Dear Partners,

Thanks to your partnership, OpenBiome continues to expand safer, easier, and cheaper access to FMT. We shipped 1,739 treatments to 62 hospitals across 28 states this quarter. As we continue to grow, the ability to identify safety patterns and concerns across the network is the key advantage of the universal donor model that we advocate for here at OpenBiome.

In Q2 we were excited to have Dr Majdi Osman join our team as Clinical Program Director driving our safety and quality program. Dr Osman is an infectious disease specialist faculty at Harvard Medical School and Boston Children’s Hospital. He trained at University College London, Harvard and the London School of Hygiene and Tropical Medicine and previously worked at the World Health Organization. We’re thrilled and honored to have Majdi leading our Clinical Program team, and hope all of you get an opportunity to interface with him at upcoming conferences or in your interactions with OpenBiome.

Thank you very much for your continued partnership and collective commitment to safety.

Sincerely,

James Burgess
Executive Director
Fellow Physicians,

Thank you for another wonderful quarter of partnership. It has been an immense pleasure to join OpenBiome as Clinical Program Director working in partnership with Dr Zain Kassam, Chief Medical Officer and our wonderful clinical team at OpenBiome. I’ve had the opportunity to engage in inspiring discussion with each of you over this quarter and look forward to getting to know many more of you over the coming months.

I would like to highlight three key updates from our safety program. Firstly, we have been excited to launch our STOOL study, which aims to capture the long-term safety profile of FMT. We encourage any sites interested in joining this study to contact us at science@openbiome.org to learn more. Armed with this data from studies like these, clinicians and scientists can drive towards evidence-based guidelines to ensure the best care for our patients in this emerging field.

Secondly, from an adverse events perspective, I’m happy to report there are no adverse events attributable to FMT reported across our network this quarter. However, adverse events reported to us provide important lessons on how we can enhance safety for patients receiving FMT. In this report a case of solitary colonic ulcer with bloody diarrhea post-FMT is outlined. Although the case was not related to FMT the finding of CMV on biopsies brought us to consider CMV testing in our donor. We continually review this question with our Clinical Advisory Board.

Given the high prevalence of CMV carriage we presume that our material is CMV positive. There is a potential risk in severely immunocompromised patients such as solid organ transplant recipients who may be CMV negative. Our current recommendation to our clinical partners is that they should communicate during the informed consent process the risk of CMV to patients. At the discretion of treating MDs, physicians may assess for CMV status in high risk patients undergoing FMT. In the case of seronegative, they may consider a seromatch directed donor approach or communicate higher risk with universal material, or provide alternate treatments.

Lastly, I would like to reiterate the importance of MTLs to our collective mission of improving access to safe FMT. Our first priority at OpenBiome is safety and the information you provide is the single most important thing. If you have feedback on how we can make MTLs easier to complete then do let us know.

Together, we are entering a new an exciting frontier of microbiota-based therapy, and we are thrilled to have the opportunity to share this journey with each of you.

Sincerely,

Majdi Osman, MD, MPH, MRCP, DTM&H
Clinical Program Director
• **Material Tracking Log submissions are mandatory** to place an order for new OpenBiome material
  - MTLs provide critical (non-patient identifying) data on delivery modalities, follow-ups being performed, and patterns of non-responses and adverse events tied to any specific donors for quality assurance
  - MTL submission is critical to enabling the full transparency of best-practices and flagging of safety patterns afforded in our universal donor model

• **No reported adverse events were determined to be related to FMT** in our network this quarter
  - Two events were evaluated which are summarized below
  - Questions like these are always welcome by reaching out to OpenBiome at 617-575-2201 ext. 1 (for Safety) or safety@openbiome.org
UPDATES TO THE Q&SP
Q2 2015

• No updates were made to the Q&SP this quarter.
There were several inquiries related to suspected adverse events that were flagged and escalated to OpenBiome in Q2 2015 in accordance with our Adverse Event Decision Algorithm. All such cases entered the “1c - Consult OpenBiome” pathway of the Decision Algorithm.

Figure 1: Path 1c excerpt from the OpenBiome Adverse Event Decision Algorithm
(Source: http://www.openbiome.org/safety)

Upon immediate debrief with the reporting institution, all cases were concluded to be not attributable to FMT material. All were reviewed in-depth by our Clinical Program Director and Chief Medical Officer.

These suspected adverse events are summarily debriefed in the following section.
Date of Suspected AE
April 12, 2015

Unit ID
52-012-K

Summary
86-year old gentleman with severe-complicated *Clostridium difficile* infection (CDI) developed a *Salmonella* infection post-FMT.

Past Medical History
1. End-stage renal disease (ESRD) on hemodialysis
2. *Klebsiella pneumoniae* urinary tract infection
3. Coronary heart disease with previous coronary artery bypass surgery
4. Congestive heart failure (Ejection fraction 45%)
5. Hypertension
6. Type 2 diabetes mellitus
7. Severe, recurrent CDI following antibiotic treatment for otitis media
   a. Multiple recurrences (>3) not responsive to standard antibiotic therapy

Clinical Course
An 86 year-old ESRD patient on hemodialysis presented with severe-complicated CDI (Modified Horn Index 4) following antimicrobial treatment for otitis media, with courses of antibiotics in September 2014, October 2014 and January 2015.

The patient did not respond to conventional anti-CDI therapy underwent FMT by colonoscopy with 250 mL of donor fecal material. Initially, the patient clinically improved post-FMT with formed daily bowel movements. However, approximately 1 week post-FMT the patient developed hematuria and presented to the emergency room on with sepsis secondary to emphysematous cystitis. Urine culture was positive for *Klebsiella pneumoniae ssp pneumoniae*.

The patient was initially treated with ceftriaxone 1g IV daily with persistently formed bowel movements. On day three of antibiotic therapy he developed loose stool with *C. difficile* and *Salmonella infantis* (Group C1) detected on stool culture. Blood cultures were negative.

On assessment no overt risk factors for *Salmonella* were identified including contact with other Salmonella cases, food exposures, travel or pets. It is not clear whether there were
any other Salmonella cases reported in the ward. The patient was not admitted to ICU and remained stable throughout admission.

The patient was discharged on trimethoprim-methoxazole and cephalexin for *Salmonella* and oral vancomycin for CDI with close outpatient gastroenterology follow-up. On follow-up assessment the patient was doing well after three weeks of bactrim and vancomycin, and passing formed stools.

The OpenBiome team was contacted and given the clinical context, a detailed collaborative investigation was immediately conducted in keeping with OpenBiome's SAFE protocol and included strict donor material quarantining during the investigation.

As part of the investigation the donor was clinically reassessed and found to not have any risk factors including contact with other *Salmonella* cases, food exposures, travel or pets. The safety aliquot for the donor material was tested and returned negative for *Salmonella* and was otherwise non-contributory.

**Assessment**

An 86 year-old ESRD patient on hemodialysis presented with *Salmonella* diarrhea and *Klebsiella* emphysematous cystitis post-FMT. Given the temporality and clinical context this adverse event (NIH Grade 4) triggered a full investigation for a possible FMT source of *Salmonella*.

As outlined above the donor was reassessed and no risk factors for *Salmonella* were identified. Given the negative safety aliquot and non-contributory clinical evaluation, both the clinical site physicians and the OpenBiome physicians independently determined the *Salmonella* infection was not attributable to FMT.

From data based on our quality assurance program Donor 52 is noted to have an 87% efficacy (n=124) without any related adverse events.

**Best-Practices Learned**

1. Although there is emerging, promising data for using FMT to treat severe-complicated CDI not responsive to standard therapy, clinicians should comprehensively review the risks, benefits and alternatives during the FMT informed consent process.

2. Infection control could offer further support in evaluating adverse events where there may be a suspected infectious etiology. As in this case, further information on
the source of Salmonella or further cases on the ward may offer insights into the source of infection.
Summary
74-year old gentleman with recurrent C. difficile infection (CDI) developed bloody diarrhea 1 day post-FMT likely secondary to ischemic colitis.

Past Medical History
1. Stage IV chronic kidney disease (not on dialysis)
2. Hypertension
3. Type 2 diabetes mellitus (insulin controlled)
4. Gout
5. Allergic rhinitis

Clinical Course
Briefly, a 74-year old gentleman with Stage IV chronic kidney disease (CKD), not on hemodialysis, presented with recurrent CDI associated diarrhea. Over a course of six months the patient received several courses of antibiotic therapy, including metronidazole, vancomycin taper and fidoxamixicin. The patient did not respond to antibiotics.

A fecal microbiota transplant (FMT) was performed by nasogastric tube with 30 mL of donor fecal material with confirmatory placement by radiograph. There were no complications during the procedure.

Importantly the patient’s anti-hypertensive medications were held for the FMT and there was a systolic blood pressure of 170mmHg and diastolic blood pressure of 103mmHg identified in the medical records. This is suggestive of hypertensive urgency peri-procedure although blood pressure was not closely monitored on the general medical ward so it is unclear the maximum blood pressure.

The patient was admitted overnight for observation following FMT due to moderate nausea post-procedure. The patient was discharged the following day feeling well with normally formed bowel movements.

The patient developed bloody diarrhea day 1 post-FMT and subsequently presented to the ER day 5 post-FMT with ongoing bloody diarrhea and no associated symptoms. The patient underwent negative stool testing including: Campylobacter jejuni, Clostridium
difficult toxin A/B, Shigella, Salmonella, Vibrio, Yersinia, E. coli, Cryptosporidium, Cyclospora, Entamoeba histolytica, Giardia lamblia, Adenovirus, Astrovirus, Norovirus, Rotavirus and Sapnovirus.

It is unknown whether the patient had previously experienced bloody diarrhea prior to FMT nor if they had any symptoms of inflammatory bowel disease, ischemic colitis or radiation colitis.

A CT was performed that revealed inflammation in the mesentery at the sigmoid colon with edema. Subsequent colonoscopy showed a deep ulceration at the mid-proximal descending colon. Internal hemorrhoids were also detected. The location of the ulcer was classic for ischemic colitis, and it is worth noting the patient had an unremarkable colonoscopy in 14 months prior.

Biopsy immunohistochemistry returned with “rare” CMV although no viral inclusions were detected. The patient did have a positive CMV viral DNA on serum evaluation; however, the baseline CMV status is unknown. The patient was empirically treated with ganciclovir without significant benefit but was discharged with the plan for close outpatient care.

Shortly after, the patient was readmitted with fever (105°F), respiratory distress, an acute abdomen and ongoing clinical decline consistent with abdominal sepsis from a bowel perforation. After a goals of care discussion, the next of kin opted for the patient to undergo rescue colectomy. The etiology was confirmed as likely perforation and thought secondary to ulcer extension +/- potentially iatrogenic exacerbation during colonoscopy. Unfortunately, according to the most responsible physician, the colon was preserved in paraffin and deep culture assessment is no longer possible.

**Assessment**

A 74-year old gentleman with multiple co-morbidities developed colitis with subsequent perforation following onset of symptoms 1 day post-FMT by nasogastric delivery.

This NIH Grade 4 adverse event was reported to OpenBiome and following an initial triage conversation between the reporting clinicians and OpenBiome’s Clinical Program Director we conducted an in-depth review of the case. A detailed collaborative investigation was immediately conducted in keeping with OpenBiome’s SAFE protocol and included strict donor material quarantining during the investigation.

After an in depth investigation with the most responsible physician, an infectious disease and a gastroenterology specialist on our Clinical Advisory Board, OpenBiome’s Clinical Program Director and Chief Medical Officer, there was consensus that the outcome was not related to FMT. Given the incubation period of CMV is approximately 4-12 weeks,
and the patient developed bloody diarrhea Day 1 post-FMT, a CMV infection from FMT was determined improbable.

It is possible the patient may have been CMV positive at baseline, as his status is unknown, however, the absence of viral inclusions and 'rare' CMV make it less likely to be the source of the patient's robust symptoms. Overall, the consensus opinion was that given the patient's multiple ischemic colitis risk factors including uncontrolled hypertension, end-stage renal disease, diabetes on insulin as well as the location of the ulcer, the diagnosis of ischemic colitis was deemed most probable and felt not to be related to FMT.

From data based on our quality assurance program Donor 52 is noted to have an 87% efficacy (n=124) without any related adverse events.

**Best-Practices Learned**

1. Although this adverse event was determined to unlikely have been caused by CMY it offers an opportunity to outline our approach to CMV as we do not currently screen our donors for CMV. As FMT use increases this is becoming an important question and one that we are continually reviewing with our Clinical Advisory Board.

There have been a few documented cases of CMV colitis in the context of FMT but no reported cases in the context of FMT for rCDI. A case report in NEJM (Hohmann et al 2014) reported CMV colitis in an ulcerative colitis patient after home FMT. This patient did not have CDI. Another small study published in Gastroenterology (Rosser et al 2015) assigned ulcerative colitis patients to either treatment with feces from healthy donors or control group receiving autologous fecal microbiota. One patient did get CMV however interestingly they were in the control group receiving their own fecal microbiota.

Given the high prevalence of CMV carriage we assume that our material is CMV positive. There is a potential risk in severely immunocompromised patients such as solid organ transplant recipients who may be CMV negative. Our current recommendation to our clinical partners is that they should communicate during the informed consent process the risk of CMV to patients. At the discretion of treating MDs, physicians may assess for CMV status in high risk patients undergoing FMT. In the case of seronegative, they may consider a seromatch directed donor approach or communicate higher risk with universal material, or provide alternate treatments.
There were no changes to the OpenBiome Adverse Event Watch List this past quarter. 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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<th>Threat Type</th>
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