

**SER-109 and the Prevention of
Clostridium difficile Infection (CDI) in
Patients with Multiple Recurrent
Infections**

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SER-109 and the Prevention of Recurrent *Clostridium difficile* infection (CDI)



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- The foundation for the SER-109 development program is based on scientific knowledge that has emerged on the importance of the human microbiome in states of health and disease.

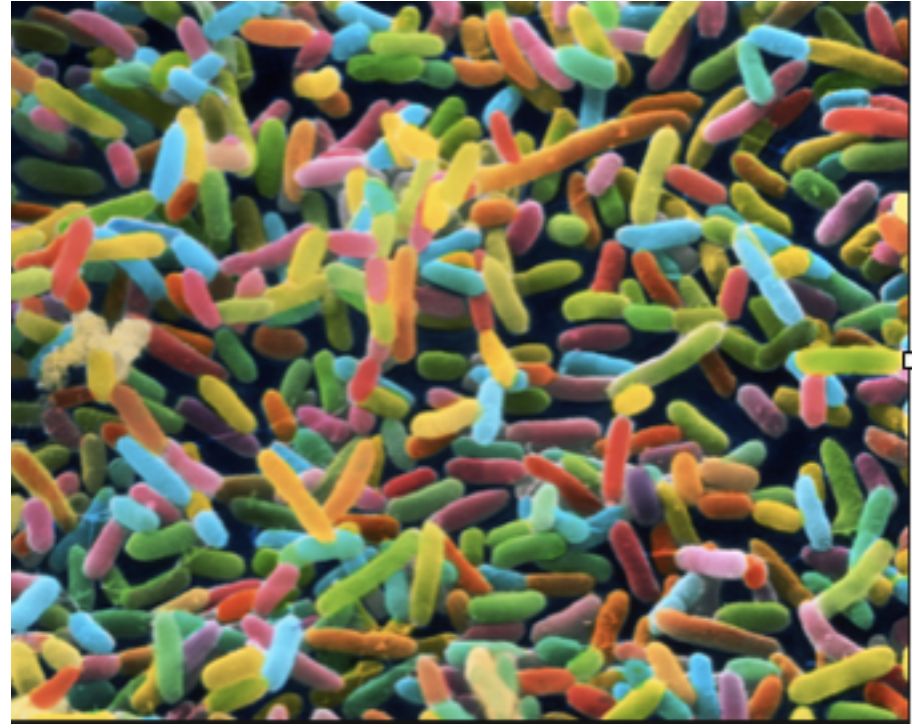


The Human Microbiome Project

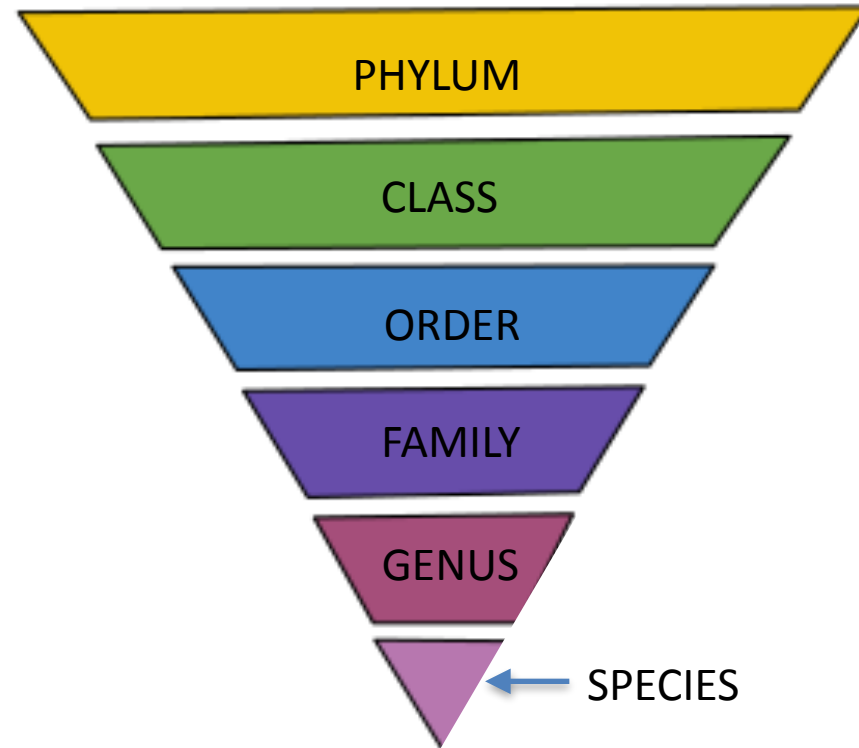


The Human Microbiome Project

- **The Human Microbiome Project has shown that 100 trillion bacteria live in a healthy person's gut**
- The diversity of the bacteria in our gut help us live a healthy life by:
 - Breaking down sugars
 - Releasing energy from dietary sources
 - Building up proteins
 - Reducing inflammation
 - Other important functions

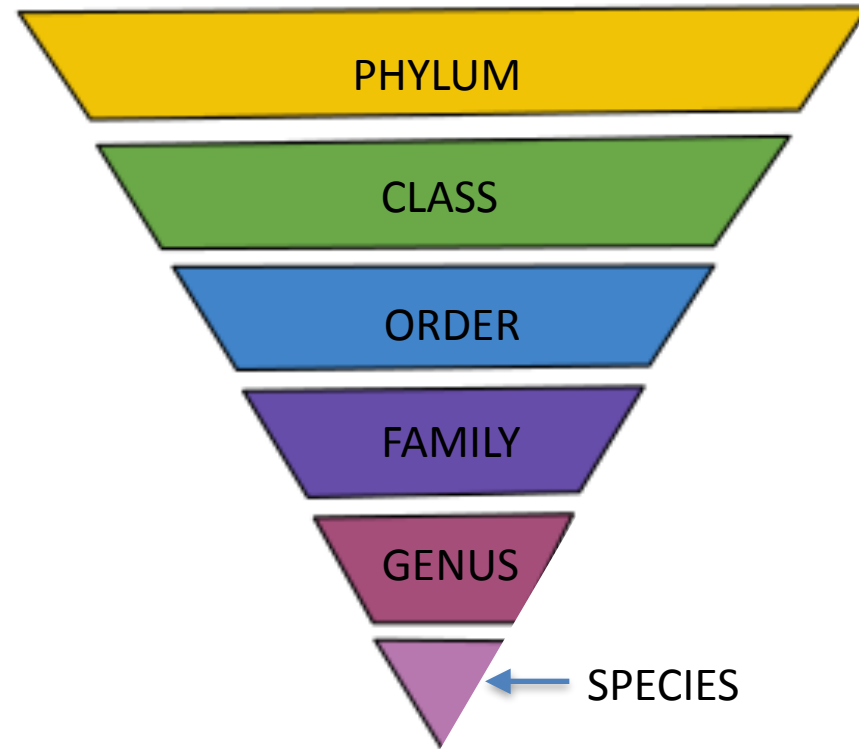


The classification system for Bacteria



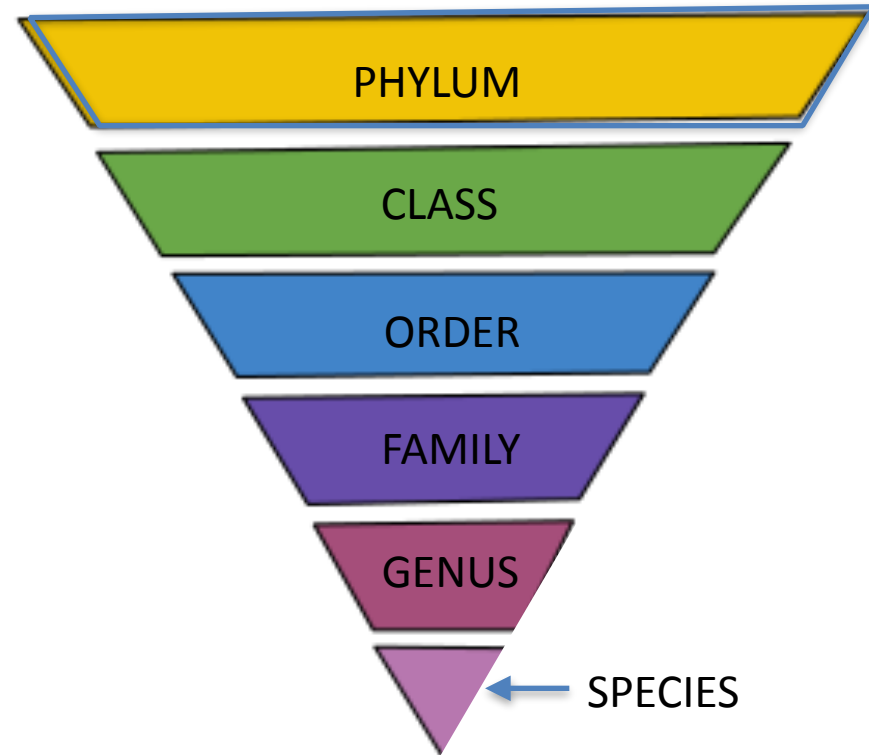
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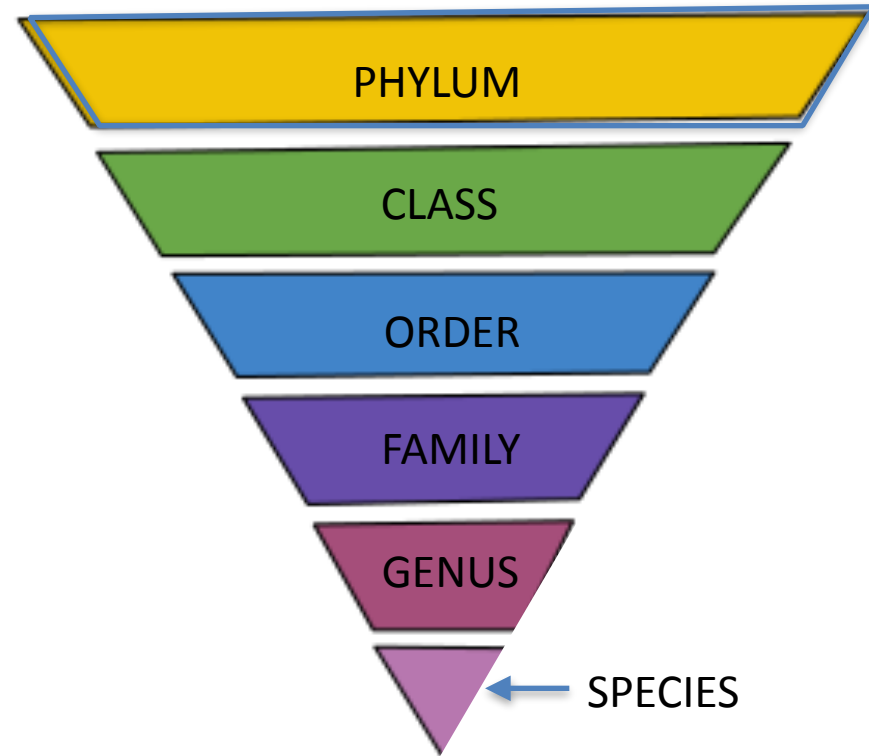
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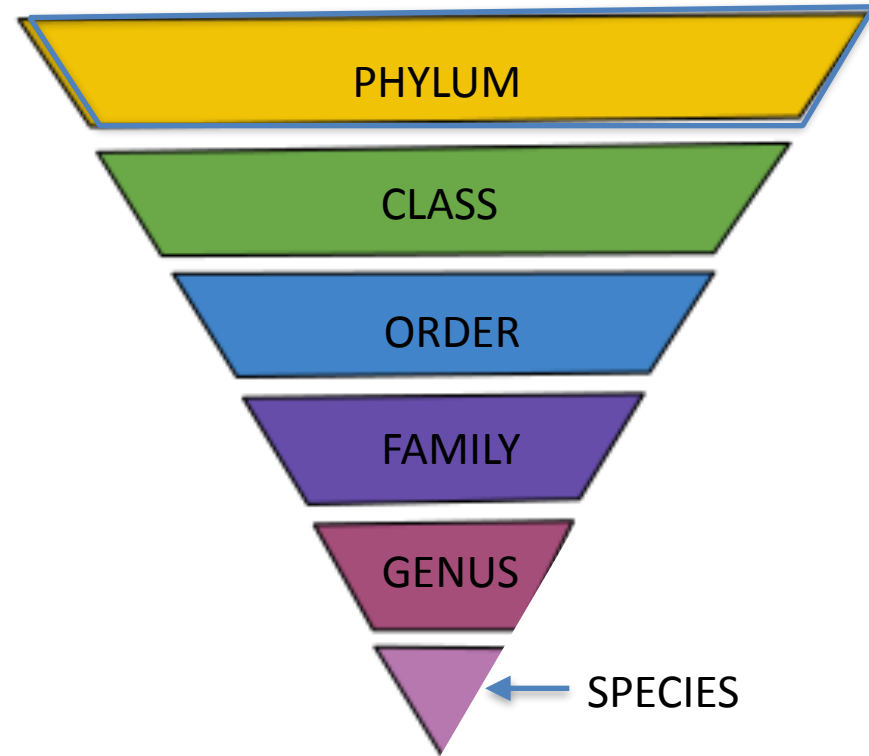
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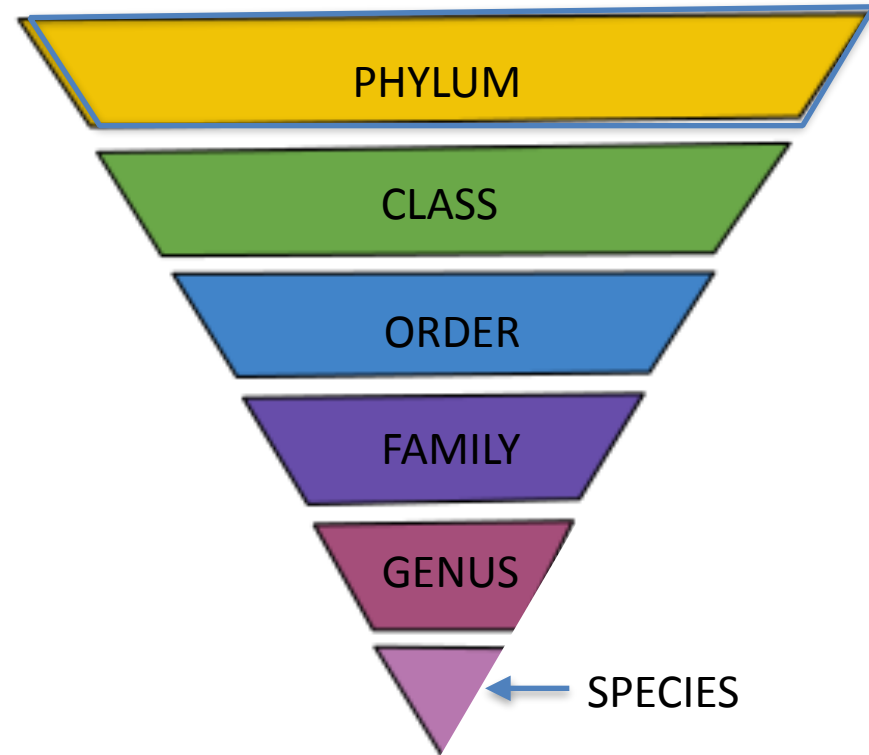
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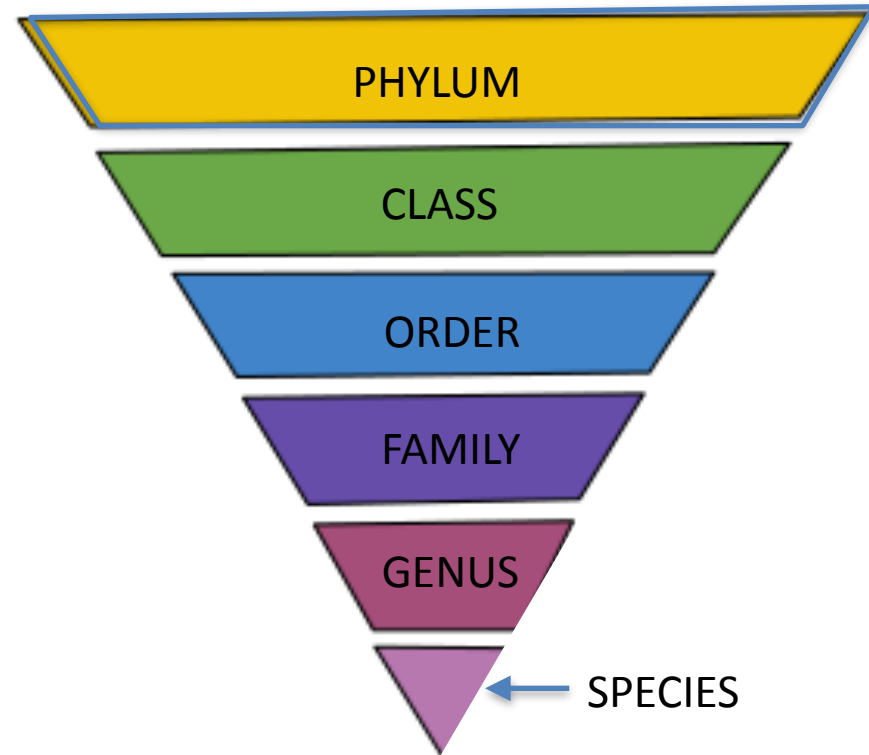
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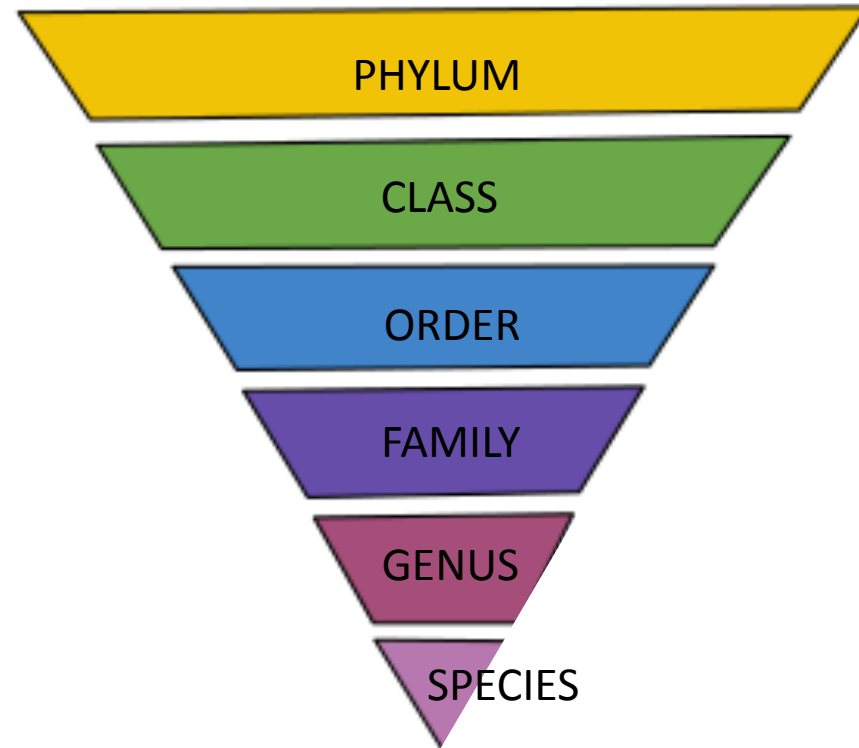


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 - **Firmicutes**
 - **Bacteroidetes**
- Thus, there is great similarity among the phyla that exist among healthy persons

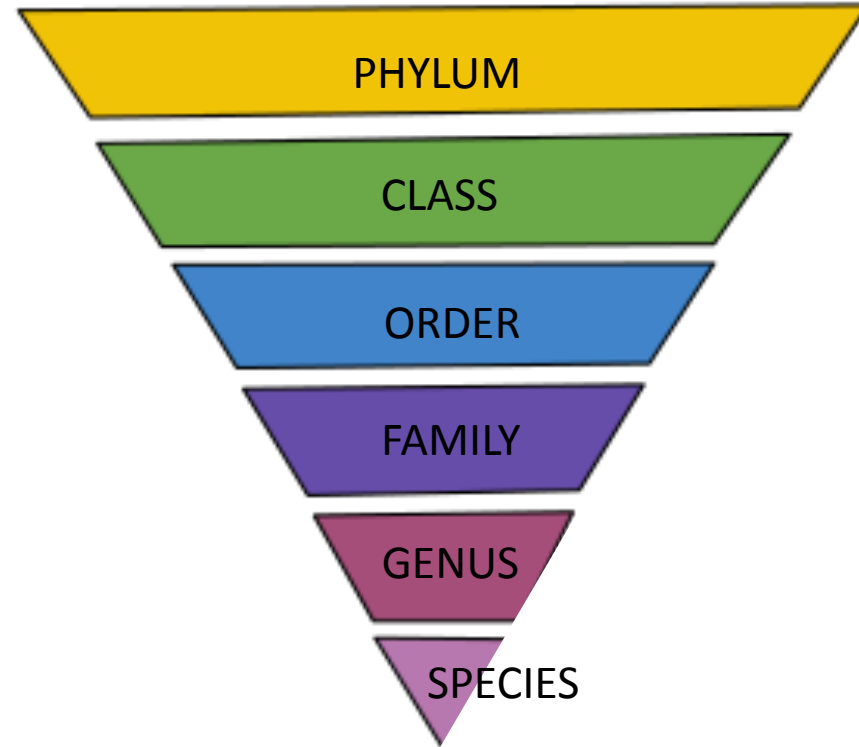


There is no single “healthy microbiome”



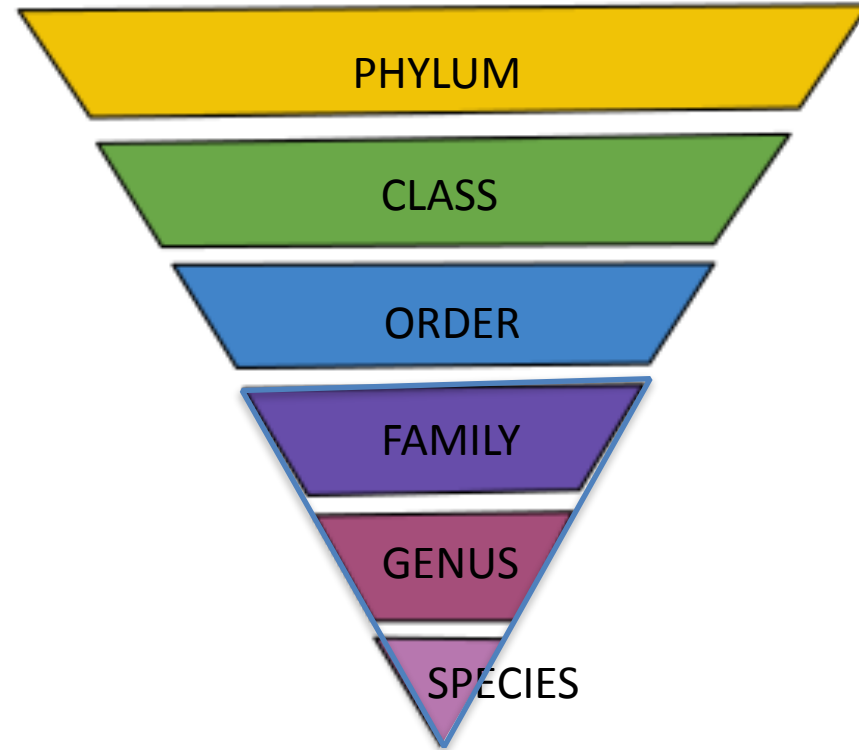
There is no single “healthy microbiome”

- On the family, genus and species level, there is a wide variety of what constitutes “health” from person to person



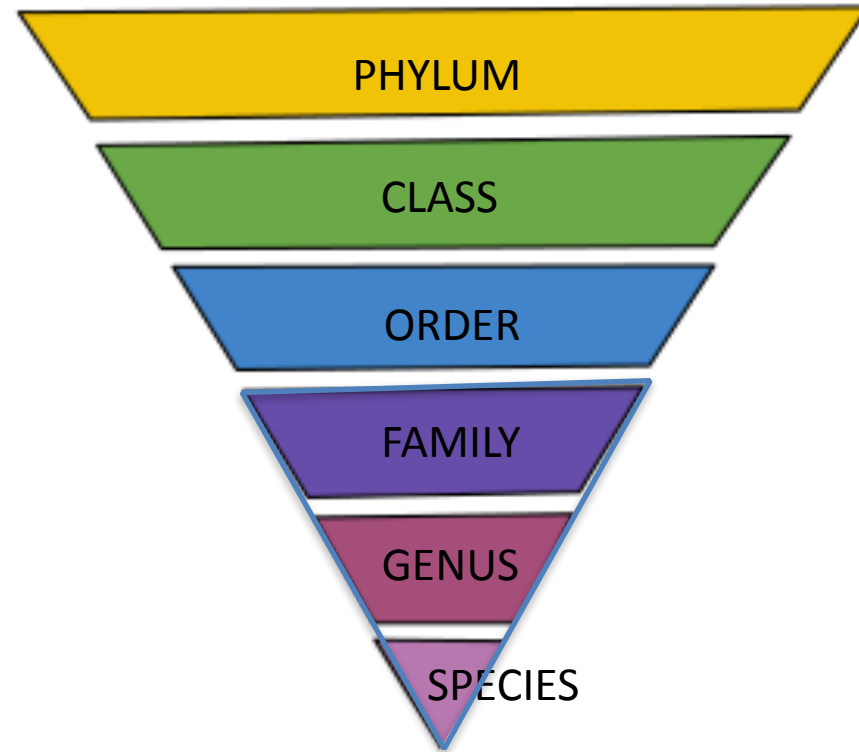
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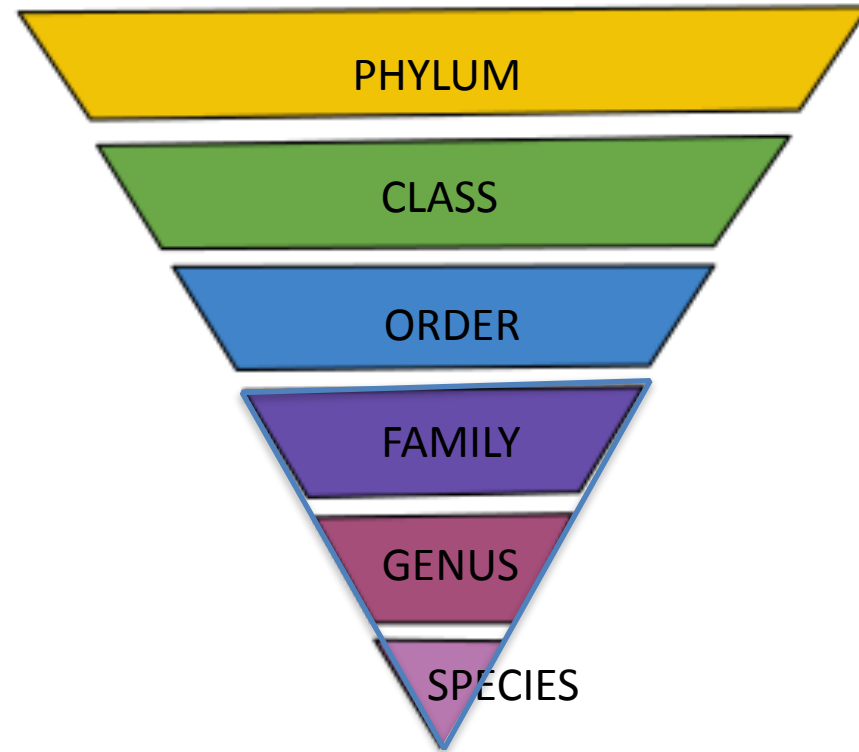
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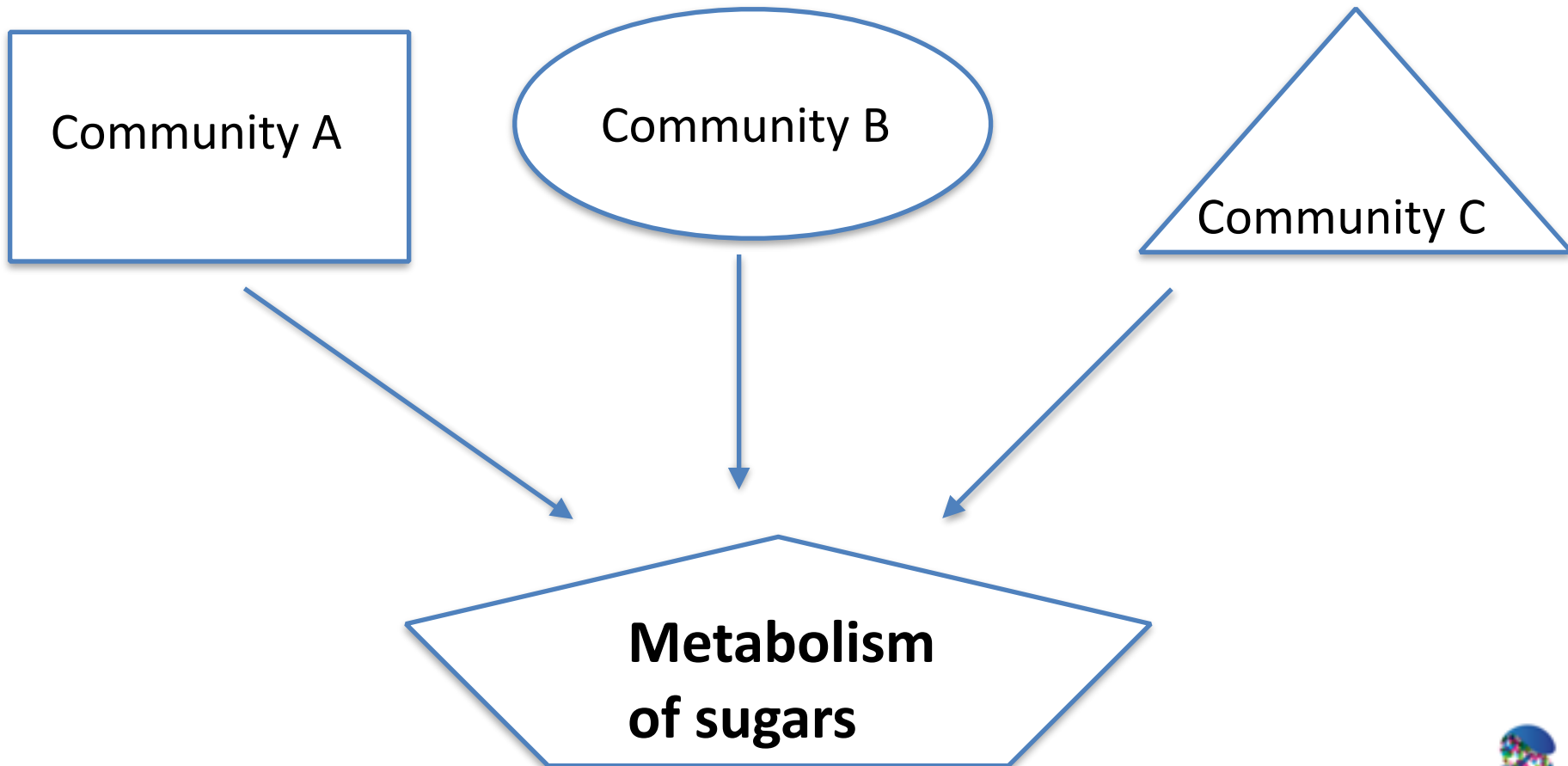
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- **Thus, there is no single profile of a “healthy microbiome”**



Diversity vs Function

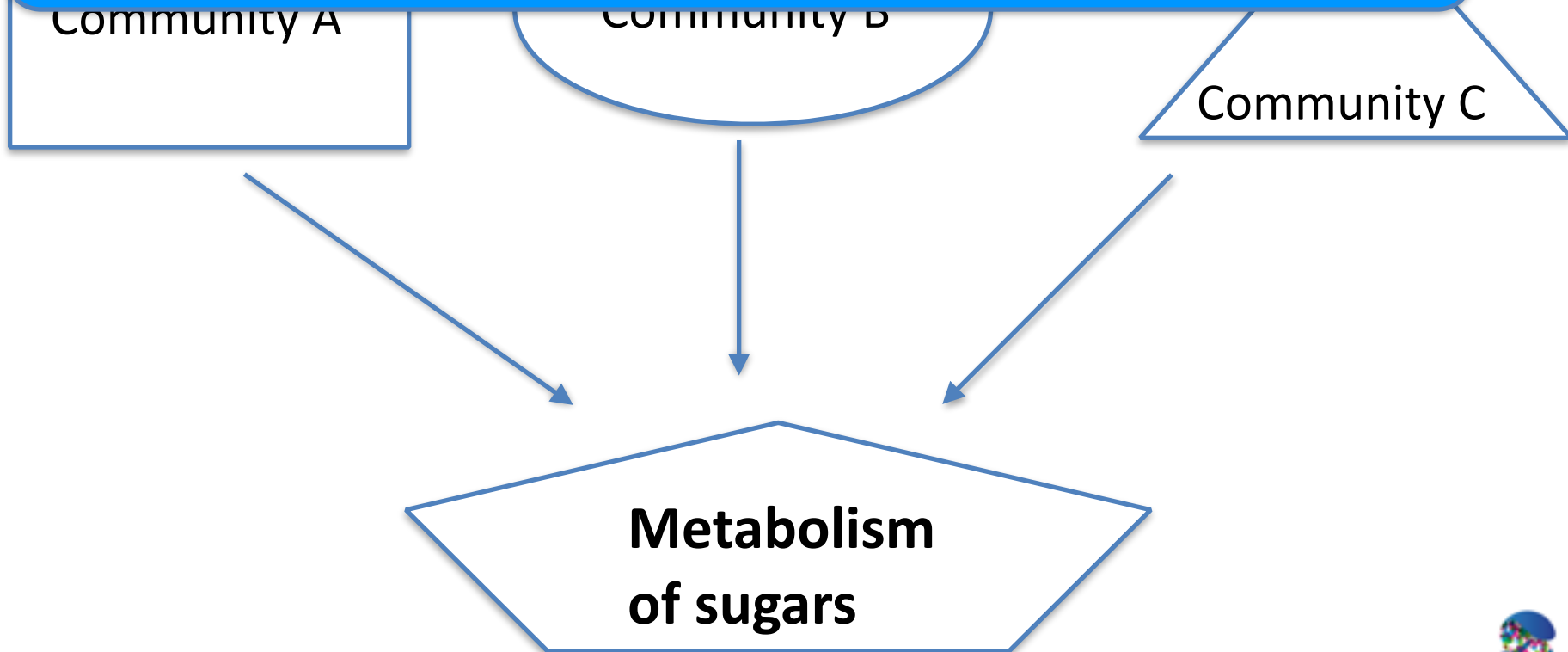
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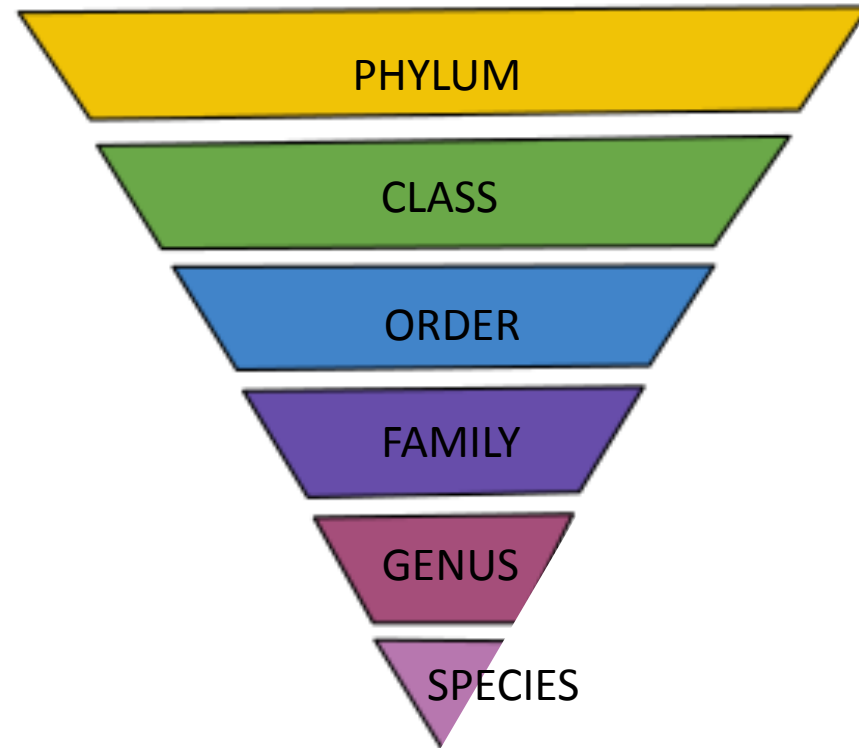
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The microbiome as a functional organ is similar among healthy individuals

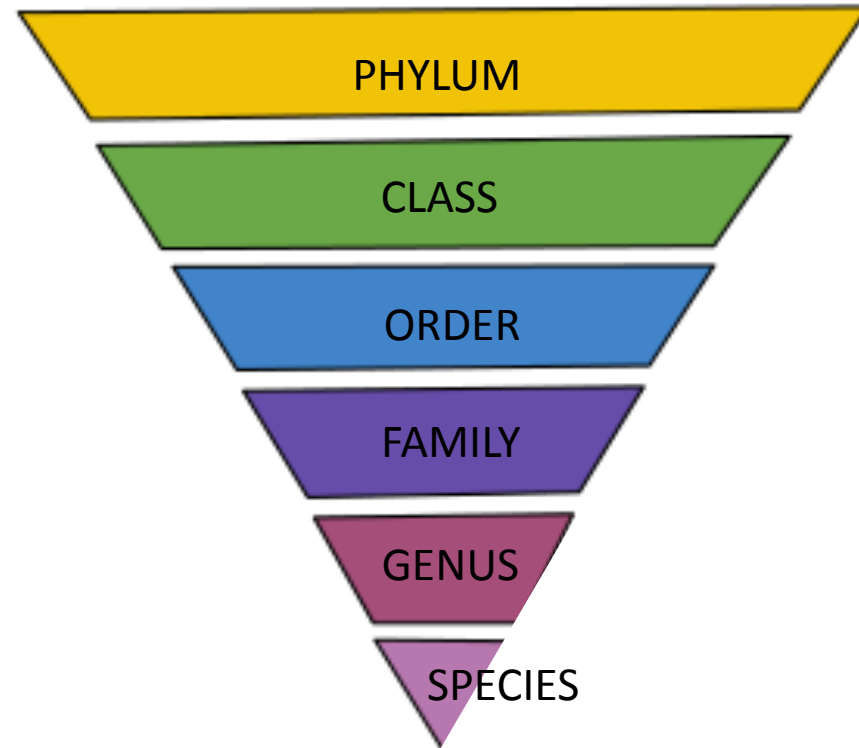


Where does Clostridia fit in the scheme of things?



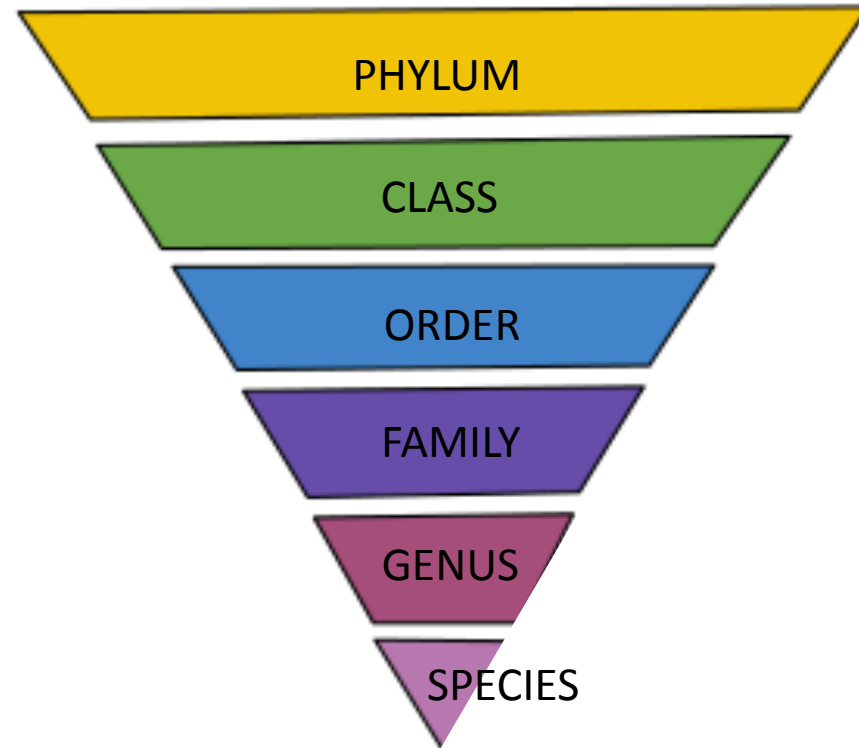
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- *Clostridium difficile* is one of the Firmicutes, which includes other spore-forming bacteria
- Within the Firmicutes, there are many other bacteria that are essential to the health of the host, including many helpful Clostridia. Thus, only some Clostridial species are potentially harmful.



Antibiotics harm the healthy gut microbiome



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- We know that the leading risk factor for CDI are antibiotics, which disrupt the gut microbiome by wiping out important bacteria that live normally in a healthy person
 - Antibiotic use leads to a less diverse population of bacteria
- Hypothesis: This lack of diversity allows *C. difficile* to flourish and cause inflammation of the gut with diarrheal disease.



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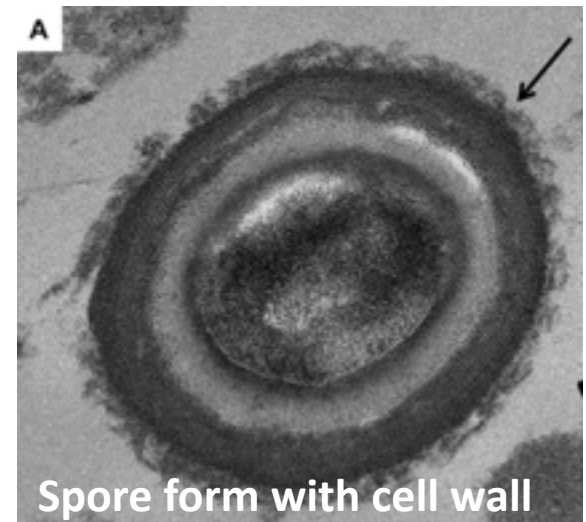
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 - Increasing the populations of bacteria that help *C.difficile* spores to germinate and cause disease
- *These concepts form the underlying rationale for the development of SER-109 to prevent recurrent C. difficile infection*



What is SER-109?

- SER-109 is an ecology of approximately 50 bacterial spores
- The spores are enriched from stool donations obtained from healthy, screened donors
- SER-109 has been shown to prevent recurrence of CDI in preclinical studies in animals



Why does SER-109 only use spores?

- **Advantages of spores**

- Dormant forms of bacteria that are very hearty
 - Resistant to air, heat and many solvents
 - In the manufacturing of SER-109, we are able to use ethanol which kills other potentially harmful germs, including bacteria, fungi and viruses
 - *But the spores remain intact*
- The potential for transmission of harmful pathogens is dramatically reduced



Why use only spores?

- The number of spores can be measured and calculated based on the composition of the spore wall
 - This provides consistency of dosing
 - These spores also represent only a fraction (<0.1%) of the complex species of organisms found in stool that have been identified to date (and many more that have not), thus allowing a more focused therapeutic approach
- In general, spores are resistant to stomach acid allowing them to reach the intestine where they can germinate and grow into a living ecology of bacteria.
- SER-109 is formulated into capsules for oral delivery



Donor Screening

- Lean donors <50 years of age undergo rigorous screening process including:
 - A thorough medical and family history
 - A general physical examination
 - Laboratory screening to eliminate donors with any signs of metabolic abnormalities (elevated sugars or fats) or autoimmune diseases (like Rheumatoid arthritis or Lupus)
 - Donors also undergo screening of blood and stool for any sign of infection



SER-001: Study design

- Open-label study conducted at four US sites with two dosing arms (Cohort 1 and Cohort 2)
- Adult patients (18 to 90 years of age) with ≥ 3 CDI episodes in the previous 12 months
- Eligible patients:
 - Clinical response to CDI antibiotics immediately before enrollment
 - Able to give informed consent to receive a donor-derived product



Treatment Protocol

- Day-2: Antibiotics for CDI completed
- Day-1: Bowel lavage
- Day-0: Enter one of the SER-109 dosing arms
 - If during 8-week period following dosing, CDI recurred, repeat administration of CDI antibiotics followed by SER-109 was allowed



SER-001: An investigative study evaluating SER-109 for prevention of recurrent CDI

Efficacy phase

- The primary efficacy measure was the ability of SER-109 to prevent recurrent CDI up to 8 weeks after dosing
 - CDI recurrence was defined as >3 unformed bowel movements in a 24-hour period with laboratory confirmation of *C. difficile* in the stool



SER-001: An investigative study evaluating SER-109 for prevention of recurrent CDI

Safety phase:

- Adverse events, laboratory values, vital signs, and physical examination findings were measured before and after SER-109 dosing over 24 weeks



Secondary objectives: Alterations in Gut Microbiota Composition

- The impact of SER-109 on the gut microbiome was examined by looking at microbial diversity - the number of different types of organisms in the gut



Patient Characteristics

	<i>COHORT 1</i>	<i>COHORT 2</i>
AGE	64.7	59.1
GENDER	10 (66.7%)	10 (66.7%)



Primary endpoint achieved in 26 of 30 patients (86.7%)

Patients with recurrent CDI responsive to antibiotics (n=30)

Cohort 1 (n=15)

Approximate mean dose 10(9) spores

Yes

**Achieved
Primary
Endpoint
(n=13)**

No

**Cohort 1 (n=2)
Cohort 2 (n=2)**

Cohort 2 (n=15)

Approximate mean dose 10(8) spores

Yes

**Achieved
Primary
Endpoint
(n=13)**

No

Only 1 patient required more than one SER-109 treatment



What happened to the four patients who did not meet the primary endpoint?

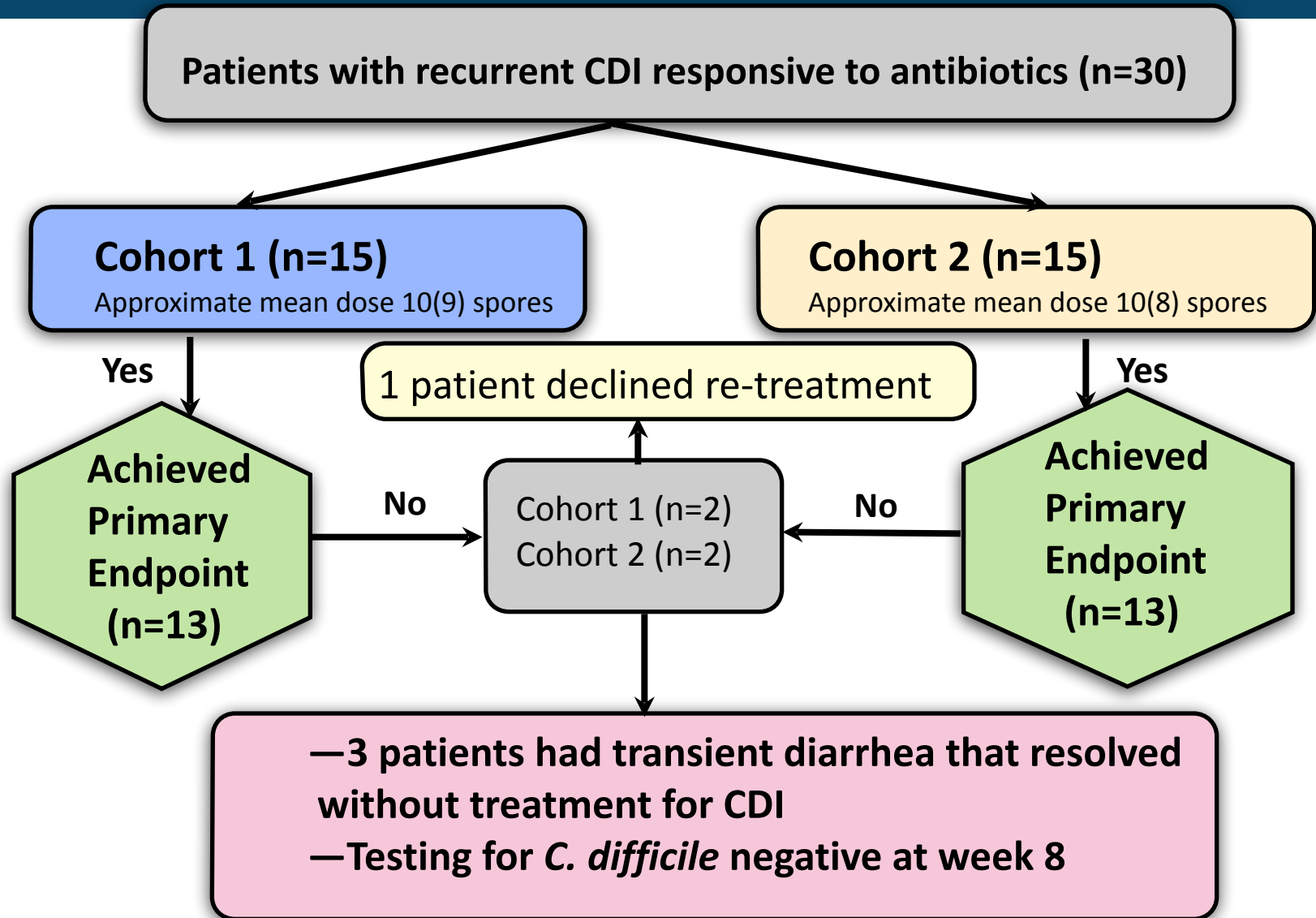
1 patient with recurrent diarrhea declined re-dosing with SER-109 and left study

Cohort 1 (n=2)
Cohort 2 (n=2)

- 3 patients had transient diarrhea that resolved without CDI treatment
- Testing for *C. difficile* negative at week 8



Clinical Resolution Achieved in 29 of 30 patients (96.7%)



Adverse Events during 24 weeks of follow-up

- The most common drug-related adverse events included mild diarrhea, nausea and abdominal pain, which occurred mainly within the first 3 days following dosing.
- Seven serious adverse events documented in four patients considered not to be drug-related by the investigators.



Did any patients have recurrent CDI during the safety phase? (weeks 8-24)

29 patients entered safety phase

1 patient left
for personal reasons

2 patients were lost
to follow-up

26 of 29 patients completed the safety phase

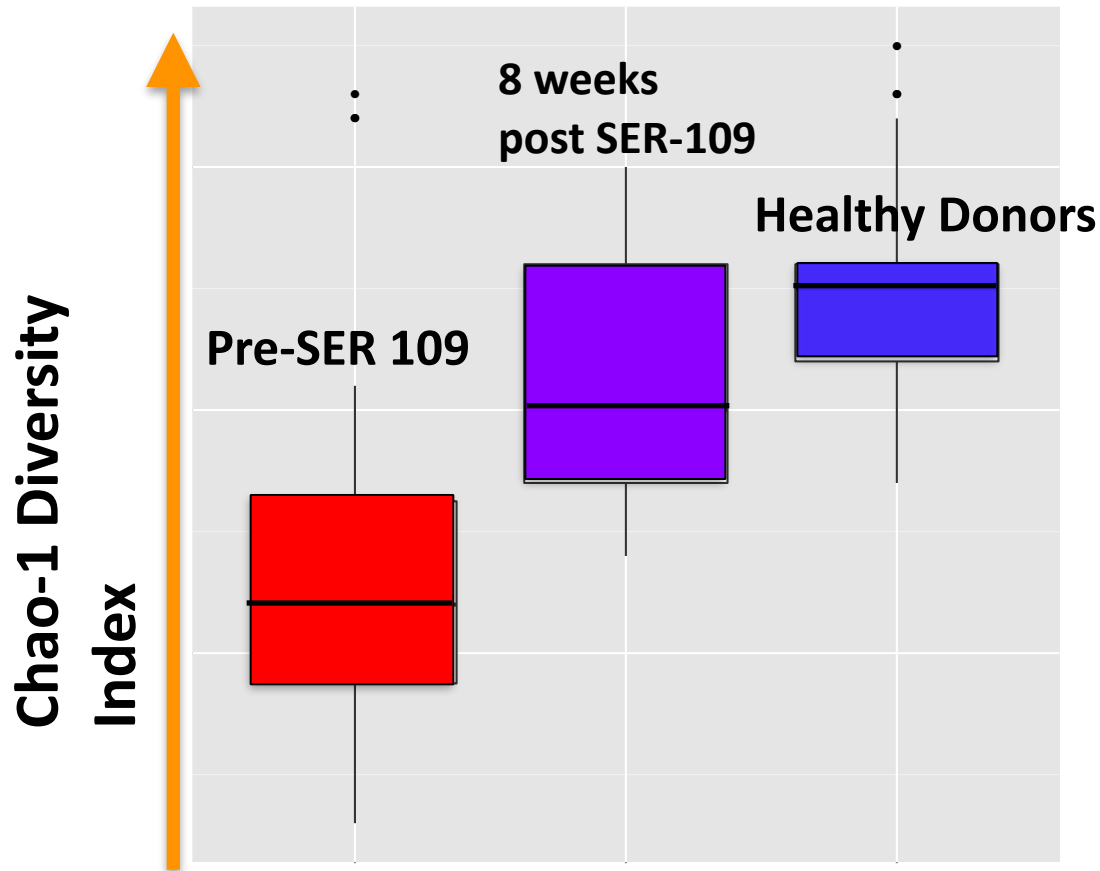
**1 patient relapsed
without clear
risk factors**

**23 without CDI
recurrence**

**2 patients relapse
after non-CDI
antibiotics**



Improvements in the Microbiome Occurred in Parallel with Clinical Resolution



SER-109 increases the microbiome diversity towards the level of diversity seen in healthy donors



Summary of SER-109 profile



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- Limitations of this trial are its small size and lack of a placebo-controlled design



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- Primary endpoints are safety and efficacy



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- Assess measures of quality of life and health outcomes through week 24 after dosing of SER-109 vs placebo





SERESTM
THERAPEUTICS