

Novel Small Molecule Antibiotic Targeting *C. difficile*



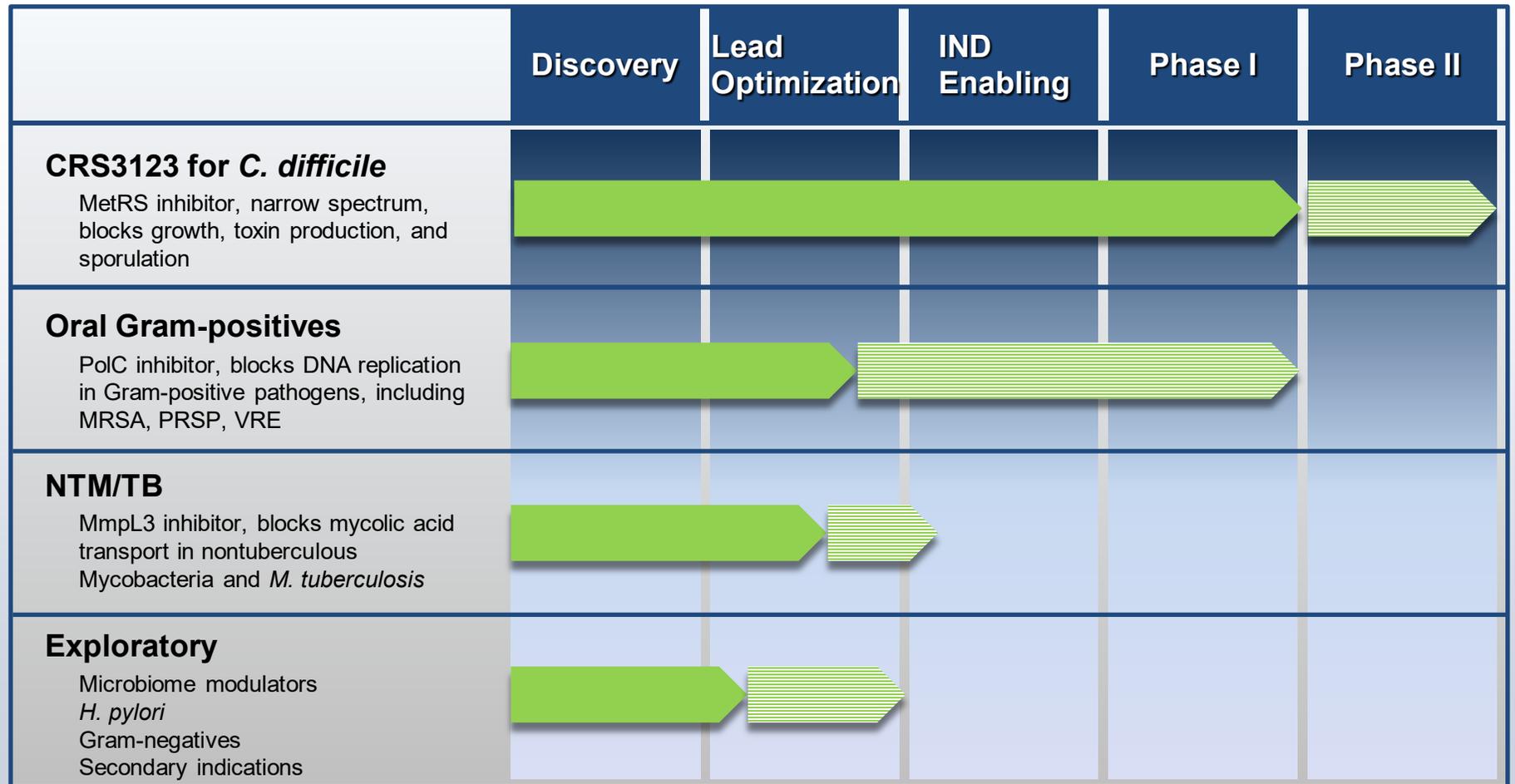
Urs Ochsner, PhD
Crestone, Inc.

PACCARB – February 27, 2020

Crestone, Inc., a Small Business Focused on Antibiotics

BACKGROUND

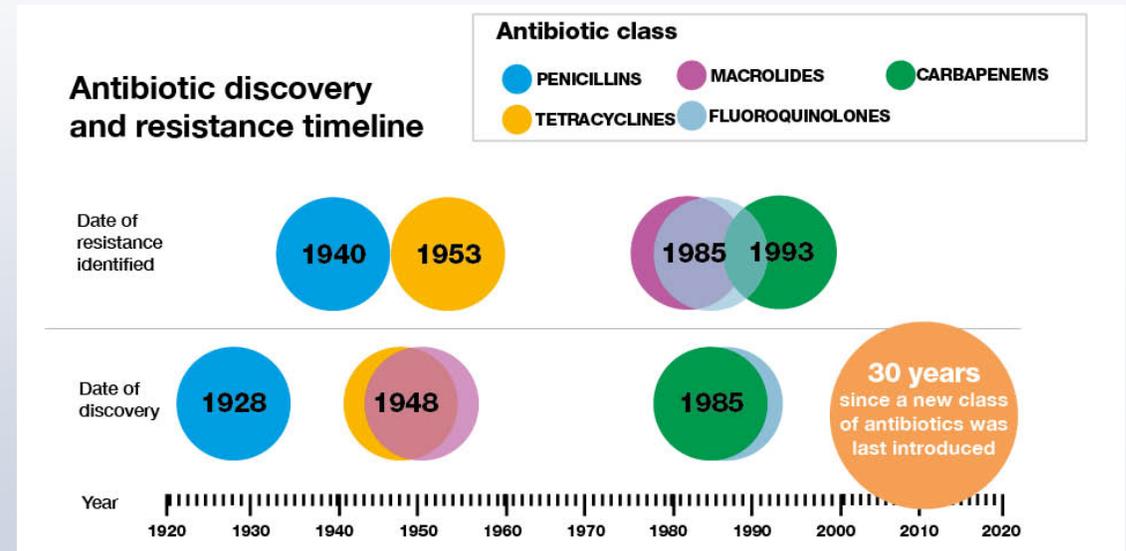
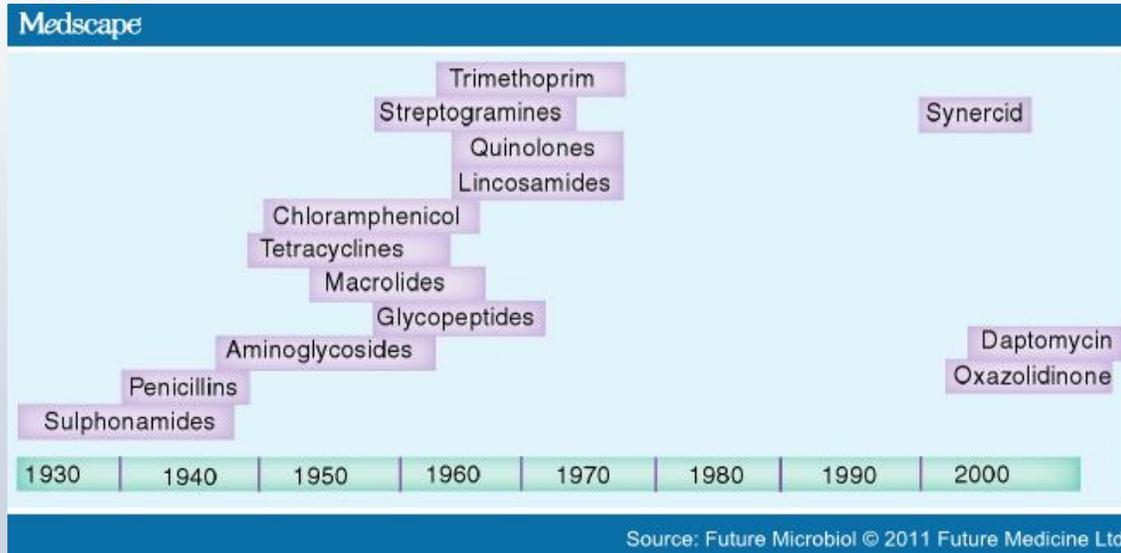
- Founded in 2009
- Boulder, Colorado
- Novel mode-of-action
- Funded through grants and contracts
- Active pipeline (current activities)
- One clinical-stage program (CDI)
- Promising pre-clinical stage programs
- Runway of 4 years



 Completed
  Current activities

Past Success of Antibiotics: Broad-spectrum Activity

- Nearly all antibiotics discovered by 1985 are broad-spectrum, and commercially successful
- Very few new antibiotics are discovered, clinical use of old antibiotic classes remains high
- Antibiotic overuse is leading to resistance development and collateral damage (e.g. *C. difficile*)



AMR Threats Today and in 2050 – What Should We Do?

- **AMR Report CDC (2019)**

- 2,868,700 antibiotic-resistant infections occur **in the United States** each year, and 35,900 people die.
- In addition, 223,900 people in the United States required hospital care for *C. difficile* and at least 12,800 people died in 2017.

- **Global problem now and in the future (O’Neill Report 2016)**

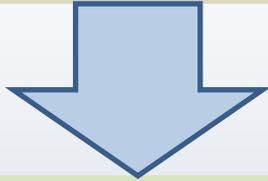
- 700,000 people **in the world** die of resistant infections every year.
- By 2050, 10 million lives a year and a cumulative 100 trillion USD of economic output are at risk due to drug-resistant infections.
- Antibiotics are an essential part of modern medicine (surgery, caesarean sections, joint replacements, chemotherapy for cancer)

- CDC (2019). Antibiotic Resistance Threats in the United States. Atlanta, GA: U.S. Department of Health and Human Services, CDC.
- O’Neill, J. (2016) Tackling Drug-Resistant Infections Globally: Final Report and Recommendations.

Post-Antibiotic Era Challenges and Opportunities

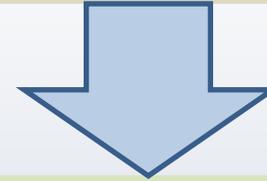
The specter of losing antibiotics as an essential part of modern medicine

- Supply and demand problem
- Antibiotic management and antimicrobial stewardship



Changes needed

- Preservation of existing antibiotics
- Reduction of demand
- Increase in supply
- Accountability



New approaches

- New antibiotics with novel mode of action
- Narrow spectrum agents
- Non-traditional approaches
- Vaccines

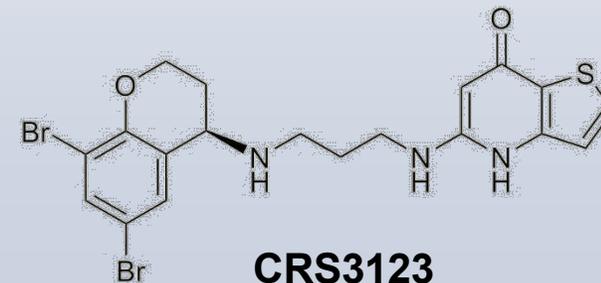
C. difficile Infection (CDI)

- **CDI often follows treatment with broad-spectrum antibiotics due to disruption of healthy gut microbiota**

- **Old suboptimal drugs** such as metronidazole and vancomycin are also broad-spectrum and further disturb the gut microbiota and/or delay its recovery
- **Recurrence** is high (20-40%)
- Selection of **vancomycin-resistant Enterococci** (VRE)
- Change in CDI **treatment guidelines** in 2018: Metronidazole no longer widely recommended

- **New agents to treat CDI**

- Cadazolid, surotomycin, LFF-571 have shown no advantage over vancomycin – all are broad-spectrum!
- **Narrow spectrum agents**
 - Fidaxomicin (FDA-approved 2011, Merck)
 - Ridinilazole (Phase 3, Summit Therapeutics)
 - CRS3123 (Phase 2, Crestone, Inc.)



Narrow-spectrum Agent CRS3123 for CDI Treatment

- **CRS3123 mode of action**

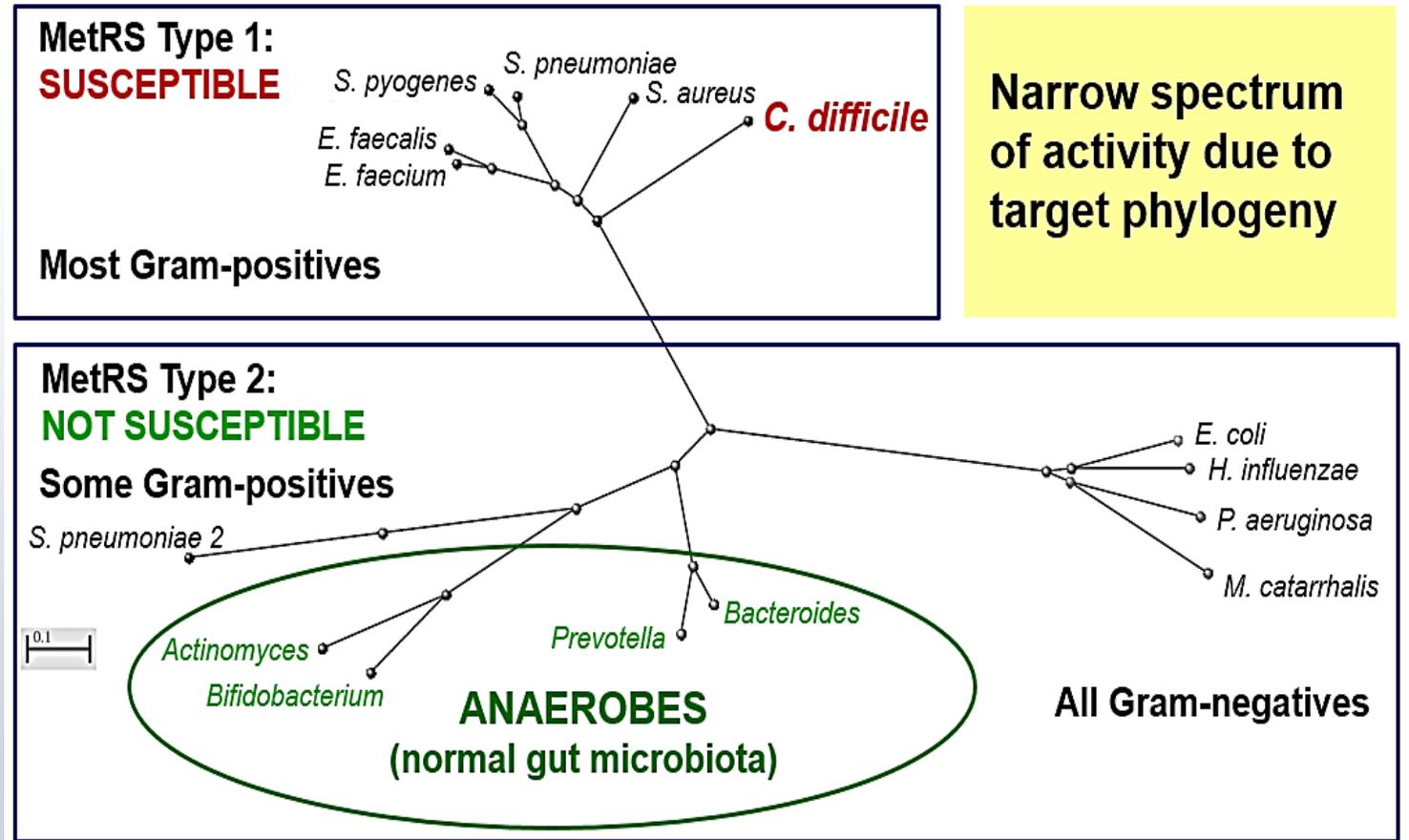
- Inhibits protein synthesis (essential target MetRS)
- Blocks toxin production
- Inhibits spore formation

- **Phase 1 (SAD/MAD)**

- Safe and well tolerated
- Minimal disturbance of healthy gut microbiota

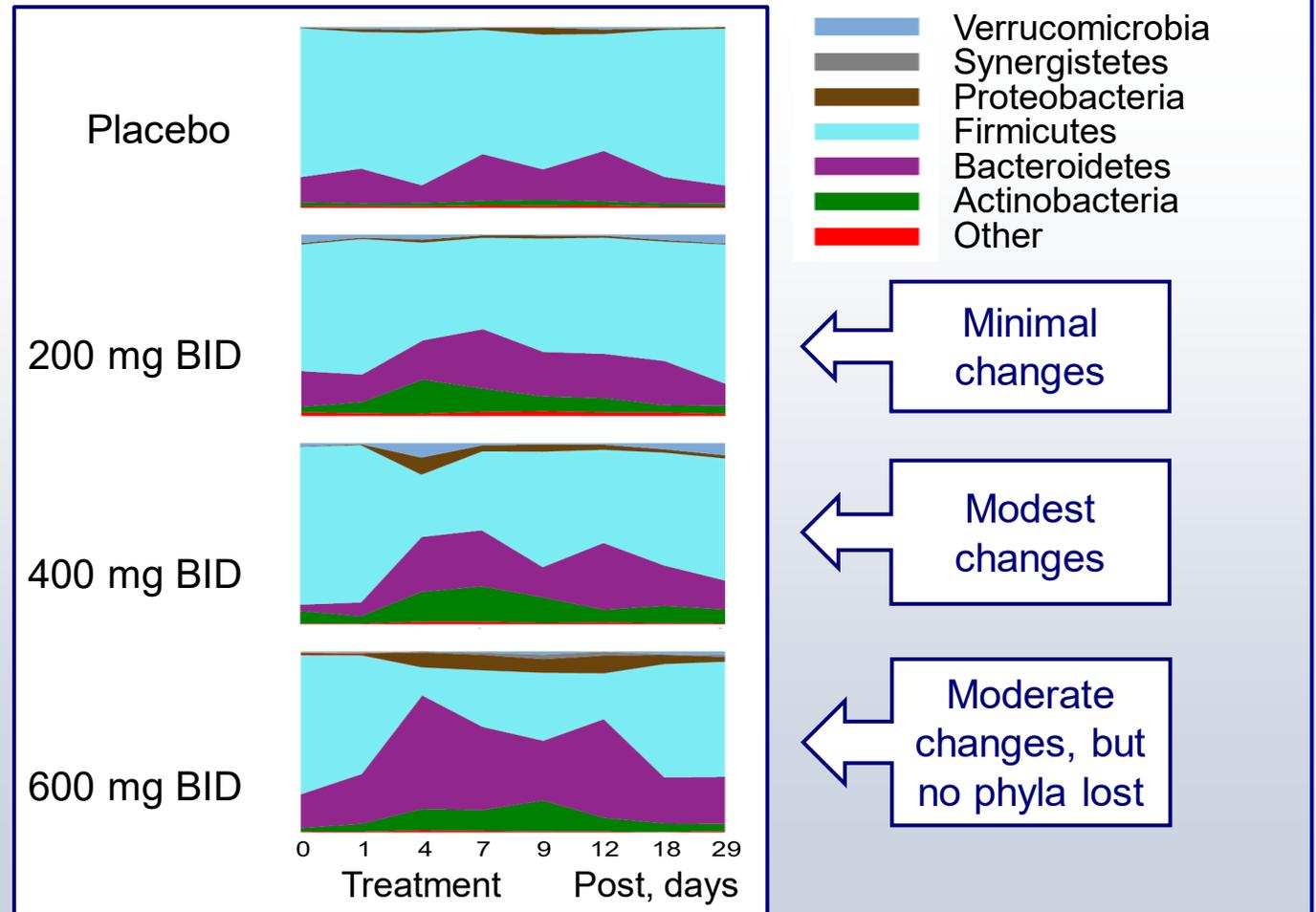
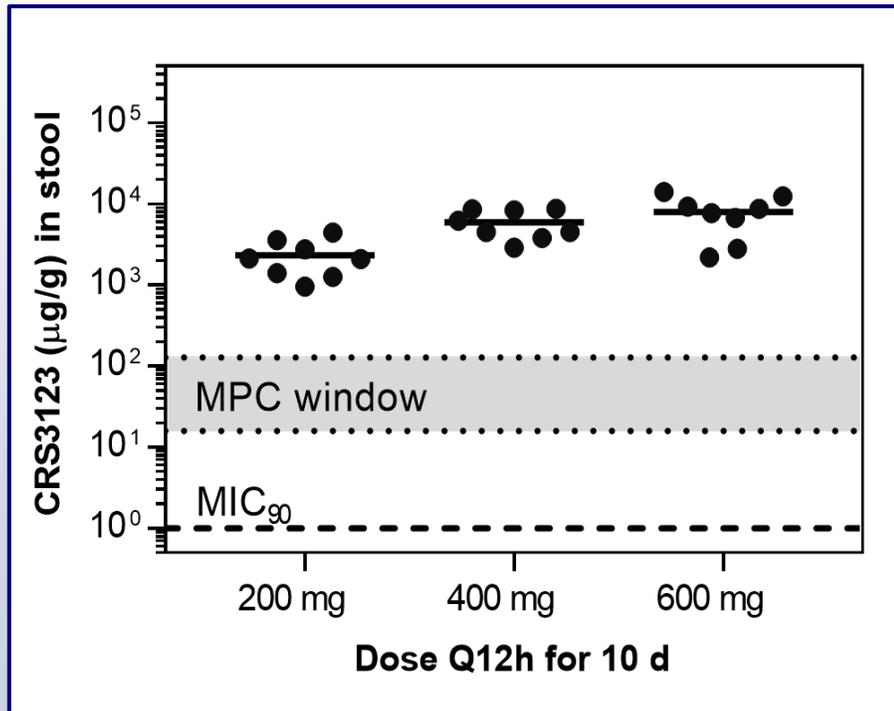
- **Phase 2 (ongoing)**

- Faster relief of symptoms?
- Lower recurrence rates?



Minimal Effect on Normal Gut Microbiota

- Low systemic absorption
- High accumulation in the gut
- Sparing of the normal gut microbiota



Advantages of Narrow-spectrum CDI Agents

- **Improved Patient Outcomes**

- Faster relief of symptoms
- Reduction in recurrence rates

- **Reduced Economic Burden**

- Shorter hospital stays
- Fewer follow-up visits to healthcare providers
- Reduction in directly attributable healthcare costs (\$1B estimated in 2017 for CDI (CDC, 2019))

- **Public Health Benefit**

- Low propensity for collateral damage (e.g. selection of VRE)
- Antibiotic stewardship
- Value added

ISSUES:
Drug pricing
Hospital reimbursement
Limited market segment

VANCOMYCIN-RESISTANT
ENTEROCOCCI (VRE)

THREAT LEVEL **SERIOUS**



54,500

Estimated cases
in hospitalized
patients in 2017



5,400

Estimated
deaths in 2017



\$539M

Estimated attributable
healthcare costs in 2017

THANK YOU!

- **NIAID and DMID – funding of Phase 1 and Phase 2 clinical studies**
- **Crestone, Inc. scientists, consultants and collaborators**
- **PACCARB for the invitation**



Boulder, Colorado