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Preventing the Silent Pandemic: Antibiotic Stewardship and COVID-19

Rapid Reviews of Co-Infection and Antibiotic Prescribing in COVID-19

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May 27, 2021
Public Health Ontario Grand Rounds

Objectives

- Explain the potential implications of COVID-19 to antimicrobial resistance.
- Discuss rapid review findings on bacterial infection and antimicrobial prescribing in COVID-19.
- Discuss antibiotic stewardship strategies at the patient and population level.

What will be the net impact of COVID-19 on antimicrobial resistance (AMR)?

a. Increased AMR

b. No Change in AMR

c. Decreased AMR

d. Unsure


FIRST OPINION
Antibiotic resistance: the hidden
threat lurking behind Covid-19
PEW
TOPICS PROJECTS FEATURES ABOUT GET INVOLVED SEARCH
Superbugs in the News: How COVID-19 Is Increasing Antibiotic Use
A collection of articles exploring the nexus of the coronavirus and antibiotic resistance
thebmj covid-19 Research
Feature
How covid-19 is accelerating the threat of antimicrobial resistanc
BMJ 2020 ; 369 doi: https://doi.org/10.1136/bmj.m1983 (Published 18 May 2020)
Cite this as: BMJ 2020;369:m1983
SCIENCE 04.23.2020 07:00 AM
Covid-19 May Worsen the Antibiotic Resistance Crisis
The disease can't be treated with these drugs, b
otic use is rising anyway, in ICUs and among the worried well.
THE CORONAVIRUS CRISIS
Why Antibiotic Resistance Is More Worrisome Than Ever
May 14, 2020 · 10:31 AM ET
SUSAN BRINK
Health
Why overuse of antibiotics
lasting impact in health care
Doctor's N
increasing antib
Why has the WHO said a 'worrying
infections are becoming resistant to
of bacterial
es?
-19 is
ance

AMR in the Era of COVID-19 [1]

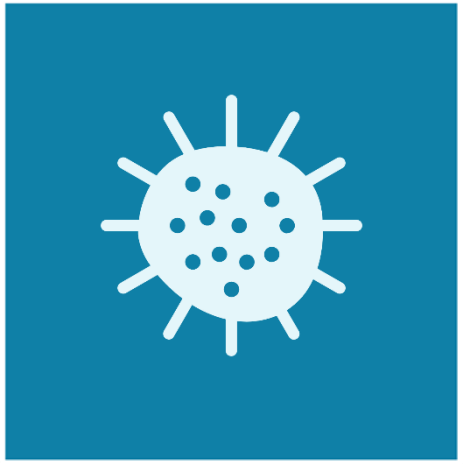
Will AMR Increase?

- Concern for co-infection increases antibiotic prescribing in patients with COVID-19
- Difficulty differentiating bacterial from viral etiology
- COVID-19 has affected AMR epicenters (China, Italy, USA)

Will AMR Decrease?

- Physical distancing
- Hand hygiene
- Reduced influenza rates
- Shifts in healthcare utilization
- Travel restrictions

Rapid Review Objectives:



To determine the prevalence of bacterial infection in patients with COVID-19 and to identify the most common co-infecting respiratory organisms in these individuals

To determine the prevalence of antibiotic prescribing and identify the predictors of antibiotic use in patients with COVID-19

Methods: Rapid Review

- Inclusion criteria
  - Studies evaluating humans with lab-confirmed SARS-CoV-2
  - All healthcare settings and age groups
  - Any study design except case studies, series < 10 patients, reviews

AND

  - Co-infection Rapid Review:

Study indicates number of patients with respiratory bacterial infection +/- bacteremia

  - Antibiotic Prescribing Rapid Review:

Study indicates number of patients prescribed antibiotic therapy

Search Methodology

- MEDLINE, OVID Epub and EMBASE databases for published literature
- Dates of search: January 1, 2019 to April 16, 2020 (co-infection) / June 9, 2020 (antibiotic)
- Assistance from a medical library information specialist
- Search concepts include:
  - COVID-19 terms
  - Epidemiology, descriptive cohort study terms
  - Co-infection/bacterial infection terms *OR*
  - Antibiotic prescribing terms
- Protocols registered with PROSPERO

Primary Analyses

Bacterial Infection Rapid Review

Estimate the overall proportion of confirmed acute bacterial infections in patients with COVID-19

Stratified by co-infection (on initial presentation) and secondary infection (during the course of the illness)

Stratified by severity

Antibiotic Infection Rapid Review

Estimate the overall prevalence of antibiotic prescribing among patients with COVID-19.

Stratified by region

Stratified by severity of COVID-19

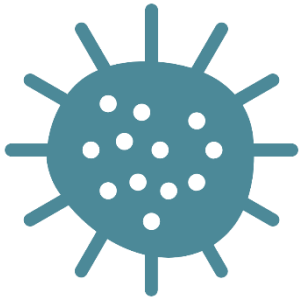
Stratified by month of study completion

Stratified by age group

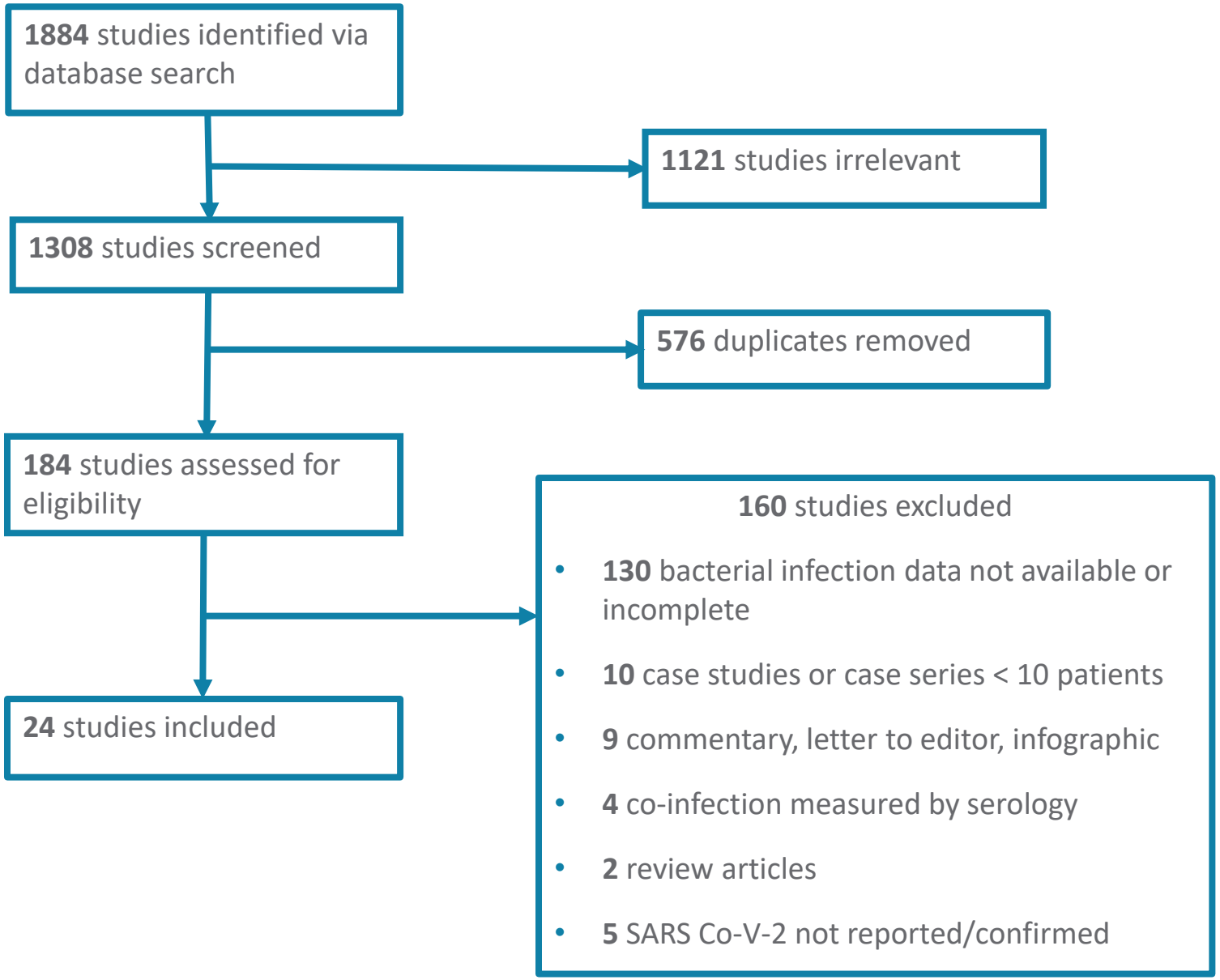
Statistics

- Proportions of patients with 1) bacterial infection or 2) antibiotic prescribed were estimated using random-effects meta-analysis
- Results illustrated using forest plots
- Heterogeneity estimated using I^2 statistic
- Meta-regression to identify predictors of co-infection and predictors of antibiotic prescribing in COVID-19 at the study level

Co-Infection Rapid Review Results



Study Flow Diagram:
Bacterial Infection Rapid Review



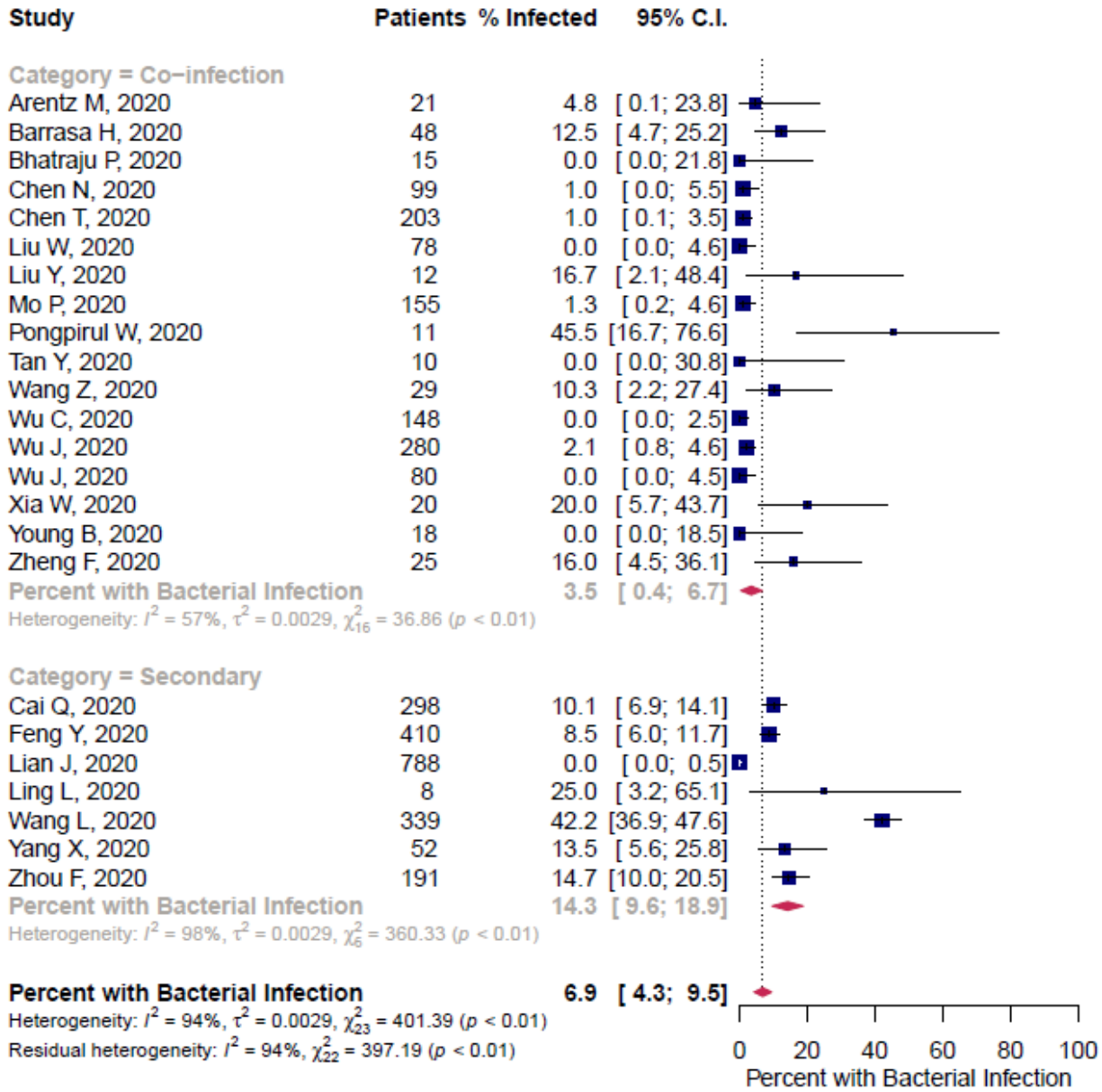
Source: Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al.[2] Used with permission.

Results: Co-Infection

- 24 retrospective studies
- Region: n= 21 in Asia
- Setting: n=19 hospitalized, n=5 critically ill
- Age group: n=18 adult
- Patients: 3338 of 3506 patients evaluated for bacterial infection
- Co-infection (n=11 explicit, 6 implicit) vs. secondary infection (n=7)
- Bacteriological testing method:
  - Culture (respiratory +/- blood) = 10
  - Nucleic acid amplification = 2
  - Not specified = 12

Results: Co-Infection

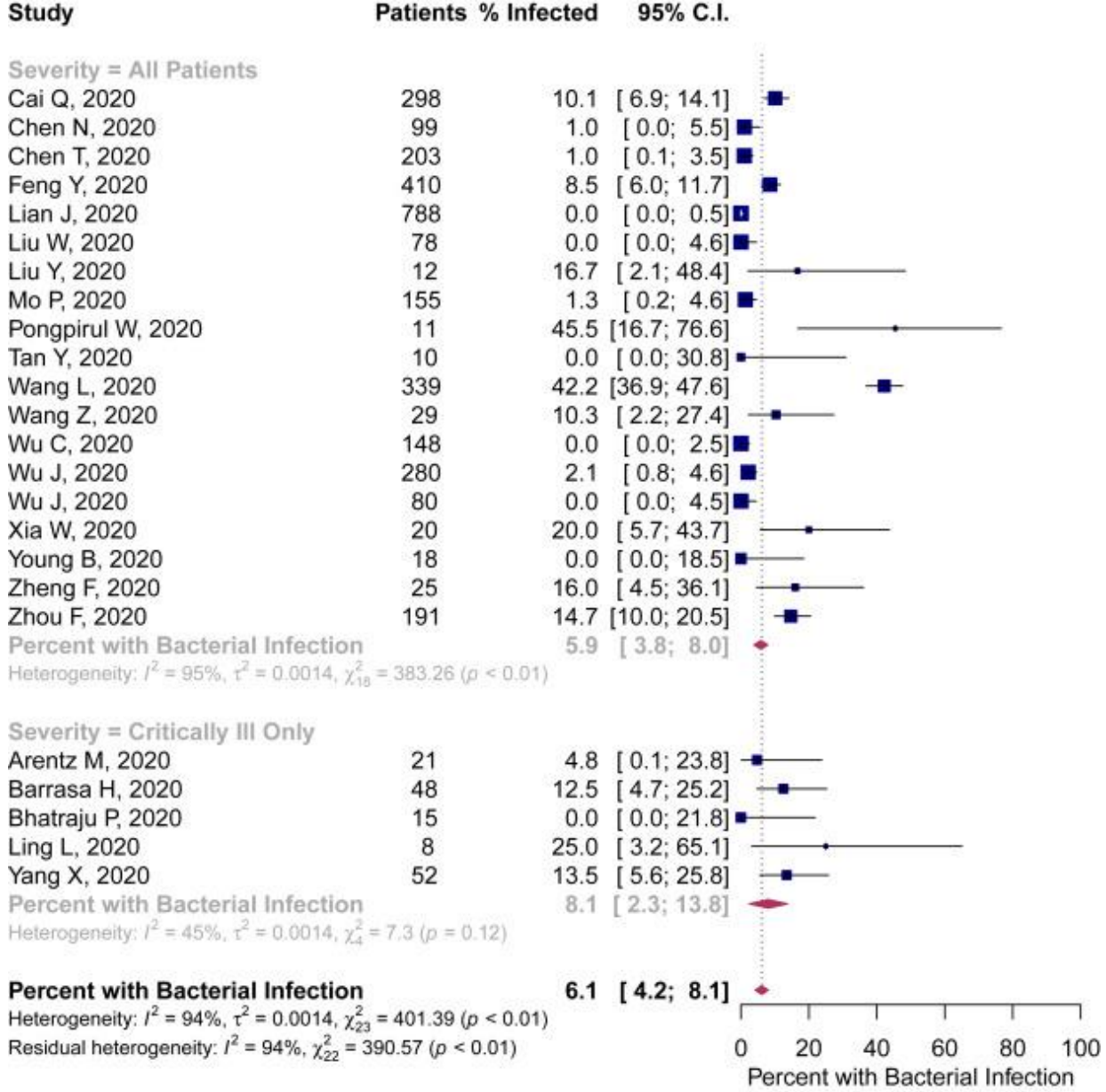
Overall 6.9% of patients with COVID-19 had a concurrent bacterial infection



Source: Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al.[2] Used with permission.

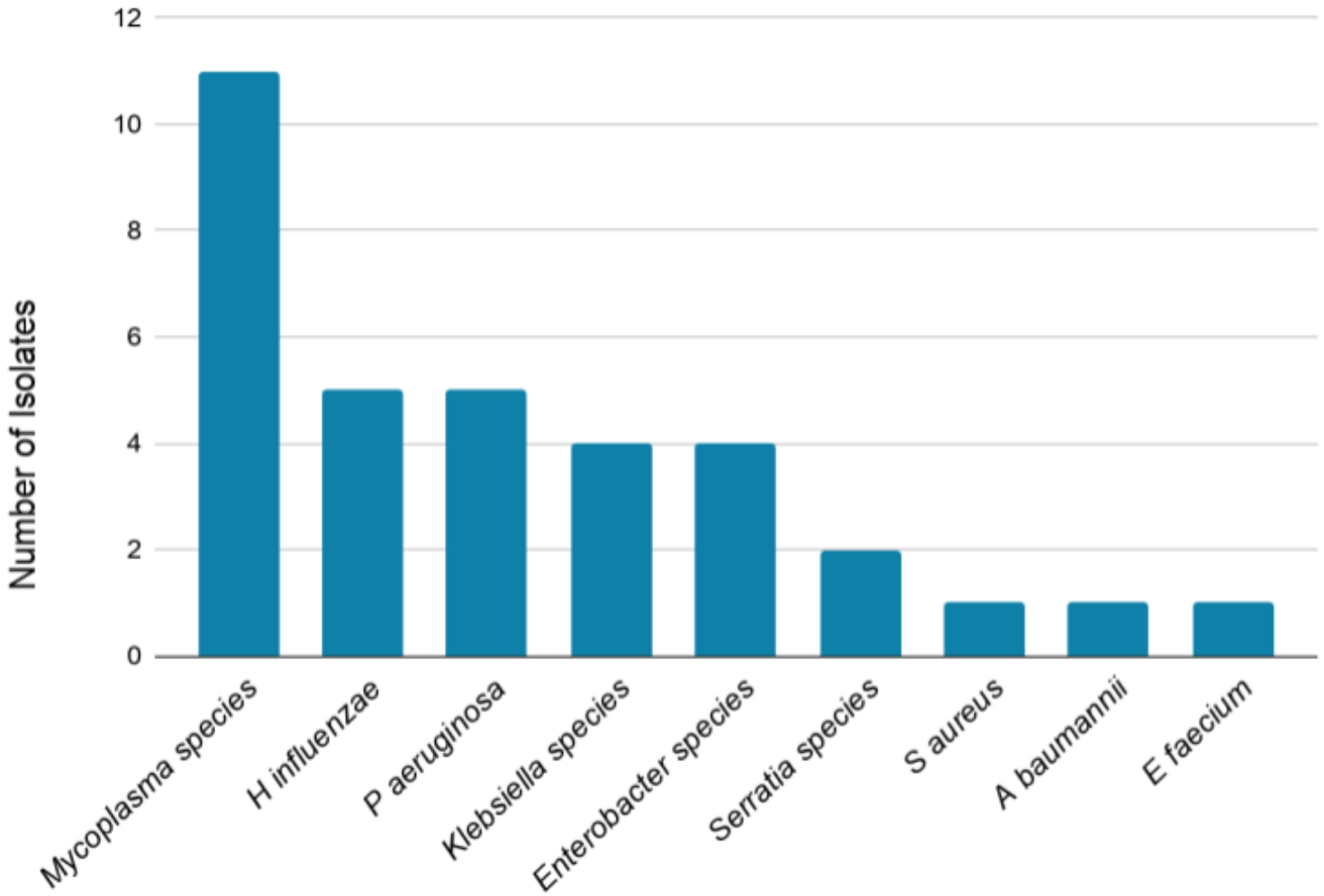
Results: Co-Infection

- Bacterial infection is less common in hospitalized patients on the wards compared to those in the ICU



Source: Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al.[2] Used with permission.

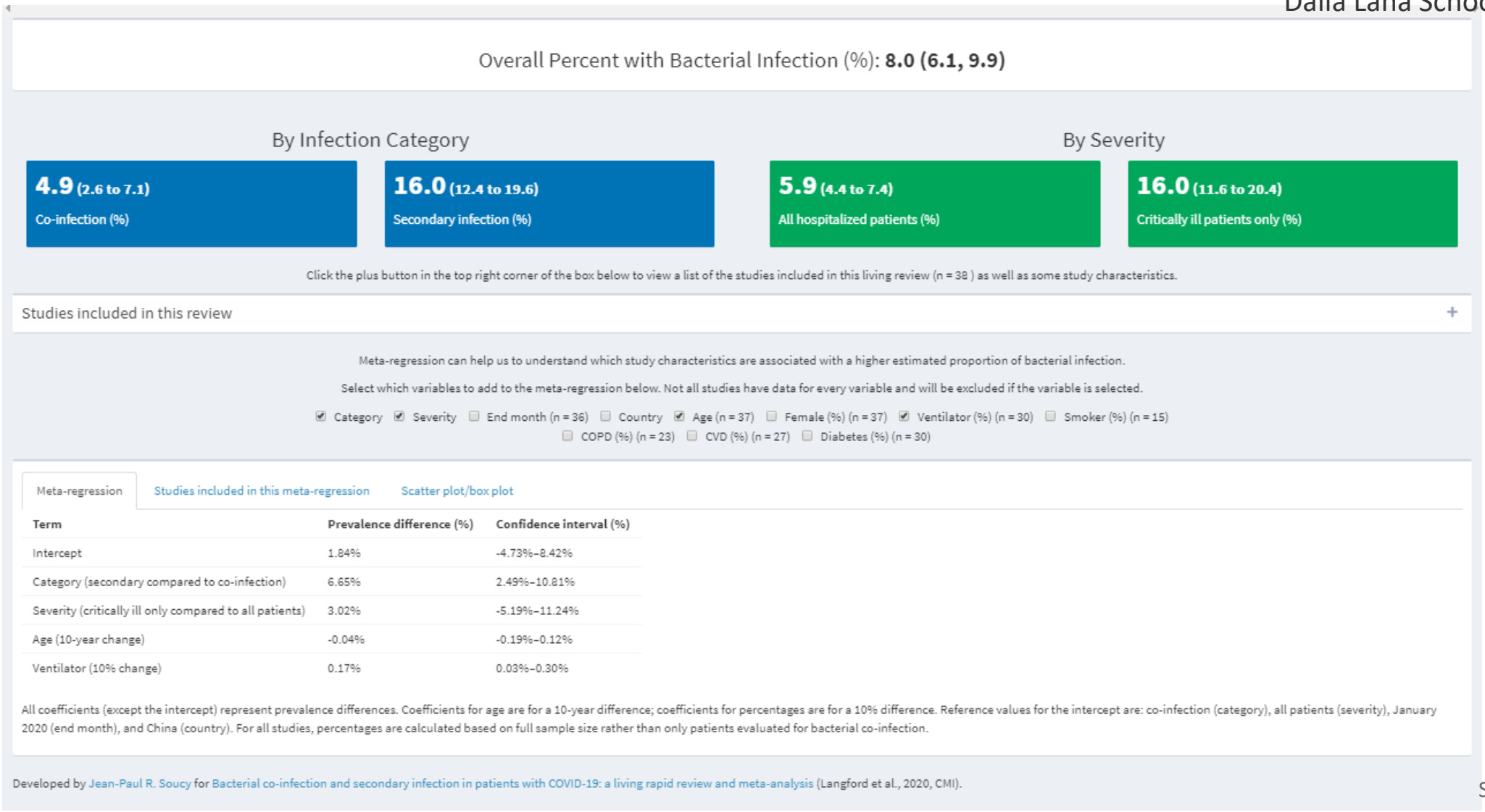
Bacteria Isolated in Patients with COVID-19



Source: Langford BJ, So M, Raybardhan S, Leung V, Westwood D, MacFadden DR, et al.[2] Used with permission.

Co-Infection Dashboard: www.tarrn.org/COVID

Developed by Jean-Paul Soucy
PhD candidate
Dalla Lana School of Public Health



Overall Percent with Bacterial Infection (%): **8.0 (6.1, 9.9)**

By Infection Category

4.9 (2.6 to 7.1)
Co-infection (%)

16.0 (12.4 to 19.6)
Secondary infection (%)

By Severity

5.9 (4.4 to 7.4)
All hospitalized patients (%)

16.0 (11.6 to 20.4)
Critically ill patients only (%)

Click the plus button in the top right corner of the box below to view a list of the studies included in this living review (n = 38) as well as some study characteristics.

Studies included in this review +

Meta-regression can help us to understand which study characteristics are associated with a higher estimated proportion of bacterial infection.

Select which variables to add to the meta-regression below. Not all studies have data for every variable and will be excluded if the variable is selected.

☑ Category ☑ Severity ☐ End month (n = 36) ☐ Country ☑ Age (n = 37) ☐ Female (%) (n = 37) ☑ Ventilator (%) (n = 30) ☐ Smoker (%) (n = 15)
☐ COPD (%) (n = 23) ☐ CVD (%) (n = 27) ☐ Diabetes (%) (n = 30)

Meta-regression | Studies included in this meta-regression | Scatter plot/box plot

Term	Prevalence difference (%)	Confidence interval (%)
Intercept	1.84%	-4.73%–8.42%
Category (secondary compared to co-infection)	6.65%	2.49%–10.81%
Severity (critically ill only compared to all patients)	3.02%	-5.19%–11.24%
Age (10-year change)	-0.04%	-0.19%–0.12%
Ventilator (10% change)	0.17%	0.03%–0.30%

All coefficients (except the intercept) represent prevalence differences. Coefficients for age are for a 10-year difference; coefficients for percentages are for a 10% difference. Reference values for the intercept are: co-infection (category), all patients (severity), January 2020 (end month), and China (country). For all studies, percentages are calculated based on full sample size rather than only patients evaluated for bacterial co-infection.

Developed by Jean-Paul R. Soucy for Bacterial co-infection and secondary infection in patients with COVID-19: a living rapid review and meta-analysis (Langford et al., 2020, CMI).

Source: © 2020, TARRN[3]

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

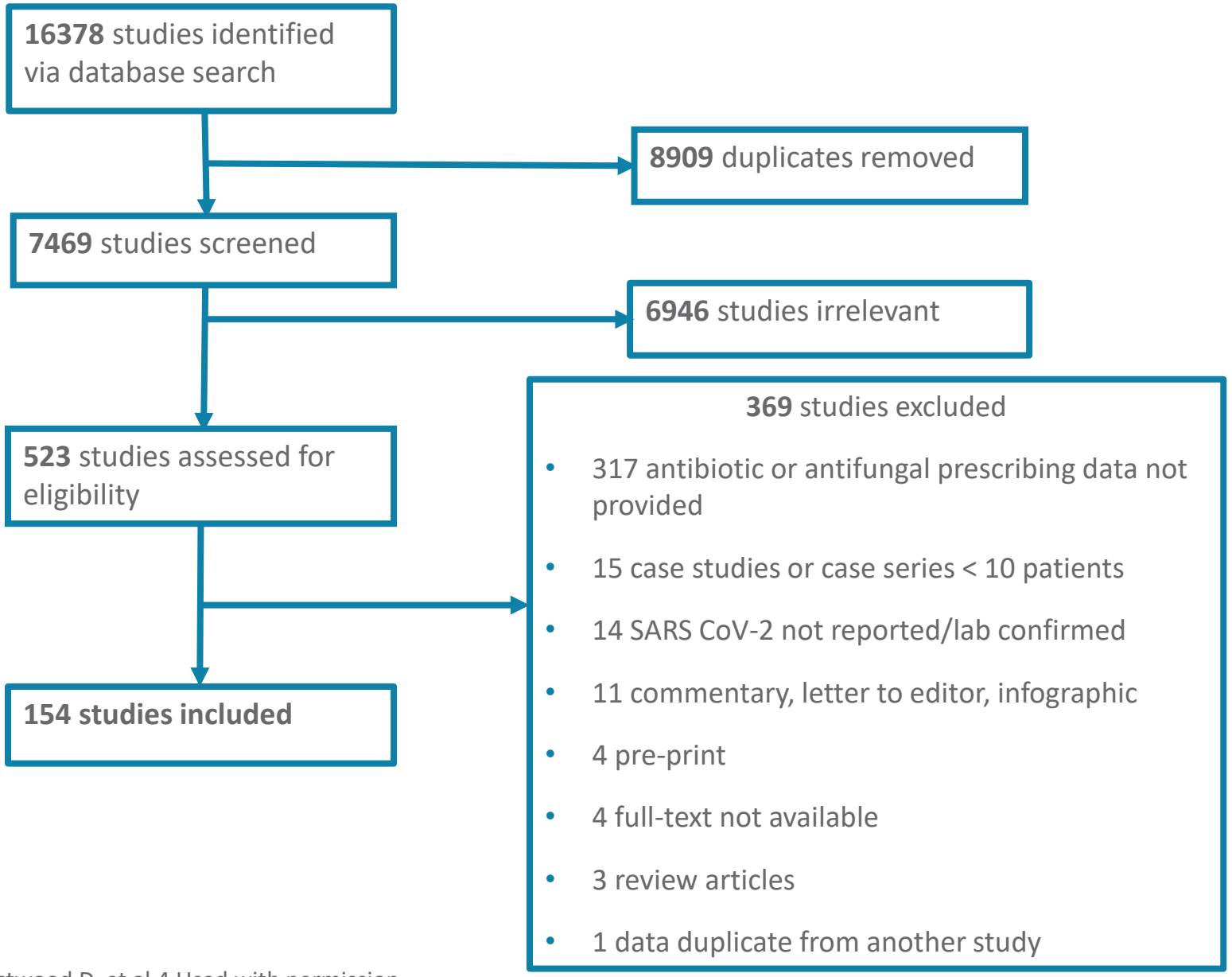
71.9% **Antibiotic Prescribing**

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

Antibiotic Prescribing Rapid Review Results

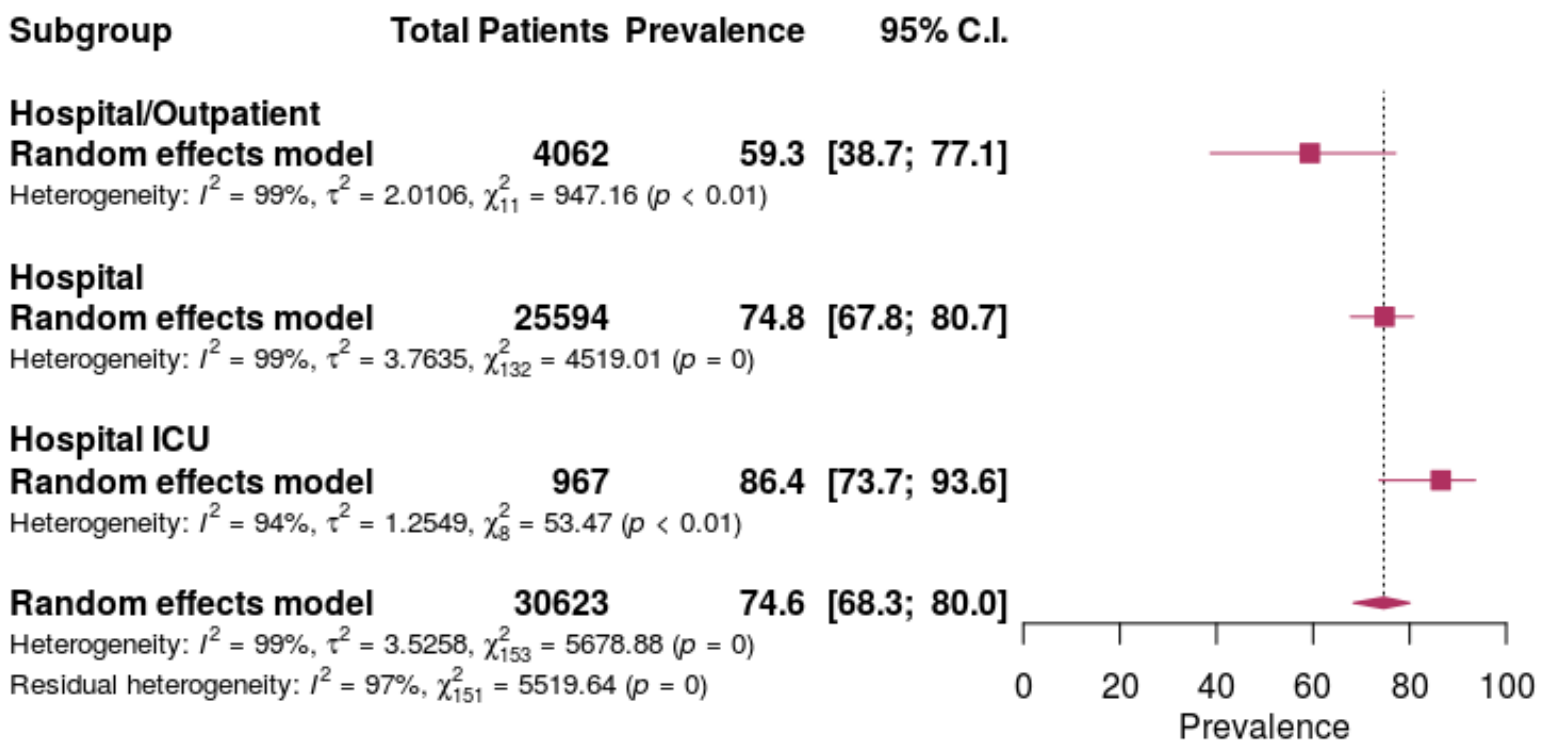
Study Flow Diagram: Antibiotic Prescribing Rapid Review



Source: Langford BJ, So M, Raybardhan S, Leung V, Soucy JR, Westwood D, et al.4 Used with permission

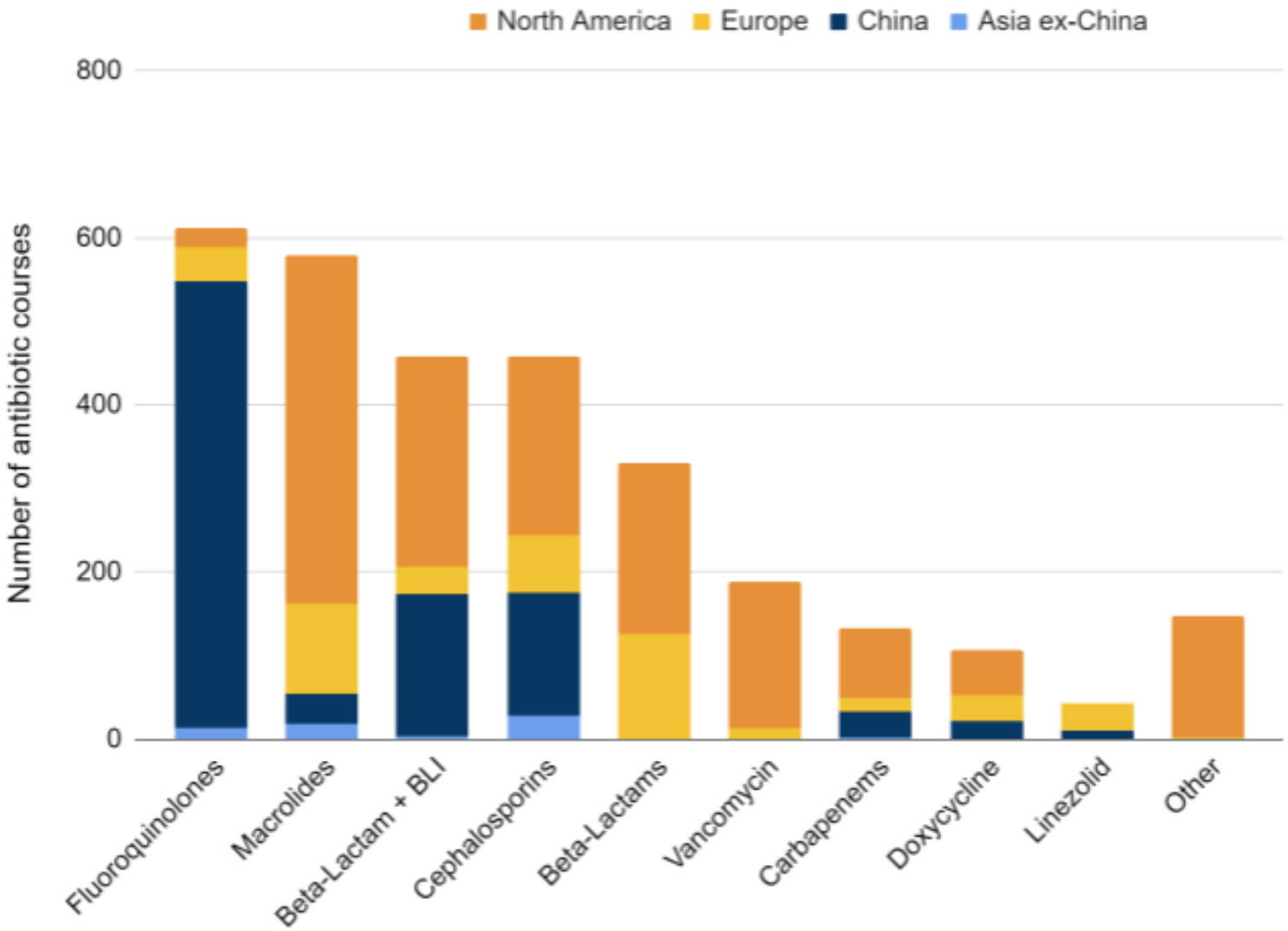
Results: Antibiotic Prescribing

Overall **74.6%** of patients with COVID-19 received at least one antibiotic



Source: Langford BJ, So M, Raybardhan S, Leung V, Soucy JR, Westwood D, et al.[4] Used with permission.

Results: Antibiotic Prescribing



Source: Langford BJ, So M, Raybardhan S, Leung V, Soucy JR, Westwood D, et al.[4]

Antibiotic Prescribing in Patients with COVID-19

Rapid Review and Meta-analysis

154
Studies included

35,263
COVID-19 Patients

December 2019 to
May 2020

74.6%
Antibiotic Prescribing

8.6%
Bacterial Co-infection

Unnecessary antibiotic use is estimated to be **high in patients with COVID-19**

Geographic Region
No clear difference in prescribing

Older Age
Associated with higher prescribing

Mechanical Ventilation
Associated with higher prescribing

Langford BJ, So M, Raybardhan S, Leung V, Soucy JPR, Westwood D, Daneman N. MacFadden DR, Clinical Microbiology and Infection. 2021.

TARRN

Strengths and Limitations

- Strengths
  - Large number of studies spanning several continents
  - Meta-regression quantifies risk of co-infection and antibiotic prescribing based on study factors. Helps identify opportunities for antimicrobial stewardship
- Limitations
  - High degree of heterogeneity among studies
    - Differences in bacterial detection methods and detail provided on methodology
  - Challenges in distinguishing true infection from colonization
  - Minimal data on co-pathogens
  - Cannot differentiate between antibiotics used empirically on admission vs. for secondary infections later in hospitalization

Next Steps

- Update to bacterial infection in COVID-19 living review
- Over 25,000 studies screened
- Approximately 100-150 for inclusion
- Additional variables that may increase infection risk:
  - Corticosteroid use
  - Tocilizumab use
- Meta-regression to evaluate the predictors of bacterial infection in patients with COVID-19

www.tarrn.org/COVID

Impact of COVID-19 on Antibiotic use in Hospitals and Communities

Study	Setting	Direction	Details
Vaughn VM 2020[5]	Hospital	?	N=1705, from 38 hospitals in Michigan, USA. 56.6% were prescribed early empiric antibiotics despite 3.5% co-infection rate Median duration was 3 days, range between hospitals 27-84% prescribing 55% had antibiotics stopped within 1 day of negative result. Of those who did not have confirmed bacterial infection, 65% received more than 5 days.
Buehrle DJ 2020[6]	Hospital	↑	Single-centre in Pennsylvania, USA. Antibiotic days of therapy per 1000 bed days increased by 8.1/month.
Abelenda-Alonso[7] 2020	Hospital	↑	Single-centre in Catalonia, Spain. Biphasic increase in amoxicillin-clavulanate, then “broad spectrum” as a result of empiric recommendations to use antibiotics in all patients COVID-19, then an increase in critically ill patients.

Impact of COVID-19 on Antibiotic use in Hospitals and Communities

Study	Setting	Direction	Details
Malcolm W 2020[8]	Community	↓	921 GP practices in Scotland, UK Peak in antibiotic prescribing in early March 2020 followed by a 34% reduction in prescribing by the end of May 2020.
PHAC 2020[9]	Community	↓	Canada-wide antibiotic dispensing data from Canadian CompuScript database (IQVIA). 30% decrease in April/May 2020, compared to 2019.
Buehrle DJ 2020[10]	Community	↓	USA-wide antibiotic dispensing data from National Prescription Audit database (IQVIA). Antibiotic use decreased by 13-56% for top 10 antibiotics. Respiratory antibiotics did not return to pre-pandemic levels.
Shah S 2020[11]	Community (Dentistry)	↑	National Health Service (UK) antibiotic dispensing related to dental prescriptions. Antibiotic prescribing increased by 25% from April-July 2020 compared to April-July 2019.

What approach can be used to reduce antimicrobial overuse in COVID-19?

a. Avoid empiric use in low risk patients.

b. Re-evaluate antibiotic use at 48 hours

c. Restrict antibiotics in COVID-19 patients

d. All of the above

e. A and B

Recommendations for Pre-Emptive Antibiotics in COVID-19

Guideline	Pre-Emptive Antibiotics Recommended? Mild	Moderate	Critical	Statement
World Health Organization 2020[12]	✗	✗	✓	"We recommend for patients with… severe COVID-19…empiric antimicrobials to treat all likely pathogens… and this should be done as soon as possible… ideally with blood cultures obtained first. Antimicrobial therapy should be assessed daily for de-escalation."
Surviving Sepsis Campaign 2020[13]	N/A	N/A	✓	"In mechanically ventilated patients with COVID-19 and respiratory failure, we suggest using empiric antibacterials. Assess for de-escalation daily, and re-evaluate… based on the microbiology results and the patient's clinical status." (weak recommendation)
National Institute for Health and Care Excellence (NICE) 2020[14]	✗	✗	✗	"If there is confidence that the clinical features are typical for COVID-19, it is reasonable not to start empirical antibiotics. Empirical antibiotics should be started if there is clinical suspicion of bacterial infection, including characteristic symptoms, localised chest findings."
Dutch Working Party on Antibiotics 2020[15]	✗	✗	△	"We generally suggest restrictive use of antibacterial drugs in patients with proven or a high likelihood of COVID-19. This especially applies for patients upon admission who are mild to moderately ill"
Ontario Clinical Practice Guidelines 2021[16]	✗	✗	✗	Critically Ill: "Do not add… unless bacterial co-infection is strongly suspected" Mild-Moderate: "Antibacterial therapy is not routinely recommended outside clinical trials or where other indications would justify its use"

Ontario COVID-19 Drugs and Biologics Clinical Practice Guidelines Working Group

Antimicrobial and Immunomodulatory Therapy in Adult Patients with COVID-19

SCIENCE TABLE

Recommendations in this document apply to patients >18 years of age. Click the medication names in the table to view the associated science briefs.

Recommendations are based on the best available data and may change as additional data becomes available.

Infectious diseases consultation (where available) is recommended before any investigational treatment is offered to a patient with COVID-19 outside of a clinical trial.

Click for dosing and pharmacologic considerations for medications approved or under investigation for management of COVID-19.

SEVERITY OF ILLNESS	RECOMMENDATIONS
Critically Ill Patients Patients requiring ventilatory and/or circulatory support, including high-flow nasal oxygen, non-invasive ventilation, invasive mechanical ventilation, or ECMO. These patients are usually managed in an intensive care setting.	● Dexamethasone 6 mg PO/IV daily for 10 days (or until discharge if sooner) **is recommended** for critically ill patients. ● Tocilizumab **is recommended** for patients who are critically ill with suspected or confirmed COVID-19, who: are on optimal dexamethasone therapy; AND are within 14 days of hospital admission (or within 14 days of a new COVID-19 diagnosis if nosocomially acquired). ◆ **Ivermectin:** There is **insufficient evidence** to support the use of ivermectin in the treatment of critically ill patients with COVID-19 outside of clinical trials or where other indications would justify its use. Individuals who require ivermectin for other established non-COVID indications may use it if they develop COVID-19. ◆ **Vitamin D:** There is **insufficient evidence** to support the use of vitamin D in the treatment of critically ill patients with
	■ Bacterial co-infection is uncommon in COVID-19 pneumonia at presentation. **Do not add empiric antibiotics for bacterial pneumonia** unless bacterial infection is strongly suspected. Continue empiric antibiotics for no more than 5 days, and de-escalate on the basis of microbiology results and clinical judgment.
	◆ **Bamlanivimab** is **not recommended outside of clinical trials.**
Moderately Ill Patients Patients newly requiring low-flow supplemental oxygen. These patients are usually managed in hospital wards.	● Dexamethasone 6 mg PO/IV daily for 10 days (or until discharge if sooner) **is recommended** for moderately ill patients. ● Tocilizumab **is recommended** for patients who are moderately ill with suspected or confirmed COVID-19, who: have ◆ **Ivermectin:** There is **insufficient evidence** to support the use of ivermectin in the treatment of moderately ill patients with COVID-19 outside of clinical trials or where other indications would justify its use. Individuals who require ivermectin for other established non-COVID indications may use it if they develop COVID-19.
	◆ **Antibacterial therapy** is **not routinely recommended outside of clinical trials** or where other indications would justify its use.
	● **Remdesivir** 200 mg IV on day 1, then 100 mg IV daily for 4 days **is recommended** for patients who are moderately ill with suspected or confirmed COVID-19. ◆ **Bamlanivimab** is **not recommended outside of clinical trials**. ◆ **Interferon** (with or without combination of lopinavir-ritonavir and ribavirin) is **not recommended outside of clinical trials**. ◆ **Antibacterial therapy** is **not routinely recommended outside of clinical trials** or where other indications would justify its use.
Mildly Ill Patients Patients who do not require new or additional supplemental oxygen from their baseline status, intravenous fluids, or other physiological support. These patients are usually managed in an ambulatory/outpatient setting.	■ **Dexamethasone** is **not recommended** for mildly ill patients. ◆ **Ivermectin:** There is **insufficient evidence** to support the use of ivermectin in the treatment of mildly ill patients with COVID-19 outside of clinical trials or where other indications would justify its use. Individuals who require ivermectin for
	◆ **Antibacterial therapy** is **not routinely recommended outside of clinical trials** or where other indications would justify its use.
	◆ **COVID-19 convalescent plasma** is **not recommended outside of clinical trials** (unavailable outside of clinical trials). ◆ **Interferon** (with or without combination of lopinavir-ritonavir and ribavirin) is **not recommended outside of clinical trials**. ◆ **Antibacterial therapy** is **not routinely recommended outside of clinical trials** or where other indications would justify its use.

NOT RECOMMENDED for any patient severity: ■ **Hydroxychloroquine** or **chloroquine** ■ **Lopinavir/ritonavir**

Source: Ontario COVID-19 Drugs and Biologics Clinical Practice Guidelines Working Group, 202116

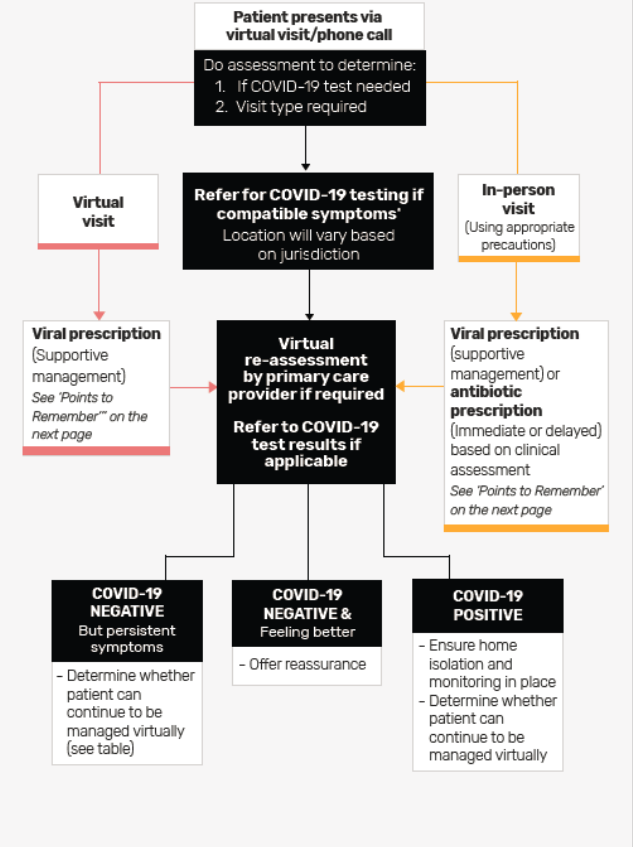
Version 2.0 | Updated April 6, 2021
https://doi.org/10.47326/ocsat.cpg.2021.2.0

Recommendations for Antibiotics in COVID-19[16]

Recommendation	Strength	Quality of Evidence
Avoid empiric antibiotics if proven or high likelihood of COVID-19, especially in mild-moderate illness	Weak	Very Low
Empiric antibiotics are reasonable in COVID-19 if radiological and/or inflammatory findings are compatible with bacterial co-infection or patient is immunocompromised (e.g., AIDS, prolonged steroids, immunosuppressants)	Weak	Good Practice
If starting antibiotics, blood and sputum cultures should be taken before starting antibiotics	Strong	Good Practice
If starting antibiotics, empiric atypical coverage is not likely unless patient is severely ill or high risk of Legionella	Weak	Very Low
Stop antibiotics if sputum, blood (and urinary antigen if taken) are negative at 48 hours	Weak	Good Practice
Total duration should be five days for patients with bacterial co-infection as long as there are improvements in signs and symptoms of pneumonia	Weak	Good Practice

Managing Respiratory Tract Infections in the Era of COVID-19

MANAGING RTIs: VIRTUAL CARE AND COVID-19



	INDICATIONS FOR VIRTUAL VISIT	INDICATIONS FOR IN-PERSON VISIT
SUSPECTED OR CONFIRMED COVID-19	• Fever • Respiratory symptoms • No shortness of breath	• Shortness of breath or hypoxia (if monitoring available) • Concerns of dehydration • Suspicion of secondary bacterial infection • Any red flags**
EAR PAIN (In children over 6 months of age)	• Symptoms <48 hours • Fever <39°C • Pain controlled with oral pain medication • Otherwise feels well	• Symptoms >48 hours despite adequate pain medications • Fever ≥39°C • Feels unwell
SORE THROAT	• Mild symptoms <48 hours • Low suspicion for bacterial pharyngitis, e.g.: ○ Over 15 years of age ○ No fever ○ Presence of cough or runny nose	• Persistent or worsening symptoms >48 hours, or • High suspicion of bacterial pharyngitis, e.g.: ○ Severe pain ○ No cough or runny nose ○ Fever without alternate cause
SINUS CONGESTION	• Mild symptoms <7 days • No red flags***	• Presence of red flags***
COPD EXACERBATION	• Patient able to do their activities of daily living • Patient known to provider and reliable for virtual follow-up	• Patient is too short of breath to do their activities of daily living
SUSPECTED PNEUMONIA	• Should be assessed in-person	• Assess clinically
INFLUENZA-LIKE ILLNESS, BRONCHITIS, COMMON COLD, ASTHMA	• High fever controllable with antipyretic • Cough • Congestion • Body aches • Mild GI symptoms	• Concerns of dehydration • Suspicion of secondary bacterial infection • Any red flags**

Source: © Choosing Wisely Canada. License: CC BY-NC-ND 4.0[17]

Case 1

56M with new fever and productive cough

PMH: hypertension

On Exam: 97% on RA, RR=22/min

T= 38.6C, not in respiratory distress

Labs: WBC 7.4 $x10^9$

Imaging: bilateral ill defined patchy opacities in all lung zones

NP swab for COVID-19 and influenza

Conclusions

- COVID-19 presents a risk for worsening antimicrobial resistance
- Bacterial co-infection in COVID-19 is uncommon (<10%)
- Antibacterial prescribing in COVID-19 is frequent (70-75%)
- Efforts should be made to improve the quality of antibiotic prescribing
  - Avoid empiric antibiotics in COVID-19 unless clear evidence of bacterial pneumonia or severely ill or immunocompromised
  - If prescribing antibiotics in COVID-19, blood and sputum cultures should be performed prior to antibiotic treatment
  - Antibiotics should be re-assessed at 48h and discontinued if COVID-19 positive and blood and sputum cultures negative

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