Antimicrobial stewardship in COVID-19

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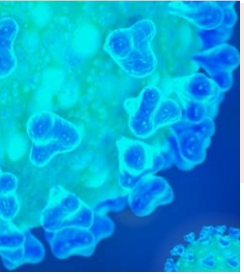
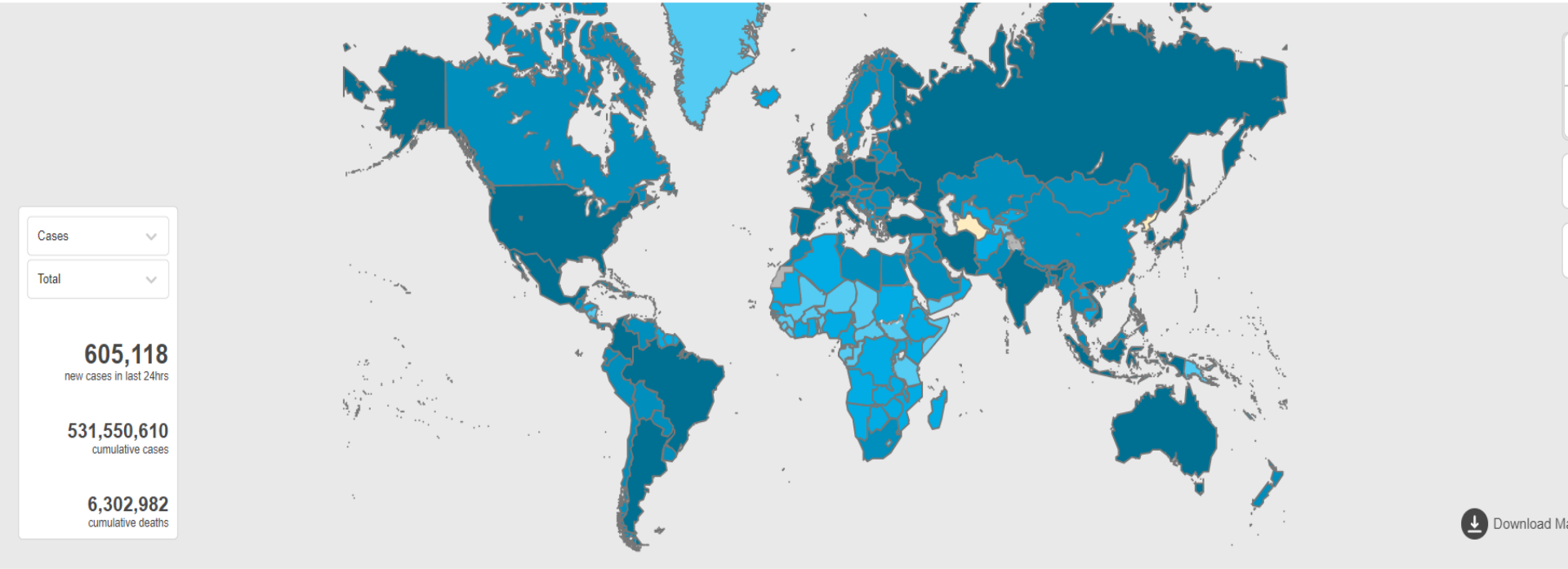


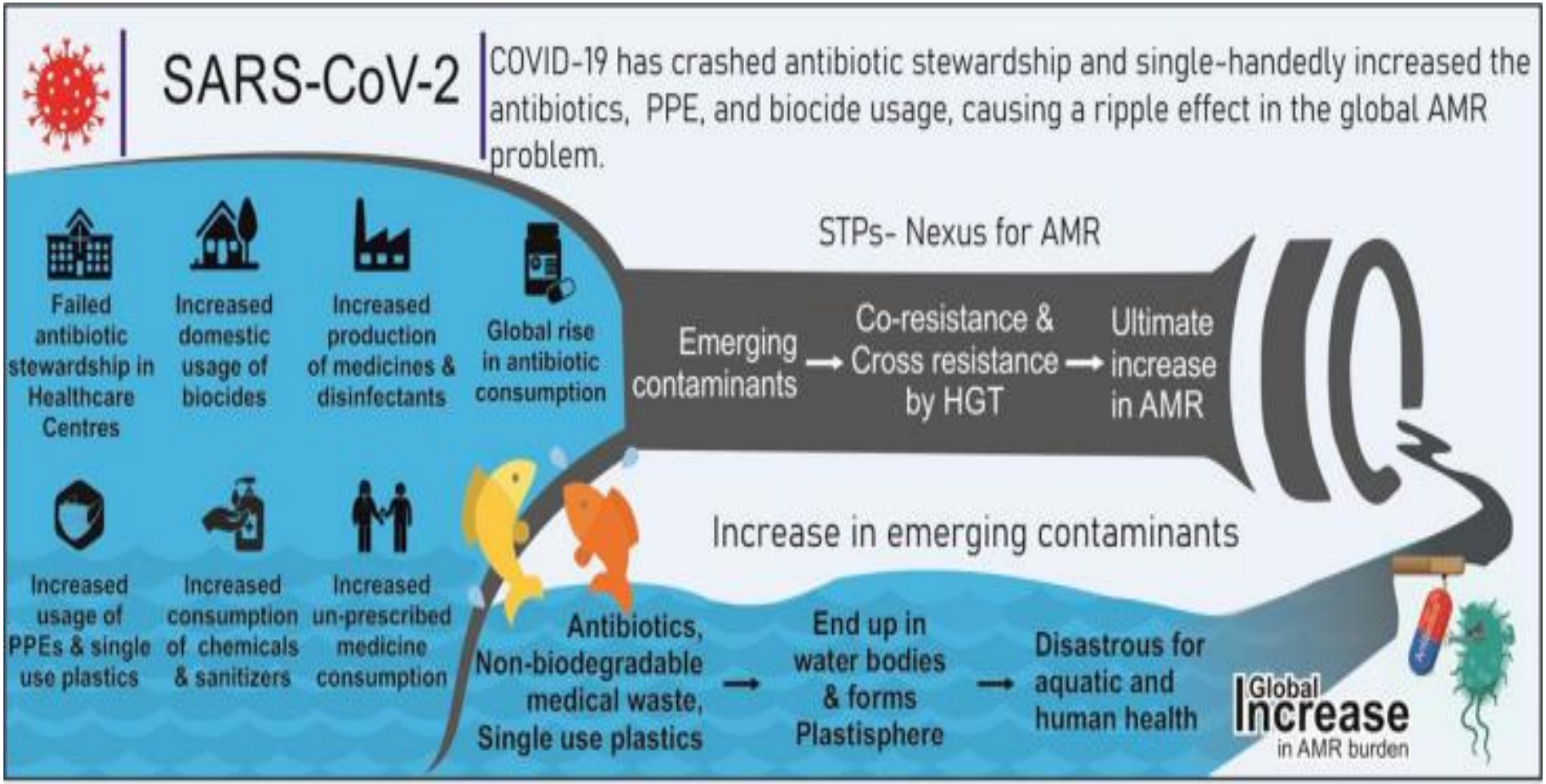
Outline

- Epidemiology of COVID-19
- COVID -19 and antibiotic consumption
- Secondary and Co-infections in COVID-19
- Case based approach to antimicrobial stewardship in COVID-19

COVID-19 epidemiology



Globally, as of **5:10pm CEST, 9 June 2022**, there have been **531,550,610 confirmed cases** of COVID-19, including **6,302,982 deaths**, reported to WHO. As of **6 June 2022**, a total of **11,854,673,610 vaccine doses** have been administered.



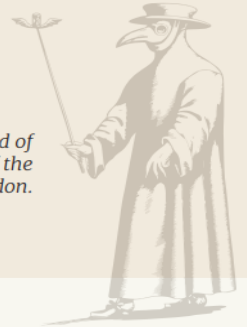
Ukuhor HO. *J Infect Public Health*. 2021;14(1):53-60. doi:10.1016/j.jiph.2020.10.018

Pandemics throughout history

Global Pandemics by Death Toll

Worldwide Smallpox Epidemic	1877 – 1977**	500,000,000
Spanish Flu	1918 – 1919	50,000,000
Plague of Justinian	483 – 565	30,000,000 – 50,000,000
HIV/AIDS	1981 – Present	32,000,000+ so far
Bubonic Plague/Black Death	1347 – 1351	25,000,000
Cocoliztli	1545 – 1547	5,000,000 – 15,000,000
Mexico Smallpox Epidemic	1519 – 1520**	5,000,000 – 8,000,000
Antonine Plague	165 – 180	5,000,000
Cholera	1817 – 1975***	3,798,000 – 4,798,000
The Great Plagues	1348 – 1665*	3,000,000
Russia Typhus Epidemic	1918 – 1922	2,500,000
Japanese Smallpox Epidemic	735 – 737**	2,000,000
COVID-19	2019 – Present	6,700,000 as on 1 June, 2022
Hong Kong Flu	1968 – 1970	1,000,000
Europe Smallpox Epidemic	1870 – 1875**	500,000
Swine Flu	2009 – 2010	151,700 – 575,400
Yellow Fever	1800 – 1802	100,000 – 150,000

*The Great Plagues consisted of around 40 resurgences of the bubonic plague, primarily in London.



Quarantine was invented during the Black Plague. Sailors would not leave their ships for 40 days to avoid spreading the illness; the word comes from the Italian word for 40, "quaranta."

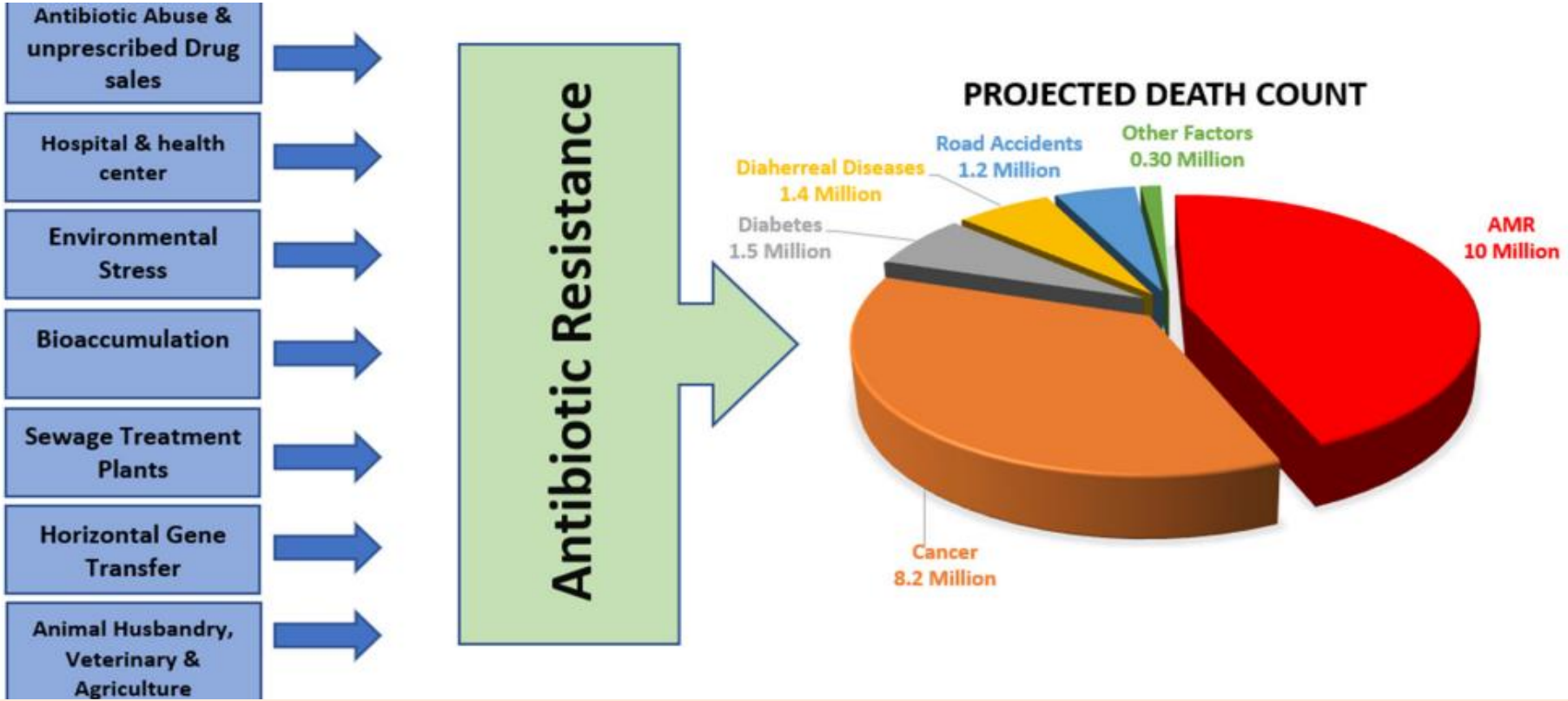
5,000,000

Smallpox

**Smallpox is most often associated with the 16th century, when it decimated the native population of Mexico. However, it resulted in the most casualties during the last 100 years of its existence. Between 1877 and 1977, smallpox was responsible for the deaths of an estimated 500,000,000 people.

Japanese Smallpox Epidemic
735 – 737
2,000,000

Mexico Smallpox Epidemic
1519 – 1520
5,000,000 – 8,000,000



Anthropogenic disturbances increase antibiotic resistance in the environment either directly or indirectly. **Due to the pandemic, there is a surge in antibiotic usage in various sectors, especially health care centers and pharmaceutical industries which will escalate the existing antimicrobial resistance burden**.

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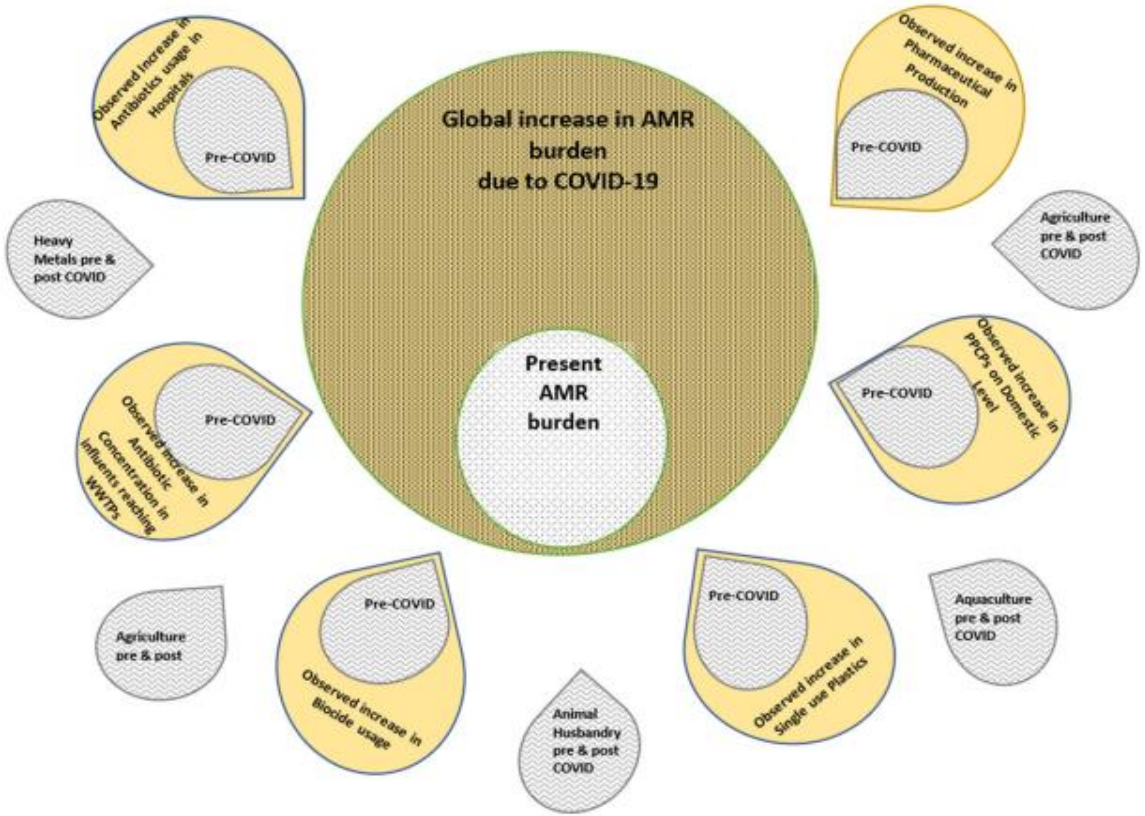
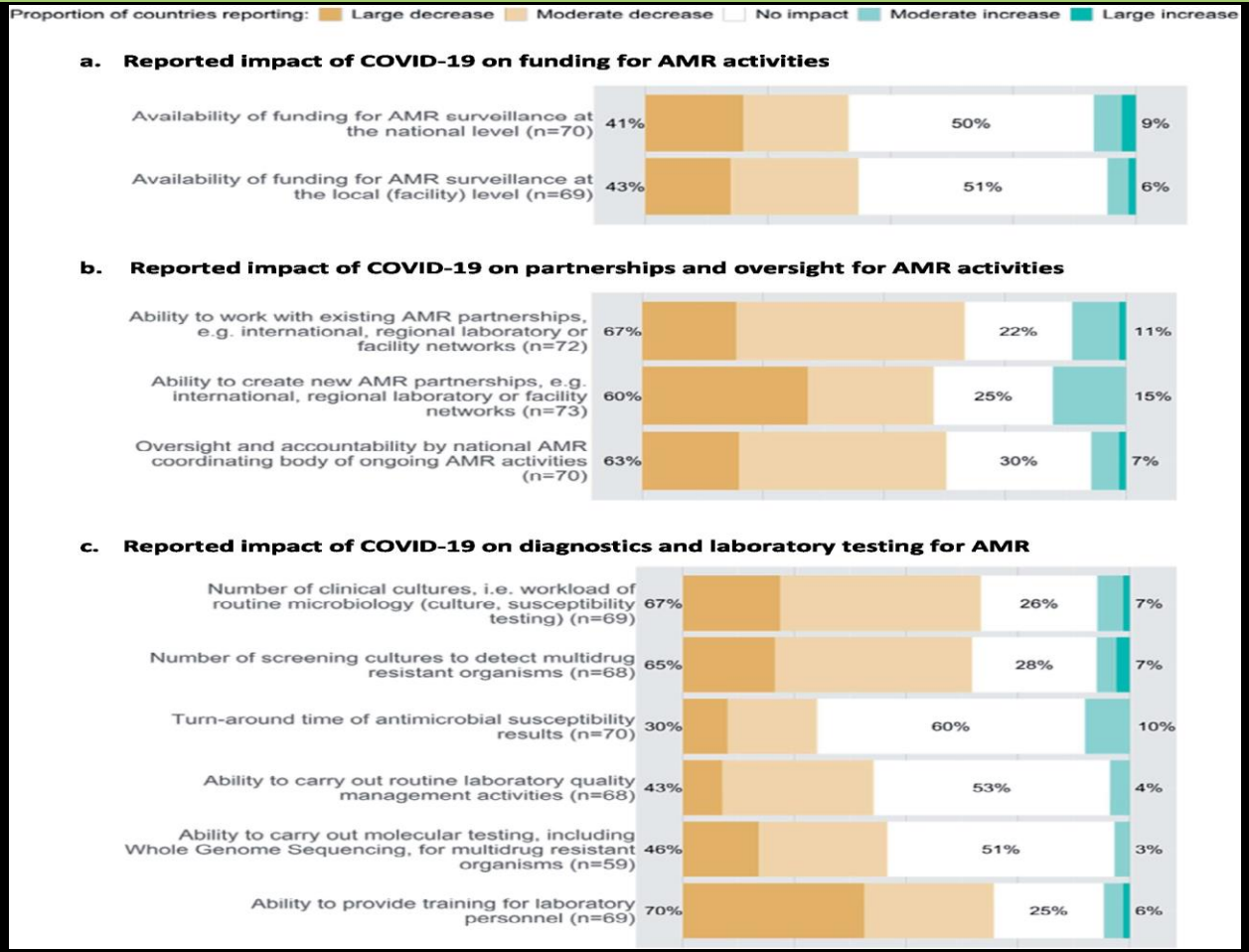


[COVID-19 and antimicrobial resistance: A cross-study - PMC (nih.gov)]

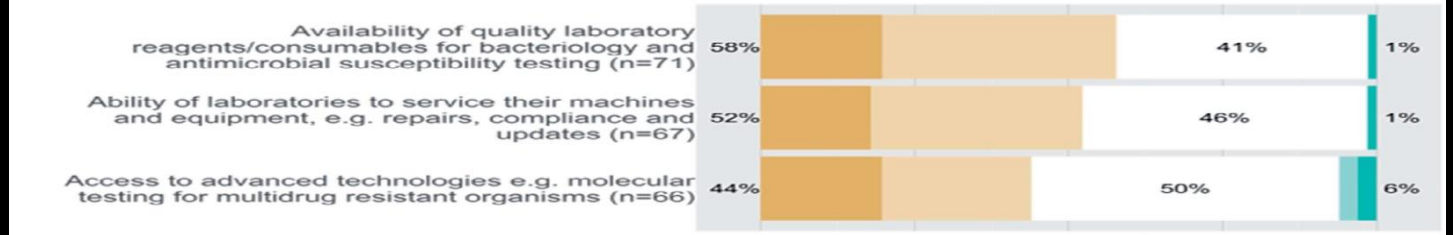
Some contributors of Antimicrobial Resistance have increased significantly due to the pandemic, while others remain unchanged. Antibiotics, biocides, and single-use plastics have drastically increased in the environment- predominantly in aquatic habitats. These factors act synergistically in promoting Antimicrobial Resistance. Consequently, this existing problem will possibly increase in the Post-COVID-19 Era.

Impacts of COVID-19 on AMR in GLASS countries (n = 73).

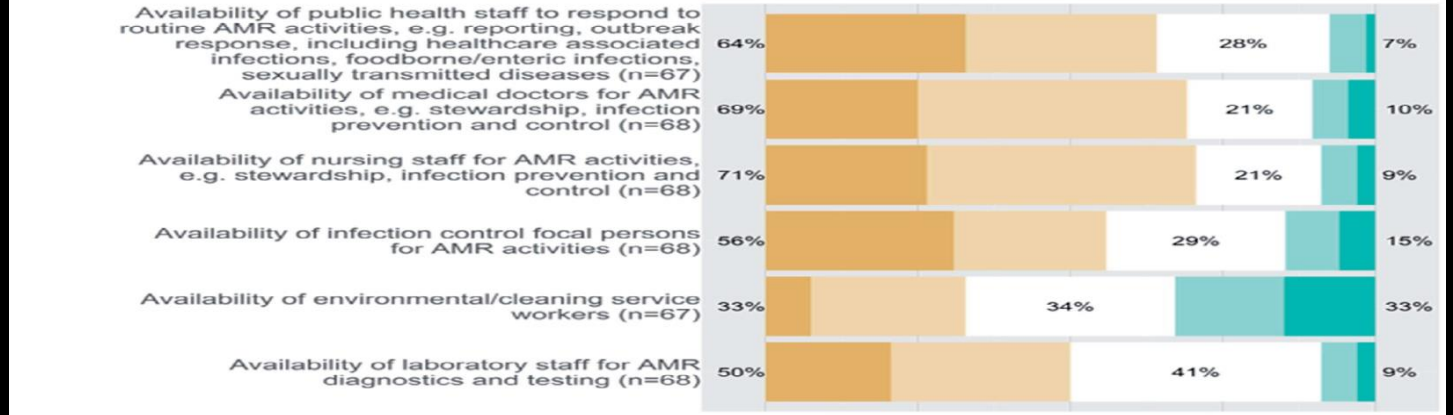


J Antimicrob Chemother, Volume 76, Issue 11, November 2021, Pages 3045–3058, https://doi.org/10.1093/jac/dkab300

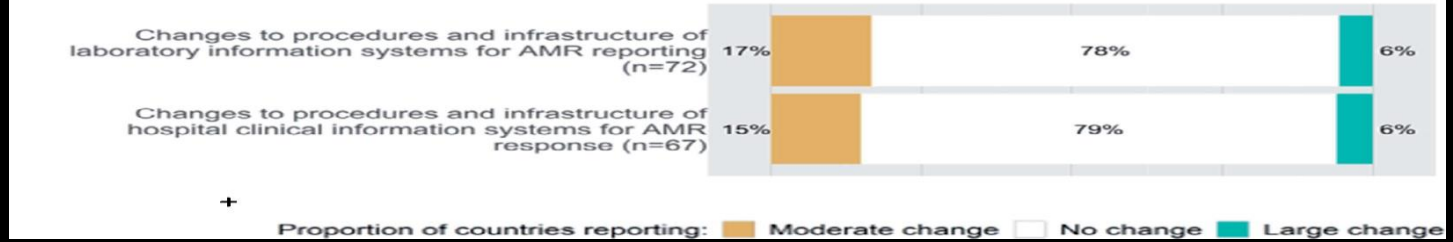
d. Reported impact of COVID-19 on laboratory supplies and equipment for AMR activities



e. Reported impact of COVID-19 on the availability of staff responsible for AMR activities

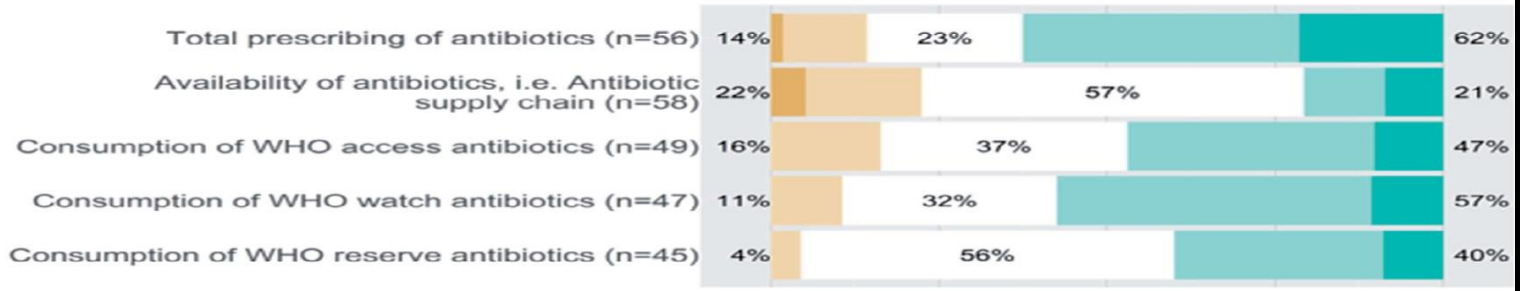


f. Reported impact of COVID-19 on AMR data information systems +

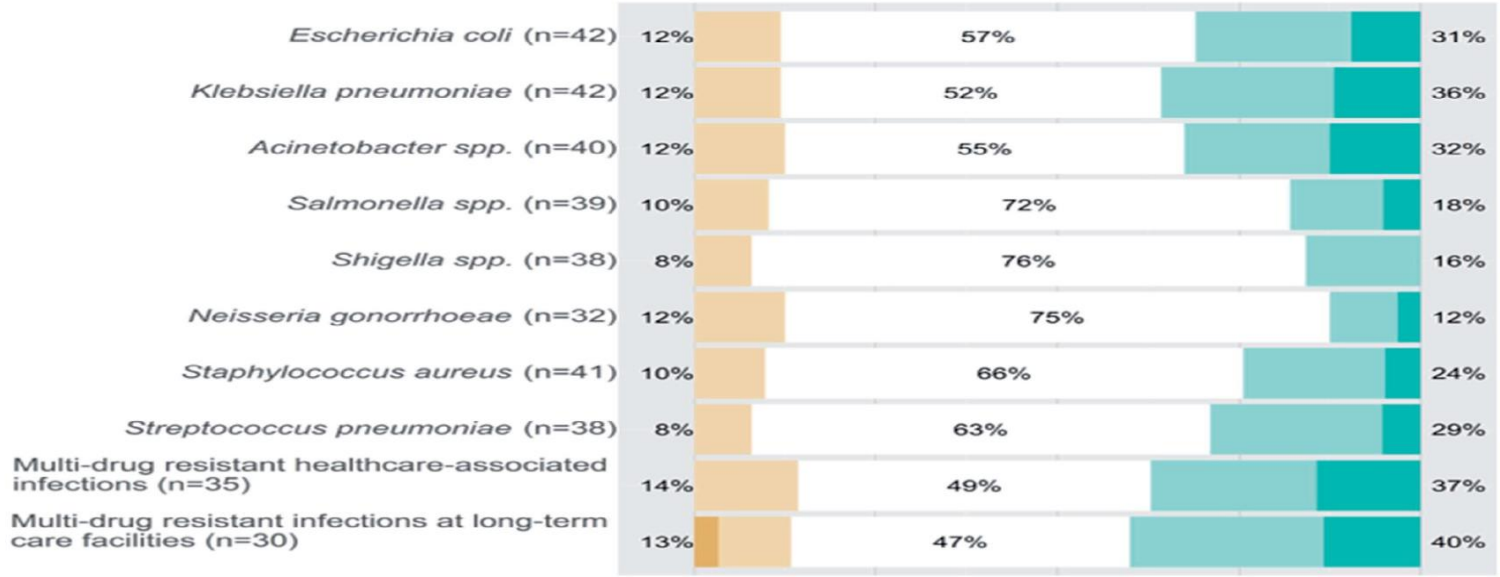


J Antimicrob Chemother, Volume 76, Issue 11, November 2021, Pages 3045–3058, https://doi.org/10.1093/jac/dkab300

i. Reported impact of COVID-19 on antibiotic consumption



j. Reported impact of COVID-19 on antimicrobial resistance rates



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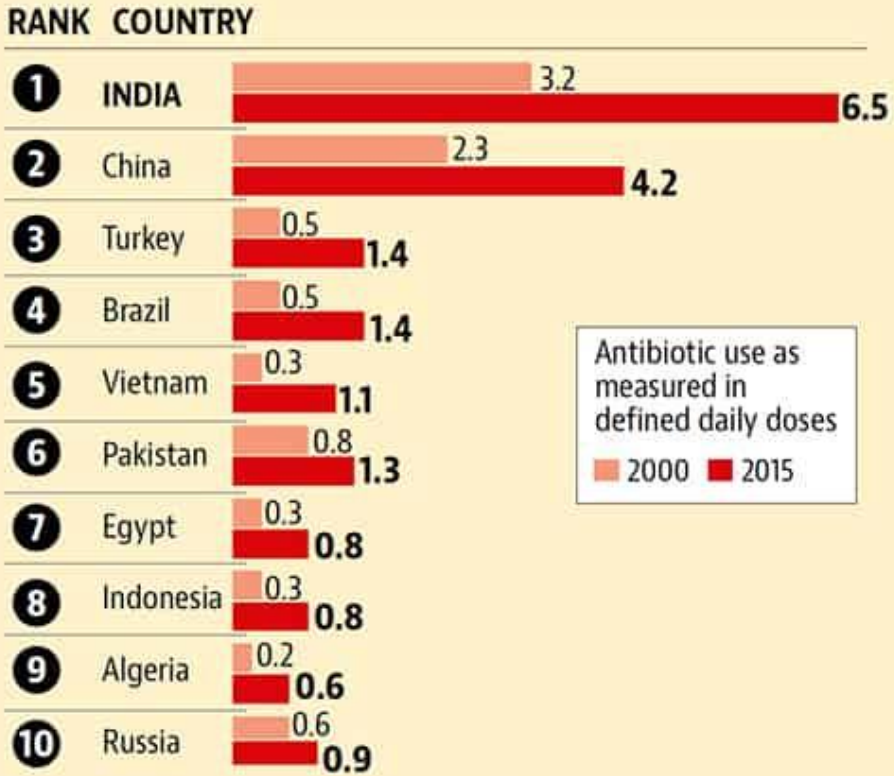
Global antibiotic consumption rates increased by 46 percent since 2000

Pre covid

- Global antibiotic consumption rates increased by 46 % in the last two decades in 204 countries from 2000 to 2018, as per data through the Global Research on Antimicrobial Resistance (GRAM) Project.
- The key findings:
  - In high-income countries, consumption rates remained stable between 2000 and 2018
  - In low- and middle-income countries, there was a 76% increase observed between 2000 and 2018 (from 7·4 to 13·1 DDD per 1000 per day).
  - The largest increases in antibiotic consumption rates were seen in the North Africa and Middle East region (111% increase) and South Asia (116%).
  - The highest rates of broad-spectrum penicillin consumption were observed in the High-Income super-region and the lowest in South Asia.
  - In South Asia, consumption rates for **fluoroquinolones increased 1.8 fold** and for **third-generation cephalosporin 37 fold** during the study period.

https://www.ox.ac.uk/news/2021-11-16-global-antibiotic-consumption-rates-increased-46-percent-2000

Countries with highest increase in consumption



Rank according to volume increase; Source: Proceedings of the National Academy of Sciences

ET Healthworld.com
From The Economic Times

Antibiotics for Covid cases worsen India's superbug crisis

covid patients: Antibiotics for Covid cases worsen India's superbug crisis, Health News, ET HealthWorld (indiatimes.com)

India's antibiotic use doubles in 15 years, common infections harder to treat: Study | Health - Hindustan Times

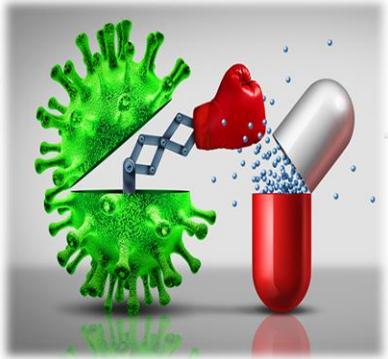
ANTIBIOTIC USE IN A PANDEMIC

(a) Inappropriate use will lead to a break in the global supply chain potentially leading to antibiotics not being available for those who need them

(b) The increased workload associated with parenteral administration of antibiotics for nurses involved in COVID-19 patient care

(c) Unintended negative long-term consequences associated with antibiotic overuse potentially leading to increased morbidity and mortality in the future.

REASONS FOR ANTIBIOTIC ABUSE IN COVID19



- Clinicians initiate antibiotics when symptoms suggest bacterial pneumonia which are often similar to COVID-19
- Indiscriminate use of HCQ and azithromycin combinations, quinolones and penicillins for prophylaxis in COVID-19
- Empirical use of antibiotics to prevent bacterial coinfections in COVID-19
- Even though COVID19 is a viral illness not affected by antibiotics many small studies from healthcare settings suggest that above 90% of the cohort are on antibiotics

Case 1

- 53 yr old male Shop keeper
- Fever (up to 102° F) with myalgia x 3 days duration
- Dry cough x 1 day
- No sore throat ,rhinorrhoea ,diarrhoea or dyspnoea
- Hypertensive well controlled on ACE inhibitors
- No other co-morbidities
- No addictions
- No travel history / Not from a hotspot or containment zone

Physical examination and Labs

- On Examination
  - Temp 100.6 F
  - HR 108/min
  - BP 130/80 mm of Hg
  - Sp02 – 99% on Room air
  - Systemic Exam – Unremarkable
- Routine tests like CBC, LFT,
  - S. Creatinine, are within normal limits

What is your diagnosis?

1. Dengue fever
2. Malaria
3. Leptospirosis
4. Scrub typhus
5. COVID-19
6. Intercurrent viral illness

What is the next step you would like to take ?

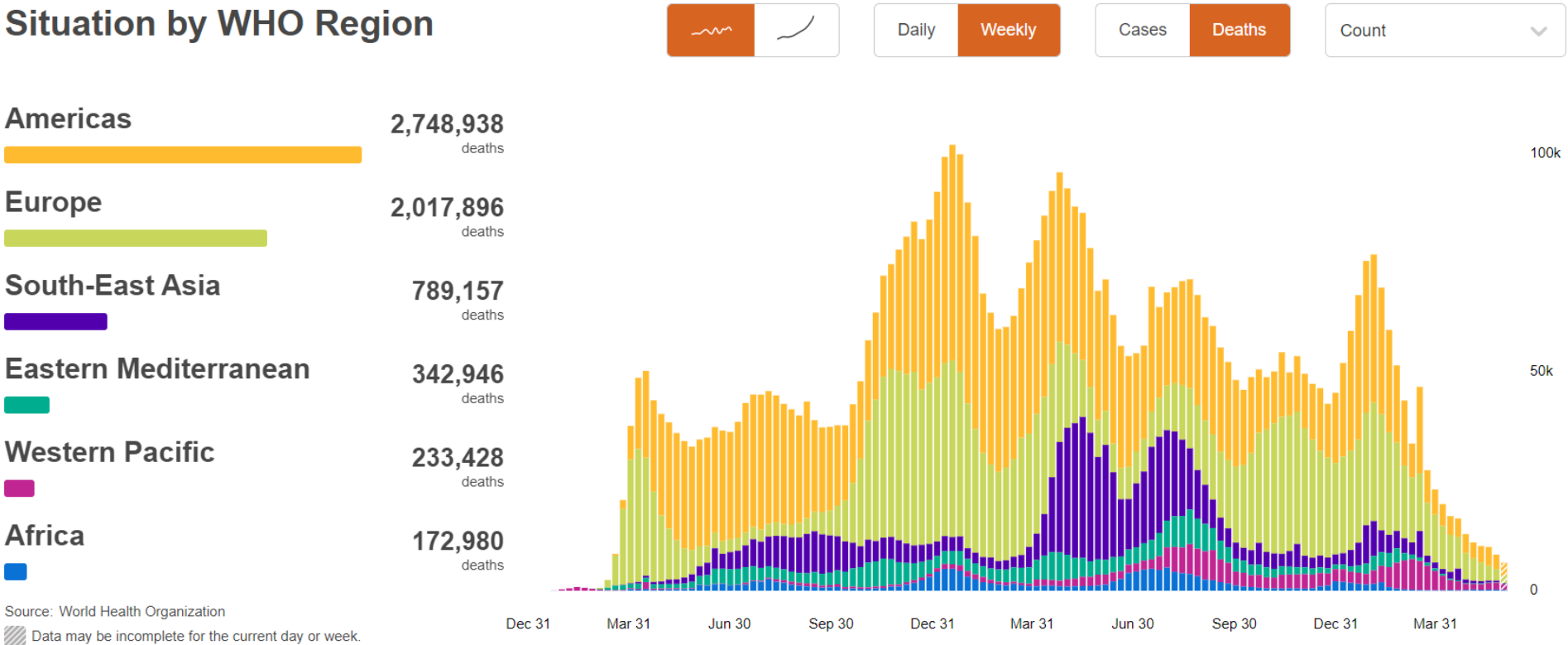
1. Malarial parasite smear, Dengue, Scrub typhus and Leptospirosis serology
2. Order a RT- PCR on a nasopharyngeal swab
3. Start antibiotics
4. Self isolation at home and ask the patient to come back if develops cough and breathlessness
5. Admit for evaluation

He comes back to the OPD 1 day later and the COVID-19 PCR comes back as positive, he has a runny nose, but no breathlessness, vitals are stable

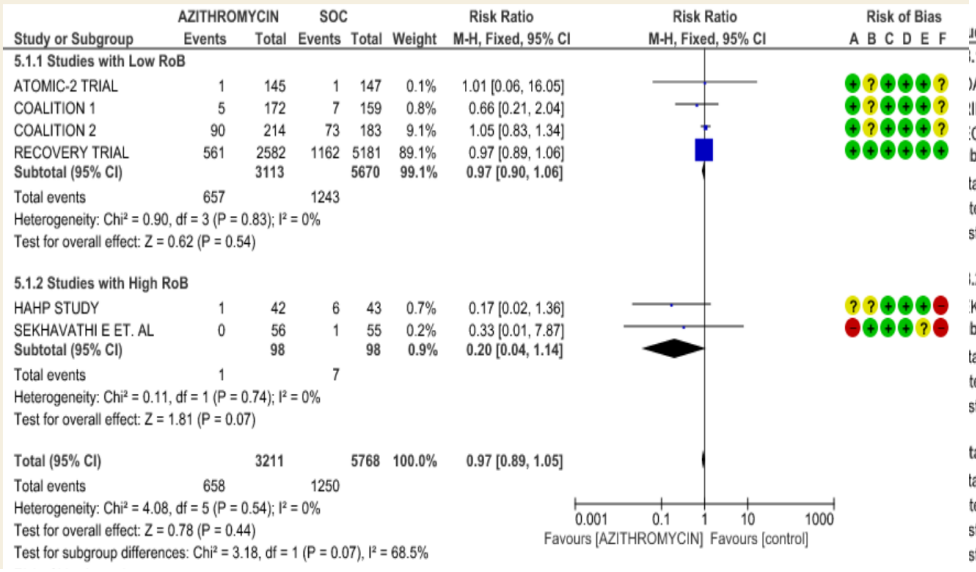
- **What treatment would you like to start for the patient and why?**

- Azithromycin
- Hydroxychloroquine
- Remdesivir
- Casirivimab-Imdevimab
- Piperacillin-Tazobactam

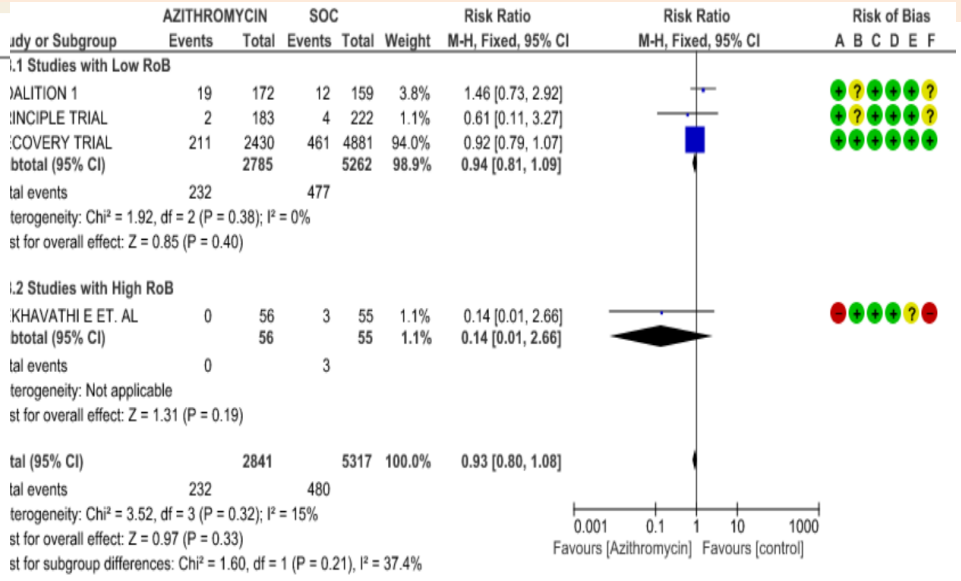
Things to consider



Azithromycin



Mortality



Progression to IMV

RECOMMENDATION: The group recommends against the use of Azithromycin for COVID-19 infection in all categories of severity (strong recommendation). There was high certainty evidence to demonstrate that Azithromycin did not impact mortality or progression of illness in the treatment of COVID-19 infection.

DATE OF RECOMMENDATION: 27th September 2021

https://indiacovidguidelines.org

We do not recommend use of azithromycin for treatment of COVID-19 infection (strong recommendation).

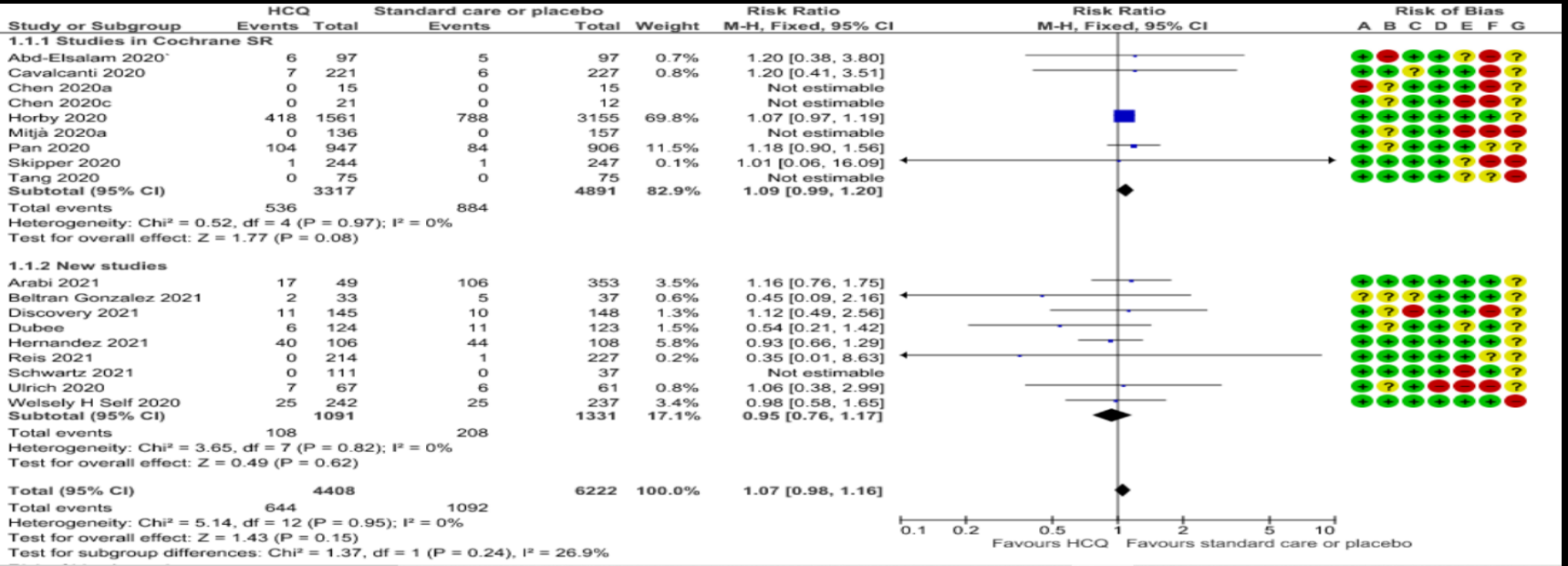
Hydroxychloroquine or Chloroquine

RECOMMENDATION: We do not recommend Hydroxychloroquine (HCQ) or Chloroquine for treating COVID-19. There is no demonstrable benefit and there is potential toxicity.

DATE OF RECOMMENDATION: 4th February 2022

https://indiacovidguidelines.org

We do not recommend HCQ or Chloroquine for treating COVID-19 (strong recommendation)



illness. There is no mortality benefit and it does not reduce progression to intensive care. It may reduce hospitalization or medically attended visits.

DATE OF RECOMMENDATION: 04th May 2022

https://indiacovidguidelines.org

We do not recommend Intravenous Remdesivir in all patients with non severe COVID-19 illness (conditional recommendation)

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gottlieb,2022	0	279	0	283		Not estimable
Total (95% CI)		**279**		**283**		**Not estimable**
Total events	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

Risk Ratio M-H, Fixed, 95% CI

Risk of Bias A B C D E F

0.01 0.1 1 10 100
Favours Remdesivir Favours Placebo

Mortality

Study or Subgroup	Remdesivir Events	Remdesivir Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Gottlieb,2022	2	279	15	283	100.0%	0.14 [0.03, 0.59]
Total (95% CI)		**279**		**283**	**100.0%**	**0.14 [0.03, 0.59]**
Total events	2		15			

Heterogeneity: Not applicable
Test for overall effect: Z = 2.67 (P = 0.007)

Risk Ratio M-H, Fixed, 95% CI

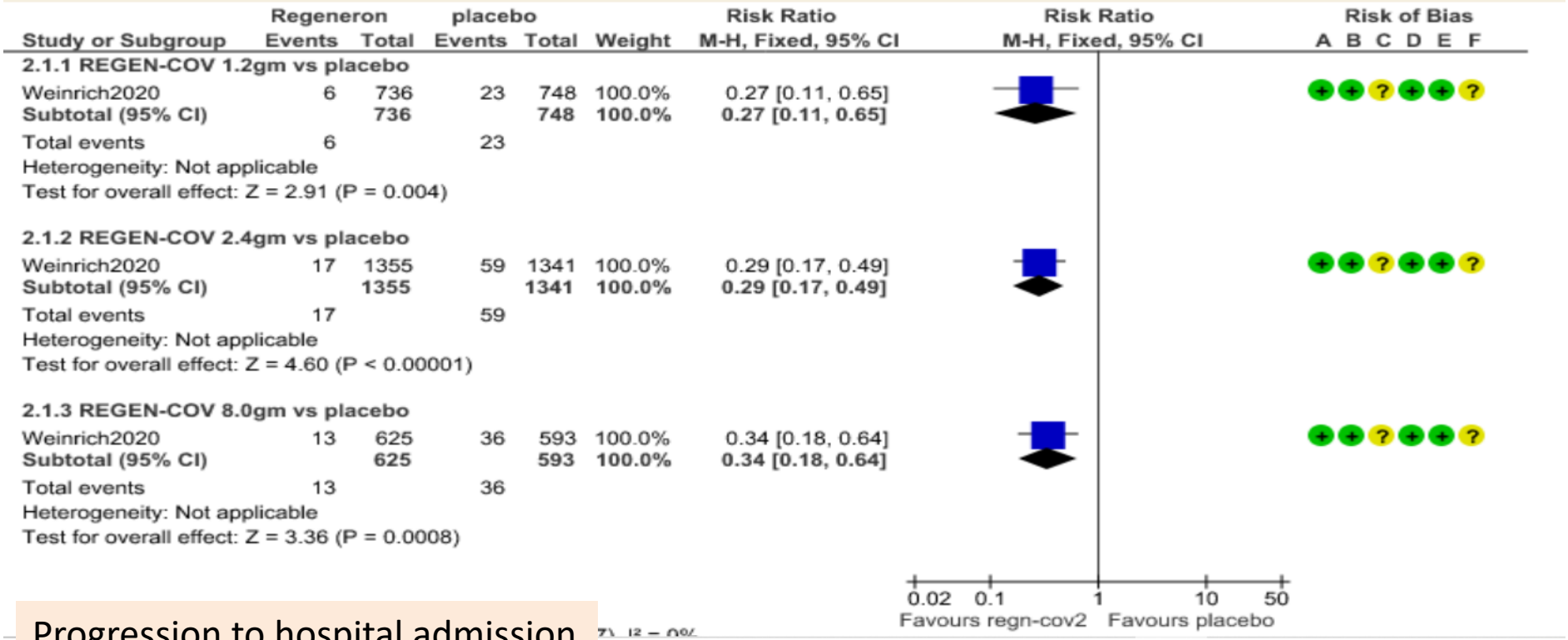
Risk of Bias A B C D E F

0.01 0.1 1 10 100
Favours Remdesivir Favours Placebo

Progression to hospital admission

We do not recommend Casirivimab-Imdevimab for patients with mild COVID-19 and no risk factors for progression to severe disease (Strong recommendation)

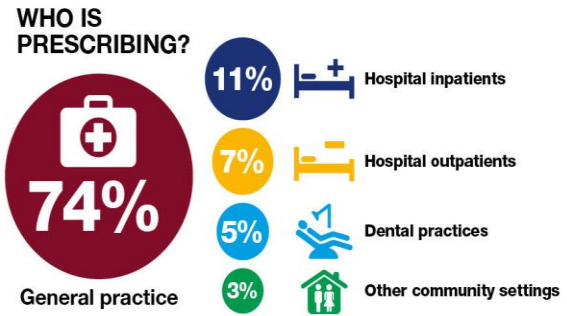
We recommend Casirivimab-Imdevimab for use within 10 days of symptom onset in those with ≥ 1 risk factors for progression to severe disease with a non Omicron variant of COVID-19 (Conditional recommendation)



Progression to hospital admission

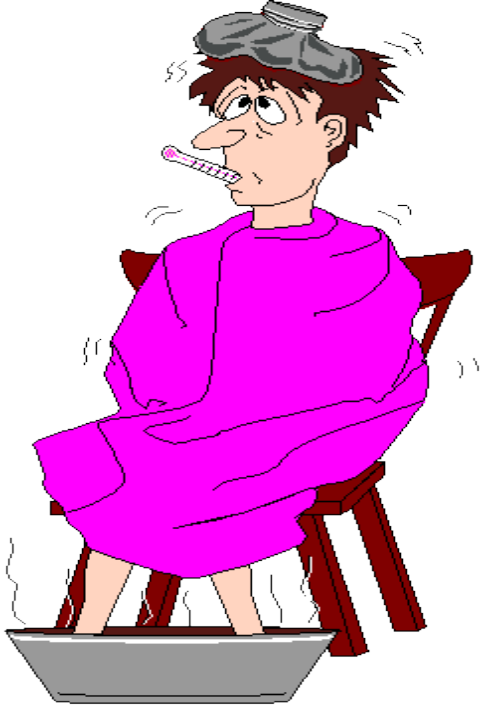
COVID-19 AND AMS

- The Omicron variant has a 59% lower risk of hospital admission, 44% lower risk of hospital attendance and 69% lower risk of death vs delta variant cases – therefore mild COVID-19 probably does not need any form of treatment
- Antibiotics or antivirals not indicated



www.gov.uk/ AMR publications, CDC

Lancet 2022; 399: 1303–12 Published Online March 16, 2022 https://doi.org/10.1016/ S0140-6736(22)00462-7



Approach to pneumonia during the COVID19 pandemic

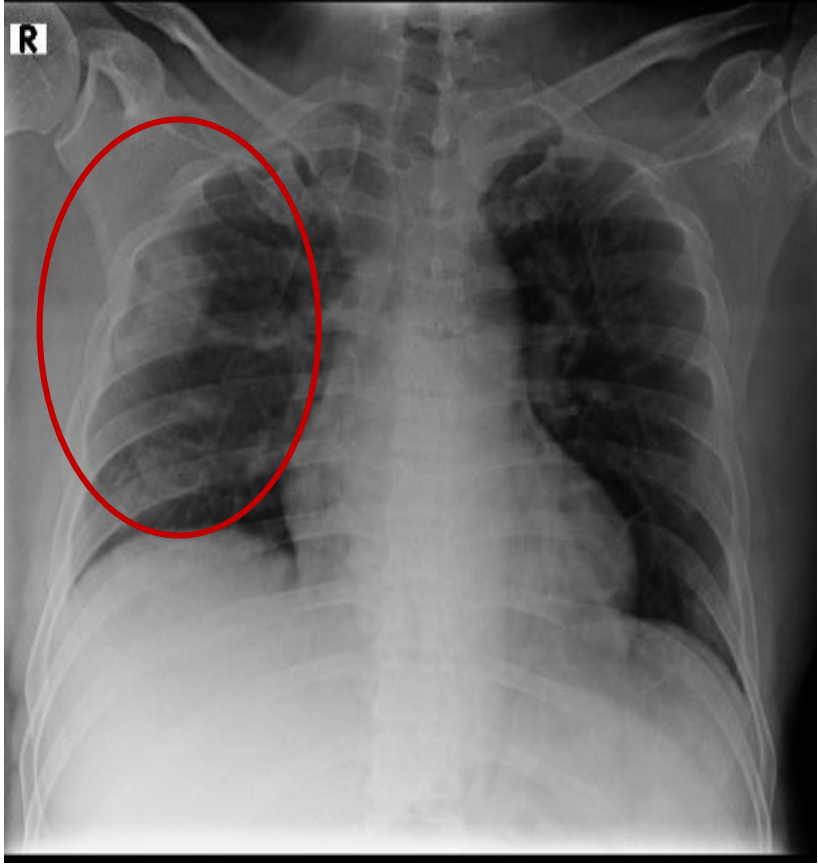
Case 2

- 43 yr. old male
- Fever for 4 days duration – moderate - high grade
- Dry cough x 3 days duration
- No URI symptoms, cough ,diarrhoea , sore throat
- Worsening breathlessness for 1 day and hence referred
- Newly diagnosed uncontrolled Diabetic on OHA's
- No other co-morbidities
- History of contact with returnees from a religious meeting in Delhi

On Examination:

RR 36/min ; BP 110/70 mm Hg
PR 118/min ; SpO2 92%
Temp=100° F
GCS 15/15
Systemic Exam : Right upper zone crepitations +

- Started on Piperacillin-Tazobactam while awaiting results



•Patient diagnosed with SARI
(Severe acute Respiratory Infection)
•Admitted to the ward

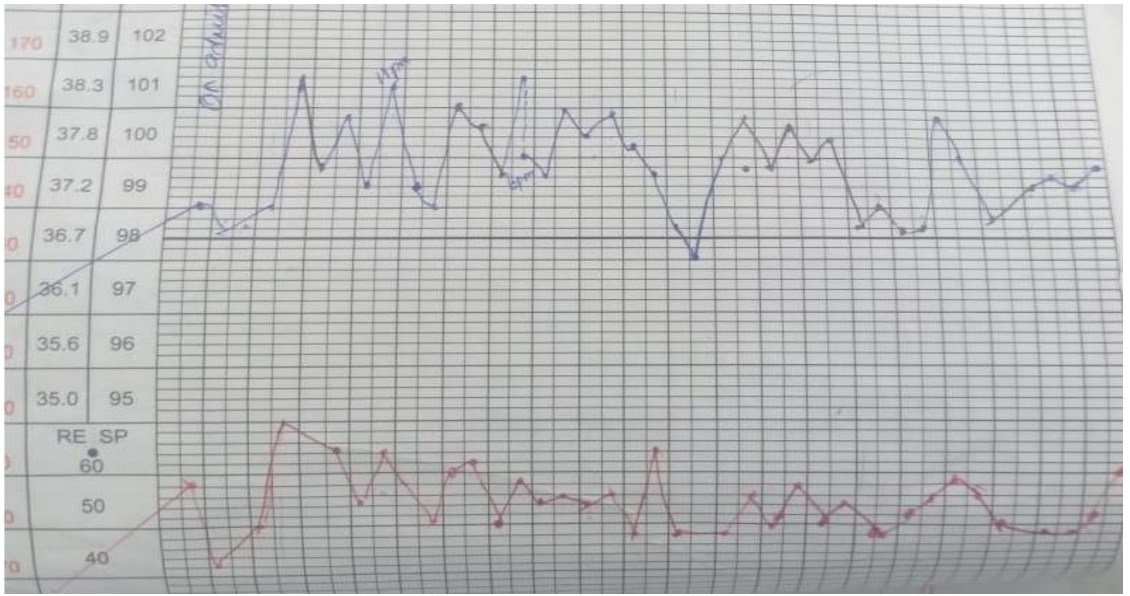
What is your diagnosis and how would you treat?

1. Viral pneumonia other than COVID-19
2. COVID-19 pneumonia
3. Bacterial pneumonia
4. Tuberculosis
5. Pulmonary aspergillosis
6. Pulmonary mucormycosis

COVID 19 PCR comes positive

Course in the hospital

- Not hypoxic, cough becomes productive
- Continues to have low grade fevers
- It is now 10 days, d-Dimer, Ferritin are showing a downward trend



Questions to the panel

What would you like to do next?

1. Change antibiotics
2. Send further tests
3. Stop antibiotics
4. Send a procalcitonin for a de-escalation of antibiotics
5. Put down the fevers to long covid syndrome

1. **Change antibiotics:** Patient is improving, not needed
2. **Send further tests:** Probably prudent
3. **Stop antibiotics:** Definite response, could definitely do so
4. **Send a procalcitonin for a de-escalation of antibiotics:** Probably not required, obvious clinical response
5. **Put down the fevers to long covid syndrome:** Does not fit in to the clinical case definition of post acute COVID-19 sequelae

A clinical case definition of post COVID-19 condition by a Delphi consensus

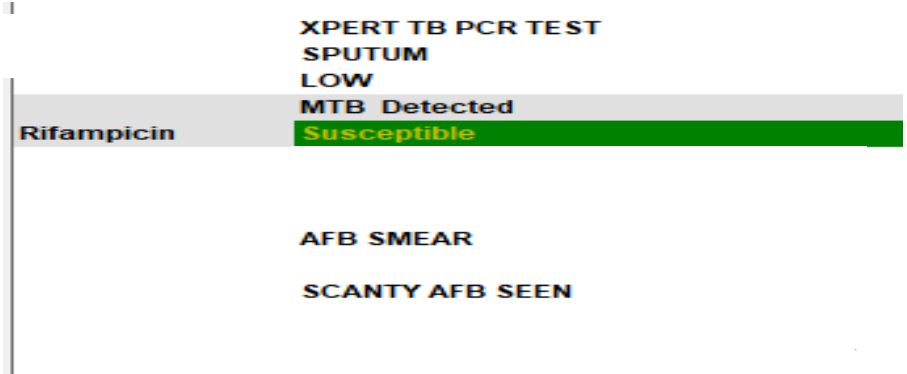
6 October 2021

World Health Organization

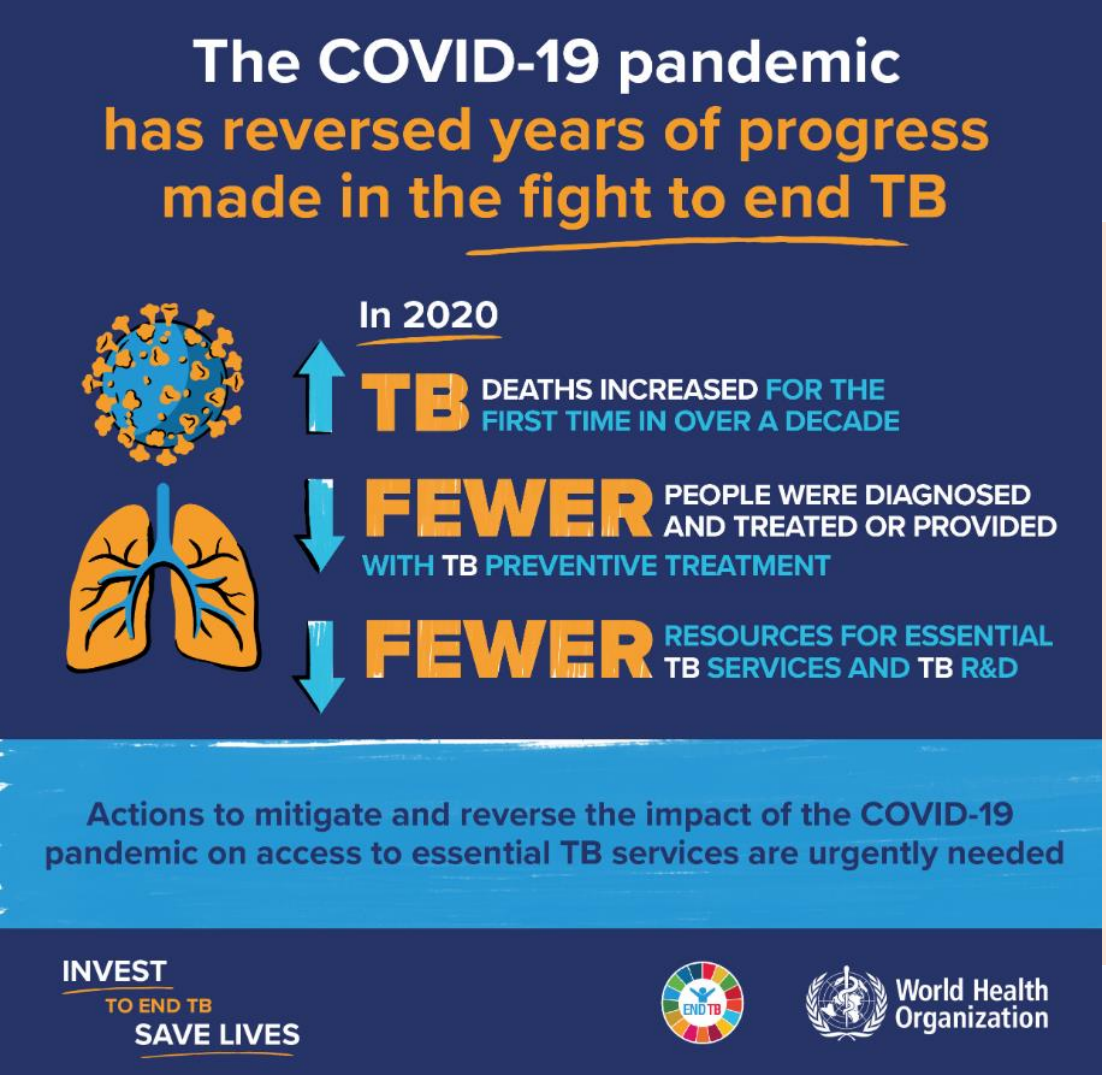
Post COVID-19 condition occurs in individuals with **a history of probable or confirmed SARS-CoV-2** infection, **usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.** Common symptoms include **fatigue, shortness of breath, cognitive dysfunction** but also others (see **Table 3** and **Annex 2**) which generally have an **impact on everyday functioning.** Symptoms may be **new onset,** following initial recovery from an acute COVID-19 episode, or **persist** from the initial illness. Symptoms may also **fluctuate** or **relapse** over time. A separate definition may be applicable for children.

ID comes in for a consult

- He actually takes a detailed history and realises that the patient has been sick for a month
- He has had weight loss of 5 kg over 6 months
- Chest X rays are reviewed, finally sputum tests done



	XPERT TB PCR TEST
	SPUTUM
	LOW
	MTB Detected
Rifampicin	Susceptible
	AFB SMEAR
	SCANTY AFB SEEN



EUROPEAN RESPIRATORY JOURNAL
ORIGINAL RESEARCH ARTICLE
TB/COVID-19 GLOBAL STUDY GROUP

Tuberculosis and COVID-19 co-infection: description of the global cohort

The TB/COVID-19 Global Study Group

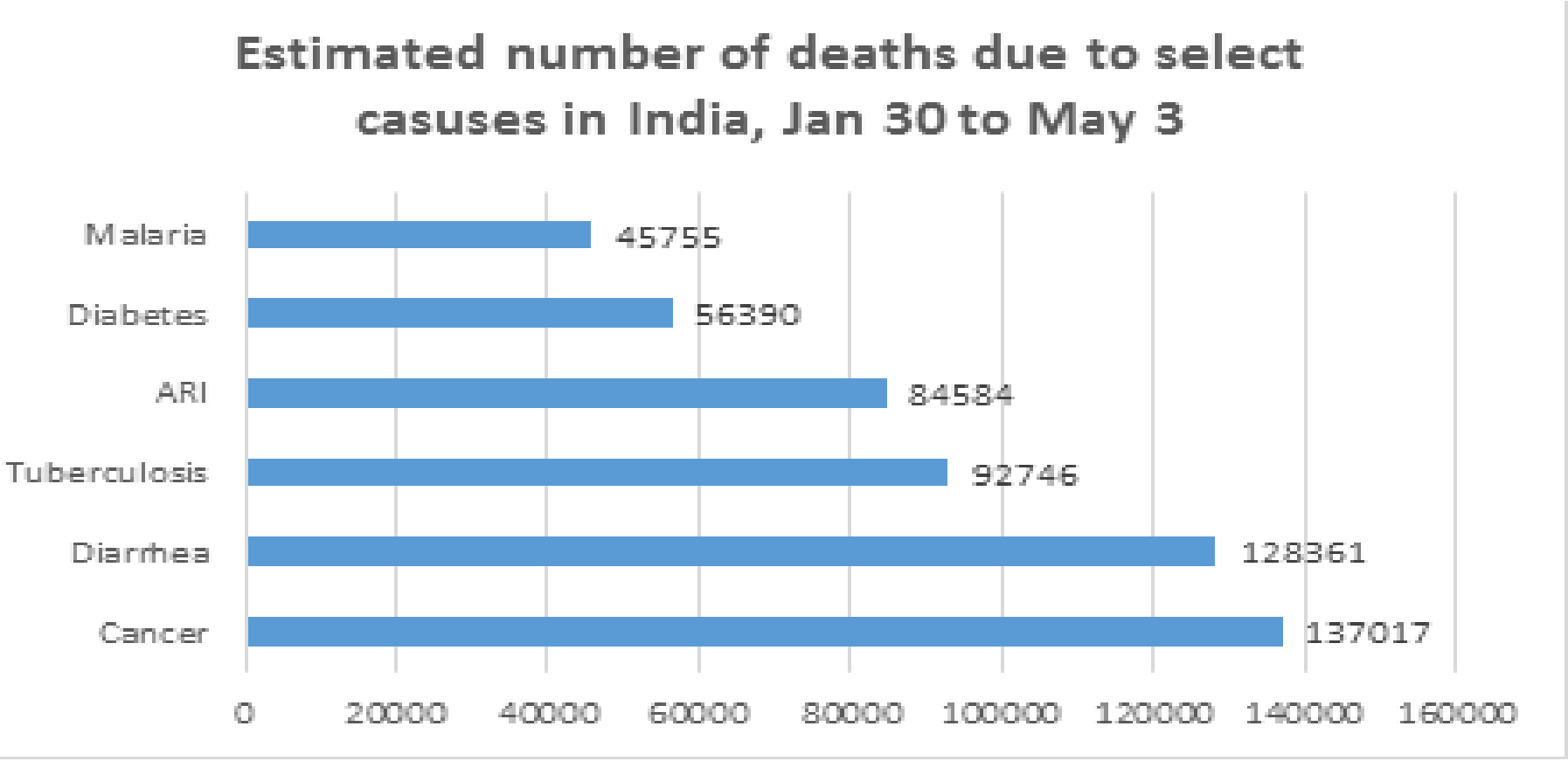
- 18% decrease in TB case notifications between 2019-2020 (7.1-5.8 million cases)
- 20% increase in TB deaths expected
- TB diagnosed concomitantly with or after diagnosis of COVID-19
- 12.6% higher case fatality rate with co-infection vs susceptible TB alone 1-2%
- COVID-19 patients with TB have a 2.7 times higher mortality
- Higher age, male gender and need for invasive ventilation were predictors of mortality

Eur Respir J 2022; 59: 2102538 [DOI: 10.1183/13993003.02538-2021]

COVID-19 and AMS

- START SMART AND THEN FOCUS
- A COMMUNITY ACQUIRED PNEUMONIA EVEN IF PRESENT NEEDS ONLY 7 DAYS OF TREATMENT
- WHEN RESPONSE IS DELAYED THEN LOOK FOR AN ALTERNATIVE CAUSE
- TB AND BACTERIAL PNEUMONIA HAVE BEEN REPORTED AS CO-INFECTIONS

Non-COVID-19 Patients Are Paying the Price of India's Efforts Against the Coronavirus



Case - History

- 49 year old gentleman, diabetic, hypertensive, asthmatic with obstructive sleep apnoea and dyslipidaemia
- Fever and cough for 6 days, headache for 1 day on 23.03.2020
- no h/o chills/ rigors/ haemoptysis / chest pain/ breathlessness
- He travelled to the UK (Feb 23,2020- March 17,2020)
- On 18 March 2020,he developed fever associated with nasal stuffiness, cough and mild yellowish expectoration -relieved by antipyretics
- Two episodes of loose stools, non mucoid, non- bloody with no abdominal pain or vomiting
- Past h/o: surgery in 2016 for distal ureteric calculus, November 2018- hospitalized for left lower lobe pneumonia

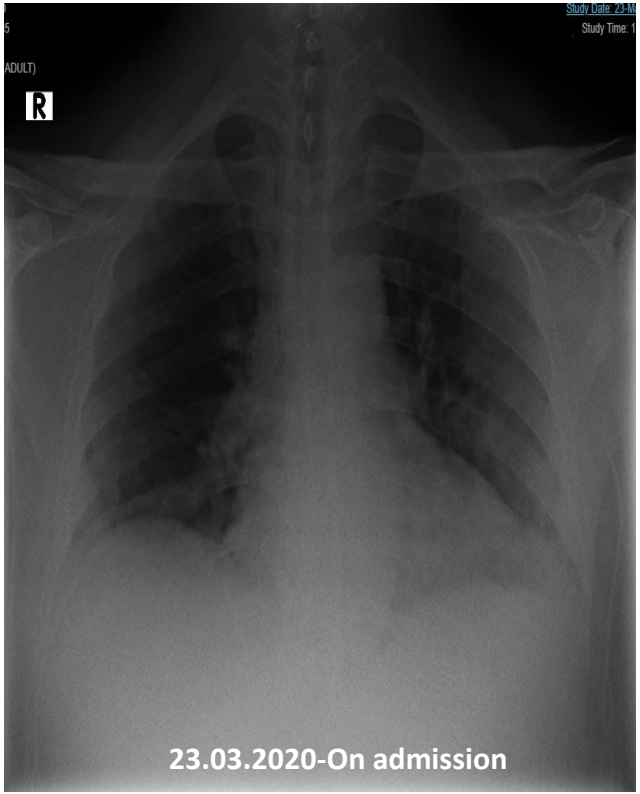
Examination

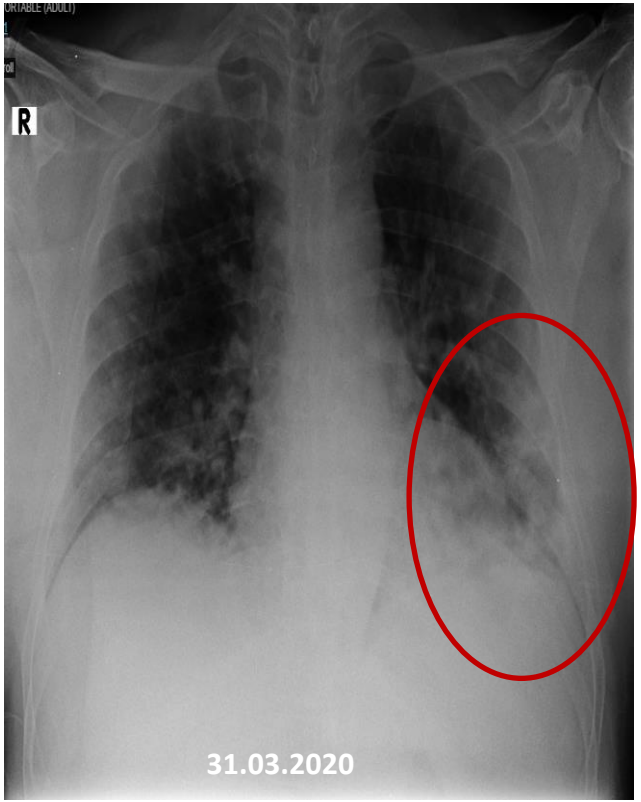
- General Exam: Conscious, oriented, HR=82/min, BP=130/90mmHg, RR=22/min, JVP not elevated, afebrile
- At presentation he was maintaining saturation at room air and was haemodynamically stable not requiring inotropic support.
- CVS: S1 S2+
- RS: Respiratory system: Pharynx- no congestion, no enlarged tonsils, No sinus tenderness, Trachea central, Occ basal crepitations present over left IAA,NVBS+
- Per abdomen: Soft, non tender, No organomegaly or masses palpable, No signs of free fluid per abdomen, Bowel sounds-Normal
- CNS: Normal

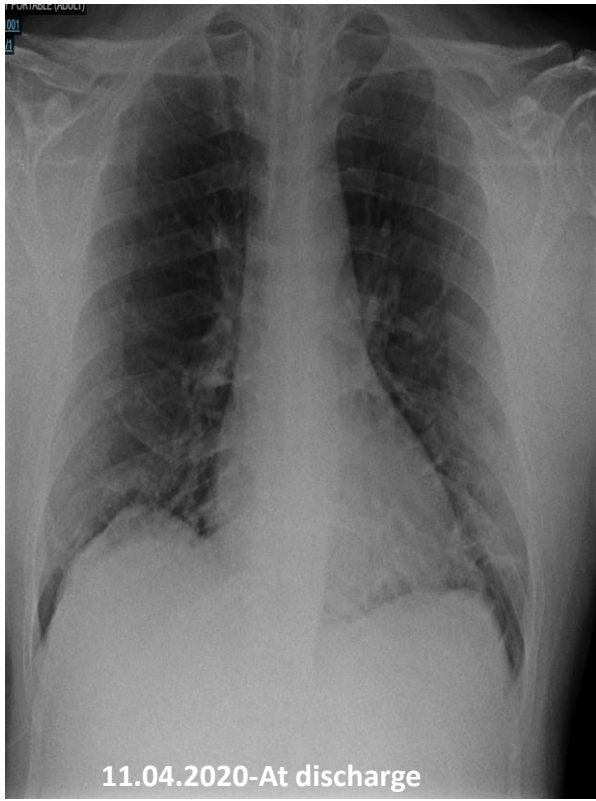
DATE	TEST	REPORT
23.03.2020	CBC:Hb-14.4, WBC :4900, Platelets:161000, DC: NE/LY/MO/EO:68/22/1/0, CRP:203, Liver Function Tests: Normal, Creat:0.97, HbA1C:8.9	
23.03.2020	PCR for multiple virus	Negative
23.03.2020	Blood C/S	No growth
26.03.2020	Qualitative SARS COV-2 PCR Screen	Positive
27.03.2020	XPERT TB PCR TEST(SPUTUM)	MTB not detected
29.03.2020	D Dimer	474ng/ml
29.03.2020	NT pro BNP	11pg/ml
11.04.2020	Chest X ray	Clearing Of Alveolar And Reticular Shadows
22.04.2020	Qualitative SARS COV-2 PCR Screen	Negative

Course in hospital

- He was initiated on Inj. Piperacillin + Tazobactam, Azithromycin and Oseltamivir after taking blood cultures and throat swab on day 1
- He tested positive for SARS COVID-19 and was initiated on Tab. Hydroxychloroquine
- In view of persistent fever with early ARDS features, a Chest X-ray was repeated on day 8 which revealed an opacity right lower zone
- Inj.Meropenem was started with which he symptomatically improved. His multiple blood cultures were negative


R
23.03.2020-On admission


R
31.03.2020


11.04.2020-At discharge

Questions to panelists

1. What is the risk of bacterial pneumonia in patients with proven or high likelihood of COVID-19?

2. What are the causative bacterial species in patients with proven or high likelihood of COVID-19 and bacterial pneumonia?

3. What are the stewardship opportunities here?

4. What is the optimal empirical antibiotic choice for patients with proven or high likelihood of COVID-19 and suspected bacterial pneumonia?

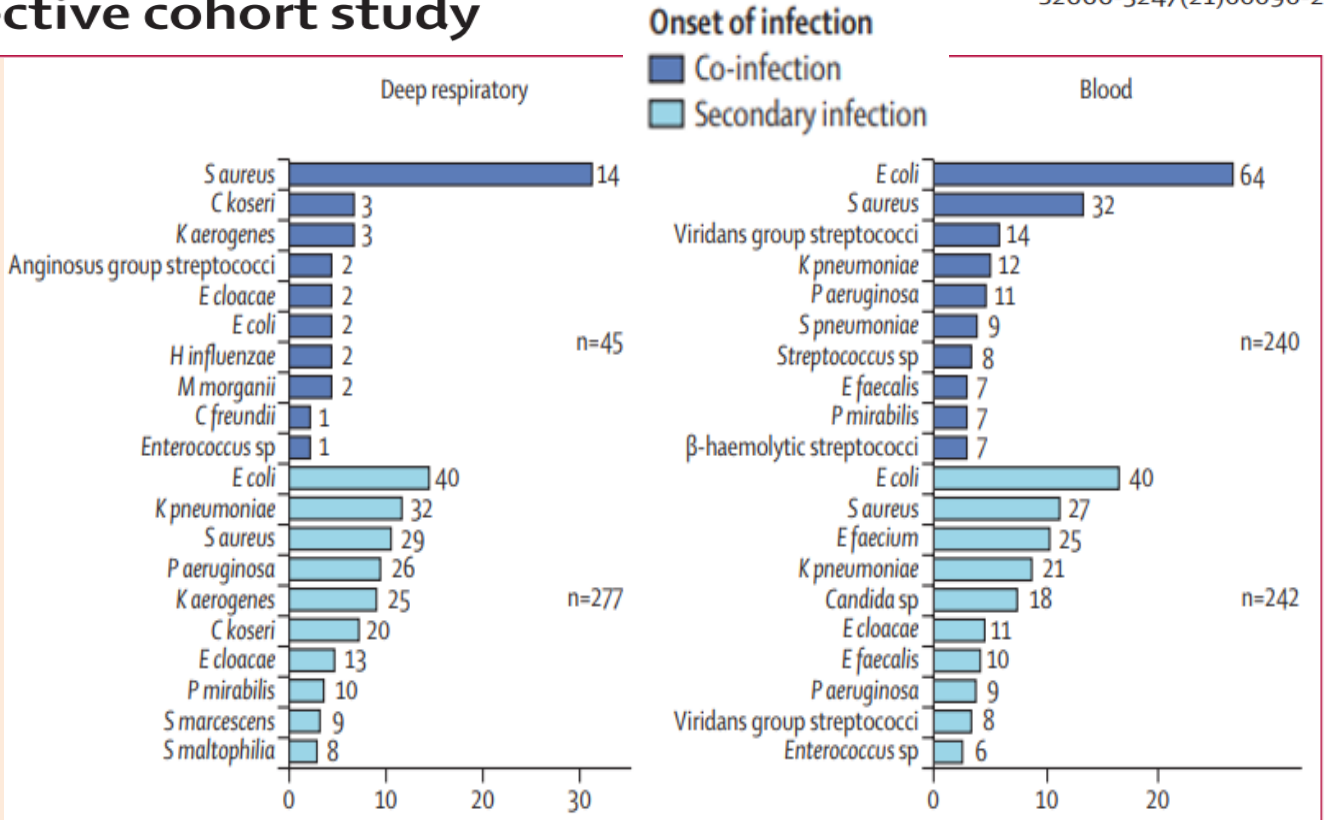
Stewardship opportunities

- Did not need Piperacillin –Tazobactam on the first day since it was a viral pneumonia
- Hydroxychloroquine is not prescribed anymore in any category of COVID-19 infection
- Meropenem as an empirical choice may be appropriate, depending on local profile and susceptibility patterns

Co-infections, secondary infections, and antimicrobial use in patients hospitalised with COVID-19 during the first pandemic wave from the ISARIC WHO CCP-UK study: a multicentre, prospective cohort study

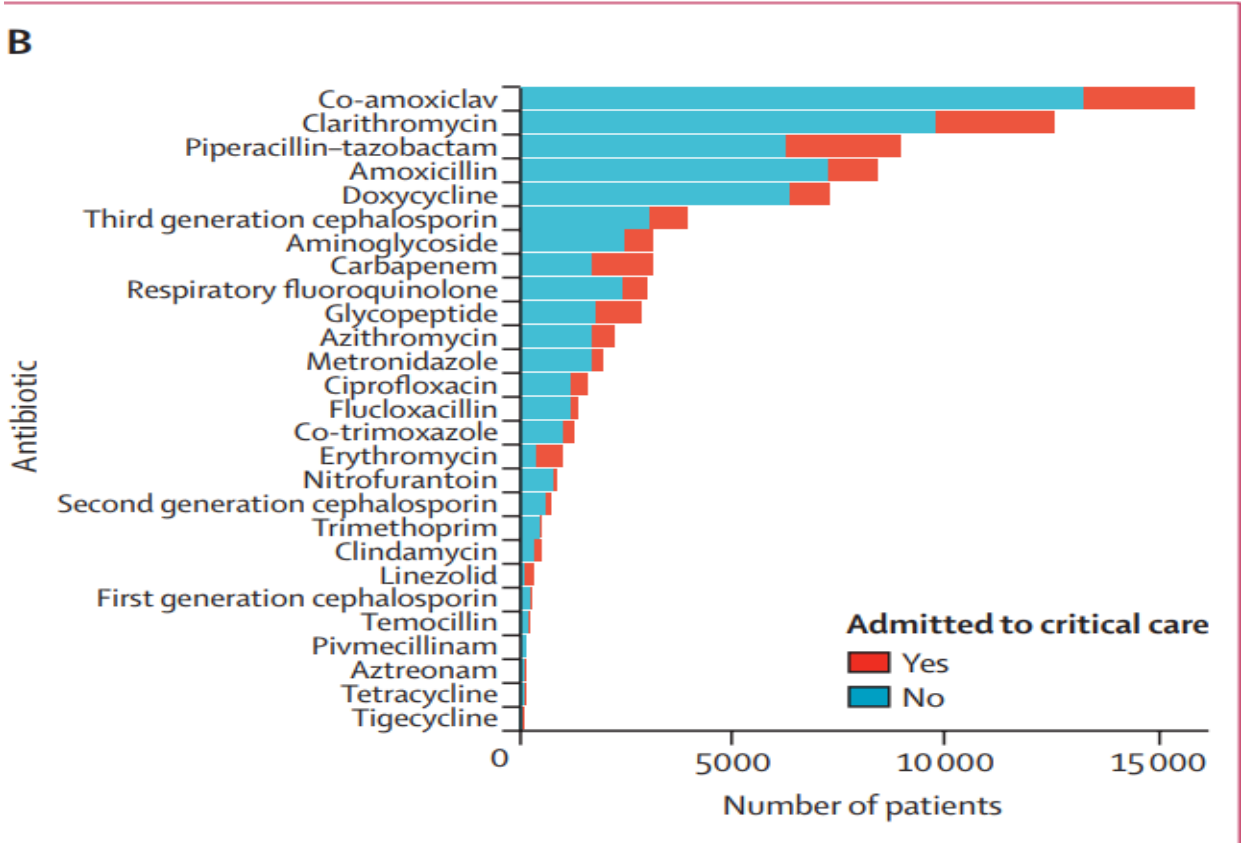
Lancet Microbe 2021; 2: e354–65
Published Online June 2, 2021
https://doi.org/10.1016/S2666-5247(21)00090-2

- Data from 48,902 patients admitted b/w Feb and June 2020
- 762/48,902 =1.5% secondary infections
- S.aureus and H.influenzae common respiratory co-infections
- E.coli and S.aureus common secondary infections
- BSI mainly E.coli and S.aureus



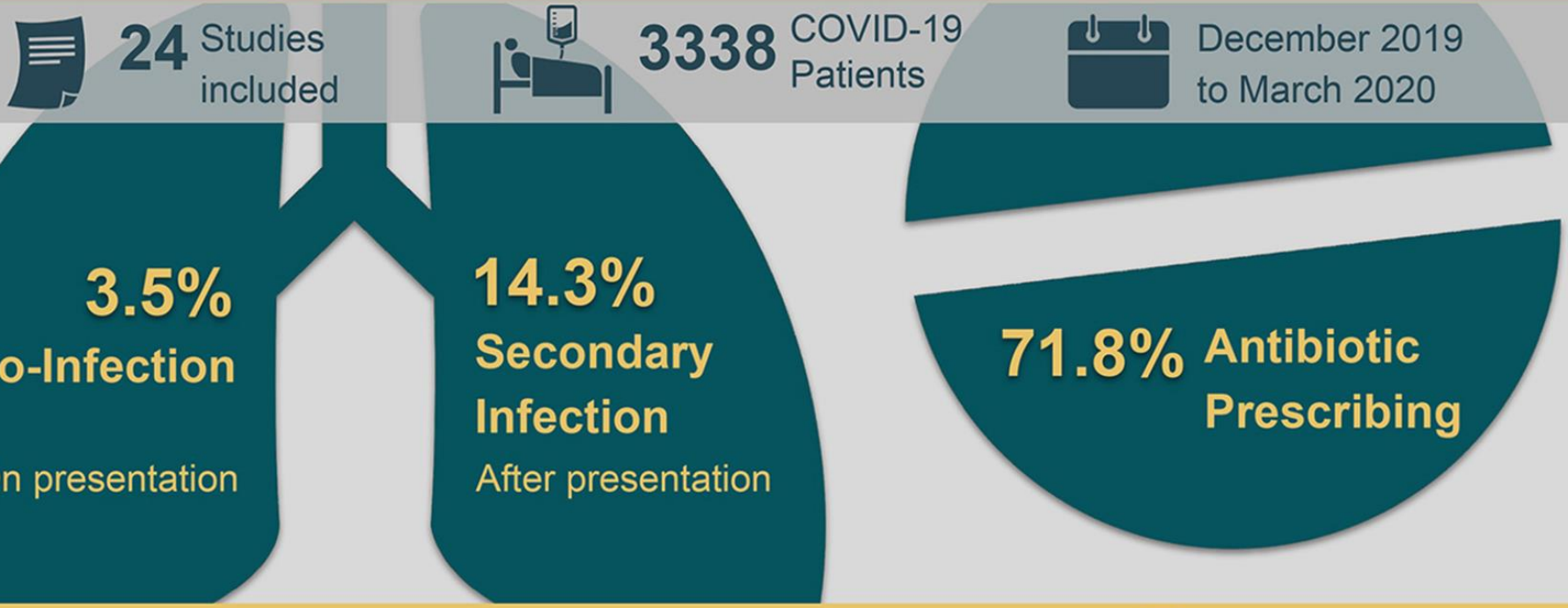
Specific antimicrobials across levels of care

- 85% of in-patients received antimicrobials
- Piperacillin Tazobactam was prescribed in 30% of the cases
- ICU: Glycopeptides and Fluoroquinolones were often prescribed
- Ward level: BL/BLI, doxycycline and Co-amoxycillin were common



Acute Bacterial Co-Infection in COVID-19

A Rapid Living Review and Meta-analysis



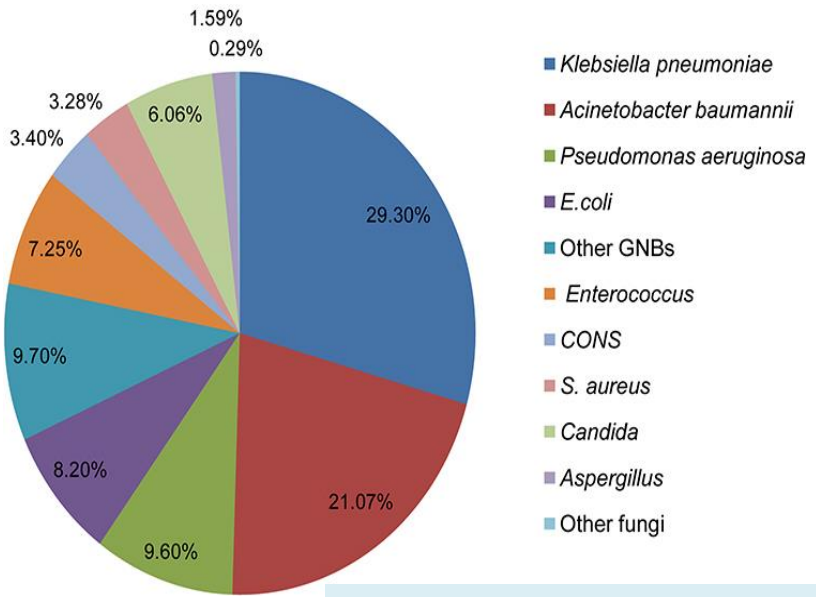
Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, Soucy JPR, Daneman N. Clinical Microbiology and Infection. 2020.

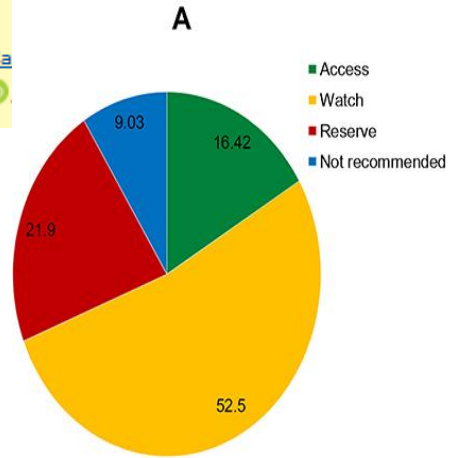
TARRN
www.tarrn.org/covid

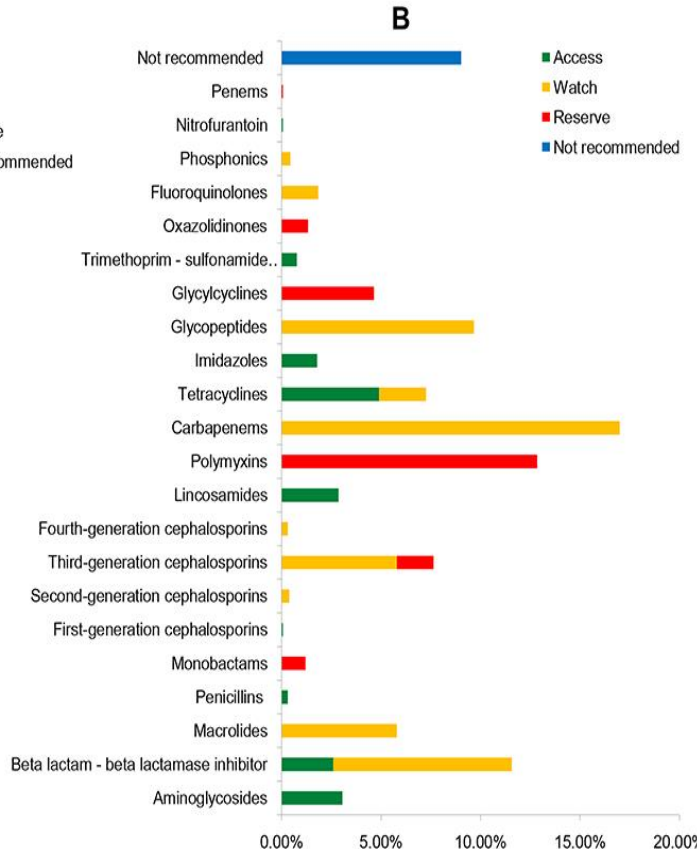
Secondary Infections in Hospitalized COVID-19 Patients: Indian Experience

Fulltext | Metrics | Get Permission | Cite this article

Authors Vijay S, Bansal N, Rao BK, Veeraraghavan B, Rodrigues C, Wa
Venkatasubramanian R, Khadanga S, Bhattacharya S, Mukherjee S



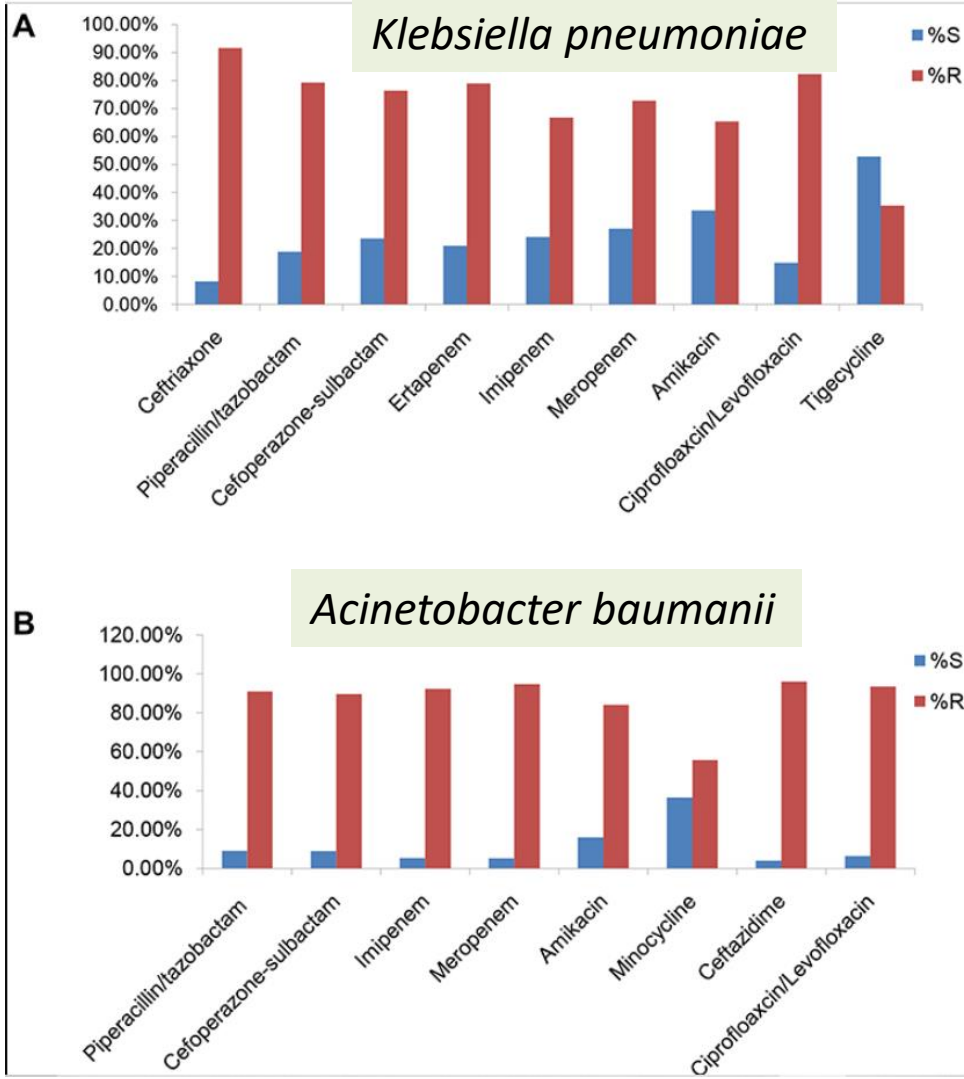




https://www.dovepress.com/secondary-infections-in-hospitalized-covid-19-patients-indian-experien-peer-reviewed-fulltext-article-IDR

Drug resistance patterns and outcomes

- Among all hospitalized 47% were infected with MDROs
- In *Klebsiella spp*, resistance against carbapenems was >70%, 3rd gen cephalosporins was >90%, fluoroquinolones was >80%
- Overall mortality was 11.6%, but in those with secondary infections it was 56% and those among MDROs it was 60.5%
- Overall gram- 72%; gram + was 11%, mixed was 8% and fungal was 4%



Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study

Fei Zhou*, Ting Yu*, Ronghui Du*, Guohui Fan*, Ying Liu*, Zhibo Liu*, Jie Xiang*, Yeming Wang, Bin Hui Li, Xudong Wu, Jiuyang Xu, Shengjin Tu, Yi Zhang, Hua Chen, Bin Cao

Zhou P, Liu Z, Chen Y, Xiao Y, Huang X, Fan X-G. Bacterial and fungal infections in COVID-19 patients: A matter of concern. Infect Control Hosp Epidemiol. :1–2

	Total (n=191)	Non-survivor (n=54)	
Outcomes			
Sepsis	112 (59%)	54 (100%)	58 (42%) <0·0001
Treatment			
Antibiotics			·0001
Antiviral tr			·0001
Corticoster			·0001
Intravenou			·0001
High-flow			·0001

Conclusion:

A study of 191 patients in two Wuhan hospitals showed that 50 percent of those who died tested positive for secondary infections compared to only one of the 137 survivors

Table 1. Secondary Infection or Coinfection in COVID-19 Patients

Patients With Secondary Infection or Coinfection, n/N (%)			Antibiotics Use Rate, n/N (%)			Procalcitonin ≥0.25 ng/mL, n/N (%)			
Total	Nonsurvivors	Survivors	Total	Nonsurvivors	Survivors	Total	Nonsurvivors	Survivors	Reference
28/191 (15)	27/54 (50)	1/137 (1)	181/191 (95)	53/54 (98)	128/137 (93)	20/164 (12)	16/51 (31)	4/113 (4)	Zhou et al[2]
9/52 (17)	4/32 (13)	5/20 (25)	49/52 (94)	30/32 (94)	19/20 (95)	...	...	...	Yang et al[8]
4/41 (10)	4/13 (31)	0/28 (0)	41/41 (10)	13/13 (100)	28/28 (100)	5/39 (13)	3/12 (25)	2/27 (7)	Huang et al[7]

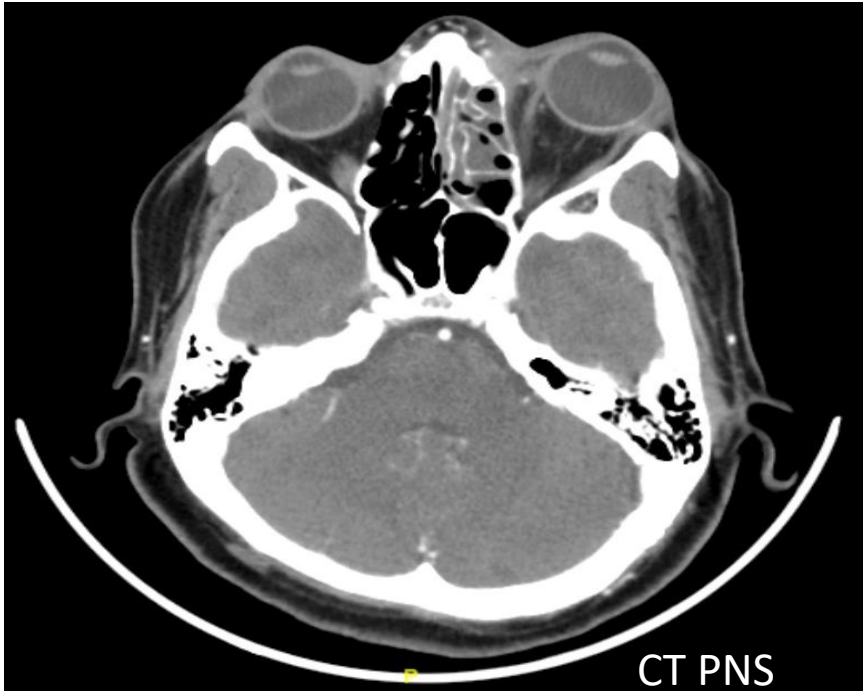
Note. Patients were classified in to ICU and non-ICU patients instead of nonsurvivors and survivors in the study by Huang et al.[7]

Case history

- A 52 year old lady housewife from Andhra Pradesh
  - Had 5 days of low grade fever dry cough with no SOB, found to have mild COVID-19 with SARS CoV-2 Nasopharyngeal swab RT PCR positivity,
  - Treated symptomatically & improved.
- One week later she started noticing left cheek swelling pain & redness which later turned into black eschar
- There was also left eye swelling with protrusion of the eye with progressive diminution of vision & complete ptosis of the same duration.
- H/O type II diabetes mellitus of 8 years duration which was well controlled still 2 months back
- Now high sugars following COVID-19 with AC >300mg/dl and HbA1C:9.7% requiring insulin to control.

On examination

- -Mild pallor +
- Systemic examination: RS CVS PA and CNS were normal
- Left eye no PL, proptosis, frozen eye, left eye lid swelling with conjunctival suffusion (left II, III, IV & VI cranial nerve palsy)
- Left cheek 2X2 black eschar with loosened left upper jaw tooth and tenderness with visible underlying osteomyelitic bone and pus discharge.
- Rigid nasal endoscopy showed: left middle and inferior turbinates necrotic with pus discharge from left maxillary and ethmoid sinuses.



- Left maxillary and ethmoid sinus soft tissue thickening with erosions of sinuses
- Soft tissue thickening with fat stranding in the left premaxillary region with maxillary osteomyelitis, retro-maxillary region extending into the pterygomaxillary and sphenopalatine region
- Left eye proptosis with soft tissue thickening along the medial wall of the orbit and left periorbital, intra, extraconal spaces, superior orbital fissure, optic canal, erosions in the medial wall of the left orbit.
- Left cavernous sinus enhancement with no evidence of thrombosis or ICA vasculitis
- No intra orbital or cerebral abscess / focal cerebritis or infarcts.

Course in hospital

- She underwent Endoscopic Nasal debridement with
  - Premaxillary and retro-maxillary clearance
  - Left inferior partial maxillectomy wit mucosal flap reconstruction
  - Left orbital decompression.
- Biopsy: *Mucor spp*
- She received 14 days of lipid emulsion amphotericin B @ 5mg/kg/day dose which she tolerated well except for mild hypokalemia which was corrected.
- Her sugars well controlled with Insulin
- At the end of IV amphotericin B therapy she was started on oral posaconazole 300mg OD after loading dose.
- Her Posaconazole trough level after 2 weeks of therapy was 3050ng/ml,
- She tolerated the drug well without major side effects.

Follow up

- On follow-up at end of 3 months of therapy
  - Left cheek healed with scarring and healthy underlying flap with no oroantral fistula.
  - Left proptosis is decreased with left ptosis improved and left eye pthsis bulbi
  - Her repeat rigid nasal endoscopy: showed healthy nasal mucosa and sinuses
- Repeat CT PNS showed
  - Clear sinuses with sclerotic left maxillary and left ethmoid sinues,
  - Post left maxillectomy status with resolving osteomyelitic changes.
  - Residual soft tissue thickening in the left orbital intra & extraconal areas(significantly improved comared to previous scan) with osteomyelitic changes in the the left infrior and medial orbital walls.
  - No cavernous sinsus enchancement or thrombosis, no ICA vasculitis, normal visulised cerebral parenchyma.

- She received total 4 months of oral posaconazole and at 6 months & 9 months of followup she has resolving disease with no recurrence.

Questions to panelists

- What are the various fungal infections that were found to occur as superinfections in COVID-19 infection
- COVID-19 infection in India showed an explosion of COVID associated mucormycosis. What were the possible reasons for this explosion of cases?
- Is there a pathogenetic mechanism to explain a possible synergy between COVID and Mucorales spp?
- What are the various options to treat Mucormycosis available in India and could you give us an idea of the various costs involved?

Epidemiology of COVID associated Mucormycosis

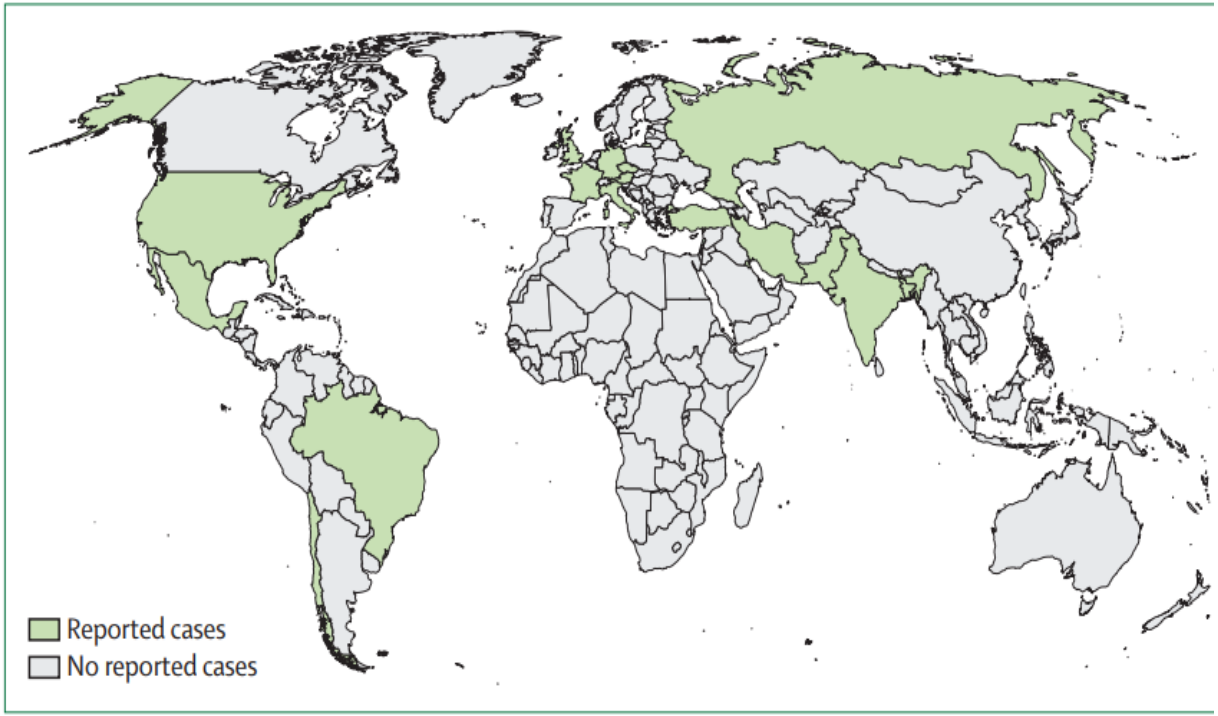
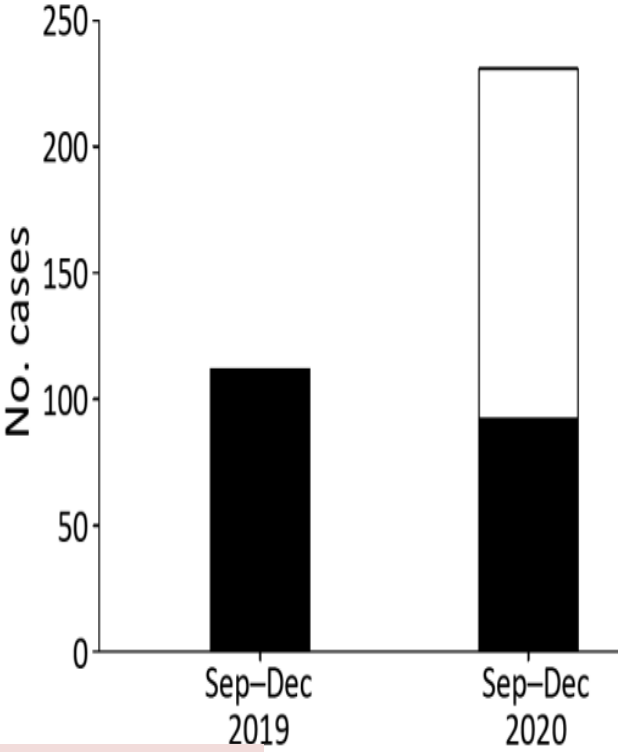


Figure 1: **Global distribution of 80 COVID-19-associated mucormycosis cases**



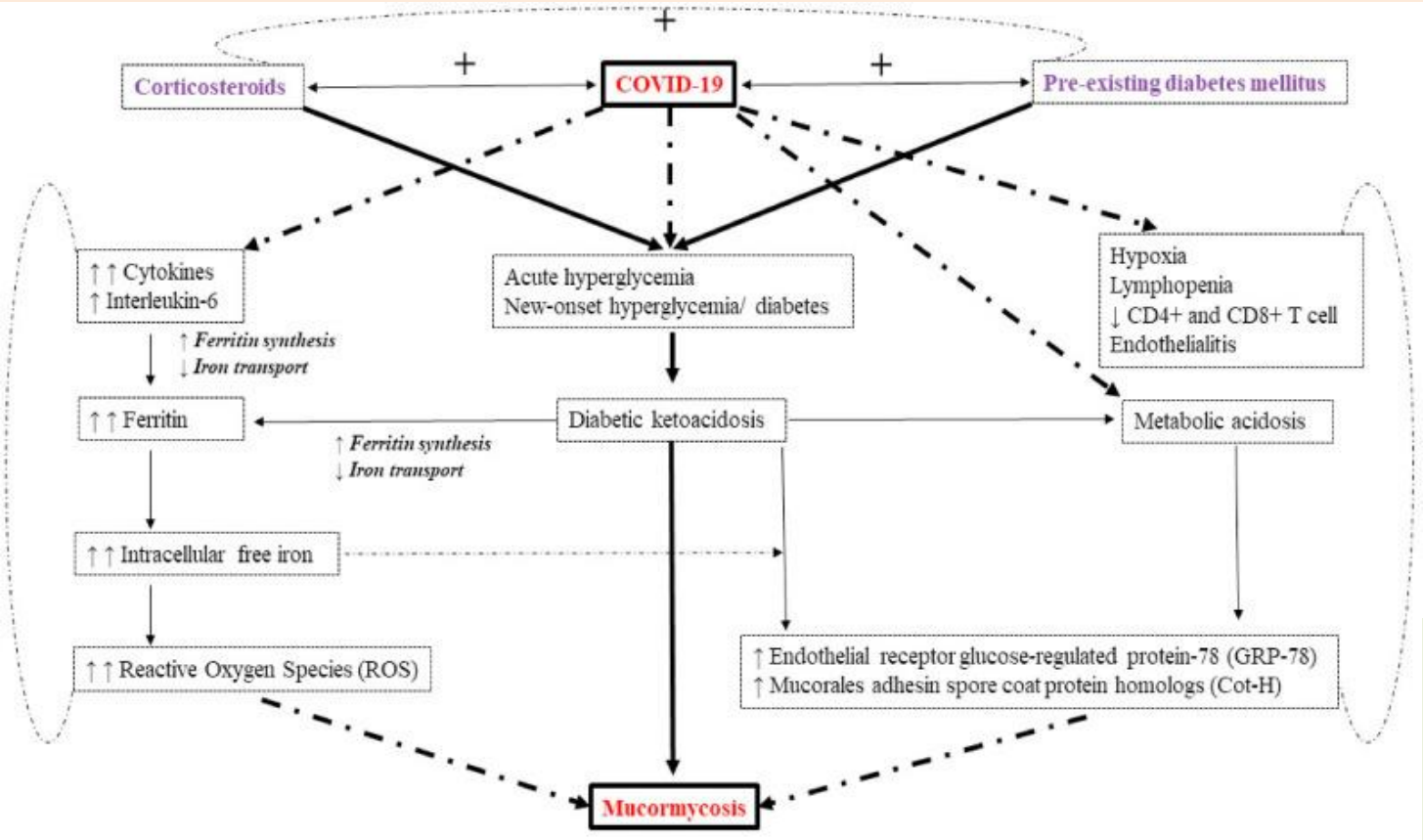
Lancet Microbe 2022 Published Online January 25, 2022 https://doi.org/10.1016/ S2666-5247(21)00237-8

Table 1. Baseline characteristics among patients with mucormycosis, with and without COVID-19, India*

Variables	CAM, n = 187	Non-CAM, n = 100	p value
Mean age, y (SD)	56.9 (12.5)	46.9 (16.4)	0.0001
Sex			0.003
M	150 (80.2)	64 (64.0)	
F	37 (19.8)	36 (36.0)	
Underlying disease			0.0001
None	0	19 (19.0)	
COVID-19 only	61 (32.6)	0	
Glucocorticoids for COVID-19	48/61 (78.7)	NA	
Diabetes mellitus	113 (60.4)	67 (67.0)	
Traumatic inoculation (dental s		0)	
Hematological malignancy		)	
Renal transplantation			
Other†		)	
Glucocorticoids	146 (78.1)	6 (6.0)	0.0001
Site of involvement			
Rhino-orbital	117 (62.6)	50 (50.0)	0.07
Rhino-orbito-cerebral	44 (23.5)	34 (34.0)	0.07
Pulmonary	16 (8.6)	6 (6.0)	0.42
Renal	1 (0.5)	1 (1.0)	0.66
Other (e.g., cutaneous, stomach)	5 (2.7)	9 (9.0)	0.03
Disseminated	4 (2.1)	0	0.41
Sequential	79 (42.5)	11 (11.0)	
Combined medical and surgical therapy	131 (70.1)	73 (73.0)	0.60
Outcome			
Death ≤6 weeks	70 (37.4)	40 (40.0)	0.67
Death ≤12 weeks (n = 256)	75/170 (44.1)	42/86 (48.8)	0.51

Emerging Infectious Diseases • www.cdc.gov/eid •
Vol. 27, No. 9,, September 2021

Pathogenesis

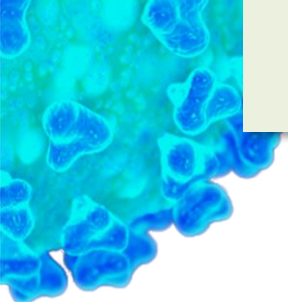


Singh AK, Singh R, Joshi SR, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. *Diabetes Metab Syndr*. 2021;15(4):102146. doi:10.1016/j.dsx.2021.05.019

Pathogenesis

- Mean spore counts are high in outdoor air in the hospital environment, new construction activities in the hospital setting can make the fungal spores airborne
- *Rhizopus arrhizus* is the most common, followed by *Mucor, Rhizomucor, Lichtheimia, Apophysomyces, Saksenaea, Cunninghamella*, and other species
- ACE2 protein allows entry of SARS-CoV-2 into pancreatic islet cells and may injure the beta cells causing diabetes
- *Rhizopus spp* interacts with GRP78 on nasal epithelial cells via CotH3 to invade and damage the nasal epithelial cells and this expression of GRP78 and CotH3 is significantly enhanced by high glucose, iron, and ketones (the hallmark of DKA)
- Hyperferritinemia, occurs in COVID-19. In DKA, acidosis temporarily dislocates iron bound to transferrin and b-hydroxybutyrate, indirectly compromises the ability of transferrin to chelate iron. This increased iron can permit the growth of *R.arrhizus*
- Endothelial dysfunction, zinc deficiency and steroids contribute

AMSP considerations in COVID



- Avoid antifungal prophylaxis
- COVID associated pulmonary aspergillosis and COVID associated mucormycosis need appropriate diagnostic tests for confirmation
- CMV activation rare, confirm diagnosis before starting antivirals
- Altered PK-PD in COVID; risk for underdosing and overdosing

Int. J. Antimicrob. Agents 2021, 58, 106409

Case history

- A 61 y old lady diabetic, hypertensive for 30 yrs, Hypothyroid with CKD since 2018 presented to a local hospital with

  Fever on and off x 7days

  Altered sensorium on and off x 6 days

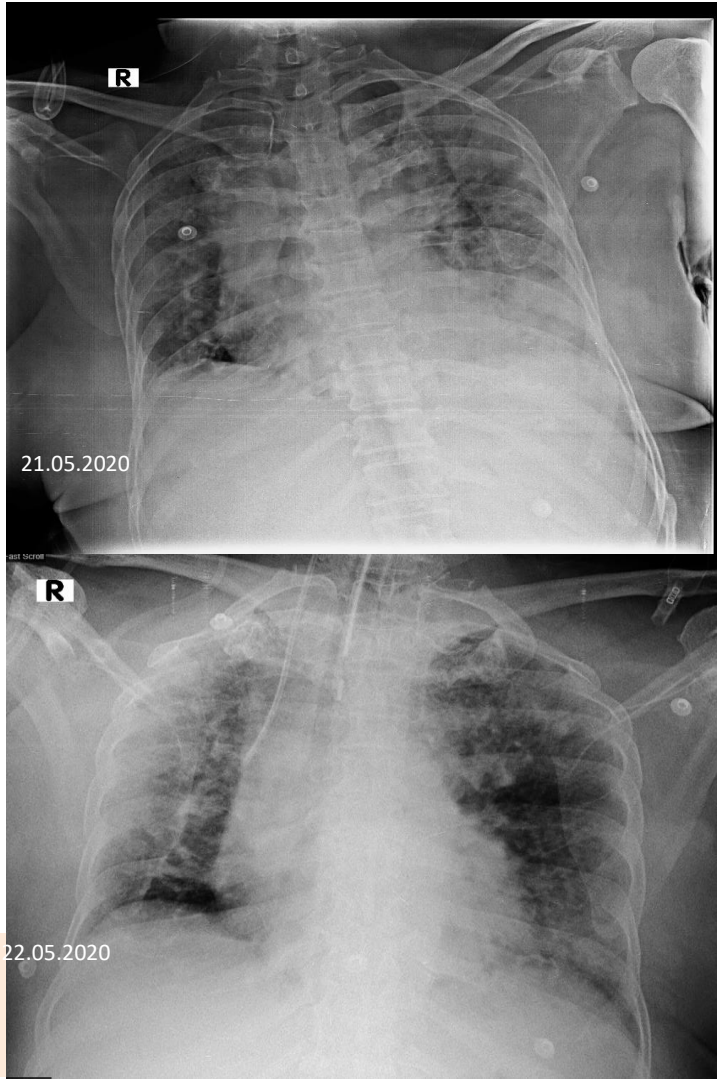
  Loose stools for 2 days and Shortness of breath x 1 day

- Past medical h/o: Buttock abscess under review in surgery.
- O/E : SpO2 45% which improved to 97% on 15L O_2, GCS 14/15, HR= 108/min, RR 45/min, Temp 98°F, BP 90/50 which later improved to 120/70,

  - She had cold peripheries, was dehydrated, had pedal edema and her JVP was not elevated

- RS: B/L basal crepitations
- CVS, CNS and Abdomen were within normal limits

TEST	REPORT
HB:11.3, WBC:15500, Plt:342000,RBC:3.97, Cr.1.73	
Urine analysis:RBC:46/ hpf. WBC:73/hpf,EC:4-5/ hpf	
Qualitative PCR for SARS COV-2 Swab	Positive
C/S blood	No growth
WBC	25400
Trop T	88.2pg/ml
CKMB mass	9.0ng/ml
TSH	1.660
Procalcitonin	0.049ng/mL



She was prescribed with Inj. Meropenem 1gm q8h and Inj.Azithromycin 500 od + Tab. HCQ 200mg

Questions to panelists

- Do you think if the patient has bacterial infection that warrants antibiotics?
- Could a biomarker based antimicrobial strategy be implemented here?
- How can you confirm bacterial vs viral co-infection in a patient with COVID-19?
- What would be the stewardship opportunities here?

AMSP IN COVID-19

- Avoid antibiotics in COVID-19 infection unless critically ill (septic shock)
- For both CAP or HAP which may occur as co-infections or superinfections, use narrow spectrum antibiotics as far as possible empirically
- Use local antibiograms to choose or modify initial appropriate antibiotic therapy
- **Antimicrobial stewardship programs (ASPs) should be included in disaster planning or emergency response preparedness efforts**

Mild COVID-19

- Antibiotics should be avoided.

Moderate COVID-19

- Antibiotics should not be used if there is no evidence of bacterial pneumonia.
- Standard empiric community acquired pneumonia coverage per local guidelines typically adequate if patients do not have risk factors for *Pseudomonas aeruginosa* or MRSA.

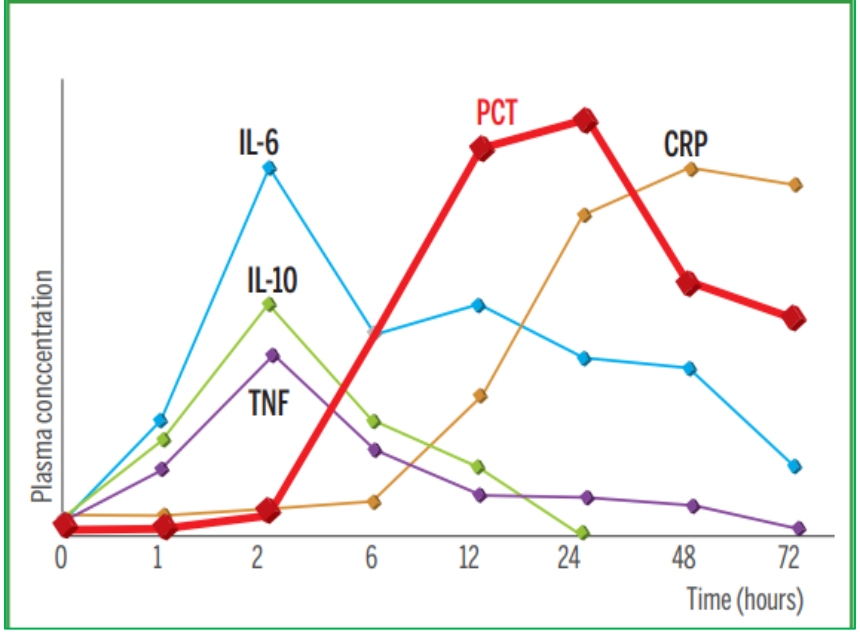
Severe COVID-19

- Antibiotics can be considered as part of standard empiric sepsis coverage if shock is present.

PROCALCITONIN BASED AMSP for diagnosis and guidance of antibiotic therapy

- Diagnostic tools and biomarkers which assess a patient's risk of having an infection, and their response to antibiotic therapy are useful
- Procalcitonin (PCT), increasingly used in AMSP
- During bacterial infections, PCT blood levels rise within 4-6 hours. Its kinetics then mirror the severity of infection. PCT levels drop by about 50% daily when infection is controlled and responds adequately to antibiotics

Figure 1: Kinetic profiles of different biomarkers of bacterial infection.
Adapted from Meisner M. Procalcitonin: Experience with a new diagnostic tool for bacterial infection and systemic inflammation. J Lab Med 1999;23:263-72 [1].



Utility of Procalcitonin

- Based on this regulation and kinetics, many studies have documented the clinical utility of PCT for different clinical settings and infections.
  - PCT may differentiate between bacterial and viral infections
  - PCT can aid in decision-making on antibiotic discontinuation for patients with suspected or confirmed sepsis
  - PCT used to monitor therapy for respiratory infections has led to a more tailored use of antibiotics with a reduction in antibiotic exposure. lower risk of antibiotic-associated side effects, shorter length of hospital stays, and lower overall costs due to antibiotic savings

1.Uzzan B, Cohen R, Nicolas P, et al. Procalcitonin as a diagnostic test for sepsis in critically ill adults and after surgery or trauma: a systematic review and meta-analysis. Critical Care Medicine 2006, 34(7):1996-2003.

2.Schuetz P, Briel M, Christ-Crain M, et al. Procalcitonin to Guide Initiation and Duration of Antibiotic Treatment in Acute Respiratory Infections: An Individual Patient Data Meta-Analysis. Clin Infect Dis 2012;55(5):651-623.

3.De Jong A, van Oers JA, Beishuizen A, et al. Efficacy and safety of procalcitonin guidance in reducing the duration of antibiotic treatment in critically ill patients: a randomised, controlled, open-label trial. The Lancet Infectious Diseases. Published online 29 February 2016. doi.org/10.1016/S1473-3099(16)00053-0

Figure 10: Protocol for procalcitonin (PCT)-guided antibiotic therapy in patients with suspected or confirmed LRTI.
Adapted from Albrich WC, et al. Arch Intern Med. 2012;172(9):715-722 [69].

PCT result (ng/mL)	<0.10	0.10 - 0.25	0.26 - 0.50	>0.50
Recommendation regarding use of Abx	STRONGLY DISCOURAGED	DISCOURAGED	RECOMMENDED	STRONGLY RECOMMENDED

FOLLOW-UP IF NO ANTIBIOTIC THERAPY IS INITIATED:

- Repeat PCT measurement within 6-24 h (also in outpatients if symptoms persist/worsen)
- Differential diagnosis? e.g, pulmonary embolism, congestive heart failure, tumor, BOOP, viral, fungal

Antibiotic therapy can be considered for:

1. **Admission to the ICU or IMC**: (a) respiratory instability (respiratory rate ≥30/min or O2 saturation <90% with 6 L O2/min); (b) hemodynamic instability (systolic blood pressure for at least 1 h <90 mm Hg, despite adequate volume replacement or need for vasopressors)
2. **Life-threatening comorbidity**: (a) imminent death; (b) severe immunosuppression (neutrophils <500/µL; for HIV: CD4 <350/µL); (c) chronic infection or other non-respiratory infection requiring antibiotics (eg, endocarditis, TB)
3. **Complications and difficult-to-treat-organisms**: Legionella (antibiotics ≥10 d), abscess, empyema
4. **(a) PCT <0.10 ng/L**: CAP PSI V (>130) or CURB-65 >3 points, COPD GOLD IV;
   (b) PCT 0.10-0.25 ng/L: CAP PSI IV and V (>90), CURB-65 >2, COPD GOLD stages III and IV, SaO2 <90% despite 30 minutes of intensive oxygen therapy.

Falsely low PCT: eg, parapneumonic effusion, loculated infection (empyema), early phase of infection, fungal, most severe immunosuppression

FOLLOW-UP IF ANTIBIOTIC THERAPY IS INITIATED:

Follow-up if antibiotic therapy is initiated:

- **Check PCT on control days 2-3, 4-5, 6-8, and every 2 days after day 8 for guidance of antibiotic therapy**
- **To stop ongoing antibiotic therapy, use the same cutoff values as above**
- **For outpatients, duration of antibiotic therapy depends on last PCT value**: (≥0.25 ng/mL 3 d, ≥0.50 ng/mL 5 d, ≥1.0 ng/mL 7 d)
- **For initially very high PCT (e.g. >5 ng/mL), follow the relative decline of PCT if patients show clinical improvement** :
  - Decline ≥80% of peak: stop recommended
  - Decline ≥90% of peak: stop strongly recommended
- **Persistently elevated PCT**: suspect complicated course (resistant organism, MOF, abscess...)
- **Falsely elevated PCT**: eg, severe SIRS and shock, ARDS, trauma, postoperative, tumor (eg, medullary thyroid cancer, SCLC), fungal, malaria

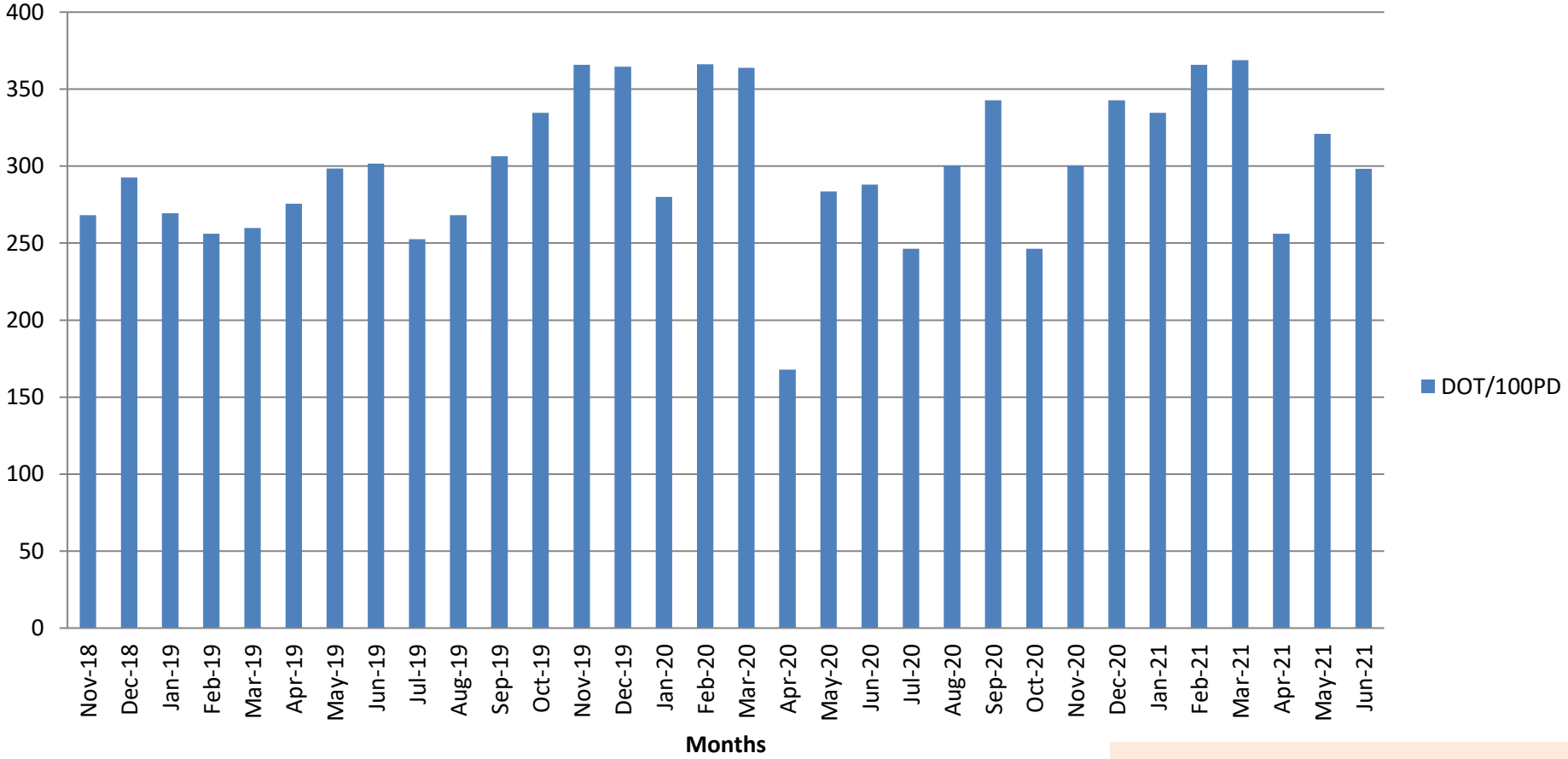
ARDS, acute respiratory distress syndrome; BOOP, bronchiolitis obliterans with organizing pneumonia; CAP, community-acquired pneumonia; COPD GOLD, chronic obstructive pulmonary disease Global Initiative for Chronic Obstructive Lung Disease; CURB-65, confusion, serum urea nitrogen, respiratory rate, blood pressure, and age 65 years or older; HIV, human immunodeficiency virus; ICU, intensive care unit; IMC, intermediate care unit; MOF, multiple organ failure; PSI, Pneumonia Severity Index; SCLC, small-cell lung cancer; SIRS, sepsis inflamma

Booklet_procalcitonin-educational-booklet-offered-by-biomerieux.pdf

Challenges and Innovations in AMSP

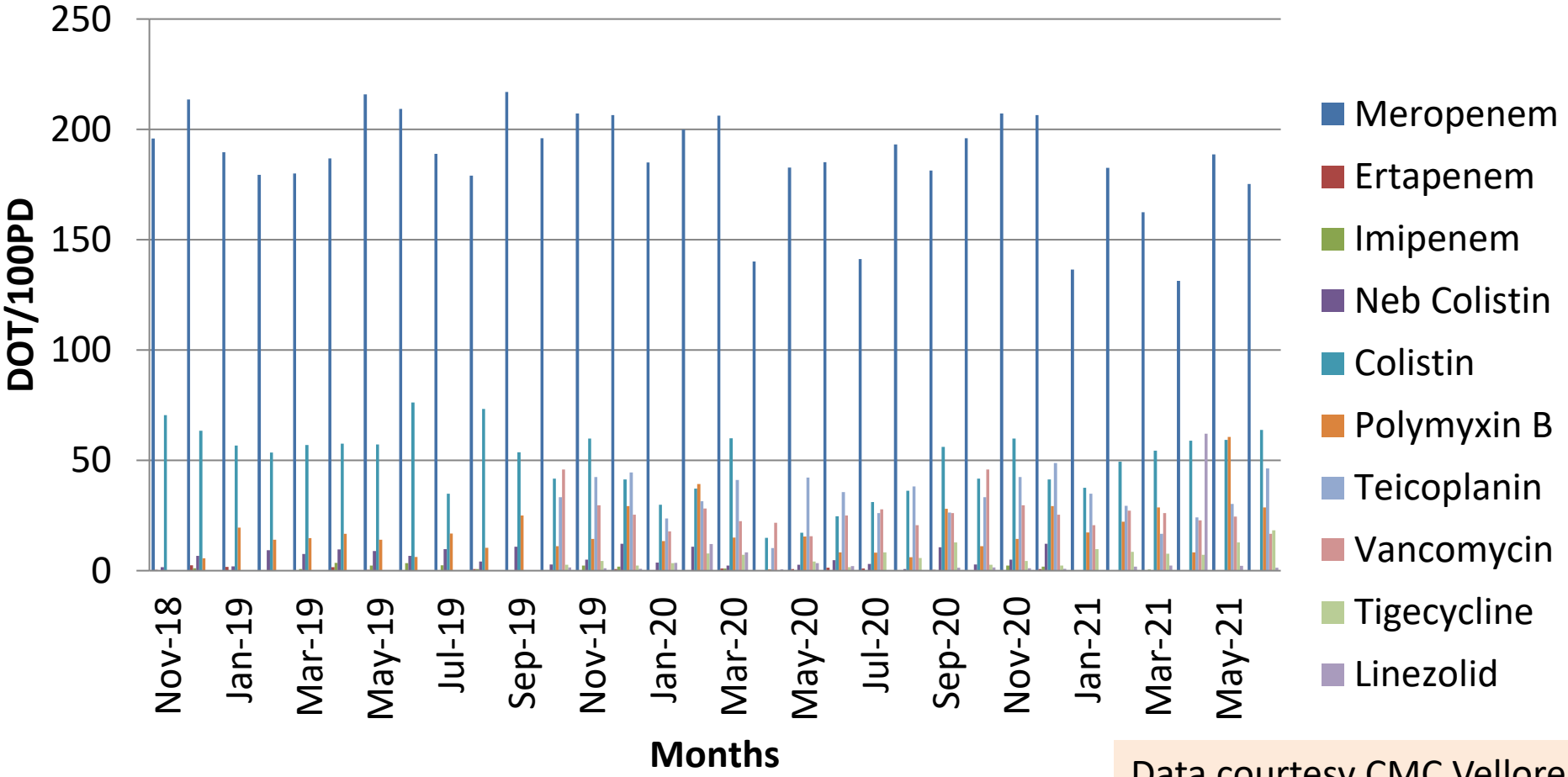
CHALLENGE	INTERVENTION
Antimicrobial use: Reduced compliance to guidelines, use of restricted antimicrobials, broad spectrum agents, multiple agents, increased duration and difficulty in de-escalation	Review of antiviral and antimicrobial therapy in COVID-19 pathway Pre-authorization and restricted use Follow up AMS review of COVID negative Biomarker based surveillance
Decreased surveillance of MDROs	Use EMR for surveillance
Difficulty in diagnosis of co-infections	Procalcitonin and urinary antigens
Antimicrobial shortages	Updated guidelines according to availability and access
Face to face meetings not possible	Electronic media and resources

Antibiotic use before and during covid-19 pandemic



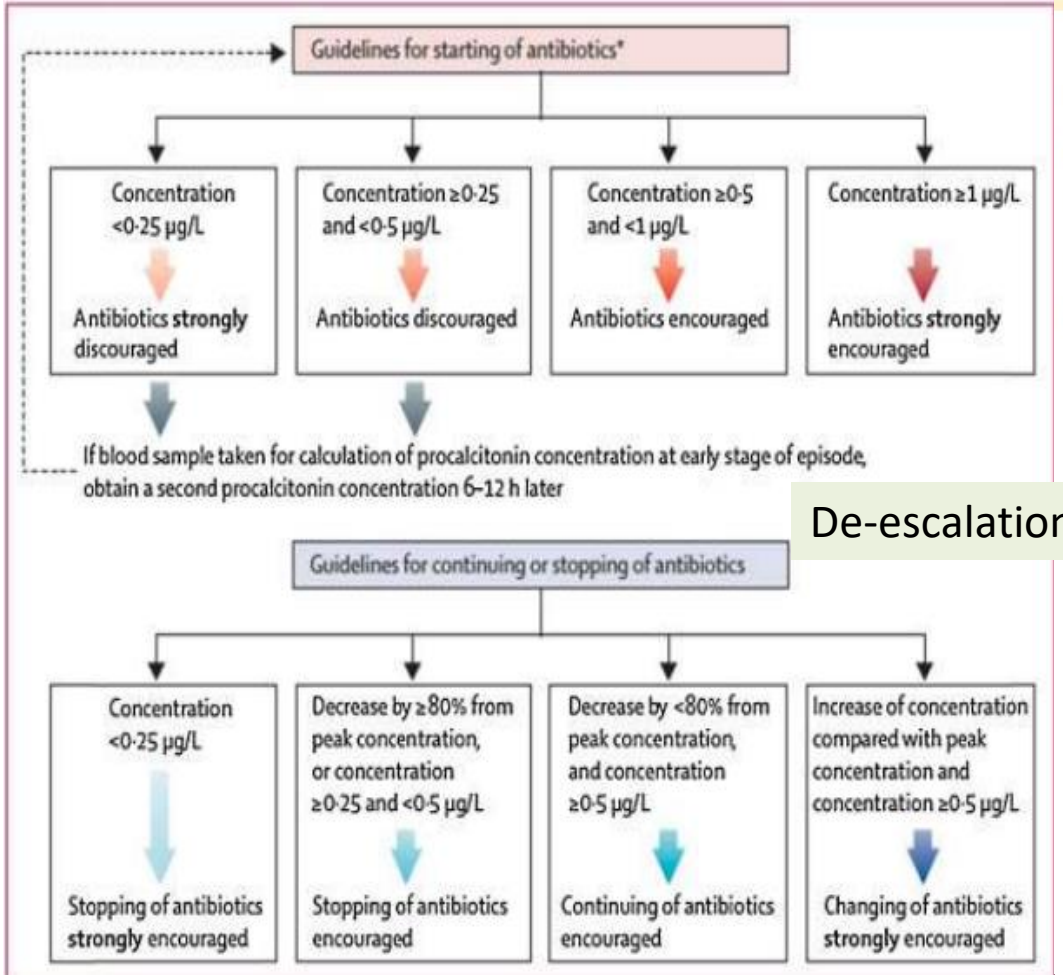
Data courtesy CMC Vellore

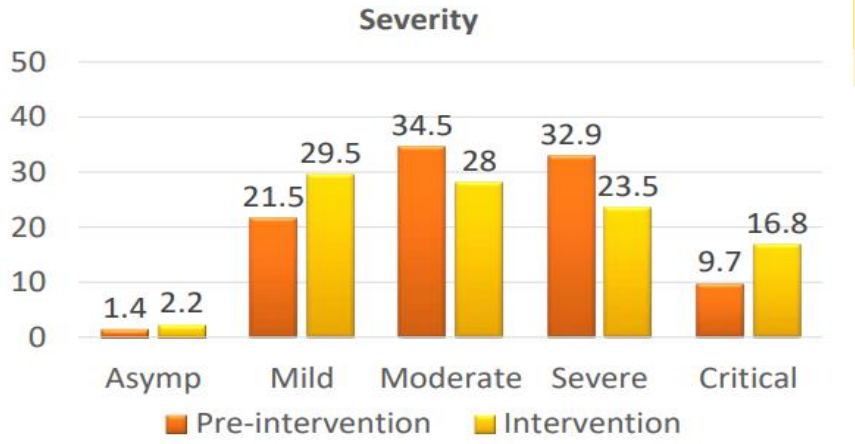
Antibiotic use before and during covid-19 pandemic



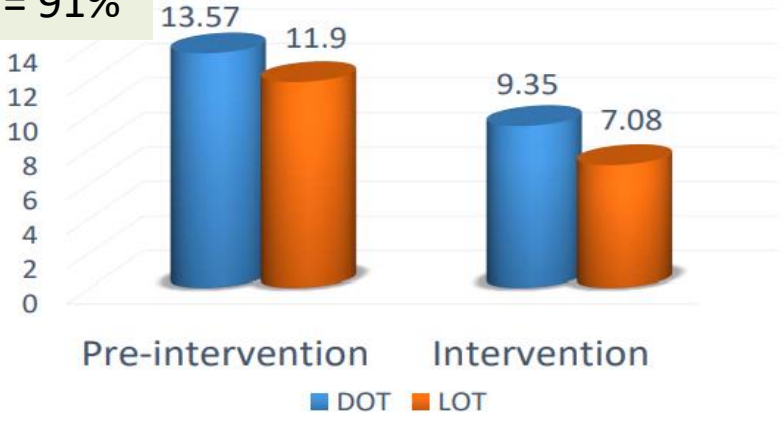
Data courtesy CMC Vellore

Development & Implementation of a Biomarker-based Remotely-delivered Antimicrobial Stewardship (AMS) Strategy during the COVID-19 Pandemic

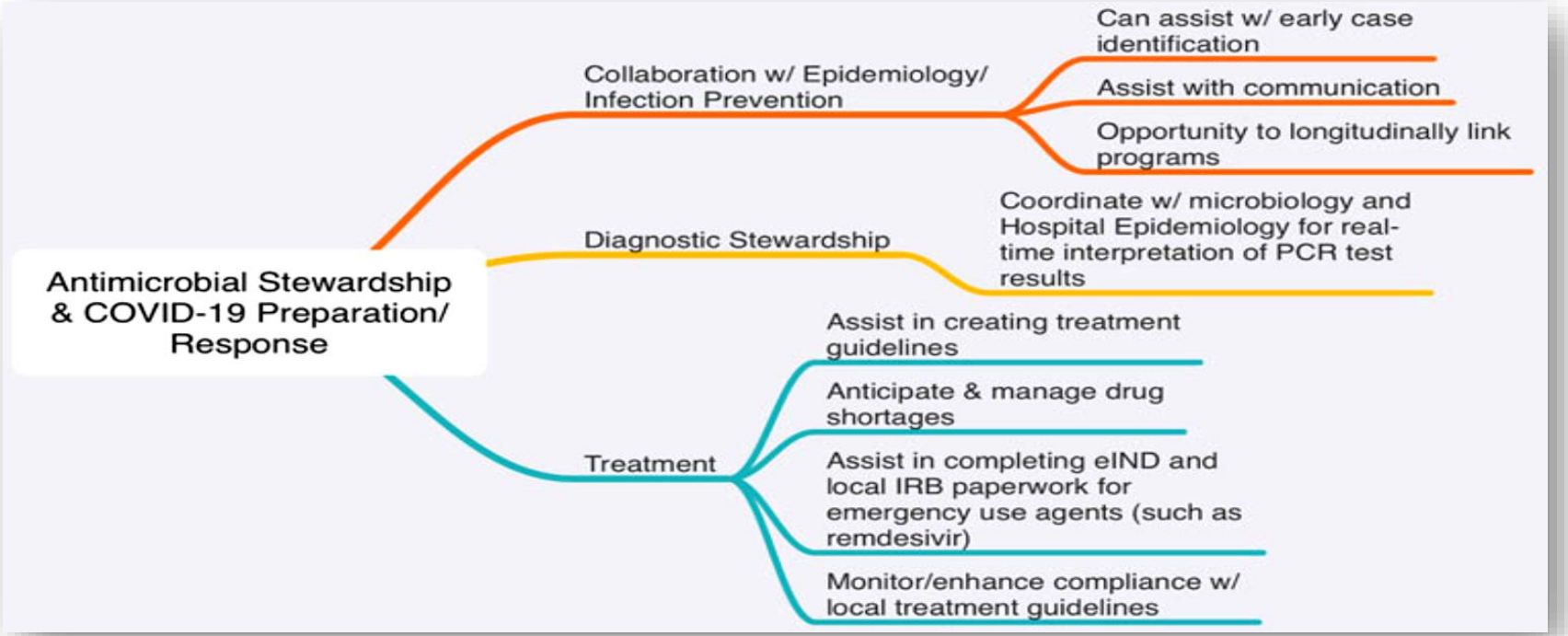




De-escalation = 91%



Opportunities for antimicrobial stewardship programs to assist COVID-19 response preparation and planning efforts



Stevens MP, Patel PK, Nori P. Involving antimicrobial stewardship programs in COVID-19 response efforts: All hands on deck. Infect Control Hosp Epidemiol. :1–2.

Summary

- COVID-19 had a collateral effect on antimicrobial resistance due to injudicious use of antibiotics
- Co-infections and Secondary infections though treated empirically were <5% and 20% respectively
- The unnecessary use of antibiotics is a prime driver of antimicrobial resistance, a global public health crisis.
- Optimizing antibiotic stewardship during COVID-19 will likely require a combination of traditional stewardship approaches and effective implementation of host-response biomarkers and rapid COVID-19 diagnostics

A schema of community engagement in AMSP

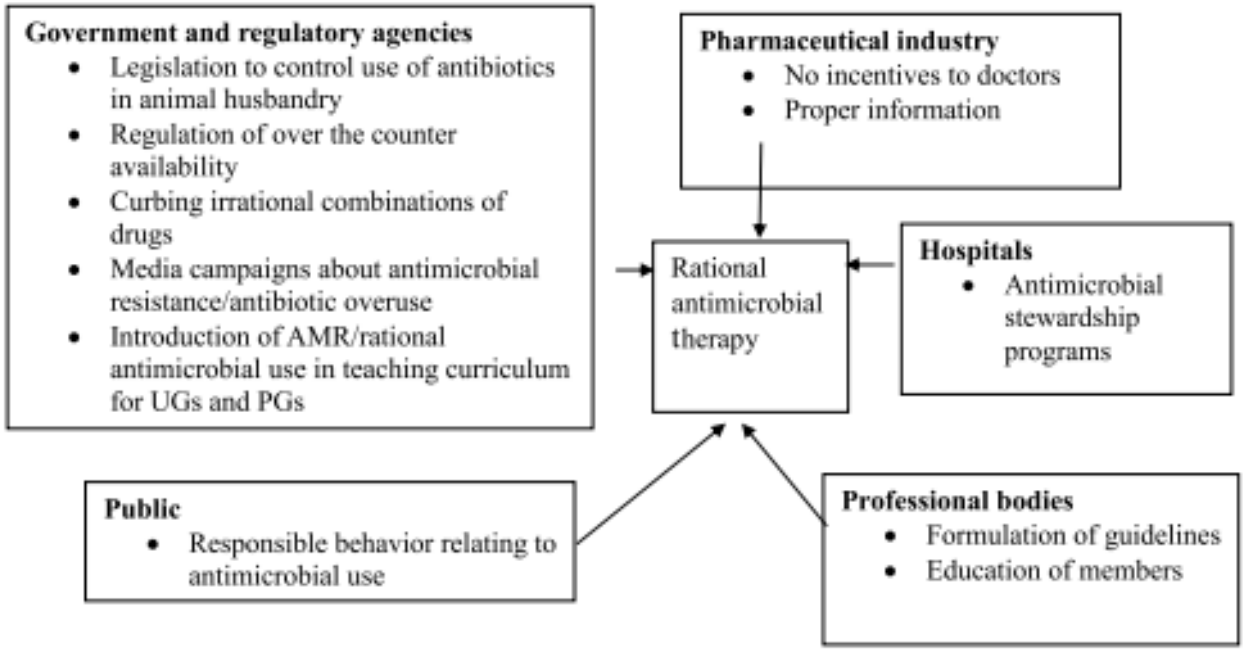


Fig. 2 Schematic representation of some interventions to promote rational antimicrobial therapy