Lessons Learned: A Global Perspective

COVID-19: Singapore

Matthias Maiwald

Senior Consultant in Microbiology Dept. Pathology & Lab. Medicine KK Women's & Children's Hospital, Singapore

Adj. Assoc. Prof., Dept. Microbiology & Immunology Yong Loo Lin School of Medicine, National University of Singapore



matthias (dot) maiwald (at) singhealth (dot) com (dot) sg



Background: Singapore was hit quite badly by the 2003 SARS outbreak

Country or region \$	Cases +	Deaths +	Fatality (%)
Mainland China ^[a]	5,327	349	6.6
* Hong Kong	1,755	299	17.0
Taiwan ^{[b][6][7]}	346	73	21.1
Canada	251	44	17.5
Singapore	238	33	13.9
* Vietnam	63	5	7.9
Total excluding Mainland China	2,769	454	16.4
Total (29 territories)	8,096	811	9.6

separately by the WHO. b. ^ After 11 July 2003, 325 Taiwanese cases were 'discarded'. Laboratory

information was insufficient or incomplete for 135 of the discarded cases; 101 o these patients died.

Singapore also had 5 deaths among healthcare workers

Painful Lesson:

 Due to its exposed location as trade and travel hub, SG is extremely vulnerable to imported infections!





Since 2003, Singapore kept doing pandemic planning:

Our hospital's Emerging Infectious Diseases Pages

> Page from 2015 (when MERS, Ebola and Flu A H7N9 were around)

Credit: KKH Infection Control



Exercise "Sparrowhawk" (I and II)

- Mock patient with serious infection arrives at the hospital
- Role-play
- Conducted for Ebola 2015 – Enhanced PPE with respirators
- For "Respiratory X" disease – Full PPE with N95 mask, eye protection, gowns, gloves



Images: KKH Infection Control Unit



Singapore National Centre for Infectious Diseases (NCID)

- Purpose-built medical facility within the public healthcare system
- 17 wards, 330 beds, 2 ICUs
- High-level isolation ward capable of handling Ebola, Marburg, anthrax
- Research and diagnostic facilities
- National Public Health Laboratory (NPHL)
- Formally opened on 7 Sept. 2019 (just in time)





Images: Wikipedia (top), NCID (bottom)

KK Women's and Children's **Hospital (KKH)**



- 830-bed pediatric & OB/Gyn hospital
- Tertiary-level academic teaching hospital for National University of Singapore (NUS) and Duke-NUS
- My workplace -- I am a clinical microbiologist at the hospital's Department of Pathology & Laboratory Medicine
- Relatively small microbiology section

Images: Unabiz (top), Google Maps, User KSY (bottom)







Laboratory testing for 2019 novel coronavirus (2019-nCoV) in suspected human cases Interim guidance 17 January 2020

WHO/2019-nCoV/laboratory/2020.3



https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/laboratory-guidance

Early PCR Assays (Jan 2020)

- Drosten Group, Charité, Berlin Germany
- School of Public Health, University of Hong Kong, Hong (Leo Poon, Daniel Chu and Malik Peiris)
- China CDC (National Institute for Viral Disease Control and Prevention)
- Department of Medical Sciences, Ministry of Public Health, Thailand
- National Institute of Infectious Diseases, Tokyo, Japan

PCR protocol available 13 Jan 2020

Berlin, 13.01.2020

Diagnostic detection of Wuhan coronavirus 2019 by real-time RT-PCR

-Protocol and preliminary evaluation as of Jan 13, 2020-

Victor Corman, Tobias Bleicker, Sebastian Brünink, Christian Drosten Charité Virology, Berlin, Germany

Olfert Landt, Tib-Molbiol, Berlin, Germany

Marion Koopmans Erasmus MC, Rotterdam, The Netherlands

Maria Zambon Public Health England, London

Additional advice by Malik Peiris, University of Hong Kong

RESEARCH

Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR

Victor M Corman¹, Olfert Landt², Marco Kaiser², Richard Molenkamp³, Adam Meijer⁴, Daniel KW Chu⁵, Tobias Bleicker¹, Sebastian Brünink¹, Julia Schneider¹, Marie Luisa Schmidt¹, Daphne GJC Mulders³, Bart L Haagmans³, Bas van der Veer⁴, Sharon van den Brink⁴, Lisa Wijsman⁴, Gabriel Goderski⁴, Jean-Louis Romette⁶, Joanna Ellis⁷, Maria Zambon⁷, Malik Peiris⁵, Herman Goossens⁸, Chantal Reusken⁴, Marion PG Koopmans³, Christian Drosten¹

- Charité Universitätsmedizin Berlin Institute of Virology, Berlin, Germany and German Centre for Infection Research (DZIF), Berlin, Germany
- 2. Tib-Molbiol, Berlin, Germany
- 3. Department of Viroscience, Erasmus MC, Rotterdam, the Netherlands
- National Institute for Public Health and the Environment (RIVM), Bilthoven, the Netherlands University of Heard Keng, Keng, China.
- 5. University of Hong Kong, Hong Kong, China
- Université d Aix-Marseille, Marseille, France
 Public Health England, London, United Kingdom
- Public Health England, London, United Kingdom
 Department of Medical Microbiology, Vaccine and Infectious Diseases Institute, University of Antwerp, Antwerp, Belgium

Correspondence: Christian Drosten (christian.drosten@charite.de)

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Corman Victor M, Landt Olfert, Kalser Marco, Molenkamp Richard, Meljer Adam, Chu Daniel KW, Bleicker Toblas, Brünink Sebastlan, Schnelder Julia, Schmidt Marie Luisa, Mulders Daphne GJC, Haagmans Bart L, van der Veer Bas, van den Brink Sharon, Wijsman Lisa, Goderski Gabriel, Romette Jean-Louis, Ellis Joanna, Zambon Maria, Peiris Malik, Goossens Herman, Reusken Chantal, Koopmans Marion PG, Drosten Christian. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill. 2020;25(3):pil=2000045. https://doi.org/10.2807/1560-7917.ES.2020.25;3.2000045

Adoption of Testing in Singapore

National Public Health Laboratory (NPHL)

 Started testing; designed own PCR (N gene, ORF1ab gene); JAMA 2020

JAMA | Original Investigation

Epidemiologic Features and Clinical Course of Patients Infected With SARS-CoV-2 in Singapore

Barnaby Edward Young, MB, BChir; Sean Wei Xiang Ong, MBBS; Shirin Kalimuddin, MPH; Jenny G. Low, MPH; Seow Yen Tan, MBBS; Jiashen Loh, MBBS; Oon-Tek Ng, MPH; Kalisvar Marimuthu, MBBS; Li Wei Ang, Msc; Tze Minn Mak, PhD; Sok Kiang Lau, PhD; Danielle E. Anderson, PhD; Kian Sing Chan, MBBS; Thean Yen Tan, MBBCh; Tong Yong Ng, MBBS; Lin Cui, PhD; Zubaidah Said, MSc; Lalitha Krurpatham, MPH; Mark I-Cheng Chen, PhD; Monica Chan, BMBS; Shawn Vasoo, MBBS; Lin-Fa Wang, PhD; Boon Huan Tan, PhD; Raymond Tzer Pin Lin, MBBS; Vernon Jian Ming Lee, PhD; Yee-Sin Leo, MPH; David Chien Lye, MBBS; for the Singapore 2019 Novel Coronavirus Outbreak Research Team MAM. 2020;323(15):1488-1494. doi:10.1001/jama.2020.3204 Published online March 3, 2020. Corrected on March 20, 2020.

Other Labs (public & private)

- Adopted various published PCR assays
- Subseq. commercial assays, e.g.
 - TIB Molbiol Berlin, Germany
 - Fortitude Kit, A*Star Singapore
 - Roche cobas 6800 or 8800 (semi-automated)

We at KKH

• PCR testing started 11 Feb 2020

Subsequently

- Ramping up test capacity (~500/day at KKH)
- Some bigger public labs 1500-2500 per day
- Private labs expanded
- Singapore (pop. 6.6 m) reached test capacity ~70,000 PCRs per day in ~27 labs

Serology

- KKH started Abbott N protein assay in May 2020
- Some labs offer S protein assays (vacc. & infect.)
- Surrogate neutralization assays (cPass Test)

Virus Characterization

 Positive samples from public hospitals sent to NPHL (Natl' Public Health Lab) for whole-genome sequencing and virus culture

Biosafety of Testing

- Needed to design lab protocols
- (1) Microbiology & Mol. Micro. Lab
- (2) Other Clinical Laboratories
- (a) "Respiratory type" specimens (higher risk)
- (b) "Non-respiratory" specimens (lower risk)
- COVID suspect specimens double-bagged and labeled





Photos: M. Maiwald

- For (a): Biosafety cabinets (BSCs), goggles, N95 masks, gowns, gloves for specimen processing
- Pregnant women & staff on immunosuppressant medication exempted

LESSONS LEARNED: A GLOBAL PERSPECTIVE



Early COVID-19 Timeline in SG



Escalation of the Situation

- Until late March 2020, SG did very well
- Cases were under control with aggressive isolation and contact tracing efforts
- Shops, schools were open, public life unaffected

Then, cases emerged at Foreign-Worker Dormitories (from 30 March)

- SG has ~300,000 low-income foreign workers, mostly in construction (e.g. India, Bangladesh, Myanmar)
- Housed in crammed conditions, e.g. 15-20
 people in one bedroom
- Virus got foothold, spread like 'wildfire'
- All dormitories quarantined (Armed Forces involved)
- Comprehensive testing and relocation strategy to Government Quarantine Facilities (GQFs)







Photos: Channel NewsAsia from AFP, Reuters, MINDEF



Subsequent Timeline in SG

Timeline until 17 Apr. 2020 1400 55.395 56,435 Dorm residents Imported Feb 1 Travel restrictio on all mainland China arrivals SHN for all travellers entering from ASEAN, Japan Travellers from Iran, northern Italy, S Korea not allowed to transit All short-term visitors barred from entering or transiting Returning Singapore residents from UK, US must serve SHN All returning travelle must serve SHN at 1200 49.375 a must complete **Community Cases** 41 833 1000 Total: 569 Dorm Residents 800 Imported Cases All Cases Total: 1.218 Mar 21 First 2 deaths announced Apr 1 Lee Ah Mooi Old Age Home cluster First cluster at Yong Thai Hang medical ball 200 1 34 5 101824 4047677785 9096106 130 178 243509 40 Apr 11 Apr 18 Apr 25 May 2 May 16 May 16 May 23 May 30 Jun 6 Jul 11 Jul 18 Jul 25 Jun 13 Jun 20 Jun 27 Community Cases Transatt Hills "5th Wave' reb 7 DORSCON Orange declar Imported Cases Entertainment venues closed, social gatherings limited to 10 people, mass gatherings cancelled Total: 3,263 Isolated before Detection 700 650 600 Detected through Surveillance 550 500 1. In Antalationally 450 400 350 300 250 --> 3 distinct epi curves Dorm Residents **Community Cases** Apr 1-Apr 3-Apr 7-Apr 9-Apr 11-Apr 11-Apr 115-Apr 115lan 18 lan 20 lan 22 lan 24 lan 26 lan 28 lan 28 lan 30 Feb 1 Feb 3 Feb 5 Feb 7 Feb 9 Mar Mar Mar Mar Mar Mar Mar Mar 30 - Apr 4 Key clusters at S11 Dormitory, Westlite Toh Guan, Mustafa Centre Apr 5 S11 Dormitory and Westlite Toh Guan Apr 9 Link found between Mustafa Centre and Image: Channel NewsAsia g 1000 & Ministry of Health ofca **Dorm Residents** 500 7 Apr: Start of "Circuit Breaker", i.e. SG lockdown Jan 17 Jan 23 Jan 23 Feb 10 Feb 10 Feb 22 Mar 11 Mar 12 Apr 12 Apr 22 Apr 22 Apr 22 Apr 22 Apr 22 May 4 Jun 3 Jun 9 - School closures, only essential businesses open - Public mask wearing, social distancing Date From 2 Jun: Reopening in phases 30 Mar: Start Image: Ministry of Health Situation Reports "4th Wave" of dorm cases LESSONS LEARNED: A GLOBAL PERSPECTIVE

Timeline until 30 Aug. 2020

Coping with Increased Testing

 Increasing test demand, tests from dorms and Government Quarantine Facilities (GQFs) distributed across public and private labs

Testing in high-prevalence settings is challenging!

- Many samples with low-level or borderline amplification curves (stages of infection)
- Extensive re-testing with confirmatory assays is necessary!



Advent of COVID-19 Rapid Testing

Rapid PCR (singleplex)

 E.g. Cepheid GeneXpert SARS-CoV-2 (monoplex; ~45 min)





Rapid PCR (multiplex)

 E.g. BioFire FilmArray RP 2.1 multiplex PCR with 19 pathogens & SARS-CoV-2 (~45 min)



1	Res	piratory Panel 2.1		0	3
					www.BioFireDx.com
R	un Summary				
	Sample ID:	RP2.1example	R	un Date:	04 April 2020
	Detected:	Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2	s) _		5:21 PM
	Equivocal:	⇔Influenza A		ontrois;	rasseu
	Liquitoeni.	- Indettea A	_		
R	esult Summary	/ Mensee			
-	Not Detected	Adenovinus			
	Not Detected	Coronavirus 229F			
	Not Detected	Coronavirus HKU1			
	Not Detected	Coronavirus NL63			
	Not Detected	Coronavirus OC43			
Detected Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)					
	Not Detected	Human Metapneumovirus	,		
	Not Detected	Human Rhinovinus/Enterovirus			
-	Equivocal	Infuenza A			
-	Not Detected	Influenza B			
	Not Detected	Parainfluenza Virus 1			
	Not Detected	Parainfluenza Virus 2			
	Not Detected	Parainfluenza Virus 3			
	Not Detected	Parainfluenza Virus 4			
	Not Detected	Respiratory Syncytial Virus			
_		Bacteria			
	Not Detected	Bordetella parapertussis (IS1001)			
	Not Detected	Bordetella pertussis (ptxP)			
	Not Detected	Chlamydia pneumoniae			
	Not Detected	Mycoplasma pneumoniae			
R	un Details				
	Pouch:	RP2.1 v1.0 Pro	locol:	NPS2 v3	3.2
	Run Status:	Completed Ope	rator:	JDoe	
	Serial No.:	01234567 Instru	ment:	TM8CC8	F3
	a set block	012245			

Antigen Rapid Tests (ARTs)

- E.g. BD Veritor (~30 min)
- Disadvantage: Sensitivity ~70-80%



Images: Manufacturer Websites



Timeline of Pandemic Response Measures, Singapore

Time	Phase	Key events or measures
Jan 2020	NA	First imported case reported
Feb 7	Pandemic Level 3	 Non-essential large events (>1,000 people) deferred Daily health monitoring at workplace (including temperature) Public reminded of personal hygiene and social distancing Persons who are unwell to seek medical attention and wear masks
Mar 23	(DORSCON Orange)	 Social gatherings limited to 10 persons Closure of entertainment venues (e.g. cinemas, bars) Intl' travel restrictions & stay-home notices (SHNs) for return residents
Apr 7	Lockdown ("Circuit Breaker")	 F&B outlets: no dine-in, only takeaways/deliveries Suspension of non-essential businesses Restricted commute, work from home encouraged School closures –full home-based learning Full closure of recreational venues (e.g. museums, theme parks) Use of masks strongly encouraged outside of home
Apr 13		 Mandatory mask-wearing outside of home (>2 years old)
Apr 20		 Temperature screening & contact traceability logs at all outlets No social home visits/gatherings
Jun 2	Re-opening Phase 1	 Phased re-opening of selected businesses Phased re-opening of schools
Jun 19	Re-opening Phase 2	 F&B outlets: dine-in resumed; no more than 5 persons per table Safe distancing measures remain in place Masks outside of home remain compulsory
Dec 28 – May 7, '21	Re-opening Phase 3	 Gathering limit increased to 8 persons per table or household Mask-wearing & safe distancing measures remain in place

NA, not applicable; DORSCON, Disease Outbreak Response System Condition; F&B, food and beverage.

LESSONS LEARNED: A GLOBAL PERSPECTIVE



COV

D-19

SG Timeline up to June 2021

Note different

axis scales Phase 2 Re-opening Phase 1 Phase 3 (high alert) (high alert) $2020 \leftarrow // \rightarrow 2021$ Pandemic Lvl 3 Lockdown Re-opening Re-opening **DORSCON** Orng (Circuit Breaker) Phase 2 Phase 3 **Circuit Breaker** Imported cases, Imported Cases mostly detected in quarantine Local transmission in clusters; airport cluster, **Community Cases** Occasional hospital cluster 40 spillover Stay-Home Notice for **Dorm Residents** travelers from high-**Routine Rostered** 1000 **Dorms largely** Testing (RRT) in Rise of risk countries 21 days under control Healthcare Staff dorm cases 500 (from 4 May) implemented Mar 2020 May 2020 Jul 2020 Sep 2020 Nov 2020 Jan 2021 Mar 2021 May 2021 Isolated before Detection Detected through Surveillance Dorm (Prior to Classification on 24th Aug) — Moving Average (7-days)

Spike in Cases Apr/May 2021

- Until March 2021, SG did well; dorms under control
- \rightarrow Then, community cases rose
- Led to several case clusters, e.g.
 - Airport; TTS Hospital; Westgate Shopping Mall
- Presumably imported; return residents & relatives
- Hospital Cluster: 48 cases, 3 deaths
- Commonly B.1.617.2 variant of concern (VOC), i.e. Delta (Indian) variant
- Presumably escaped 14-d Quarantine
- Presumed that pats. are longer infectious/shedding
- → Govt. tightened measures
- 21-d quarantine for 'high-risk countries'
- 'Heightened Alert' measures 8 May 2021
- Back to Phase 2 Reopening (from Ph. 3) 16 May

Singapore's virus situation since April 28

7-day moving averages*

Total new cases Community cases Unlinked cases

NOTE: *The 7-day moving average refers to the average of the cases on a given day, the three preceding days and the three following days.



After Case Spike & Hospital Cluster

• Hospital (TTSH) closed for new admissions; deferment of non-urgent cases

All Public Hospitals

- Enhanced PPE regulations; e.g. N95 (not surgical) masks for all patient-fronting areas
- All newly admitted patients to be COVID-19 PCR-tested
- All symptomatic patients in Emergency Depts. (EDs) to be ART (antigen) and PCR-tested
- All hospital staff to be PCR-tested:
 - a) Initial "sweep" testing of all staff within 2 weeks
 - b) Subsequent Rostered Routine Testing (**RRT**) of all staff, every 14 days (non-vaccinated 7 d)

Consequences

- Massive PCR testing demand KKH has >6500 staff; SGH (Singapore General) ~18,000
- Needed to further ramp up test capacity
- KKH implemented 3:1 pooling (at the lab) of staff specimens; help from other departments
- Other hospitals implemented pooling at the point of swabbing (e.g. 3 staff swabs 1 tube)
- ART (Antigen Rapid Testing) in EDs not yet implemented; details unclear

Case of Paucisymptomatic Child

- 6 mo/old infant admitted for testing & isolation b/c mother was infected
- Asymptomatic except mild fever 38.5°C
- Low Ct value 13.7
 ≈ 6 billion virus copies per NP swab
- NP samples pos. up to day 16
- Child likely highly infectious



A Well Infant With Coronavirus Disease 2019 With High Viral Load

Kai-qian Kam,^{1,©} Chee Fu Yung,¹ Lin Cui,² Raymond Tzer Pin Lin,² Tze Minn Mak,² Matthias Maiwald,³ Jiahui Li,¹ Chia Yin Chong,¹ Karen Nadua,¹ Natalie Woon Hui Tan,¹ and Koh Cheng Thoon¹

¹Infectious Disease Service, Department of Pediatrics, KK Women's and Children's Hospital, Singapore, Singapore, ²National Public Health Laboratory, National Centre for Infectious Diseases, Singapore, Singapore, and ³Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore, Singapore

A well 6-month-old infant with coronavirus disease 2019 (COVID-19) had persistently positive nasopharyngeal swabs up to day 16 of admission. This case highlights the difficulties in establishing the true incidence of COVID-19, as asymptomatic individuals can excrete the virus. These patients may play important roles in human-to-human transmission in the community.

Keywords. COVID-19; SARS-CoV-2; infant; 2019 novel coronavirus. Clin Infect Dis. 2020 Jul 28; 71: 847-849.

 Our lab's lowest recorded Ct value:
 9.7 (in an adult)
 ≈ 100 billion virus copies per NP swab Clinical Infectious Diseases

CORRESPONDENCE

Online ahead of print. ciaa1376.

Saliva Is Not a Useful Diagnostic Specimen in Children With Coronavirus Disease 2019 (COVID-19)

TO THE EDITOR—Saliva specimens have shown promise for diagnosing coronavirus disease 2019 (COVID-19) in adults, with a sensitivity of 50.5-96%[1–8]. However, in children, the utility of saliva specimens is uncertain; thus, we compared saliva with nasopharyngeal (NP) swabs for diagnosing COVID-19 in children.

Chia Yin Chong,^{1,2,3,4} Kai-Qian Kam,^{1,2,3,} Jiahui Li,^{1,2,3} Matthias Maiwald,^{3,5,6} Liat Hui Loo,⁵ Karen Donceras Nadua,^{1,2,3} Natalie Woon Hui Tan,^{1,2,3,4} Chee Fu Yung,^{1,3,4} and Koh Cheng Thoon^{1,2,3,4}

¹Infectious Diseases, Department of Pediatrics, KK Women's and Children's Hospital, Singapore, Republic of Singapore, ²Yong Loo Lin School of Medicine, National University of Singapore, Singapore, Republic of Singapore, ³Duke-NUS Medical School, Singapore, Republic of Singapore, ⁴Lee Kong Chian School of Medicine, Imperial College London, London, United Kingdom, Nanyang Technological University, Singapore, Republic of Singapore, ⁵Department of Pathology and Laboratory Medicine, KK Women's and Children's Hospital, Singapore, Republic of Singapore, and ⁶Department of Microbiology and Immunology, National University of Singapore, Republic of Singapore, Republic of Singapore

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Salivarys NP swappy (ngired)

- 18 infected children; 12 asympt., 8 mildly symptomatic
- 5 pats. (28%) had only negative saliva
- Saliva Ct values significantly higher than NP Ct values
- Saliva sensitivity highest at only 53% on days 4-7
- Conclusion --> Saliva is not a good specimen



Day of illness/diagnosis	Day 1-3	Day 4-7	Day 8-10	Day 11-15
Number of pairs of nasopharyngeal and saliva specimens	16	18	11	8
Sensitivity of saliva specimen	46.7%	52.9%	25%	33.3%
Nasopharyngeal mean cycle threshold ± SD	$\textbf{25.9} \pm \textbf{6.8}$	$28.9\ \pm 6.6$	$\textbf{32.3} \pm \textbf{7.5}$	39.2 ± 7.3
Saliva mean cycle threshold \pm SD	38.5 ± 7.2	39.1 ± 6.1	42.0 ± 6.2	43.1 ± 5.0
P value	<0.001	<0.001	0.009	0.27

Ε

Disappearance and reappearance of respiratory viruses during COVID-19 response measures

- Routine Respiratory Pathogens (RP) multiplex PCR testing (BioFire)
- Around Dec 2019/Jan 2020 Large proportion of positives Mainly Flu A/B
- COVID restrictions set in -
 - DORSCON Orange in Feb '20; Hard Lockdown ("Circuit Breaker") in Apr '20
 - Reopening Phase 1 in Jun '20; Phase 2 later in Jun '20; Phase 3 in Jan '21

Observations

- Around Apr '20, noticed that <1/10 of RP PCRs had pathogens
- What is going on? All disappeared?
- About ~13 weeks after reopening, EV/RV reappeared; later AdV
- Into 2021, other viruses reappeared

Wan WY, Thoon KC, Loo LH, Chan KS, Oon LLE, Ramasamy A, Maiwald M. Broad decline and subsequent differential re-emergence of respiratory viruses during COVID-19 pandemic response measures, Singapore 2020. MedRxiv. 2021. https://doi.org/10.1101/2021.03.23.21251968. (Non-peer-reviewed pre-print).

LESSONS LEARNED: A GLOBAL PERSPECTIVE

EV = enterovirus RV = rhinovirus AdV = adenovirus









Singapore's Vaccination Programme

- 14 Dec 2020: Pfizer-BioNTech mRNA vaccine approved; 1st shipment arrived 21 Dec
- Vaccine free for all Singaporeans, permanent & long-term residents
- 30 Dec 2020: Start with Healthcare & Frontline Workers
- 3 Feb 2021: Moderna mRNA vaccine approved
- From Feb 2021: Start with elderly; sequentially moved to lower age groups
- 18 May 2021: Pfizer-BioNTech vaccine approved for 12-15 y/o
- 18 May 2021: Vaccine interval (1st to 2nd dose) extended from 3-4 wks to 6-8 wks
- 1 Jun 2021: Mass vaccination drive incl. students >12 y/o
- 2 Jun 2021: CoronaVac (China) limited approval





Sources: Wikipedia; Google; Our World in Data

Public Health Measures

Singapore has been exemplary in contact tracing, isolating and identifying clusters

Classical Contact Tracing Smartphone App TraceTogether

TraceTogether Token



TraceTogether and SafeEntry

- Since June 2021, TraceTogether App/Token are mandatory for entry at public places and shopping malls
- Serves for access control and contact tracing





Conclusions and Outlook

- Singapore generally manages the crisis very well benefitted from preparedness
- As of 11 Jun 2021, 62,245 cases, 34 deaths remarkably low death rate
- Outbreak in the foreign workers' dormitories led to rapid spread; majority of SG's cases
- July '20-May '21 relatively few restrictions mask-wearing, safe distancing, gathering limits
- Clusters sparked by imported cases Apr/May 2021 sparked new temp. restrictions

On the Ground

- Work on the ground is challenging large testing demands for our small lab
- No major PPE shortages stockpiles before the pandemic (e.g. 18 M N95 masks; ~3 p.p.)
- Temporary lab reagent shortages overcome with centralized procurement & alternatives

Capacity Building & Maintaining

- Completion of NCID (long planned) in 2019 was fortuitous
- Our lab was underresourced & understaffed improved & rec'd help from hospital leaders
- Maintaining clinical & lab capacity, staffing & skill sets essential for outbreak response

Future

• Still unclear how pandemic will progress – but many countries now see cases coming down

THANK YOU !

