	600 mg BD	___	$231 (China)	$20	$1.45
Lopinavir/ritonavir (14 Days)	400/100 BD	$503 (US)	$9 (Global Fund)* $15 (South Africa)	$4	$0.28
Hydroxychloroquine (14 Days)	400 mg OD	$19 (China)	$2 (India)	$1	$0.08
Chloroquine (14 days)	155 mg OD	$93 (US)	$0.20 (Bangladesh)	$0.30	$0.02
Azithromycin (14 days)	500 mg OD	$63 (US)	$5 (India)	$1.40	$0.10
Sofosbuvir/daclatasvir (14 days)	400/60 OD	$18,610 (US)	$6 (Pakistan)	$5	$0.39
Pirfenidone (28 days)	801 mg TD	$9606 (US)	$100 (India)	$31	$1.09
Tocilizumab (Per dose)	560 mg BD	$3383 (US)	$510 (Pakistan)	___	___

*Median price available to a range of low- and middle-income countries. OD: once daily; BD: two times daily; TD: three times daily; IV: intravenous.

Hill et all in the Journal of Virus Eradication (2020).

Relatively cheap to make because not complicated

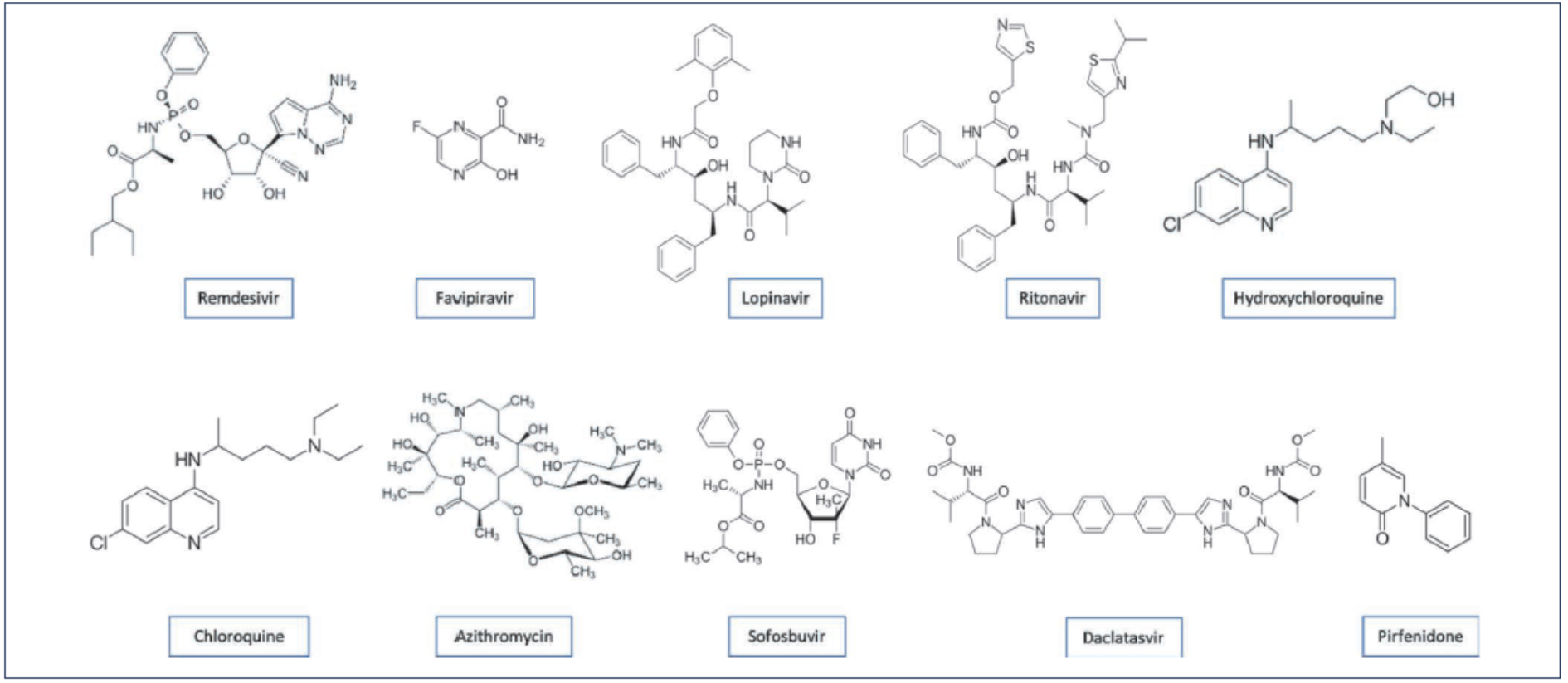


Figure 1. Chemical structures of candidate drugs

A few select treatment costs...being inexpensive to make is not unusual

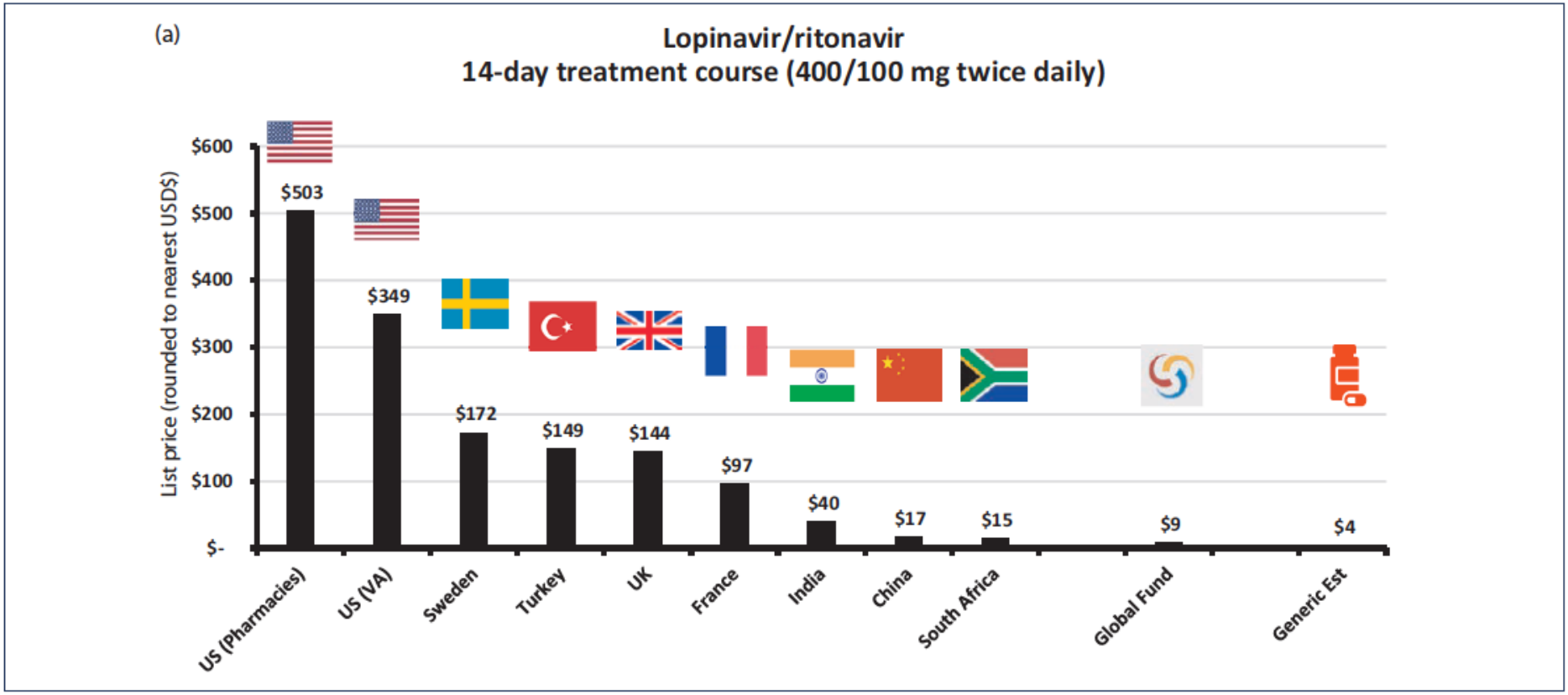


Figure 3. (a) List price cost of lopinavir/ritonavir in selected countries for 14-day treatment (400/100 mg twice daily).

A few more treatment costs

It is not unusual for current antivirals To be generically very cheap.

Why are we doing cost effectiveness analysis

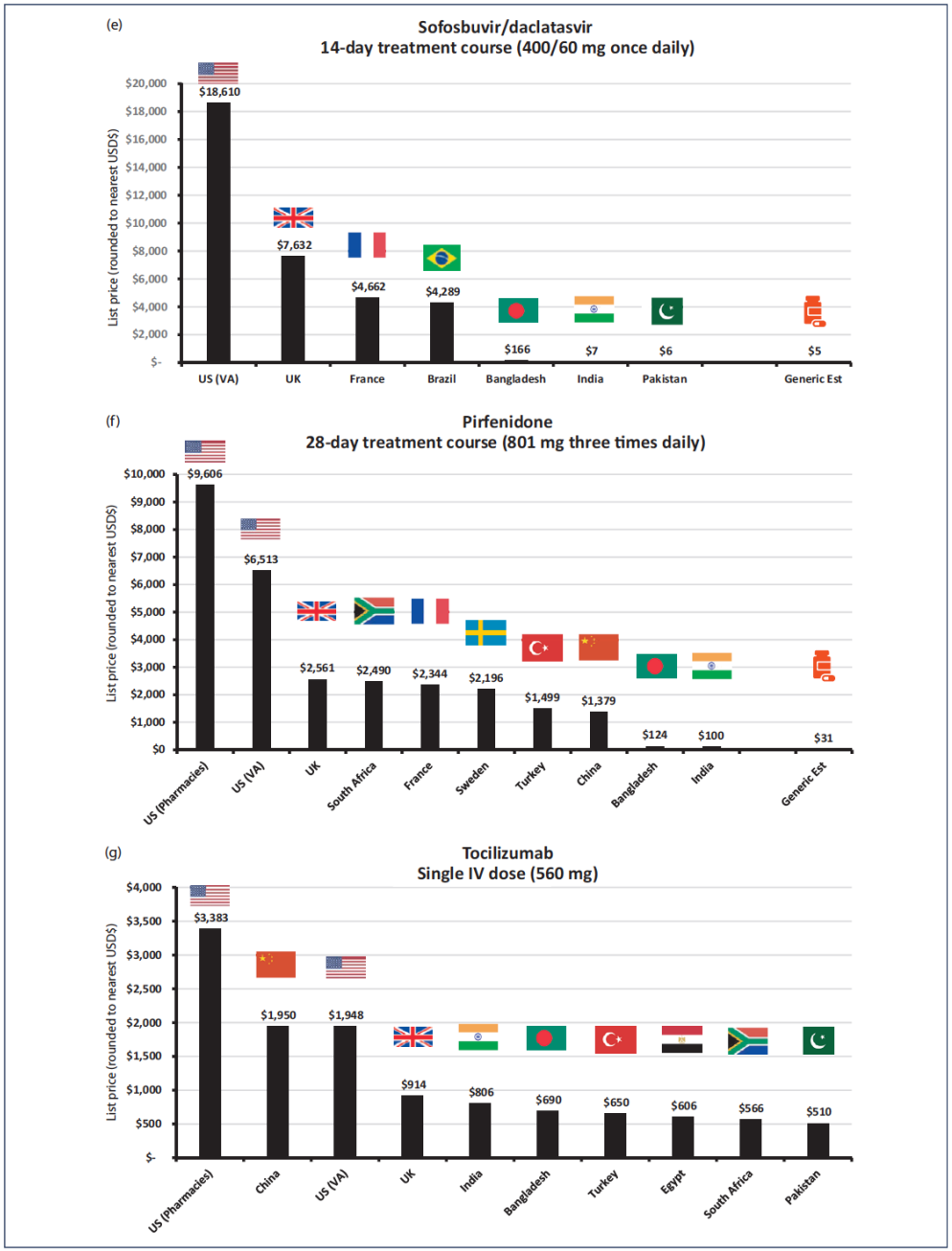


Figure 3, cont'd. (e) List price cost of sofosbuvir/daclatasvir in selected countries for 14-day treatment (400/60 mg once daily). (f) List price cost of pirfenidone in selected countries for 28-day treatment (801 mg three times daily). (g) List price cost of IV tocilizumab in selected countries for single dose (560 mg).

Calculating the treatment costs of Remdesivir

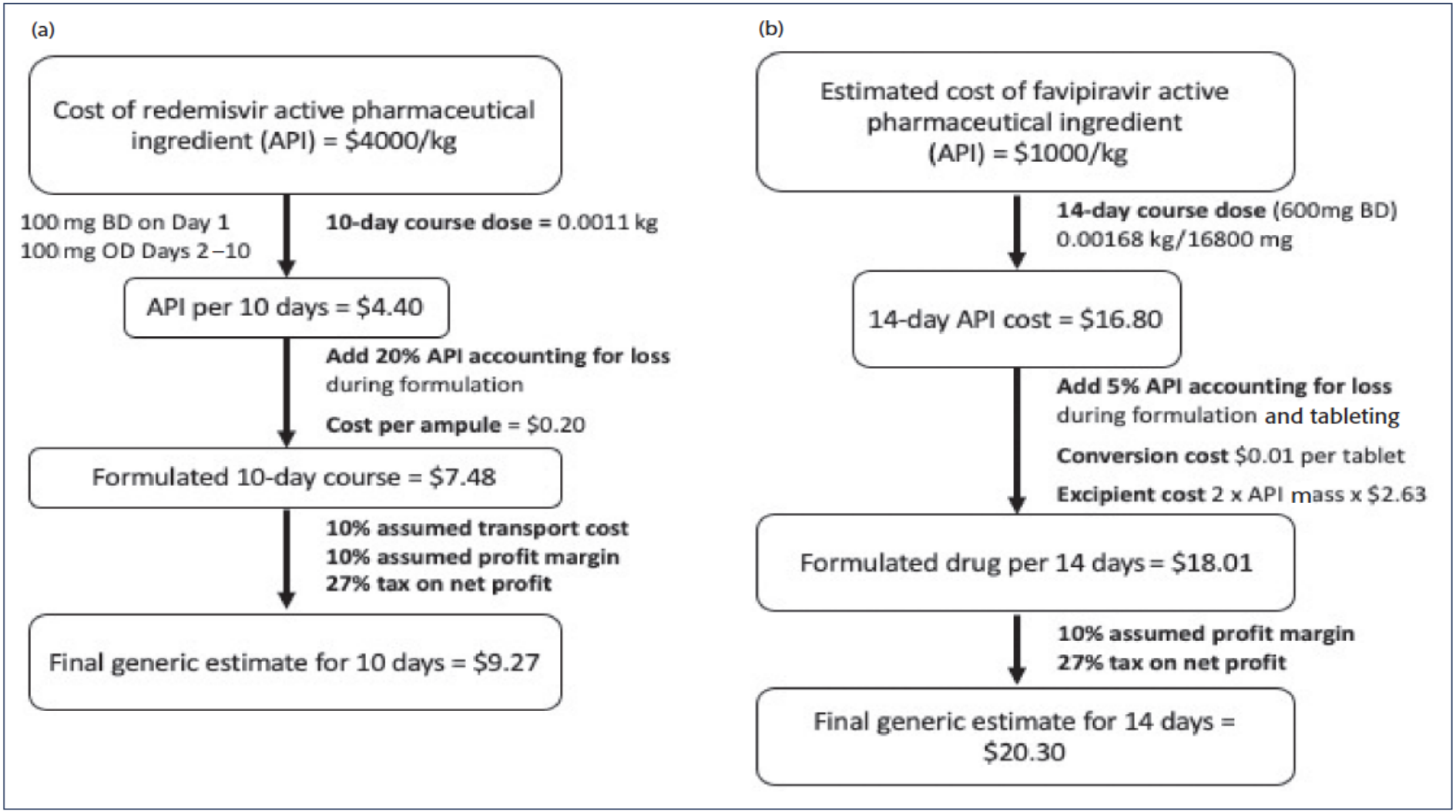


Figure 2. (a) Flowchart to show the calculation of treatment costs for remdesivir. (b) Flowchart to show the calculation of treatment costs for favipiravir. OD: once daily; BD; twice

Cost Recovery model results

Table 1. Cost Recovery Model Results

Minimal Marginal Cost*	Manufacturer R&D Costs	Public Investment in R&D Costs	Total Cost Recovery Pricing Options
$10-$600	Prior to COVID-19: *No data available*	Prior to COVID-19: $70 million	Option 1. Minimal marginal cost only: **$10-$600**
	Directly related to COVID-19: **$1 billion** projected by Gilead for 2020	Directly related to COVID-19: *No data available*	Option 2. Minimal marginal cost and 2020 projected manufacturer R&D costs: **$1,010-$1,600**¥

**Per 10-day course of treatment*

¥ *Assuming all costs recovered over 1 million patients receiving a 10-day treatment course*

$600 is the midpoint of generic prices being offered at time of the study

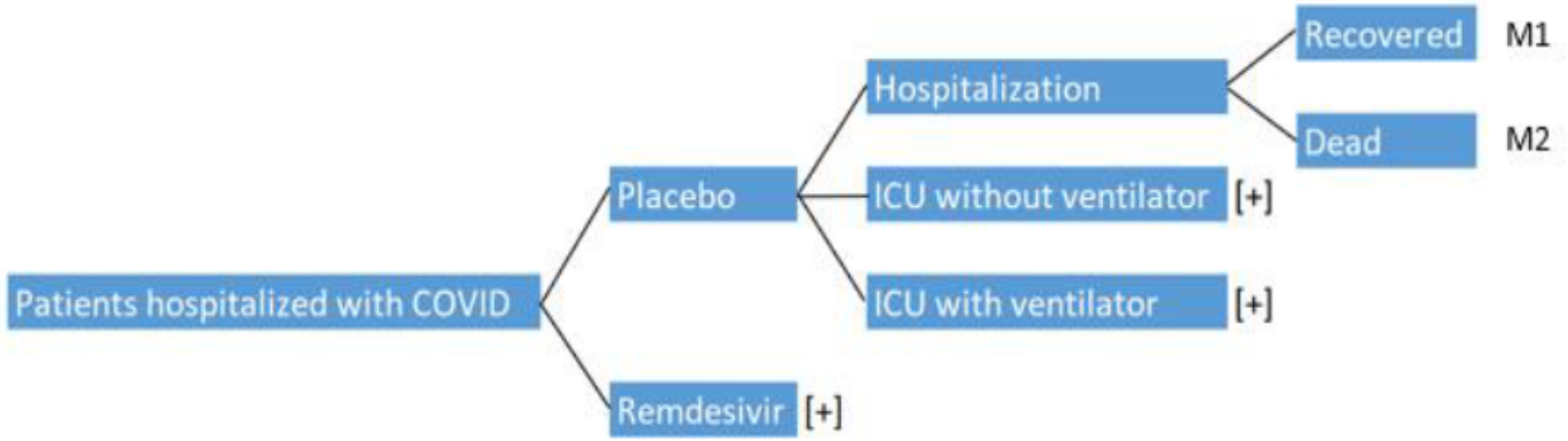
ICER-COVID Model 2: Remdesivir Cost-Effectiveness Analysis

- **Objective:** estimate the cost-effectiveness and corresponding cost-effectiveness price benchmarks of Remdesivir plus standard of care **versus standard of care alone** for hospitalized patients with COVID-19 and lung involvement.

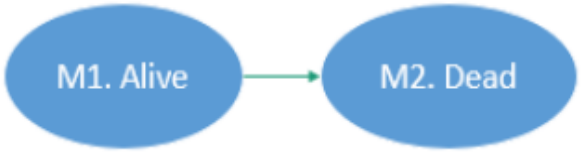
- What is 'standard of care'? And why is it part of the description?
- What if standard care changes?
- How will this affect analysis of other COVID-19 interventions?

Model 2: Decision Tree

Appendix Figure 1. Decision Tree Schematic



Appendix Figure 2. Markov Model



Evidence of treatment effectiveness taken from Adaptive COVID-19 Treatment Trial (ACTT-1) and other sources

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Final Report

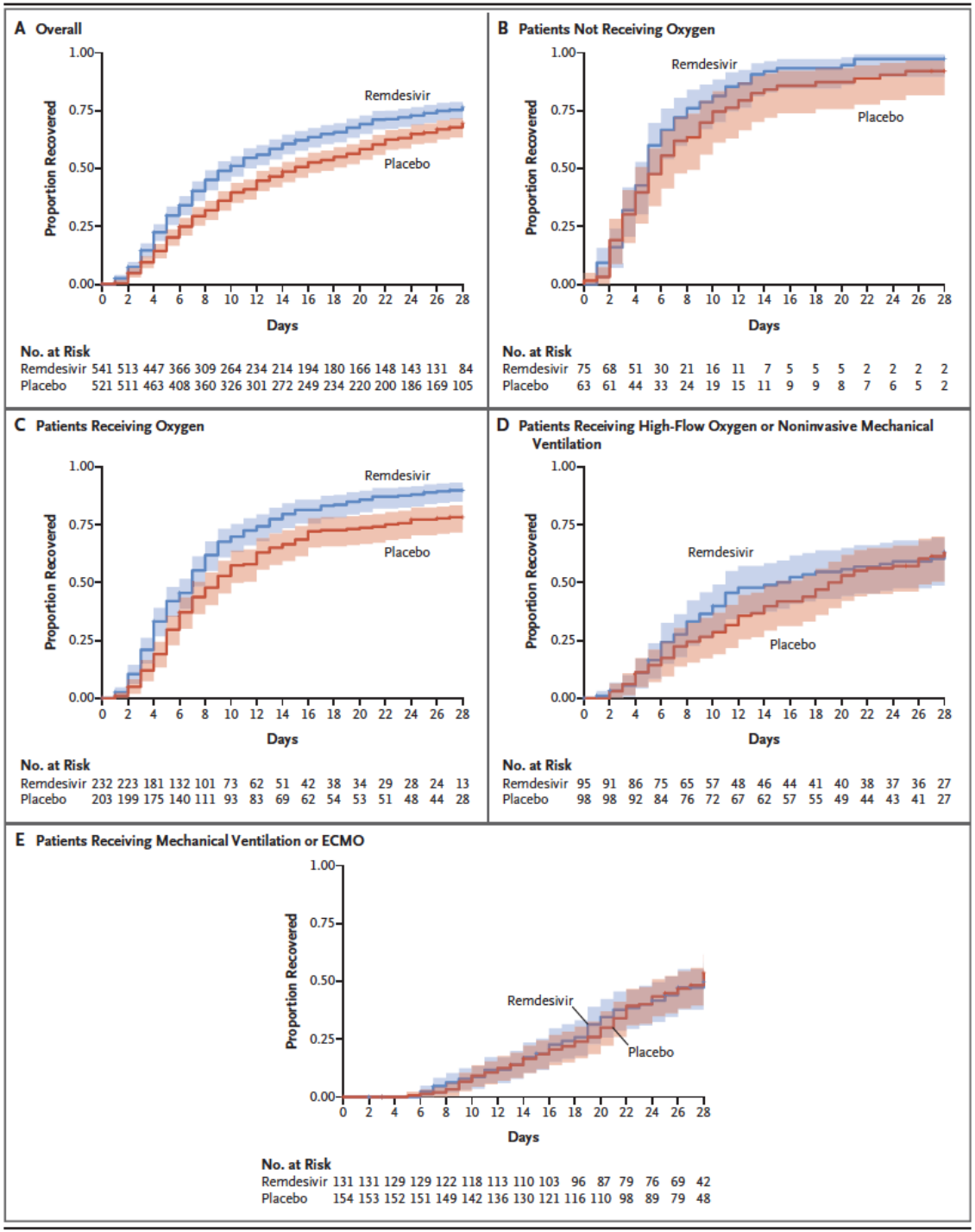
J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

SHORT BREAKOUT

- Please study the next three slides…
- Provide a comment on each

Results from the trial

Please discuss



Time to recovery

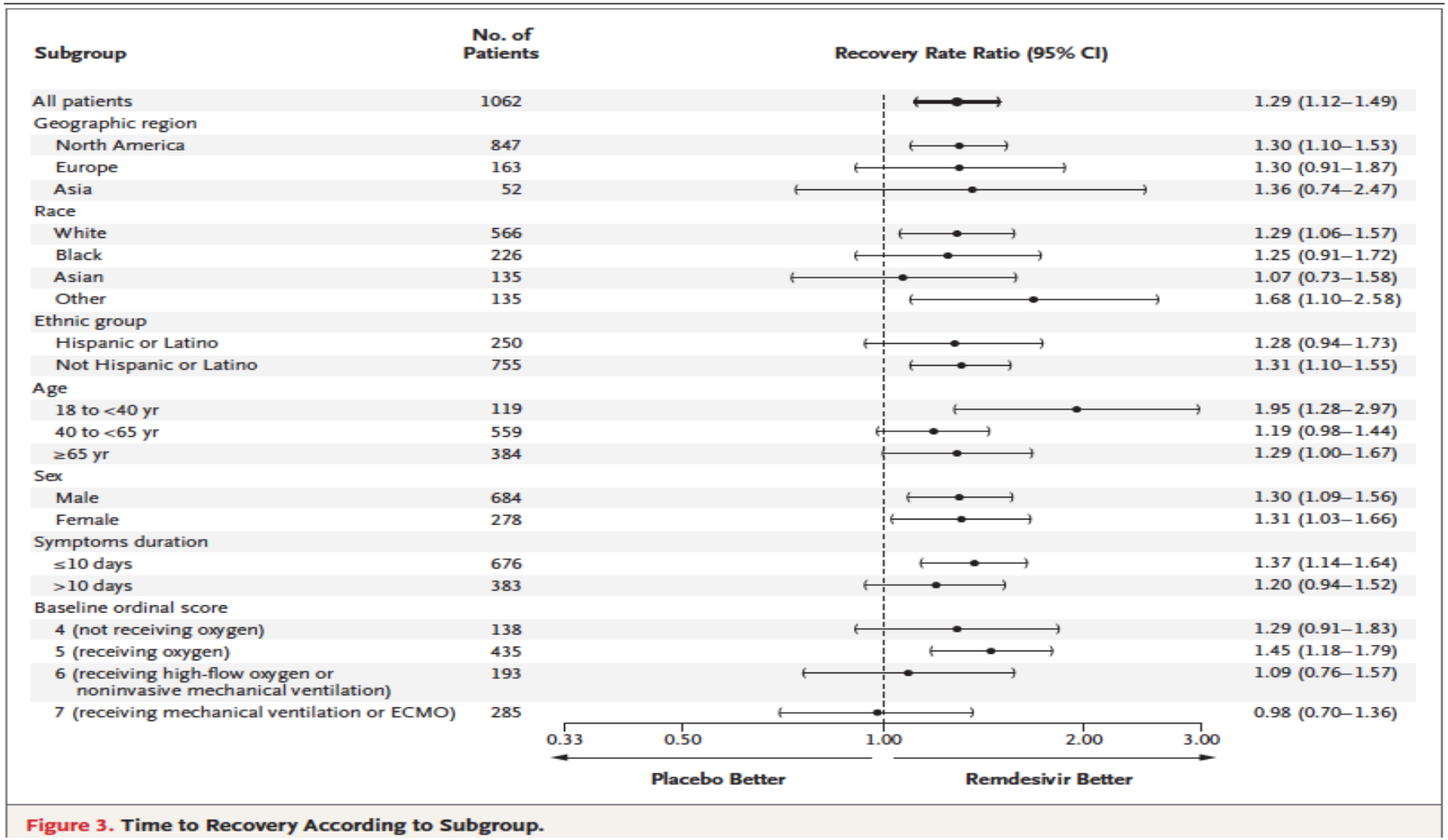


Figure 3. Time to Recovery According to Subgroup.

Please discuss...

Secondary outcomes

Spot the more interesting observations…

Table 3. Additional Secondary Outcomes.

	Remdesivir (N=541)	Placebo (N=521)	Rate Ratio (95% CI)
Median time to clinical improvement (95% CI) — days			
Improvement of one category on ordinal scale	7.0 (6.0 to 8.0)	9.0 (8.0 to 11.0)	1.23 (1.08 to 1.41)
Improvement of two categories on ordinal scale	11.0 (10.0 to 13.0)	14.0 (13.0 to 15.0)	1.29 (1.12 to 1.48)
Discharge or National Early Warning Score ≤2 for 24 hr*	8.0 (7.0 to 9.0)	12.0 (10.0 to 15.0)	1.27 (1.10 to 1.46)
			Difference (95% CI)
Hospitalization			
Median duration of initial hospitalization (IQR) — days†	12 (6 to 28)	17 (8 to 28)	−5.0 (−7.7 to −2.3)
Median duration of initial hospitalization among those who did not die (IQR) — days	10 (5 to 21)	14 (7 to 27)	−4.0 (−6.0 to −2.0)
Patients rehospitalized — % (95% CI)	5 (3 to 7)	3 (2 to 5)	2 percentage points (0 to 4)
Oxygen			
Median days receiving oxygen if receiving oxygen at baseline (IQR)	13 (5 to 28)	21 (8 to 28)	−8.0 (−11.8 to −4.2)
New use of oxygen			
No. of patients/total no.	27/75	28/63	
Percent of patients (95% CI)	36 (26 to 47)	44 (33 to 57)	−8 (−24 to 8)
Median days receiving oxygen (IQR)	4 (2 to 12)	5.5 (1 to 15)	−1.0 (−7.6 to 5.6)
Noninvasive ventilation or high-flow oxygen			
Median days of noninvasive ventilation or high-flow oxygen use during study if receiving these interventions at baseline (IQR)	6 (3 to 18)	6 (3 to 16)	0 (−2.6 to 2.6)
New use of new noninvasive ventilation or high-flow oxygen use during the study			
No. of patients/total no.	52/307	64/266	
Percent of patients (95% CI)	17 (13 to 22)	24 (19 to 30)	−7 (−14 to −1)
Median days of use during the study (IQR)	3 (1 to 10.5)	4 (2 to 23.5)	−1.0 (−4.0 to 2.0)
Mechanical ventilation or ECMO			
Median days of mechanical ventilation or ECMO during study if receiving these interventions at baseline (IQR)	17 (9 to 28)	20 (8 to 28)	−3.0 (−9.3 to 3.3)
New use of mechanical ventilation or ECMO during study			
No. of patients/total no.	52/402	82/364	
Percent of patients (95% CI)	13 (10 to 17)	23 (19 to 27)	−10 (−15 to −4)
Median days of use during the study (IQR)	21.5 (9 to 28)	23 (12 to 28)	1.0 (−6.0 to 8.0)

(Back to the method) CEA Model Settings:

- Perspective: Health System (always give the perspective)
- Time Horizon: Lifetime (always give a time horizon)
- Outcomes: Incremental costs, incremental QALYs, incremental evLYG (equal value of life-years gained, through hospital recovery or death..we don't focus on this for now)
- Structure:
  - **short-term decision tree**
    - duration in highest hospital level of care
    - probability of death from highest hospital level of care
  - **long-term Markov model**
    - health states of alive and dead with average age-based costs and consequences
- Population: hospitalized patients with COVID-19 and lung involvement (always… well, you know the drill by now

CEA Model Assumptions:

- All those who recover in either the standard of care or Remdesivir treatment arm are assigned **age- and gender-based probability of death**, quality of life, and average healthcare costs
- Treatment costs for Remdesivir are in addition to a bundled hospital payment
- **No cost or disutility for potential adverse events** separate from the cost and disutility of the admission
- **Cost and outcomes discounted at 3% per year**.

- What do you think of some of these assumptions?
- What are your initial thoughts on the price of the antiviral?

Decision tree populated by:

- Costs,
- quality-adjusted life years (QALYs)

- Lifetime costs and outcomes of remdesivir and standard of care by assigning the age-based average survival, healthcare costs, and utility for **all those who recovered from the COVID-19 hospital event in a Markov Model**
- perspective of the healthcare sector
- Scenario analysis in which there is a **cost savings from a reduction in length of stay**.
- Health system capacity measures, healthcare personnel impacts, and **impacts beyond that of the health system** were **not included in this analysis**.

- Again, what do you think of some of these assumptions?

Uncertainty

- Substantial clinical evidence uncertainty remains for Remdesivir.
- In particular, the comparative Remdesivir adjusted mortality benefit in ACTT-1 did **not reach statistical significance, and the mortality benefit is a driver of the cost-effectiveness findings.**
- Added scenario analyses assuming use of dexamethasone as part of standard care

Cost effectiveness results

*Table 2. Cost-effectiveness price benchmarks**

Threshold	Base-case (assuming mortality benefit)	Scenario analysis assuming no mortality benefit	Scenario analysis assuming dexamethasone in standard of care
$50,000 per QALY and per evLYG	**$4,580 - $5,080**	**$310**	**$2,520 - $2,800**
$100,000 per QALY and per evLYG	$18,640 - $19,630	$620	$12,120 - $12,700
$150,000 per QALY and per evLYG	$32,700 - $34,180	$930	$21,730 - $22,590

evLYG=equal value of life years gained

QALY=quality-adjusted life year

**For all cost-effectiveness price benchmarks that include a range, the lower value was derived from QALYs and the higher value was derived from evLYGs.*

IF remdesivir extends life and improves quality of life versus standard of care

BREAKOUT SESSION

- Please look at the following slides of information (to end of Topic 1).
- What are the implications for cost effectiveness of Remdesivir?
- In general, what are the challenges of doing cost effectiveness of new drugs and vaccines during a pandemic?

BUT…

BIOPHARMADIVE

BRIEF

Gilead's COVID-19 drug doesn't prevent deaths, large WHO study finds

By Ned Pagliarulo

Published Oct. 16, 2020

Squaring the WHO trial results with the NIH trial results is difficult, according to Taison Bell, an assistant professor of medicine and infectious disease doctor at the University of Virginia. But he said the SOLIDARITY results do not rule out a role for Veklury, when given at the right time to the right patients.

The SOLIDARITY manuscript, for example, presented results for patients on low- and high-flow oxygen together, whereas ACTT-1 separated data from those two groups and found a much larger benefit for those on low-flow oxygen support.

WHO SOLIDARITY

- What are the implications of this?

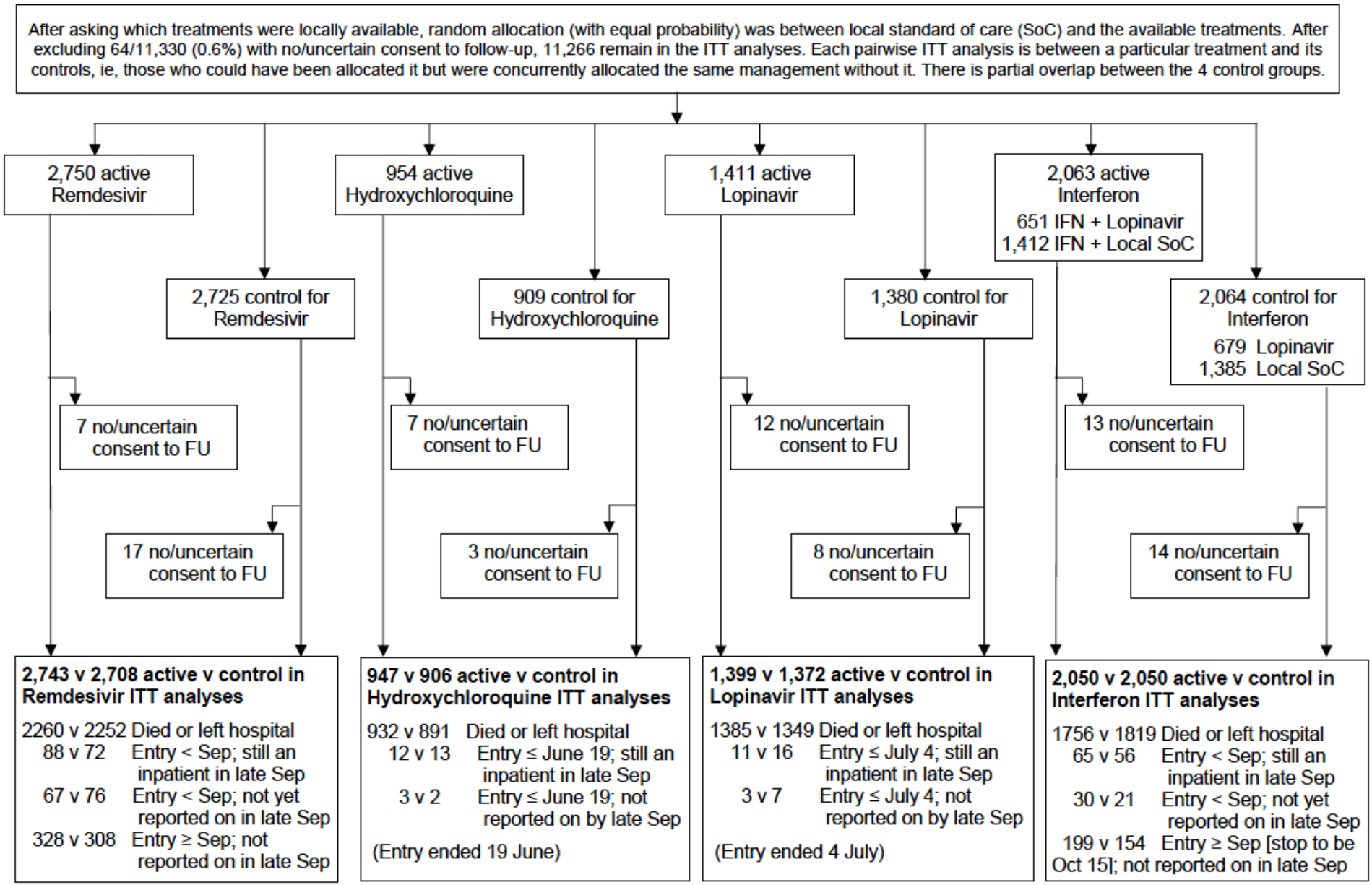
MedRxiv (October 15) version

Repurposed antiviral drugs for COVID-19 –interim WHO SOLIDARITY trial results

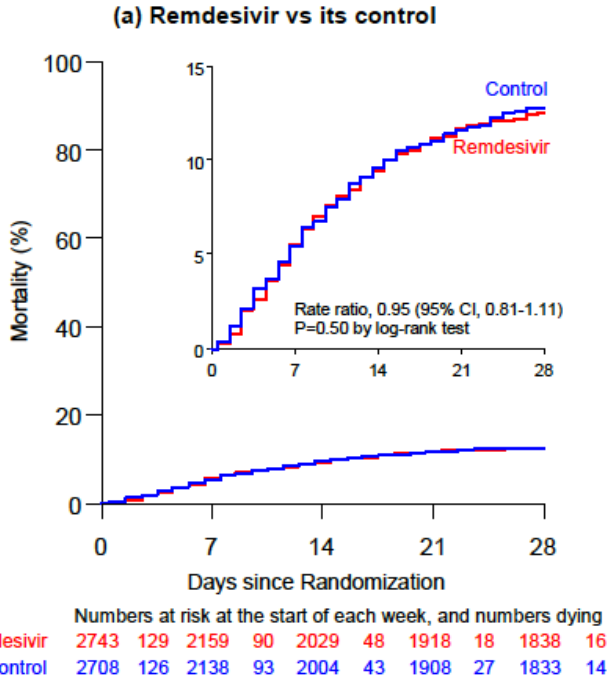
WHO Solidarity trial consortium*

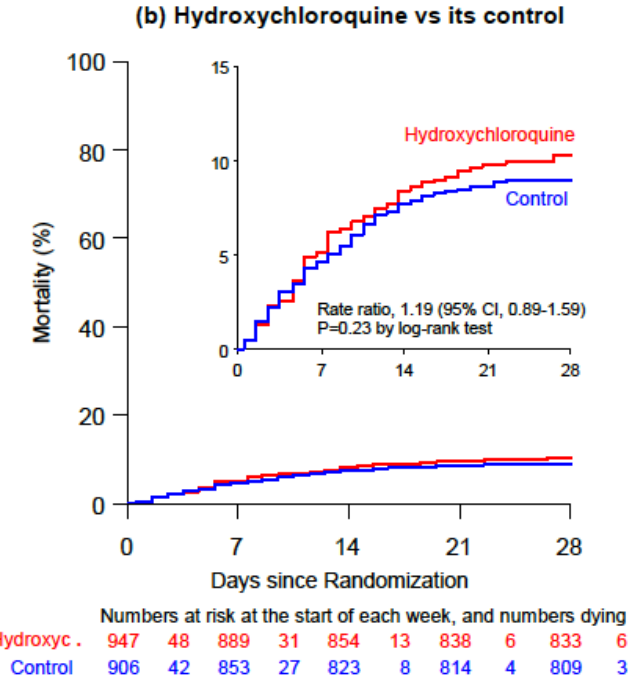
*A complete list of SOLIDARITY Trial investigators is provided in the Supplementary Appendix.

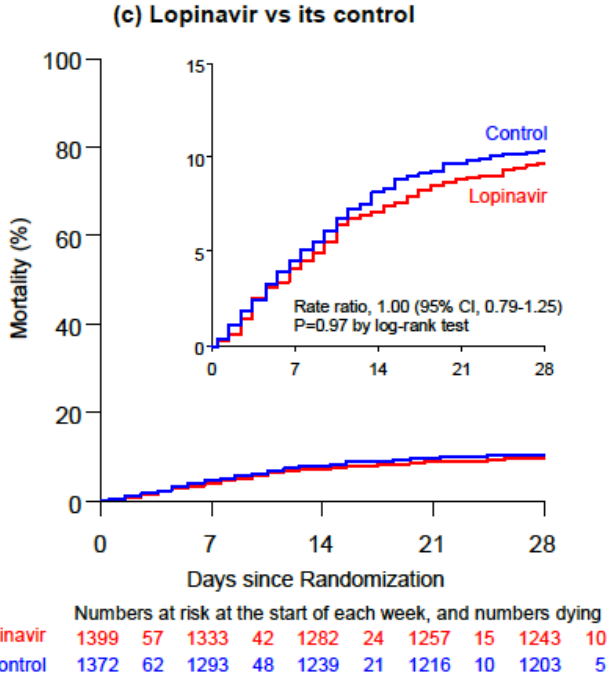
Figure 1. WHO Solidarity Trial – information to October 4, 2020 on entry, follow-up (FU) and intent-to-treat (ITT) analyses

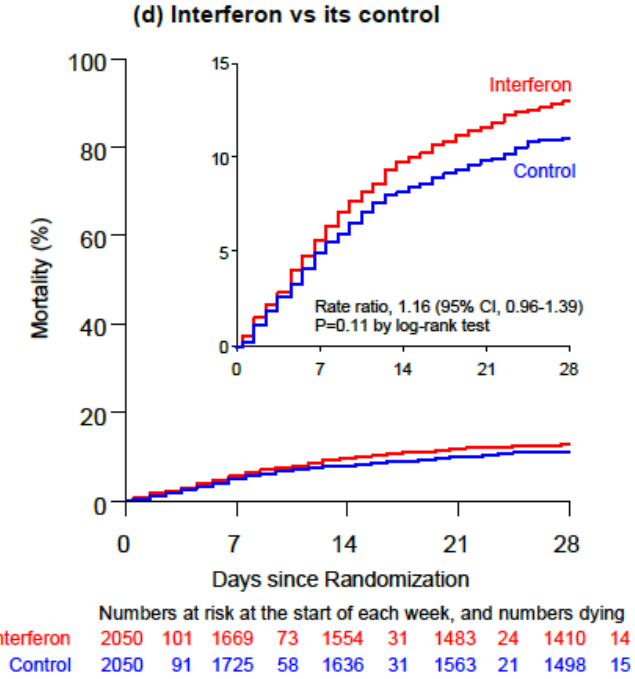


Effects on 28 –day mortality



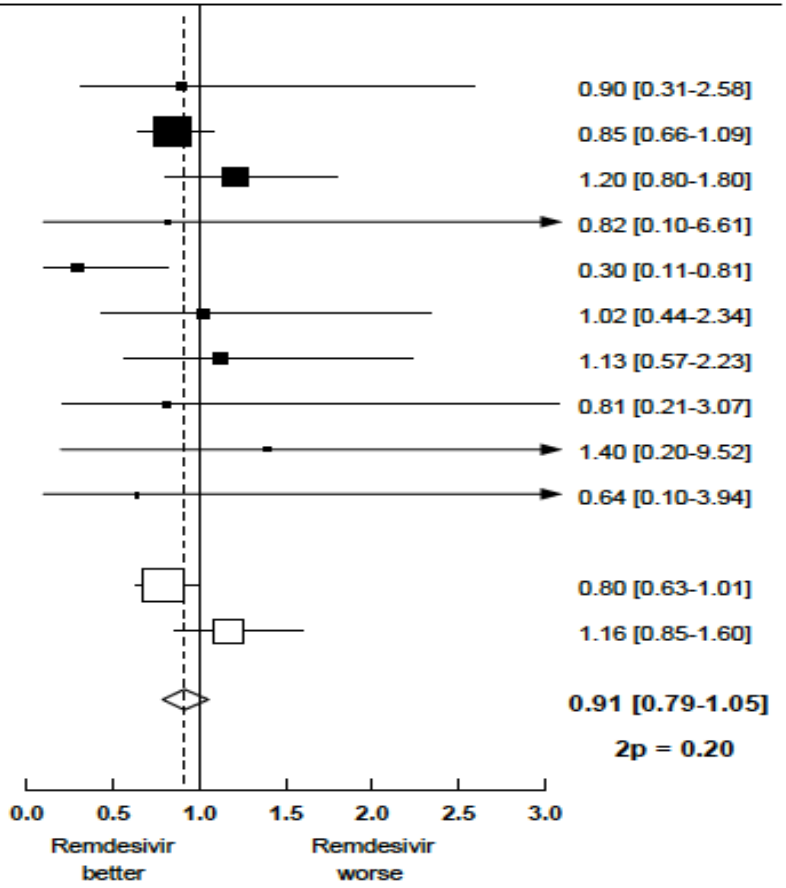






Remdesivir vs control: Meta-analysis in trials of random allocation of hospitalised COVID-19 patients

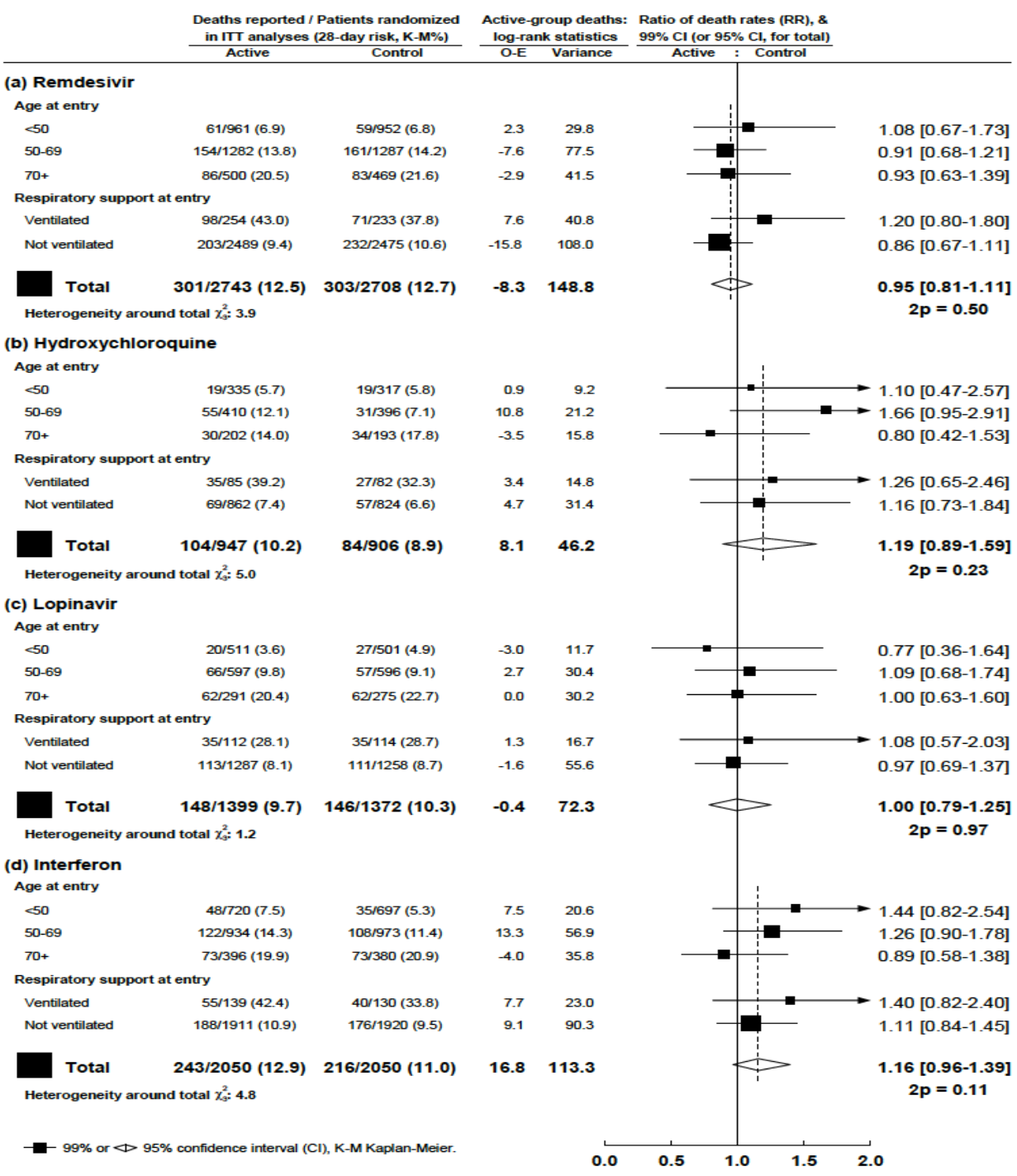
Trial name, and initial respiratory support	Deaths reported / Patients randomized in ITT analyses (28-day risk, K-M%) Remdesivir	Control	Remdesivir deaths: Observed-Expected (O-E)*	Var (O-E)	Ratio of death rates (RR), & 99% CI (or 95% CI, for total) Remdesivir : Control
Solidarity: no O_2	11/661 (2.0)	13/664 (2.1)	-0.6	6.0	0.90 [0.31-2.58]
Solidarity: low/hi-flow O_2	192/1828 (12.2)	219/1811 (13.8)	-16.9	101.8	0.85 [0.66-1.09]
Solidarity ventilation	98/254 (43.0)	71/233 (37.8)	7.6	40.8	1.20 [0.80-1.80]
ACTT: no O_2	3/75 (4.1)	3/63 (4.8)	-0.3	1.5	0.82 [0.10-6.61]
ACTT: low-flow O_2	9/232 (4.0)	25/203 (12.7)	-8.0	6.7	0.30 [0.11-0.81]
ACTT: hi-flow O_2 or non-invasive ventilation	19/95 (21.2)	20/98 (20.4)	0.2	9.6	1.02 [0.44-2.34]
ACTT: invasive ventilation	28/131 (21.9)	29/154 (19.3)	1.7	14.3	1.13 [0.57-2.23]
Wuhan: low-flow O_2	11/129 (8.5)	(7/68) x2† (10.3)	-0.8	3.7	0.81 [0.21-3.07]
Wuhan: hi-flow O2 or ventilation	11/29 (37.9)	(3/10) x2† (30.0)	0.6	1.8	1.40 [0.20-9.52]
SIMPLE: no O_2	5/384 (1.3)	(4/200) x2† (2.0)	-0.9	2.0	0.64 [0.10-3.94]
Subtotals					
Lower risk groups (with no ventilation)	231/3309 (7.0)	282/3277 (8.6)	-27.6	121.6	0.80 [0.63-1.01]
Higher risk groups	156/509 (30.6)	126/505 (25.0)	10.1	66.5	1.16 [0.85-1.60]
Total	**387/3818 (10.1)**	**408/3782 (10.8)**	**-17.5**	**188.2**	**0.91 [0.79-1.05]**
					2p = 0.20



■-/-□- 99% or ◁▷ 95% confidence interval (CI), K-M Kaplan-Meier.

* Log-rank O-E for Solidarity, O-E from 2x2 tables for Wuhan and SIMPLE, and w.log$_e$HR for ACTT strata (with the weight w being the inverse of the variance of log$_e$HR, which is got from the HR's CI). RR is got by taking log$_e$RR to be (O-E)/V with Normal variance 1/V. Subtotals or totals of (O-E) and of V yield inverse-variance-weighted averages of the log$_e$RR values.

Rate ratios of any death stratified by age and respiratory support at entry



An early study across ten hospitals in China (randomised, double-blind, placebo-controlled)

Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial

Yeming Wang, Dingyu Zhang*, Guanhua Du*, Ronghui Du*, Jianping Zhao*, Yang Jin*, Shouzhi Fu*, Ling Gao*, Zhenshun Cheng*, Qiaofa Lu*, Yi Hu*, Guangwei Luo*, Ke Wang, Yang Lu, Huadong Li, Shuzhen Wang, Shunan Ruan, Chengqing Yang, Chunlin Mei, Yi Wang, Dan Ding, Feng Wu, Xin Tang, Xianzhi Ye, Yingchun Ye, Bing Liu, Jie Yang, Wen Yin, Aili Wang, Guohui Fan, Fei Zhou, Zhibo Liu, Xiaoying Gu, Jiuyang Xu, Lianhan Shang, Yi Zhang, Lianjun Cao, Tingting Guo, Yan Wan, Hong Qin, Yushen Jiang, Thomas Jaki, Frederick G Hayden, Peter W Horby, Bin Cao, Chen Wang*

Summary

Background No specific antiviral drug has been proven effective for treatment of patients with severe coronavirus disease 2019 (COVID-19). Remdesivir (GS-5734), a nucleoside analogue prodrug, has inhibitory effects on pathogenic animal and human coronaviruses, including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in vitro, and inhibits Middle East respiratory syndrome coronavirus, SARS-CoV-1, and SARS-CoV-2 replication in animal

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April 29, 2020
https://doi.org/10.1016/
S0140-6736(20)31022-9

Some outcomes

	Remdesivir group (n=158)	Placebo group (n=78)	Difference*
Time to clinical improvement	21·0 (13·0 to 28·0)	23·0 (15·0 to 28·0)	1·23 (0·87 to 1·75)†
Day 28 mortality	22 (14%)	10 (13%)	1·1% (−8·1 to 10·3)
Early (≤10 days of symptom onset)	8/71 (11%)	7/47 (15%)	−3·6% (−16·2 to 8·9)
Late (>10 days of symptom onset)	12/84 (14%)	3/31 (10%)	4·6% (−8·2 to 17·4)
Clinical improvement rates			
Day 7	4 (3%)	2 (3%)	0·0% (−4·3 to 4·2)
Day 14	42 (27%)	18 (23%)	3·5% (−8·1 to 15·1)
Day 28	103 (65%)	45 (58%)	7·5% (−5·7 to 20·7)
Duration of invasive mechanical ventilation, days	7·0 (4·0 to 16·0)	15·5 (6·0 to 21·0)	−4·0 (−14·0 to 2·0)
Duration of invasive mechanical ventilation in survivors, days‡	19·0 (5·0 to 42·0)	42·0 (17·0 to 46·0)	−12·0 (−41·0 to 25·0)
Duration of invasive mechanical ventilation in non-survivors, days‡	7·0 (2·0 to 11·0)	8·0 (5·0 to 16·0)	−2·5 (−11·0 to 3·0)
Duration of oxygen support, days	19·0 (11·0 to 30·0)	21·0 (14·0 to 30·5)	−2·0 (−6·0 to 1·0)
Duration of hospital stay, days	25·0 (16·0 to 38·0)	24·0 (18·0 to 36·0)	0·0 (−4·0 to 4·0)
Time from random group assignment to discharge, days	21·0 (12·0 to 31·0)	21·0 (13·5 to 28·5)	0·0 (−3·0 to 3·0)
Time from random group assignment to death, days	9·5 (6·0 to 18·5)	11·0 (7·0 to 18·0)	−1·0 (−7·0 to 5·0)

Some other figures

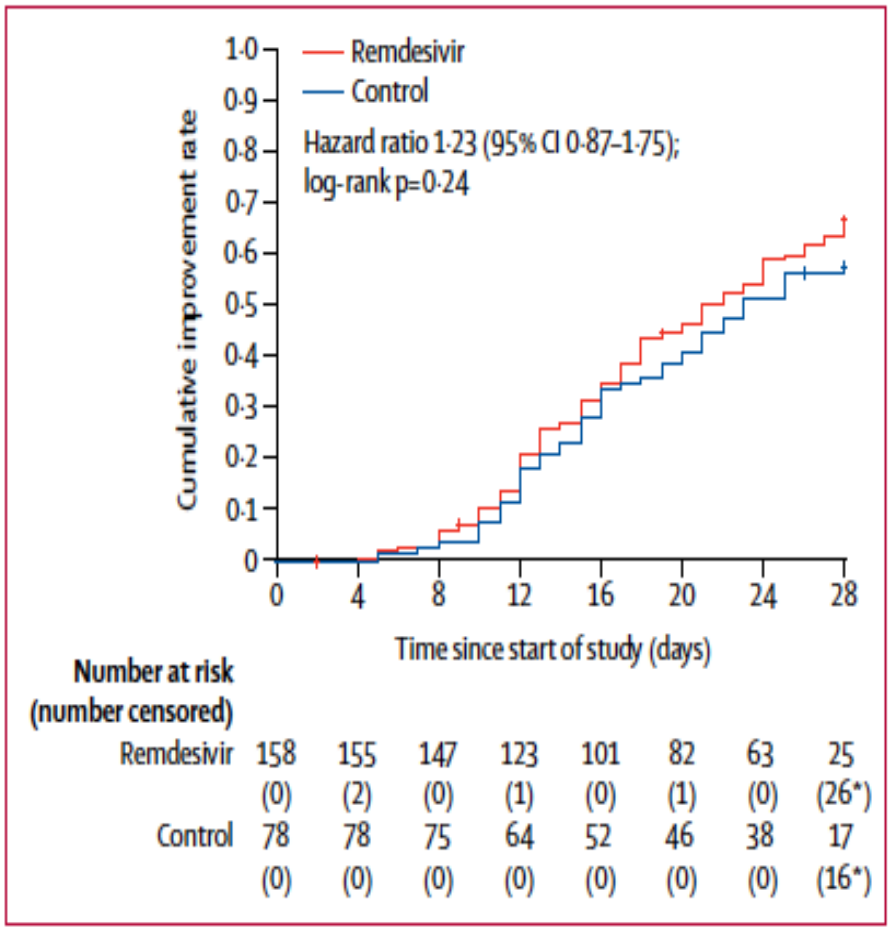


Figure 2: **Time to clinical improvement in the intention-to-treat population**
Adjusted hazard ratio for randomisation stratification was 1·25 (95% CI 0·88–1·78). *Including deaths before day 28 as right censored at day 28, the number of patients without clinical improvement was still included in the number at risk.

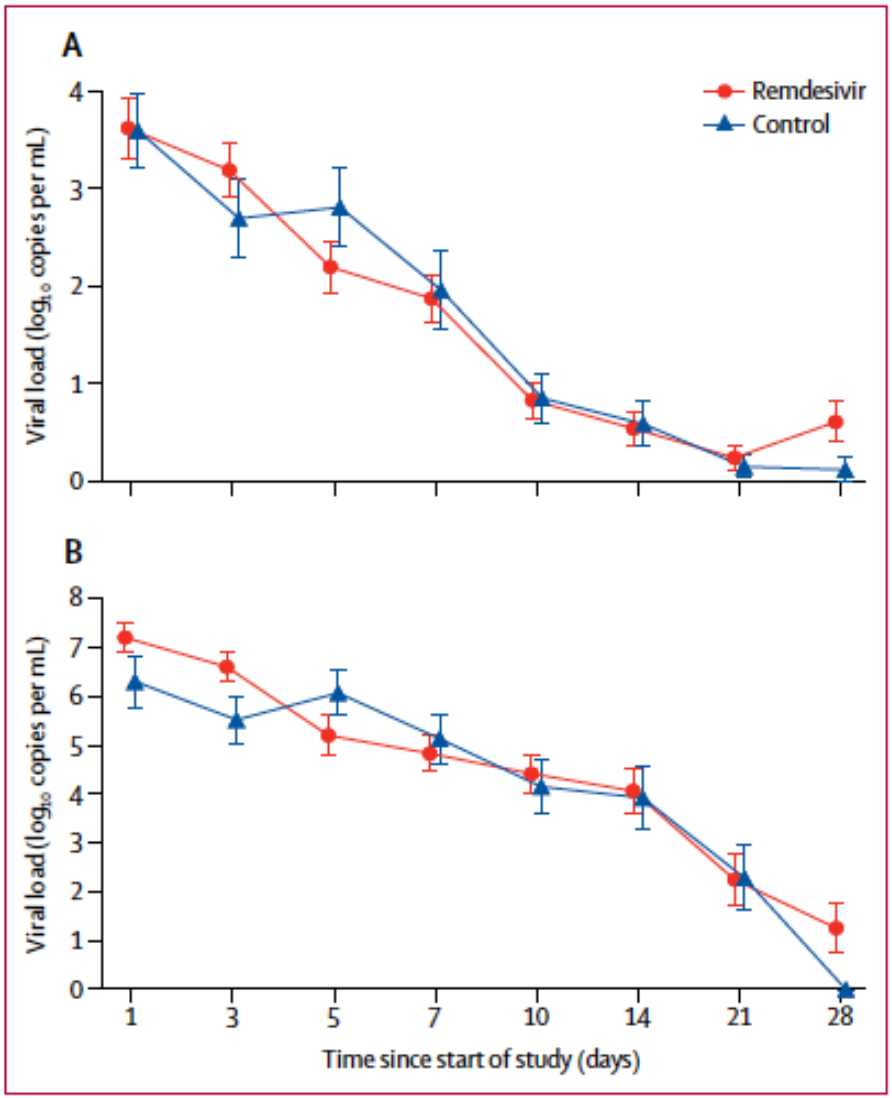


Figure 3: **Viral load by quantitative PCR on the upper respiratory tract specimens (A) and lower respiratory tract specimens (B)**

WHO SOLIDARITY

RESULTS

In 405 hospitals in 30 countries 11,266 adults were randomized, with 2750 allocated Remdesivir, 954 Hydroxychloroquine, 1411 Lopinavir, 651 Interferon plus Lopinavir, 1412 only Interferon, and 4088 no study drug. Compliance was 94-96% midway through treatment, with 2-6% crossover. 1253 deaths were reported (at median day 8, IQR 4-14). Kaplan-Meier 28-day mortality was 12% (39% if already ventilated at randomization, 10% otherwise). Death rate ratios (with 95% CIs and numbers dead/randomized, each drug vs its control) were: Remdesivir RR=0.95 (0.81-1.11, p=0.50; 301/2743 active vs 303/2708 control), Hydroxychloroquine RR=1.19 (0.89-1.59, p=0.23; 104/947 vs 84/906), Lopinavir RR=1.00 (0.79-1.25, p=0.97; 148/1399 vs 146/1372) and Interferon RR=1.16 (0.96-1.39, p=0.11; 243/2050 vs 216/2050). No study drug definitely reduced mortality (in unventilated patients or any other subgroup of entry characteristics), initiation of ventilation or hospitalisation duration.

CONCLUSIONS

These Remdesivir, Hydroxychloroquine, Lopinavir and Interferon regimens appeared to have little or no effect on hospitalized COVID-19, as indicated by overall mortality, initiation of ventilation and duration of hospital stay. The mortality findings contain most of the randomized evidence on Remdesivir and Interferon, and are consistent with meta-analyses of mortality in all major trials. (Funding: WHO. Registration: ISRCTN83971151, NCT04315948)

WHO SOLIDARITY

- What are the lessons of the WHO SOLIDARITY trial for cost effectiveness and decision-making in general?

2) (PPE) PROTECTING PUBLIC HEALTH WORKERS

RESEARCH ARTICLE

Cost-effectiveness and return on investment of protecting health workers in low- and middle-income countries during the COVID-19 pandemic

Nicholas Risko[1]*, Kalin Werner[2], O. Agatha Offorjebe[3], Andres I. Vecino-Ortiz[4], Lee A. Wallis[2], Junaid Razzak[1]

1 Johns Hopkins University School of Medicine, Baltimore, MD, United States of America, 2 University of Cape Town, Cape Town, South Africa, 3 University of Southern California Keck School of Medicine, Los Angeles, CA, United States of America, 4 Johns Hopkins University Bloomberg School of Public Health, Baltimore, MD, United States of America

"In scenarios where PPE remains scarce, 70-100% of HCWs will get infected, irrespective of nationwide social distancing policies,"

What are the consequences of this… and of avoiding this...

The objective

- To predict the health and economic consequences of **immediate investment in personal protective equipment (PPE) for health care workers (HCWs) in low- and middle income countries (LMICs)**
- Need to estimate cases and mortality for HCWs
- Need data to calculate cost effectiveness and return on investment (ROI) analysis
- using a decision-analytic model with **Bayesian multivariate sensitivity analysis and Monte Carlo simulation**.
- Data and model sources:
  - World Health Organization Essential Supplies Forecasting Tool
  - College of London epidemiologic model.

The urgency

- 80% of the world's population lives in LMICs
- fragile health systems with few resources make HCWs vulnerable to COVID-19
- Already shortage of HCWs
- Any more depletion due to illness, death or absenteeism could threaten the stability of LMIC health systems
- Global bidding war for PPE
- Export restrictions, supply chain disruptions

Not just LMICs…

Risk of COVID-19 among front-line health-care workers and the general community: a prospective cohort study

Long H Nguyen, David A Drew*, Mark S Graham*, Amit D Joshi, Chuan-Guo Guo, Wenjie Ma, Raaj S Mehta, Erica T Warner, Daniel R Sikavi, Chun-Han Lo, Sohee Kwon, Mingyang Song, Lorelei A Mucci, Meir J Stampfer, Walter C Willett, A Heather Eliassen, Jaime E Hart, Jorge E Chavarro, Janet W Rich-Edwards, Richard Davies, Joan Capdevila, Karla A Lee, Mary Ni Lochlainn, Thomas Varsavsky, Carole H Sudre, M Jorge Cardoso, Jonathan Wolf, Tim D Spector, Sebastien Ourselin†, Claire J Steves†, Andrew T Chan†, on behalf of the COronavirus Pandemic Epidemiology Consortium‡*

Summary

Background Data for front-line health-care workers and risk of COVID-19 are limited. We sought to assess risk of COVID-19 among front-line health-care workers compared with the general community and the effect of personal protective equipment (PPE) on risk.

Methods We did a prospective, observational cohort study in the UK and the USA of the general community, including

Lancet Public Health 2020; 5: e475–83

Published Online July 31, 2020 https://doi.org/10.1016/S2468-2667(20)30164-X

In late March 2020, 48% of healthcare facilities in the US were out or nearly out of N-95 respirators, 68% reported insufficient gowns (US Association for Professionals in Infection Control and Prevention)

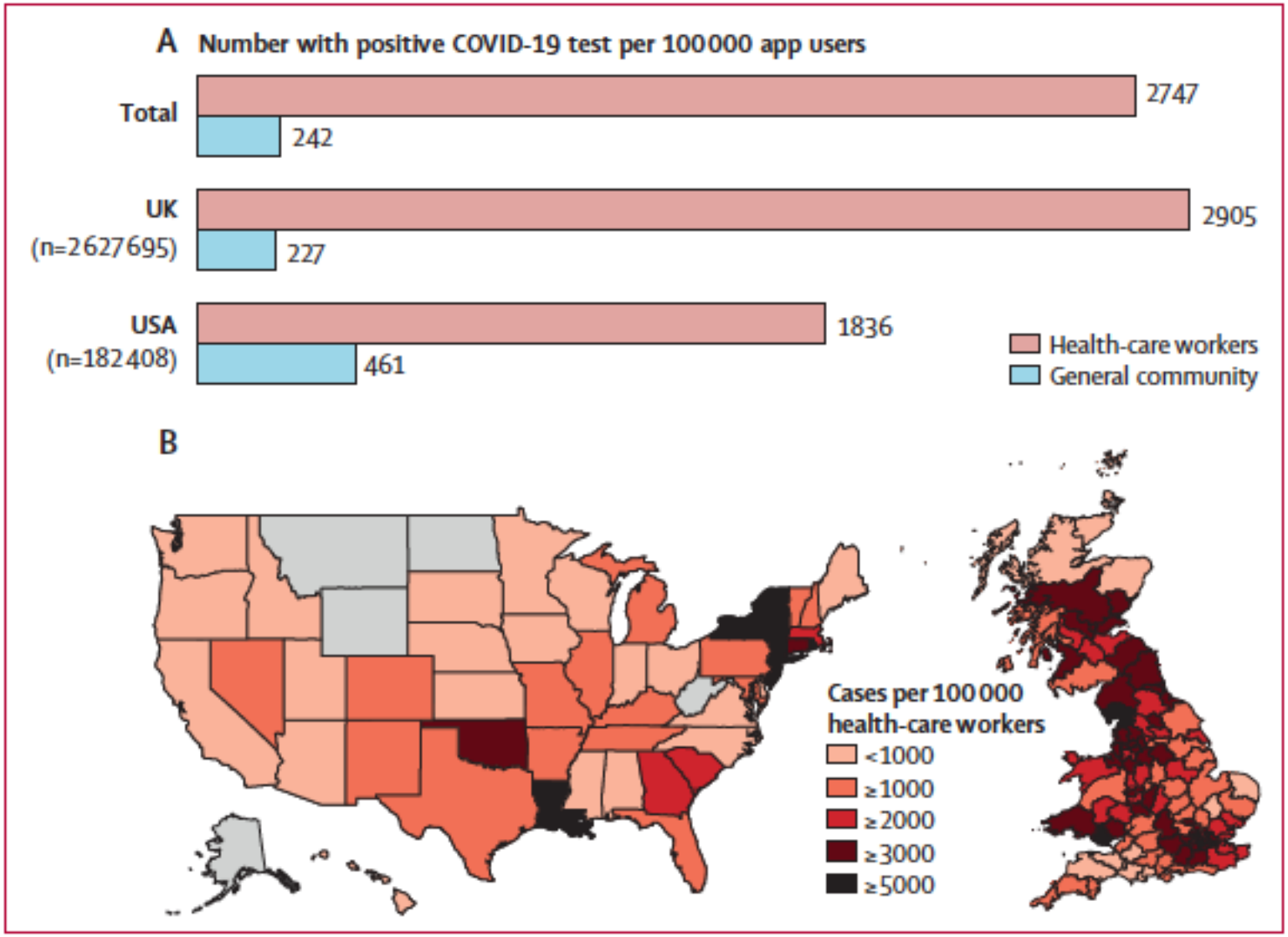


Figure: **Risk of testing positive for COVID-19 among front-line health-care workers**
(A) Between March 24 and April 23, 2020, considerable disparities were noted in prevalence of a positive COVID-19 test among front-line health-care workers compared with the general community, in both the UK and the USA. (B) Prevalence of a positive COVID-19 test reported by front-line health-care workers in the UK and the USA. Regions in grey did not have sufficient data for analysis. app=COVID-19 Symptom Study smartphone application.

US and UK

	Event/ person-days	Incidence (30-day)	Age-adjusted hazard ratio (95% CI)	Multivariate-adjusted hazard ratio (95% CI)	Health-care workers reporting reuse of PPE	Health-care workers reporting inadequate PPE
General community	3623/32 980 571	0·33%	1 (ref)	1 (ref)	..	..
Front-line health-care worker						
Inpatient	564/184 293	9·18%	23·58 (21·20–26·25)	24·30 (21·83–27·06)	23·7%	11·9%
Nursing homes	118/52 901	6·69%	16·48 (13·60–19·97)	16·24 (13·39–19·70)	15·4%	16·9%
Outpatient hospital clinics	51/45 217	3·38%	10·75 (8·10–14·27)	11·21 (8·44–14·89)	16·3%	12·2%
Home health sites	36/38 642	2·79%	7·79 (5·58–10·87)	7·86 (5·63–10·98)	14·7%	15·9%
Ambulatory clinics	44/66 408	1·99%	6·64 (4·90–9·01)	6·94 (5·12–9·41)	19·3%	11·8%
Other	73/64 310	3·41%	9·42 (7·42–11·96)	9·52 (7·49–12·08)	12·0%	13·8%

Model was stratified by 5-year age group, calendar date at study entry, and country and adjusted for sex (male or female), history of diabetes (yes or no), heart disease (yes or no), lung disease (yes or no), kidney disease (yes or no), current smoking (yes or no), and body-mass index (17·0–19·9 kg/m^2, 20·0–24·9 kg/m^2, 25·0–29·9 kg/m^2, and ≥30·0 kg/m^2). Ambulatory clinics include free-standing (non-hospital) primary care or specialty clinics and school-based clinics. PPE=personal protective equipment.

Table 5: **Front-line health-care workers and risk of testing positive for COVID-19, by site of care delivery (prespecified secondary analysis)**

Method

- Uses standard guidelines for cost effectiveness analyses
- Base case = full PPE supply maintains a low rate of HCW infection
- Compare to a scenario where inadequate PPE leads to higher rates of HCW infection.
- Seek:
  - cost per HCW case averted
  - cost per HCW death averted
- Results as incremental cost-effectiveness ratio (ICER): ratio of cost per each unit of effect.
- Return on Investment (ROI) analysis comparing societal economic gains from having HCWs fully protected against exposure, with current investment required to afford the PPE.
- (and a few other things)

Basics model…

- Basic Susceptible-Infectious-Removed (SIR) model, a standard epidemic model
- The three scenarios analyzed for their varying impact on case and mortality counts, from ICL model
  - unmitigated pandemic spread;
  - suppression with intensive social distancing after reaching a trigger of 1.6 deaths per 100,000 population per week;
  - suppression after reaching 0.2 deaths per 100,000 population per week.
- If PPE remains scarce and there is less than full suppression, 100% of HCWs are infected.

Imperial College model

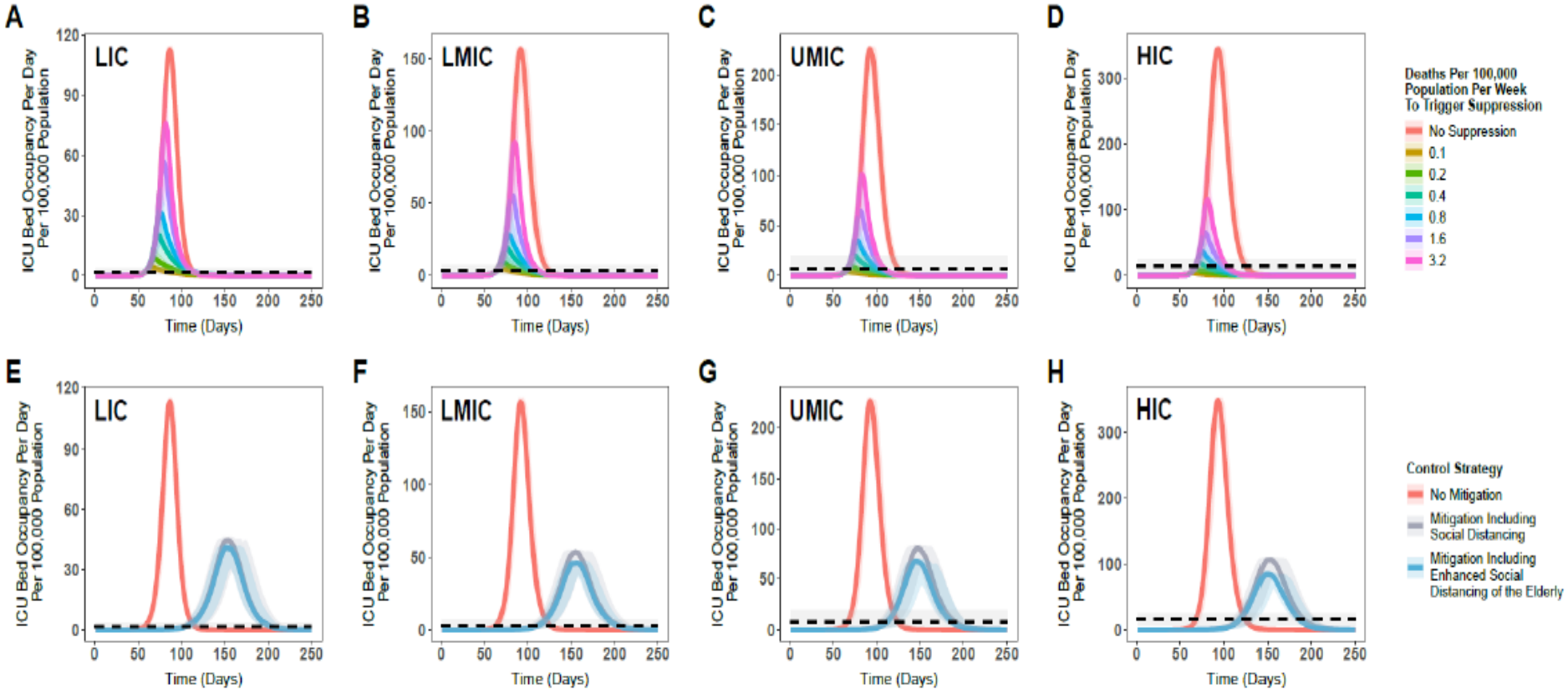


Figure 6: The impact of various control strategies in representative settings. Using an age-structured SEIR model along with demographies and contact patterns representative of LIC, LMIC, UMIC and HIC countries (columns left to right) the impact of different control strategies was. ICU bed occupancy per day per 100,000 population is shown in all figures. The top row shows impact of suppression (triggered at times dependent on when the rate of deaths per week increases beyond certain defined thresholds) and the bottom row shows mitigation (involving either mitigation involving general social distancing across the whole population or mitigation involving whole population social distancing as well as enhanced social distancing of the elderly)

Imperial model

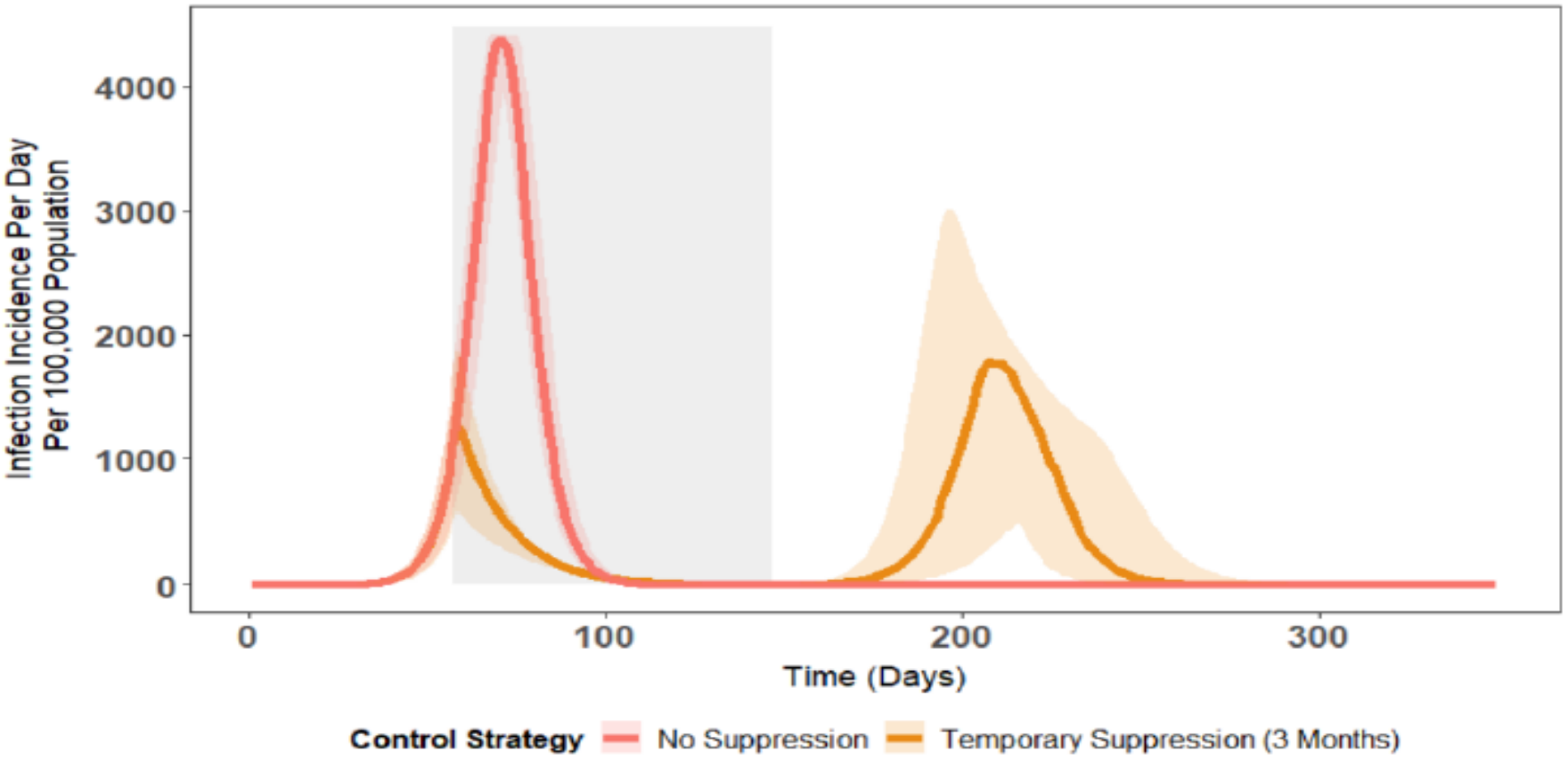


Figure 7: The impact of temporary suppression on infection incidence in a representative lower income setting. In this example, suppression is maintained for 3 months but is then stopped and contact patterns are assumed to return to previous levels.

Basics model…

- Default settings
  - medium clinical attack rate of 20%,
  - targeted testing strategy for all severe/critical patients
  - 10% of mild/moderate cases being tested
- incidence data for each country
- projected PPE costs
- Estimates of national mortality and hospitalizations from published projections calculated by the WHO Collaborating Center for Infectious Disease Modeling at the Imperial College of London (ICL)
- Bayesian sensitivity analysis of policy impact on **workforce depletion**.

BREAKOUT SESSION

- Now I have given you the basics, please study the next few slides (to end of Topic 2) for a few minutes to acquaint yourselves with the results.
- When we come back, I want someone to explain the sensitivity analysis
- And someone to explain the ROI results

Cases per strategy

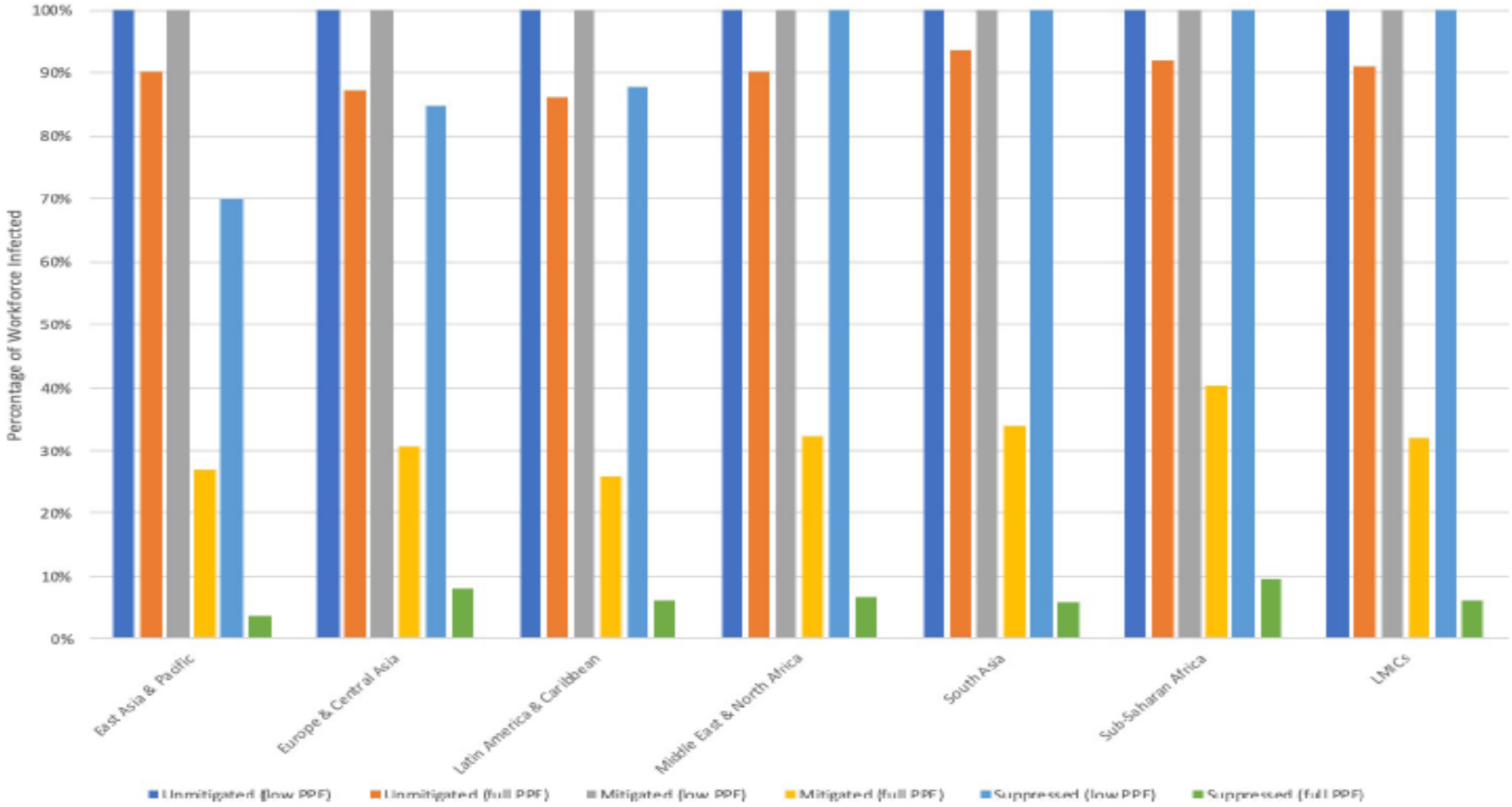


Fig 4. Cumulative HCW cases as a percentage of total workforce, by strategy.

Mortality of HCW per strategy

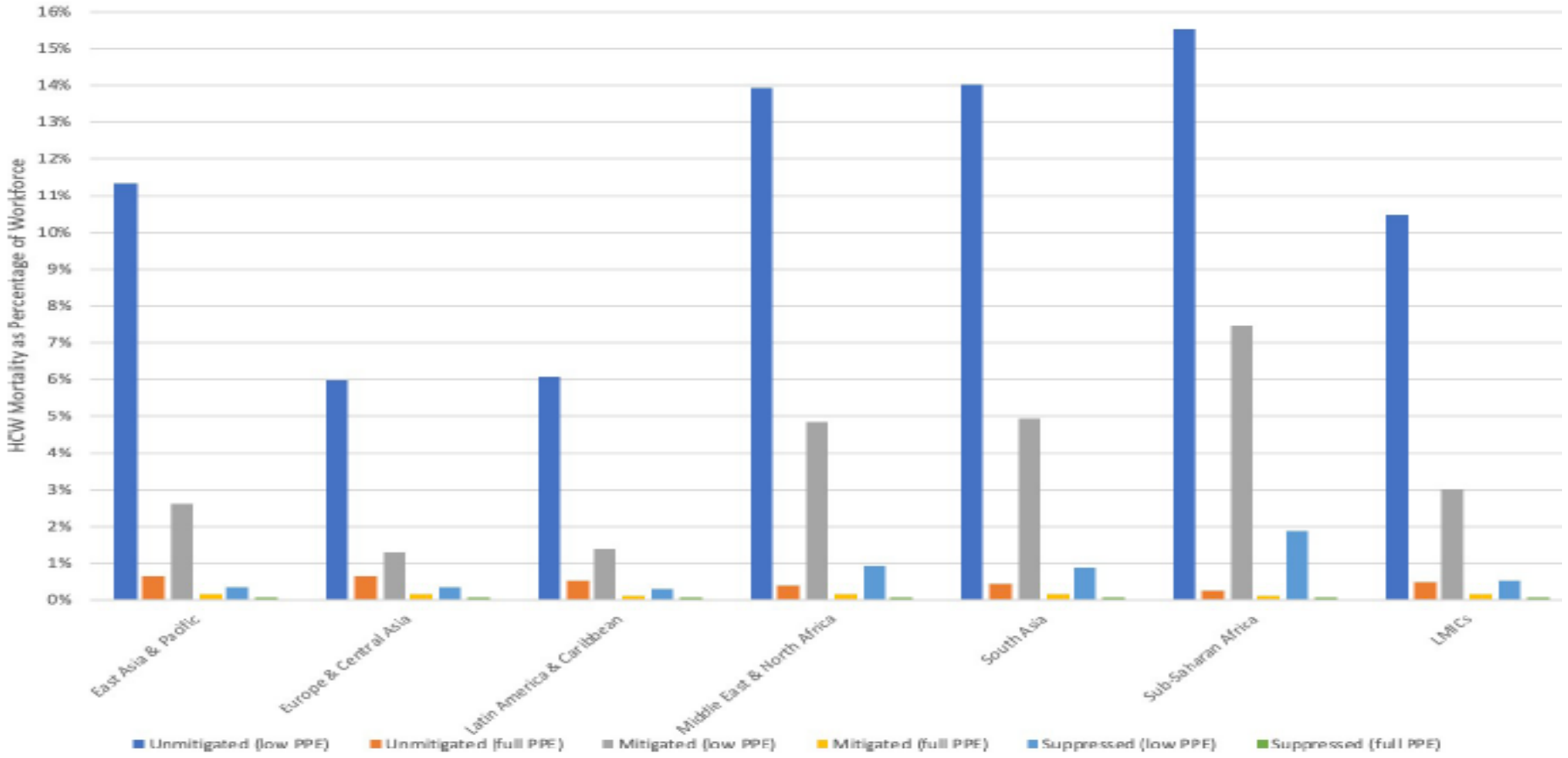


Fig 5. Cumulative HCW mortality as a percentage of total workforce, by strategy.

Key model parameters

Table 1. Key model parameters.

Parameter	Value	Distribution	Source
Epidemiologic Variables			
LMIC deaths (millions)	15.82 (13.45–18.19)	lognormal	15,17
LMIC cases (millions)	1,146 (974.3–1,318)	lognormal	15,17
HCW infections as % of total infections (*full PPE case*)	0.42 (0.36–0.49)	lognormal	20–28
HCW infections as % of total infection (*limited PPE case*)	14.5 (4.0–25.0)	lognormal	20–28
Case acuity mix % (*mild/moderate/critical*)	80.0/13.8/6.20	beta	17
Case fatality (%)	1.38 (1.23–1.53)	lognormal	17
Utilization Inputs	**Value (range for sensitivity analysis)**		
Mean hospital days for severe infection	11 (6–21)	lognormal	Estimate
Days of work missed for infection (*mild/moderate/severe*)	13/28/40	lognormal	Estimate
Cost Inputs (2020 USD)			
Nitrile gloves (per pair)	0.06 (0.01–2.63)	gamma	15
Polypropylene contact gown	0.80 (0.69–4.40)	gamma	15
Plastic face shield	0.60 (0.50–3.28)	gamma	15
N-95 Mask	0.70 (0.58–0.92)	gamma	15
Liquid soap (per liter)	0.90 (0.85–1.15)	gamma	15
Hospital bed per day	Varies by country	gamma	23
GDP per capita	Varies by country	gamma	20
Number of HCW per country	Varies by country	lognormal	22

* Assumes HCW are at same risk as rest of population.

**2019 US bulk purchase price at the facility level.

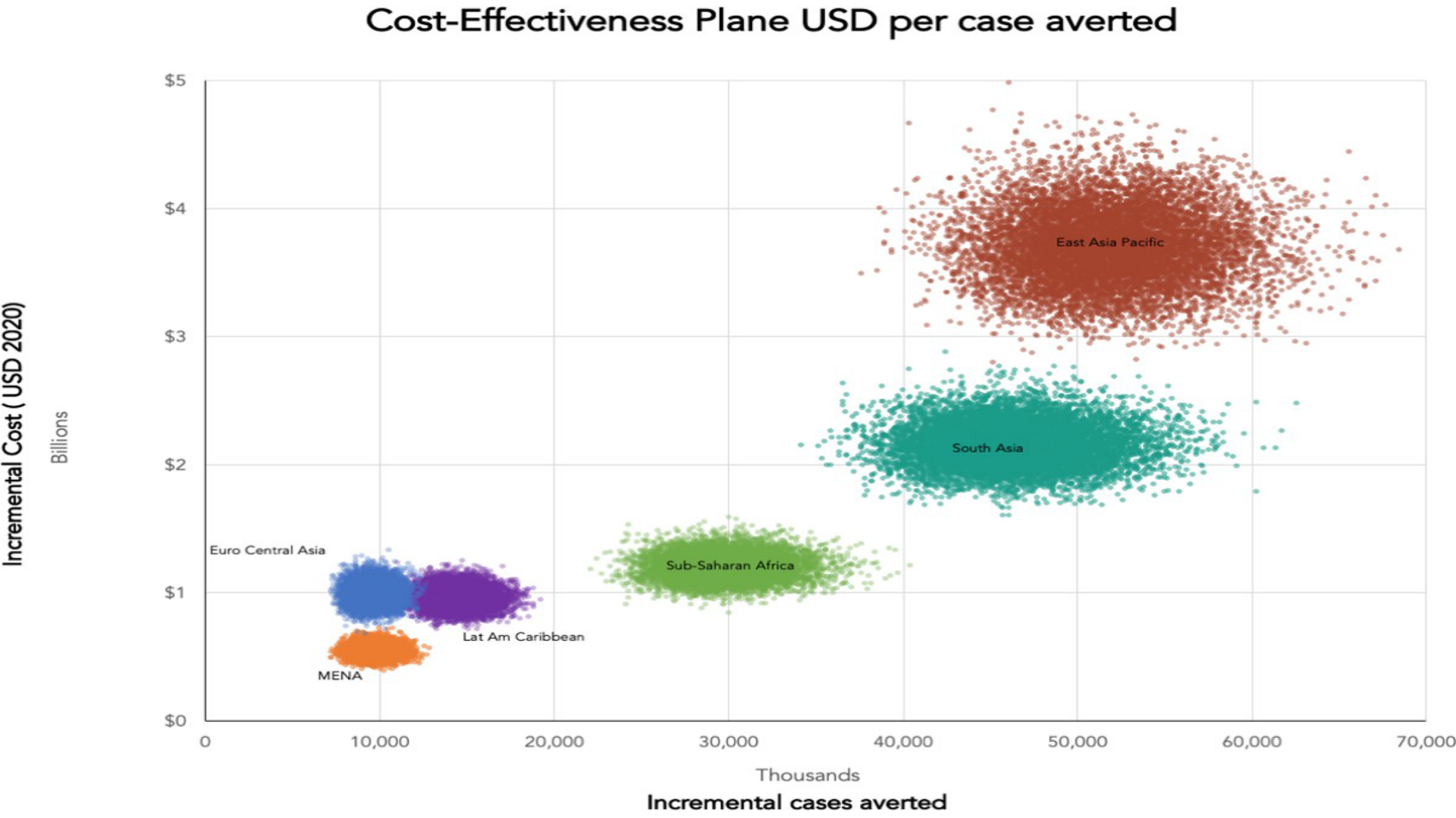
Costs

- Estimate PPE resource use and costs: WHO COVID-19 Essential Supplies Forecasting Tool (ESFT).
- Costs of labor and healthcare utilization: WHO Choosing Interventions that are Cost-Effective (WHO-CHOICE).
- Projections for each LMIC for a 30-week period starting August of 2020 and incorporating costs related to the "hygiene" and "PPE" outputs into decision analytic model.
- Costs in 2020 US dollars (USD) from the societal perspective.
- **Lost future productivity due to early mortality included in assessment of the economic impact.**
- **Training costs** (lost investment in HCWs that have died or as to replace them) **not included** (so, tends to underestimate the economic benefit of averted mortality).

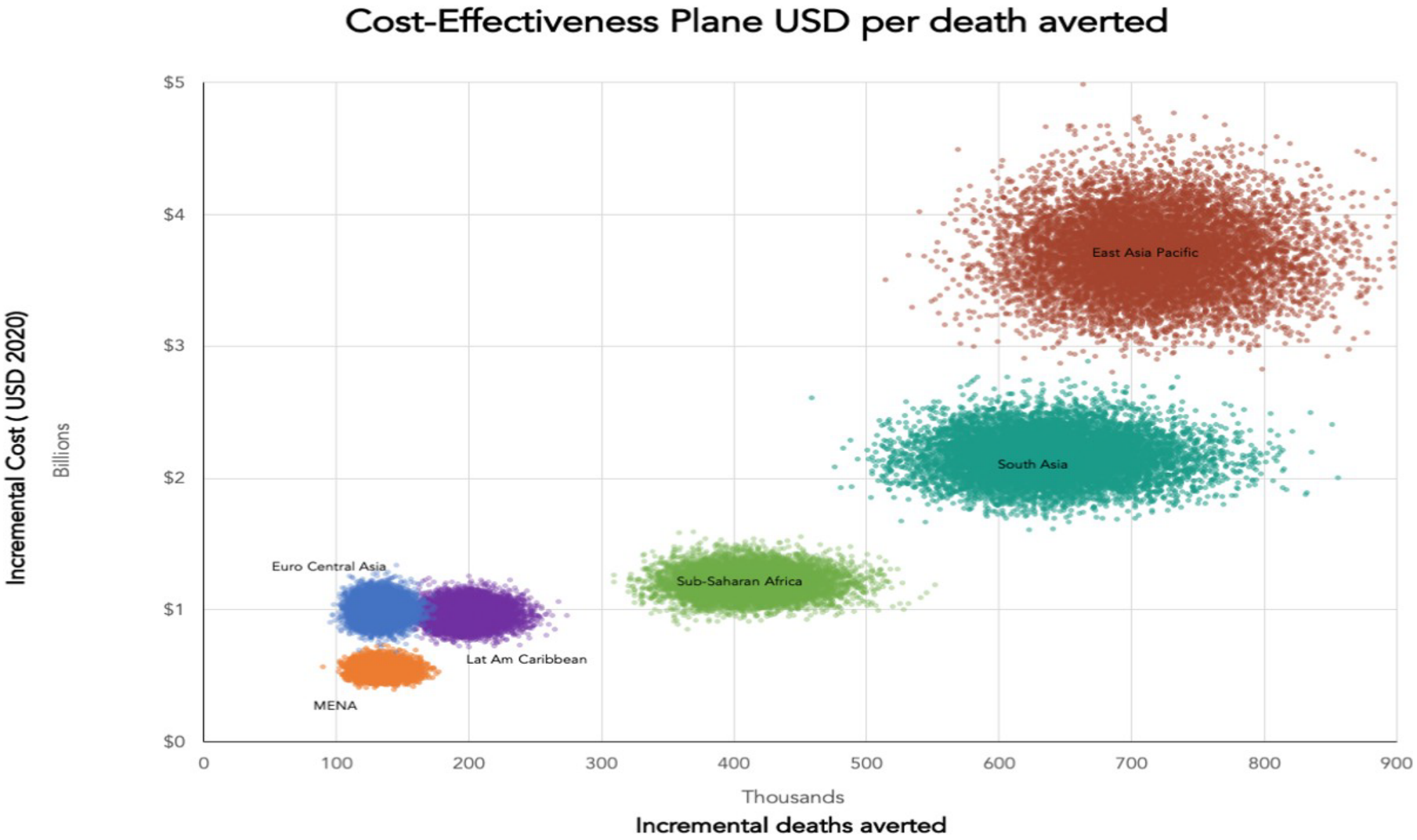
Sensitivity analysis

- Bayesian multivariate sensitivity analysis to consider uncertainty surrounding all key parameters.
- 10,000 run Monte Carlo simulation randomly re-sampled across the input distributions for each model parameter for each regional projection.
- Distributions:
  - Beta distributions for sampling within the 95% confidence interval of probability variables.
  - gamma distributions for cost variables.
  - lognormal distribution for the remaining parameters.

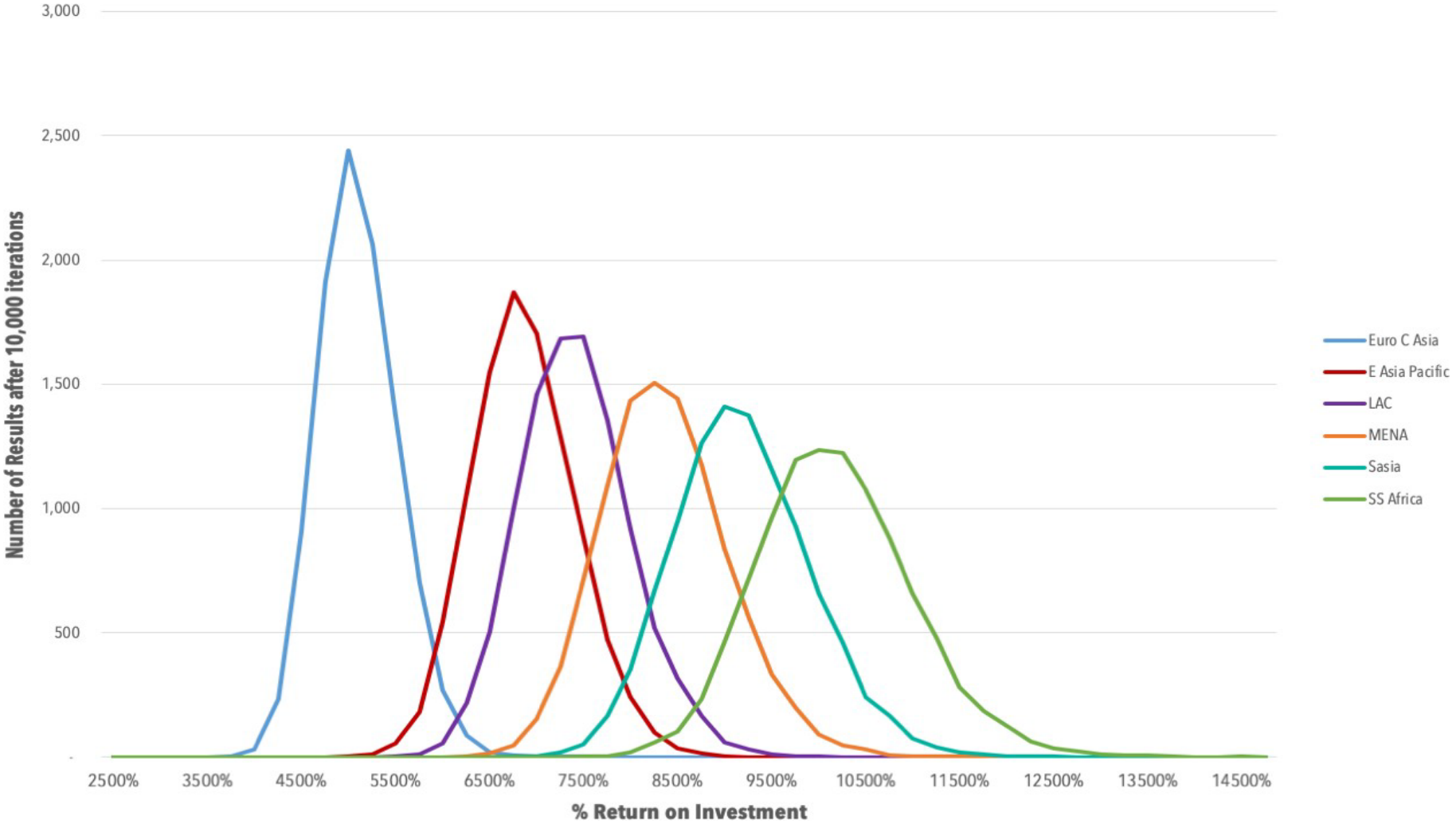
Cost effectiveness scatter plots… (by world bank region)



Cost effectiveness scatter plots…



Return to investment (per region generated by Monte Carlo simulation)



ROI numbers

- The societal ROI **from productivity gains** is estimated to be $755.3 billion USD, yielding the
- equivalent to 7,932% ROI

Table 2. Results of cost-effectiveness analysis by region*.

	Incremental Change			Cost-effectiveness Ratios		
Region	HCW Cases Averted (in millions)	HCW Deaths Averted	Investment (in millions)	Cost per Case Averted	Cost Per Death Averted	Economic Gains (in millions)
East Asia & Pacific	51.9 (49.3 to 54.5)	713,277 (677,963 to 748,590)	$3,711 (3,526 to 3,895)	$72 (67 to 78)	$5,237 (4,862 to 5,611)	$257,421 (247,433 to 267,407)
Europe & Central Asia	9.61 (9.11 to 10.1)	132,632 (125,831 to 139,433)	$993.4 (946.2 to 1,040)	$104 (97 to 111)	$7,541 (7,014 to 8,069)	$51,769 (49,839 to 53,698)
Latin America & Caribbean	14.5 (13.7 to 15.2)	200,069 (189,920 to 210,219)	$959.9 (914.6 to 1,005)	$67 (62 to 71)	$4,830 (4,496 to 5,164)	$72,125 (69,623 to74,986)
Middle East & North Africa	9.72 (9.25 to 10.2)	133,895 (127,364 to 140,427)	$544.7 (518.7 to 570.6)	$56 (53 to 60)	$4,094 (3,811 to 4,376)	$46,024 (44,187 to 47,865)
South Asia	46.4 (44.1 to 48.7)	640,080 (608,652 to 671,507)	$2,158 (2,056 to 2,260)	$47 (44 to 50)	$3,393 (3,163 to 3,623)	$200,343 (191,551 to 209,135)
Sub-Saharan Africa	29.8 (28.4 to 31.3)	412,148 (392,387 to 431,909)	$1,202 (1,144 to 1,259)	$41 (38 to 43)	$2,934 (2,735 to 3,132)	$123,442 (117,922 to 128,961)
LMIC aggregated	161.8 (153.9 to 169.8)	2,232,260 (2,122,083 to 2,342,436)	$9,557 (9,100 to 10,014)	$59 (55 to 63)	$4,309 (4,010 to 4,608)	$755,314 (724,335 to 786,293)

95% confidence intervals are derived using the standard error of the simulation results.

*All monetary values are in 2020 US dollars, rounded to nearest dollar.

A note…

“In the absence of perfect data, we have endeavored to make all assumption as conservative as possible and to rigorously explore them in our sensitivity analysis”

Results

- An investment of $9.6 billion USD would adequately protect HCWs in all LMICs.
- This would result in 4,863,299 fewer HCW cases and 67,283 fewer HCW deaths.
- Would save 2,299,543 lives across LMICs, costing $59 USD per HCW case averted.
- Mean incremental cost-effectiveness ratio of $59 USD per HCW case averted and $4,309 USD per HCW life saved.
- The societal ROI would be $755.3 billion USD, the equivalent of a 7,932% return.

3) PANDEMIC CONTROL

The Great Plague of Milan (1639) (no social distancing…and no face masks)

What antivirals?

Systematic Review of Pandemic Control interventions

Evidence-Based, Cost-Effective Interventions To Suppress The COVID-19 Pandemic: A Systematic Review

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Methods

- PRISMA systematic review guidelines, MEDLINE (1946 to April week 2, 2020) and Embase (1974 to April 17, 2020) were searched using a range of terms related to pandemic control. Articles reporting on the
- Effectiveness or cost-effectiveness of at least one intervention
  - higher-quality evidence (randomized trials)
  - lower-quality evidence (other study designs)
- Many decisions of unknown cost-effectiveness
- even of lower quality, is better than no evidence at all?

Step	Searches	Results
1	pandemic control.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]	108
2	pandemic interventions.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]	15
3	non-pharmaceutical interventions.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]	283
4	outbreak control.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]	1314
5	epidemic control.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]	981
6	epidemic interventions.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]	30
7	outbreak interventions.mp. [mp=ti, ab, hw, tn, ot, dm, mf, dv, kw, fx, dq, nm, kf, ox, px, rx, ui, sy]	35
8	1 or 2 or 3 or 4 or 5 or 6 or 7	2742
9	remove duplicates from 8	1653

They found

- 1,653 papers
- 62 included
- **Higher-quality evidence (Randomized trial evidence) only available for effectiveness of hand washing and face masks.**
- All other interventions, lower-quality evidence.
- **Most cost effective:**
  - Swift contact tracing and case isolation, surveillance networks, protective equipment for healthcare workers, and early vaccination (when available).
- **Less cost effective**
  - home quarantines and stockpiling antivirals are less cost-effective.
- **Least cost effective**
  - workplace and school closures effective but costly.
  - less cost effective the later they are.
  - H1N1 influenza, contact tracing was estimated 4,363 times more cost-effective than school closures ($2,260 vs. $9,860,000 per death prevented).
- Combinations are more cost-effective than single interventions

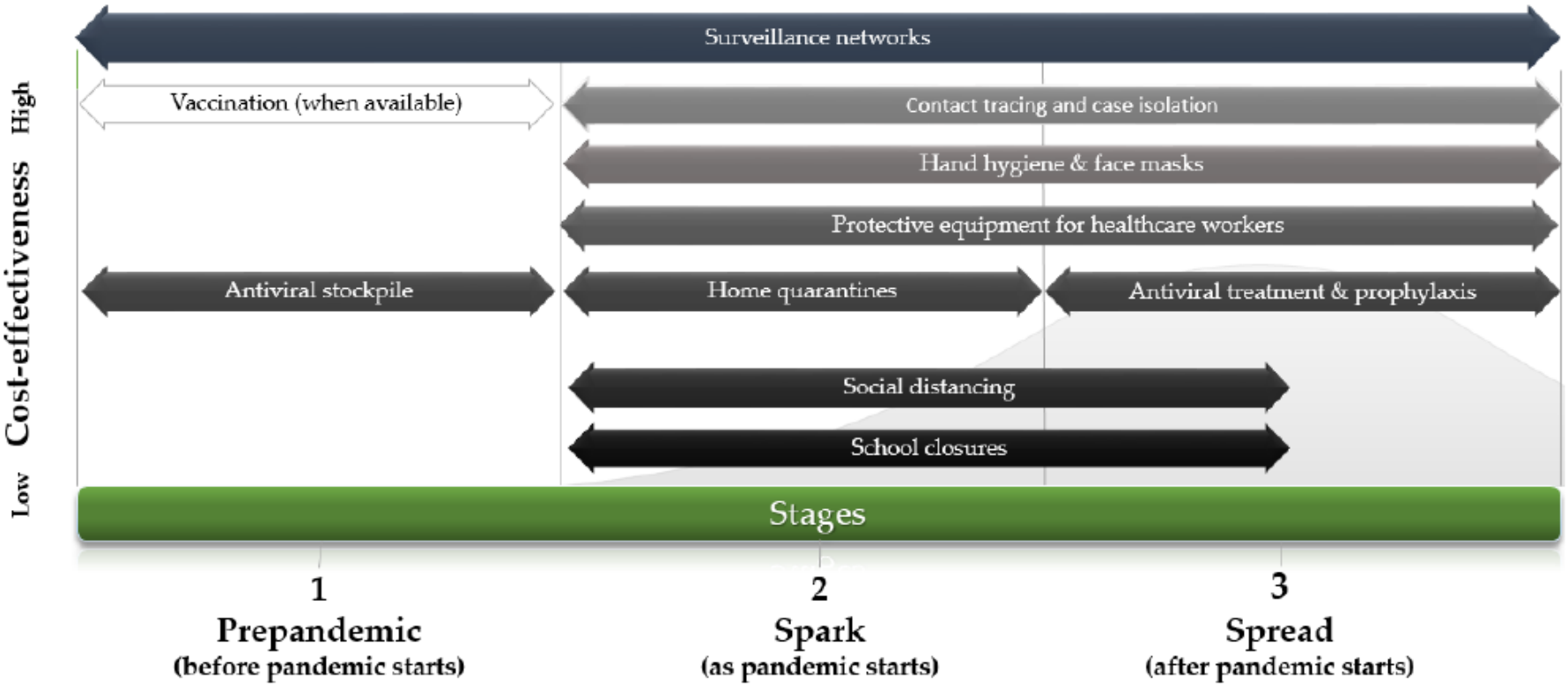
- Does this reflect your own experiences?

Timing and Severity

- **TIMING:** Adopting as early as possible a combination of interventions that includes hand washing, face masks, ample protective equipment for healthcare workers, and swift contact tracing and case isolation is likely to be the most cost-effective strategy.
- **TIMING:** Vaccination past the peak of infections, and long-term school closures late in the outbreak are less cost-effective.
- **VIRUS SEVERITY:** Cost-effectiveness of interventions depends on virus severity. For SARS-CoV-2, estimates of case fatality rate range from 1% to 7.2% (Onder et al. 2020).
- **Latest IFR about 1.15% in richer economies and 0.23% in Africa** https://www.imperial.ac.uk/news/207273/covid-19-deaths-infection-fatality-ratio-about/

Cost effectiveness and stage of pandemic

Figure 1—Cost-effectiveness of interventions in COVID-19, by stage



Cost-effectiveness of strategies for COVID-19 epidemic control

The paper we will look at:

Cost-effectiveness of public health strategies for COVID-19 epidemic control in South Africa: a microsimulation modelling study

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Guy Harling, ScD[4,5,6,7]
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Prof. Elena Losina, PhD[3,13,14,15]
Prof. Kenneth A. Freedberg, MD[1,3,8,16,17]
Pooyan Kazemian, PhD[1,3*]
Mark J. Siedner, MD[1,3,5,8*]

Note the number of co-authors… If
You ever do this, you will rarely,
If ever, do it on your own!

What they did: dynamic microsimulation model

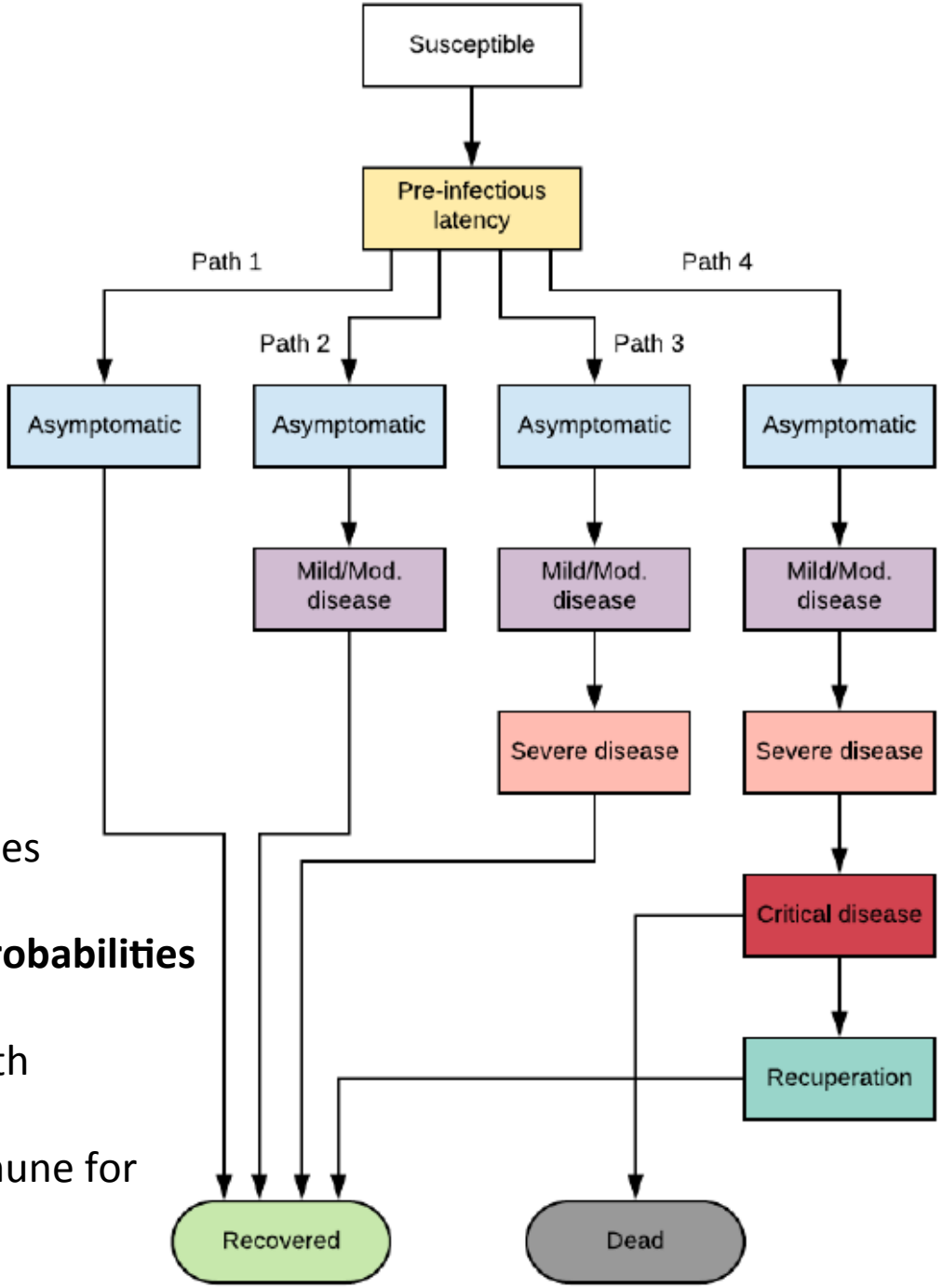
- Clinical and Economic Analysis of COVID Interventions (CEACOV) model
- dynamic state-transition Monte Carlo microsimulation model
- **Four modules**
  - 1) Natural history of disease (stages, age-depedent probability of transition along the path, (next slide)
  - 2) Transmission
  - 3) Interventions including testing
  - 4) Resource utilization

- Each model simulation starts with 1 million individuals.
- Starting with SARS-CoV-2 infection prevalence of 0·1% (to seed the model)
- Use model to project outcomes over 360 days, including daily and cumulative infections **(detected and undetected)**, deaths, resource utilization, and healthcare costs from the **health sector perspective without discounting**.
- (any comments on these?)
- Extrapolated the results to the KwaZulu-Natal population of 11 million.

Running the model

- Outside the model, calculate the average lifetime years-of-life saved (YLS) from each averted COVID-19 death during the 360-day model horizon:
  - **16·8 life-years**
- Average non-HIV public health expenditures in South Africa
  - **$600/year per Capita**
- ICER estimates include healthcare costs during the 360-day model horizon and YLS over a lifetime from averted COVID-19 deaths during the 360-day model horizon.
- **ICER less than $3,250/YLS is cost effective**
- Any comments?

Illustration of health states and disease paths in the CEACOV model



Susceptibility by age-stratified probabilities (0-19, 20-59, ≥ 60)
All paths are based on **age-dependent probabilities**

Critical disease-> daily probability of death

Recovered = no risk of transmission, immune for simulation purposes

Model Calibration

- Populated with with COVID-19 natural history data from published literature.
- Used estimates of the basic reproduction number (R0) and viral shedding duration in various disease states to calculate transmission rates.
- Calibrated transmission rates to construct an effective reproduction number (Re) corresponding to South African estimates in May 2020 (NICD) , after implementation of physical distancing and lockdown policies.
  - Changes over time as social interventions alter the number of contacts and infectivity per contact.
- Evaluated alternative epidemic growth scenarios with Re=1.1, Re=1.2, or Re=2.6
- Note: homogenous mixing presumed.

BREAKOUT SESSION

- Look at the next few slides (to end of all the flow charts) and work out how each module of the model is being set up
- Please don't get buried in the details… just get a feel for it.
- When ready, approach some of the questions on the 'BACK AFTER BREAKOUT' slide

Natural history parameters

Table S1. Additional natural history input parameters for a model-based analysis of COVID-19 intervention strategies in KwaZulu-Natal, South Africa.

Parameter	Value				Source
Disease path probability*, stratified by age, %	Asymp.	Mild/Mod.	Severe	Critical	†
0-19y	29.93	69.78	0.25	0.03	
20-59y	17.90	80.38	0·80	0.93	
≥60y	17.10	76.37	1.40	5.16	
Duration of health states, stratified by disease path, days	Asymp.	Mild/Mod.	Severe	Critical	†
Pre-infectious latency	2.6	2.6	2.6	2.6	
Asymptomatic	9.5	2.0	2.0	2.0	
Mild/moderate disease	--	10.0	6.5	3.0	
Severe disease	--	--	10.5	7.1	
Critical disease	--	--	--	11.9	
Recuperation after critical disease	--	--	--	5.7	
Mortality probability among those with critical COVID-19 disease, stratified by age, daily, %	0-19y	20-59y	≥60y		†
Without hospital care	11.7500	16.6200	20.3300		
With hospital care	0.0006	0.3800	5.0000		

COVID-19: coronavirus disease 2019. y: years. Asymp.: asymptomatic. Mod.: moderate.

*Disease path probability refers to the likelihood that an individual, once infected with SARS-CoV-2, will eventually progress to the specified COVID-19 disease state

Natural History

- Duration in each state, **age-dependent probability of developing severe or critical disease, and age-dependent mortality for those with critical disease**.
- Individuals in asymptomatic, mild/moderate, severe, critical, or recuperation states of COVID-19 may transmit infection to susceptible individuals at state-dependent daily rates.
- The number of daily infections is a function of the proportion of susceptible people in the population, the distribution of disease states among those with COVID-19, and interventions that influence transmission.
- Time to development of pneumonia (from literature: Wang et al.15);
- Time to ICU admissions (from literature: Zhou et al.14);

Life Expectancy and Years-of-Life Lost

Years-of-life lost (YLL) = the average number of years a person would have lived had s/he not died from COVID-19.

The absolute number of YLL were:

$$YLL_{age\ i} = Deaths_{age\ i} * LE_{age\ i}$$

Where,
$Deaths_{age\ i}$ is the number of deaths from COVID-19 in the age stratum,
$LE_{age\ i}$ is the life expectancy in South Africa in the age stratum.

(This is equation 4 in a moment…)

To get that… first we need age-stratified deaths and age-stratified life expectancy

1. Age-stratified distribution of cases: We used the published South Africa National Institute for Communicable Disease for Communicable Diseases (NICD) COVID-19 epidemiology report.[18]

2. Age-stratified distribution of deaths: We used data from the South Africa NICD COVID-19 update report.[19]

3. Calculate life expectancy: Published South Africa life tables are stratified by sex. Our model analysis was not stratified by sex. Therefore, we generated a standard abridged life table, not stratified by sex.
    I. To create a life table for South Africa, we used the following data:
        a. All-cause mortality: World Health Organization disease burden and mortality[20]
        b. Age- and sex-stratified population size: United Nations World Population Prospects 2019[21]
    II. Using SAS software (Cary, North Carolina, USA), we generated a life table. From this, we estimated the expected life-years at any given age.

4. Calculate the age-stratified absolute number of YLL:

$$YLL_{age\ i} = Deaths_{age\ i} * LE_{age\ i}$$

Now we need to know what the intervention might do according to the model!

5. Calculate the total absolute number of YLL, base case:

$$YLL_{base\ case} = \sum YLL_{age\ i}$$

6. Calculate the mean YLL:

$$Mean\ YLL = \frac{\sum YLL_{age\ i}}{\sum Deaths_{age\ i}}$$

7. Calculate the absolute number of YLL associated with different intervention strategies: We used the mean YLL to estimate intervention-specific YLL

$$YLL_{intervention\ j} = Mean\ YLL * Deaths_{intervention\ j}$$

The estimates for YLL for each COVID-19 death were 16.8 (undiscounted) and 12.5 (discounted 3%/year).

(By the way, are you comfortable with discounting?)

Transmission: Basically, what do we presume R0 to be?

- R0 assumed 2.6 for individuals with asymptomatic and mild/moderate disease
- R0 is one-tenth of 2.6 for individuals with severe and critical disease (from literature)
- Why is this?
- viral shedding times in days
  - Asymptomatic 9.5
  - mild/moderate 12
  - Severe 19
  - critical 24

  (all from literature)

Resource Utilization and Costs

- Costs from the health sector perspective.
- Adjusted to 2019 United States dollars, using South Africa-specific inflation and exchange rates.
- Costs of clinical care from Mahomed et al. and Netcare Hospitals.
- Cost of PCR testing, including personnel and supplies, from the Africa Health Research Institute
- Costs and sources are in extensive:

Costs 1…

Table S12. Cost of supplies for isolation centres and quarantine centres.

Item	Cost, USD*	Quantity	Sub-total, per month, USD	Vendor information
Tent assembly and rental	41,052.63	1	6,842.11†	David Pam Jang Traders, Durban, KZN
Food (3 precooked meals)	12.00	15,000	180,000.00	Functionfoods, Richards Bay, KZN
Computers	1,373.68	20	4,578.95†	First Technology, Umhlanga, KZN
Monitors	263.16	40	1,754.39†	First Technology, Umhlanga, KZN
Wireless router	31.53	10	52.54†	Makro, Springfield, KZN
Portable LED light	11.53	100	192.11†	Makro, Springfield, KZN
Bed	172.50	500	14,375.00†	Kendon Medical Supplies (PTY) LTD, Johannesburg, GP
Mattress	43.58	500	3,631.58†	Surgical and General Supplies, Durban, KZN
Bedding	12.11	500	1,008.77†	Kendon Medical Supplies (PTY) LTD, Johannesburg, GP
Cots	68.70	100	1,144.96†	Kendon Medical Supplies (PTY) LTD, Johannesburg, GP
Biohazardous waste bin	10.00	100	166.69†	Compass Medical Waste Services, Westville, KZN
Biohazardous waste bags	0.35	100	5.91†	Compass Medical Waste Services, Westville, KZN
Refrigerator	807.84	10	1,346.40†	Makro, Springfield, KZN
Privacy screens	106.41	500	8,867.61†	Kendon Medical Supplies (PTY) LTD, Johannesburg, GP
File cabinet	142.05	100	2,367.54†	Makro, Springfield, KZN
Computer desk	52.58	50	438.16†	Makro, Springfield, KZN
Whiteboard	47.32	20	157.72†	Makro, Springfield, KZN
Lock box	133.76	50	1,114.69†	Kendon Medical Supplies (PTY) LTD, Johannesburg, GP
Tape dispenser	2.88	100	288.42	Makro, Springfield, KZN
Tape	1.04	100	104.21	Makro, Springfield, KZN
General waste bin	5.53	100	552.63	Makro, Springfield, KZN
General waste bags	2.47	100	247.11	Makro, Springfield, KZN
Cleaning products	5.66	100	566.11	Makro, Springfield, KZN
Fire extinguisher	29.96	50	1,498.03	Fire Check, Durban, KZN
Laundry service	1.23	500	616.46	Kingsdale Steam Laundry CC, Durban, KZN
Portable toilet	18.16	100	1,815.79	Sanitech, Durban, KZN
Wheelchair accessible toilet	92.61	20	1,852.11	Sanitech, Durban, KZN
Portable toilet (services)	21.18	120	2,542.11	Sanitech, Durban, KZN
Gloves	0.05	90,000	4,902.63	Lasec SA (PTY) LTD, Westville, KZN
Disposable gowns	1.97	45,000	88,519.74	Surgical and General Supplies, Durban, KZN
Face shields	1.73	45,000	77,636.84	Surgical and General Supplies, Durban, KZN
Face masks	0.79	75,000	59,013.16	Surgical and General Supplies, Durban, KZN
Microwave oven	63.11	10	631.05	Makro, Springfield, KZN
Disposable cups	1.52	900	1,371.32	Makro, Springfield, KZN
Disposable plates	2.10	900	1,892.37	Makro, Springfield, KZN
Portable sink	42.37	500	21,184.21	Sanitech, Durban, KZN
Portable sink (services)	18.16	120	2,178.95	Sanitech, Durban, KZN
Biohazard spill kit	47.82	100	4,781.58	SpillTech, Congella, KZN
Infrared thermometer	111.97	100	11,197.37	Surgical and General Supplies, Durban, KZN
Stethoscopes	2.42	500	1,210.53	Kendon Medical Supplies (PTY) LTD, Johannesburg, GP
Toilet and sink deliveries	120.21	10	1,202.05	Sanitech, Durban, KZN

USD: United States dollars. KZN: KwaZulu-Natal, South Africa. GP: Gauteng, South Africa.

*Cost estimates were obtained in May 2020.

†Cost amortized over six months.

Costs 2

Table S13. Cost of supplies for contact tracing.

Item	Cost, USD*	Quantity	Sub-total, per month, USD	Vendor information
Infrared thermometer	111.97	2	223.95	Surgical and General Supplies, Durban, KZN
Stethoscopes	2.42	2	4.48	Kendon Medical Supplies (PTY) LTD, Johannesburg, GP
Gloves	0.05	200	10.89	Lasec SA (PTY) LTD, Westville, KZN
Disposable gowns	1.97	600	1,180.26	Surgical and General Supplies, Durban, KZN
Face shields	1.73	600	1,035.16	Surgical and General Supplies, Durban, KZN
Face masks	0.79	600	472.11	Surgical and General Supplies, Durban, KZN

USD: United States dollars. KZN: KwaZulu-Natal, South Africa. GP: Gauteng, South Africa.

*Cost estimates were obtained in May 2020

Costs 3

Table S14. Personnel costs.

Category	Monthly salary, USD*	Quantity	Sub-total, per month, USD	Source
Isolation centres				
Nurse (junior professional)	1,494.84	40	59,793.68	Median AHRI position payscale
Nurse (senior professional)	2,111.21	8	16,889.68	Median AHRI position payscale
Nursing assistant	916.79	40	36,671.58	Median AHRI position payscale
Janitorial staff (3 days per week)	697.26	10	6,972.63	Median AHRI position payscale
Project manager	2,661.41	1	2,661.41	Median AHRI position payscale
Unarmed security guard	1200.51	10	12,005.05	Republic Watch Security, Mtubatuba, KZN
Quarantine centres				
Nurse (junior professional)	1,494.84	5	7,474.21	Median AHRI position payscale
Nurse (senior professional)	2,111.21	2	4,222.42	Median AHRI position payscale
Nursing assistant	916.79	10	9,167.89	Median AHRI position payscale
Janitorial staff (3 days per week)	697.26	5	3,486.32	Median AHRI position payscale
Project manager	2,661.41	1	2,661.41	Median AHRI position payscale
Unarmed security guard	1200.51	10	12,005.05	Republic Watch Security, Mtubatuba, KZN
Contact tracing and mass screening				
Nurse (junior professional)	1,494.84	2	2,989.68	Median AHRI position payscale

USD: United States dollars. KZN: KwaZulu-Natal, South Africa. AHRI: Africa Health Research Institute

*Cost estimates were obtained in May 2020.

Costs 3

Table S15. Transportation costs.

Category	Descriptor / Unit	Value, USD*	Quantity	Sub-total, per month, USD	Source
Isolation centres					
Transport for 99 staff members	Cost per kilometre	26.05	200	5,210.53	AHRI commercial quote
Quarantine centres					
Transport for 23 staff members	Cost per kilometre	6.05	200	1,210.53	AHRI commercial quote
Contact tracing and mass screening					
Transport for 2 staff members	Cost per kilometre	0.26	6000	1,578.95	AHRI commercial quote
Cost of leasing additional vehicle	Cost per month	435.22	1	435.22	AHRI commercial quote

USD: United States dollars. AHRI: Africa Health Research Institute

*Cost estimates were obtained in May 2020.

Costs 4

Table S16. Per-patient costs of testing and interventions.

Category	Daily cost per patient, USD				Source
	Supplies	Personnel	Transportation	Total	
Isolation centres	34.26	9.00	0.35	43.60	*
Quarantine centres	34.26	2.60	0.08	36.94	*
Contact tracing and mass screening	0.98	1.00	0.67	2.64	†
Hospital care (non-ICU)	73.70	91.70	--	165.40	Netcare Hospitals[24]
ICU care	875.00	1,089.00	--	1,964.00	Mahomed et al.[23]
Ventilator, mechanical	93.60	--	--	93.60	Netcare Hospitals[24]
PCR testing	26.40	0.50	--	26.90	AHRI communication

USD: United States dollars. ICU: intensive care unit. PCR: polymerase chain reaction. AHRI: Africa Health Research Institute.

*The per-patient costs of isolation and quarantine centres were estimated based on the total monthly expenses of an alternate care site with the capacity to treat 500 patients daily, for 30 days per month. The total costs included personnel, fixed costs to establish the centres, supplies, and transportation. We assumed that fixed costs were amortized over 6 months (tables S12-S15).

†The per-instance costs of contact tracing and symptom screening were calculated based on the total monthly expenses and screening capacity of a community health worker team (tables S13-S15). We estimated that a two-person team working 20 days per month could conduct approximately 3000 screens per month, visiting an average of 30 five-person households per day.

Some costs

- Costs of additional intervention strategies from data supplied by the Africa Health Research Institute.
- Daily per-person costs of isolation and quarantine centre beds were based on the cost of a 500-person tent and personnel requirements.
- Per-person cost of contact tracing and mass symptom screening (including personnel, supplies, and transportation) assumed on basis that community health workers could visit 30 households per day, with 5 individuals per house, 20 days per month:

$$Per\ person\ contact\ tracing\ cost = \frac{Monthly\ cost\ of\ contact\ tracing}{Days\ per\ month \times Households\ per\ day \times Individuals\ per\ house}$$

(the same per-person cost was applied for mass symptom screening)

Costs of tests, etc.

- Per-unit costs of resources the same regardless of the total quantity.
- Costs of the various interventions included expenses associated with personnel, supplies, personal protective equipment, and transportation of specimens and personnel.
- No additional costs of staff training.
- The per-test cost (reagents and personnel and specimen transportation)
- No cost of additional machines or training new technicians
- How account for this uncertainty? To reflect uncertainty in our estimates, we varied costs between 50% and 200% of their base case value in sensitivity analyses.

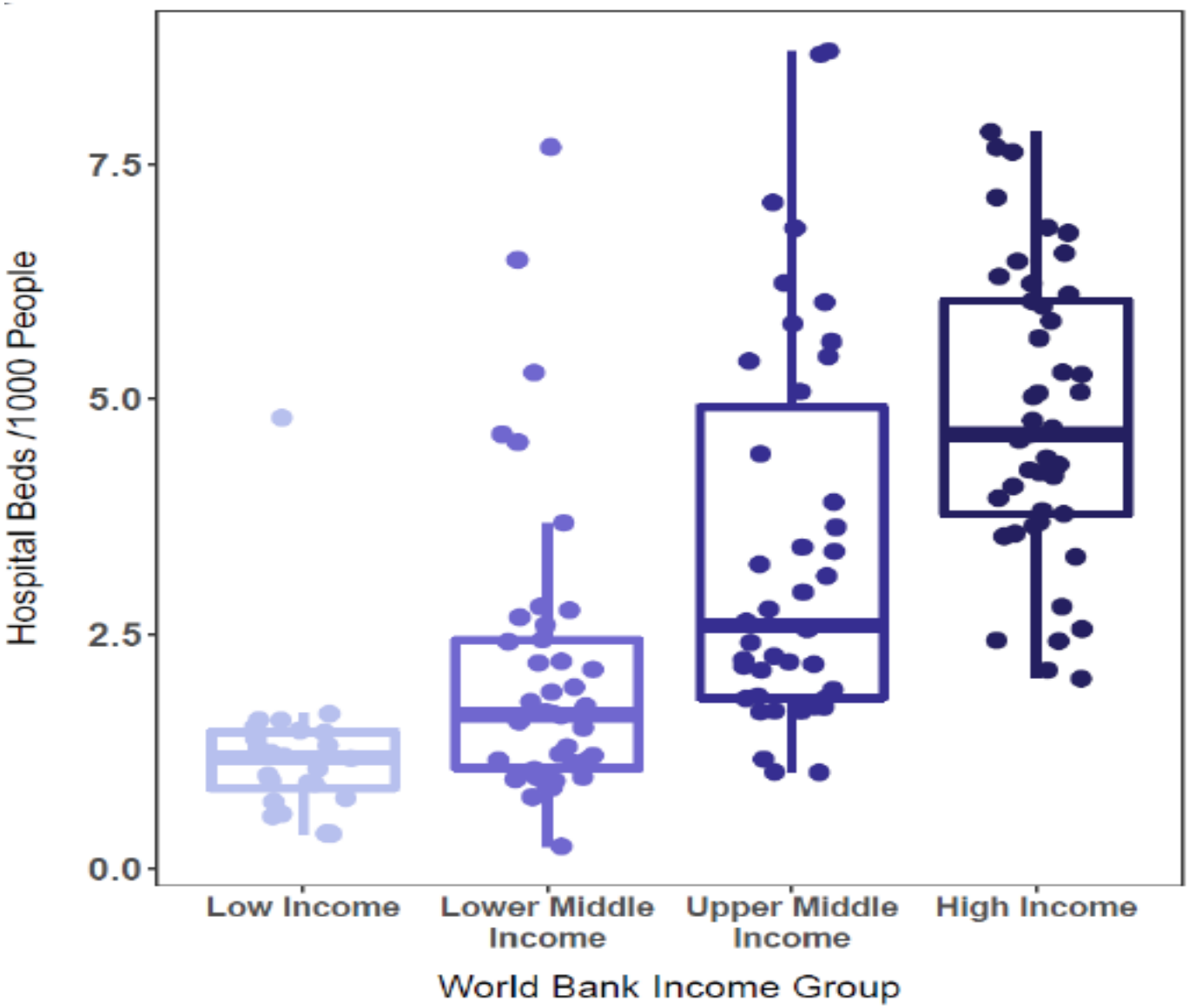
ICU or non-ICU beds

- Number of ICU and non-ICU hospital beds available in KwaZulu-Natal (KZN) based on data reported by the South Africa Department of Health:

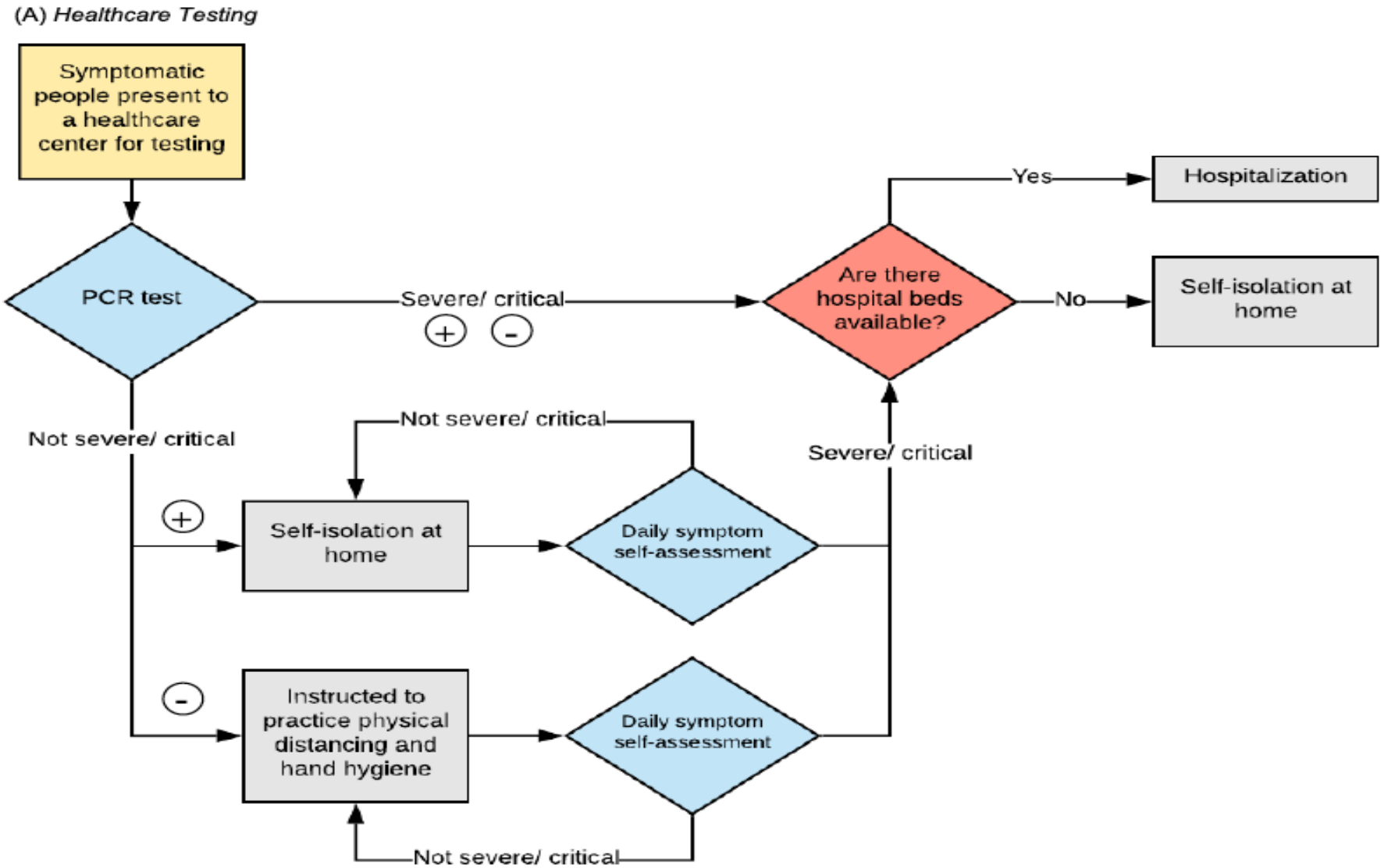
$$(a)\ \ ICU\ hospital\ beds_{KZN} = \frac{Total\ (non-ICU\ and\ ICU)\ hospital\ beds_{KZN}}{Total\ (non-ICU\ and\ ICU)\ hospital\ beds_{South\ Africa}} \times ICU\ hospital\ beds_{South\ Africa}$$

$$(b)\ \ non-ICU\ hospital\ beds_{KZN} = \frac{Total\ (non-ICU\ and\ ICU)\ hospital\ beds_{KZN}}{Total\ (non-ICU\ and\ ICU)\ hospital\ beds_{South\ Africa}} \times non-ICU\ hospital\ beds_{South\ Africa}$$

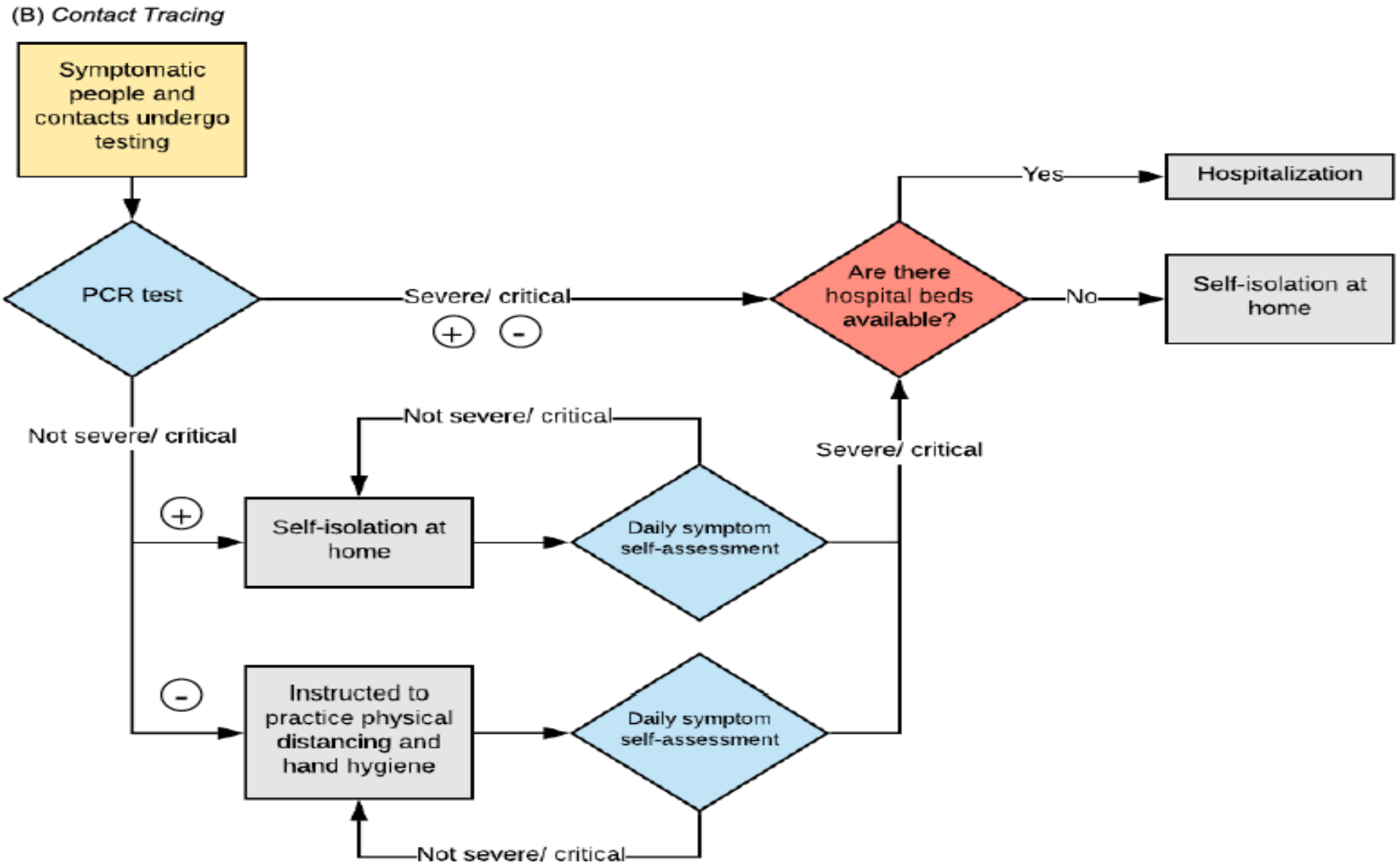
Hospital beds…A reminder



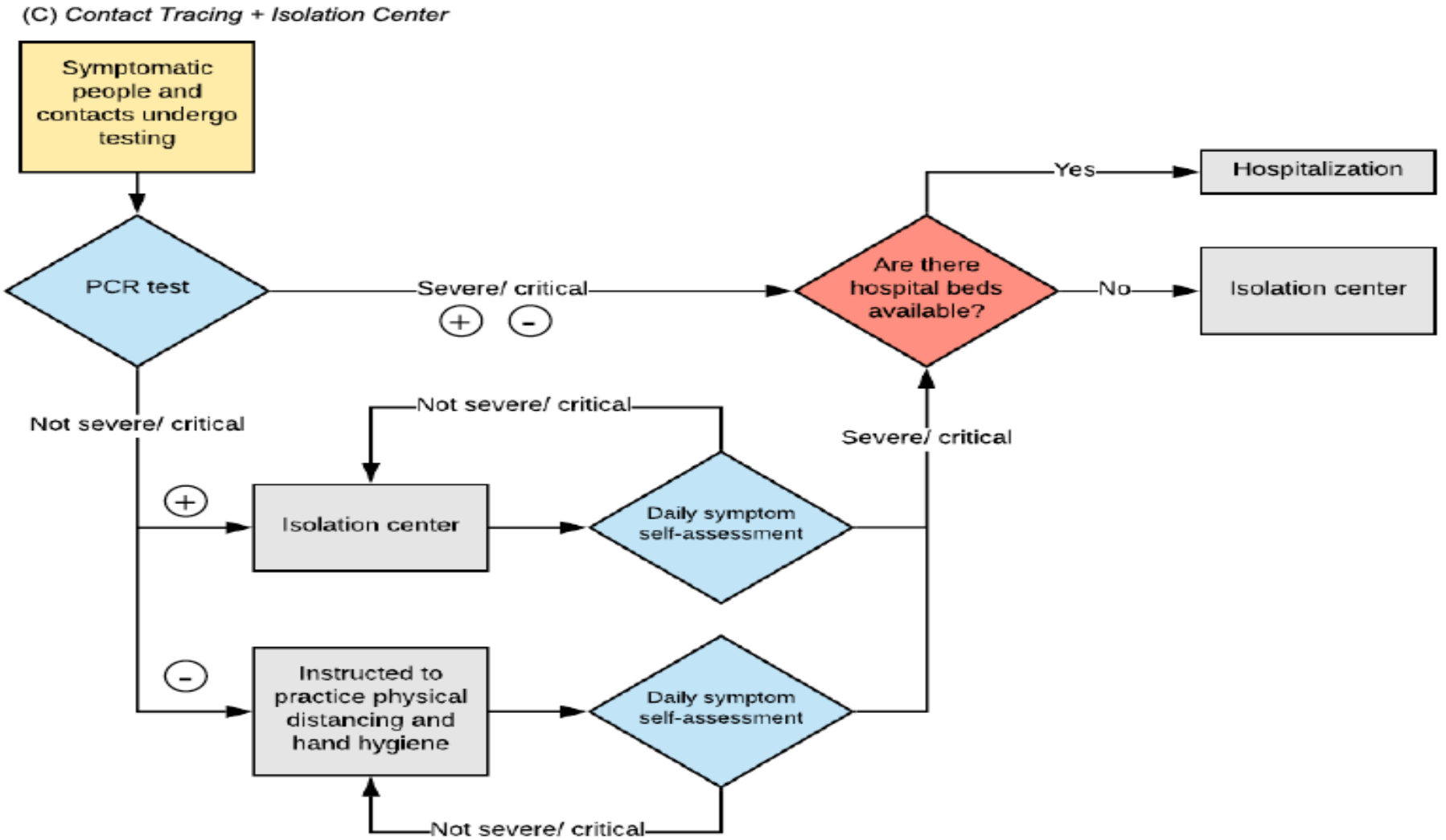
Flowchart: Healthcare testing



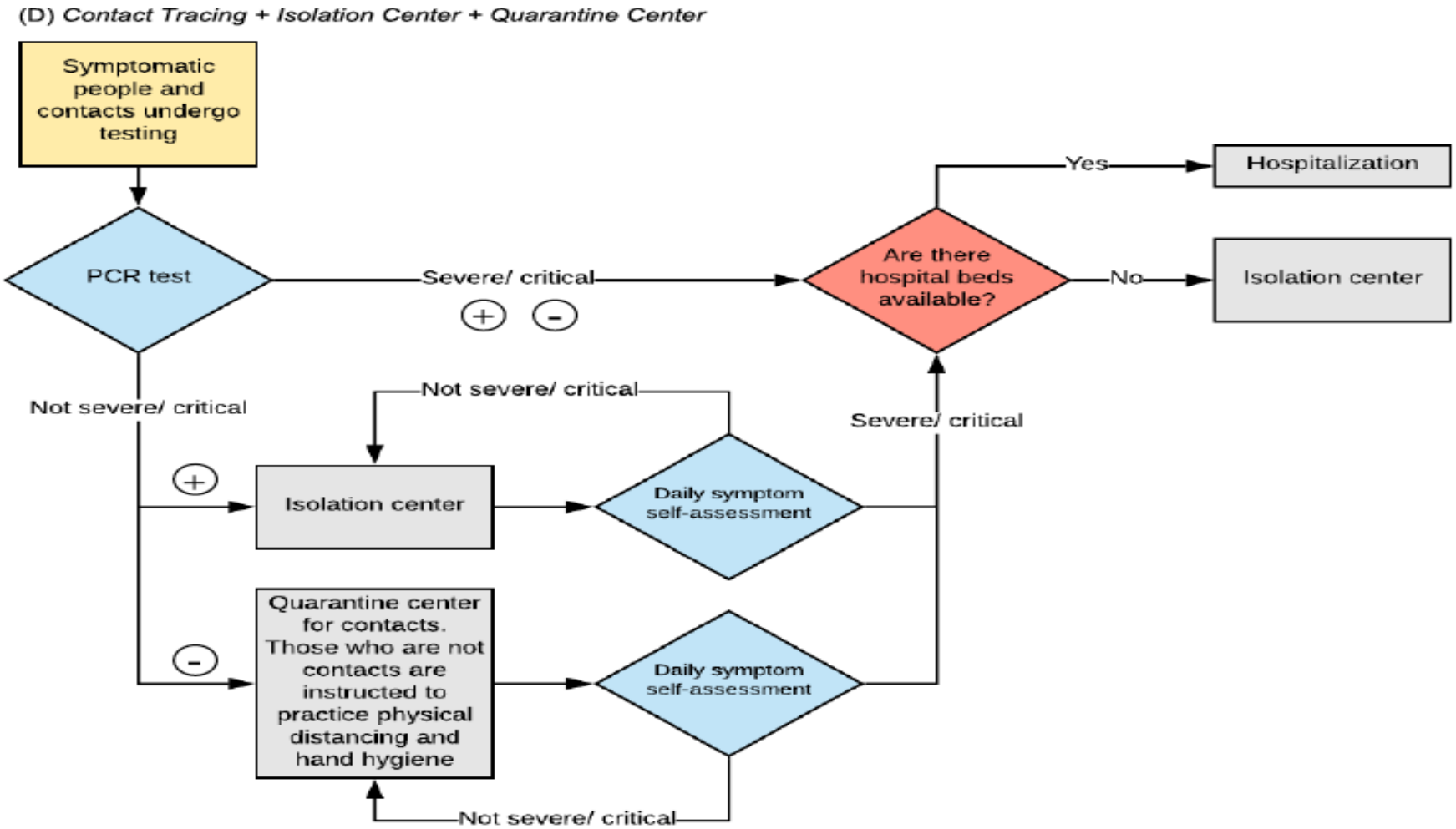
Flowchart: contact tracing



Flowchart: contact tracing plus isolation



Flowchart: contact tracing plus isolation plus quarantine



BACK AFTER BREAKOUT

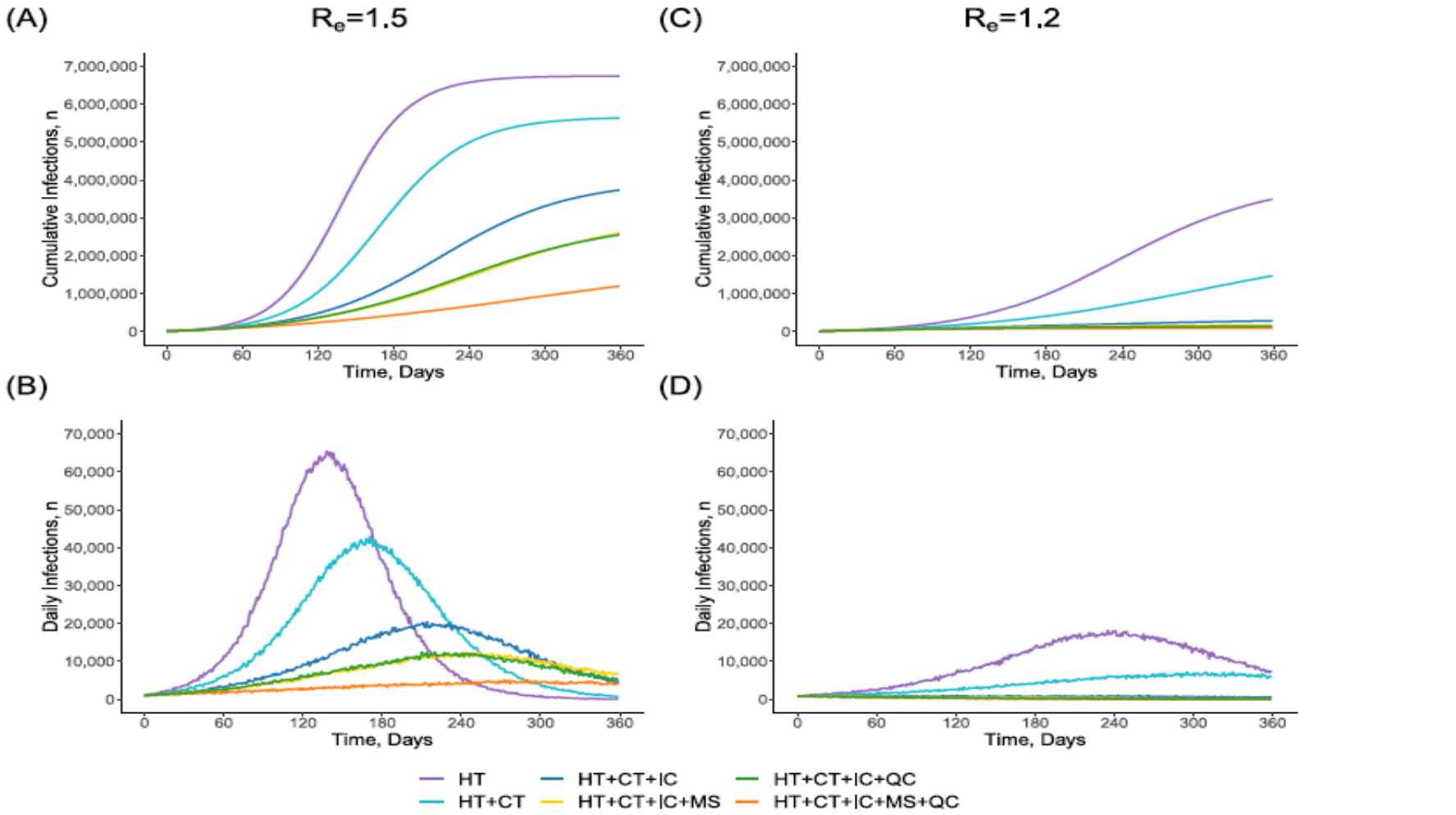
- What do you think of the natural history parameters?
- How are they used in the model?
- Where did all that cost data come from? Would I be available in your own country?
- How did the flow charts work?
- Could you just apply this model to your own country?

What was evaluated (now we need to explore some results)

- Evaluate clinical and economic outcomes and cost-effectiveness of epidemic control strategies
  - HT: Healthcare Testing (at healthcare centres);
  - CT: Contact Tracing
  - IC: Isolation Centres (cases not requiring hospitalisation);
  - MS: community health worker-led Mass Symptom Screening and molecular testing for symptomatic individuals
  - QC: Quarantine Centres (household contacts testing negative).
- The primary outcome was the incremental cost-effectiveness ratio (ICER), the difference in COVID-19-related healthcare costs (2019 US dollars [US$]) during the 360-day model simulation, divided by lifetime years-of-life saved (YLS) per COVID-19 death averted during the 360-day model simulation.
- **Not include costs beyond the 360-day model horizon**.
- in terms of undiscounted healthcare costs, cost-effectiveness threshold from literature of $3,250 per year-of-life saved

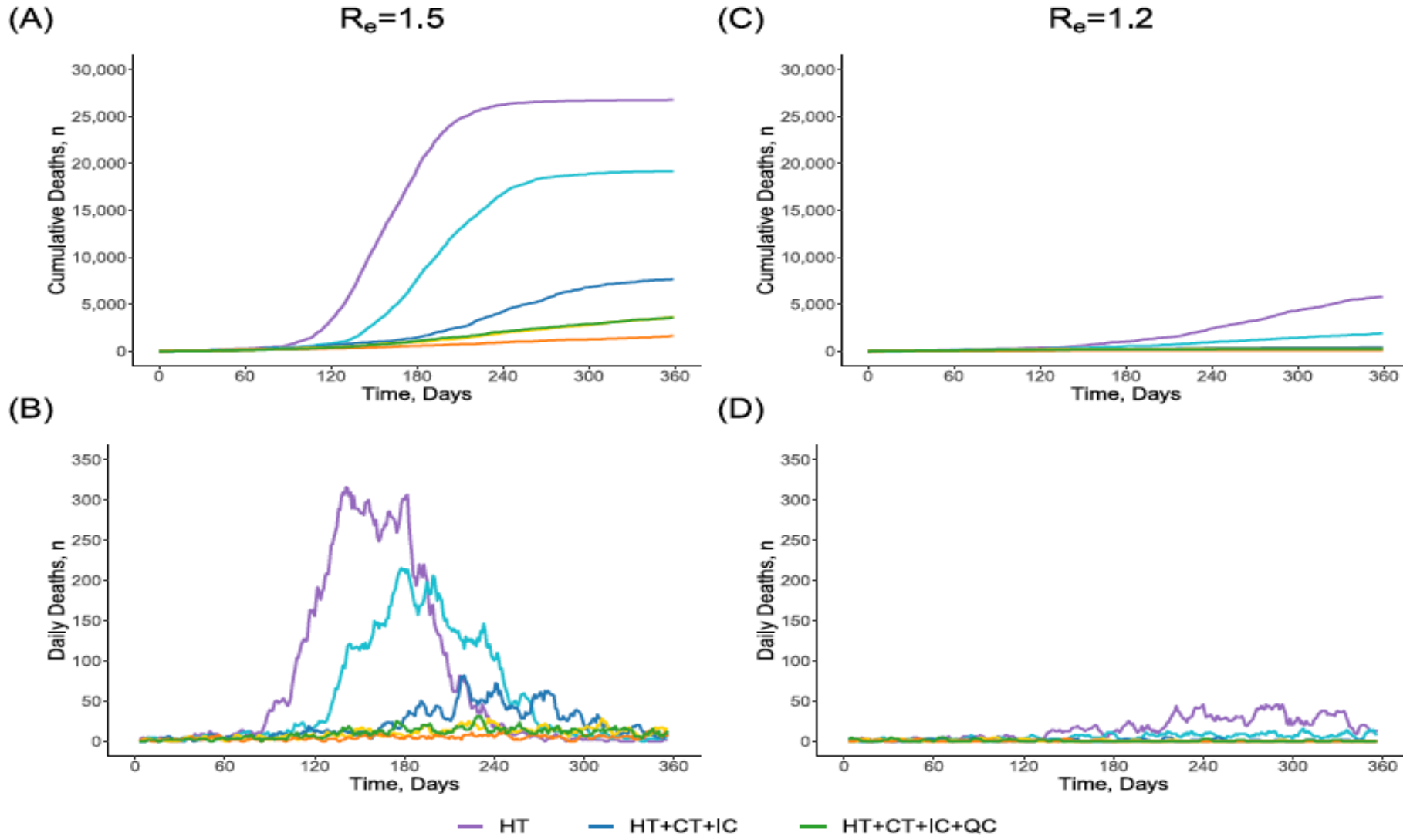
Model-projected cumulative and daily SARS-CoV-2 infections by intervention strategy

Figure S3. Model-projected cumulative and daily SARS-CoV-2 infections by intervention strategy in KwaZulu-Natal



Deaths by intervention strategy

Figure S4. Model-projected cumulative and daily COVID-19 deaths by intervention strategy in KwaZulu-Natal



What do strategies achieve?

Table S2. Intervention-related input parameters for a model-based analysis of COVID-19 intervention strategies in KwaZulu-Natal, South Africa.

Intervention Strategies	*HT*	*HT+CT*	*HT+CT +IC*	*HT+CT +IC+MS*	*HT+CT +IC+QC*	*HT+CT +IC+MS+QC*	Source
Cumulative probability of undergoing testing, over health state duration, %							
Susceptible	0	Variable	Variable	Variable	Variable	Variable	*
Pre-infectious latency	0	10 (5-20)	10 (5-20)	12.5 (6.25-25)	10 (5-20)	12.5 (6.25-25)	Asm.
Asymptomatic	0	10 (5-20)	10 (5-20)	12.5 (6.25-25)	10 (5-20)	12.5 (6.25-25)	Asm.
Mild/moderate disease	30	35 (33-40)	35 (33-40)	40 (35-50)	35 (33-40)	40 (35-50)	Asm.
Severe disease	100	100	100	100	100	100	Asm.
Critical disease	100	100	100	100	100	100	Asm.
Recovered	0	Variable	Variable	Variable	Variable	Variable	*
Reduction in onward transmission, % (range)							
Home isolation/quarantine	50 (25-75)	50 (25-75)	50 (25-75)	50 (25-75)	--	--	Asm.
Isolation centre	--	--	95 (75-99)	95 (75-99)	95 (75-99)	95 (75-99)	Asm.
Quarantine centre	--	--	--	--	95 (75-99)	95 (75-99)	Asm.

COVID-19: coronavirus disease 2019. Asm.: assumption. HT: healthcare testing. CT: contact tracing within households. IC: isolation centre. MS: mass symptom screen. QC: quarantine centre.

Are you comfortable with this?

ICER

- The ICER is the difference between two strategies in costs divided by the difference in life-years. The displayed life-years and costs are rounded, but the ICER was calculated with non-rounded life-years and costs.
- Strategies are listed in order of ascending costs, per convention of cost-effectiveness analysis.
- In the base case, contact tracing and mass symptom screening cost $3/person.

Uncertainties and sensitivity

- Epidemiologic models of interventions generally suggest **efficacy depends on transmission dynamics and intervention adherence**
- Uncertainties about epidemic dynamics
  - two main epidemic scenarios over 360 days,
  - effective reproduction numbers (Re) of 1·5 and 1·2.
  - Seeking strategies with incremental cost-effectiveness ratio (ICER) <US$3,250/year-of-life saved (YLS) cost-effective.
- Sensitivity analysis
  - Varied Re, molecular testing sensitivity, and efficacies and costs of interventions

LAST BREAKOUT

- Please look at the slides to end of part 4.
- What works?
- What are the limitations of this analysis?
- Can you just use it in your own country?

Sensitivity analysis: Dominance or not?

- USD: United States dollars.
- YLS: year-of-life saved.
- HT: healthcare testing.
- CT: contact tracing within households.
- IC: isolation centre.
- MS: mass symptom screen.
- QC: quarantine centre

- DOMINATED: strong dominance, resulting in more life-years lost and higher costs than an alternative strategy.
- dominated: extended dominance, resulting in an ICER higher than that of an alternative strategy that results in fewer life-years lost.

Varying the costs of contact tracing and mass symptom screening

Table S3. Sensitivity analysis: varying the costs of contact tracing and mass symptom screen strategies.

Cost	Strategy	Total life-years lost, n	Total health care costs over 360 days, 2019 USD	ICER, 2019 USD/YLS
Base case	*HT*	450,940	437,000,000	--
	HT+CT+IC+MS+QC	27,220	581,000,000	340
	HT+CT	322,970	588,000,000	DOMINATED
	HT+CT+IC+MS	60,930	668,000,000	DOMINATED
	HT+CT+IC	128,890	780,000,000	DOMINATED
	HT+CT+IC+QC	60,190	965,000,000	DOMINATED
Contact tracing and mass symptom screening cost changed to 50% of base case value	*HT*	450,940	437,000,000	--
	HT+CT+IC+MS+QC	27,220	551,000,000	270
	HT+CT	322,970	584,000,000	DOMINATED
	HT+CT+IC+MS	60,930	637,000,000	DOMINATED
	HT+CT+IC	128,890	778,000,000	DOMINATED
	HT+CT+IC+QC	60,190	963,000,000	DOMINATED
Contact tracing and mass symptom screening cost changed to 200% of base case value	*HT*	450,940	437,000,000	--
	HT+CT	322,970	596,000,000	dominated
	HT+CT+IC+MS+QC	27,220	640,000,000	480
	HT+CT+IC+MS	60,930	729,000,000	DOMINATED
	HT+CT+IC	128,890	786,000,000	DOMINATED
	HT+CT+IC+QC	60,190	970,000,000	DOMINATED

USD: United States dollars. ICER: incremental cost-effectiveness ratio. YLS: year-of-life saved. HT: healthcare testing. CT: contact tracing within households. IC: isolation centre. MS: mass symptom screen. QC: quarantine centre. DOMINATED: strong dominance, resulting in more life-years lost and higher costs than an alternative strategy. dominated: extended dominance, resulting in an ICER higher than that of an alternative strategy that results in fewer life-years lost.

Varying cost of hospitalization

Table S4. Sensitivity analysis: varying the cost of hospitalisation.

Cost	Strategy	Total life-years lost, n	Total health care costs over 360 days, 2019 USD	ICER, 2019 USD/YLS
Base case	*HT*	450,940	437,000,000	--
	HT+CT+IC+MS+QC	27,220	581,000,000	340
	HT+CT	322,970	588,000,000	DOMINATED
	HT+CT+IC+MS	60,930	668,000,000	DOMINATED
	HT+CT+IC	128,890	780,000,000	DOMINATED
	HT+CT+IC+QC	60,190	965,000,000	DOMINATED
Hospital (non-IC) bed daily cost changed to WHO estimate ($56/day)*	*HT*	450,940	381,000,000	--
	HT+CT	322,970	535,000,000	dominated
	HT+CT+IC+MS+QC	27,220	568,000,000	440
	HT+CT+IC+MS	60,930	641,000,000	DOMINATED
	HT+CT+IC	128,890	743,000,000	DOMINATED
	HT+CT+IC+QC	60,190	938,000,000	DOMINATED
Hospital (non-ICU) bed daily cost changed to 50% of base case value	*HT*	450,940	395,000,000	--
	HT+CT	322,970	548,000,000	dominated
	HT+CT+IC+MS+QC	27,220	571,000,000	420
	HT+CT+IC+MS	60,930	647,000,000	DOMINATED
	HT+CT+IC	128,890	752,000,000	DOMINATED
	HT+CT+IC+QC	60,190	945,000,000	DOMINATED
Hospital (non-ICU) bed daily cost changed to 200% of base case value	*HT*	450,940	521,000,000	--
	HT+CT+IC+MS+QC	27,220	600,000,000	190
	HT+CT	322,970	669,000,000	DOMINATED
	HT+CT+IC+MS	60,930	709,000,000	DOMINATED
	HT+CT+IC	128,890	837,000,000	DOMINATED
	HT+CT+IC+QC	60,190	1,007,000,000	DOMINATED
ICU bed daily cost changed to 50% of base case value	*HT*	450,940	281,000,000	--
	HT+CT	322,970	419,000,000	dominated
	HT+CT+IC+QC+MS	27,220	521,000,000	570
	HT+CT+IC+MS	60,930	541,000,000	DOMINATED
	HT+CT+IC	128,890	609,000,000	DOMINATED
	HT+CT+IC+QC	60,190	831,000,000	DOMINATED
ICU bed daily cost changed to 200% of base case value	*HT+CT+IC+MS+QC*	27,220	700,000,000	--
	HT	450,940	748,000,000	DOMINATED
	HT+CT+IC+MS	60,930	922,000,000	DOMINATED
	HT+CT	322,970	927,000,000	DOMINATED
	HT+CT+IC	128,890	1,124,000,000	DOMINATED
	HT+CT+IC+QC	60,190	1,234,000,000	DOMINATED

In the

Varying test parameters

Table S5. Sensitivity analysis: varying PCR testing parameters.

PCR testing parameter	Strategy	Total life-years lost, n	Total health care costs over 360 days, 2019 USD	ICER, 2019 USD/YLS
Base case	*HT*	450,940	437,000,000	--
	HT+CT+IC+MS+QC	27,220	581,000,000	340
	HT+CT	322,970	588,000,000	DOMINATED
	HT+CT+IC+MS	60,930	668,000,000	DOMINATED
	HT+CT+IC	128,890	780,000,000	DOMINATED
	HT+CT+IC+QC	60,190	965,000,000	DOMINATED
PCR sensitivity changed to 50%	*HT*	450,940	437,000,000	--
	HT+CT	322,970	581,000,000	dominated
	HT+CT+IC+MS+QC	31,850	583,000,000	350
	HT+CT+IC+MS	78,520	672,000,000	DOMINATED
	HT+CT+IC	152,040	717,000,000	DOMINATED
	HT+CT+IC+QC	57,590	870,000,000	DOMINATED
PCR sensitivity changed to 90%	*HT*	450,940	437,000,000	--
	HT+CT	322,970	596,000,000	dominated
	HT+CT+IC+MS	51,110	613,000,000	440
	HT+CT+IC+MS+QC	28,150	651,000,000	1660
	HT+CT+IC	92,410	810,000,000	DOMINATED
	HT+CT+IC+QC	60,000	956,000,000	DOMINATED
PCR result return time changed to 1 day	*HT*	563,720	495,000,000	--
	HT+CT	390,750	639,000,000	dominated
	HT+CT+IC+MS+QC	23,520	653,000,000	290
	HT+CT+IC+MS	102,970	963,000,000	DOMINATED
	HT+CT+IC	206,300	995,000,000	DOMINATED
	HT+CT+IC+QC	56,850	1,146,000,000	DOMINATED
PCR result return time changed to 7 days	*HT*	401,500	405,000,000	--
	HT+CT+IC+MS	65,190	537,000,000	dominated
	HT+CT+IC+MS+QC	29,440	541,000,000	370
	HT+CT	296,860	569,000,000	DOMINATED
	HT+CT+IC	118,520	691,000,000	DOMINATED
	HT+CT+IC+QC	70,000	874,000,000	DOMINATED

USD: United States dollars. ICER: incremental cost-effectiveness ratio. YLS: year-of-life saved. PCR: polymerase chain reaction. HT: healthcare testing. CT: contact tracing within households. IC: isolation centre. MS: mass symptom screen. QC: quarantine centre. DOMINATED: strong dominance, resulting in more life-years lost and higher costs than an alternative strategy. dominated: extended dominance, resulting in an ICER higher than that of an alternative strategy that results in fewer life-years lost.

In the base case, the PCR test has a 70% sensitivity and a 5-day result return time.

Varying cost of tests

Table S6. Sensitivity analysis: varying the cost of the PCR test.

Cost	Strategy	Total life-years lost, n	Total health care costs over 360 days, 2019 USD	ICER, 2019 USD/YLS
Base case	*HT*	450,940	437,000,000	--
	HT+CT+IC+MS+QC	27,220	581,000,000	340
	HT+CT	322,970	588,000,000	DOMINATED
	HT+CT+IC+MS	60,930	668,000,000	DOMINATED
	HT+CT+IC	128,890	780,000,000	DOMINATED
	HT+CT+IC+QC	60,190	965,000,000	DOMINATED
PCR test cost changed to 50% of base case value	*HT*	450,940	416,000,000	--
	HT+CT	322,970	508,000,000	dominated
	HT+CT+IC+MS+QC	27,220	528,000,000	260
	HT+CT+IC+MS	60,930	605,000,000	DOMINATED
	HT+CT+IC	128,890	714,000,000	DOMINATED
	HT+CT+IC+QC	60,190	905,000,000	DOMINATED
PCR test cost changed to 200% of base case value	*HT*	450,940	478,000,000	--
	HT+CT+IC+MS+QC	27,220	686,000,000	490
	HT+CT	322,970	748,000,000	DOMINATED
	HT+CT+IC+MS	60,930	793,000,000	DOMINATED
	HT+CT+IC	128,890	912,000,000	DOMINATED
	HT+CT+IC+QC	60,190	1,086,000,000	DOMINATED

USD: United States dollars, ICER: incremental cost-effectiveness ratio, YLS: years of life saved, PCR: polymerase

In the base case, the PCR test cost $26/test

Varying availability of hospital and ICU beds

Table S7. Sensitivity analysis: varying the availability of hospital beds and ICU beds.

Number of hospital and ICU beds	Strategy	Peak daily resource use, n		Total life-years lost, n	Total health care costs over 360 days, 2019 USD	ICER, 2019 USD/YLS
		Hospital (non-ICU) beds	ICU beds			
Base case	*HT*	4,686	748	450,940	437,000,000	--
	HT+CT+IC+MS+QC	638	341	27,220	581,000,000	340
	HT+CT	3,443	748	322,970	588,000,000	DOMINATED
	HT+CT+IC+MS	1,320	715	60,930	668,000,000	DOMINATED
	HT+CT+IC	1,925	748	128,890	780,000,000	DOMINATED
	HT+CT+IC+QC	1,375	737	60,190	965,000,000	DOMINATED
Number of hospital and ICU beds reduced *	*HT*	4,466	374	564,280	308,000,000	--
	HT+CT	3,190	374	438,160	447,000,000	dominated
	HT+CT+IC+MS+QC	638	341	27,220	581,000,000	510
	HT+CT+IC+MS	1,210	374	115,000	600,000,000	DOMINATED
	HT+CT+IC	1,782	374	235,380	646,000,000	DOMINATED
	HT+CT+IC+QC	1,199	374	120,740	904,000,000	DOMINATED

ICU: intensive care unit. USD: United States dollars. ICER: incremental cost-effectiveness ratio. YLS: year of life saved. HT: healthcare testing. CT: contact tracing within households. IC: isolation centre. MS: mass symptom screen. QC: quarantine centre. DOMINATED: strong dominance, resulting in more life-years lost and higher costs than an alternative

In the base case, the numbers of available hospital (non-ICU) beds and ICU beds are 26,220 and 748 per 11 million people, respectively.

Varying effective reproduction number

Table S8. Sensitivity analysis: varying the effective reproductive number.

Effective reproduction number (R_e)	Strategy	Total life-years lost, n	Total health care costs over 360 days, 2019 USD	ICER, 2019 USD/YLS
1.1	*HT+CT+IC+QC*	2,590	110,000,000	--
	HT+CT+IC	3,700	114,000,000	DOMINATED
	HT+CT	8,330	127,000,000	DOMINATED
	HT+CT+IC+MS	2,040	167,000,000	dominated
	HT+CT+IC+MS+QC	1,300	171,000,000	47,410
	HT	37,960	182,000,000	DOMINATED
1.2	*HT+CT+IC+QC*	3,890	139,000,000	--
	HT+CT+IC	6,850	141,000,000	DOMINATED
	HT+CT+IC+MS	4,260	183,000,000	DOMINATED
	HT+CT+IC+QC+MS	2,040	190,000,000	27,590
	HT+CT	32,040	276,000,000	DOMINATED
	HT	97,600	393,000,000	DOMINATED
1.5	*HT*	450,940	437,000,000	--
	HT+CT+IC+MS+QC	27,220	581,000,000	340
	HT+CT	322,970	588,000,000	DOMINATED
	HT+CT+IC+MS	60,930	668,000,000	DOMINATED
	HT+CT+IC	128,890	780,000,000	DOMINATED
	HT+CT+IC+QC	60,190	965,000,000	DOMINATED
2.6	*HT*	933,730	353,000,000	--
	HT+CT	890,210	532,000,000	4,130
	HT+CT+IC	838,360	1,170,000,000	dominated
	HT+CT+IC+MS	811,510	1,317,000,000	9,970
	HT+CT+IC+QC	795,580	2,380,000,000	dominated
	HT+CT+IC+MS+QC	758,910	2,634,000,000	25,040

USD: United States dollars. ICER: incremental cost-effectiveness ratio. YLS: year-of-life saved. HT: healthcare testing. CT: contact tracing within households. IC: isolation centre. MS: mass symptom screen. QC: quarantine centre. DOMINATED: strong dominance, resulting in more life-years lost and higher costs than an alternative strategy. dominated: extended dominance, resulting in an ICER higher than that of an alternative strategy that results in fewer life-years lost.

Varying effectiveness of contact tracing and mass symptom screening

Table S9. Sensitivity analysis: varying the efficacies of contact tracing and mass symptom screening.

Efficacies of contact tracing and mass symptom screening for case detection	Strategy	Total life-years lost, n	Total health care costs over 360 days, 2019 USD	ICER, 2019 USD/YLS
Changed to 50% of base case value (less efficacious)	*HT*	450,940	437,000,000	--
	HT+CT	393,350	582,000,000	dominated
	HT+CT+IC	269,080	849,000,000	dominated
	HT+CT+IC+MS	220,560	893,000,000	1,980
	HT+CT+IC+QC	215,930	1,343,000,000	dominated
	HT+CT+IC+MS+QC	143,520	1,350,000,000	5,930
Base case	*HT*	450,940	437,000,000	--
	HT+CT+IC+MS+QC	27,220	581,000,000	340
	HT+CT	322,970	588,000,000	DOMINATED
	HT+CT+IC+MS	60,930	668,000,000	DOMINATED
	HT+CT+IC	128,890	780,000,000	DOMINATED
	HT+CT+IC+QC	60,190	965,000,000	DOMINATED
Changed to 200% of base case value (more efficacious)	*HT+CT+IC+QC*	6,110	164,000,000	--
	HT+CT+IC+MS+QC	2,220	183,000,000	4,810
	HT+CT+IC+MS	6,110	197,000,000	DOMINATED
	HT+CT+IC	20,190	282,000,000	DOMINATED
	HT	450,940	437,000,000	DOMINATED
	HT+CT	196,860	608,000,000	DOMINATED

Varying effectiveness of isolation and quarantine

Table S10. Sensitivity analysis: varying the efficacies of isolation and quarantine centres.

Efficacies of isolation and quarantine centres in transmission reduction, %	Strategy	Total life-years lost, n	Total health care costs over 360 days, 2019 USD	ICER, 2019 USD/YLS
75 (less efficacious)	*HT*	450,940	437,000,000	--
	HT+CT	322,970	588,000,000	1,180
	HT+CT+IC	217,970	894,000,000	dominated
	HT+CT+IC+MS	144,630	909,000,000	1,800
	HT+CT+IC+MS+QC	107,230	1,376,000,000	12,490
	HT+CT+IC+QC	192,410	1,493,000,000	DOMINATED
95 (base case)	*HT*	450,940	437,000,000	--
	HT+CT+IC+MS+QC	27,220	581,000,000	340
	HT+CT	322,970	588,000,000	DOMINATED
	HT+CT+IC+MS	60,930	668,000,000	DOMINATED
	HT+CT+IC	128,890	780,000,000	DOMINATED
	HT+CT+IC+QC	60,190	965,000,000	DOMINATED
99 (more efficacious)	*HT*	450,940	437,000,000	--
	HT+CT+IC+MS+QC	19,440	437,000,000	1
	HT+CT	322,970	588,000,000	DOMINATED
	HT+CT+IC+MS	51,300	614,000,000	DOMINATED
	HT+CT+IC	115,190	751,000,000	DOMINATED
	HT+CT+IC+QC	49,630	803,000,000	DOMINATED

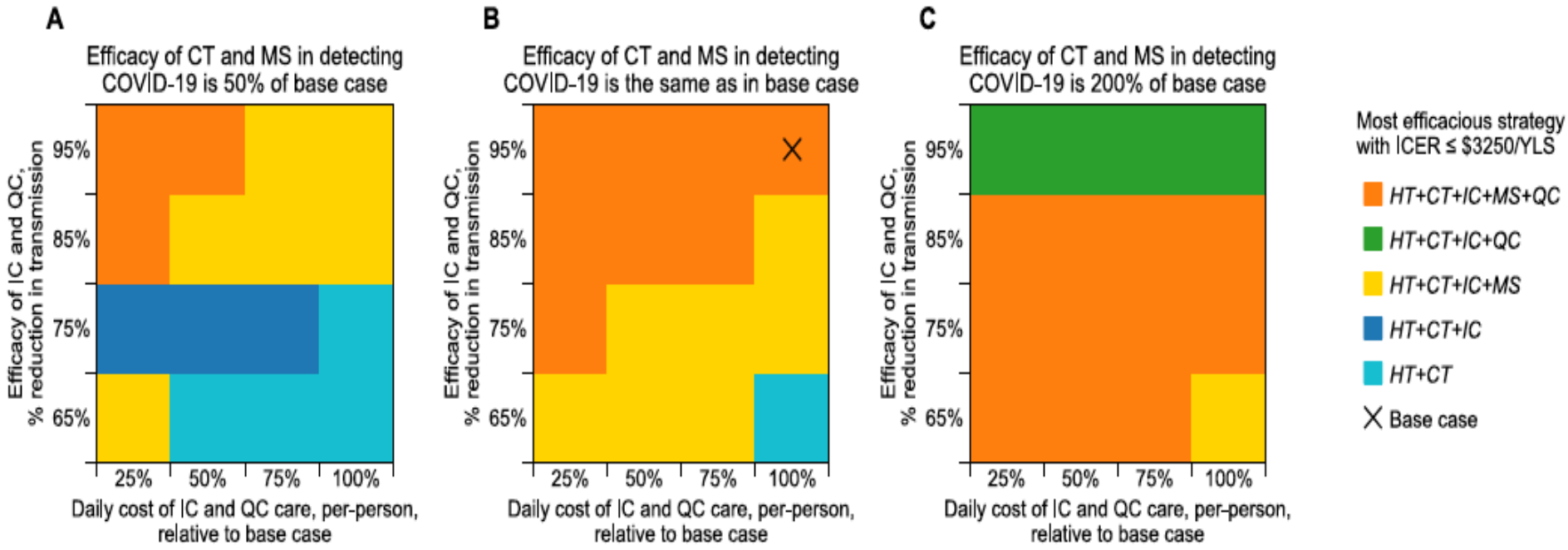
Varying cost of isolation and quarantine

Table S11. Sensitivity analysis: varying the cost of isolation and quarantine centres.

Cost of isolation and quarantine centres	Strategy	Total life-years lost, n	Total health care costs over 360 days, 2019 USD	ICER, 2019 USD/YLS
Base case	*HT*	450,940	437,000,000	--
	HT+CT+IC+MS+QC	27,220	581,000,000	340
	HT+CT	322,970	588,000,000	DOMINATED
	HT+CT+IC+MS	60,930	668,000,000	DOMINATED
	HT+CT+IC	128,890	780,000,000	DOMINATED
	HT+CT+IC+QC	60,190	965,000,000	DOMINATED
Isolation centre and quarantine centre costs changed to 25% of base case values	*HT+CT+IC+MS+QC*	27,220	373,000,000	--
	HT	450,940	437,000,000	DOMINATED
	HT+CT+IC+MS	60,930	528,000,000	DOMINATED
	HT+CT+IC+QC	60,190	568,000,000	DOMINATED
	HT+CT	322,970	588,000,000	DOMINATED
	HT+CT+IC	128,890	598,000,000	DOMINATED
Isolation centre and quarantine centre costs changed to 50% of base case values	*HT*	450,940	437,000,000	--
	HT+CT+IC+MS+QC	27,220	442,000,000	10
	HT+CT+IC+MS	60,930	575,000,000	DOMINATED
	HT+CT	322,970	588,000,000	DOMINATED
	HT+CT+IC	128,890	659,000,000	DOMINATED
	HT+CT+IC+QC	60,190	700,000,000	DOMINATED
Isolation centre and quarantine centre costs changed to 200% of base case values	*HT*	450,940	437,000,000	--
	HT+CT	322,970	588,000,000	dominated
	HT+CT+IC+MS	60,930	854,000,000	dominated
	HT+CT+IC+MS+QC	27,220	858,000,000	990
	HT+CT+IC	128,890	1,023,000,000	DOMINATED
	HT+CT+IC+QC	60,190	1,495,000,000	DOMINATED

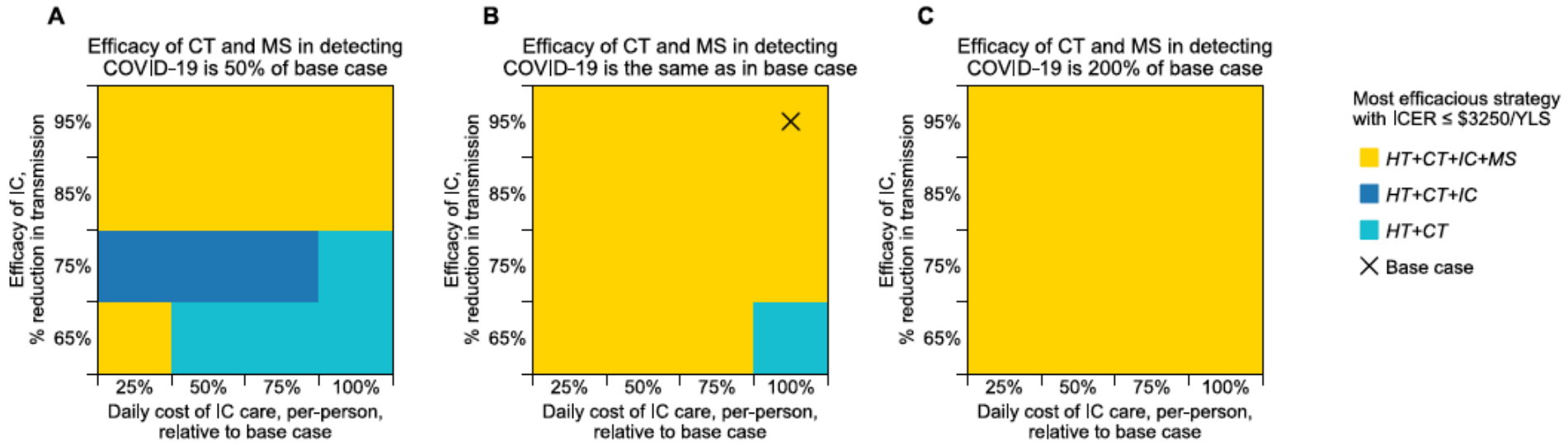
So what is an effective strategy?

Figure S5. Multi-way sensitivity analysis demonstrating cost-effectiveness of strategies across a range of assumptions about the efficacies and costs of key public health interventions.



So what is an effective strategy?

Figure S6. Multi-way sensitivity analysis demonstrating cost-effectiveness of strategies across a range of assumptions about the efficacies and costs of key public health interventions, excluding quarantine centres as an option.



A summary of findings

- With Re 1·5, HT resulted in the most COVID-19 deaths over 360 days. Compared with HT.
- HT+CT+IC+MS+QC reduced mortality by 94%, increased costs by 33%, and was cost-effective ICER $340/YLS).
- In settings where quarantine centres cannot be implemented, HT+CT+IC+MS was cost-effective compared with HT (ICER $590/YLS).
- With Re 1·2, HT+CT+IC+QC was the least costly strategy, and no other strategy was cost-effective.

4) COST-EFFECTIVENESS OF VACCINES

The potential public health and economic value of a hypothetical COVID-19 vaccine in the United States: use of cost-effectiveness modeling to inform vaccination prioritization

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Funding: Moderna, Inc.

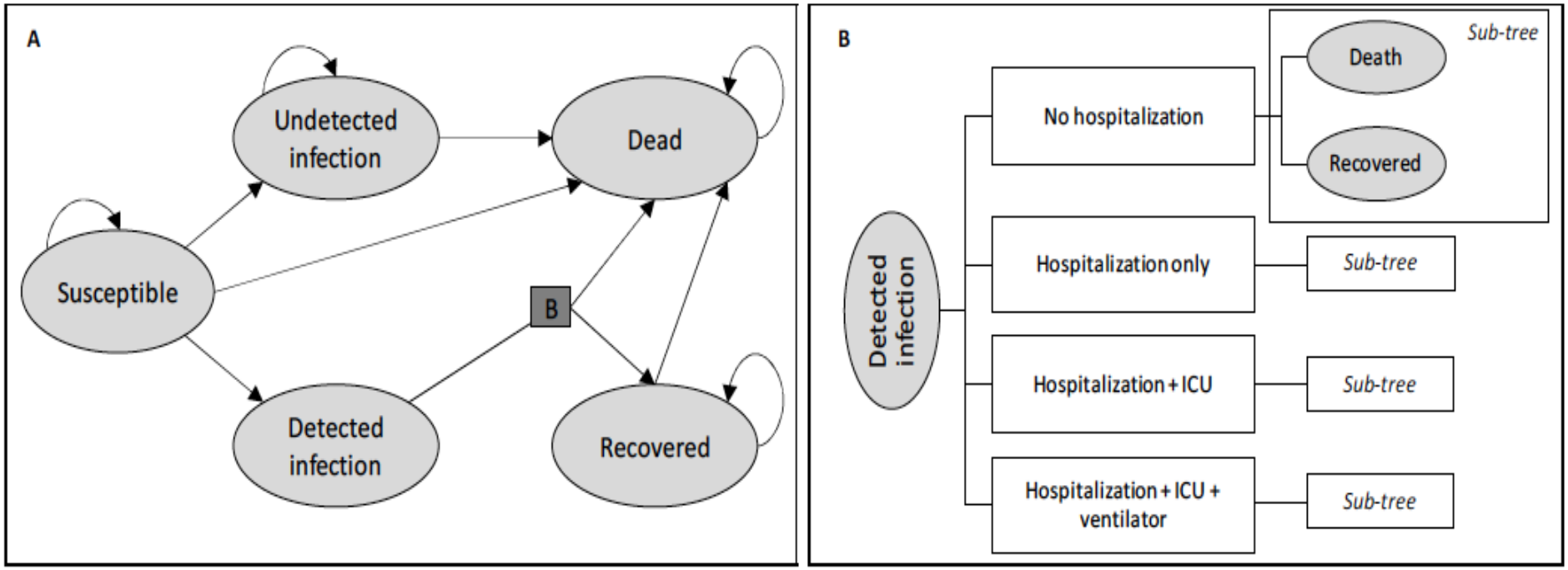
What was done

- Mathematical model to assess the public health and economic impacts in the US of a **hypothetical vaccine** for SARS-CoV-2.
- **Markov cohort model** used to compare COVID-19 related direct medical costs and deaths, versus without implementation of a **60% efficacious vaccine**.
- Base case efficacy for single dose
  - 40% for those aged <55
  - 25% for those aged 55+
- To prioritize vaccine if constrained supply, three tier-based vaccination prioritization, population divided based on:
  - Simple age-based;
  - risk and age;
  - occupation and age;
- Outcomes of model, including estimates of clinical outcomes and vaccine cost-effectiveness by vaccination tier

- Outcomes compared across one year under various supply assumptions
- For each prioritization strategy, the incremental cost per quality-adjusted life-year(QALY) gained versus no vaccine was calculated overall and by tier.

The model

Figure 1. Structure of the model of SARS-CoV-2 infection and COVID-19 progression. (A) Markov health states showing allowed transitions. (B) Probability tree linking transitions from the "Detected Infection" state in the Markov model. Arrows represent the movements between the health states. Death from "Detected infection" is due to COVID-19 while death from all other health states is due to other causes.



BREAKOUT SESSION

- Now you have some feel for the basic model, please quickly go through all the ingredients list on the next few slide.
- Are there any ‘ingredients’ you are not happy with? (pick one each and critique it)
- How do you interpret the vaccine supply diagram? What is going on?
- Tell a story with the ICER? Can you spot any particularly interesting ones?
- Would you recommend the vaccine being analysed?
- What else do you want to know?
- What are any downside?
- Someone to discuss the Tornado diagram please!

Transition probabilities

Transition probability	0-9 yrs	10-17 yrs	18-29 yrs	30-39 yrs	40-49 yrs	50-59 yrs	60-64 yrs	65-69 yrs	70-79 yrs	80+ yrs
Detected infections with no serious medical conditions										
Detected infection → No hospitalization	96·62%	97·95%	97·46%	95·40%	93·21%	90·39%	84·87%	84·87%	71·95%	69·39%
Detected infection → Hospitalization	2·58%	1·59%	1·90%	3·58%	5·26%	6·29%	9·89%	9·89%	18·15%	20·27%
Detected infection → Hospitalization with ICU	0·42%	0·20%	0·31%	0·55%	0·70%	1·42%	1·96%	1·96%	4·04%	4·24%
Detected infection → Hospitalization with ICU + ventilator	0·38%	0·27%	0·33%	0·47%	0·84%	1·90%	3·29%	3·29%	5·86%	6·10%
No hospitalization → Dead	0·04%	0·04%	0·06%	0·04%	0·04%	0·11%	0·12%	0·12%	2·29%	19·57%
Hospitalization → Dead	0·27%	0·32%	0·34%	0·20%	0·41%	0·67%	0·93%	0·93%	17·71%	43·02%
Hospitalization with ICU → Dead	1·84%	2·94%	2·69%	1·72%	4·11%	4·93%	6·49%	6·49%	34·56%	65·77%
Hospitalization with ICU + ventilator → Dead	10·40%	12·12%	16·08%	12·41%	31·47%	36·69%	62·16%	62·16%	67·58%	76·12%
Detected infections with serious medical conditions*										
Detected infection → No hospitalization	73·01%	86·37%	82·30%	76·11%	70·62%	63·72%	50·16%	50·16%	35·32%	37·95%
Detected infection → Hospitalization	20·96%	10·24%	13·79%	18·48%	22·28%	23·14%	33·19%	33·19%	41·97%	41·10%
Detected infection → Hospitalization with ICU	2·94%	1·70%	1·95%	2·41%	3·53%	5·22%	6·07%	6·07%	9·91%	8·92%
Detected infection → Hospitalization with ICU + ventilator	3·09%	1·69%	1·96%	3·00%	3·57%	7·92%	10·58%	10·58%	12·81%	12·03%
No hospitalization → Dead	0·12%	0·22%	0·34%	0·41%	0·77%	1·33%	4·60%	4·60%	12·94%	33·12%
Hospitalization → Dead	0·24%	0·99%	0·99%	1·87%	4·46%	2·96%	16·10%	16·10%	31·69%	49·18%
Hospitalization with ICU → Dead	1·75%	5·74%	6·04%	11·32%	10·80%	13·24%	31·91%	31·91%	49·58%	72·33%
Hospitalization with ICU + ventilator → Dead	14·87%	22·50%	42·67%	61·23%	71·16%	70·86%	67·28%	67·28%	69·47%	86·74%
All individuals[12]										
Susceptible → Dead Never detected infection → Dead Recovered → Dead	0·00142%	0·00049%	0·00196%	0·00306%	0·00510%	0·01184%	0·02021%	0·02842%	0·05343%	0·19912%

Model parameters

Parameter	Base-case value	Source
Vaccine coverage rates		
First dose		
18 to 49 years	34·9%	[8]
50 to 64 years	47·3%	[8]
65+ years	68·1%	[8]
Second dose (all ages)	87·5% of proportion receiving first dose	[9]
Population distribution at baseline		
Susceptible	92·7%	
Undetected Infection	5·2%	Estimated from IHME data[18]
Recovered	2·1%	Estimated from IHME data[18]
SARS-CoV-2 incidence		
Detected infection	Appendix Table A4	Described in Appendix
Undetected infection	1·05 times detected infection rates	Described in Appendix
Decision tree transition probabilities	Appendix Table A2	Described in Appendix
Non-COVID-19 mortality rates	Appendix Table A2	[19]
Vaccine efficacy (against detected and undetected SARS-CoV-2 infection)		
First dose, age 18-49 years	24·0%	Assumption
First dose, age 50-59 years	19·5%	Assumption
First dose, age 60+ years	15·0%	Assumption
Second dose, all ages	60·0%	Assumption
Costs		
Vaccine (per dose)	$35·00	Assumption
Vaccine administration (per dose)	$14·44	Code CPT90471[24]
COVID-19 treatment: ambulatory care only (per event)	$228·98	Physician visit ($112) + ED visit ($582 x 20.1% with visit*)[25]
COVID-19 treatment: hospitalization without ICU or ventilator (per event)	$16,924·00	Physician visit ($112) + hospitalization ($16,812)[25]
COVID-19 treatment: hospitalization with ICU as highest level of care (per event)	$37,429·00	Physician visit ($112) + midpoint of hospitalization and hospitalization with ventilator ($37,317)[25]
COVID-19 treatment: hospitalization with ICU + ventilator as highest level of care (per event)	$57,934·00	Physician visit ($112) + hospitalization with ventilator ($57,822)[25]
Health state utility parameters		
Detected infection symptoms disutility weight	0·19	Described in Appendix
Detected infection hospitalization as highest setting disutility weight	0·30	Described in Appendix
Detected infection hospitalization with ICU as highest setting disutility weight	0·50	Described in Appendix
Detected infection hospitalization with ICU + ventilator as highest setting disutility weight	0·60	Described in Appendix
Event durations		
COVID-19 symptoms among all confirmed infections	14 days	Described in Appendix
Hospitalization among detected infections not requiring ICU or ventilator	6 days	Described in Appendix

Virus attack rate

Table A4. Weekly attack rates for SARS-CoV-2 by age group used for the base-case and sensitivity analyses

Age group	Base-case scenario	Worst scenario	Best scenario	Base-case scenario (additional deaths in under 50 years)
0 to 9 years	0·0020%	0·0023%	0·0009%	0·0079%
10 to 17 years	0·0085%	0·0099%	0·0038%	0·0345%
18 to 29 years	0·0095%	0·0110%	0·0042%	0·0384%
30 to 39 years	0·0197%	0·0229%	0·0088%	0·0812%
40 to 49 years	0·0318%	0·0370%	0·0145%	0·0646%
50 to 59 years	0·0458%	0·0534%	0·0203%	0·0458%
60 to 64 years	0·0401%	0·0500%	0·0182%	0·0401%
65 to 69 years	0·0300%	0·0330%	0·0132%	0·0300%
70 to 79 years	0·0264%	0·0307%	0·0118%	0·0233%
80+ years	0·0483%	0·0564%	0·0214%	0·0434%

SARS-CoV-2 Attack Rate from IHME

Duration of symptoms

Table A5. Duration of symptoms assumed to calculate disutility decrement for each severity of symptoms in the base-case and in sensitivity analyses

Event	Estimated duration (days)			
	Base-case	Lower values for sensitivity analysis	Higher values for sensitivity analysis	Source
COVID-19 symptoms among all detected infections	14	7	21	[21]
Hospitalization among detected infections not requiring ICU or ventilator*	6	3	10	[22]
Hospitalization among detected infections with ICU as highest level of care*	15	9	15	[7]
Hospitalization among detected infections with ventilator as highest level of care*	15	9	15	[7]

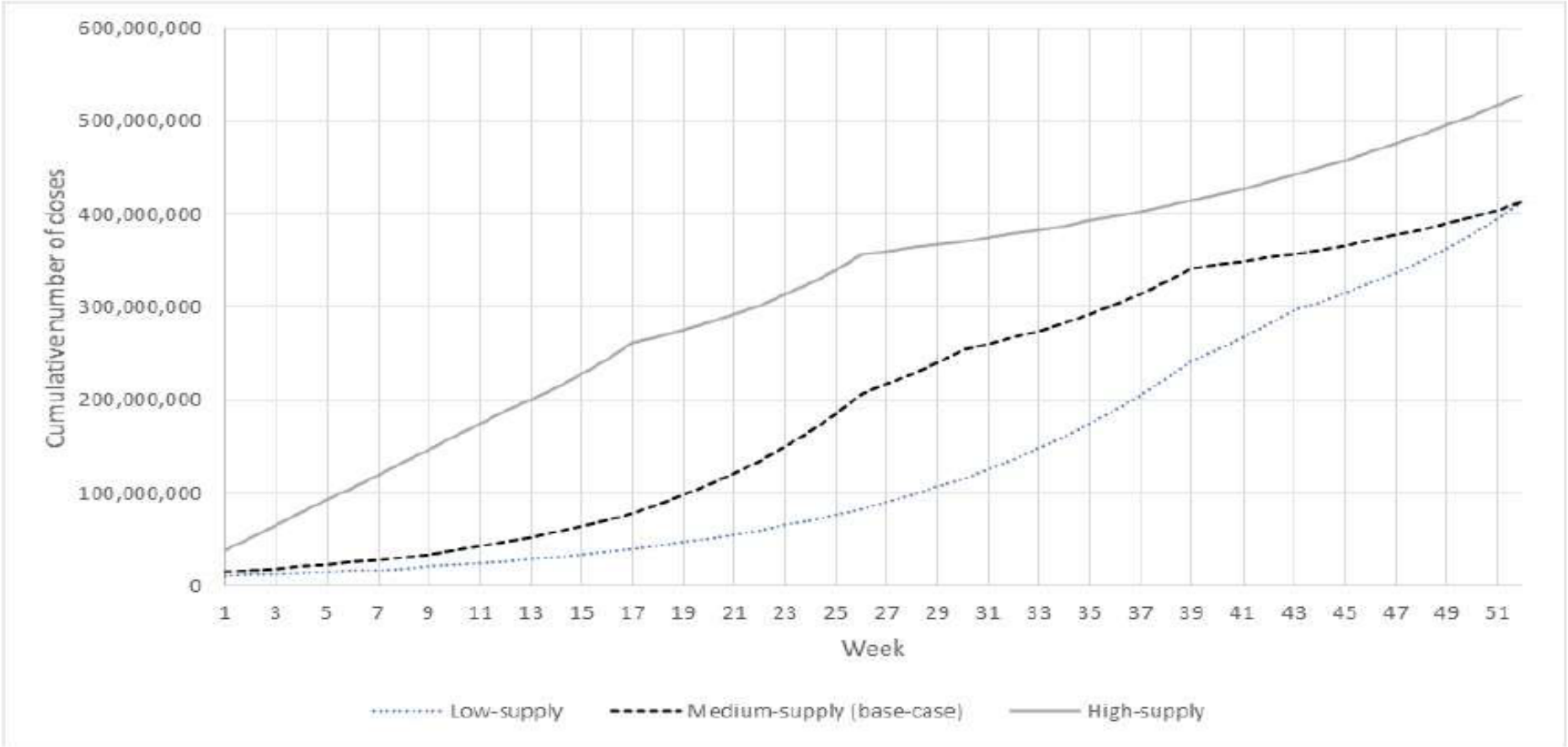
Hospitalization data

Hospitalization among detected infections with ICU as highest level of care	15 days	Described in Appendix
Hospitalization among detected infections with ventilator as highest level of care	15 days	Described in Appendix

ED, emergency department; ICU, intensive care unit; IHME, Institute for Health Metrics and Evaluation.
*Proportion of patients who have an ED visit is assumed to be equal to 20·1% which is the average rate of hospitalization observed in our model, consistent with the approach utilized by Fiedler and Song, 2020.[25]

Vaccine supply

Figure A1. Cumulative estimated weekly vaccine supply curve



Population eligibility

Table A1. Summary of population eligible for vaccination by tier*

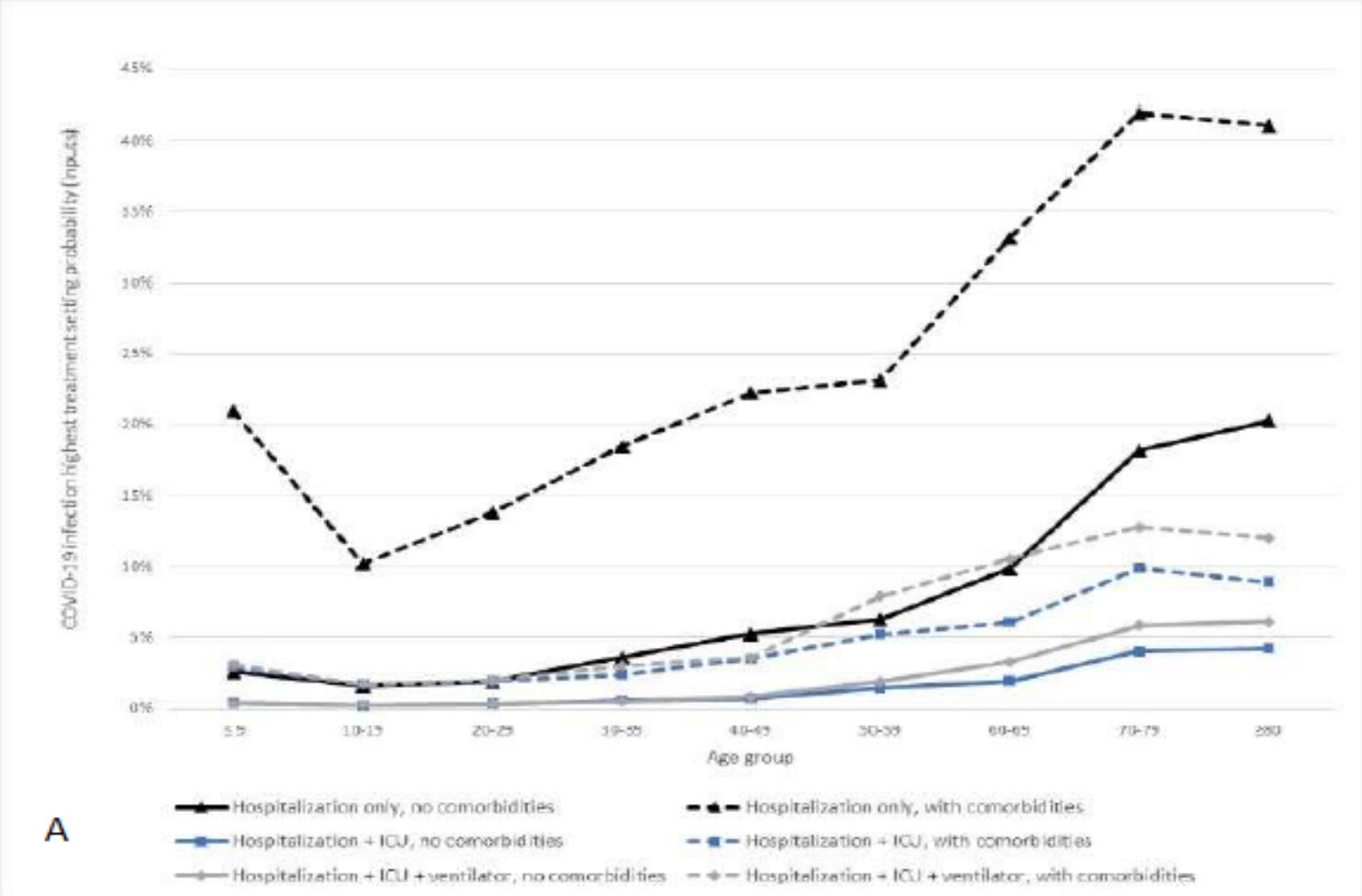
Strategy	Vaccination tier			
	1	2	3	4
1. Age-based				
Subgroup	65+ years	50-64 years	18-49 years	n/a
# eligible for vaccination[2]	56,051,566	63,292,950	139,327,967	-
2. Risk-group-based				
Subgroup	Nursing homes; 65+ years with or without serious medical conditions	Serious medical condition, 18-64 years and no serious medical condition, 50-64 years	No serious medical condition, 18-49 years	n/a
# eligible for vaccination[2,3,19]	56,282,700	92,599,345	109,790,438	-
3. Occupational/age groups				
Subgroup	Priority† and other critical occupations‡	65+ years	50-64 years	18-49 years
# eligible for vaccination[2,4,20]	21,700,000	54,706,166	57,390,550	124,875,767

Outcomes under various vaccine supply scenarios

Table 3. Base-case population-level outcomes under various vaccine supply scenarios

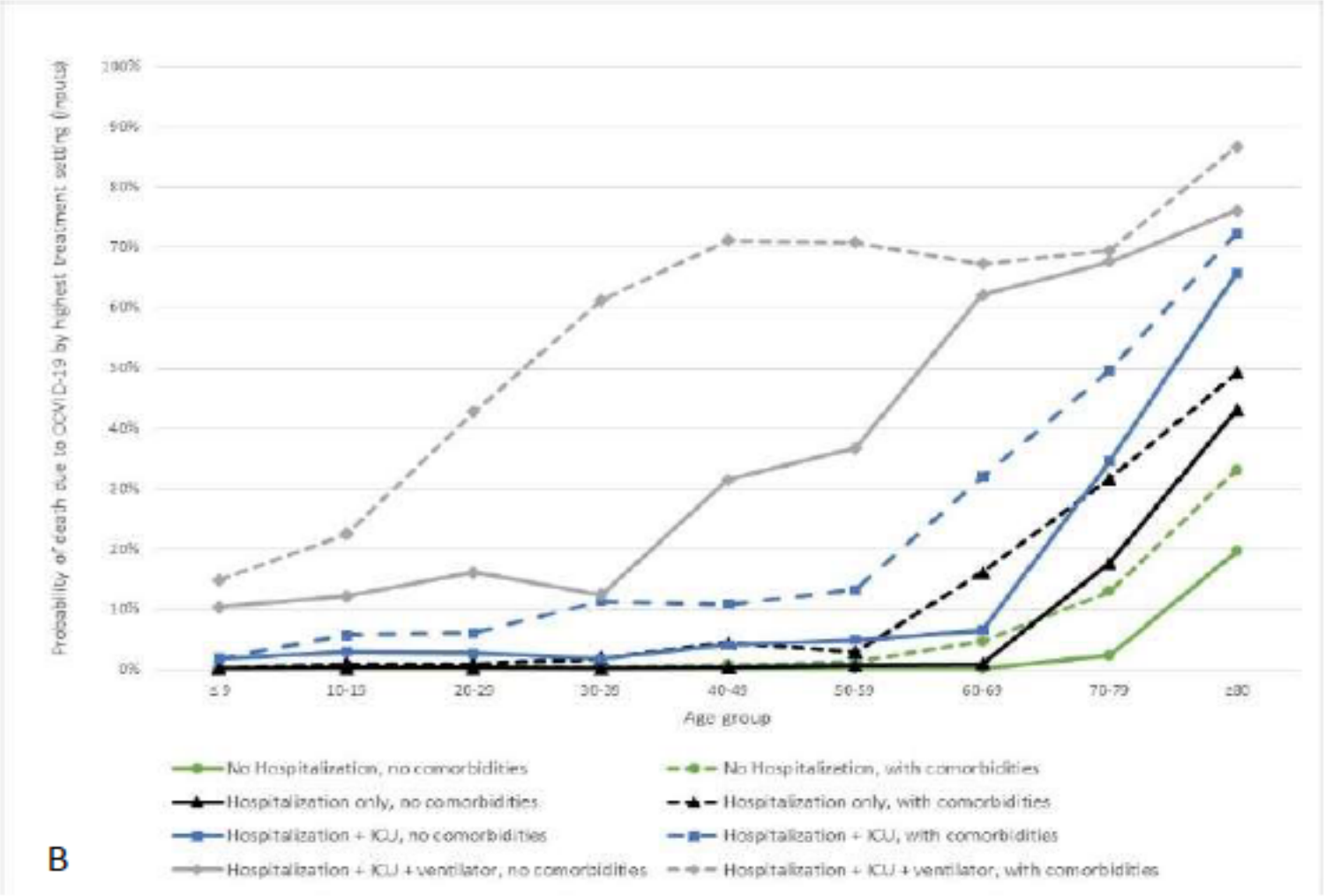
Vaccine supply scenario	Vaccination strategy	Deaths		Hospitalizations		Detected infections		Costs (millions)		
		Total	Difference from base-case	Total	Difference from base-case	Total	Difference from base-case	Hospitali-zations	Vacci-nation	Total
No vaccine	**n/a**	**264,602**		**726,115**		**3,601,719**		**$20,628**	**$0**	**$20,628**
Low	Age-based	204,253	-23%	595,040	-18%	3,149,627	-13%	$16,895	$10,823	$27,718
Low	Risk-group-based	204,298	-23%	594,838	-18%	3,153,147	-12%	$16,895	$10,823	$27,718
Low	Occupational/age-based	210,668	-20%	604,383	-17%	3,156,372	-12%	$17,161	$10,823	$27,984
Low	No priority	221,785	-16%	621,556	-14%	3,171,221	-12%	$17,653	$10,823	$28,476
Medium	Age-based	194,092	-27%	566,570	-22%	3,011,973	-16%	$16,085	$10,823	$26,908
Medium	Risk-group-based	194,131	-27%	566,463	-22%	3,014,785	-16%	$16,087	$10,823	$26,910
Medium	Occupational/age-based	198,237	-25%	572,768	-21%	3,017,299	-16%	$16,263	$10,823	$27,086
Medium	No priority	207,305	-22%	586,539	-19%	3,028,438	-16%	$16,657	$10,823	$27,480
High	Age-based	181,526	-31%	528,585	-27%	2,819,933	-22%	$15,002	$10,823	$25,825
High	Risk-group-based	181,412	-31%	527,716	-27%	2,821,040	-22%	$14,983	$10,823	$25,806
High	Occupational/age-based	182,097	-31%	529,569	-27%	2,821,455	-22%	$15,030	$10,823	$25,854
High	No priority	187,591	-29%	539,108	-26%	2,835,583	-21%	$15,307	$10,823	$26,130
Immediate	Age-based	179,775	-32%	520,452	-28%	2,760,399	-23%	$14,776	$10,823	$25,599
Immediate	Risk-group-based	179,775	-32%	520,452	-28%	2,760,399	-23%	$14,776	$10,823	$25,599
Immediate	Occupational/age-based	179,775	-32%	520,452	-28%	2,760,399	-23%	$14,776	$10,823	$25,599

Probability of being admitted to hospital by highest level of care received



A

probabilities of death by treatment location



Expected number of deaths in one year period

Table A3. Expected* number of deaths in a 1-year period compared to the model predicted* number of deaths following calibration of the SARS-CoV-2 attack rates

Age group	Base-case scenario		Worst scenario		Best scenario		Base-case scenario (additional deaths in under 50 years)	
	Expected	Predicted	Expected	Predicted	Expected	Predicted	Expected	Predicted
0 to 9 years	39	39	46	46	18	18	158	158
10 to 17 years	132	132	153	153	59	59	526	526
18 to 29 years	960	960	1,116	1,116	431	431	3,840	3,840
30 to 39 years	2,840	2,840	3,301	3,301	1,276	1,276	11,362	11,362
40 to 49 years	7,463	7,463	8,674	8,674	3,354	3,354	14,925	14,925
50 to 59 years	21,626	21,626	25,135	25,135	9,718	9,718	21,626	21,626
60 to 69 years	47,584	47,584	55,306	55,306	21,384	21,384	47,584	47,584
70 to 79 years	67,684	67,684	78,668	78,668	30,417	30,417	59,935	59,935
80+ years	116,274	116,274	135,143	135,143	52,253	52,253	104,647	104,647
Total	**264,602**	**264,602**	**307,542**	**307,542**	**118,910**	**118,910**	**264,602**	**264,602**

*Expected number of deaths were the calibration targets generated using the IHME predictions as described in the text. The predicted numbers were generated by our model after calibration of the age-specific attack rate for SARS-CoV-2.

Costs in base-case

Table A6. Summary of costs used in the base-case and sensitivity analyses

Resource	Medicare costs*	Medicaid costs	Commercial costs
Physician visit	$112	$80	$129
Emergency department visit	$582	$540	$1,312
Hospitalization without ventilator	$16,812	$13,780	$34,890
Hospitalization with ICU	$37,317	$30,588	$74,866
Hospitalization with ICU/ventilator	$57,822	$47,396	$114,842

ICER: Age-based

Table A7. Detailed cost-effectiveness analysis results

Strategy / Sensitivity analysis	Vaccination tier ICER ($/QALY gained)				Overall strategy	
	1	2	3	4	ICER ($/QALY gained)	Change from base-case ICER
1. Age-based						
*Subgroup**	*65+ yrs*	*50-64 yrs*	*18-49 yrs*	*n/a*		
# eligible for vaccination[2]	*56,051,566*	*63,292,950*	*139,327,967*	-		
Base-case	**Vaccination Dominates†**	**$8,000**	**$94,000**	**n/a**	**$8,200**	-
Vaccine cost $50/dose	$2,300	$14,000	$130,000	n/a	$14,000	71%
Vaccine cost $100/dose	$11,000	$33,000	$240,000	n/a	$32,000	290%
Infection incidence: worst case, mandates easing	Vaccination Dominates†	$4,900	$79,000	n/a	$5,800	-29%
Infection incidence: best case, universal masks	$10,000	$31,000	$220,000	n/a	$30,000	266%
Higher death rates in <50 years	$490	$8,000	$25,000	n/a	$6,600	-20%
Higher undetected infection incidence (1.5x)	Vaccination Dominates†	$8,200	$94,000	n/a	$8,400	2%
2nd dose vaccine efficacy: 50%	$1,400	$12,000	$120,000	n/a	$12,000	46%
2nd dose vaccine efficacy: 70%	Vaccination Dominates†	$5,300	$78,000	n/a	$5,700	-30%
Vaccine efficacy: single dose efficacy 40%, all ages	Vaccination Dominates†	$7,600	$94,000	n/a	$7,700	-6%
Duration of disutilities: low	Vaccination Dominates†	$8,100	$96,000	n/a	$8,300	1%
Duration of disutilities: high	Vaccination Dominates†	$7,900	$92,000	n/a	$8,200	0%
Unit costs: commercial[18]	Vaccination Dominates†	Vaccination Dominates†	$80,000	n/a	Vaccination Dominates†	n/a
Unit costs: Medicaid[18]	$1,300	$10,000	$96,000	n/a	$10,000	22%
Low mortality, low ventilator use	Vaccination Dominates†	$8,500	$110,000	n/a	$8,500	4%
Low mortality, high ventilator use	Vaccination Dominates†	$8,400	$110,000	n/a	$8,500	4%
High mortality, low ventilator use	Vaccination Dominates†	$7,300	$83,000	n/a	$7,900	-4%
High mortality, high ventilator use	Vaccination Dominates†	$7,300	$83,000	n/a	$7,900	-4%
Baseline utility -10%	Vaccination Dominates†	$8,900	$100,000	n/a	$9,100	11%
Baseline utility +10%	Vaccination Dominates†	$7,300	$86,000	n/a	$7,500	-9%

ICER: Age based (cont.)

Infection incidence: best case, universal masks	$10,000	$36,000	$790,000	n/a	$30,000	266%
Higher death rates in <50 years	$480	$5,300	$110,000	n/a	$6,600	-20%
Higher undetected infection incidence (1.5x)	Vaccination Dominates†	$10,000	$340,000	n/a	$8,400	2%
2nd dose vaccine efficacy: 50%	$1,400	$15,000	$420,000	n/a	$12,000	46%
2nd dose vaccine efficacy: 70%	Vaccination Dominates†	$7,300	$290,000	n/a	$5,700	-30%
Vaccine efficacy: single dose efficacy 40%, all ages	Vaccination Dominates†	$9,900	$340,000	n/a	$7,700	-6%
Duration of disutilities: low	Vaccination Dominates†	$10,000	$370,000	n/a	$8,300	1%
Duration of disutilities: high	Vaccination Dominates†	$10,000	$320,000	n/a	$8,200	0%
Unit costs: commercial[18]	Vaccination Dominates†	Vaccination Dominates†	$310,000	n/a	Vaccination Dominates†	n/a
Unit costs: Medicaid[18]	$1,300	$12,000	$350,000	n/a	$10,000	22%
Low mortality, low ventilator use	Vaccination Dominates†	$11,000	$440,000	n/a	$8,500	4%
Low mortality, high ventilator use	Vaccination Dominates†	$11,000	$450,000	n/a	$8,500	4%
High mortality, low ventilator use	Vaccination Dominates†	$9,500	$270,000	n/a	$7,900	-4%
High mortality, high ventilator use	Vaccination Dominates†	$9,400	$270,000	n/a	$7,900	-4%
Baseline utility -10%	Vaccination Dominates†	$11,000	$370,000	n/a	$9,100	11%
Baseline utility +10%	Vaccination Dominates†	$9,400	$320,000	n/a	$7,500	-9%

ICER, risk-based

2. Risk-group-based						
*Subgroup**	*Nursing homes; serious medical condition, 65+ yrs with or without serious medical condition*	*Serious medical condition, 18-64 years; no serious medical condition, 50-64 yrs*	*No serious medical condition, 18-49 yrs*	*n/a*		
# eligible for vaccination[2,3,19]	*56,282,700*	*92,599,345*	*109,790,438*	-		
Base-case	**Vaccination Dominates†**	**$10,000**	**$340,000**	**n/a**	**$8,200**	-
Vaccine cost $50/dose	$2,300	$17,000	$450,000	n/a	$14,000	71%
Vaccine cost $100/dose	$11,000	$38,000	$830,000	n/a	$32,000	290%
Infection incidence: worst case, mandates easing	Vaccination Dominates†	$7,000	$290,000	n/a	$5,800	-29%

ICER: By occupation

3. Occupational/age groups						
Subgroup[*] *# eligible for vaccination*[2,4,20]	*Priority*[§] *and other critical occupations*[§] *21,700,000*	*65+ yrs* *54,706,166*	*50-64 yrs* *57,390,550*	*18-49 yrs* *124,875,767*		
Base-case	**$20,000**	**Vaccination Dominates**[†]	**$8,000**	**$94,000**	**$8,200**	-
Vaccine cost $50/dose	$29,000	$2,300	$14,000	$130,000	$14,000	71%
Vaccine cost $100/dose	$60,000	$11,000	$33,000	$240,000	$32,000	290%
Infection incidence: worst case, mandates easing	$15,000	Vaccination Dominates[†]	$4,900	$79,000	$5,800	-29%
Infection incidence: best case, universal masks	$56,000	$10,000	$31,000	$230,000	$30,000	266%
Higher death rates in <50 years	$12,000	$450	$8,000	$25,000	$6,600	-20%
Higher undetected infection incidence (1.5x)	$20,000	Vaccination Dominates[†]	$8,200	$95,000	$8,400	2%
2nd dose vaccine efficacy: 50%	$26,000	$1,400	$12,000	$120,000	$12,000	46%
2nd dose vaccine efficacy: 70%	$15,000	Vaccination Dominates[†]	$5,200	$79,000	$5,700	-30%
Vaccine efficacy: single dose efficacy 40%, all ages	$19,000	Vaccination Dominates[†]	$7,600	$94,000	$7,700	-6%
Duration of disutilities: low	$20,000	Vaccination Dominates[†]	$8,100	$96,000	$8,300	1%
Duration of disutilities: high	$19,000	Vaccination Dominates[†]	$7,900	$92,000	$8,200	0%
Unit costs: commercial[18]	$8,800	Vaccination Dominates[†]	Vaccination Dominates[†]	$80,000	Vaccination Dominates[†]	n/a
Unit costs: Medicaid[18]	$22,000	$1,300	$10,000	$97,000	$10,000	22%
Low mortality, low ventilator use	$21,000	Vaccination Dominates[†]	$8,500	$110,000	$8,500	4%
Low mortality, high ventilator use	$21,000	Vaccination Dominates[†]	$8,400	$110,000	$8,500	4%
High mortality, low ventilator use	$18,000	Vaccination Dominates[†]	$7,300	$84,000	$7,900	-4%
High mortality, high ventilator use	$18,000	Vaccination Dominates[†]	$7,300	$84,000	$7,900	-4%
Baseline utility -10%	$22,000	Vaccination Dominates[†]	$8,900	$100,000	$9,100	11%
Baseline utility +10%	$18,000	Vaccination Dominates[†]	$7,300	$86,000	$7,500	-9%

Base-case cost effectiveness analysis

Strategy	Vaccination tier ICER ($/QALY gained)				Overall strategy
	1	2	3	4	ICER ($/QALY gained)**
1. Age-based					
*Subgroup**	*65+ yrs*	*50-64 yrs*	*18-49 yrs*	*n/a*	
# eligible for vaccination	*56,051,566*	*63,292,950*	*139,327,967*	-	
Base-case	**Vaccination Dominates†**	**$8,000**	**$94,000**	**n/a**	**$8,200**
2. Risk-group-based					
*Subgroup**	*Nursing homes; serious medical condition, 65+ yrs with or without serious medical condition*	*Serious medical condition, 18-64 years; no serious medical condition, 50-64 yrs*	*No serious medical condition, 18-49 yrs*	*n/a*	
# eligible for vaccination	*56,282,700*	*92,599,345*	*109,790,438*	-	
Base-case	**Vaccination Dominates†**	**$10,000**	**$340,000**	**n/a**	**$8,200**
3. Occupational/age groups					
*Subgroup**	*Priority‡ and other critical occupations§*	*65+ yrs*	*50-64 yrs*	*18-49 yrs*	
# eligible for vaccination	*21,700,000*	*54,706,166*	*57,390,550*	*124,875,767*	
Base-case	**$20,000**	**Vaccination Dominates†**	**$8,000**	**$94,000**	**$8,200**

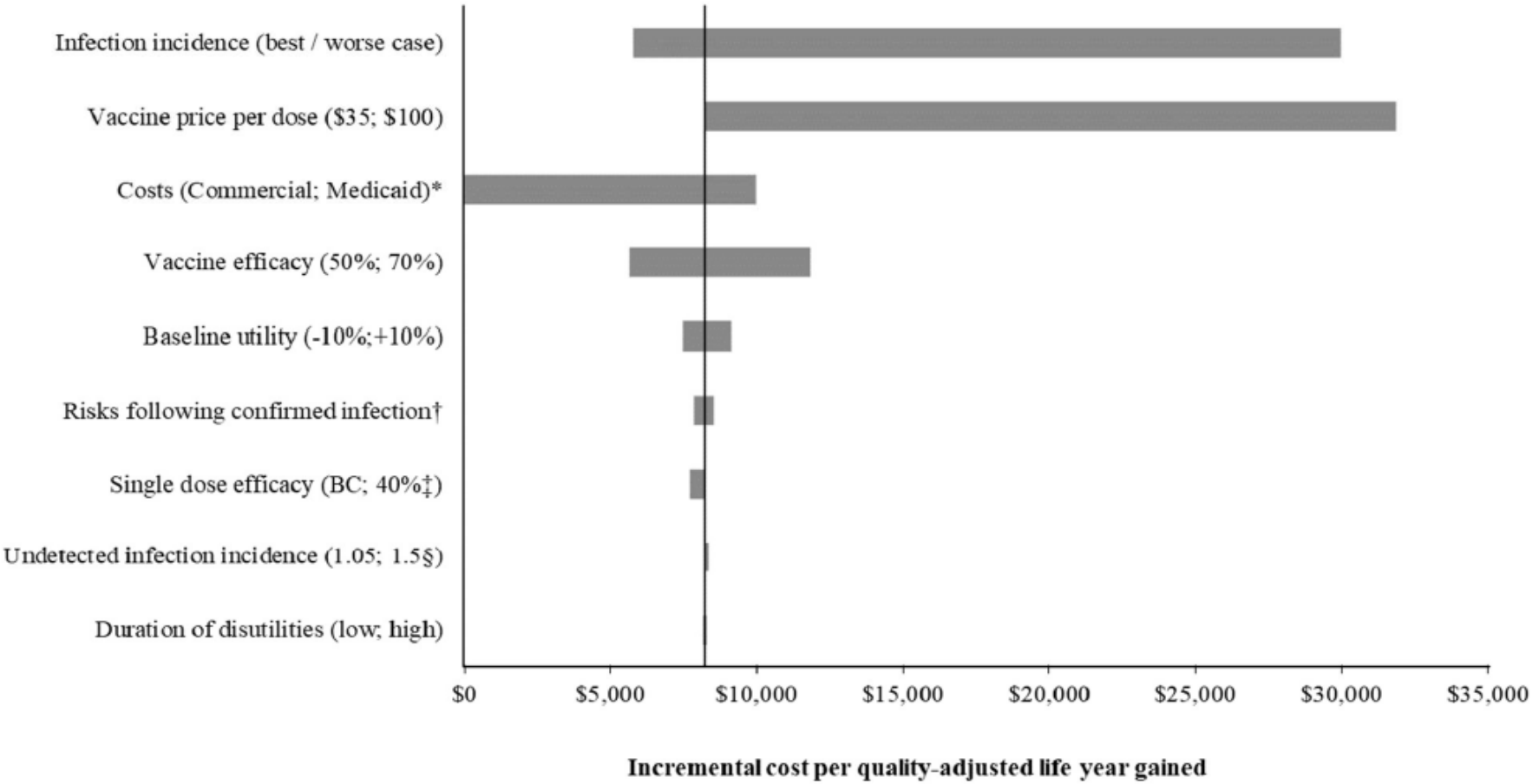
Results

- Overall, the cost per QALY gained for all vaccination strategies was $8,200 versus no vaccination.
- For the tiers at highest risk of complications from COVID-19, vaccination was cost-saving compared to no vaccination.
- The cost per QALY gained increased as the risk of hospitalization and death within each tier decreased.
- **Under the most optimistic supply scenario and the most efficient prioritization scenario, the vaccine may prevent 32% of expected deaths.**
- As supply becomes more constrained, prioritization is required to optimize the prevention of deaths.

- What are the implications of this?

Tornado diagram

Figure 2. Tornado diagram showing the impact of the sensitivity analyses on the overall incremental cost per quality-adjusted life-year gained of vaccination compared to no vaccination**



What price could the firm charge?

Table A8. The vaccine unit price required so that the cost per quality-adjusted life-year gained equals at least $50,000, by tier and overall, under base-case assumptions

Strategy	Vaccine price per dose to achieve a cost per QALY ≥ $50,000 vs no vaccination				
	Tier 1	Tier 2	Tier 3	Tier 4	Overall*
Base-case incidence					
1. Age-based	$328	$143	$15	n/a	$150
2. Risk-group-based	$328	$127	Not possible†	n/a	$150
3. Occupational/age groups	$84	$329	$143	$15	$150
Worst-case incidence					
1. Age-based	$378	$174	$20	n/a	$176
2. Risk-group-based	$378	$154	Not possible†	n/a	$176
3. Occupational/age groups	$101	$379	$174	$19	$176
Best-case incidence					
1. Age-based	$140	$58	Not possible†	n/a	$60
2. Risk-group-based	$140	$50	Not possible†	n/a	$60
3. Occupational/age groups	$31	$141	$58	Not possible†	$60

What do you think of the logic of this?

Group discussion: What are the strengths and weaknesses of this model? What else might you want to consider? (e.g. what about other vaccines? Other interventions, etc.)

However…(to read in your own free time, not now)...

CRITICAL EVIDENCE QUESTIONS FOR COVID-19 VACCINES POLICY MAKING

STRATEGIC ADVISORY GROUP OF EXPERTS (SAGE) ON IMMUNIZATION WORKING GROUP ON COVID-19 VACCINES

Table of Contents

In particular…

SARS-CoV-2 and COVID-19 Epidemiology

I. What is the evidence on the breadth and magnitude of the burden of disease over time, including in different populations and epidemiologic settings?

II. What is evidence on the epidemic trajectory with and without non-pharmaceutical and pharmaceutical interventions?

III. What is the evidence that specific sub-populations are at increased risk of severe disease and death when infected?

- Age groups
- Sex
- Individuals with specific co-morbidities
- Individuals likely to be exposed to higher viral inoculum (e.g. health workers at high or very high risk of infection)
- Specific subpopulations of equity concern (e.g. racial and ethnic groups, socially disadvantaged groups, vulnerable populations)
- Pregnant and lactating women

In particular

IV. What is the evidence that specific sub-populations are at increased risk of infection?

For example:

- Frontline health workers and caregivers
- Essential workers, where physical distancing is not feasible
- Individuals in work or other settings, where physical distancing is not feasible
- Individuals living in densely populated areas, including slums, prisons, and refugee settings

V. What is the evidence that specific settings are associated with higher transmission?

For example:

- Long term care facilities
- Densely populated areas, including slums, refugee settings and prisons
- Workplace where physical distancing is challenging or infeasible to implement
- School or University settings
- Congregate housing
- Mass gatherings such as sport, cultural or other public events, religious gatherings and pilgrimages
- Tourism and travel

In particular

VI. What is the evidence on the demand for healthcare services, including the proportion of COVID-19 cases requiring health care at different levels of intensity (primary care/outpatient, secondary or tertiary care/inpatient, ICU, high-flow oxygen, ventilator) in different population subgroups (e.g. age groups) and geographic settings?

VII. What is the evidence on the long-term sequelae associated with COVID-19 disease, and, in infected persons, what is the evidence of the incidence and duration of long-term sequelae in different population subgroups (e.g. age groups) and geographic settings?

VIII. What is the evidence on the effects of specific treatment/clinical management options on reducing severe disease and mortality?

In particular…

Indirect effects of COVID-19 pandemic

IX. What is the evidence of health-related indirect effects of the COVID-19 pandemic in different populations?

For example:

- Increased burden of disease of other health conditions, through disruption of health care services causing delay in diagnosis and treatment of other conditions (e.g. cancer and cardiovascular diseases)
- Decreased vaccine coverages
- Interruption of screening programs for health conditions
- Mental health (e.g. problems induced by lockdowns and physically distancing interventions)

In particular…

Additional relevant questions

X. What is the evidence of economic and other societal effects of the COVID-19 pandemic, in different populations and population subgroups?

XI. What is the evidence of other indirect effects of the COVID-19 pandemic, such as restricted social contact and isolation, on different population groups?
For example:

- Educational attainment
- Poor access to food, malnutrition
- Child marriages
- Child abuse
- Domestic violence

THANK YOU