Management of Covid19

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How does covid-19 spread

1. **Inhalation** of air carrying very small fine droplets and aerosol.
    1. Risk of transmission is greatest within three to six feet of an infectious source
2. **Deposition** of virus carried in exhaled droplets and particles onto exposed mucous membranes (i.e., “splashes and sprays”, such as being coughed on).
3. **Touching mucous membranes** with hands soiled by exhaled respiratory fluids containing virus or from touching inanimate surfaces contaminated with virus.

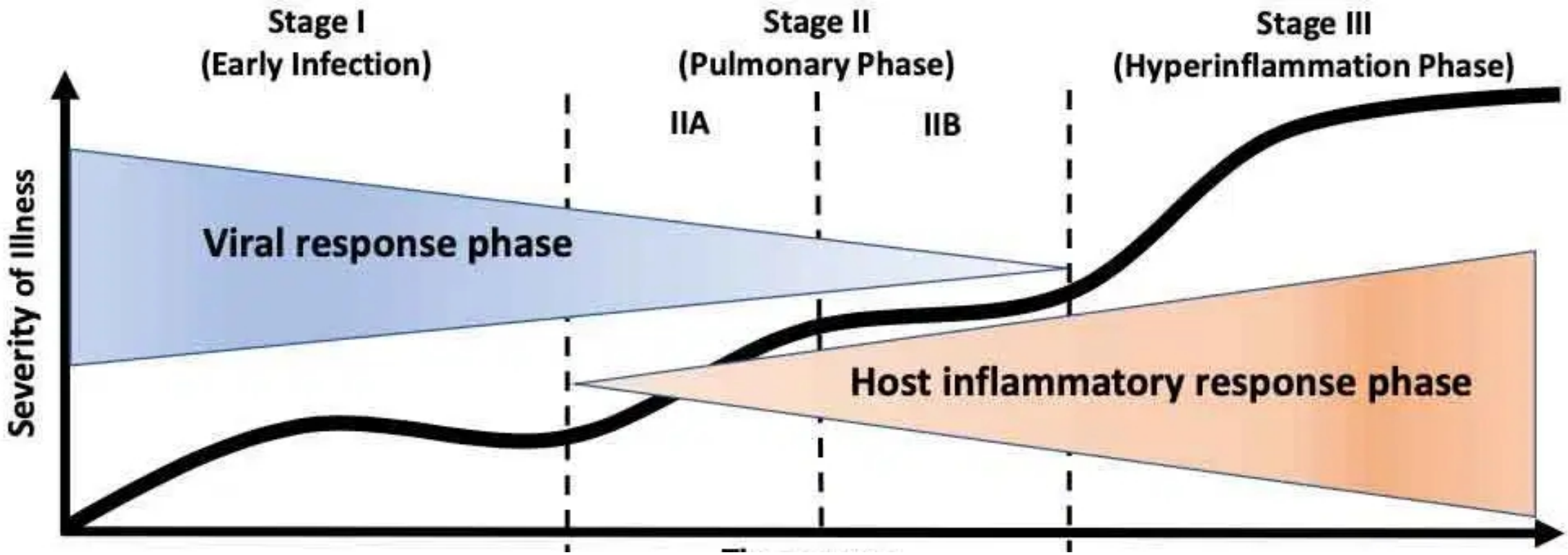
https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html

When can covid-19 transmission be airborne?

- **Enclosed spaces with inadequate ventilation or air handling**
- **Increased exhalation** of respiratory fluids if the infectious person (e.g., exercising, shouting, singing).
- **Prolonged exposure** to these conditions, typically more than 15 minutes.

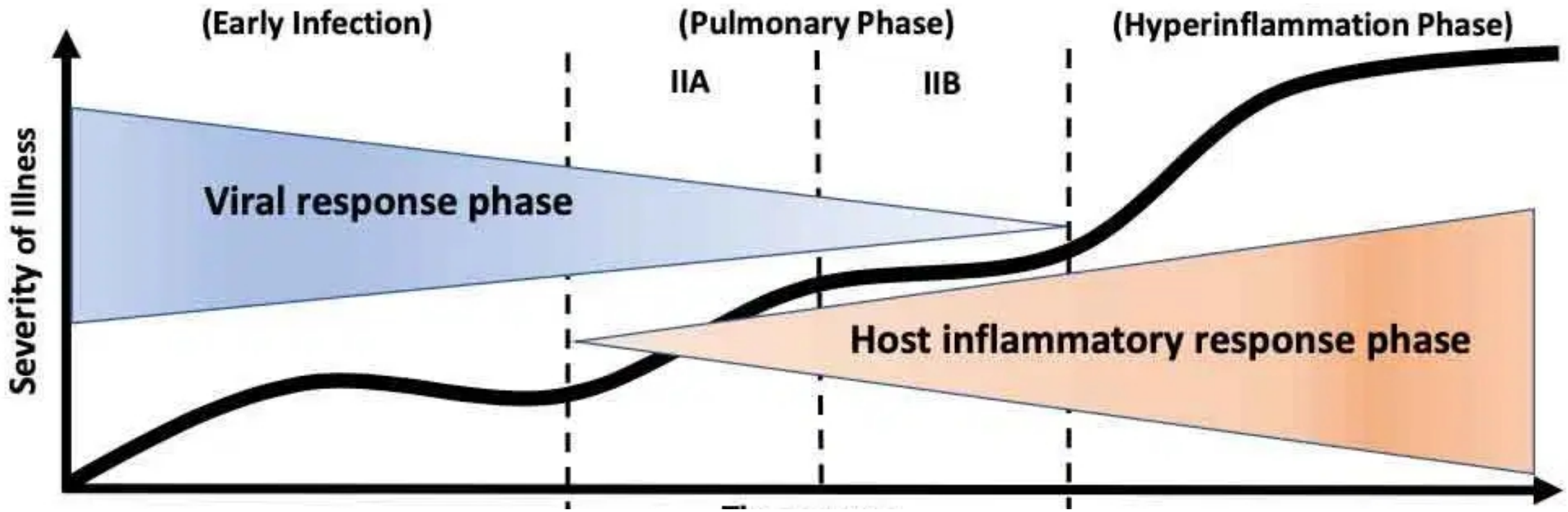
https://www.cdc.gov/coronavirus/2019-ncov/science/science-briefs/sars-cov-2-transmission.html

Natural history



Natural history

ASYMP OR FLU LIKE SX	PNUEMONIA	NP / FACE MASK	HFNC / VENT
CLINICAL CATEGORY 1 & 2	CAT 3	CAT 4	CAT 5



Diagnosing covid-19

COVID-19

- Fever or chills
- Cough
- Shortness of breath or difficulty breathing
- Fatigue
- Muscle or body aches
- Headache
- New loss of taste or smell
- Sore throat
- Congestion or runny nose
- Nausea or vomiting
- Diarrhoea

Respiratory symptoms

Body ache, fatigue

Loss of taste and smell

GI symptoms

Suspect phase – requires clinical and epidemiological criteria

Clinical criteria

- Acute onset of fever AND cough; OR

- Acute onset of **ANY TWO OR MORE** of the following signs and symptoms: Fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnea, anorexia/nausea/vomiting, diarrhoea, altered mental status.

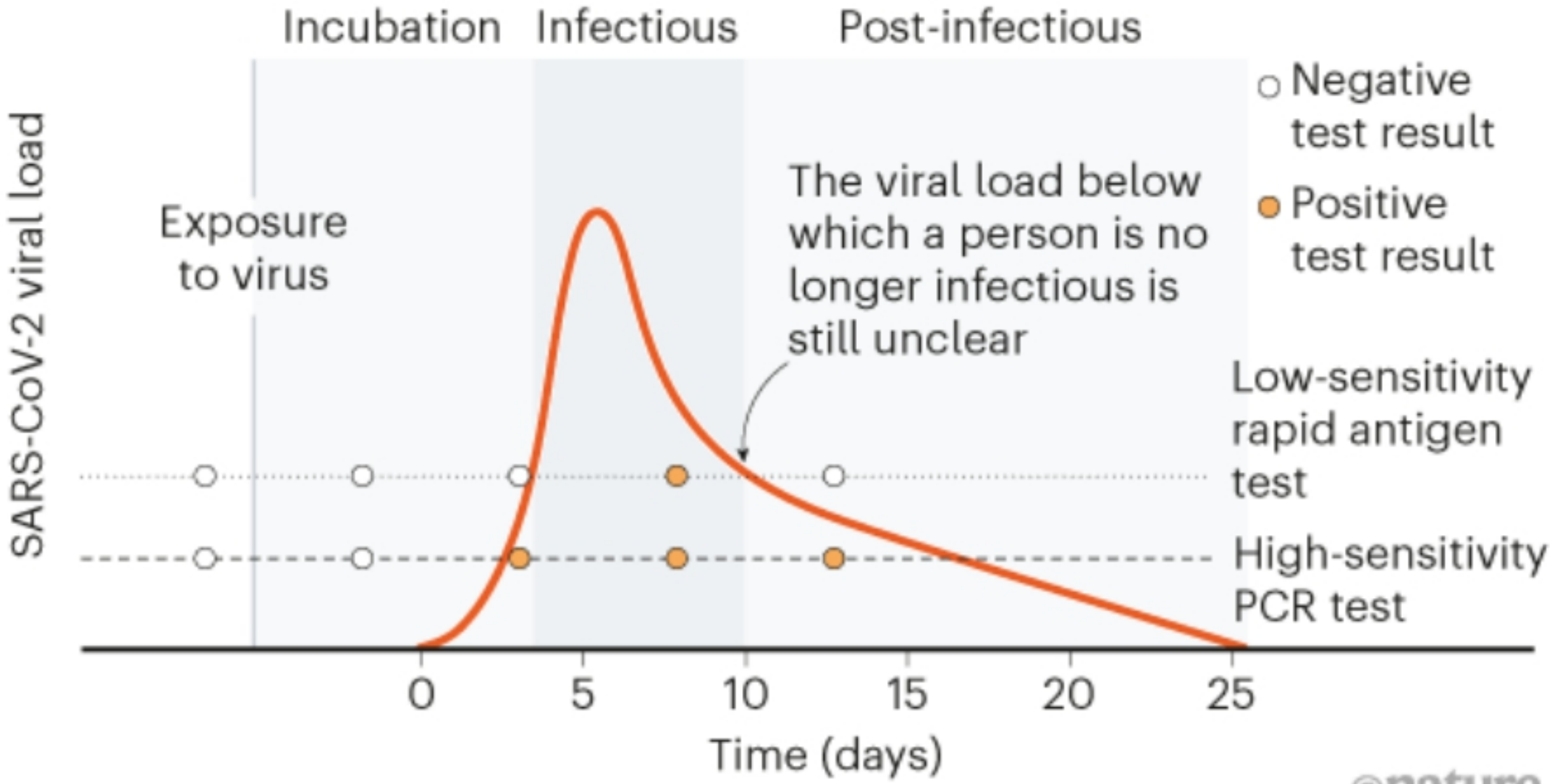
Probable Case

- **A person (alive or dead) with a positive RTK-Ag.**
- A **suspected case with chest imaging** showing findings suggestive of COVID-19 disease2.
- A patient who meets **clinical criteria** above **AND** is a c**ontact of a probable or confirmed case or** linked to a **COVID-19 cluster.**
- A person with recent onset of **anosmia** (loss of smell) or **argeusia** (loss of taste) in the absence of any other identified cases.
- **Death**, not otherwise explained, in an adult with **respiratory distress** preceding death AND **was a contact of a probable or confirmed case** or linked to a **COVID-19 cluster.**

Confirmed Case

- A person with a **positive RTK-Ag in pre-determined areas/locality with prevalence of COVID-19 > 10%.**

- A person (alive or dead) with a positive **molecular test (RT-PCR or rapid molecular).**


Incubation
Infectious
Post-infectious
SARS-CoV-2 viral load
Exposure to virus
The viral load below which a person is no longer infectious is still unclear
Negative test result
Positive test result
Low-sensitivity rapid antigen test
High-sensitivity PCR test
0
5
10
15
20
25
Time (days)
©nature

Morbidity and Mortality Weekly Report

Transmission of SARS-COV-2 Infections in Households — Tennessee and Wisconsin, April–September 2020

Carlos G. Grijalva, MD[1,*]; Melissa A. Rolfes, PhD[2,*]; Yuwei Zhu, MD[1]; Huong Q. McLean, PhD[3]; Kayla E. Hanson, MPH[3]; Edward A. Belongia, MD[3]; Natasha B. Halasa, MD[1]; Ahra Kim, MPH[1]; Carrie Reed, DSc[2]; Alicia M. Fry, MD[2]; H. Keipp Talbot, MD[1]

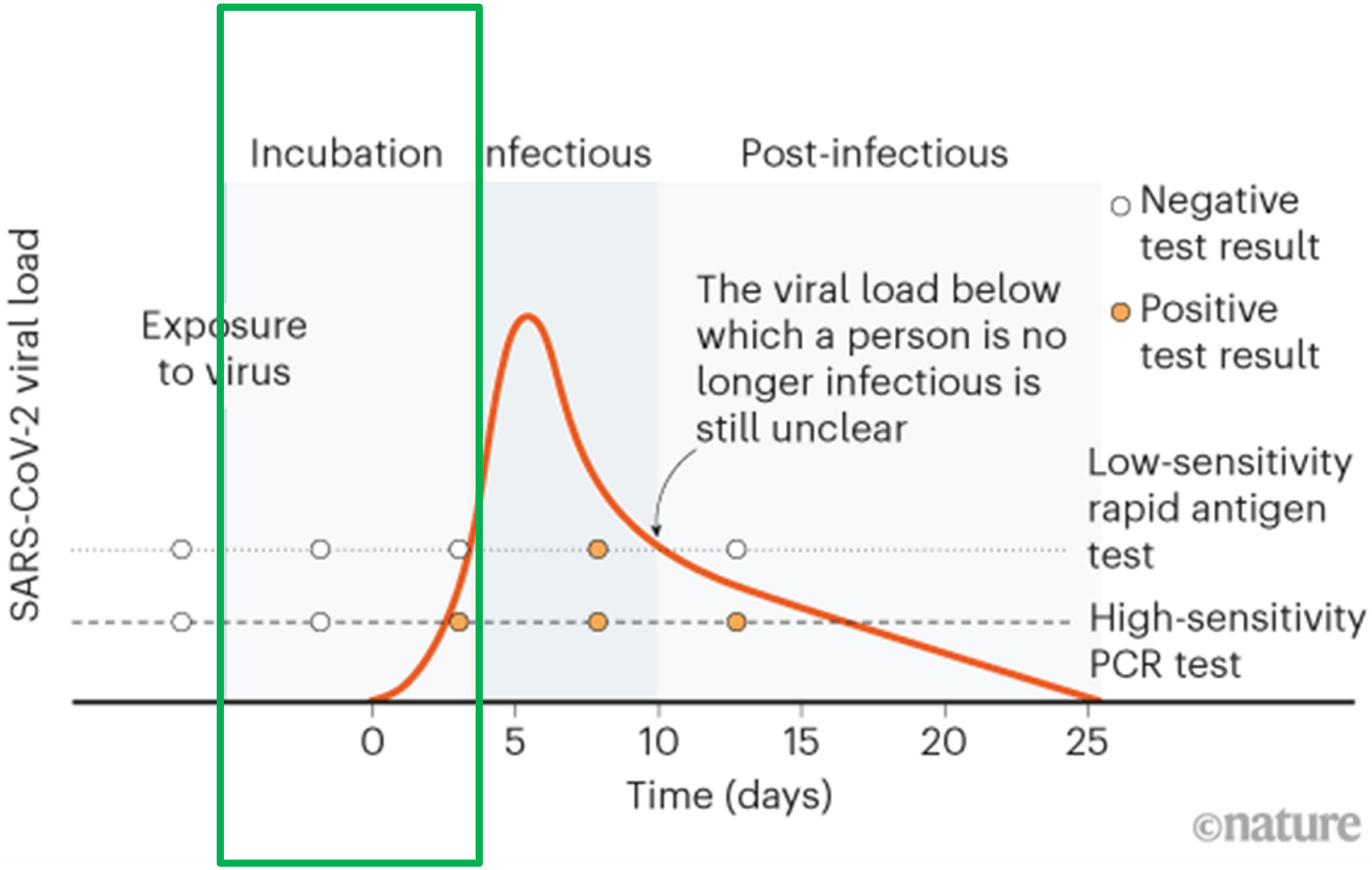
MMWR / November 6, 2020 / Vol. 69 / No. 44

75% of infections identified within 5 days of the index patient's illness onset

Incubation period

- The median incubation period of COVID-19 - 5-6 days.
- Most become positive 2 – 12 days after exposure

Health Information and Quality Authority. Evidence summary for the incubation period of COVID-19, or time to first positive test, in individuals exposed to SARS-CoV-2 2020 [updated 4 November 2020].



<u>Using PCR</u>

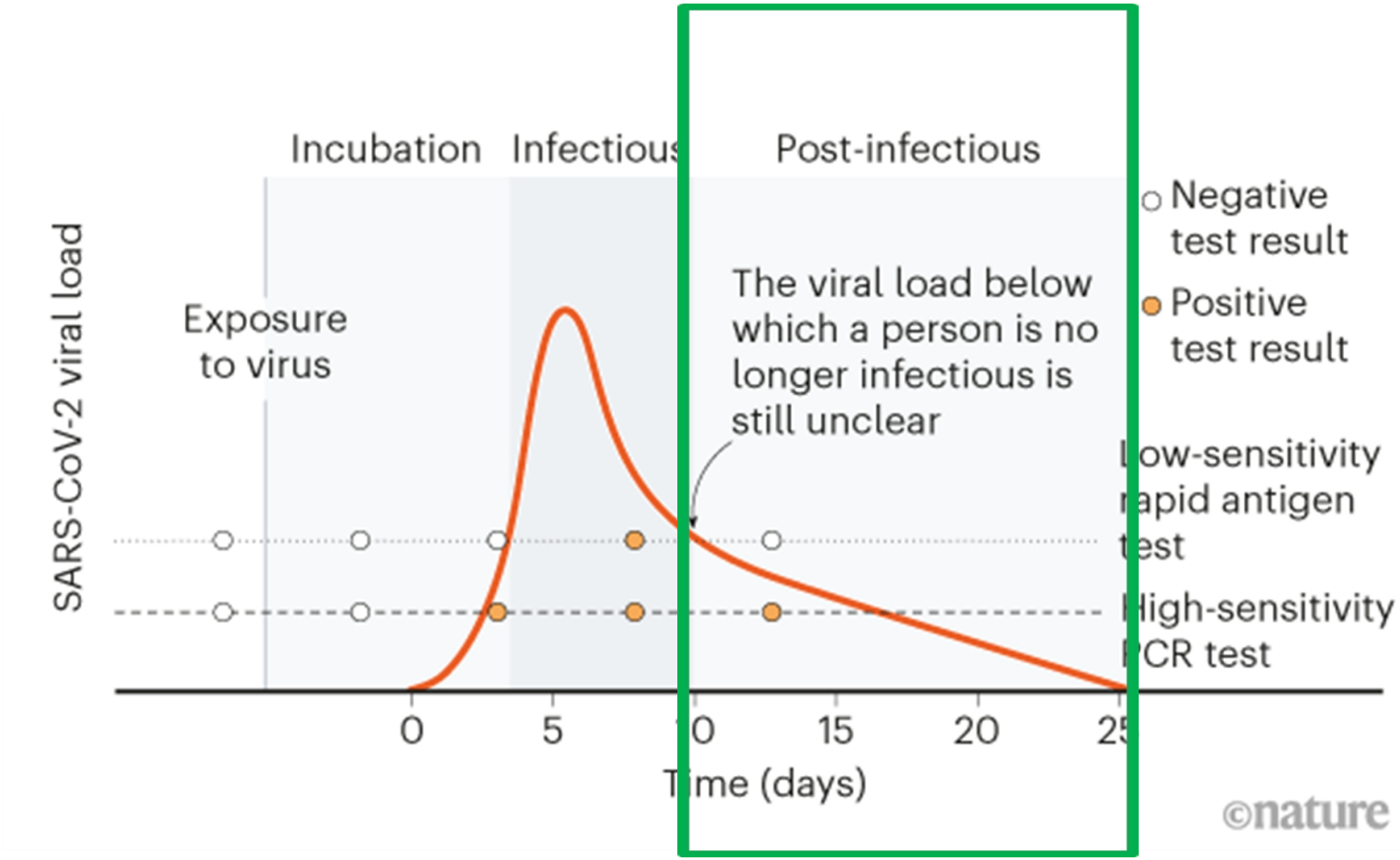
Day 5 after exposure – 38% false negative rate

Day 8 after exposure – 20% false negative rate

Kucirka LM, Lauer SA, Laeyendecker O, Boon D, Lessler J. Variation in false-negative rate of reverse transcriptase polymerase chain reaction-based SARS-CoV-2 tests by time since exposure. Ann Intern Med 2020;173:262-7. doi: 10.7326/M20-1495 pmid: 32422057

PCR positive but not infectious

- Covid PCR positive =
  - Live virus
  - Dead virus
  - Viral fragments



Antigen tests

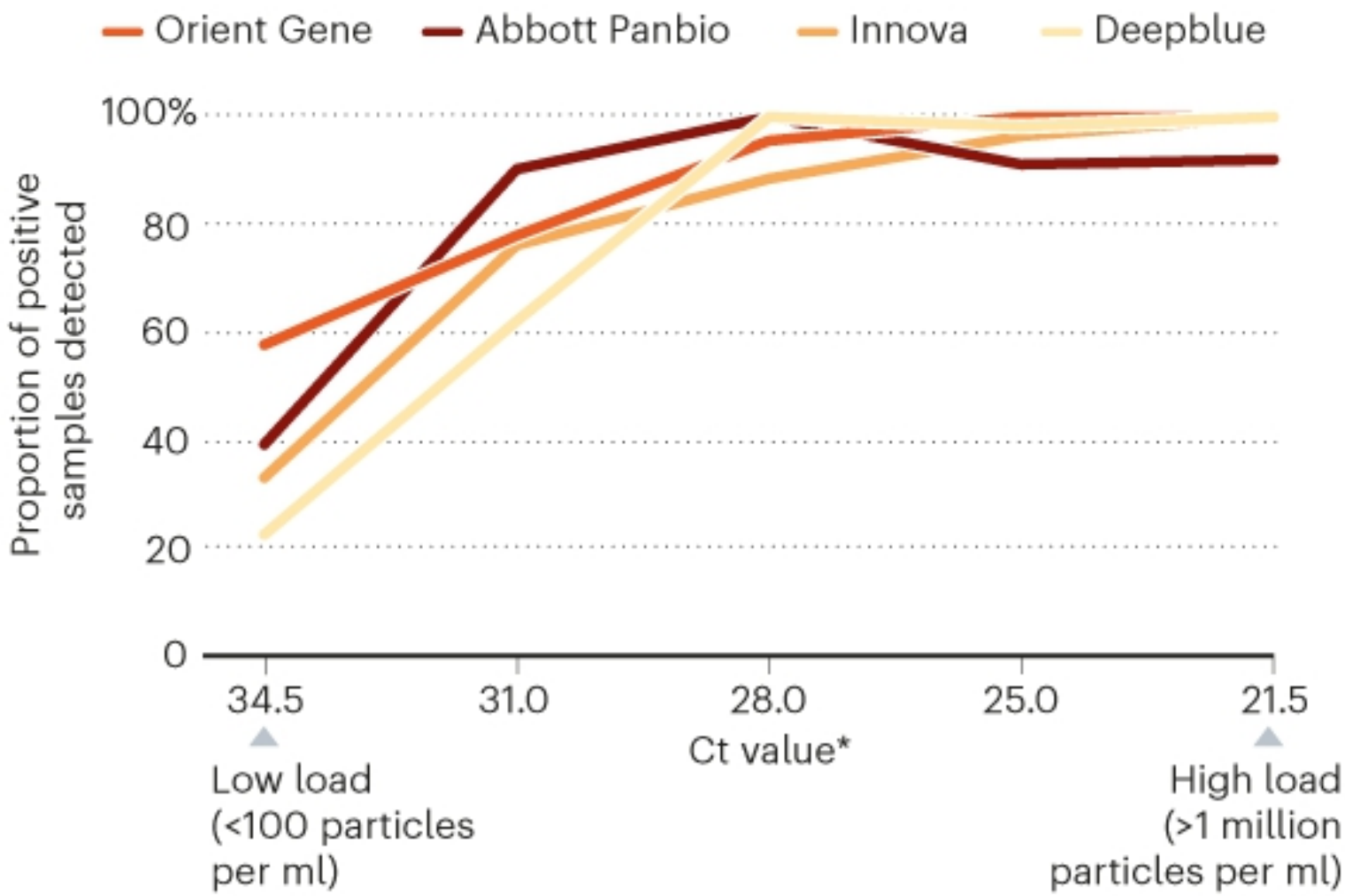
- Sensitive enough to detect cases with high viral load,
  - pre-symptomatic
  - early symptomatic cases (up to five days from symptom onset)
  - low RT-PCR cycle threshold (Ct) value <25)

- Developed for testing in symptomatic persons
- Not currently recommended for use in asymptomatic persons
-

https://www.ecdc.europa.eu/en/publications-data/options-use-rapid-antigen-tests-covid-19-eueea-and-uk

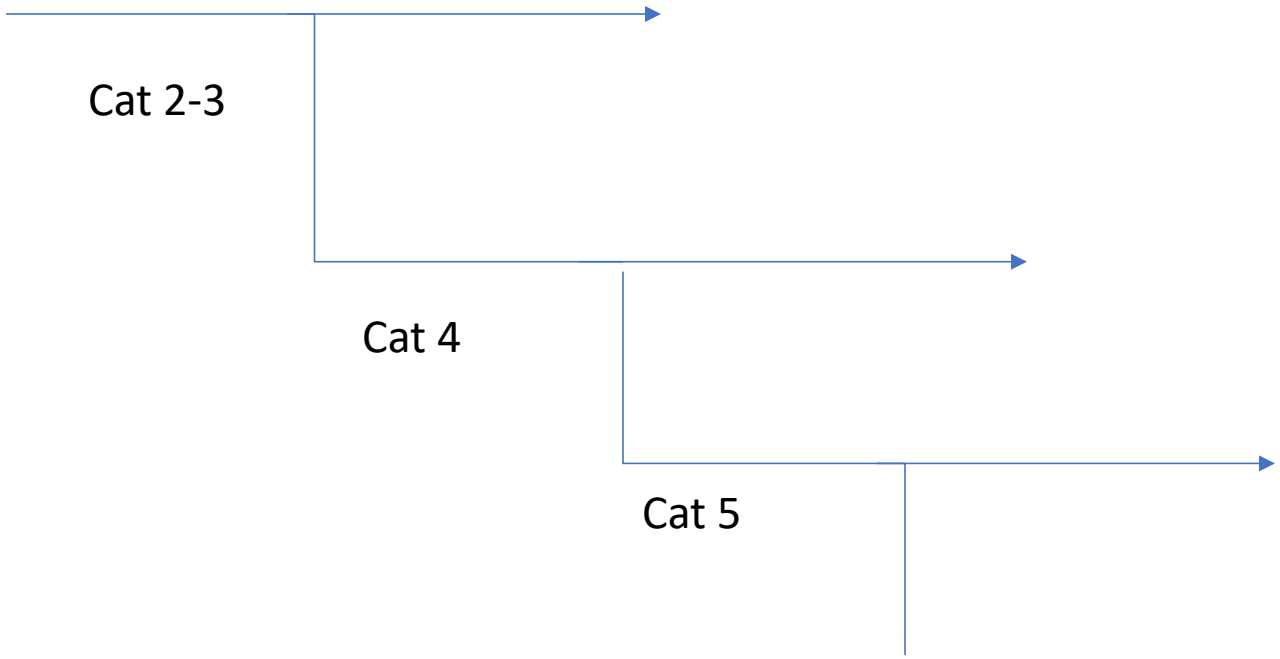
RAPID TESTS SPOT HIGH VIRAL LOADS

Antigen tests from different manufacturers tend to have similar sensitivity to high viral loads, but very different sensitivities when viral loads are low.

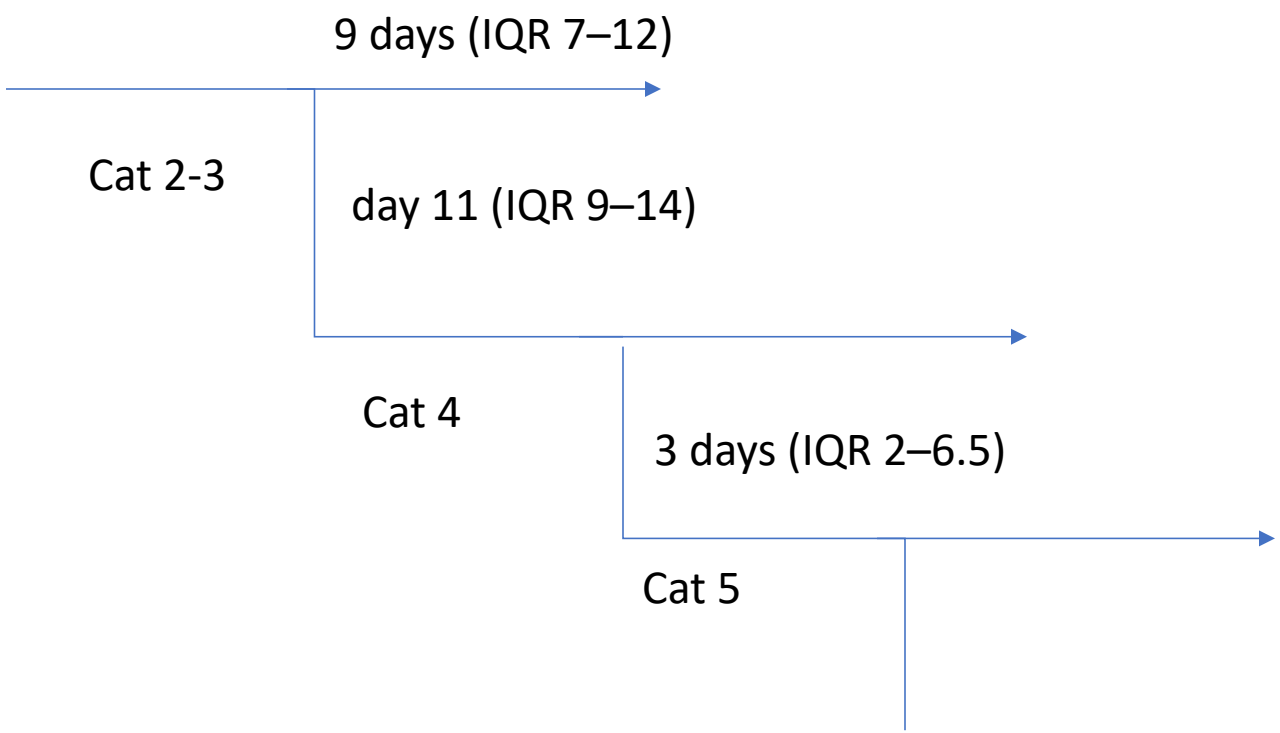


*Number of cycles of PCR needed to detect virus in a sample. Relationship between Ct and viral load can vary between laboratories.

Clinical progression



Clinical progression & timelines



Chen S, Feng H, Xu H, Huang S, Sun J, Zhou L, et al. Patterns of Deterioration in Moderate Patients With COVID-19 From Jan 2020 to Mar 2020: A Multi-Center, Retrospective Cohort Study in China. Front Med [Internet]. 2020 [cited 2021 May 12];7. Available from: https://www.frontiersin.org/articles/10.3389/fmed.2020.567296/full

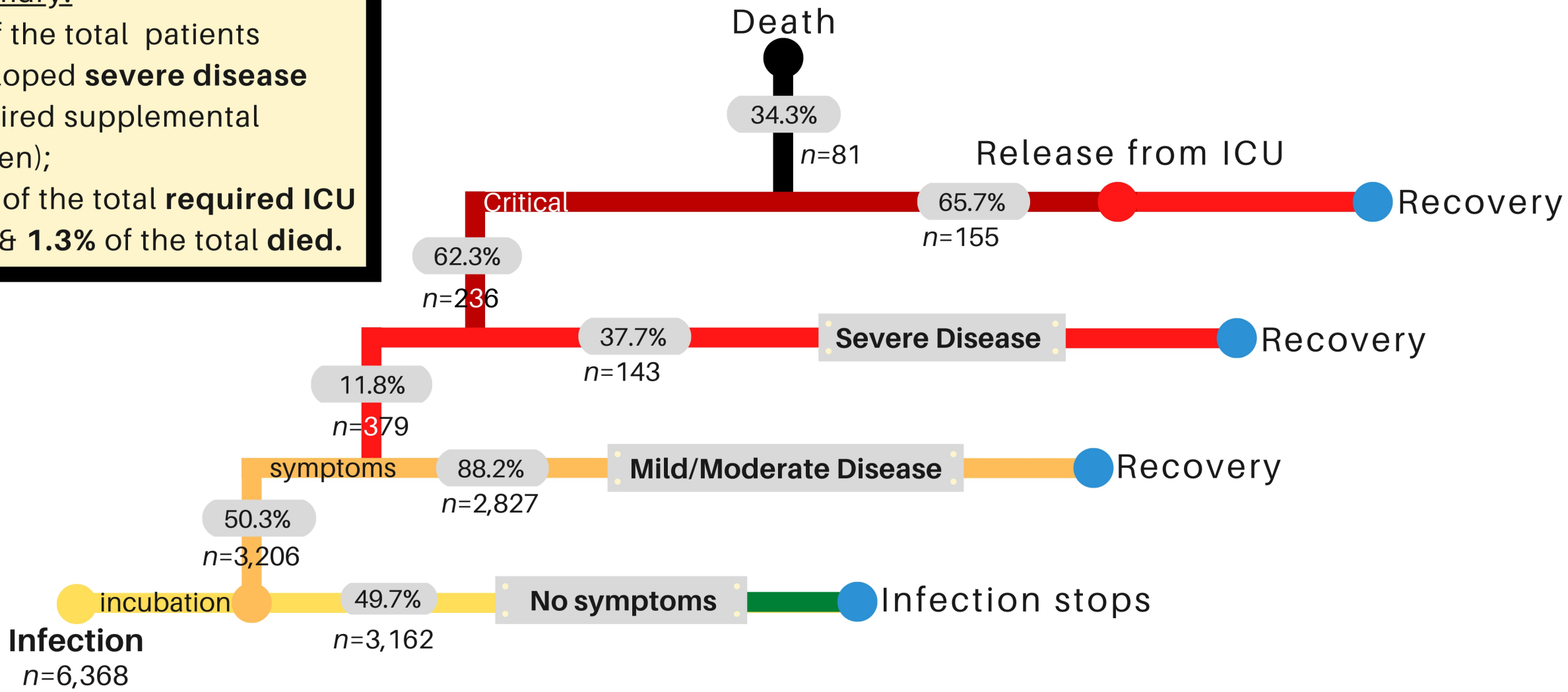
COVID-19 Clinical Course & Outcomes of 6,368 patients in Malaysia

Based on Malaysian Cohort, *n=6,368*

Summary:

6% of the total patients developed **severe disease** (required supplemental Oxygen);

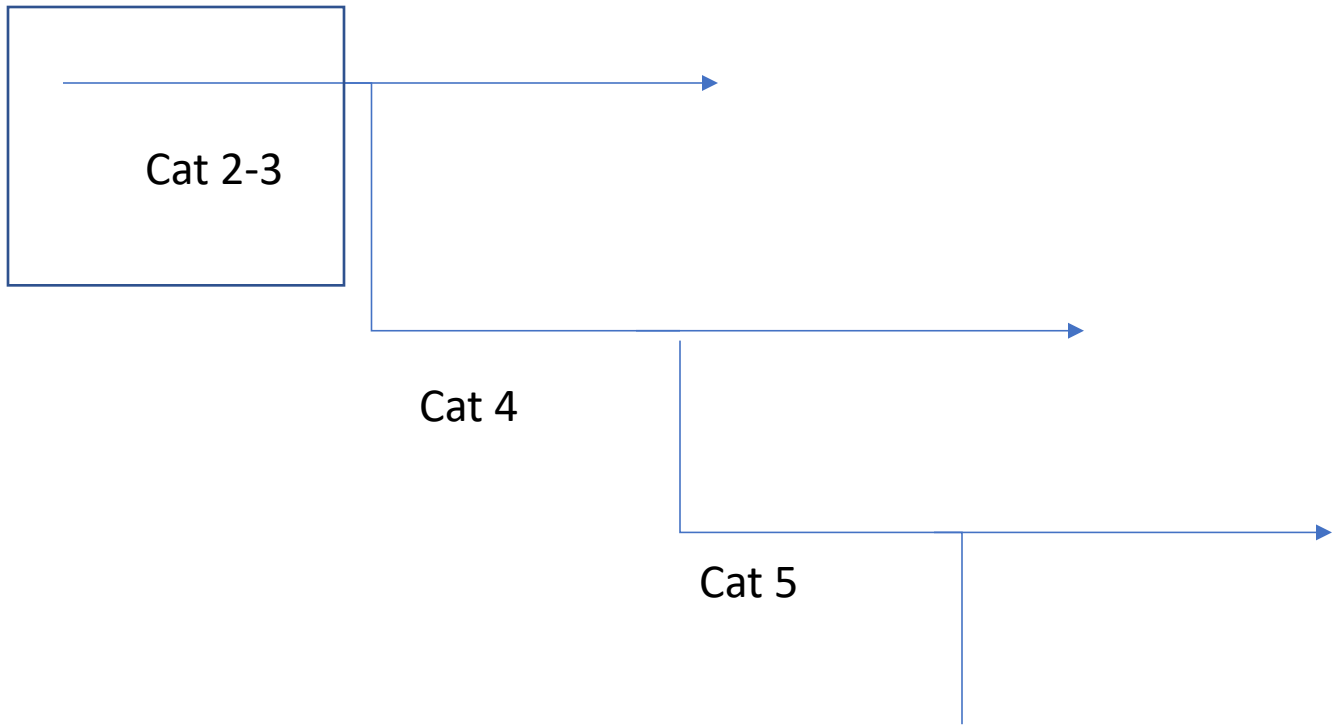
3.7% of the total **required ICU care** & **1.3%** of the total **died.**



ource: ClinData_COVID19 research team; Ministry of Health Malaysia's National Consensus Guidelines & National COVID-19 Mortality Review Committee

m BL, Chidambaram SK, Wong XC, Pathmanathan MD, Peariasamy KM, Hor CP, Chua HJ, Goh PP. **Clinical characteristics and risk factors for severe COVID-19 infections in Malaysia: A nationwide observational study.** The Lancet Regional Health-Western Pacific. 2020 Nov 1;4:100055 (*https://doi.org/10.1016/j.lanwpc.2020.100055*)

Clinical progression



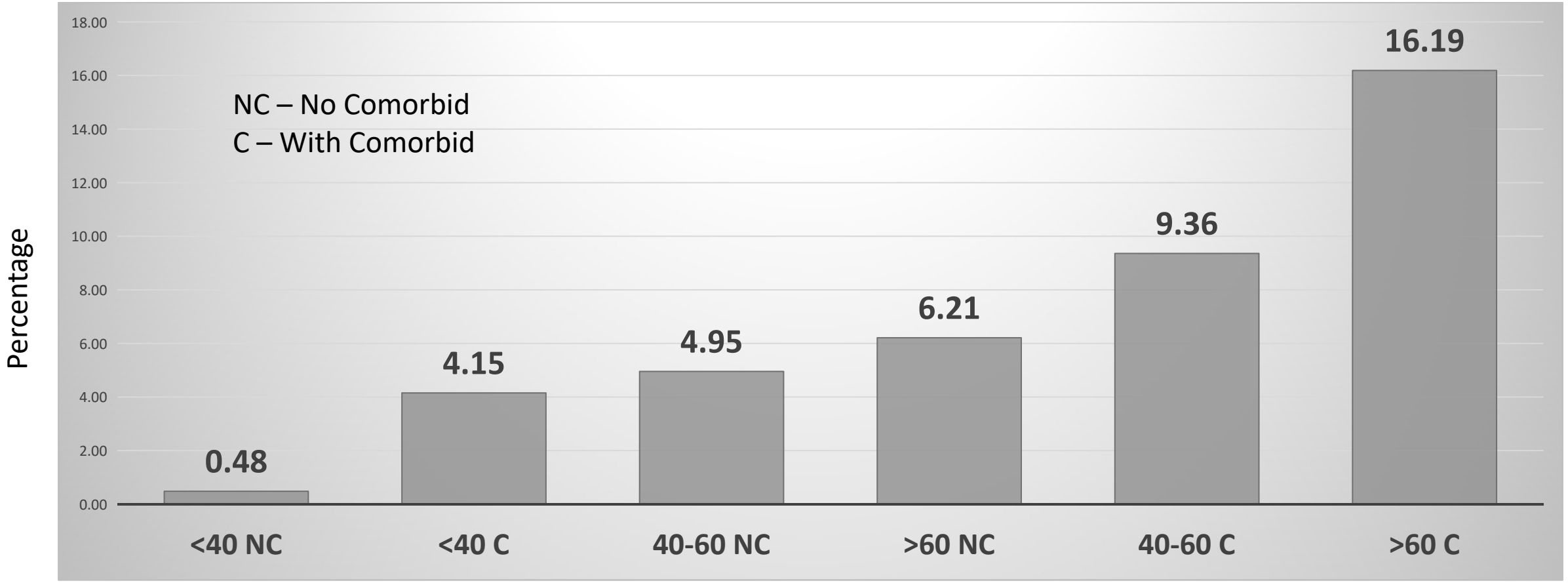
Management principles - Category 1 - 3

Risk stratification

Warning signs or symptoms

Early detection of hypoxia

Percentage deterioration - category 4/5



Data from Malaysian cohort

Risk of getting severe disease

Age group	Without underlying health conditions	With underlying health conditions
	Relative risk	Relative risk
≤ 40 without comorbid (Reference)		
≤ 40	-	8.63
41 - 50	6.19	17.71
51 - 60	12.01	24.92
61 - 70	10.77	30.4
71 - 80	34.72	49.02
≥ 81	59.52	50.5

Data from Malaysian cohort

Management principles - Category 1 - 3

Risk stratification

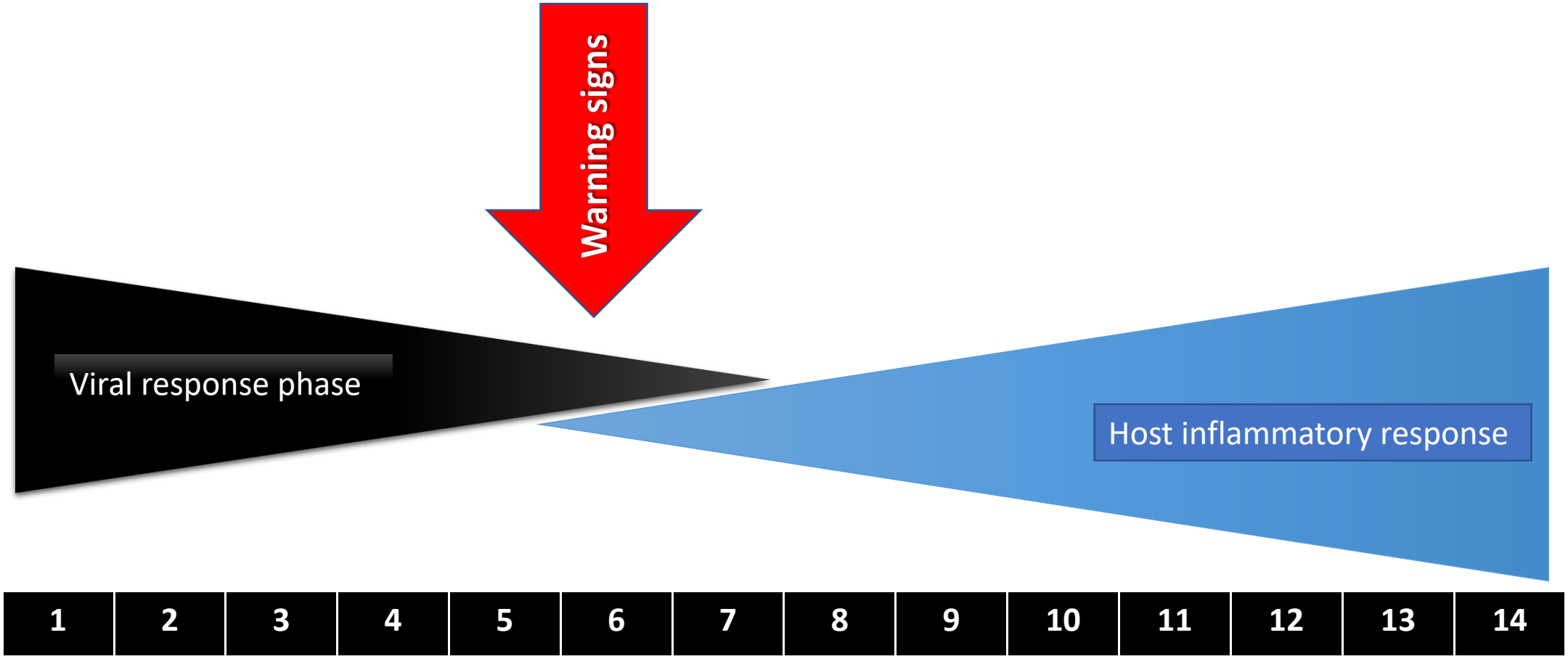
Warning signs or symptoms

Early detection of hypoxia

Mild disease – clinical category 1-3

1	2	3	4	5	6	7	8	9	10	11	12	13	14

Severe disease – Cat 4 - 5



LOOK OUT FOR WARNING SIGNS IN COVID-19 PATIENT

SYMPTOMS

Fever

Exertional dyspnoea

Persistent cough

Persistent symptoms – lethargy, poor appetite, nausea

EXAMINATION

RR > 25/min

SPO2 < 95%

Exertional hypoxia

LABORATORY

Rising CRP /
Single CRP > 5mg/dl

Dropping ALC /
Single ALC < 1

50 50

Neutrophil / lymphocyte ratio ≥ 3.13

RADIOLOGICAL

Features of severe pneumonia
/ multilobular involvement
/ rapidly worsening chest X-ray

Management principles - Category 1 - 3

Risk stratification

Warning signs or symptoms

Early detection of hypoxia

- People with **warning symptoms and signs** - look for hypoxia diligently
  - Persistent or new onset fever
  - Persistent cough
  - Lethargy (“*not up and about*”)
- Picking up hypoxia early
  - Ask for exertional dyspnoea
  - Count respiratory rate for full 1 minute
  - Do ‘1 min sit and stand test’

Picking up hypoxia early

01

Watch out for ‘silent/happy’ hypoxia

02

Watch out for patient compensating by increased respiratory effort but not feeling dyspnoeic

Monitoring category 1 -3

SCREENING QUESTIONS:

1. FEVER
2. PERSISTENT COUGH
3. DYSPNOEA AT REST OR EXERTION
4. NAUSEA OR VOMITING
5. LETHARGY

WARNING SIGNS:

1. Lethargy / Not moving around due to tiredness.
2. Confusion / reduced consciousness
3. RR>20,
4. Spo2<96,
5. Exertional desaturation ≥3%,
6. HR>100,
7. Rising CRP/Single CRP≥50mg/dl (or 5mg/l)
   - Dropping ALC
   - Increasing NLR

Bloods :

FBC/CRP/CXR/LFT/RP ± DXT

☐ Admission ☐ Warning signs

In High risk groups - Repeat FBC/CRP±CXR @ day 9/10 of illness before Discharge

Doctors / Nurses review TDS

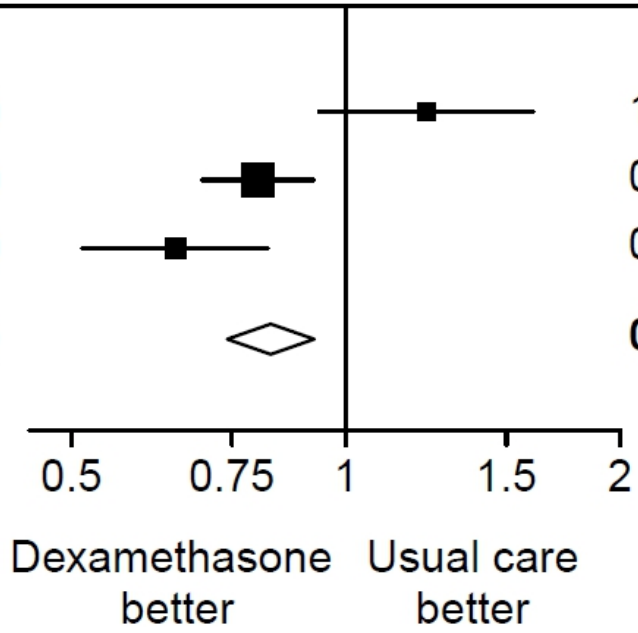
☐ Screening questions ☐ Warning signs

Don’t start steroids too early

Dexamethasone – Recovery study, UK NHS

Respiratory support at randomization	Dexamethasone	Usual care	RR (95% CI)
No oxygen received	85/501 (17.0%)	137/1034 (13.2%)	1.22 (0.93−1.61)
Oxygen only	275/1279 (21.5%)	650/2604 (25.0%)	0.80 (0.70−0.92)
Invasive mechanical ventilation	94/324 (29.0%)	278/683 (40.7%)	0.65 (0.51−0.82)
All participants	**454/2104 (21.6%)**	**1065/4321 (24.6%)**	**0.83 (0.74−0.92) p<0.001**

Trend across three categories: χ^2_1=11.49; p<0.001



- Dose used 6mg daily for 10 days

When is it too early?

- Not hypoxic
- In the first week of illness
  - *onset of disease could be subtle – so day of illness not accurate always*
- Low CRP (<50mg/l)
- Neutrophil/Lymphocyte ratio (NLR) – low (%L, % N looks like viral fever)

Antiviral treatment

How do we treat Covid-19?

No effective anti-virals

- e.g. Chicken Pox – Acyclovir

Prevention of complications

- Clotting – Heparin

Early treatment of complications

- Difficulty in breathing - Steroids

Favipiravir

- Efficacy still not proven
- Most likely to be effective in the viral phase of illness
- When do we use it?
  - In High risk groups
    - Category 3 disease

    OR
    - Symptomatic but within the 1st 7 days of illness

- Is there a role for it in patients in cat 4 ? – not known

Favipiravir

Common side effects:

- Hyperuricemia
- Diarrhoea
- Elevated transaminase
- Neutropenia

Drug interactions:

- Paracetamol – maximum 3gm per day
- Theophylline – increases Favipiravir levels
- Pyrazinamide – both cause hyperuricemia

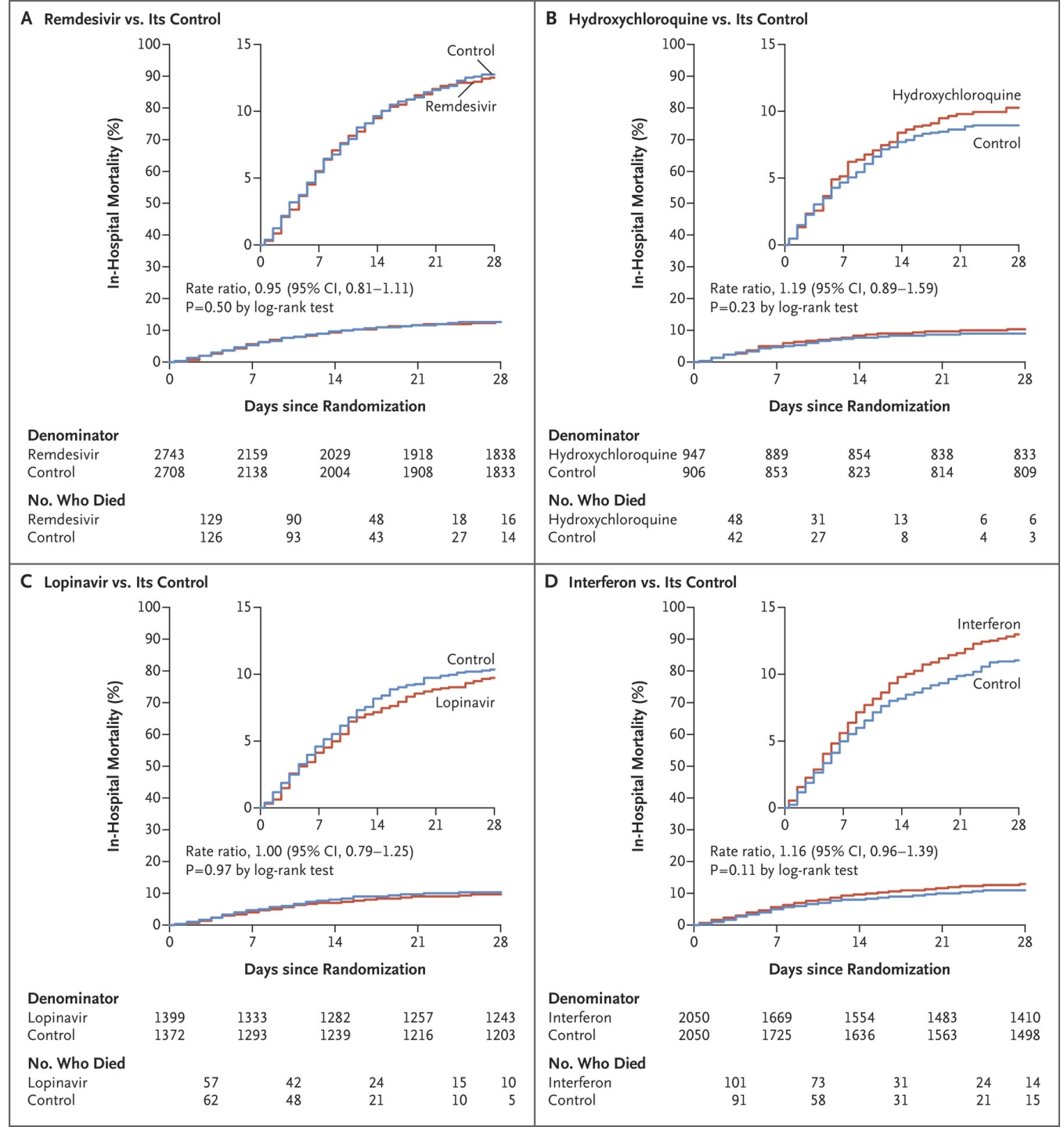
Teratogenic effect:

- Favipiravir is contraindicated for women of childbearing potential and men whose partner is of childbearing potential.
- In this group, if Favipiravir is used, they should be advised to use contraception for 7 days after the last dose of Favipiravir

- Avoid if GFR <30ml/min

Not registered drug. Requires patient consent to administer

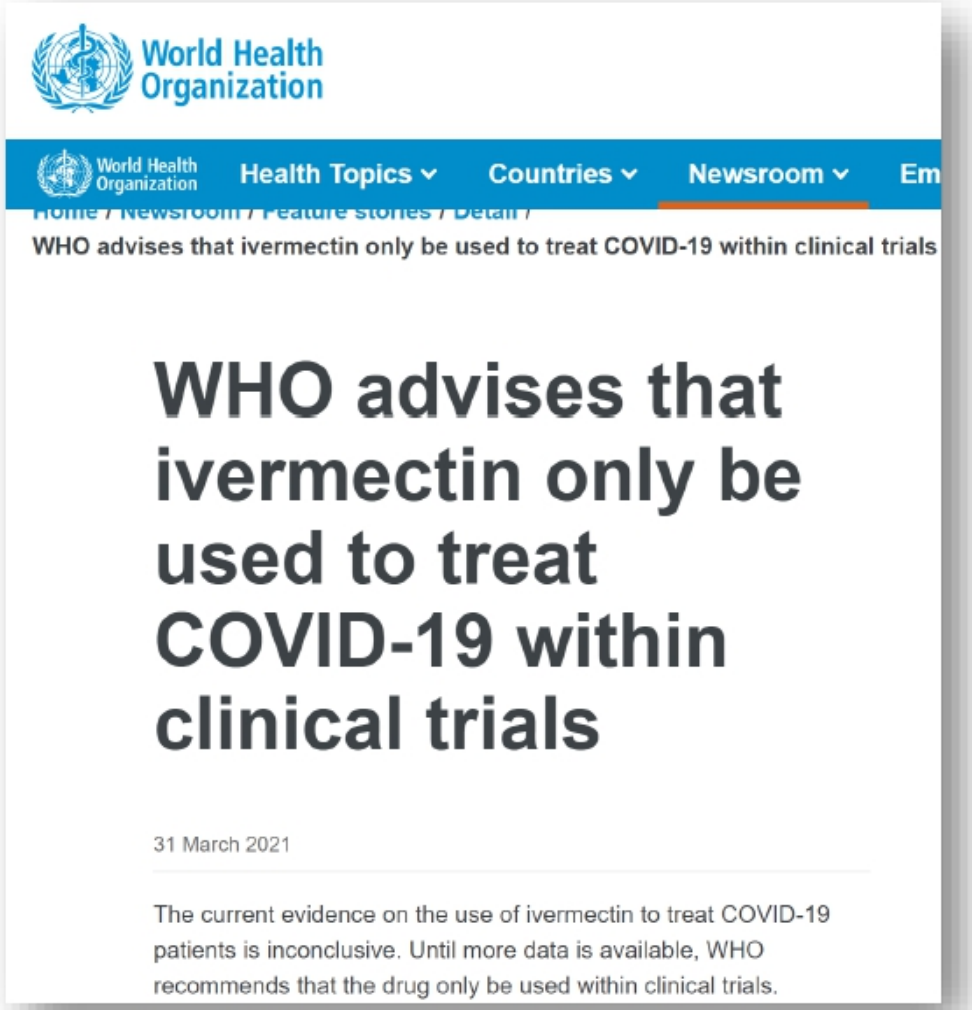
https://www.nejm.org/doi/full/10.1056/NEJMoa2023184



Ivermectin in Covid-19: Yay or nay?

- The National Institutes of Health's COVID-19 guidelines panel indicates that there are insufficient data to recommend for or against the use of ivermectin for the treatment of COVID-19 and that results from adequately powered, well-designed, and well-conducted clinical trials are needed to provide more specific, evidence-based guidance.

- WHO & IDSA suggest against ivermectin use outside of the context of a clinical trial in outpatients or hospitalized patients with COVID-19.

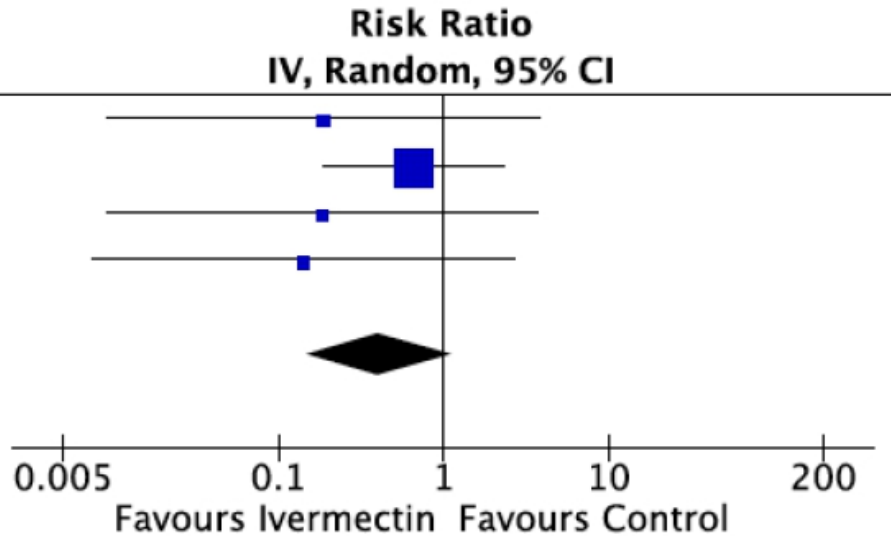


Hospitalisation, for Out-Patient trials

Study or Subgroup	Ivermectin Events	Ivermectin Total	Control Events	Control Total	Weight	Risk Ratio IV, Random, 95% CI
Bangladesh Chowdhury et al	0	60	2	56	11.3%	0.19 [0.01, 3.81]
Colombia Lopez-Medina et al	4	200	6	198	65.6%	0.66 [0.19, 2.30]
Israel Schwartz et al	0	49	2	45	11.3%	0.18 [0.01, 3.73]
Lebanon Raad et al	0	50	3	50	11.9%	0.14 [0.01, 2.70]
Total (95% CI)		**359**		**349**	**100.0%**	**0.41 [0.15, 1.14]**
Total events	4		13			

Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 1.59$, df = 3 (P = 0.66); $I^2 = 0\%$

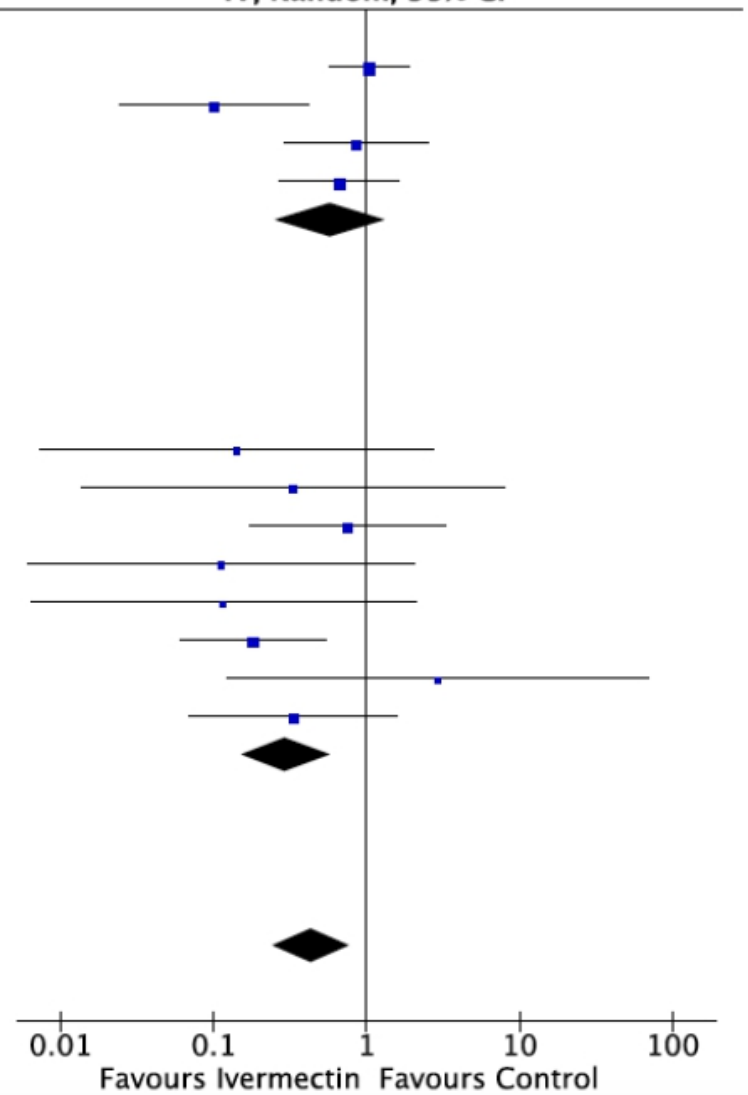
Test for overall effect: Z = 1.71 (P = 0.09)



Courtesy of Dr Andrew Hill, University of Liverpool, UK

Meta-analysis for All-cause mortality

Study or Subgroup	Ivermectin Events	Total	Control Events	Total	Weight	Risk Ratio IV, Random, 95% CI
4.3.1 Severe						
Brazil Fonseca et al	12	53	25	115	18.4%	1.04 [0.57, 1.91]
Egypt Elgazzar Severe	2	100	20	100	9.4%	0.10 [0.02, 0.42]
Mexico Gonzalez et al	5	36	6	37	12.5%	0.86 [0.29, 2.56]
Turkey Okumus et al	6	30	9	30	14.7%	0.67 [0.27, 1.64]
Subtotal (95% CI)		**219**		**282**	**55.0%**	**0.58 [0.25, 1.32]**
Total events	25		60			
Heterogeneity: $Tau^2 = 0.45$; $Chi^2 = 8.90$, df = 3 (P = 0.03); $I^2 = 66\%$						
Test for overall effect: Z = 1.30 (P = 0.19)						
4.3.2 Mild/moderate						
Bangladesh Mahmud et al	0	183	3	180	3.2%	0.14 [0.01, 2.70]
Colombia Lopez-Medina et al	0	200	1	198	2.8%	0.33 [0.01, 8.05]
Egypt Abd-Elsalam et al	3	82	4	82	9.1%	0.75 [0.17, 3.25]
Egypt Elgazzar Moderate	0	100	4	100	3.2%	0.11 [0.01, 2.04]
India Kirti et al	0	55	4	57	3.3%	0.12 [0.01, 2.09]
Iran Niaee et al	4	120	11	60	12.4%	0.18 [0.06, 0.55]
Iran Rezai et al	1	35	0	34	2.8%	2.92 [0.12, 69.20]
Iraq Hashim et al	2	70	6	70	8.4%	0.33 [0.07, 1.60]
Subtotal (95% CI)		**845**		**781**	**45.0%**	**0.30 [0.15, 0.58]**
Total events	10		33			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 5.42$, df = 7 (P = 0.61); $I^2 = 0\%$						
Test for overall effect: Z = 3.57 (P = 0.0004)						
Total (95% CI)		**1064**		**1063**	**100.0%**	**0.44 [0.25, 0.77]**
Total events	35		93			
Heterogeneity: $Tau^2 = 0.35$; $Chi^2 = 19.24$, df = 11 (P = 0.06); $I^2 = 43\%$						
Test for overall effect: Z = 2.85 (P = 0.004)						
Test for subgroup differences: $Chi^2 = 1.54$, df = 1 (P = 0.21), $I^2 = 35.1\%$						



I-TECH Study

NMRR-21-155-58433

Ivermectin Treatment Efficacy in Covid-19 High Risk Patients

A Multicenter Open-label Randomized Controlled Clinical Trial

Study design

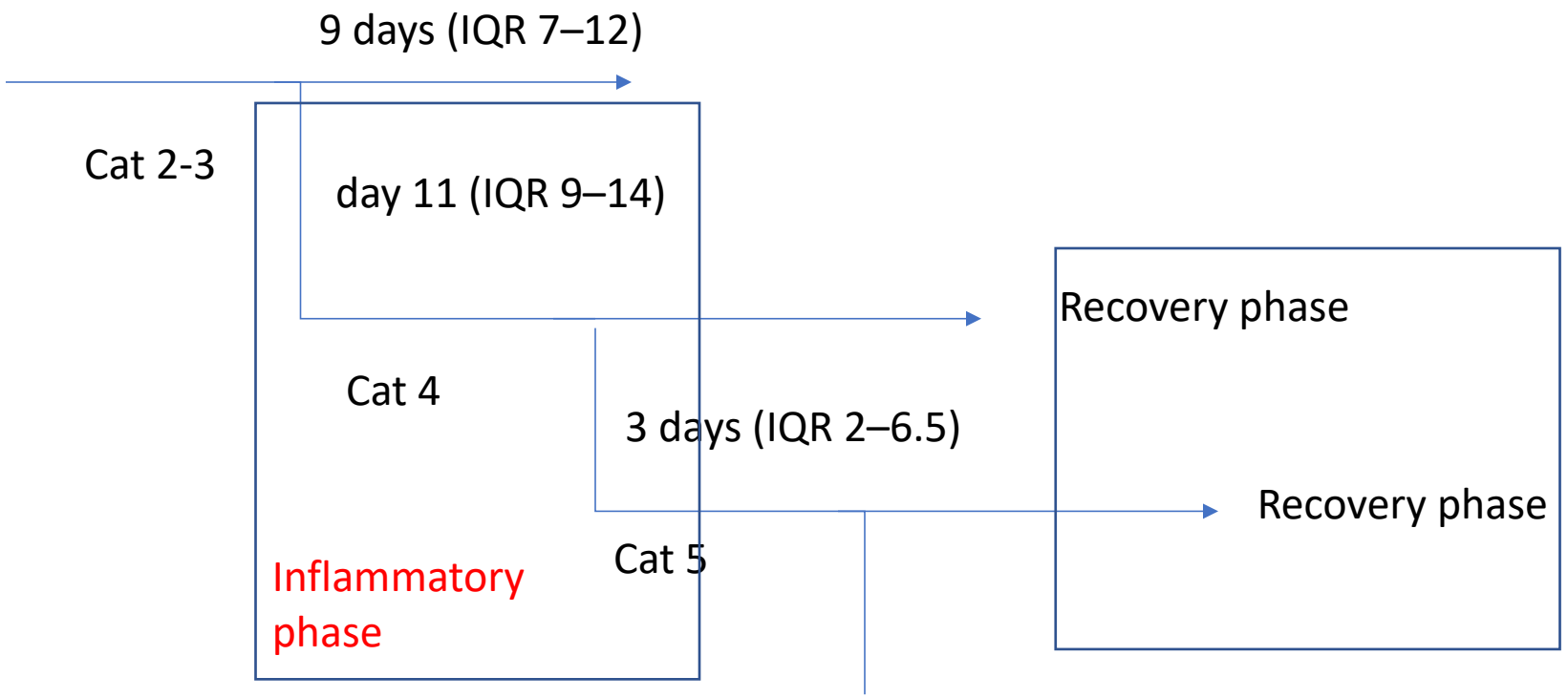
- Multicenter Open-label Randomized Controlled Clinical Trial

- Symptomatic mild-to-moderate hospitalized COVID-19 patients (clinical stage 2 or 3) who are 50 years old and above, with co-morbidities and within first 7 days of illness.
- 500 subjects (250 subjects in each arm)
- Patients are randomized 1:1

1. Treatment group: Ivermectin 0.4mg/kg/day for 5 days + standard-of-care
2. Control group: Standard-of-care only

- 1st May 2021 – 30th September 2021

Clinical progression & timelines



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Inflammatory phase vs Recovery phase

Inflammatory phase

- Second week of illness
  - *onset of disease could be subtle – so day of illness not accurate always*
- Usually preceded by ‘warning signs or symptoms’
- Increasing CRP or increasing NLR
- Progressive hypoxia

Recovery phase

- Third week of illness
  - *onset of disease could be subtle – so day of illness not accurate always*
- Clinically improving,
- Feels less breathless, not tachypnoeic at rest
- Patient feels less lethargic and starting to ambulate
- 02 requirements decreasing
- Dropping CRP

Identify recovery phase

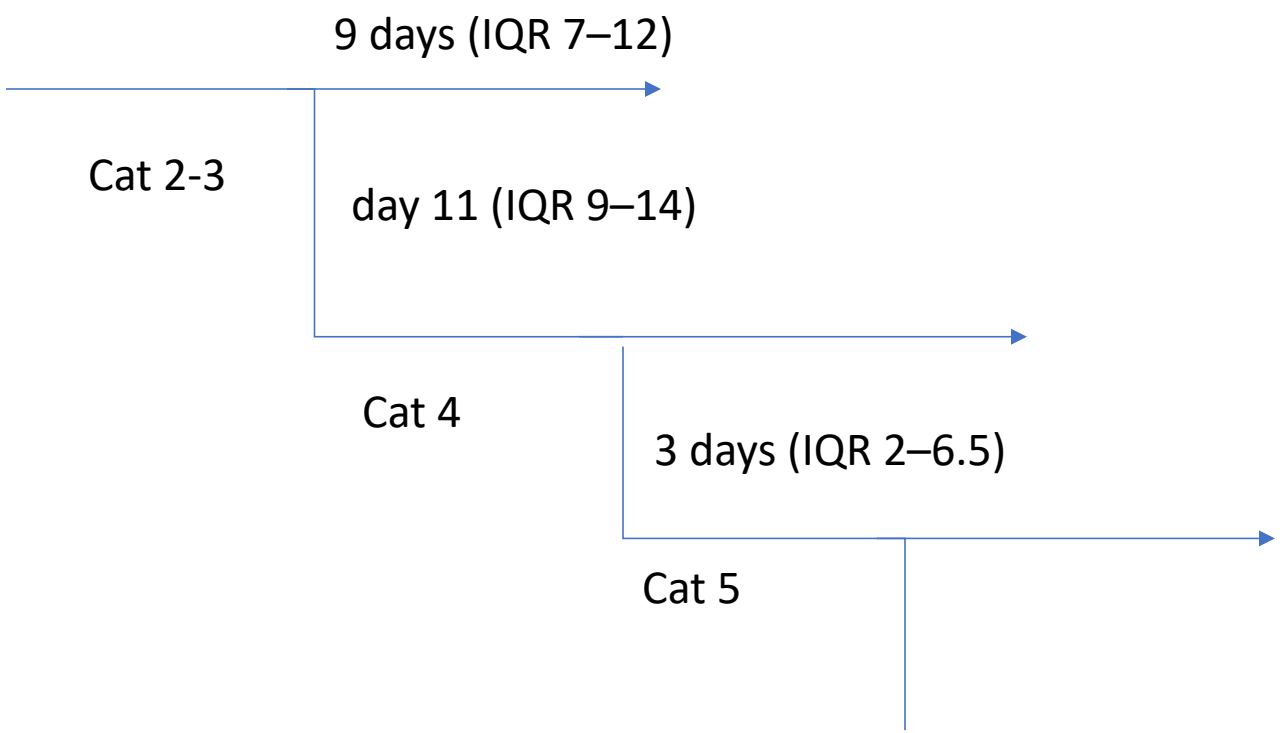
- Enables earlier step down
- Start discharge planning early

If someone is in ‘recovery phase’

- Aim for SP02 of > 92%
  - esp in those
    - who had severe disease earlier or
    - those who appear comfortable despite the lower SP02
- Switch to oral dexamethasone
- No need daily bloods
- Transfer to step-down care

*Such patients can still deteriorate due to secondary infections, PE, organising pneumonia, worsening comorbid

Clinical progression & timelines



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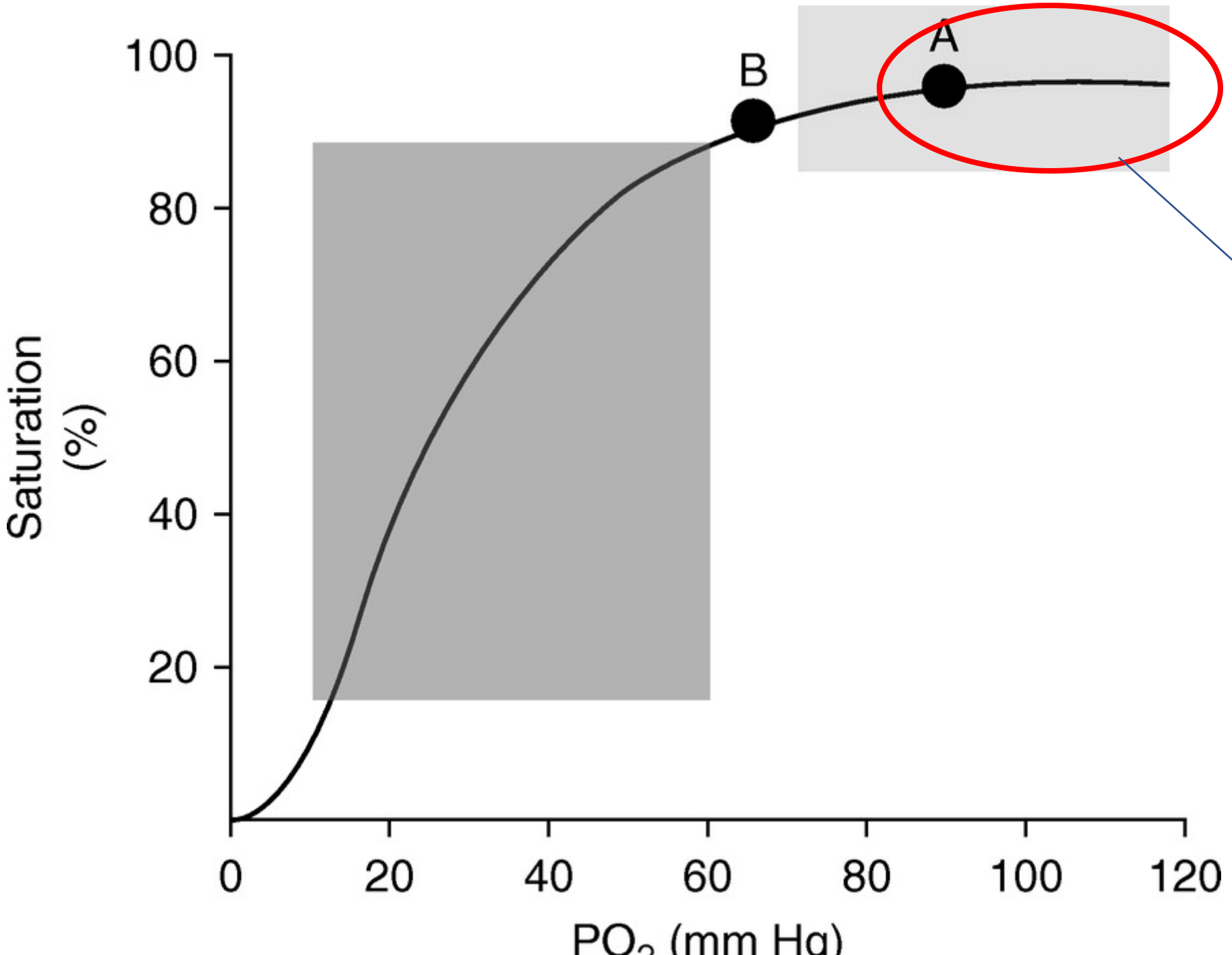
If someone is in ‘Inflammatory phase’

- Aim for a sp02 of 96%
  - Remember the 02 dissociation curve (next slide)
- Also adjust 02 requirement based on work of breathing
  - *Patient could be maintaining the saturation by breathing fast/with effort*
  - *On the other hand, patient could have hypoxia but not in respiratory distress due to shunting (happy/silent hypoxia)*
- Teach patient self-proning
- Advice complete rest in bed as much as possible



Big changes in PaO2 causes minimal or no change in SP02

Steroid conundrum

MSIC CONSENSUS STATEMENT: CORTICOSTEROIDS FOR COVID-19

27th January 2021

Malaysian Society of Intensive Care

www.msic.org.my

MSIC Working Group

Shanti Rudra Deva, Azmin Huda Abdul Rahim, Louisa Chan Yuk Li, Premela Naidu Sitaram, Muhamad Hafizzi Mohd, Nahla Irtiza Ismail, Tai Li Ling

Oxygen therapy	Steroid	Dose
Nil	Not indicated	
Nasal prongs or Facemask 5-8 L/min	IV Dexamethasone	6 mg daily x 7 – 10 days
HFNC/ NIV* or Mechanical ventilation	IV Dexamethasone	20 mg daily x 5 days then 10 mg daily for 5 days

MSIC CONSENSUS STATEMENT: CORTICOSTEROIDS FOR COVID-19

27th January 2021

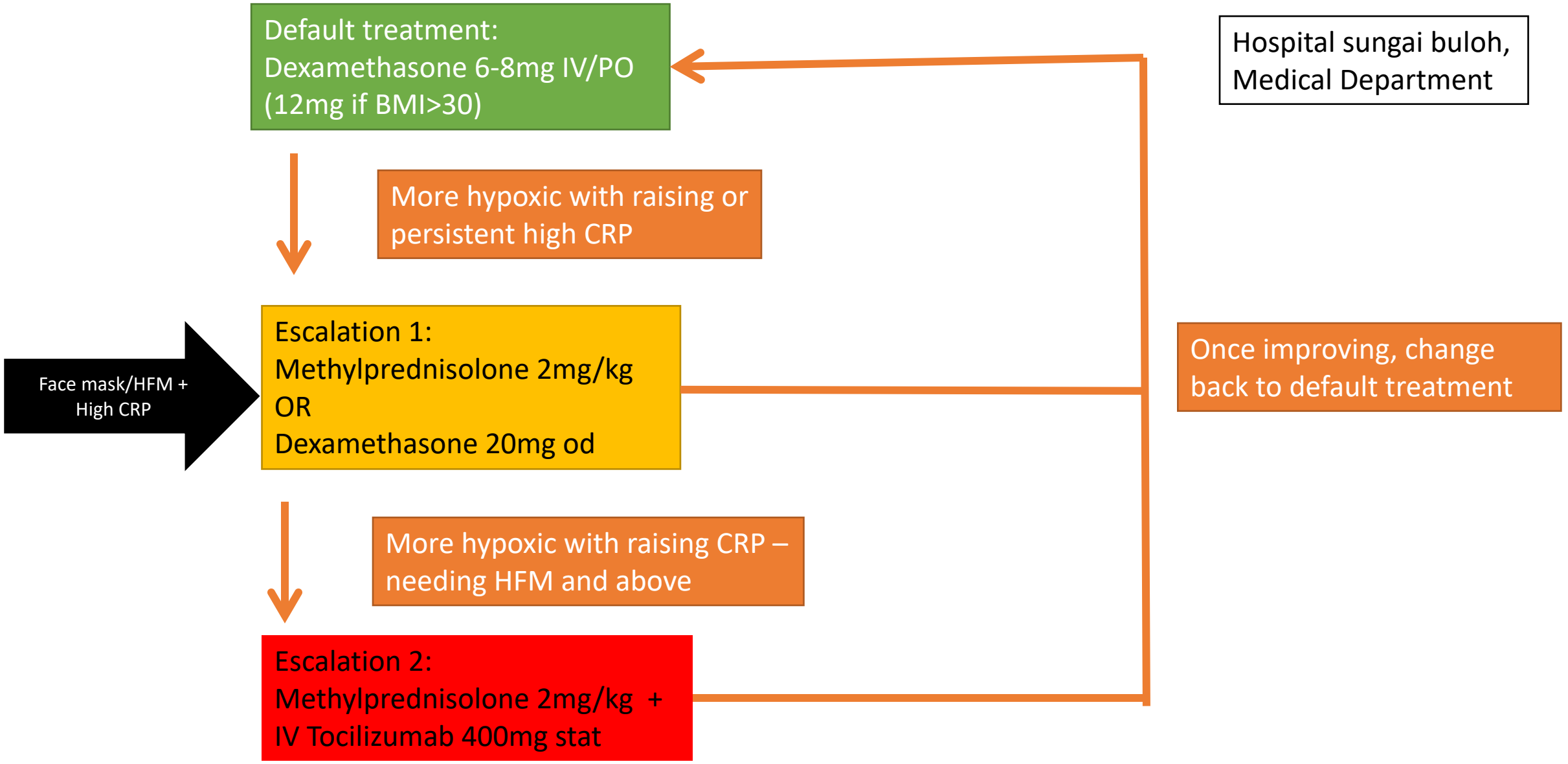
Malaysian Society of Intensive Care

www.msic.org.my

MSIC Working Group

Shanti Rudra Deva, Azmin Huda Abdul Rahim, Louisa Chan Yuk Li, Premela Naidu Sitaram, Muhamad Hafizzi Mohd, N

Weeks of pregnancy	Steroid	Comment
24 – 34 weeks	IV Dexamethasone 6 mg 12 hourly x 2 days[11] then either Prednisolone 40 mg daily x 8 days or Hydrocortisone 80 mg 12 hourly x 8 days	Dexamethasone required for foetal lung maturity
< 24 weeks or > 34 weeks	Prednisolone 40 mg daily x 10 days or Hydrocortisone 80 mg 12 hourly x 10 days	



Warning: This protocol is frequently updated as new knowledge emerges

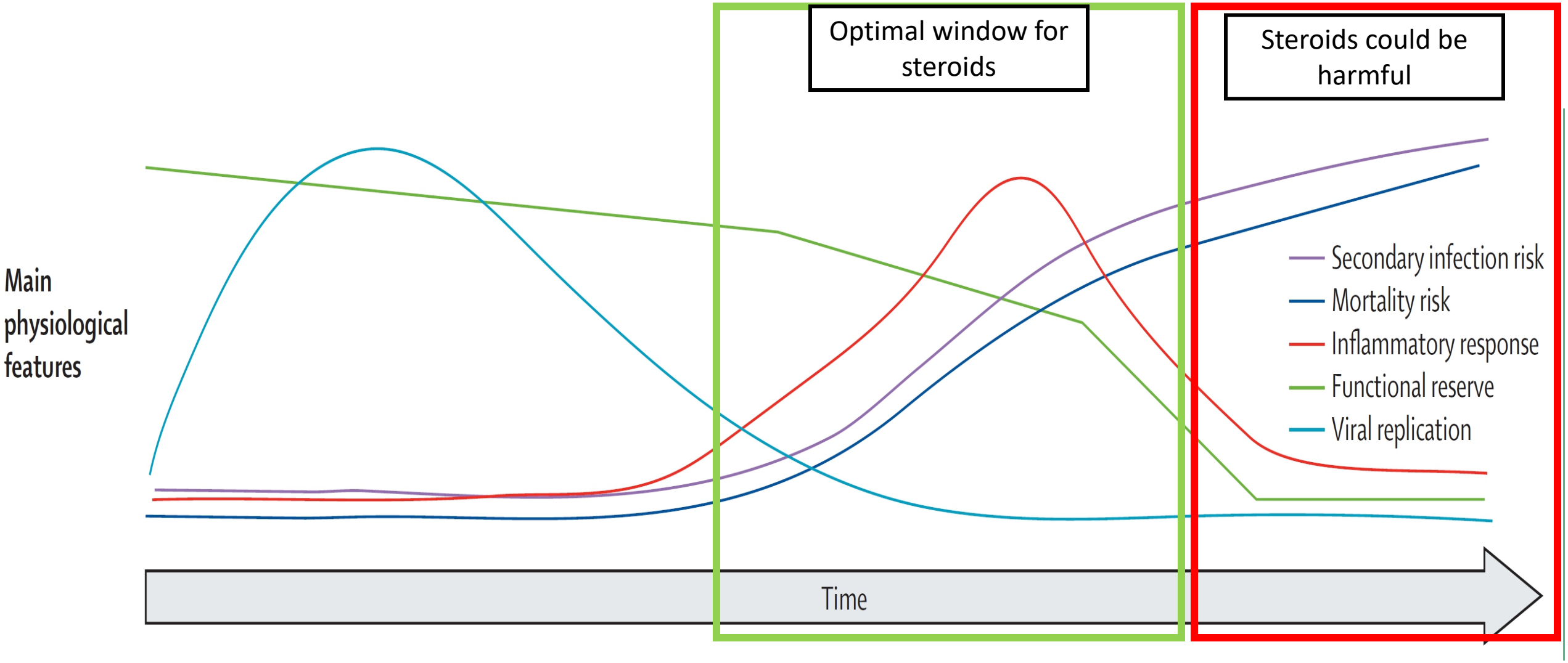
Step down to steroid dosages in guidelines - ASAP

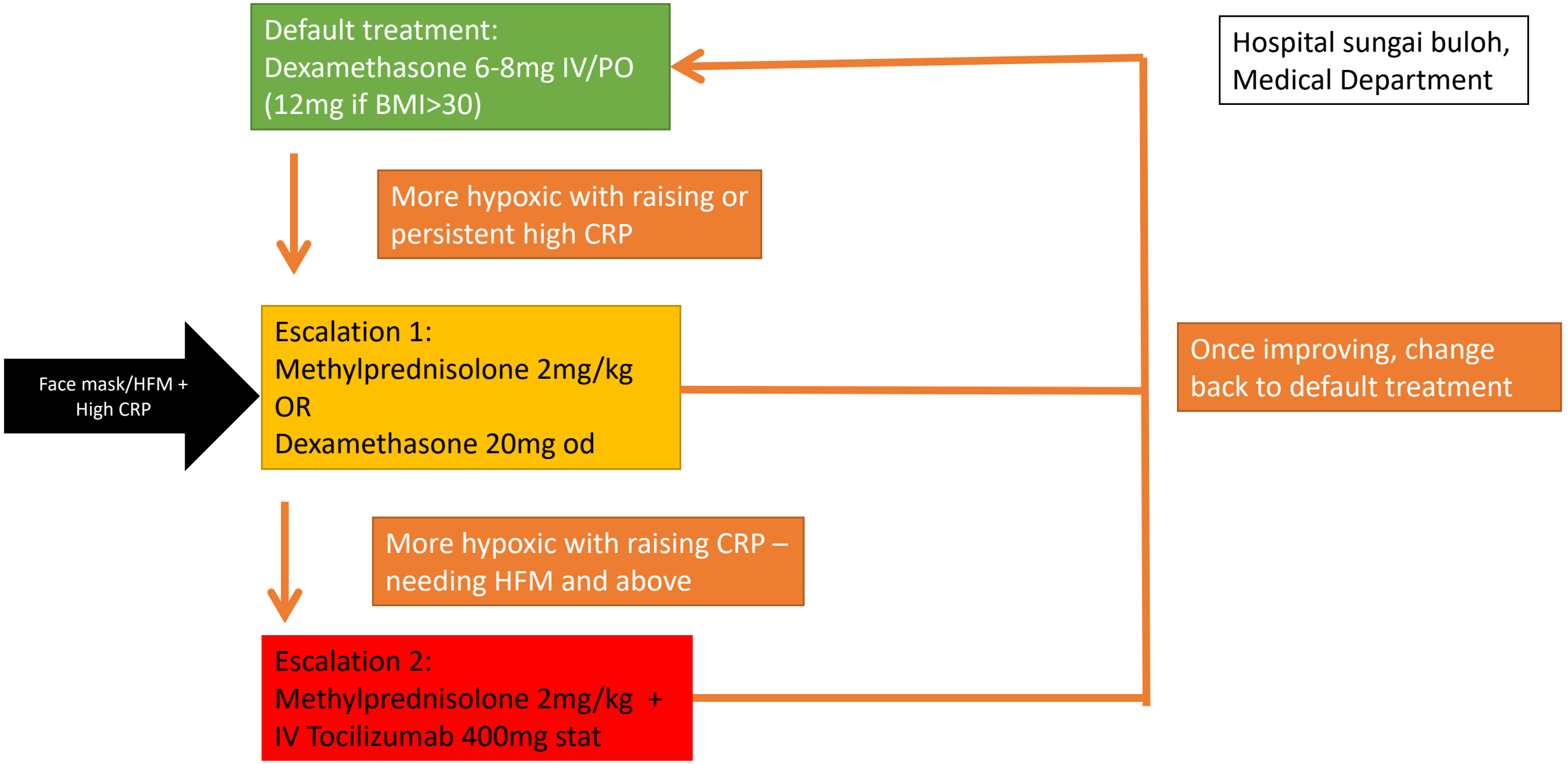
- High dose steroids – MP 2mg/kg or above are not proven therapies
- Done out of desperation – ‘Acute fibrinous organising pneumonia’
- We don’t know if high dose steroids do more harm than good in the long run

- Should be used as pulse therapy – beyond 3 days – only in exceptional cases

- As soon as patient improves – step down
- Also step down , if patient condition is static but CRP levels are down

Steroids may be harmful in late disease





Warning: This protocol is frequently updated as new knowledge emerges

NICE National Institute for Health and Care Excellence

NICE guideline

COVID-19 rapid guideline: managing COVID-19

NICE guideline

Published: 23 March 2021

www.nice.org.uk/guidance/ng191

Strong recommendation

Offer tocilizumab to adults in hospital with COVID-19 if all of the following apply:

- they are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids
- they have not had another interleukin-6 inhibitor during this admission
- there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab.

And they either:

- need supplemental oxygen and have a C-reactive protein level of 75 mg/litre or more, or
- are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

Tocilizumab

The recommended dose of tocilizumab is 8mg/kg to be administered as an intravenous infusion. The total dose should not exceed 800mg. Tocilizumab should be diluted in a 100mL bag of 0.9% sodium chloride, after removing an equivalent volume of saline (total volume 100mL) and given over 1 hour[3]. A single dose is to be administered, with the option to repeat a dose in 12-24 hours after the initial dose if there has not been sufficient clinical improvement. **Tocilizumab should not be infused concomitantly in the same IV line with other medications.**

Please take note before supplying Tocilizumab Inj.

- It comes in two strengths which are 400mg and 80mg vial.
- The price per vial as stated in the table below.

Therefore, please make sure to supply as per table below to avoid wastage.

Dose	Vials to allocate	
	Tocilizumab 400mg VIAL (RM2560.20/vial)	Tocilizumab 80mg VIAL (RM512.05/vial)
320mg	-	4
400mg	1	-
480mg	1	1
560mg	1	2
640mg	1	3
720mg	1	4
800mg	2	-

Dose: 8mg/kg stat (Max dose: 800mg)

Covid-19 Treatment

Antiviral - Favipiravir

Steroids or other immunomodulatory agents (Tocilizumab)

Anti-coagulation - LMWH

Addressing Hyper-coagulopathy

1

Full dose anti-coagulation

- **Full dose anticoagulation**
- eg. Enoxaparin – 1mg/kg 12hrly

- Confirmed VTE
- Suspect PE - sudden unexplained deterioration in oxygenation or hemodynamic instability, acute cor pulmonale
- Clotting of vascular devices (eg, venous, arterial devices, and hemodialysis devices).

2

High prophylactic dose anti-coagulation

- High prophylactic dose anti-coagulation
- eg. Enoxaparin - 0.5mg/kg 12hrly

- Category 5

3

Prophylaxis

- Prophylaxis
- eg. Enoxaparin 30-40mg daily depending on renal function

- Category 4

GARIS PANDUAN KEMENTERIAN KESIHATAN MALAYSIA

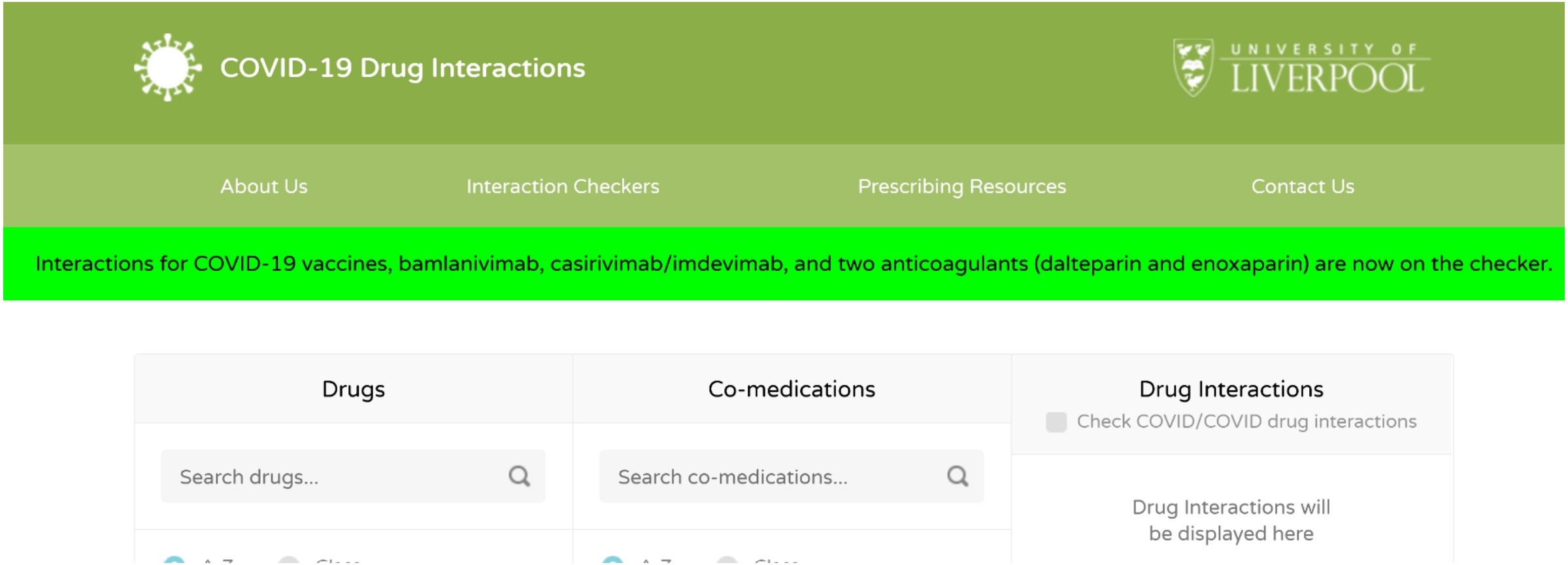
> Garis Panduan Pengurusan COVID-19 di Malaysia No.5/2020 (Kemaskini Terkini pada **11 Mei 2021**)
>
> *COVID-19 Management Guidelines in Malaysia No.5 / 2020 (Latest Update on **11 Mei 2021**)*

ANNEX 1 : Case Definition of COVID-19 (Updated on 11/05/2021)

ANNEX 2 : Management of Suspected, Probable and Confirmed COVID-19 (Updated on 5 October 2020)

- Annex 2a : Management of Suspected Case Not Required Admission (Updated on 5 October 2020)
- Annex 2b : Management of Suspected Case Required Admission (Updated on 5 October 2020)

- https://www.covid19-druginteractions.org/checker

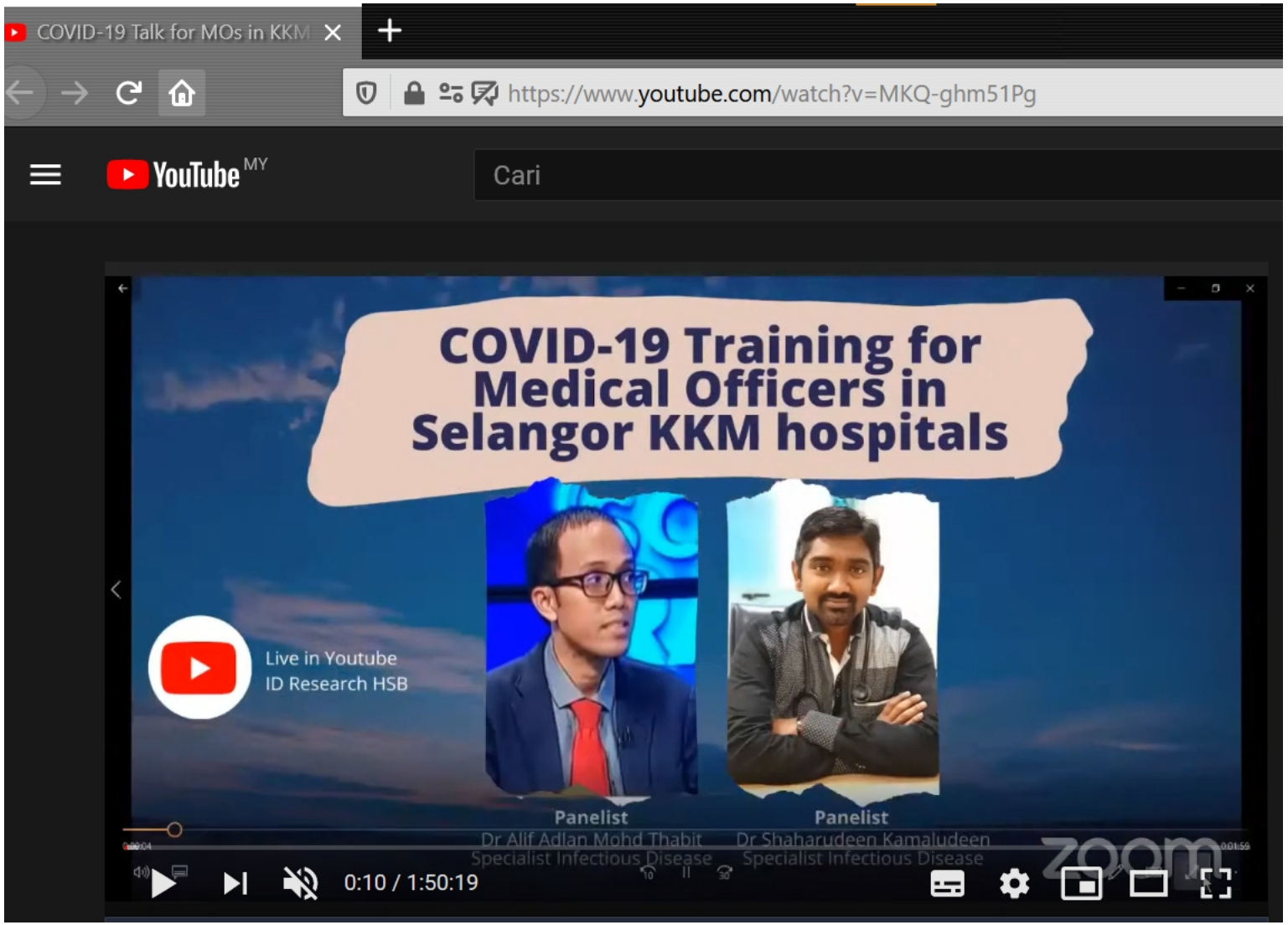


Training

Basic course

https://tinyurl.com/covid19malaysia

Severe disease management



https://www.youtube.com/watch?v=MKQ-ghm51Pg

Thank you