COVID-19 and the Impact of Secondary and Co-Infections

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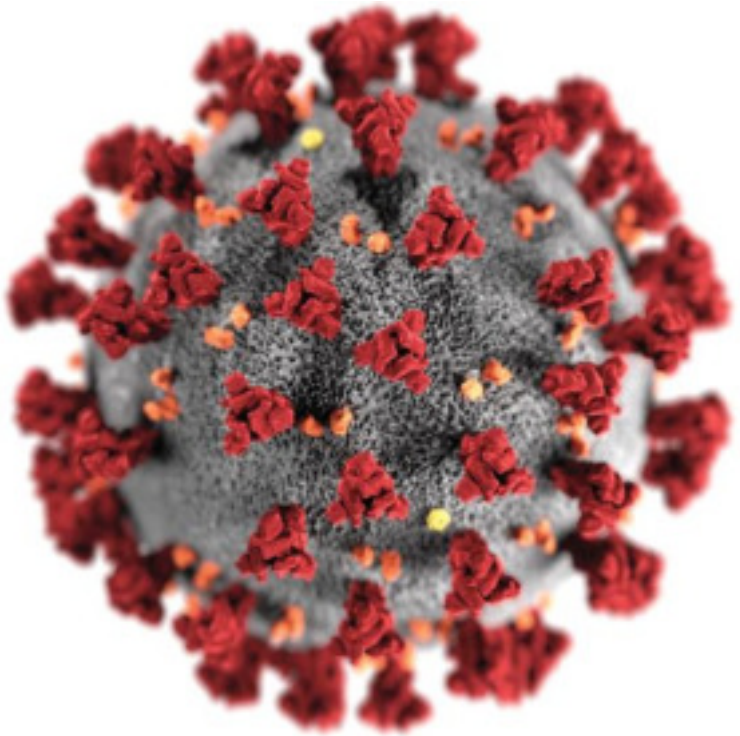
Objectives

- Review COVID-19 background as it relates to secondary and co-infections
- Understand the current limitations of traditional methods in diagnosing secondary and co-infections
- Identify appropriate COVID-19 patients at risk for secondary or co-infections to be tested with T2 Biosystems' panels
- Learn about T2 Biosystems response to COVID-19

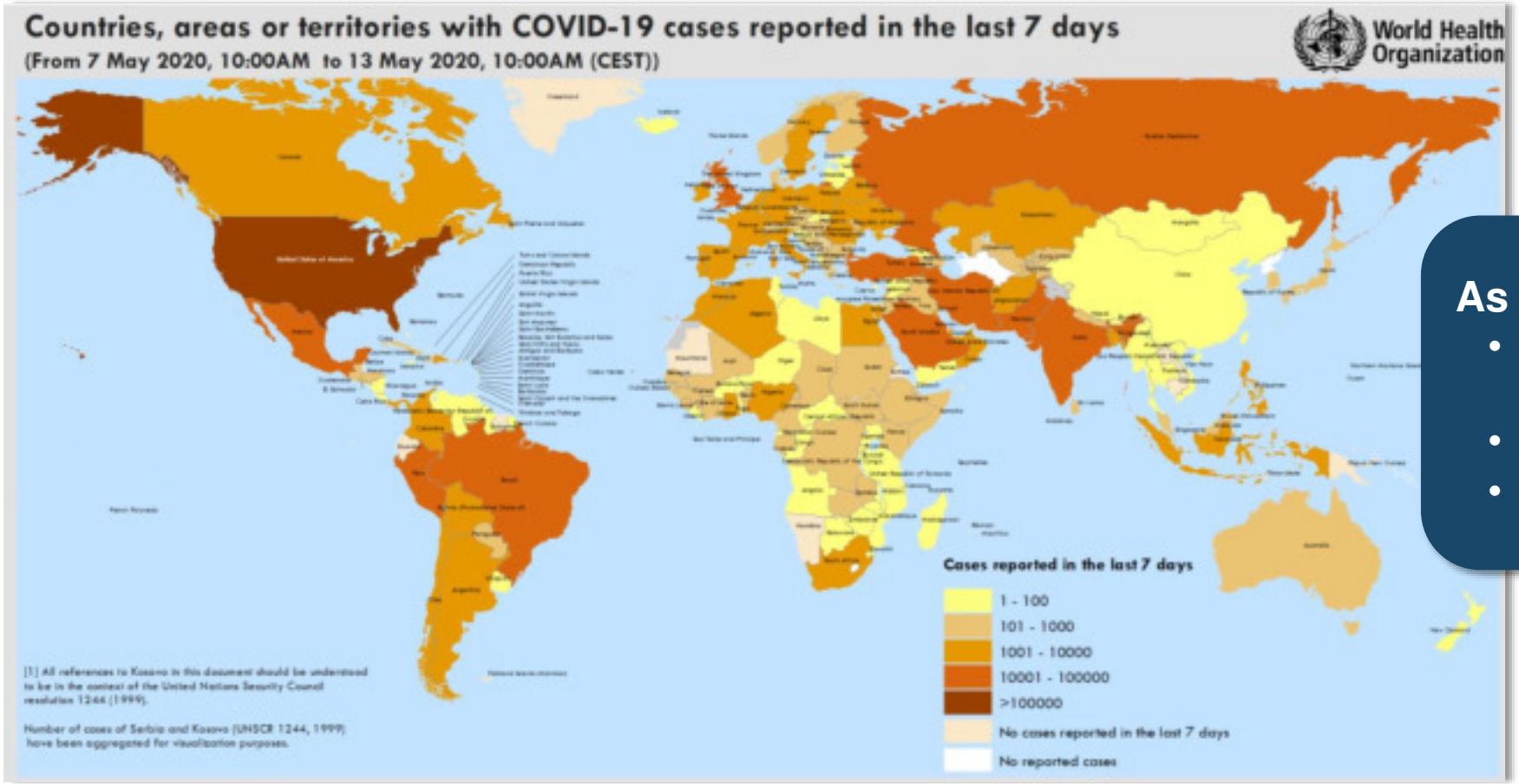


COVID-19 Overview

- SARS-CoV2 is a novel coronavirus that was first reported in China in December 2019
- Individuals of all ages are at risk for infection and severe disease with the highest probability of fatality in people aged ≥65
- At present no agent is recommended for pre or post exposure prophylaxis against SARS-CoV-2 outside of a clinical trial
- Currently there are no Food and Drug Administration (FDA)-approved drugs for COVID-19. However, an array of drugs approved for other indications, as well as multiple investigational agents, are being studied for the treatment of COVID-19 in several hundred clinical trials around the globe
  - Remdesivir has shown promise in clinical trials and has EUA but access is still challenging and formal peer-reviewed publications are pending

NIH Guidelines

COVID-19 Statistics Worldwide



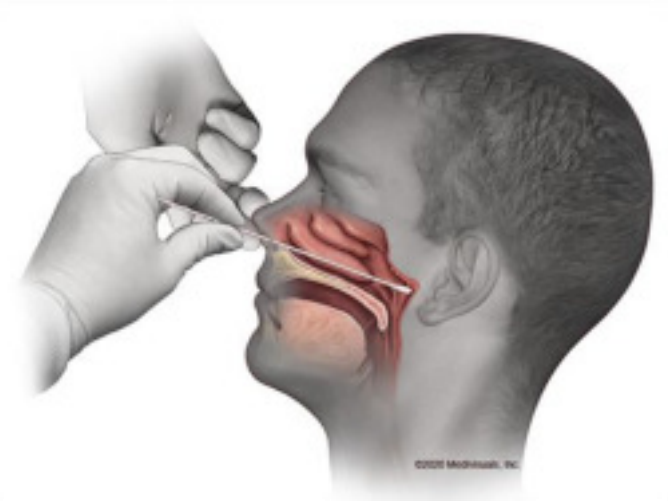
As of May 13, 2020:

- Total cases: > 4 million
  - ≈80,000 new cases/day
- Total deaths: >280,000
- 201 countries/territories

WHO Coronavirus Situation Report https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200513-covid-19-sitrep-114.pdf?sfvrsn=17ebbbe_4

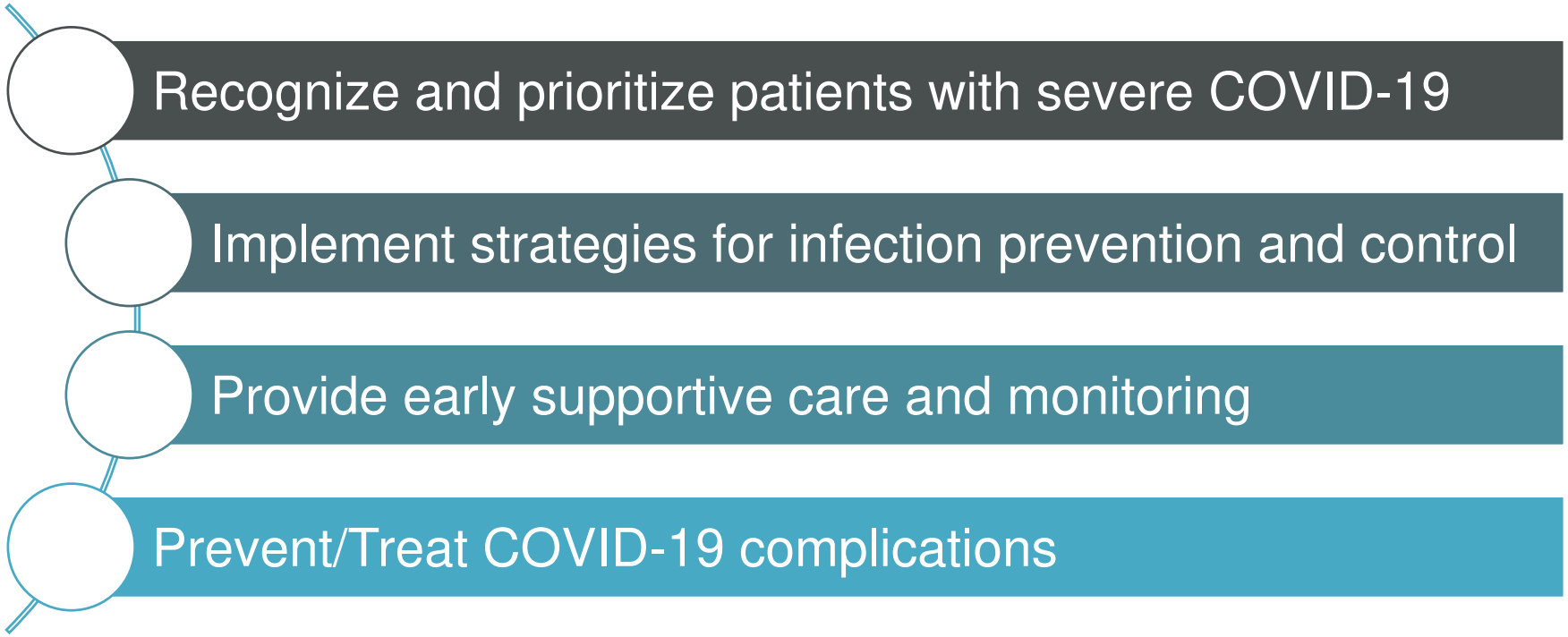
COVID-19 Diagnosis

- CDC has established a priority system for diagnostic testing for SARS-CoV-2 infection based on availability of testing[1]
- More than 70 diagnostic tests for SARS-CoV-2 infection have received Emergency Use Authorization (EUA) by the FDA
  - Most initial diagnostic tests have relied on reverse transcriptase polymerase chain reaction (RT-PCR) platforms
  - Lower respiratory tract samples have a higher yield than upper tract samples
  - Availability of testing remains a concern
  - High false negative rates have been reported in recent studies[2]



1. Centers for Disease Control and Prevention. Evaluating and testing persons for coronavirus disease 2019 (COVID-19). 2020. Available at: https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html.
2. Basu et al; Performance of the rapid Nucleic Acid Amplification by Abbott ID NOW COVID-19 in nasopharyngeal swabs transported in viral media and dry nasal swabs, in a New York City academic institution. 2020. Available at: https://www.biorxiv.org/content/10.1101/2020.05.11.089896v1.full.pdf+html

COVID-19 Treatment Goals



COVID-19 Diagnostic Challenges

- Risks of False Negatives with COVID-19 testing
  - Critically Ill Patients
    - Lack of access to investigational therapy
    - Inappropriate isolation or use of PPE causing risk to health care providers
  - Mild to Moderately Ill Patients
    - Exposure in the workplace
    - Lack of appropriate quarantine

Secondary and Co-Infections

- Secondary infections with bacterial, viral, and other pathogens are well-described in influenza, SARS, MERS and other respiratory viral illnesses
- Data regarding secondary and co-infections in COVID-19 are still emerging
- **Secondary infection**: Also known as superinfection is an infection following a previous infection especially when caused by microorganisms that are resistant or have become resistant to the antibiotics used earlier
- **Co-infection**: An infection that occurs simultaneously with the initial infection
- Superinfections and coinfections can increase pathogenesis increasing the morbidity and mortality of viral infections

Risk Factors for Secondary and Co-Infections

- Hospitalized patients, especially critically ill and mechanically ventilated are at risk for infections, independent of SARS-CoV-2
- Severe COVID-19 is associated with immune dysregulation creating opportunity for bacterial or fungal proliferation
- Cytokine release syndrome, immune exhaustion and/or lung damage may pre-dispose to superinfection

Risk Factors for Infection with Resistant Gram-negative Pathogens[1-6]
• Receipt of broad spectrum antibiotic therapy in last 90 days • Family member with MDRO infection • Current hospitalization of at least 5 days • Residing in a nursing home or long-term care facility • Hospitalized for at least 2 days within last 90 days • Chronic dialysis within 30 days • Home infusion therapy • Immunosuppressive disease and/or chemotherapy • Septic shock at the time of infection • ARDS at the time of infection

1. 2005 HCAP/HAP/VAP Guidelines. 2005
2. Patel G, et al. Infect Control Hosp Epidemiol. 2008
3. Schwaber MJ, et al. Antimicrob Agents Chemother 2008
4. Gupta N, et al. Clin Infect Dis. 2011
5. HAP/VAP Guidelines Clin Infect Dis. 2016
6. Goodman K, et al. Clin Infect Dis.2016

Diagnostic Challenges of Secondary and Co-Infections

- During 1918 and subsequent influenza pandemics, bacterial superinfections were common causes of mortality and morbidity[1]
- Studies have shown that up to 65% of laboratory-confirmed cases of influenza infection are complicated by bacterial co/superinfections with the majority being between 11-35%
- Diagnosis of secondary bacterial and fungal infections requires a high index of suspicion for infection beyond the original infection
- Conventional diagnostic tests often have poor sensitivity in identifying causative pathogens
  - In cases of community acquired pneumonia – only 44% of cases had a pathogen identified
  - 50-73%[2,3] of bacterial and fungal pathogens identified on first blood culture draw

1. Morens DM, Taubenberger JK, Fauci AS. Predominant role of bacterial pneumonia as a cause of death in pandemic influenza: implications for pandemic influenza preparedness. J Infect Dis 2008; 198(7): 962-70.
2. Clancy, C. J., & Nguyen, M. H. (2013). Finding the "missing 50%" of invasive candidiasis: how nonculture diagnostics will improve understanding of disease spectrum and transform patient care. Clinical infectious diseases, 56(9), 1284-1292.
3. Cockerill III, F. R., Wilson, J. W., Vetter, E. A., Goodman, K. M., Torgerson, C. A., Harmsen, W. S., ... & Wilson, W. R. (2004). Optimal testing parameters for blood cultures. Clinical Infectious Diseases, 38(12), 1724-1730.

Data to Date: Secondary and Co-Infections in COVID-19

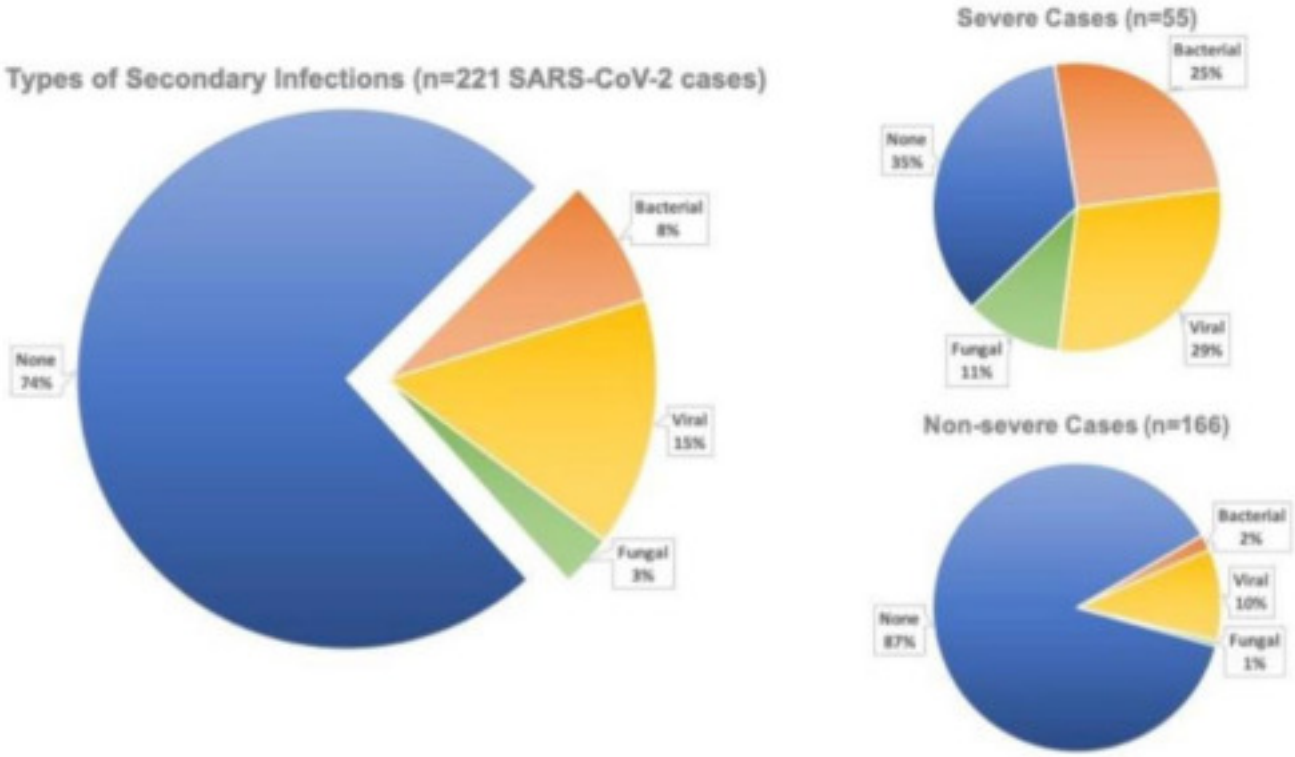


Figure 1. Types of secondary infections among COVID-19 patients, Zhongnan Hospital, Wuhan, China. Created from source data in Zhang et al., 2020.

Preliminary studies suggest secondary infections are common, especially in severe cases

Case Study: Secondary Candidemia in a COVID-19 Positive Patient

- Case Summary
  - 67 year old patient admitted with cough and fever after recent travel to New York
  - Day 1: SARS-CoV-2 PCR was positive
    - Treated with 5 day of empiric hydroxycholorquine and azithromycin
    - An additional 5 days of hydroxycholorquine was given after the first course
  - Day 15: Ampicillin/sulbactam started for suspected aspiration pneumonia
  - Day 20: Blood cultures obtained due to persistent fever
    - Sputum culture revealed *C. albicans* (colonization)
  - Day 22: Blood culture positive for yeast, identified as *C. albicans* and anidulafungin started
  - Day 27: T2Candida and blood culture were both negative
  - Patient completed 14 days of antifungal and was discharged in stable condition
- Case Analysis
  - Patient was worsening 3 weeks into hospitalization and blood cultures were obtained. Candidemia was not initially suspected, thus T2Candida not ordered initially and antifungal not started. Patient had several risk factors including: extended ICU stay, broad-spectrum antimicrobials and colonization with yeast (positive sputum culture). This highlights the importance of early suspicion and testing for both bacterial and fungal pathogens.

COVID-19 Impact on Antimicrobial Stewardship and Antibiotic Overuse

- AMR infections are estimated to cause 700,000 deaths annually worldwide
  - This number is projected to increase to 10 million per year by 2050[1]
- Data on antibiotic prescribing in COVID-19 patients has ranged from 58-100%[2-6]
- Widespread usage of antimicrobial therapy is understandable, albeit concerning
  - 25-70% of severely ill COVID-19 patients manifested evidence of sepsis[2,4,6]
  - It is difficult to exclude bacterial or fungal superinfections based on signs and symptoms, physical findings and radiology reports

1. O'Neill J. Tackling drug-resistant infections globally: Final report and recommendations 2016;
2. Zhou F. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020.
3. Cao J, Clinical Features and Short-term Outcomes of 102 Patients with Corona Virus Disease 2019 in Wuhan, China. Clin Infect Dis 2020.
4. Chen T,. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ 2020; 368: m1091.
5. Dong X, Eleven faces of coronavirus disease 2019. Allergy 2020.
6. Huang C, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020.

Role of T2 in Diagnosis of Secondary Bacterial and Fungal Infections in COVID-19 Patients

Our Comprehensive Product Portfolio is Simple to Use

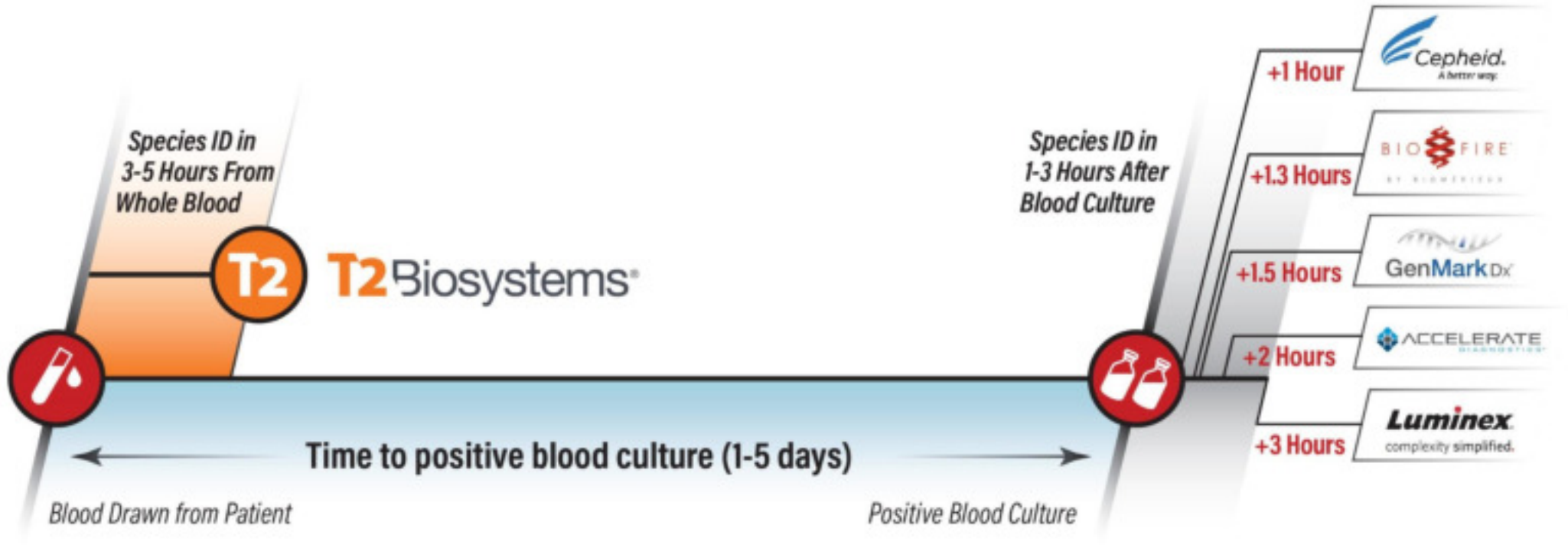
Fully-automated T2Dx Instrument

- Fast: Results in 3-5 hours
- Easy: no sample preparation
- Sensitive: ~1 CFU/mL LoD

T2Candida	T2Bacteria
Sensitivity: 91.1%[2] Specificity: 99.4%[2]	Sensitivity: 95.4%[1] Specificity: 98.0%[1]
C. albicans *C. tropicalis* *C. parapsilosis* *C. krusei* *C. glabrata*	*E. faecium* *S. aureus* *K. pneumoniae* *P. aeruginosa* *E. coli*
FDA-Cleared **CE-marked** 1-3 CFU/mL LoD	**FDA-Cleared** **CE-marked** 2-11 CFU/mL LoD

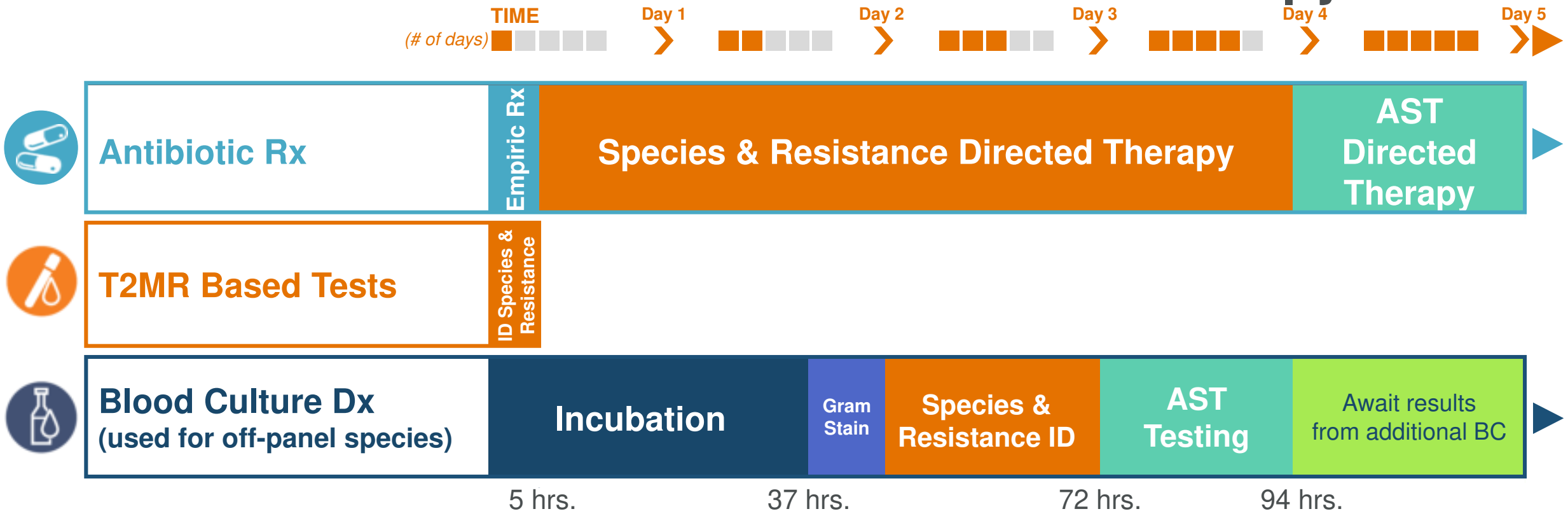
1. T2Bacteria Pivotal Clinical Study. This is a combination of samples run in both prospective and contrived arms of study. T2Bacteria showed an overall average sensitivity of 90% in the prospective arm of the study and the contrived arm an overall average PPA of 97%.
2. Mylonakis, E., Clancy, C.J., Ostrosky-Zeichner, L., et al. (2015). Clinical Infectious Diseases

Why Wait Days for Results?



*T2 Biosystems' diagnostic panels are the **only FDA-cleared** tests that provide species identification, **directly from whole blood** and within **3-5 hours of the first blood draw**, which is often before the second dose of broad-spectrum antibiotics is delivered, enabling clinicians to target therapy faster than current standard of care.*

T2MR & Blood Culture Results Influence Therapy



- T2MR Based tests enable more rapid targeted therapy based on species ID & resistance
- Across 3 studies, 94%-100% of patients are correctly treated after species ID, not after assessment of susceptibility testing, demonstrating effectiveness of antibiogram-directed therapy[1-3]
- Numerous studies indicate that this will reduce both LoS and mortality for infected patients

1. Doern et al. *J Clin Micro* 1994;
2. (2) Byl et al. Clin Infect Dis 1999;
3. Kerremans et al. J Clin Microbiol 2012

* Average Turn around times from Nguyen et al. *Annals Int Med* 2019

Role of T2: Who to Test for Secondary Infections

- **Testing populations provided by current T2Candida and T2Bacteria customers**
  - COVID-19 Patients Admitted to the ICU
  - COVID-19 Patients experiencing new fever/deterioration
  - Critically ill/septic patients who are negative for COVID-19
  - Others per institutional protocol/risk factors
- **Using T2 diagnostic panels as a stewardship tool**
  - Confidently diagnose pathogen causing secondary infection and start targeted therapy
  - Ability to more confidently stop empiric antimicrobials in specific scenarios
  - High negative predictive values allow for consideration of de-escalating antifungal and/or antibacterial therapy in appropriate cases

T2SARS-CoV-2™ Panel – in Development

- T2 Biosystems recently entered into a worldwide licensing agreement for a rapid COVID-19, novel coronavirus test developed by the Center of Discovery and Innovation at Hackensack Meridian Health, which is currently in use under EUA guidelines
- The proprietary information we licensed from Hackensack is accelerating the development of our T2SARS-CoV-2 Panel, which will run on the T2Dx Instrument
- We plan to make the T2SARS-CoV-2 Panel available to customers under the FDA Emergency Use Authorization guidelines
- At this time, we anticipate making our T2SARS-CoV-2 Panel available to U.S. customers as early as the end of this quarter

Conclusions

- Secondary infections, including antimicrobial resistant infections, are likely to occur in a clinically significant proportion of hospitalized patients with COVID-19
- Highest risk is likely in ventilated patients with longer stay and higher severity of illness
- Stewardship will be crucial for limiting broad-spectrum antimicrobial use in hospitalized patients
- Non-culture based diagnostics such as T2Bacteria and T2Candida will play a role in diagnosing secondary infections in COVID-19 patients especially where cultures may be falsely negative due to prior empiric antimicrobial exposure

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Thank You and Questions

For additional information on T2 Biosystems and our diagnostic portfolio, please visit our website (www.t2biosystems.com) or email us at info@t2biosystems.com.