Tocilizumab:
Trials, Tribulations, and Timely Treatment

Drugs & Biologics Clinical Practice Guidelines Working Group
Ontario COVID-19 Science Advisory Table

April 26, 2021

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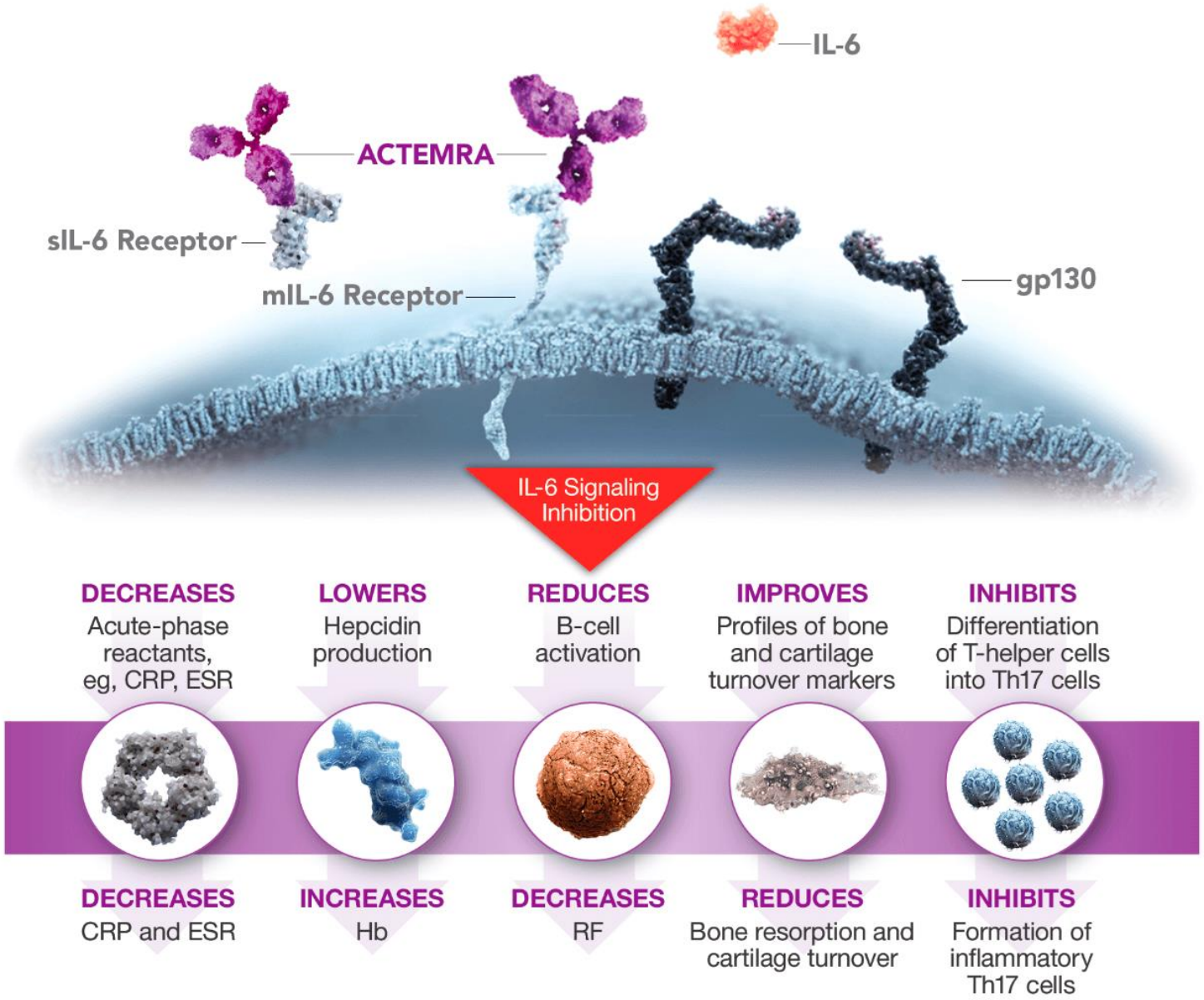
SCIENCE TABLE
COVID-19 ADVISORY FOR ONTARIO

Learning Objectives

- Summarize the data on the use of tocilizumab in patients with COVID-19
- Describe the recommended populations to receive tocilizumab
- Provide advice and considerations regarding secondary infections
- Discuss access and use of tocilizumab in the context of drug shortage

Introduction to Tocilizumab

- **Mechanism of action:**
  - Recombinant humanized interleukin-6 (IL-6) receptor antagonist
- **Indications prior to COVID-19:**
  - Adult patients with moderate to severe active rheumatoid arthritis (RA)
  - Polyarticular or systemic juvenile idiopathic arthritis
  - Giant cell arteritis
  - Diffuse large B cell lymphoma and ALL patients with CAR-T (chimeric antigen receptor T cell) induced cytokine release syndrome (CRS)



https://www.actemrahcp.com/about.html

Hypothesis for Effectiveness in COVID-19:

- Increased levels of inflammatory markers including IL-1, IL-6, TNF-alpha, D-dimers, ferritin, and CRP
- Inflammatory response results in lung injury including diffuse alveolar inflammation, neutrophilic infiltrates, and microvascular thrombosis.
- Beneficial effects of dexamethasone in COVID-19 patients with hypoxic respiratory failure suggested that additional benefit may be achieved through inhibition of more specific immunomodulatory targets such as IL-6.

Summary of RCT Evidence

Trial	They included…	Tocilizumab compared to…
CORIMUNO-19 (Hermine et al. 131 patients, 1:1 randomization)	Moderate to severe COVID On oxygen, but no IMV	standard of care
RCT-TCZ-COVID-19 (Salvarani et al. 126 patients, 1:1 randomization	Moderate to severe COVID On oxygen, but no IMV	standard of care
BACC Bay Tocilizumab Trial (Stone et al. 243 patients, 2:1 randomization)	Moderate to severe COVID On oxygen, but no IMV	placebo
COVACTA (Rosas et al. 452 patients, 2:1 randomization)	Moderate to severe COVID On oxygen, including IMV	placebo
EMPACTA (Salama et al. 389 patients, 2:1 randomization)	Moderate to severe COVID On oxygen, but no IMV	placebo
TOCIBRAS (Veigas et al. 129 patients, 1:1 randomization)	Moderate to severe COVID On oxygen, including IMV	standard of care
Wang et al. 65 patients, 1:1 randomization	Moderate to severe COVID On oxygen, including IMV	standard of care
REMAP-CAP (Gordon et al. 353 tocilizumab, 48 to sarilumab, 1:1 randomization)	**Severe COVID On oxygen, including IMV**	**standard of care**
RECOVERY (Horby and Landray et al, 4116 patients, 1:1 randomization)	**Moderate to severe COVID On oxygen, including IMV**	**standard of care**

REMAP-CAP

- Randomized, multicentred, multiplatform, adaptive trial
- 113 sites, 6 countries (UK, Netherlands, Ireland, Australia, NZ, Saudi Arabia)
- Patients enrolled between April 2020 – Nov 2020
- **Patients**: Adults in ICU with COVID-19 (proven or suspected) within 24 hours of starting respiratory/CV support
  - Invasive or non-invasive mechanical ventilation including via high-flow nasal cannula if flow > 30 L/min and FiO_2 > 0.4
  - Vasopressor or inotrope
- **Intervention:** Tocilizumab (8 mg/kg, max 800 mg), sarilumab (400 mg), vs. standard of care (control)
  - Tocilizumab could be repeated 12-24 hours post first dose

REMAP-CAP - Outcomes

- **Primary:** Respiratory and CV organ support-free days up to day 21
  - Composite ordinal outcome
  - All deaths are assigned the worst outcome (-1)
  - Among survivors, respiratory and CV organ support-free days are calculated up to day 21
    Higher number = faster recovery
    - E.g. death at day 18 = -1 days
    - E.g. off organ support at day 15 = 6 days

- **Secondary:**
  - Hospital mortality/survival
  - 90-day survival
  - Time to ICU discharge
  - Time to hospital discharge
  - WHO ordinal scale at day 14 (0 = no illness, 2 = well enough for discharge, 8 = death)
  - Progression to IMV, ECMO or death, in patients not intubated at baseline

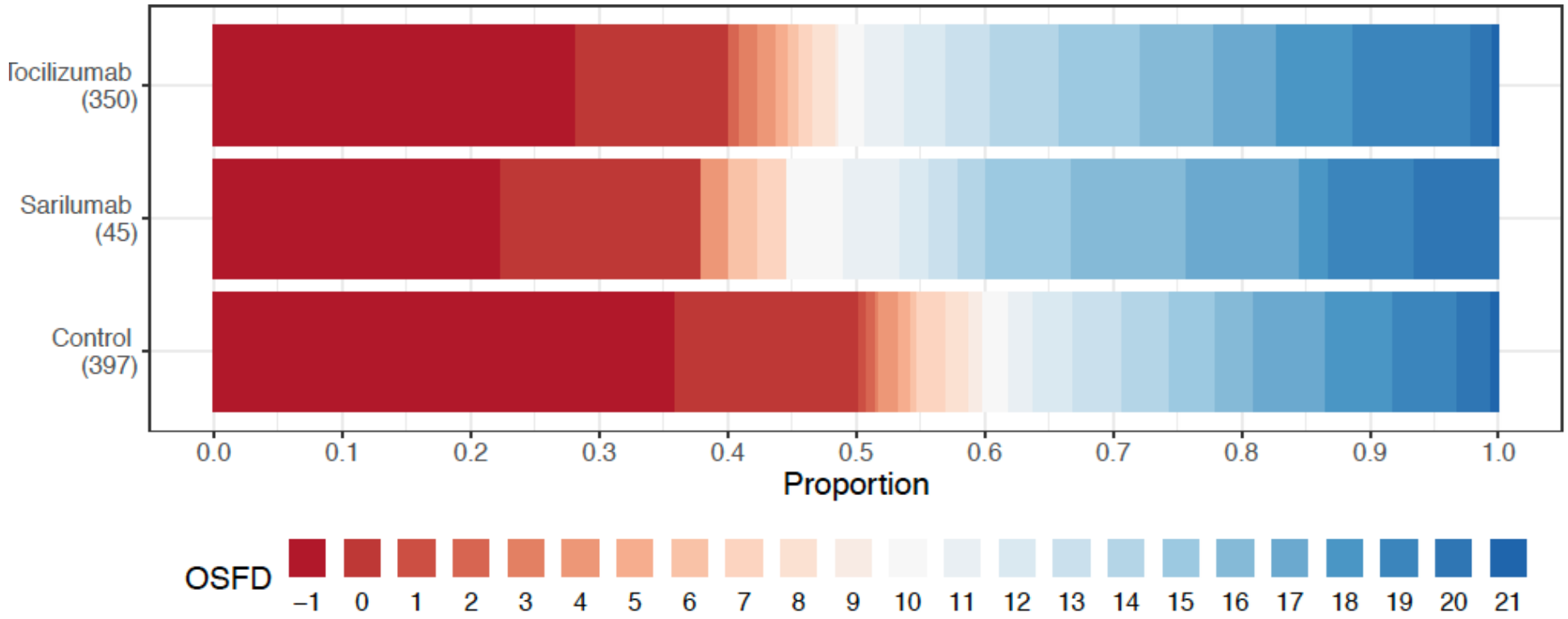
Baseline Characteristics, n=865

Characteristic	Tocilizumab (%)	Control (%)
Age (mean)	61.5	61.1
Gender (male)	73.9	70.4
Race (white)	70.2	73.8
BMI (median)	30.5	30.9
APACHE II score (median)	13	12
Diabetes	35.2	37.4
Kidney Disease	9.6	11.6
Respiratory Disease	23.5	24.4
Severe CV Disease	10.0	11.9
Time to enrollment from hospital admission (days)	1.2	1.2
Time to enrollment from ICU admission (hours)	13.1	14.0
High flow nasal cannula	28.6	27.4
Non-invasive ventilation	41.6	42.0
Invasive mechanical ventilation	29.5	30.1
Vasopressor support	17.9	19.7
PaO_2/FiO_2 (median)	115	118
C-reactive protein (median)	150	130
Corticosteroids at enrollment, or within 48 hours	**88**	

REMAP-CAP – Primary Outcome

Outcome/Analysis	Tocilizumab (N=353)	Sarilumab (N=48)	Control (N=402)
Primary Outcome, Organ support-free days (OSFDs)			
Median (IQR)	10 (-1 to 16)	11 (0 to 16)	0 (-1 to 15)
Adjusted OR - mean (SD)	1.65 (0.23)	1.83 (0.44)	1
- median (95% CrI)	1.64 (1.25 to 2.14)	1.76 (1.17 to 2.91)	1
Probability of superiority to control, %	>99.9	99.5	-
Subcomponents of OSFDs			
In-hospital deaths, n (%)	98/350 (28.0)	10/45 (22.2)	142/397 (35.8)
OSFDs in survivors, median (IQR)	14 (7 to 17)	15 (6.5 to 17)	13 (4 to 17)

REMAP-CAP – Primary Outcome



OSFD: Organ support free days is a composite ordinal outcome, all deaths are assigned the worst outcome (-1). Among survivors, respiratory and CV organ support-free days are calculated up to day 21. A higher number (DARKER BLUE) represents faster recovery

REMAP-CAP – Secondary Outcomes

Other Secondary Outcomes	
90-day Survival (time to event)	
Adjusted HR - mean (SD)	1.60 (0.21)
- median (95% CrI)	1.59 (1.24 to 2.05)
Probability of superiority to control, %	>99.9
Respiratory support-free days	
Adjusted OR - mean (SD)	1.74 (0.25)
- median (95% CrI)	1.73 (1.31 to 2.27)
Probability of superiority to control, %	>99.9
Cardiovascular support-free days	
Adjusted OR - mean (SD)	1.70 (0.26)
- median (95% CrI)	1.68 (1.25 to 2.24)
Probability of superiority to control, %	>99.9
Time to ICU discharge	
Adjusted HR - mean (SD)	1.43 (0.13)
- median (95% CrI)	1.42 (1.18 to 1.70)
Probability of superiority to control, %	>99.9

RECOVERY

- Randomized, multicentred, open label platform trial
- 131 sites in the UK
- Patients enrolled between April 2020 – Jan 2021
- **Inclusion criteria:**
  - Adults hospitalized with COVID-19 and **BOTH**:
    - Systemic inflammation: CRP $\geq$ 75 mg/L
    - Hypoxia: SaO_2 < 92% on room air, or requiring oxygen therapy
- **Exclusion criteria:**
  - Known hypersensitivity to tocilizumab
  - Evidence of active tuberculosis, bacterial, fungal, viral, or other infection
- **Intervention:** Weight-based, dose-banded tocilizumab (400-800 mg) + standard of care, vs. standard of care alone
  - Second dose could be repeated 12-24 hours later if not improvement

RECOVERY - Outcomes

- **Primary:** 28-day mortality

- **Secondary:**
  - Discharge alive from hospital within 28 days
  - Composite of requirement for invasive mechanical ventilation, including ECMO (for patients not requiring at randomization) and death

Baseline Characteristics, n=4116

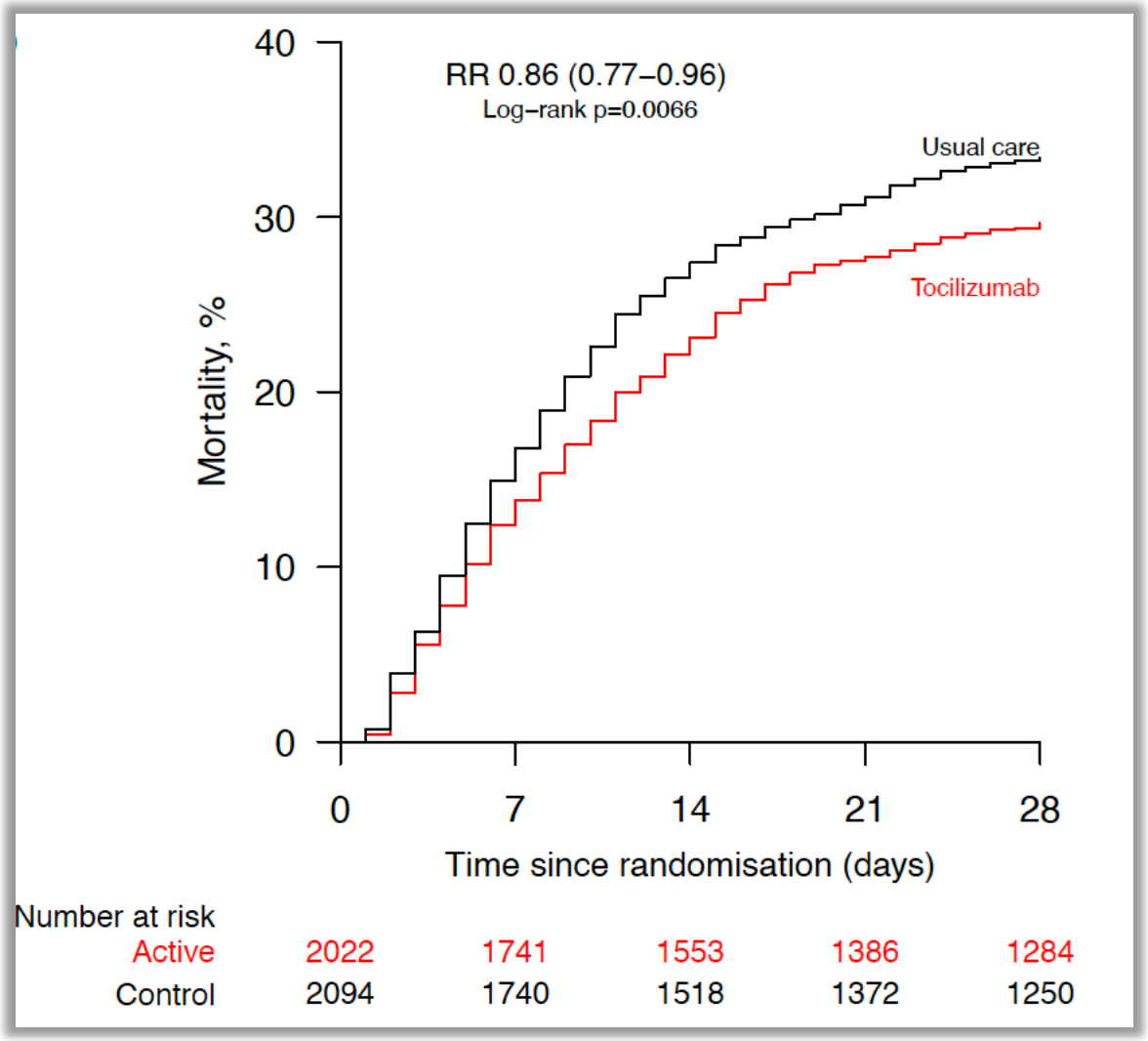
Characteristic	Tocilizumab (%)	Usual Care (%)
Age (mean)	63.3	63.9
Sex (male)	66	69
Race (white)	67	68
Diabetes	28	29
Chronic lung disease	23	23
Heart disease	22	24
# of days since symptom onset	9	10
# of days since hospitalization	2	2
No ventilator	46	45
Non-invasive ventilation	41	41
Invasive mechanical ventilation	13	14
C-reactive protein	143	144
Corticosteroids at enrollment, or within 48 hours	82	82
Remdesivir Treatment	27	29

RECOVERY Results

	Treatment allocation			
	Tocilizumab (n=2022)	Usual care (n=2094)	RR (95% CI)	p value
Primary outcome				
Total: 28-day mortality	596 (29%)	694 (33%)	0.86 (0.77-0.96)	0.0066
Secondary outcomes				
Median time to being discharged alive, days	20	>28		
Discharged alive from hospital within 28 days	1093 (54%)	990 (47%)	1.22 (1.12-1.34)	<0.0001
Receipt of invasive mechanical ventilation or death*	571/1754 (33%)	687/1800 (38%)	0.85 (0.78-0.93)	0.0005
Invasive mechanical ventilation	215/1754 (12%)	273/1800 (15%)	0.81 (0.68-0.95)	0.01
Death	471/1754 (27%)	552/1800 (31%)	0.88 (0.79-0.97)	0.01
Subsidiary clinical outcomes				
Receipt of ventilation†	233/935 (25%)	242/933 (26%)	0.96 (0.82-1.12)	0.61
Non-invasive ventilation	222/935 (24%)	223/933 (24%)	0.99 (0.84-1.17)	0.94
Invasive mechanical ventilation	45/935 (5%)	63/933 (7%)	0.71 (0.49-1.03)	0.07
Successful cessation of invasive mechanical ventilation‡	91/268 (34%)	94/294 (32%)	1.07 (0.80-1.43)	0.64
Use of haemodialysis or haemofiltration§	103/2003 (5%)	142/2075 (7%)	0.75 (0.59-0.96)	0.02

Data are n(%), n/N (%), or median (interquartile range). RR=rate ratio for the outcomes of 28-day mortality, hospital discharge and successful cessation of invasive mechanical ventilation, and risk ratio for other outcomes. * Analyses include only those on no ventilator support or non-invasive ventilation at second randomisation. † Analyses include only those on no ventilator support at second randomisation. ‡ Analyses restricted to those on invasive mechanical ventilation at second randomisation. § Analyses exclude those on haemodialysis or haemofiltration at second randomisation.

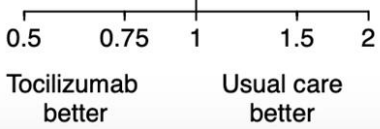
Primary Outcome - 28 Day Mortality



Subgroup Analyses of Primary Outcome

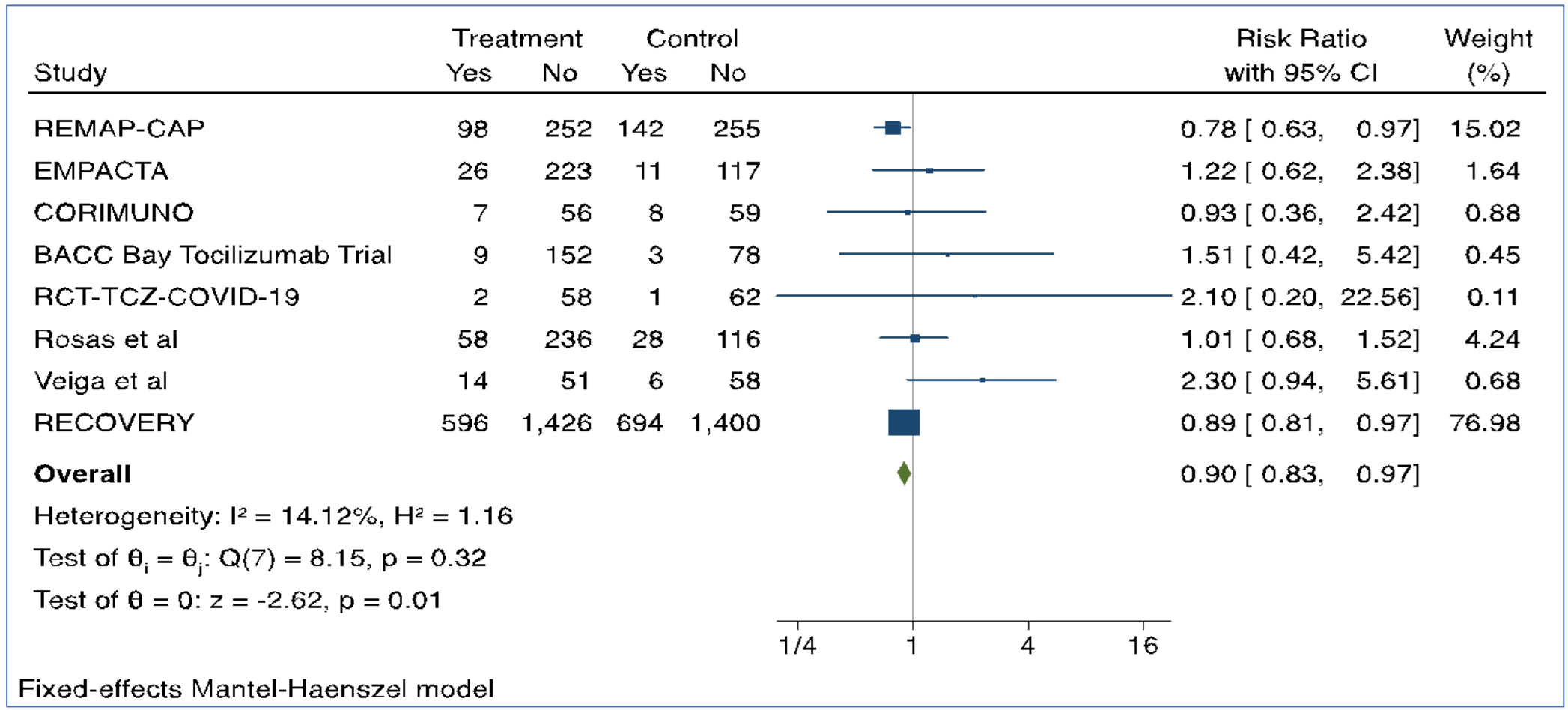
Figure 3: Effect of allocation to tocilizumab on 28–day mortality by baseline characteristics

	Tocilizumab	Usual care	RR (95% CI)
Age, years (χ^2_1=0.1; p=0.80)			
<70	256/1332 (19%)	289/1354 (21%)	0.88 (0.74–1.04)
≥70 <80	206/477 (43%)	234/480 (49%)	0.84 (0.69–1.01)
≥80	134/213 (63%)	171/260 (66%)	0.93 (0.74–1.17)
Sex (χ^2_1=2.2; p=0.14)			
Men	400/1335 (30%)	504/1437 (35%)	0.81 (0.71–0.93)
Women	196/687 (29%)	190/657 (29%)	0.98 (0.80–1.20)
Ethnicity (χ^2_1=0.3; p=0.56)			
White	429/1356 (32%)	519/1426 (36%)	0.83 (0.73–0.95)
Black, Asian, or Minority Ethnic	98/341 (29%)	110/357 (31%)	0.91 (0.69–1.20)
Unknown	69/325 (21%)	65/311 (21%)	1.00 (0.71–1.41)
Days since symptom onset (χ^2_1=0.6; p=0.46)			
≤7	210/668 (31%)	245/660 (37%)	0.81 (0.67–0.97)
>7	386/1354 (29%)	449/1433 (31%)	0.88 (0.77–1.01)
Respiratory support at randomization (χ^2_1=0.4; p=0.52)			
No ventilator support*	175/935 (19%)	202/933 (22%)	0.84 (0.69–1.03)
Non–invasive ventilation†	296/819 (36%)	350/867 (40%)	0.86 (0.74–1.01)
Invasive mechanical ventilation‡	125/268 (47%)	142/294 (48%)	0.94 (0.73–1.19)
Use of corticosteroids$ (χ^2_1=7.1; p=0.01)			
Yes	457/1664 (27%)	565/1721 (33%)	0.80 (0.70–0.90)
No	139/357 (39%)	127/367 (35%)	1.16 (0.91–1.48)
Unknown	0/1 (0%)	2/6 (33%)	
All participants	**596/2022 (29%)**	**694/2094 (33%)**	**0.86 (0.77–0.96) p=0.0066**

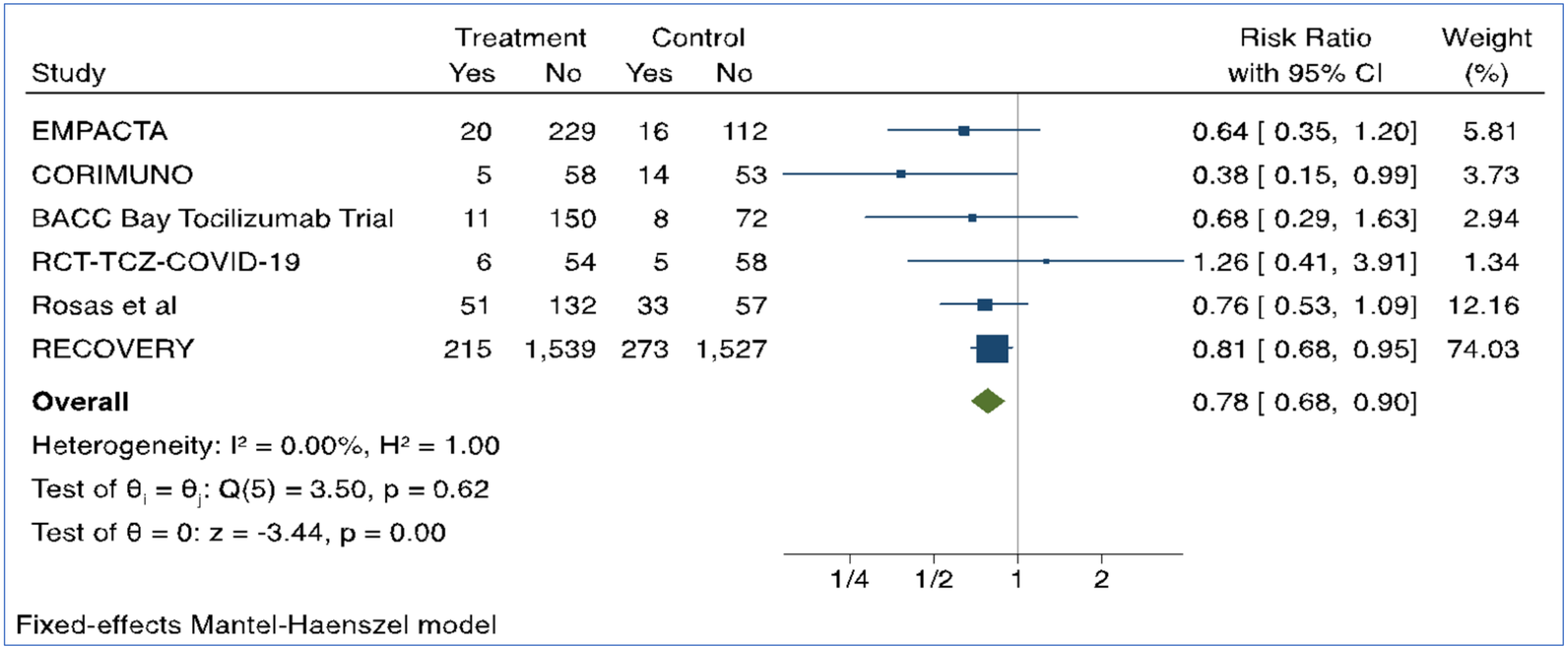


Tocilizumab: Placing Research into Context

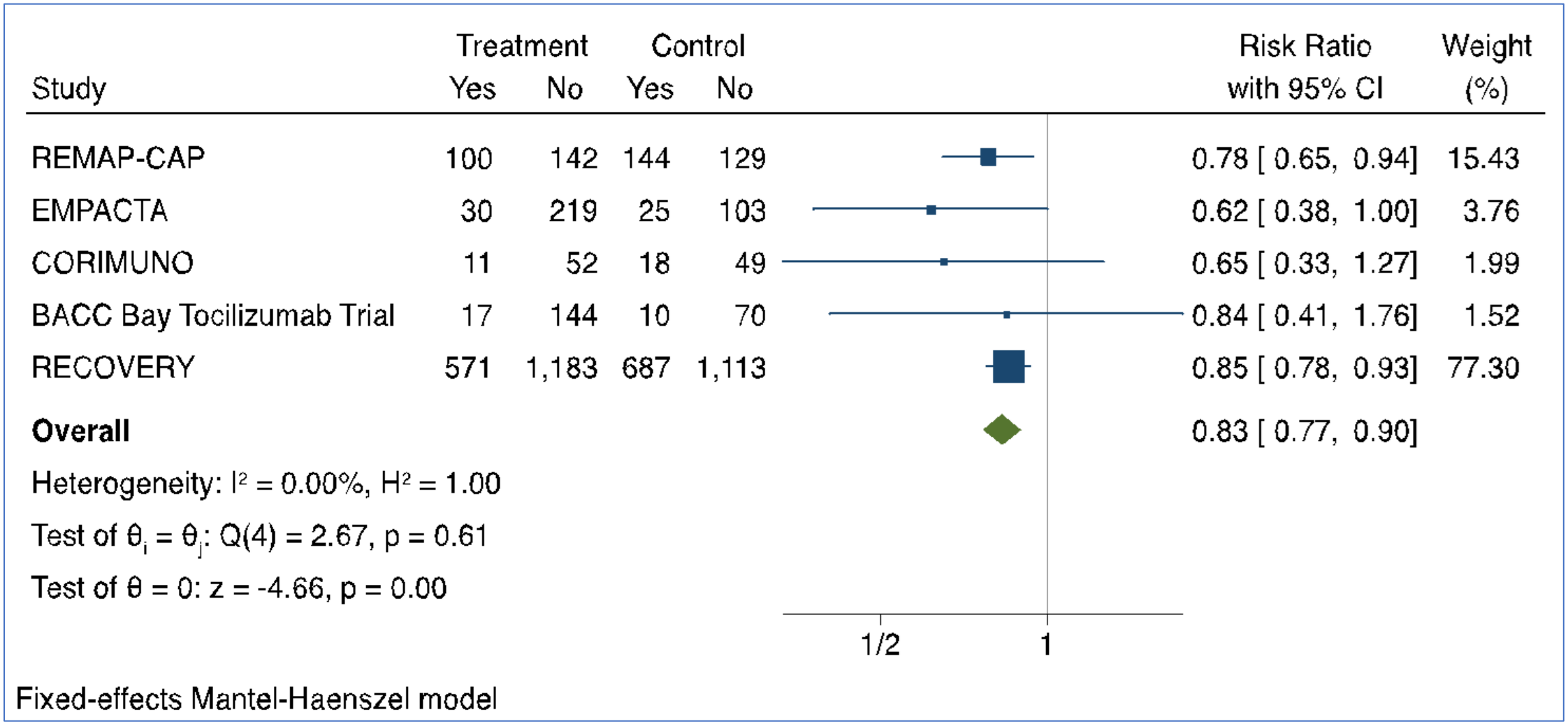
Reduced Overall Mortality



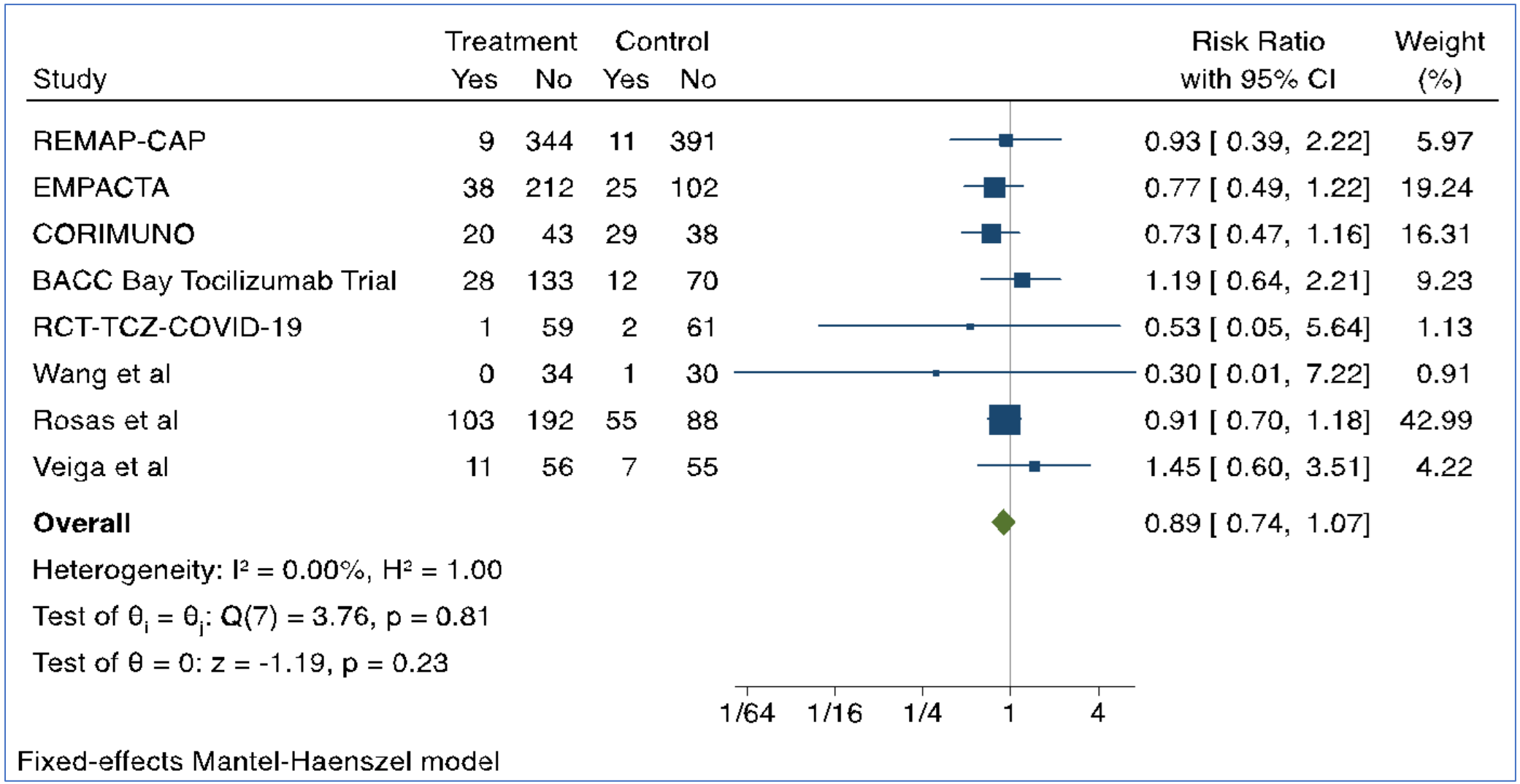
Reduced Need for Mechanical Ventilation



Reduction in Composite of Death or Mechanical Ventilation



No Increase in Severe Adverse Events



Interleukin-6 Blockade in Patients with COVID-19: Placing Research into Context

Federico Angriman,MD
Sunnybrook HSC

Bruno Ferreyro, MD
Sinai Health/UHN

Lorenzo Del Sorbo, MD
UHN

In Press Lancet Respiratory Medicine 2021

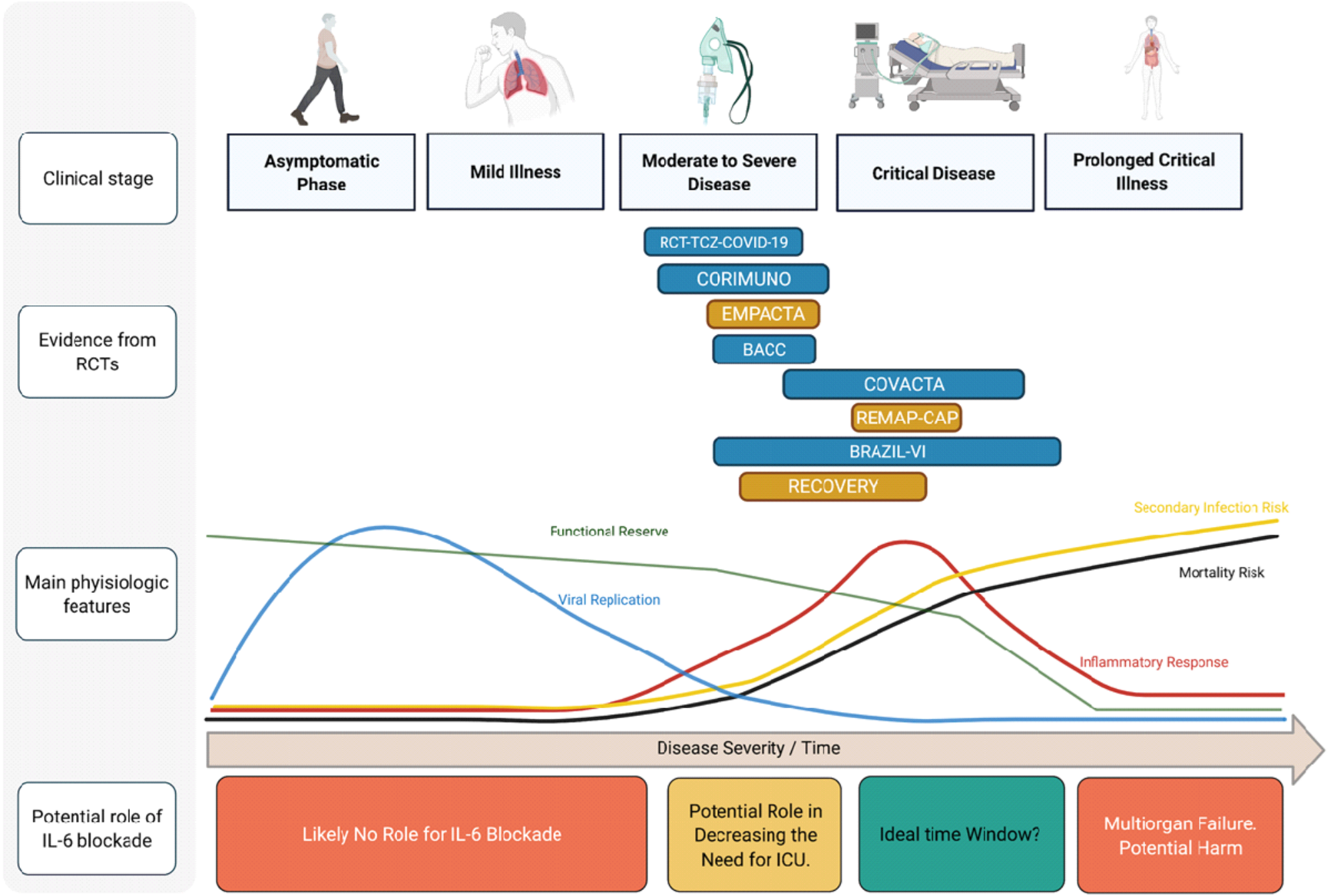


Figure Created By Angriman F, Ferreyro B, ….Del Sorbo L, In Press Lancet Respiratory Medicine 2021

ORIGINAL RECOMMENDATIONS (without supply limitations)

Recommendations: Critically Ill Patients

- Tocilizumab is **recommended** for critically ill patients receiving dexamethasone therapy (or dose-equivalent corticosteroid) AND are within 14 days of hospital admission due to COVID-19
- Critically ill is defined as patients needed **high flow nasal cannula or mechanical ventilation (no CRP criteria needed)** or those **requiring circulatory support (vasopressors/inotropes)**
- A second dose of tocilizumab may be considered after 24 hours if the patients is not improving

Recommendations: Moderately Ill Patients

- Tocilizumab is **recommended** for moderately ill **hypoxic (requiring oxygen) patients** with **evidence of systemic inflammation (ie. CRP >75 mg/L)** AND **evidence of disease progression** despite receiving dexamethasone therapy AND are within 14 days of hospital admission for COVID-19
- A second dose of tocilizumab may be considered after 24 hours if the patients is not improving

Recommendations: Mildy Ill Patients

- Tocilizumab is **not recommended** in this population outside of clinical trials

EXCLUSIONS and PRACTICAL CONSIDERATIONS

- >14 days since hospital admission OR diagnosis
- Previous intolerance to tocilizumab
- Concomitant bacterial, fungal, viral or other infection (ie active tuberculosis)

- Patients receiving tocilizumab should be monitored for potential complications including neutropenia, anemia, hepatotoxicity, secondary infections

TOCILIZUMAB DOSING

The dose of intravenous tocilizumab may be determined by a weight-based dose strategy (8 mg/kg, maximum dose 800 mg)

OR by a weight-based dose banding strategy

800 mg if weight >90kg

600 mg if weight >65 and ≤90 kg

400 mg if weight >40 and ≤65 kg

and 8mg/kg if weight ≤40 kg

Recommendations Summary

Clinical State	Recommendation
Critically Ill	• HFNC or Mechanical Ventilation or vasopressor support • Receiving dexamethasone therapy • Within 14 days of hospitalization/diagnosis
Moderately Ill	• Hypoxic requiring supplemental oxygen • CRP >75 mg/L • Deterioration after receiving dexamethasone therapy • Within 14 days of hospitalization/diagnosis
Mildly Ill	• Not Recommended

Secondary Infectic

CONTRAINDICATIONS

ACTEMRA (tocilizumab) should
tocilizumab or any of its compone
COMPOSITION AND PACKAG

Patients with active infections (se
Infections).

NB:
Contraindications listed in the the manufacturer's product monograph *may not apply* in patients with COVID-19.

RISK OF SERIOUS INFECTIONS

Serious infections including sepsis, tuberculosis (TB), invasive fungal, and other opportunistic infections have been observed with the use of biologics agents, including ACTEMRA. Hospitalization or fatal outcomes associated with infections have been reported.

Reported infections include:

- Active tuberculosis, which may present with pulmonary or extrapulmonary disease. Patients should be tested for both active and latent tuberculosis before ACTEMRA use and during therapy. Treatment should be completed prior to ACTEMRA use.
- Invasive fungal infections, including candidiasis, aspergillosis, and pneumocystis. Patients with invasive fungal infections may present with disseminated, rather than localized, disease.
- Bacterial, viral and other infections due to opportunistic pathogens.

Most patients who developed these infections were taking concomitant immunosuppressants such as methotrexate or corticosteroids, that, in addition to their rheumatoid arthritis could predispose them to infections.

Before starting treatment with ACTEMRA, all patients should be evaluated for both active and latent tuberculosis.

Treatment with ACTEMRA should not be initiated in patients with active infections including chronic or localized infections.

If a serious infection develops, interrupt ACTEMRA until the infection is controlled. Patients should be closely monitored for the development of signs and symptoms of infection during and after treatment with ACTEMRA, including the possible development of tuberculosis in patients who tested negative for latent tuberculosis infection prior to initiating therapy.

Infectious Complications (COVID-19 RCTs) 1 of 2

Trial	Duration of follow up
CORIMUNO-19 (n=131, 1:1 randomization) Moderate to severe COVID (on O2, but no IMV)	@ 28 days (absolute # serious AE lower in TCZ group) - serious bacterial infections/sepsis: TCZ=2, SOC=11 - SOC: fungal sepsis (2) and viral sepsis (1) vs TCZ=0 - lymphopenia/neutropenia: TCZ=5, SOC=0
RCT-TCZ-COVID-19 (n=126, 1:1 randomization) Moderate to severe COVID (on O2, but no IMV)	@ 14 days (absolute # AE higher in TCZ group) - "Infections/Infestations": TCZ=1 (UTI), SOC=4 (sepsis, esophageal infection, bronchial infection) - decreased neutrophils: TCZ=3 (1 mild, 2 mod), SOC=0
BACC Bay (n=243, 2:1 randomization) Moderate to severe COVID (on O2, but no IMV)	@ 28 days - infection ≥ Grade 3: TCZ=13 (8.1%), SOC=14 (17.1%) - neutropenia ≥ Grade 3: TCZ=22 (13.7%), SOC=1 (1.2%)
COVACTA (n=452, 2:1 randomization) Moderate to severe COVID (on O2, including IMV)	@ 28 days, and extension to clinical cutoff date (max 82d) - neutropenia: TCZ=4 (1.4%), SOC=0 - all infections: TCZ=126/295 (42.7%), SOC=62/143 (43.4%) - serious: TCZ=70 (23.7%), SOC=41 (28.7%) COVID-19 death: TCZ=48 (16.3%), SOC=20 (14%) - "opportunistic": TCZ=1 (0.3%), SOC=4 (2.8%) - eg. septic shock, pneumonia, sepsis, bacteremia, bacterial sepsis

Infectious Complications (COVID-19 RCTs) 2 of 2

Trial	Duration of follow up
EMPACTA (n=389, 2:1 randomization) Moderate to severe COVID (on O2, but no IMV)	@ 28 days, safety follow up visit @ 60 days - all infections: TCZ=25 (10%), SOC=16 (12.6%) - serious infection: TCZ=16 in 13 pts (5.2%), SOC=11 in 9 pts (7.1%) eg. septic shock, pneumonia (COVID-19, bacterial, "other") - ? neutropenia, but serious events TCZ=38 (15.2%), SOC=25 (19.7%)
TOCIBRAS (n=129, 1:1 randomization) Severe COVID (on O2, including IMV)	@ 14 days, safety follow up @ 29 days - secondary infections: TCZ=10/65 (15%), SOC=10/64 (16%) - TCZ: blood (5), resp (5), SSTI (1); resp+blood (1) - SOC: blood (3), resp (7), unclear (1), bacteraemia (1); resp+bacteremia (1) - severe neutropenia: TCZ=1 (1%), SOC=0; non-severe: TCZ=1 (1%), SOC=0 - non-severe thrombocytopenia: TCZ=4 (6%), SOC=0
REMAP-CAP (n=353 toci, n=48 sari, 1:1 randomization) Severe COVID (on O2, including IMV)	@ 21 days (?) - TCZ (n=353): serious AEs=9 (2.5%) → secondary bacterial (1), bleed (5) - Control (n=402): serious AEs=11 (2.7%) → thrombosis (7), bleed (4) - SARI (n=48): no serious AEs
RECOVERY (n=4116, 1:1 randomization) Moderate to severe COVID (on O2, including IMV)	@ 28 days (? further analyses specified at 6 months) → infection risk not described *"complicating bacterial infections are infrequent in [early] COVID-19, this recognised concern [with] tocilizumab would be lessened with earlier use"*

Acute Bacterial Co-Infection in COVID-19

A Rapid Living Review and Meta-analysis

24 Studies included

3338 COVID-19 Patients

December 2019 to March 2020

3.5%
Co-Infection
On presentation

14.3%
Secondary Infection
After presentation

71.9% **Antibiotic Prescribing**

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

Risk with concomitant immunosuppression (eg. dexamethasone + tocilizumab) is unclear

Bacterial co-infection: should I give concomitant antibiotic therapy?

- on initial presentation, co-infection rates are low (~3.5%)
- RECOVERY excluded patients with “active infection” (ie. on antibiotics?)

Risk of **Strongyloides:** should I give ivermectin* to treat strongyloidiasis?

- overall strongyloidiasis risk = **geographic** and **clinical** risk factors
- monotherapy tocilizumab risk is not well described
- Science Table science brief in development - stay tuned!
- ivermectin is NOT recommended for prophylaxis or treatment of COVID-19

Other infections: we need more follow-up data to describe infection risk

- eg. late bacterial co-infections, Aspergillosis, Pneumocystis pneumonia, etc.

* currently on drug shortage (estimated until Dec 2021); https://www.drugshortagescanada.ca/shortage/131914

Projected Tocilizumab Utilization

Estimating demand for tocilizumab in Canada[1]

- We used GEMINI data from 820 adult hospitalizations for COVID-19 at 6 hospitals in G.T.A. between January and June 2020.
- Applied eligibility criteria from either RECOVERY or REMAP-CAP trials, occurring during the first 14 days of hospital admission:
  - Required oxygen therapy AND C-reactive protein level ≥75 mg/L,

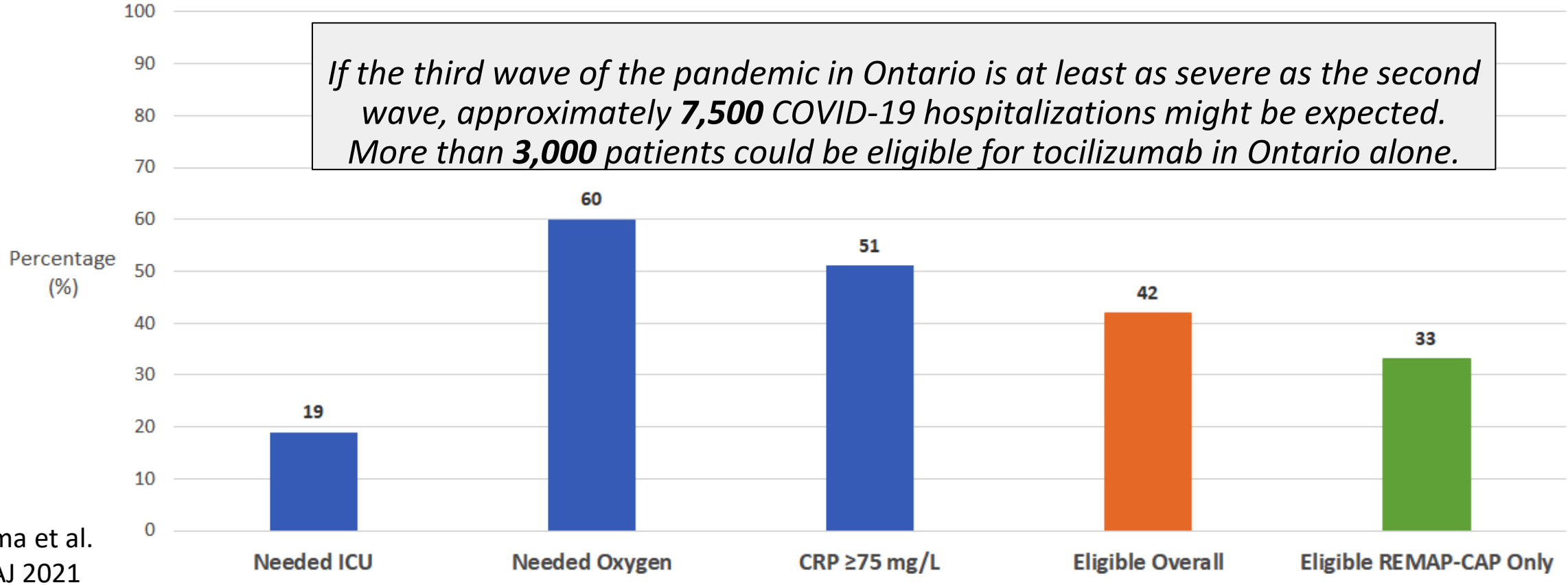
  OR
  - Required ICU admission
- Because eligibility varies by age group, we extrapolated age-specific estimates in our study population to the reported age strata for COVID-19 hospitalizations in Canada and U.S.A.

1. Verma et al. CMAJ 2021 (In Press)

Projected Tocilizumab Utilization

An estimated 42% of adults hospitalized with COVID-19 would be eligible for tocilizumab

*If the third wave of the pandemic in Ontario is at least as severe as the second wave, approximately **7,500** COVID-19 hospitalizations might be expected. More than **3,000** patients could be eligible for tocilizumab in Ontario alone.*

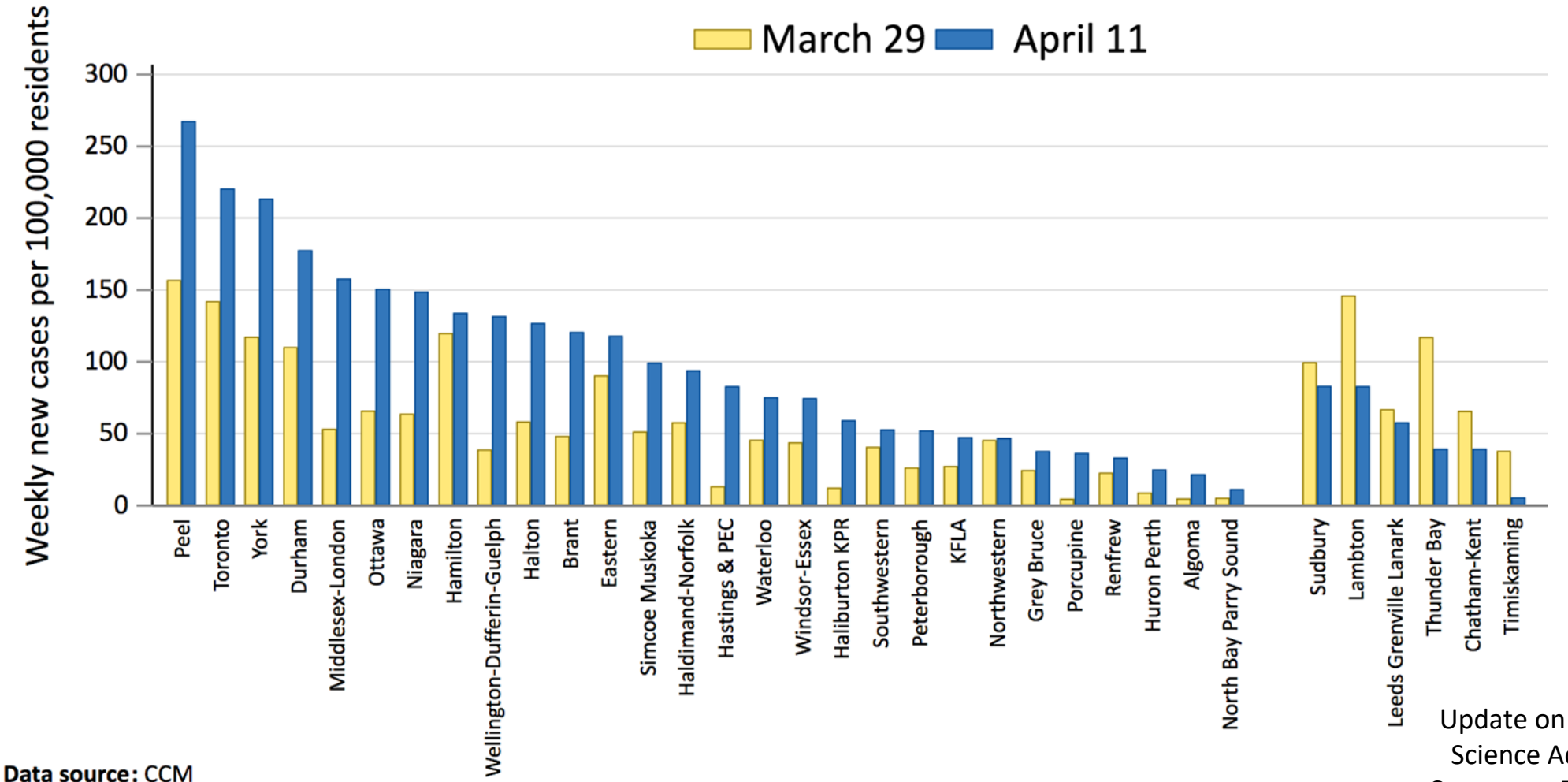


*Eligible overall refers to number of patients estimated to meet either RECOVERY or REMAP-CAP criteria

Verma et al.
CMAJ 2021
(in press)

Projected Tocilizumab Utilization

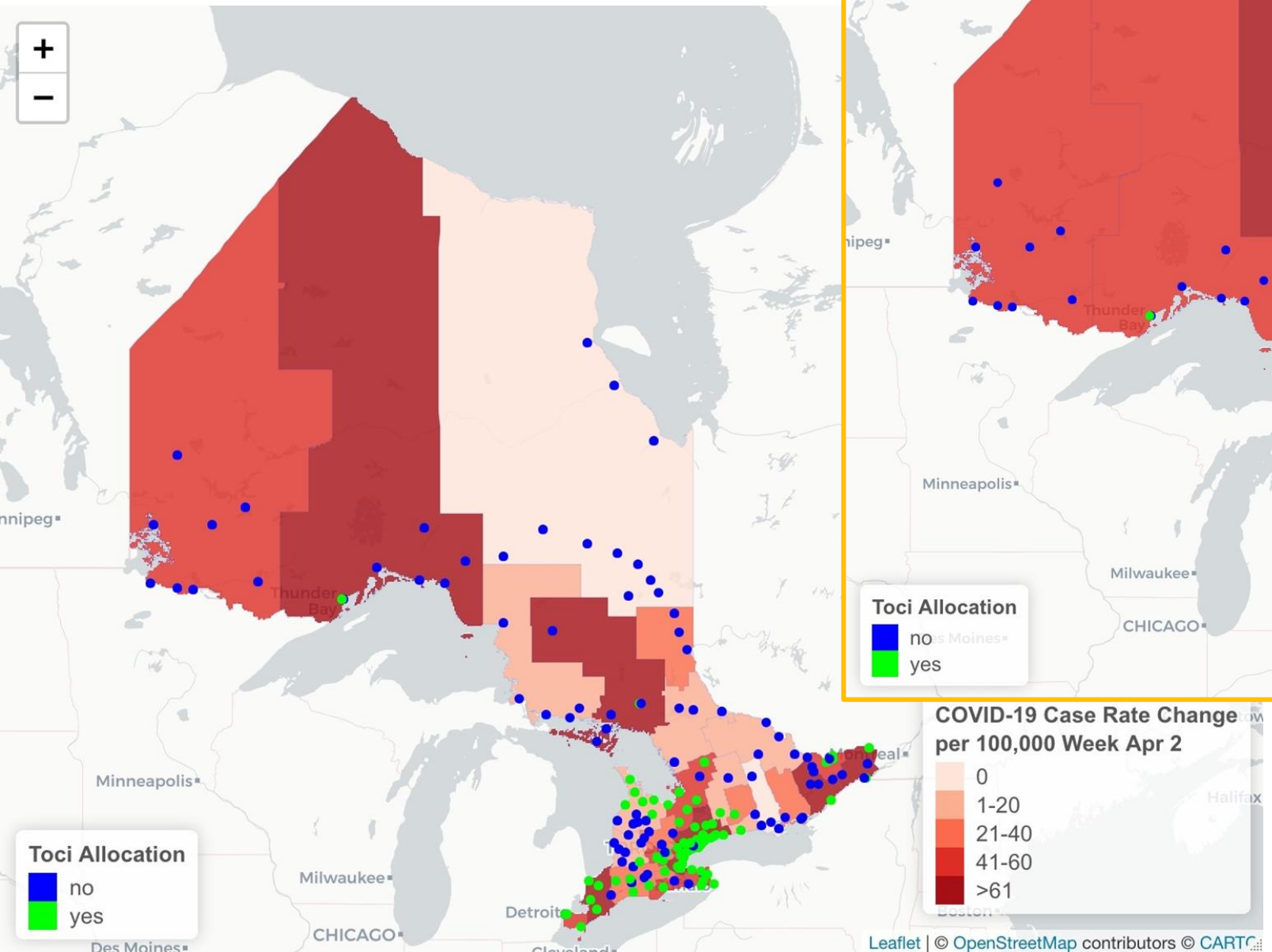
Cases are **rapidly** increasing in most Public Health Units

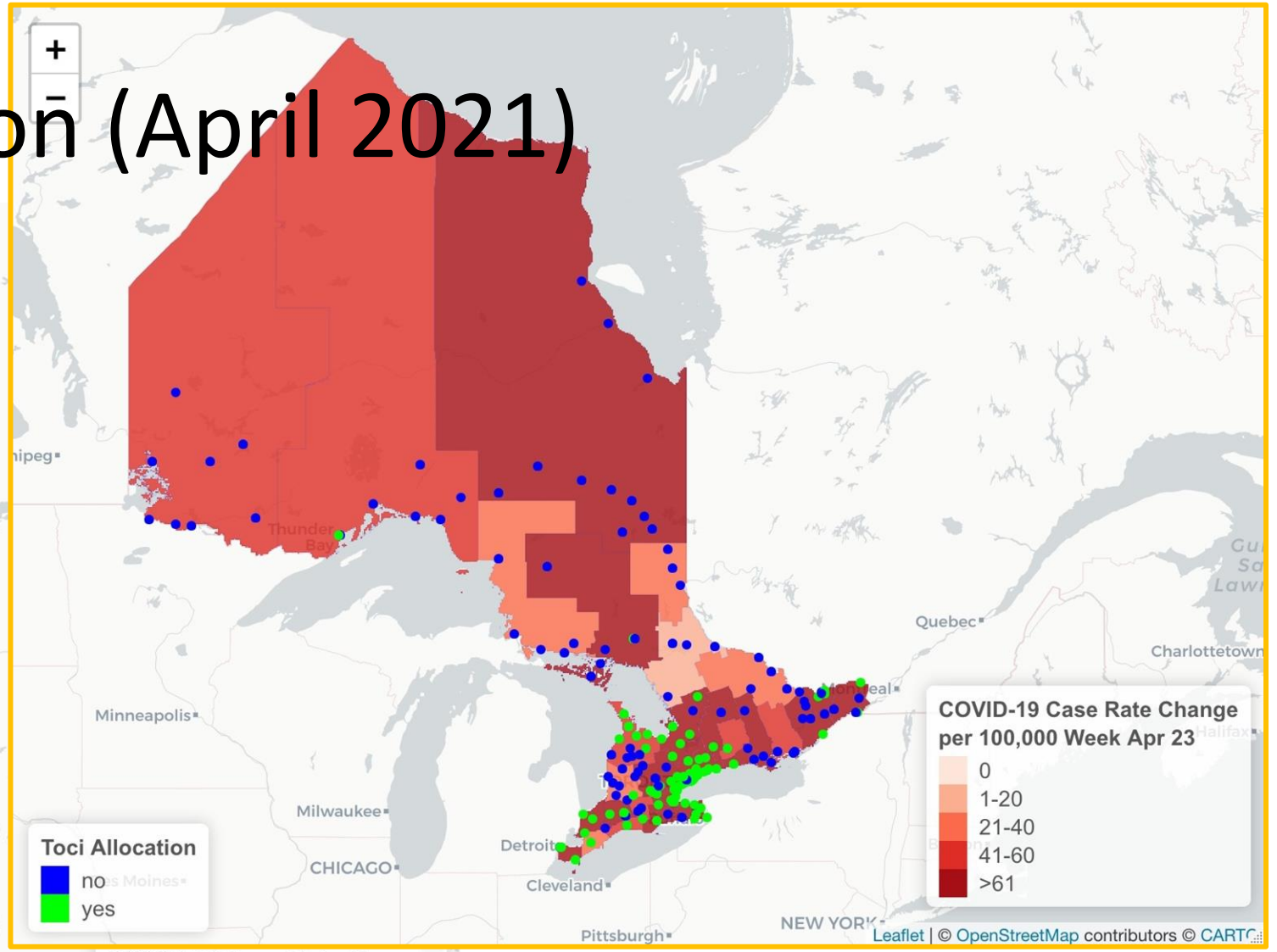


Data source: CCM
Data note: Data for the most recent day have been censored to account for reporting delays

Update on COVID-19 Projections
Science Advisory and Modelling
Consensus Tables (April 16, 2021)

Tocilizumab Allocation (April 2021)

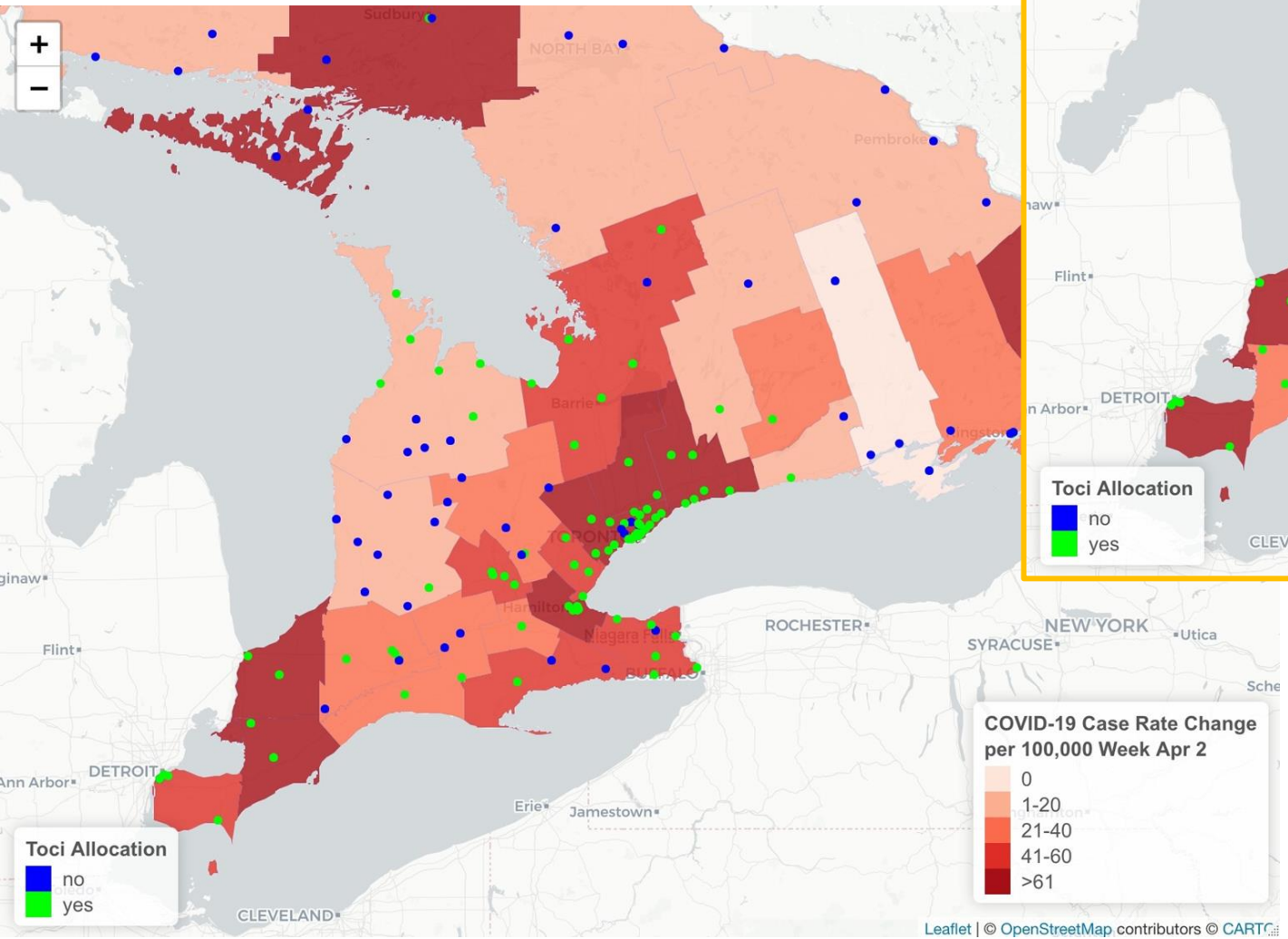


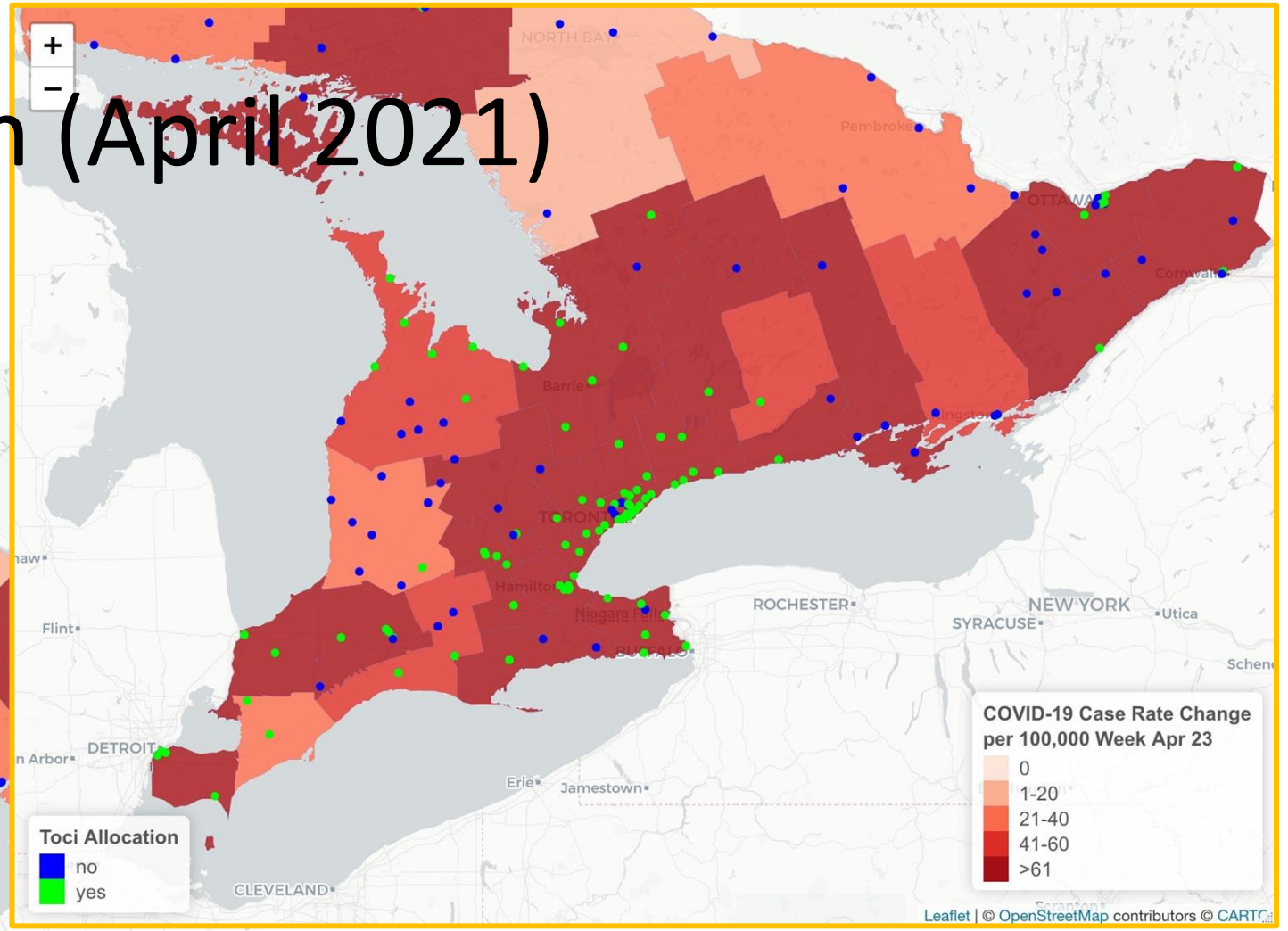


Images provided by: S. Raybardhan

Data Sources: Ontario COVID-19 Science Advisory Table's Drugs & Biologics Clinical Practice Guidelines Working Group – Tocilizumab Survey – March 8 2021; PHO Weekly Epidemiologic Summaries https://covid-19.ontario.ca/covid-19-epidemiologic-summaries-public-health-ontario

Tocilizumab Allocation (April 2021)





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Strategies to Manage Tocilizumab Supply

An ethical, evidence-based framework is required to inform allocation and use of limited tocilizumab supply. The Ontario COVID-19 Bioethics Table adapted a published Ontario drug supply shortage framework for use during the COVID-19 pandemic, that outlines a set of guiding ethical principles and three stages for managing drug supply during the COVID-19 pandemic:

- **Stage 1:** Preserve the standard of care for as many COVID-19 patients as possible by a) conserving supply, b) sharing supply, and c) procuring or accessing new supply.
- **Stage 2:** Optimize therapeutic benefit based on existing evidence within available supply (Primary Allocation Principles).
- **Stage 3:** Use a fair procedure to choose between patients (Secondary Allocation Principle) if Stage 1 and 2 efforts are insufficient to meet demand.

https://covid19-sciencetable.ca/sciencebrief/strategies-to-manage-tocilizumab-supply-during-the-covid-19-pandemic/

REVISED RECOMMENDATIONS
(taking into account supply limitations)

last updated - April 6, 2021

TOCILIZUMAB DOSING

Recommendations for Stage 2 of Tocilizumab Supply and Distribution

- The dose of tocilizumab should be reduced to 400mg
- Second doses are not recommended
- *Triaging of patients based on factors demonstrating which patients are most likely to benefit from treatment with tocilizumab has not been identified in the literature and is not recommended.*

https://covid19-sciencetable.ca/sciencebrief/strategies-to-manage-tocilizumab-supply-during-the-covid-19-pandemic/

Tocilizumab Allocation (Current State)

As of April 18, 2021:

The Ontario Critical Care COVID19 Command Centre (OCCCCC) will provide support, oversight, and accountability for the distribution of Tocilizumab in Ontario.

The OCCCCC will receive guidance from the Ontario Science Table and the Science Table's Clinical Practice Guidelines Working Group. It will also consider other expert input, as well as the relationship of Tocilizumab distribution and the overall strategy of managing critical care capacity. Jin Huh Senior Director of Pharmacy, UHN and Lead for ICU Medication Task Force, and Angie Wong, Director, Drugs and Devices Division, from Ministry of Health will provide operational support and recommendations. The OCCCCC will regularly review the supply in Ontario and ensure its distribution matches need as much as possible.

At this point in time, the OCCCCC supports and requests that clinicians adopt the Science Table's recommendation of prescribing a single dose of 400mg, when Tocilizumab is indicated. The OCCCCC does not currently recommend a randomization approach to distribution, but recognizes that as articulated by the Science Table, randomization may become the best option in the future. We are working with the Governmentt of Canada to secure addition supply and are encouraged by the initial response.

The OCCCCC was established by Ontario Health on March 28, 2020 with the following mandate:

The Ontario Critical Care COVID Command Centre, and its delegated Regional Command Centres, have been given four roles (and more may emerge):

- The authority to direct the movement of patients within and across regions to smooth the burden on critical care units and maximize the use of our critical care resources
- The authority to direct the movement of ventilators and other supplies as necessary to maximize critical care capacity
- The authority to invoke triage protocols
- The responsibility to facilitate all regions and critical care hospitals in maximizing the creation and sustainment of additional critical care capacity

CONCLUSIONS

- Tocilizumab can blunt the **inflammatory cascade** associated with COVID-19
- The effect of tocilizumab is **consistent across subgroups** of moderately ill patients with evidence of systemic inflammation or critically ill patients
- In our pooled meta-analysis, **there was evidence of a mortality benefit**. These results were largely driven by the RECOVERY trial which includes dexamethasone as the standard of care
- **More data is needed** on quantifying the infection risk, optimal dosing, and whether the results re generalizable to other IL-6 receptor antagonists

Acknowledgments

- Thank you to **Drs. Menaka Pai and Andrew Morris** for contributing slides and for their tireless dedication to, and leadership of, the COVID-19 Ontario Science Table Drugs and Biologics Clinical Practice Guidelines Working Group.
- Thank you **Drs. Fahad Razak and Amol Verma and the GEMINI research group** for sharing their analysis surrounding projections.

SCIENCE TABLE

COVID-19 ADVISORY FOR ONTARIO