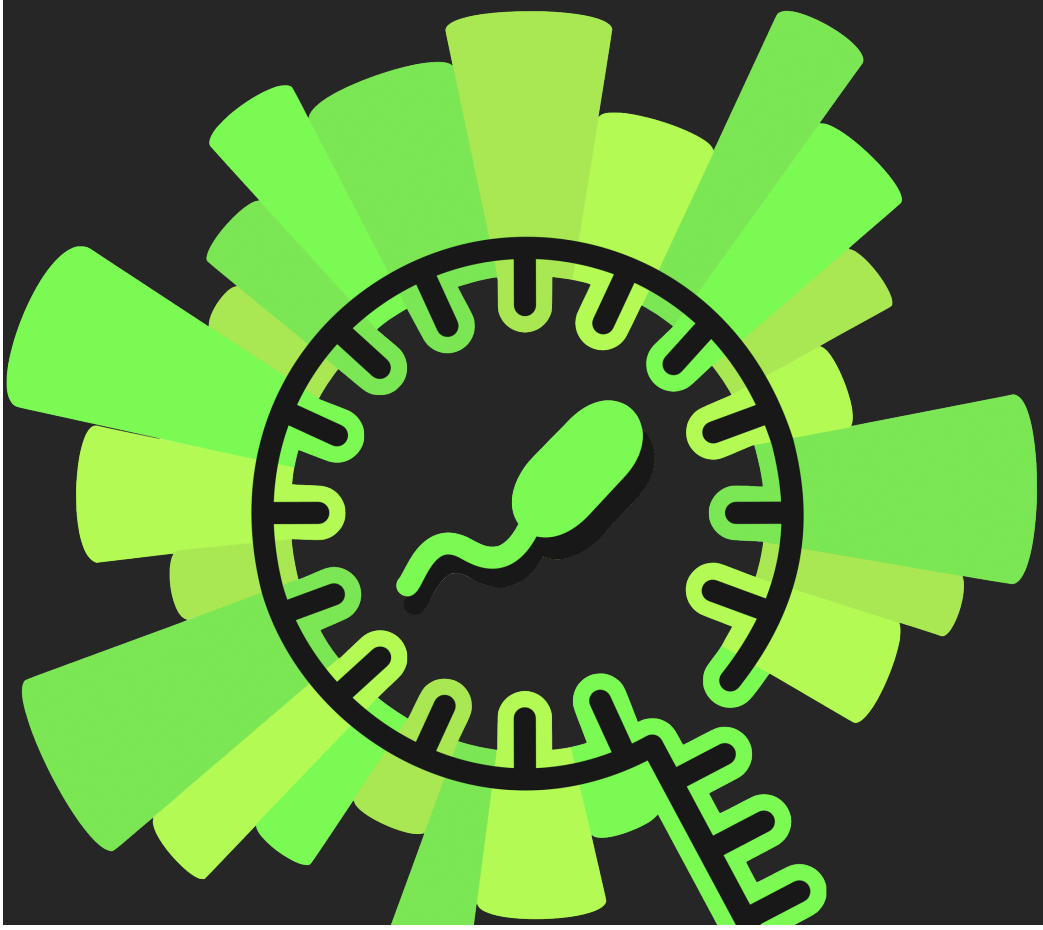
McMaster Genetically Engineered Machine

October **2017**

mGEM Human Practices:

The Promises of **Synthetic Biology in Point-of-Care Diagnostic Development** in the Canadian Clinical Context

Gregoris R, Huynh A, Machon C, Sheikh F, Bilimoria K, Lee J



CONTENTS

EXECUTIVE SUMMARY

This discussion paper highlights findings from the interviews completed from May 2017-September 2017 by the McMaster International Genetically Engineered Machine (mGEM) Human Practices team. Our team interviewed a host of stakeholders involved in the development, design, deployment, financing, policy generation, and use of diagnostic tools to identify antimicrobial resistant strains of bacteria. Antimicrobial resistance is a growing problem with over 700,000 deaths worldwide attributed to antibiotic resistant pathogens.[1] Our group sought to better understand the plausibility, prospective effectiveness, and regulatory context under which our biologically engineered organisms could be used as diagnostic tools in clinical contexts to improve patient care.

Through our four month investigation, we came across the following lessons:

Lesson #1: Antibiotic resistance is increasingly becoming a major health concern due to overprescription and poor bacterial stewardship

Lesson #2: To effectively combat antibiotic resistance, the Canadian government framed its plan of action into three major branches - surveillance, stewardship and innovation

Lesson #3: It is extremely challenging but doable to obtain crowd engagement in public health issues through multi-tiered plans

Reference:
1. Laxminarayan R, Matsoso P, Pant S, Brower C, Røttingen J, Klugman K et al. Access to effective antimicrobials: a worldwide challenge. The Lancet. 2016;387(10014):168-175.

COMMONLY OCCURRING TERMS

AMR: Short for antimicrobial resistance. A property of an organism leading them to persist against antimicrobial technologies, usually antibiotics.

AMS: Short for antimicrobial stewardship. The advocacy for education about and proper use of antimicrobial technologies, usually antibiotics, with the goal of minimizing the development of antimicrobial resistance.

Biological system: A formation of separate biological components into one system, to achieve a desired goal.

Biosensor: A device made from a biological component, usually a nucleic acid strand or an enzyme, paired with a receptor. The device detects a desired organism or chemical, and emits a signal.

C. difficile: The bacterium Clostridium difficile. Gram-positive and spore-forming, it may colonize the colon of a patient and can cause diarrhea, colonitis, and sepsis. It is a highly-prevalent hospital-acquired infection, and most strains are largely resistant to antimicrobials.

CIHR: Short for the Canadian Institutes for Health Research. A Canadian organization which designates federal funding towards health research and discovery.

Community-acquired infection: The alternative to a hospital or nosocomial infection, contracted outside of a healthcare setting.

Diagnostic test: The procedure to determine whether an organism has a bacterial or viral infection. Testing methods may be vastly different, depending on the perceived infection.

DNAzyme: A synthesized, functional strand of nucleic acids. Strands are created to act as enzymes, influencing transcription within cells to achieve a desired output.

Hospital-acquired infection: Also known as a nosocomial infection. A bacterial, viral, or fungal infection which was contracted in a hospital or healthcare facility, presenting within 72 hours of admission.

NCCID: Short for the National Collaborating Centre for Infectious Diseases. A Canadian organization which compiles knowledge and evidence within the field of infectious disease, to supplement the learning of clinicians and public health officials.

Registry of Standard Biological Parts: The catalogue of known genetic parts which are useful in the pursuit of synthetic biology innovations. The registry is accessible and expanding each year.

Synthetic Biology: The engineering of biological systems to perform tasks that they would not have done otherwise.

INTRODUCTION

Introduction to iGEM

International Genetically Engineered Machine (iGEM) is a highly accomplished synthetic biology competition targeted principally towards undergraduate students. Beginning as a course at MIT 2003, iGEM has since expanded, with 280 teams having registered worldwide for the 2015 competition. Teams are given a kit containing biological parts from the Registry of Standard Biological Parts and are asked to build their own biological systems and operate them in cells.

Introduction to mGEM

The McMaster Genetically Engineered Machine (mGEM) group is a new iGEM team hosted at McMaster University, a research-intensive university in Hamilton, Ontario, Canada. Running into our third year, mGEM consists of 40 members composing 6 subteams: Wet Lab, Dry Lab, Human Practices, Business Development, Community Outreach and Public Relations. Previous projects have included the use of light to control recombinant protein production (2015) and the use of quorum sensing with genetically-engineered lactic acid bacteria as a novel therapy for gastrointestinal tract cancers (2016). The latter project was awarded a Bronze Medal at the 2016 Jamboree. This year, the wet lab team is focused on developing a plate-based biosensor for Clostridium difficile (C. difficile) through the use of fluorescent DNAzymes. The inspiration for pursuing such a project is the growing local and global importance of developing innovative solutions to tackle antibiotic-resistant bacteria. mGEM strives to consolidate the time-consuming process of controlled protein expression and generate a simple, automated diagnostic tool. mGEM seeks to deliver uniqueness and quality, demonstrate our potential as a team, and have fun!

Applying Synthetic Biology to Address Antimicrobial Resistance

Deadly hospital-acquired infections are rising, driven by antimicrobial-resistant pathogens with no efficient point-of-care diagnostic tests. mGEM 2017 has looked to generate a sensitive and cost-efficient detection method using functional nucleic acids (known as DNAzymes), which cleave RNA in the presence of specific strains of bacteria. Known DNAzymes detecting E. coli K12 were modified to generate a novel DNAzyme detecting antimicrobial resistant strains of C. difficile. These DNAzymes were generated from a library of random oligonucleotides using in vitro selection, and contain a fluorophore-RNA-quencher motif that fluoresces when the RNA is cleaved. Machine-learning techniques looked to predict the DNA sequences' affinities for producing viable DNAzymes, while automating our fluorescent imaging analysis, and modelling DNAzyme kinetics.

Behind this kind of research lies an intrinsically human element, as no discovery is made in a social or political vacuum. This paper seeks to address the gap between our project's lab work and the transfer of scientific knowledge across communities, particularly as synthetic biology as a discipline remains in its nascent stages. By proactively engaging a variety of stakeholders, mGEM felt that our work would support building credibility surrounding synthetic biology applications in the context of a deeply risk-averse clinical technology context. To this end, consultations with the NCCID, CIHR, local politicians, and leading researchers have established both a niche for synthetic biology solutions within antimicrobial resistance, and the international need for antimicrobial stewardship action.

With its emphasis on biological engineering, synthetic biology solutions offer opportunities to harness biological organisms towards the development of clinical assays, which may demonstrate use in lower-resource areas where significant lab technology is unavailable for use. Furthermore, the specificity and broad flexibility of the toolsets used in synthetic-biology assays can help support on-the-fly technological improvements. Such themes are explored in this discussion paper through an expose of each of the interviews conducted by the mGEM Human Practices team. Summaries of stakeholder interviews are followed by an outline of the core lessons developed from the aggregate total of the interviews completed by the team.

STAKEHOLDER INTERVIEWS

From May 2017-September 2017, mGEM Human Practices interviewed a series of experts across Canada to better understand the challenges faced at various levels around antimicrobial resistance. mGEM sought to direct questions particularly focused on understanding opportunities for the prospective development of diagnostics for antimicrobial-resistant strains of bacteria in clinical contexts.

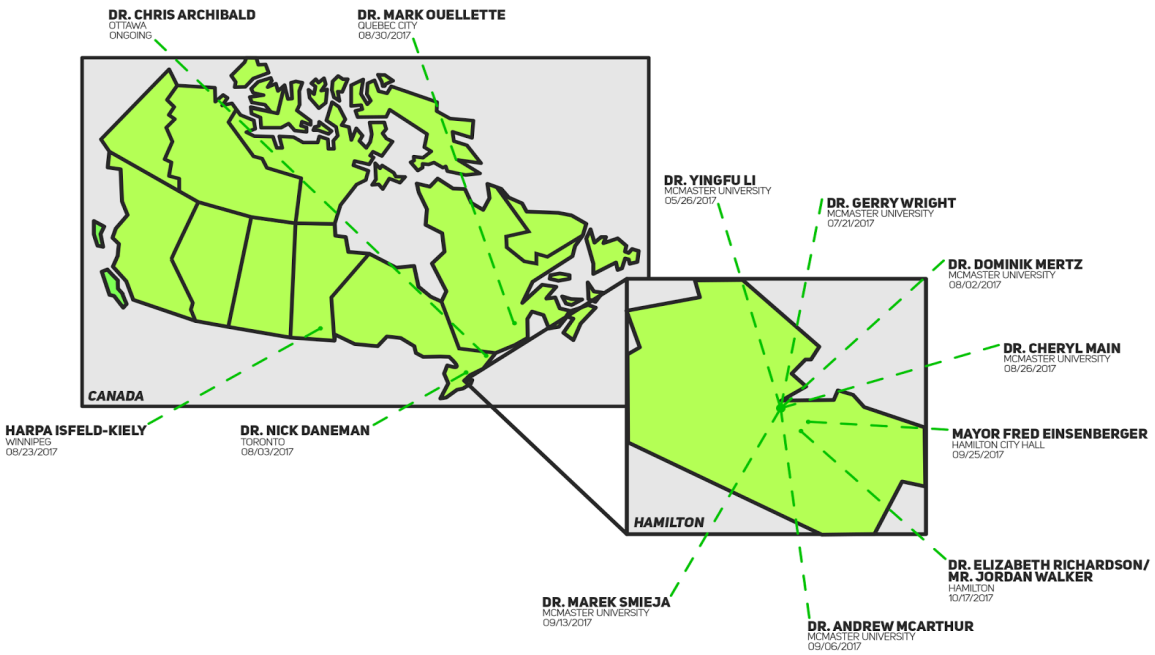


Figure 1 This map outlines the various stakeholders interviewed by the Human Practices team from May 2017- September 2017, and where they were located across Canada.

Dr. Yingfu Li

***Professor**, Dept. of Biochemistry and Biomedical Science, McMaster University*
Canada Research Chair in Chemical Biology of Nucleic Acids
May 26, 2017

During the inception of the project, as mGEM's primary advisor for the 2016-2017 year, Dr. Yingfu Li worked with mGEM to develop the theme of antibiotic-resistant bacteria. It thus followed that approaching Dr. Li for his perspective on the current stage of research regarding antibiotic resistance would serve as a strong launching pad for further research. Dr. Li outlined two major branches of research on the subject of pathogen resistance. One was improving the diagnostic method to detect bacterial strains with improved accuracy and timing. The other was developing new therapeutics to treat the novel strains. This outlining was helpful to expose how one might develop a holistic view of how antibiotic resistance is understood, and suggested that mGEM needed to approach researchers and clinicians at both branches of the resistance issue.

Dr. Li also brought attention to a factor that must be considered in the wet-lab design; balancing the needs between timing and accuracy. Dr. Li mentioned told us that a diagnostic tool that is fast in detection must sacrifice accuracy, while a tool that prioritizes accuracy sacrifices time efficiency. By relaying this to the wet-lab team, we deliberated together whether time or accuracy is more important to us, and modified the designs appropriately.

Finally, Dr. Li encouraged us to find multiple stakeholders to contact in order to fully understand the problem of antibiotic resistance. He provided names of researchers here at McMaster who would be especially helpful to mGEM, of whom the team could interview with his assistance.

Dr. Gerry Wright

Director, *Michael G. DeGroote Institute for Infectious Disease Research*
Canada Research Chair in Antimicrobial Biochemistry
July 21, 2017

mGEM further had the opportunity to interview Dr. Gerry Wright, an expert in drug development and antimicrobial resistance in the infancy of the project. The foundational knowledge developed in this meeting heavily influenced the project direction, with the first section of our discussion addressing the basics of antimicrobial resistance. Dr. Wright justified his research, which aims to identify both new antibiotics and compounds which inhibit resistance. The team learned that although sometimes resistance is due to internal mutation of the bacterial DNA (which we thought occurred most often), the most common resistance mechanism is the acquisition of resistant genes from plasmids and transposons. That is, a bacterial organism's resistance is more heavily influenced by external, rather than internal, factors.

Next, Dr. Wright discussed difficulties associated with a drug's commercialization process. Our team learned of the common decade between the discovery of a compound and the "phase two" trials of experimenting on patients. In this decade lies the transitional period referred to as the "Valley of Death", wherein most discoveries will remain, since rigorous trials often prove the compound inefficient or harmful and the cost of the years of testing is enormous.
When asked to critique our project, Dr. Wright stressed the need to determine the type of infection a patient has before administering antibiotics. In his words, the correct initial prescription of antibiotics is often a "shot in the dark", since testing for specific infections takes days, and by then the patient has already been prescribed a wide-range antibiotic which may exacerbate the infection. From this statement, we decided to focus heavily on our product's efficiency.

Dr. Dominik Mertz

***Medical Director Infection Control**, Hamilton Health Sciences*
***Associate Professor**, Division of Infectious Diseases, Department of Medicine*
August 2, 2017

mGEM had the opportunity to speak with Dr. Dominik Mertz, an Associate Professor at McMaster University, and the Medical Director of Infection Control for Hamilton Health Sciences. The team sought to interview Dr. Mertz, as his administrative role in antimicrobial resistance and infection control would be particularly helpful and interesting.

When stating that through our research, the taken to diagnose C. difficile is a significant issue, Dr. Mertz agreed. He stated, "[w]hen you have a patient in front of you who is not doing well, who needs antibiotics, the faster you know what [the infection] is, the better." The turnaround time of approximately 3-5 days between sending the sample off to the lab and yielding a result is a crucial time where patients need treatment. In the time they are not receiving C. difficile-specific antibiotics, they are often taking other, broad-spectrum antibiotics that can work to exaggerate the problem. Thus, a novel, faster technique of diagnosing C. difficile, in his view, was clearly needed.

Additionally, Dr. Mertz informed us around the lack of public awareness of antimicrobial resistance as a key problem in antimicrobial stewardship. With this in mind, we further probed Dr. Mertz about the public's perception of antimicrobial resistance and the degree of scientific literacy in the community. He did not hesitate to further support the ideas that we previously had, in saying that "another issue [besides a long laboratory turnaround time] is public awareness in terms of the use of microbial resistance". He added, "[m]any patients still expect antibiotics when they go see a doctor, even if it's not needed. Then they push the doctor to write a prescription". This concern echoed by other experts in the field whom we spoke with, particularly by Dr. Marek Smieja. It seems that physicians are sometimes pressured into prescribing antibiotics by patients who are not fully aware of the risks.

This issue of public unawareness surrounding the topic of antimicrobial resistance is not new and has patients seeking unnecessary antibiotics and not taking the full course of their prescribed antibiotics once symptoms diminish, among other hazardous actions. In light of hearing this concern from multiple healthcare professionals, we became interested in mitigating this issue. Such initiatives that we are planning on completing include a pamphlet, creating a video series directed towards the public, and appearing on Hamilton's Cable 14 News, as suggested by Mayor Fred Eisenberger.

Dr. Nick Daneman

Clinician-Scientist, *Sunnybrook Research Institute*
August 3, 2017

As a researcher in one of the country's leading hospital research centres, Dr. Nick Daneman was an an infectious disease specialist who has a particular focus in AMR stewardship, clinical epidemiology and health services research, and C. difficile. These were also all our our areas of interest, especially as C difficile AMR strands are being investigated in our wet lab work. Therefore, we wished to interview him to gain key insights into just how much C difficile is a burden on healthcare systems, how widespread it is, and how we could tackle this.

During our interview, Dr. Daneman first revealed to us that in the case of C difficile, "the majority of cases develop after admission [into a healthcare facility] or... an elderly person in a long-term care situation, or a recently discharged person who then develops symptoms in the community... The two [factors in the development of C. difficile as a disease] are: one needs to get the bug, which means oral ingestion of contaminants within the environment, and the second [factor] is antibiotics, because people have diverse, protective intestinal flora [that protect against sickness]... but antibiotics dilutes the normal bacteria and C. difficile has more of a niche to replicate and cause disease."

Dr. Daneman then detailed the processes behind the standard diagnostic test for C. difficile, which involve the use of PCRs, as they are immuno-sensitive. However, he noted that these tests are usually sent to Public Health for analysis and results, which means that they end up being stuck there for some time. He saw that if turnaround time could be reduced and the results could be known faster, the outcomes of either getting people on antibiotics should they have a positive result or spare them of unnecessary treatment on antibiotics should they be negative, would have a huge impact on patients. Another benefit that he saw was that patients could also be directed more quickly to other testing to find their proper diagnosis. Thus, he approved of our proof-of-concept for being able to fit into this needed aspect of diagnosis.

.

While mentioning the costs of C. difficile, he explained that thousands of dollars could be saved per case of prevention. Morbidity and mortality are also very high for this disease; he said that the Ontario Burden of Infectious Disease Study showed C. difficile coming out in the top ten for these factors, above all the other intestinal infections combined.

Returning to antibiotics, Dr. Daneman stressed that the issue of antibiotic and AMR stewardship and education are key in preventing C. difficile from developing into a bacterial disease. Since "any antibiotic can cause C. difficile [to become active], ...[including] the antibiotics we use to treat C. difficile," it is important to focus on "when to start, how to choose, and when to stop treatment." When his team conducted an epidemiological study on the trends of antibiotic prescription by practitioners, they saw that "the conclusion was that the prescriber was deciding [how often to prescribe antibiotics] out of habit." They thus came up with the plan to "give audit and feedback to prescribers, to try to show them where they sit as compared to their peers (e.g. 'You prescribe more antibiotics/use longer duration of antibiotics than 90% of your colleagues'.)... [as these comparison were] well-established ways to change a prescriber's behaviour." Although they only had a 10% impact on change, this was still significant because "when you're talking about 700 prescribers to 10 000 patients," the rates of prescriptions would go down by a notable figure.

> **"90% of antibiotic use is in the community... Better antimicrobial stewardship [is needed]."**

However, he still firmly believes that educating the practitioners about antibiotic overprescription is vital. Dr. Daneman saw that the next steps in tackling AMR would be to require accreditation, to have a "Requirement of Practice that every acute-care hospital in Canada needs to have an antibiotic program now, [with] long-term care also [being] a target audience." Having researched in this field extensively, and also having formerly worked under Gerry Wright, he understood the vast implications that would arise from the continued development of AMR. Lastly, he touched upon how the public also needed to become more aware of this issue so as to prevent the widespread problems surrounding AMR. Since "90% of antibiotic use is in the community, ...better antimicrobial stewardship [is needed]." He commended us on picking a very important topic, and reinforced with us that tackling this issue of AMR would be important for local, national, and global health.

.

Harpa Isfeld-Kiely

***Project Lead**, AMR and AMS*
***Senior Project Manager**, National Collaborating Centre for Infectious Disease (NCCID)*
August 23, 2017

To develop a stronger background in the broader policy dimensions of AMR, mGEM interviewed Harpa Isfeld-Kiely, a Senior Project Manager at the Canadian National Collaborating Centre for Infectious Diseases (NCCID). Our conversations focused on understanding the complexities of public education surrounding AMR, antimicrobial stewardship, the worldwide burden of disease, and Canada's political role in combatting AMR.

mGEM learned a great deal about the breadth of qualitative research done by prominent biomedical research funders such as the Wellcome Trust around science communication, and public perception of antibiotic use. This resource was helpful for us to better understand the barriers to effective science communication commonly faced by research institutions and public knowledge brokers. We were additionally informed about the existing work completed by hospitals in Canada, primarily Mt. Sinai in Toronto regarding effective hospital antimicrobial stewardship. We were additionally referred to larger action plans being developed across Canadian health institutions to support work in antimicrobial stewardship.

mGEM also discussed the large international health-economics studies projecting the estimated international number of deaths attributable to AMR bacteria, and the estimated worldwide cost for healthcare. Such arguments were particularly useful to scope the magnitude of the AMR problem in the broader context of other items on the global health agenda, such as non-communicable diseases (diabetes, cardiovascular diseases), and infectious diseases. We further discussed the functions of the Canadian government in supporting research towards point-of-care diagnostics like our wet lab project, and the leadership of Canadian policymakers on the national and international stages in strategizing against AMR. Such discussions yielded a greater understanding of the breadth of challenges presented on the policy and financing levels in supporting AMR research, and allowed us to contextualize our project in the broader AMR movement.

Dr. Cheryl Main

***Chair**, Specialty Committee of Infectious Disease*
***Senior Project Manager**, National Collaborating Centre for Infectious Disease (NCCID)*
August 25, 2017

Dr. Cheryl Main was recommended to us by one of our past interviewees due to her experiences of running educational programs in Hamilton on bacterial infections and sex education. One of HP team's main interests is improving the public awareness and engagement on antibiotic stewardship. By interviewing Dr. Main, we gained valuable insights on how public campaigns succeed and fail.

During the exchange, Dr. Main provided accounts of her work on educational programs at middle-high school boards and of the challenges experienced. She informed us that for change to occur in the minds of the public, educational programs need sustainability and longevity. She also emphasized the importance of carefully choosing words and visual aids to target the appropriate audience. For example, when catering to clinicians and other professional staff, material can carry some scientific language. However, when addressing to the general audience with mix of students, teachers and parents, basic terminology should be used to advance ideas clearly.

Furthermore, Dr. Main has executed informational campaigns for staff at the Hamilton General Hospital. Of the projects, she found installing posters at strategic locations in the wards to be especially helpful. Hearing this, the Human Practices team brainstormed initiatives that we could attempt to inform both the public and frontline staff on antibiotic stewardships. We considered flyers such as the ones developed by Dr. Main's team to be one of the most viable options for the resources that we had available.

Dr. Marc Ouellette

***Scientific Director**, CIHR III*
Canada Research Chai in Antimicrobial Resistance
August 28, 2017

In Canada, CIHR (or Canadian Institutes of Health Research) is one of three principal federal research funding agencies, and indeed the main funding agency for health research in the nation. After having interviewed several prominent researchers, we were able to get in contact with the Scientific Director of CIHR's Institute of Infection and Immunity, Dr. Marc Ouellette. Dr. Ouellette's extensive research on antimicrobial resistance, as well as his extensive oversight of the scientific community and research surrounding this topic, made him ideal in synthesizing the knowledge we gained and showing us where to go next.

As he was located in the province of Québec, we had arranged to meet with him over Skype. Before the meeting, we had particularly wanted to get his insights on the evolution and future trends in AMR, along with the current gaps in research with regards to Stewardship and diagnostics for AMR and C. difficile screening. This was so that we could tie it back to the reason we were developing an assay that could diagnose AMR-resistant bacteria.

During the meeting, several key themes emerged. Firstly, Dr. Ouellette's insights on the gaps for detection assays reverberated with previous researchers' statements: cost and rapidity were at the crux of the issue. Although there were current diagnostic assays in the field of AMR for a multitude of bacteria and their respective strains, the main focuses for future potential technologies lay in making those diagnostics more affordable, so that more healthcare centres could have access to them, and making them more rapid, especially in comparison to current techniques. Specifically, if an assay could not determine an answer "within 30, 40 minutes, then it's useless in that it has the same base as classic microbiology tests. The decision has been taken, the patient has moved on." However, he also saw that "...adding a rapid diagnostic for general bacterial infection would have a huge impact. This is the quest to everyone involved in diagnostics: to distinguish between a bacteria and a virus. Right now, looking at the RNA-seeking test, we can determine this, but it's not cheap or rapid... This is where an assay like [iGEM McMaster's] could come in and really advance molecular medicine."

Taking a broader look at the issue, Dr. Ouellette outlined how AMR was a pressing issue in Canada and around the world. He estimated that our country invests approximately $20 million each year into this issue, as it was well-represented in the House of Commons and the Canadian government. With regards to C. difficile in particular, there were no exact monetary figures, but he mentioned that this bacterial disease was a recognized crisis in hospitals and long-term care facilities that was well-funded as well. As a complex global issue, Dr. Ouellette shed light on the multi-national collaborations that are in place to tackle AMR's three pillars: surveillance, stewardship, and innovation. He remarked that he was going to a conference meeting the next day to talk to the TATFAR (Trans-Atlantic Task Force on AMR) collaboration, in which the EU (including the UK, a leader in this field), the USA, Norway, and Canada are all a part of. He saw Canada as a definite player in this issue as well, facilitating partnerships between the people and countries who have more resources and those who do not; involvement with lower-income countries and partnerships are also being formed more and more. Lastly, Dr. Ouellette mentioned the severity and wide scope of the issue around the world:

"The G7 has discussed AMR twice in a row, and it has also been discussed in their climate forum. Now, the G20 is trying to make a group with other countries for push and pull: push being the research effort, and the pull is prizes or taxbreaks. The CIHR contributed more into the pull, and the JPIAMR is a group of mostly European funders which is trying to fund internationally. Committees are being put together every week for AMR, which means there's a lot of stakes in it, and it's quite complicated because it's under the umbrella of the "One Health" concept. This concept is the human, animal, and environment health.

Challenges in developing countries are that the health systems are not the same; here in Canada I think it's reasonable, and we can use authorities to help. Some other places this system is broken, so resistant infections can spread further and complicate things. This is where I see some of the challenges. The technology we develop is also nearly impossible to make in low-income countries. This is why Ebola was such a problem: the health systems were broken."

When prompted about AMR Stewardship, Dr. Ouellette told us that the heart of this main pillar in AMR was "[to] give antibiotics to the people who need them, and the right one at the right time. It's an art, not a science, when they look at you feeling terrible." Having known of one of our interviewee's, Dr. Nick Daneman's, work surrounding the auditing of prescribers of antibiotics, Dr. Ouellette explained to us that he believed in targeting both the prescribers and the patients. Although it is a complex issue, as antibiotics are both necessary in saving lives but also could induce life-threatening consequences, he firmly stated that further education on this topic for everyone would help prevent more negative outcomes.

"Sometimes antibiotics save lives, remember that. It's just like washing your hands — it's the public and the healthcare worker. Except, this situation has dire consequences. Antibiotics are absolutely necessary, but sometimes they're not. You're a parent and you haven't slept for three days, so you try to convince your GP to give your child antibiotics. But what if you knew that your child's immune system could be harmed? It's only recently that we found antibiotics would harm your good bacteria, your microbiome, and we had no idea the role that plays in the immune system at a young age. A young baby in the first 6 months of its life: this is where antibiotics are life-saving, but also the worst. So education for all partners would help."

Finally, Dr. Ouellette foresaw future research in this field in Canada as not being as broad-scope and notable, as other countries had better funding and pharmaceutical research, but he saw the nation as being able to fill the niches in AMR research gaps. Dr. Gerry Wright's research on using molecules to help circumvent resistance was specifically mentioned, alongside immunology and alternatives to antibiotics. Stewardship was also brought up again, as he said that our methods here were strong and the field was full of the top minds in Canada. He lastly reinforced that "[we] need to protect what we have, judiciously, [through stewardship, better education]... Research on strategies to limit antibiotic use will also have impact, and Canada has a lot to offer there too."

With Dr. Ouellette's powerful insights, we were able to further understand just how important the evolving field of AMR, and specifically AMR Stewardship, are in future directions of healthcare and research. As our project could fill the gaps and needs that he mentioned, and he himself saw our work as perhaps being the next step that could be taken in diagnostics for such an issue of import, we can justify our work even more through both the scientific impact that we could have and through our decisions to now broaden education about AMR and conduct our own forms of stewardship in our local communities.

Dr. Marek Smieja

***Chief of Microbiology**, City of Hamilton*
***Founding Member**, Ontario Working Group for the Rapid Diagnosis of Emerging Infections*
Phone Interview: September 1, 2017 - IIDR Rounds: Semptember 6, 2017 –
In-person Interview: September 13, 2017

On September 13th, the Human Practices team had the opportunity to interview Dr. Marek Smieja, the Chief of Microbiology for the City of Hamilton. Dr. Smieja's extensive work with C. difficile made him an excellent resource. After interviewing him, the three most prominent lessons we learned from him were that: 1) hospitals are overflowing and the turn-around time for C. difficile tests is approximately 3-5 days; 2) a test that can be provided in a more consumer-friendly manner is much-needed; and 3) healthcare providers prescribing antibiotics should be providing patients with information regarding the risks of AMR and C. difficile.

After discussing the burden of C. difficile on the healthcare system, Dr. Smieja highlighted the importance of finding ways to redirect patients away from hospitals and move diagnostic testing upstream. In order to help alleviate this load, Dr. Smieja suggested designing a more consumer-friendly diagnostic test that can be purchased at a pharmacy, brought home by family members, or conducted by nurses in nursing homes. This would also shorten the time that patients often wait before seeking medical attention, and would hopefully allow the infection to be addressed before it worsens. Lastly, Dr. Smieja voiced concern about healthcare providers not providing patients with adequate information upon the prescription of antibiotics. He stated, "as long as people think that there are no antibiotics have no side effects, we have issues." This prompted us to ask if a pamphlet that could be distributed by such healthcare providers alongside the prescription of antibiotics would be helpful. After hearing that he was fond of the idea, the Human Practices team decided to design such a pamphlet that could be given to healthcare providers for their use.

Dr. Andrew McArthur

***Cisco Research Chair in Bioinfomatics**, McMaster University*
***Associate Professor**, Department of Biochemistry and Biomedical Sciences*
September 6, 2017

Our group was invited to attend the Michael G. DeGroote Institute for Infectious Disease Research (IIDR) Rounds, where we had the chance to discuss existing computational pipelines in the surveillance of C. difficile in St. Joseph's Hospital in Hamilton, Ontario. While this discussion was focused upon the epidemiological surveillance of C. difficile within the hospital wards, much of the clinical discussion was focused around existing tools for prevention of the spread of AMR. Spanning recommendations such as washing hands, isolating patients with diarrhea, diagnostic tools, and prophylactic antimicrobial use, we were fascinated with the host of clinical decisions required to manage C. difficile patients.

Recognizing the complexity of the clinical landscape helped us better recognize and understand the clinical context under which a technology like our prospective point-of-care diagnostic tool would fit within the broader architecture of clinical decision making. Similar in many respects to the United Kingdom, Canada is pressured under its provincial single-payer, publicly funded healthcare systems to build diligent health technology assessment studies and protocol to ensure that clinical decisions are being informed by both clinical utility and cost-effectiveness. For us, this was a significant tipping point in our understanding of the broader policy context of biotechnology development – particularly in the Canadian healthcare context. While techniques such as immunoassays and rectal swabs yield strong results, it is difficult to assess at what point in the clinical algorithm they should be deployed to ensure the ideal balance of clinical utility and cost-effectiveness.

Mr. Fred Eisenberger

***Mayor**, City of Hamilton*
September 25, 2017

With insights from leading researchers across Canada, we reached out to Mr. Fred Eisenberger, the Mayor of Hamilton, to figure out how we could effectively convey this information to the citizens of Hamilton. Specifically, we wanted to know how we could create effective workshops for high school students, campaigns for the general Hamilton community and resources that could be given to patients receiving antibiotics in order to foster a scientifically literate community and to bring awareness to issues surrounding antimicrobial resistance. Mr. Eisenberger's extensive work in the Hamilton community and his focus on developing the next generation of healthcare leaders made him the best choice to help us develop a platform to share our research.

We started the meeting off by discussing the McMaster iGEM team, our research, and the negative effects of C. difficile in Hamilton. The mayor proceeded by asking a series of questions to determine the scope of the problem and those who are most likely to be affected. With new knowledge from researchers such as Dr. Daneman, we were able to explain that in the case of C difficile,

> **"The majority of cases develop after admission [into a healthcare facility] or... [in] an elderly person in a long-term care situation, or a recently discharged person who then develops symptoms in the**

Thus, we wanted to develop a point of care diagnostic tool to prevent patients from acquiring a C. difficile infection in the first place. While our wet-lab team has made tremendous progress, the mayor pointed out that we should focus our efforts on what we can do now.

So after our discussion of the wet-lab project and the issues surrounding C. difficile that are relevant to Hamilton, we focused the remainder of our meeting on education and outreach opportunities. We started by asking Mayor Eisenberger for information regarding the most effective ways of communicating with the public and bringing awareness to antimicrobial resistance. He laughed and said that while social media platforms are a good starting point, “good old-fashioned T.V. and radio” are still a great way of communicating with a wider audience, especially those who may not be active on social media. He said that once we had a solid message and had fully developed our content, he would help us to broadcast our message using mass media platforms such as the Cable 14 news. He also connected us with a number of local community groups such as the Social Planning Research Council, and the Public Health Sector of Hamilton led by Dr. Elizabeth Richardson. The mayor showed tremendous support for our project and the work we are hoping to do in the community.

The mayor's encouragement, insight on our outreach initiatives, and contacts with local community organizations and Dr. Elizabeth Richardson have been invaluable and showcases the impact students can have. We look forward to contacting these organizations, engaging with community members and speaking to Dr. Elizabeth Richardson, the Medical Officer of Health, to better understand how the McMaster iGEM team can word to address issues in the Hamilton community.

Dr. Elizabeth Richardson and Mr. Jordan Walker

***Medical Office of Health**, City of Hamilton*
***Manager**, Hamilton Infectious Disease Prevention and Control (Respectively)*
October 17, 2017

With Mayor Eisenberger's help, we arranged a meeting with Dr. Richardson and Mr. Walker with the intention of further integrating McMaster iGEM with the City of Hamilton and its healthcare communities. The preparation for this meeting involved an inter-subteam assessment of the future of McMaster iGEM, and how to commit to projects which will truly benefit our city. We had the opportunity to discuss upcoming initiatives within Hamilton's Public Health sector, and our interviewees' own goals in the execution of these projects.

An issue we discussed in depth was the recent spike of Legionnaires' disease which occurred in Hamilton and the Greater Toronto Area over the past summer. Mr. Walker expressed that the largest obstacle in combating Legionella bacteria was the difficulty that researchers faced in tracking the source of the infection, since the bacteria exists in warm water sources and airborne mists. The current diagnostic method involves a urine antigen test which, although providing a sufficient diagnosis, does not give any hint to where an individual contracted the disease. Legionnaire's struck our team as an intricate and pressing issue, with the potential for synthetic biology application in both diagnostic and therapeutic techniques.

Other prevalent issues we discussed within Hamilton's healthcare system include:

- Lyme disease from tick bites
- Tobacco consumption and smoking in youth
- Sexually transmitted infections and antibiotic delivery for syphilis, gonorrhea, and chlamydia
- Opioids and safe injection sites
- Mental health determinants

We recognise the potential of mGEM's future projects to connect with the City of Hamilton's public health sector, and for our Human Practices and Outreach teams to provide support to their own campaigns. This meeting was invaluable for our careful consideration of the future of McMaster iGEM as a community-integrated, education-based research team.

Dr. Theresa Tam

Director of the Surveillance and Epidemiology Division,
Centre for Communicable Diseases and Infection, Public Health Agency of Canada
Ongoing

After interviewing many researchers from across Canada, speaking with the Mayor of Hamilton and most recently meeting with Dr. Richardson and Mr. Walker from the public health sector in Hamilton, we decided to contact the Public Health Agency of Canada (PHAC) to better understand antimicrobial resistance on a national scale. Dr. Theresa Tam, Chief Public Health Officer, provided us with a number of resources including the Canadian Antimicrobial Surveillance System 2016 Report, the Antimicrobial Resistance in Common Hospital Pathogens in Ontario Report, and the Federal Action Plan on Antimicrobial Resistance. These resources have been invaluable in helping us better understand the scope of AMR. After all, "AMR is a cross-cutting issue with roles and responsibilities shared by the federal, provincial, and territorial governments".

After we have had a chance to thoroughly analyze all the information we have received, we will be contacting Dr. Chris Archibald, the Director of the Surveillance and Epidemiology Division, in the Centre for Communicable Diseases and Infection Control to discuss our project, outreach initiatives and how we can continue to address healthcare issues like AMR in Canada. With insights from both Dr. Tam and Dr. Archibald, we will be able to continue the development of our outreach initiatives for both students and communities, and be able to broaden the scope of our project.

Lessons Learned

Lesson 1: Antibiotic resistance is increasingly becoming a major health concern due to overprescription and poor bacterial stewardship

One of the common recurring themes presented in the interviews was the over-prescription of antibiotics and the pressures it causes on producing new strains of resistant bacteria. It was most directly described by Dr. Ouellette, and other clinicians Drs. Mertz and Daneman have also mentioned its challenges. mGEM HP team believes that programs that will change the public's expectations on prescription of antibiotics will significantly improve the prevention of resistant strains.

Lesson 2: To effectively combat antibiotic resistance, the Canadian government framed its plan of action into three major branches - surveillance, stewardship and innovation

The terms surveillance, stewardship and innovation were used to describe the three pillars of AMR strategy in Canada. It was introduced to us by Dr. Ouellete but constantly emerged as the main themes of future interviews. We have considered our Wet Lab product to be as part of the innovation pillar as it is expected to improve diagnostics of identified strains. However, HP team also examined the stewardship pillar as it has most potential for us to make a difference in our community through educational programs. Finally, researchers such as Dr. McArther and Dr. Daneman has worked in the surveillance pillar to study the epidemiology of c.difficile resistance.

Lesson 3: It is extremely challenging but doable to obtain crowd engagement in public health issues

Our discussions with the public officer Dr. Elizabeth Richardson and Mr. Jordan Walker cemented our hopes that crowd engagement over AMR is possible, through multi-tiered intervention plan and persistence. Much of our interviewees were asked the question, "What can we do to increase the public's interest in the issue of bacterial resistance?". Together, variety of initiatives were discussed such as poster campaigns, infographs, workshops, parents conference, and discussion panels. In the future we hope to reflect on the past challenges and advantages experienced by each initiative and develop a reasonable plan to impact the local community.

CONCLUSION

Synthetic biology tools have strong promise to address the challenges presented to human health by antimicrobial resistance. The 2017 McMaster iGEM team sought to justify this statement through proof-of-concept experiments, using a functional nucleic acid strand as a rapid diagnostic tool for antimicrobial-resistant strains of E. coli and C. difficile. Stakeholder integration is essential to the development of an effective, accessible product. In meeting with AMR experts, we were further able to justify our DNAzyme project by establishing the need for rapid diagnostic technology, especially for hospital-acquired C. difficile infections.

From these interviews, we learned first and foremost that AMR is an ever-growing health concern, both for Canadians and internationally. To effectively combat antibiotic resistance, the Canadian government framed its plan of action into three major branches: surveillance, stewardship and innovation. As students, we were encouraged to engage in the stewardship pillar and promote education about antibiotic use, since poor antimicrobial stewardship is leading to a proliferation of antimicrobial resistance through inefficient prescription and duration of antibiotic treatments. We explored avenues of community health education, but found that it is extremely challenging to reframe AMR in a way that the general public will understand and engage with. Our interviewees suggested a multi-tiered AMS campaign to target both clinicians and patients.

McMaster iGEM plans to continue its commitment to public engagement within the City of Hamilton's most pressing healthcare issues. Through this project, we connected with municipal and national experts who were happy to see students pursuing health research. Thus, we plan on expanding our team initiatives next season with a revived emphasis on education and mentorship for university and high school students, in the fields of both synthetic biology and public health.