Dear Partners,

This past quarter has been exciting for OpenBiome. We grew from 60 partners across 20 states at the beginning of July to over 110 partners in over 30 states by the end of September. We are humbled and honored to partner with each new hospital to serve patients in need. Our clinical mission is to expand access to fecal microbiota transplants – to make them safer, easier, cheaper, and more widely available. This is only made possible through you.

To fulfill our mission of expanding access to safer FMT, I think of our approach in two angles. First and foremost, OpenBiome is responsible for providing rigorously screened treatments for your use. The consolidation and update of our Quality & Safety Program (Q&SP) this summer is representative of our commitment to that end.

The second part of our approach is our trust in our partners. We rely on each of you to promote best practices in FMT and escalate concerns. We appreciate an abundance of caution, and I was grateful to see many of our partners reach out with questions and concerns. None of the adverse events, detailed in the pages to follow, were attributable to OpenBiome material, but we always want to know about these events so we can watch for patterns in our network and share best practices whenever possible.

On behalf of the entire organization at OpenBiome, I thank you for making both sides of this partnership so powerful and effective. I look forward to continuing to work with you.

Sincerely,

James Burgess
Executive Director
Fellow Clinicians,

I want to echo James’ gratitude for each of OpenBiome’s partners. The strength and integrity of our Quality & Safety Program (Q&SP) is rooted in your contributions. This past quarter has been a testament to each clinician’s deep commitment to patient safety. This quarter, I have had the opportunity to connect with several of you: sometimes to answer safety-related questions, other times to navigate suspected adverse events. It is important to me to put a face and person behind these interactions. Together, we share the responsibility for disseminating the wealth of experience and knowledge in this emerging field, and I am humbled to walk with each of you in the journey to expanded safe access to FMT.

The details in this report will convey a comprehensive and transparent clinical picture of the suspected adverse events in our network. They serve as opportunities to learn from each other and continue to lead in the field of FMT safety.

Additionally, as many of you are aware, I am excited to kickoff our long-term FMT safety study, aptly named the STOOL study. This FDA-registered, multi-center longitudinal cohort study will explore the short and long-term safety profile of FMT. To our knowledge, this will be the largest and longest longitudinal safety study on FMT, and we are excited to move forward with our clinical partners in a unified fashion. Overall, OpenBiome is humbled to have the opportunity to leave a meaningful footprint upon the promising field of FMT. We have much to accomplish together.

Sincerely,

Zain Kassam, MD, MPH, FRCPC
Chief Medical Officer
• 2 Adverse Events were reported in our network this quarter
  o Both AEs were concerns of potential infectious diseases
  o Neither was directly attributable to OpenBiome material (determined upon safety aliquot testing)
  o The AE Decision Algorithm is working and is removing decision-making uncertainty from AE responses, enabling swift response times

• The FDA continues to encourage MedWatch Form 3500 submissions
  o The data is useful as they continue to gather safety data on FMT
  o OpenBiome is here to support you in the submission process. We submit a MedWatch Form 3500A subsequent to your MedWatch Form 3500

• Lower delivery continues to be our favored delivery modality
  o Literature suggests that lower delivery (colonoscopy/enema) is more efficacious than upper delivery
  o Nasogastric delivery may have more associated adverse events although more research is required

• We need greater Material Tracking Log compliance among partners
  o MTLs are used to ensure all OpenBiome material is traceable in the rare and unlikely event of an AE that requires escalation or recall across the network
  o MTLs never contain any patient identifying information and are strictly used to detect and prevent any patterns of clinical concern (e.g., non-response) to optimize quality assurance
  o Partners must maintain and submit an MTL (indicating whether a unit has been used or is still in inventory) to order new OpenBiome material
UPDATES TO THE Q&SP
Q3 2014

The FDA has requested that partners submit MedWatch Form 3500s, not Form 3500As.

As the FDA continues to exercise enforcement discretion, it has clarified that all adverse events should be reported using Form 3500 (for voluntary reporting). We have already started to include a hard copy of MedWatch Form 3500 with every shipment and a soft copy of MedWatch Form 3500 in our shipping confirmation emails.

When OpenBiome receives notification of an adverse event, we then submit a MedWatch Form 3500A separately on our end to the FDA. In addition to the original details from the partner’s Form 3500, OpenBiome will add additional details derived from screening of safety aliquots, relevant donor screens, etc. in its Form 3500A submission.

The Adverse Event Decision Algorithm has been updated to include a node for AEs that are neither attributable to an FMT procedure nor OpenBiome material, but occur around the same time as an FMT and raise cause for concern.

The ‘Rev Aug 2014’ version of the OpenBiome Adverse Event Decision Algorithm had two primary response pathways based on whether the AE was attributable to the procedure or the material used in an FMT. The majority of our Q3 2014 AEs were in an adjacent pathway, where an AE appeared to surface chronologically close to FMT delivery, but was not attributable to the procedure or material.

In this event, OpenBiome and its partner would follow a response pathway similar in principle to the two that already exist:

1. The partner immediately notifies OpenBiome of the suspected AE
2. The partner submits MedWatch Form 3500 and to the FDA & OpenBiome
3. The partner and OpenBiome conference to determine attribution, debrief any key takeaways, and agree upon any necessary next steps

While this pathway is short and straightforward, the underlying principle is that of over-reporting. The FDA welcomes the voluntary MedWatch Form 3500 reporting from its partners on AEs that surround an FMT delivery, but may not be due to the FMT itself. OpenBiome will do its part to provide additional details on its material when necessary to ensure that the AE is classified and interpreted correctly.
There were 2 suspected adverse events reported in Q3 2014. AE Debriefs on each of these adverse events are in the subsequent pages of this report. All identifying patient information has been removed.

1. *Giardia* infection – FMT attribution: Unlikely source

2. *Salmonella* infection – FMT attribution: Unlikely source
23-year-old gentleman with recurrent CDI on background of C-5 quadriplegia with Giardia infection status post-FMT

Date of AE
September 9, 2014

Unit ID
05-075-I

Past Medical History
1. C-5 quadriplegia secondary to trauma complicated by neurogenic bladder and bowel treated with bisacodyl, senna, docusate at baseline
2. Femoral DVT
3. Osteomyelitis at donor iliac graft site
4. GERD
5. Recurrent CDI
   a. Multiple recurrences (>3), including 1 hospitalization, after antibiotics for UTI
   b. Previous treatments include: several courses of Vancomycin including a Vancomycin taper and Vancomycin suppressive therapy

Clinical Course
Briefly, the patient was diagnosed with recurrent CDI (positive C. difficile PCR) and clinical diarrhea which was non-responsive to standard therapy on background of negative stool studies including Giardia antigen, Campylobacter antigen, Cryptosporidium EIA, and stool culture. The patient underwent FMT via NG but continued to have diarrhea post-procedure. Stool studies were retested (Day 35 post-FMT) and the patient was found to have a positive stool Giardia antigen and C. difficile PCR. Subsequently, the patient was treated with a course of metronidazole and repeat testing for both Giardia and C. difficile were negative with accompanying clinical resolution.

Successive donor testing was documented as pan-negative and the safety aliquot used for the patient’s FMT was negative for stool O&P and Giardia antigen. In terms of exposures, the patient had no recent travel/camping history or ingestion of any water from streams. It was unclear if there were any rehabilitation pool exposures. Of importance, the patient did have wells but water supplied by private company and the local public health department is inquiring regarding Giardia status.

Assessment
23-year-old gentleman with C-5 paraplegia and recurrent CDI (modified Horn Index 3) and Giardia positive testing following FMT. Given safety sample used in actual FMT was negative for O&P and
Giardia EIA, it seems unlikely that the FMT was the source of the event. The possibility of a false positive Giardia test (with ongoing CDI) exists, however, Giardia EIA testing conventionally has a specificity between 99-100% and a sensitivity ranging from 94-99%. Given the clinical context, an environmental exposure source seems most probable. Overall, Giardia should not be routinely tested in non-responsive FMT cases, particularly if pre-testing was negative. However, if the clinical history suggests a new exposure, it is reasonable to consider targeted stool testing.

**Plan**

1. No further assessment required.
56-year-old woman with recurrent CDI on background of a subtotal colectomy with *Salmonella* infection post-FMT.

**Date of AE**
August 19, 2014

**Unit ID**
05-097-E

**Past Medical History**
1. Colonic inertia treated by subtotal colectomy
2. Seizure disorder
3. Migraines
4. Head injury with chronic partial left VI palsy
5. BPPV
6. Hypothyroid
7. Carpal tunnel syndrome
8. Adhesive capsulitis
9. Recurrent CDI
   a. Multiple recurrences (>3), including last CDI recurrence in July 2014 leading to ongoing Vancomycin suppressive therapy

**Clinical Course**
Briefly, the patient was admitted for recurrent CDI not responsive to standard therapy and FMT conducted by EGD. The patient did well after the procedure and was discharged home the same day. Day 1 post-FMT, the patient was doing well in the morning and opted to eat a shrimp-based lunch at a local seafood restaurant. Later that evening, the patient started to have diffuse crampy 10/10 abdominal pain with approximately 15 non-bloody, watery stools, without response to loperamide. She did endorse concomitant nausea for which she took phenergan with minimal relief. She denied any fevers/chills. The patient was admitted to hospital and a stool work up conducted. *C. difficile* PCR was negative; however, stool cultures grew 2+ *Salmonella* (Salmonella serovar Saintpaul) which was sensitive to levofloxacin. The patient was started on ciprofloxacin with a clinical improvement and discharge home after a brief admission.

Successive donor testing was documented as pan-negative and the safety aliquot used for the patient’s FMT was **negative** for *Salmonella*. Public health officials were notified regarding the event and potential food contamination investigation.
Assessment
56-year-old woman with recurrent CDI on background of a subtotal colectomy (modified Horn Index 2) with *Salmonella* infection. Given safety sample used in actual FMT was negative for *Salmonella*, it seems unlikely that the FMT was the source of the event. It appears much more likely that the *Salmonella* event was linked to contaminated food given the temporal relationships of the infection, and clinical context.

Plan
1. No further assessment required.
There were no changes to the OpenBiome Adverse Event Watch List this past quarter. Of the 2 adverse events reported, none were specifically attributable to the procedure or material used in FMT. For reference, an image capture of the AE Watch List is included here. This document will be updated and circulated to all partners in the event of an AE attributable to OpenBiome material.

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