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Meta-Analysis of Response Rates Among Placebo-Treated Patients from Five Clinical Trials of Experimental Recurrent *Clostridium difficile* Therapeutics

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Background

- Recurrent *Clostridium difficile* infections (rCDI) has been recognized as an urgent health threat.
- Numerous therapeutics are being developed to reduce recurrence and have been evaluated in clinical trials.
- RBX2660 is a standardized microbiota-based drug manufactured from live human-derived microbes and was evaluated in PUNCH CD 2, a randomized, placebo-controlled Phase 2b trial for rCDI.
- Twenty (20) PUNCH CD 2 patients in the placebo arm met response criteria of no CDI recurrence within 8 weeks.
- To contextualize this placebo response observation, we conducted a meta-analysis of response rates among placebo-treated patients in additional rCDI trials.

Methods

- Five (5) blinded, randomized, and placebo-controlled trials were included in this meta-analysis [1-5].
- Studies required patients to have ≥1[5] or >2[1-4] prior CDI recurrences.
- All patients completed standard-of-care antibiotic course prior to experimental treatment.
- Four (4) studies tested a vehicle placebo administered by the same route as the active treatment (oral, intravenous, or enema) [1,2,4,5], and 1 study tested an autologous fecal transplant administered via enema.
- Response to treatment was defined as no CDI recurrence within 8-12 weeks.
- The proportional response rates with 95% confidence interval were calculated and compared in aggregate and among studies.

Disclaimer: This analysis was funded by Rebiotix Inc., Roseville, MN.

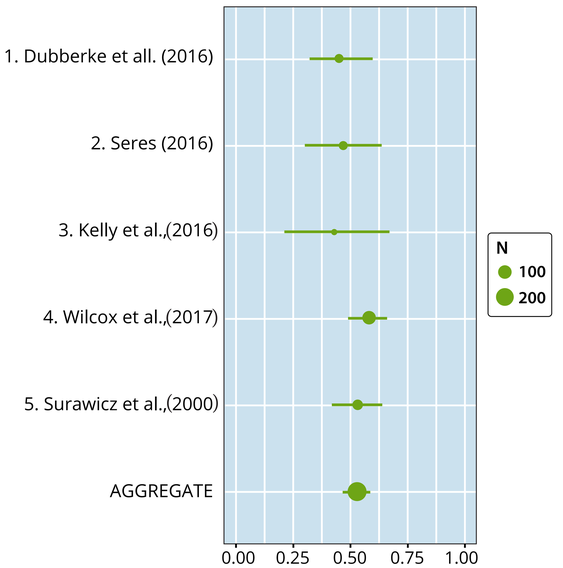
Results

- A total of 154 of 292 placebo-treated patients (53%) met study-specific response criteria.
- Placebo response rates ranged from 43%-58%.
- No study group presented a significantly different outcome from the aggregate cohort.
- No correlation of response with placebo administration route was observed.

Table 1: Randomized, controlled, double-blind studies included in this meta-analysis.

REF	LEAD AUTHOR (YEAR)	EXPERIMENTAL TREATMENT	PLACEBO (n)	DELIVERY	PLACEBO RESPONDERS (%)
1	Dubberke (2016)	RBX2660	Saline (44)	Enema	20 (45.5%)
2	Seres (2016)	SER-109	Glycerol/Saline (30)	Oral	14 (46.7%)
3	Kelly (2016)	Heterogenous FMT	Autologous FMT (14)	Enema	6 (42.9%)
4	Wilcox (2017)	Bezlotoxumab, Bezlotoxumab + actoxubab	Saline (126)	Intravenous	73 (57.9%)
5	Surawicz (2000)	*Saccharomyces boulardii*	Vehicle (78)	Oral	41 (52.6%)

Figure 1. Placebo Response Rates are Similar in Clinical Trials Evaluating Treatments for Recurrent *Clostridium difficile* Infection.



The Forest plot shows the placebo success rate for each study included in the meta-analysis with the addition of the aggregate result. Placebo group size (N) is represented by circle diameter.

References

1. Dubberke E et al. Presented at Infectious Diseases Week 2016, New Orleans, LA.
2. Seres Therapeutics [news release]. Cambridge, MA: Seres Therapeutics, Inc. communication; July 29, 2016. http://ir.serestherapeutics.com/phoenix.zhtml?c=254006&p=irol-newsArticle&ID=2240833. Accessed May 16, 2017.
3. Kelly CR et al. *Ann Intern Med.* 2016:165:609-616
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Conclusion

- This meta-analysis demonstrates that response rates for blinded placebo-treated patients are consistent among 5 trials of experimental rCDI therapeutics, including a phase 2B trial of RBX2660.
- This analysis provides a useful framework for interpreting published rCDI trials, and for designing and interpreting future rCDI therapeutics trials.
- Further evaluation of placebo response in rCDI patients is warranted.