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Pandemic Driven Innovation: Development of an Alternative Respiratory Pathogen Self-Collection Device

Thang Nguyen
University of Nebraska Medical Center

PANDEMIC DRIVEN INNOVATION: DEVELOPMENT OF AN ALTERNATIVE RESPIRATORY PATHOGEN SELF-COLLECTION DEVICE

by

Thang T. Nguyen

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Supervisory Committee:

Michael Wadman, MD	Jane Meza, PhD
James McClay, MD	Deepak Khazanchi, PhD

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Thang T. Nguyen, Ph.D.

University of Nebraska, 2020

Supervisor: Michael C. Wadman, MD

The SARS-CoV-2 virus outbreak has underscored numerous weak links in our biodefense countermeasures against highly communicable diseases. Many believe it was our lack of an effective testing model that allowed the virus to become a global pandemic within a short period. The gold standard collection method for the SARS-CoV-2 virus involves mechanical debridement of the nasopharyngeal cavity with a stiff swab applicator, which has been known to cause pain and injury to patients, subsequently resulting in low patient acceptance of the procedure. Due to the invasive nature of the nasopharyngeal swab collection method, it may not be conducive to the implementation of a mass or distance testing model. This dissertation attempted to develop an alternative specimen collection method for respiratory pathogens using a fluid debridement mechanism as opposed to the traditional mechanical swab debridement method. By adopting the design principles of design thinking, design control, and human factors engineering (HFE), this project was successful in developing a working prototype of the proposed concept. A pilot study was conducted to validate engineering parameters and the diagnostic validity of the study device. Data from the pilot study demonstrated the study device was successful in debriding the nasopharyngeal cavity for epithelial cells as confirmed by polymerase chain reaction (PCR) testing for the RNase P gene target. The study device had a 100% capture rate while maintaining consistently low cyclic threshold (CT) values indicating adequate specimen cellularity.

TABLE OF CONTENTS

INTRODUCTION

The SARS-CoV-2 virus has proven to be a highly pathogenic virus allowing it to rapidly become the center of a global pandemic within a short period. Infected individuals go on to develop the illness known as COVID-19, which has demonstrated itself to be an extremely virulent disease. Like many other countries, delays in the United States' (US) implementation of a mass testing model has hampered our ability to deploy critical containment actions such as contact tracing [1, 2]. As of October 1st, the US leads the world in COVID-19 infection and death rates [3].

In this dissertation, I evaluated the current literature on respiratory tract infection (RTI) diagnostic standards, particularly as they apply to a patient self-collection model. The diagnostic fidelity of self-collected specimens has demonstrated similar sensitivity and specificity for certain RTIs [4] and sexually transmitted infections [5] when compared to a healthcare worker collected specimen. The current gold standard collection method for respiratory pathogens such as influenza and SARS-CoV-2 is the nasopharyngeal swab method. The literature suggests patients are not accepting of the traditional nasopharyngeal swab method as it is invasive, painful, and has the potential for injury. This method of collection also places healthcare workers at risk for potential cross-infection as it requires prolonged close contact with potentially infected individuals. To compound the issue, the nasopharyngeal swab method has the tendency to trigger the patient's coughing or sneezing reflexes. In their attempts to mitigate the cross-infection risk, healthcare workers are required to utilize an exorbitant amount of personal protective equipment (PPE) to administer the procedure, resulting in global supply shortages. Using the literature data, I proposed an alternative specimen collection method to procure respiratory pathogens from the nasopharyngeal cavity. My proposed method will be designed for self-administration by the patient but can also be administered by the healthcare worker in a traditional healthcare setting.

By adopting the fluid dynamic principles used in traumatic wound care, I was able to establish engineering parameters for a nasopharyngeal cavity fluid debridement concept. I framed the overall project with the following research question and hypothesis.

Research Question: Can fluid irrigation of the nasopharyngeal cavity debride for epithelial cells?

Hypothesis: Pressurized fluid irrigation of the nasopharyngeal cavity will debride the mucosal tissue of epithelial cells.

This dissertation work is an encapsulation of three manuscripts that outlines the progressive work involved in developing an alternative respiratory self-collection device. In the first manuscript, I outlined the literature review process that established the foundational knowledge base for this project but more importantly, it provided greater insight into the proposed problem. The second manuscript involved the design and prototyping processes for the study device. I outlined the process of adopting the US Food and Drug Administration's (FDA) design control principle and utilizing it to progress the initial concept through the design, fabrication, and preliminary testing phases. An Institutional Review Board (IRB) approved pilot study was conducted to validate my concept and test my hypothesis. The third manuscript outlines the pilot study process and outcome data.

CHAPTER 1: Design Principles and Project Aims

At the onset of this project, the need for a systematic design and development template was quickly determined to be essential to the project's success. Design-related failures are the leading cause of medical device errors resulting in injuries to the patient [6]. Given the fact that this project is primarily focused on the development of a novel medical device, much of my design process was guided by the FDA's design control principle [7], which was established as a development template for medical device manufacturers. With that being said, I also co-opted many elements from other design principles such as human factors engineering (HFE) [8] and design thinking [9]. HFE and design control are both heavily referenced in many of the FDA's medical device manufacturing guidelines [7, 8]. Nevertheless, all three principles provide systematic approaches to problem-solving and have several shared attributes, such as problem definition and iterative design [7, 10]. With my project being developed in an academic setting, lacking in the experience and resources available in most corporate projects, it was important to seamlessly blend elements from each design principle as applicable to my project goals. In this chapter, I will discuss how these design principles influenced my process.

As the foundation of my doctoral curriculum was heavily rooted in design thinking and its application in the entrepreneurial process, it was natural for me to begin assessing my problem using a design thinking lens. Design thinking is an iterative problem-solving technique [9-11] in which failure of the initial proposed solution(s) are embraced as learning lessons to quickly iterate upon for the next proposed solution [12]. In fact, design thinking encourages the pursuit of ideas that may not be fully formed, knowing there is a high probability of failure [12]. This iterative process is repeated until the team is satisfied with the refined solution. Design thinking also aids the design team in developing a better understanding of the problem as it affects the end-user; this practice is commonly referred to as empathy building and is the first phase of the design thinking process [9, 10].

As previously mentioned, my project is academically driven and is limited by the resources available to an academic center. The cost of conducting large focus groups to develop a comprehensive empathetic foundation is not feasible within the current scope of this project. The hosting of focus groups requires time, adequate facilities, and possibly funds to pay the participants. Nonetheless, in an effort to develop the empathy needed to better define the problem, I drew from my personal experiences with the target audience while relying on the literature data to provide some degree of generalizable user traits. I also conducted iterative one-on-one design sessions with a small group of voluntary subject experts (physicians and nurses), allowing their feedback to outline my project goals. The use of volunteer participants allowed me to gather preliminary data using relatively limited resources because volunteers tend to be flexible with scheduling and may not require payment for their time.

Once the empathy-building is completed and the problem is better defined, I proposed a potential solution as part of the ideate phase. In this phase, the objective is to consider all possible solutions to the identified problem, regardless of the solution's feasibility or practicality. It may be advantageous to the project to have a team with diverse education and experience backgrounds generating ideas during the ideate phase. The team may choose to advance a single proposed solution or a group of proposed solutions for further development, although it is important to consider the team's available resources when attempting to evaluate multiple concepts simultaneously.

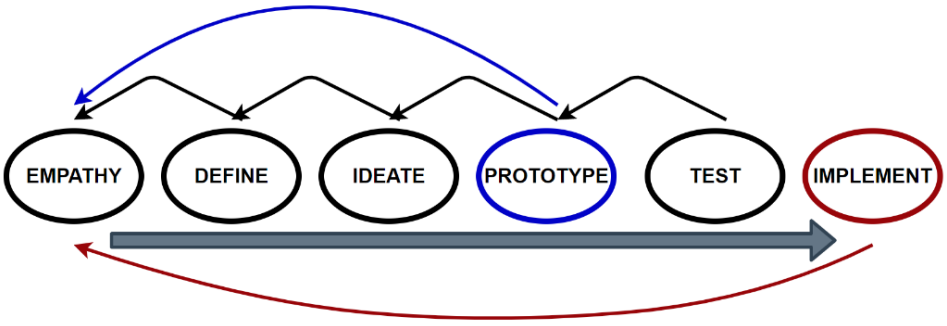

Figure 1. Design thinking flow diagram.

As the proposed solution(s) progresses through each design thinking phase, there will be inevitable modifications to the concept, for this reason, it is important to review the iterative designs to ensure it remains true to the original project goals. The iterative flow of design thinking is depicted in Figure 1 [9]. The prototyping and testing phases are often conducted jointly in a process known as continuous or concurrent engineering [13]. In this style of prototyping, early test data is rapidly integrated into a revised prototype for repeat validation testing. The process of concurrent engineering may be resource intensive as it requires cohesive teamwork and assiduous analysis of the test data to ensure potential design flaws are immediately addressed [13]. However, concurrent engineering can advance the development timeline at a much faster pace. In the implementation phase, a market-ready version of the product is tested on a small sample of the target audience to validate its performance against the original project goals. The state in which a product is determined to be market-ready may differ between design teams; if regulatory approval is not needed, this designation is often left for the team to decide. In the design thinking process, it is sometimes encouraged to test a "half-baked" product in hopes of gaining real-world performance data [12]. It is possible for more than one proposed solution to advance through all the stages of development, resulting in multiple market-ready products. In these situations, simultaneous validation tests can be conducted using multiple population samples with the experimental variable being the differences between the prototypes.

It is important to note, my development process deviated from the design thinking principle after the ideate phase. I felt the principle of design control provided more granular oversight across the design processes as it relates to the precision engineering of a medical device. In design control, proposed modifications to the current design are required to have an accompanying justification explaining why this modification contributes to the project goals; this is the review process of design control [6]. By reviewing all design modifications to the product, it provided me with an opportunity to revisit the foundational design elements of the device to

ensure negating effects do not occur. The principles of design thinking, design control, and HFE all have overlapping elements allowing for a seamless blending of the three principles [7, 10].

In general, all new medical devices must undergo regulatory review to determine their efficacy and safety before the product can be sold to the public [6]. As part of the submission process for regulatory review, the FDA requires all manufacturers of class II and III medical devices to maintain a detailed design log as applicable to the development of the product [6]. This requirement also applies to a subgroup of class I medical devices as specified in Title 21 of the Code of Federal Regulations [6]. The design log is a natural byproduct of the design control process as the design team is required to maintain diligent documentation of all modifications to the product along with the change rationale(s) [6]. The purpose of the design log is to provide an easily understood decision tree as it pertains to the design parameters and modifications made to the device during the development process; this allows the regulatory reviewer to validate whether specific product requirements are met [6].

When applying the principle of design control, the project is first framed by identifying a user need or a problem in need of solving [7]. This step is similar to the empathy and definition phases utilized in the design thinking process. The most common technique used to develop empathy is to observe the end-user and collect data on their interactions with a product in question [12]. Although there is some empathy-building in the design control principle, the process is not as in-depth as the empathy-building in the design thinking process. Empathy-building is a vital part of the development process as much of the latter design work is driven by the data synthesized during this phase [9]. The process of empathy-building provides the team with better clarity on the problem they are attempting to solve, along with insight on the target audience [9]. The empathy-building phase of design thinking is its core differentiating factor from other design principles such as design control and HFE. Design thinking focuses heavily on

defining your target audience and understanding the variables that drive their desires and actions [9].

Design teams often spend the bulk of their initial work gathering data on their end-users through direct observations, focus groups, or market pattern analysis [9, 14]. It is through this process that the design team can develop a representation of their target audience known as the user persona [14, 15]. The user persona is often based on inferences made about the user from market data, but it can also be based on hypothetical assumptions made about the user by the design team [14, 15]. The purpose of the user persona is to provide the team with a tangible target to focus their design work [14, 15]. Studies have shown the use of a user persona has beneficial effects on the idea generation process by promoting creativity [14]. If design choices are made based on a faulty user persona, the end-product may have inherent design flaws resulting in its ultimate failure. This type of failure can be appreciated when considering the poor market reception of the Chevrolet Nova automobile when it was made available in the Latin American markets. Despite being a wildly successful product in America, General Motors failed to realize the product's name, Nova, translates to "doesn't go" in Spanish [16, 17]. This is a clear example of the importance of the empathy work needed to develop a strong user persona for your target audience.

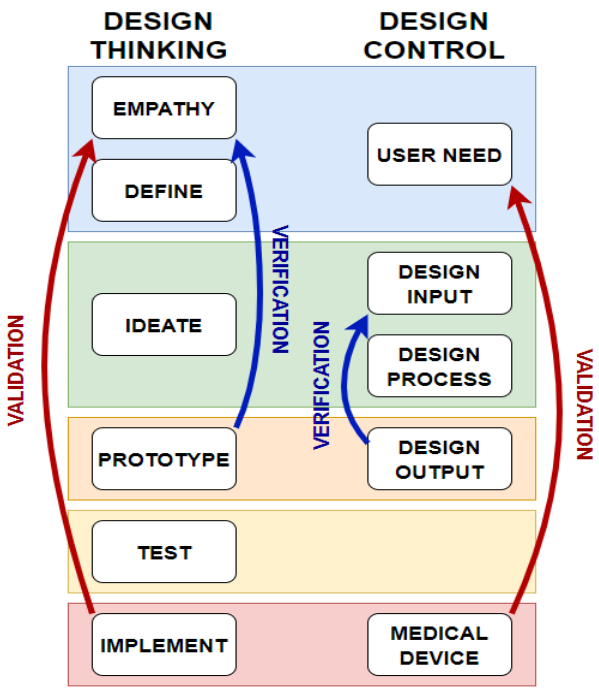

Figure 2. Comparison of design thinking and design control.

When comparing design thinking with design control, there is a memetic resemblance between the two principles, and their differentiating factors are in the nuances of their approaches to problem-solving. Figure 2 depicts a comparison of the development process for both principles [7, 9]. Both principles are cyclic in nature, encouraging the design team to continuously review their progress to ensure the outputs are consistent with the original project goals. Where the principles differ is in their overview of the project. For instance, the empathy-building and problem definition phases receive a heavier focus in design thinking, whereas, in design control, the ideation and solution refinement phases receive more attention. Design thinking can be considered a high-level problem-solving approach as the design team is tasked with constructing generalizable user personas to guide the design process and anticipate potential user reactions to the product being evaluated. Design thinking also tends to focus more on the ecosystem in which the product resides, as opposed to viewing the product as a singular variable. This viewpoint is helpful in visualizing multifaceted problems involving multiple systems, potentially requiring

simultaneous modifications to numerous variables to affect the desired change. On the other hand, design control provides a more granular evaluation of the problem as it is primarily focused on a user need [7]. For instance, when developing my proposed pathogen collection device, it was important to safeguard the irrigation mechanism from causing discomfort to the end-user. This was a specific requirement of the device that surfaced during the design thinking empathy-building process, but it was not the focus of the empathy. I would offer the lower patient acceptance of our current respiratory pathogen collection procedure is the broader problem of focus. Although design control cycles are generally geared toward addressing a particular problem, the design team can conduct simultaneous cycles to address more than one problem. The caveat to this is the need to ensure the design outputs of each cycle does not negate another design output or the original project goal. This reaffirms the importance of the verification and validation cycles, which functions as a quality control process to prevent negative design outcomes from occurring, potentially leading to patient injuries.

The FDA prioritizes the prevention of medical device-related injuries and has adopted HFE as a development principle for medical device manufacturers [8]. HFE is complementary to the process of design control, as demonstrated in Figure 3. Although the verification and validation phases of design thinking and design control may prevent potential medical device-related injuries through better engineering parameters, injury prevention is not the focus of these phases. This is in contrast with HFE, which is a robust toolset intended to aid the design team in validating the safety of their product. These validation tools can be employed during the design process as well as at the end of a development cycle, allowing for a multitiered validation approach, further strengthening the safety claims of the product [8].

In Figure 3, the red boxes illustrate the seamless incorporation of HFE principles into the design control cycle. For example, in the development of my pathogen collection device, there was feedback from an early tester expressing concerns regarding the device’s size and their

inability to operate it due to severe arthritis in their hands. This feedback is an example of incorporating potential user capabilities and limitations in the design process [8, 18], which drove the design decision to reduce the overall device size. The smaller device size facilitated easier gripping of the syringe mechanism, which alleviated the user's concerns. This process of rapid iterative prototyping based on early user feedback is an example of concurrent engineering [13].

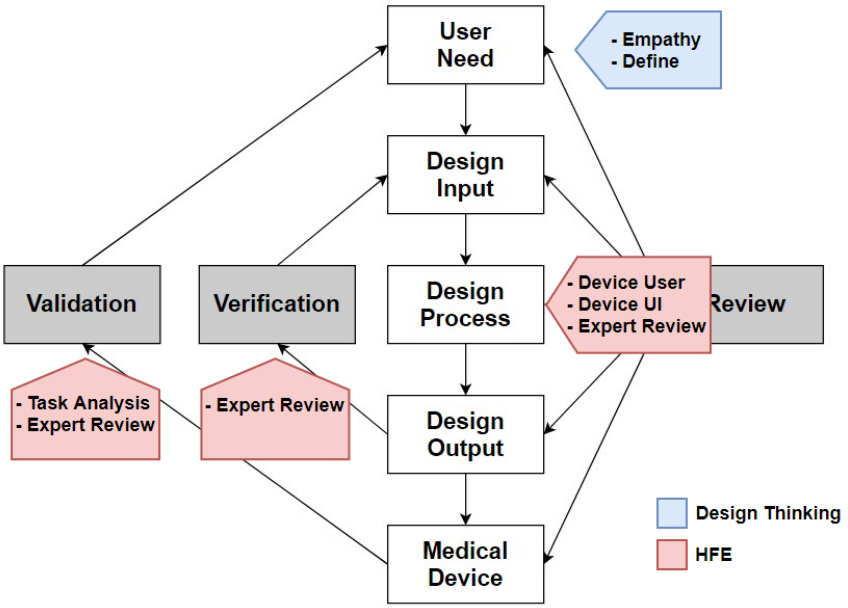

Figure 3. Blending of design thinking (blue) and human factors engineering (red) elements to the design control cycle (grayscale).

Once my device was ready for final testing, a task analysis validation was conducted to observe how real users would use the device and to identify where potential use errors could occur in the procedure [8]. A task analysis includes observation of users interacting with the product in an environment as close to the real-world as possible [8]. To provide an accurate simulation of the real world, the design team must have a clear vision of when, where, and how the users are most likely to interact with the product. Since my product was being developed in an academic center with healthcare workers as a subset of the target audience, my task analysis validation was conducted using emergency room physicians and nurses in an emergency department. All usage instructions or visual aids should be as close to final production as

possible. It should be noted; a comprehensive task analysis should also include users from the general population pool. However, during this phase of development, the decision was made to focus initially on healthcare workers. Future studies include validation studies with emergency department patients.

The end-users were provided instructions on how to assemble the product and how to self-administer the collection procedure. The users were then allowed to freely use the product under direct observation by me without any troubleshooting guidance. As a result of the task analysis, three use errors were discovered that could result in potential injury to the user. The first use error occurred when the device was used while the user stood in an upright position with their neck held in a neutral position. This positioning caused an excessive amount of irrigation solution to drain back into their throat and to the contralateral nostril. The second use error involved a user continuing to talk during the irrigation procedure, which triggered their gag reflex. The third user error involved the product assembly procedure. It was noticed some users were not completely inserting the syringe into the product housing, leading to leakage of the irrigation fluid and a reduction in irrigation pressure. Although no injuries were observed during these validation tests, concerns were raised regarding the potential for an aspiration injury related to the first two use errors. This led to the development of visual aids depicting a 15-degree flexion at the neck during the use of the device. Usage instructions were also updated to include verbiage instructing the user to hold their breath during the irrigation procedure. In repeat testing, the first two identified use errors were prevented by the modifications made to the product. As for the third use error, a few design modifications to the housing component are being evaluated that would provide a visual or tactile feedback indicating the syringe was properly inserted.

In summary, in my effort to formulate a systematic development template that is applicable to my project scope and development setting, I was successful in blending elements from three unique design principles – design thinking, design control, and HFE. Design control

and HFE are both widely adopted by the FDA and have become critical components to the regulatory approval process for medical devices [7, 8]. The core of my development process was based on the principle of design control because it provided me with a focused examination of the problem, which facilitated the precise engineering needed to develop a medical device. This is in contrast to the broad view provided by the design thinking process, which was used to develop a stronger appreciation for end-user traits that would affect their interactions with my product. Medical device designers and manufacturers must demonstrate unfaltering attention to detail as they strive to produce safe and effective medical devices. By adopting HFE principles into my development process, I was able to utilize the robust validation toolsets outlined in the Center for Devices and Radiological Health (CDRH) development guidelines to test for and to eliminate potential use errors [8].

The outline of my dissertation work is framed by the following *project aims* and the manuscripts presented in this dissertation are the resultant of these aims.

Project Aim 1: Adoption of the FDA's Design Control principle into an academically driven innovation project.

Project Aim 2: Applying Design Control to the development of a novel medical device.

Project Aim 3: Validate the efficacy of the proposed medical device.

CHAPTER 2: Manuscript 1

A Literature Review of the Efficacy of Self-Collection for Respiratory Tract Infection Diagnostics

Introduction

Respiratory tract infections (RTIs) are prevalent communicable diseases and is the third leading cause of death worldwide [19, 20]. It is estimated that a new infectious disease emerges at a rate of one per year [21], making early disease detection critically important. Within the past few decades, we have seen an increase in cases of novel respiratory illnesses such as SARS (severe acute respiratory syndrome), H1N1 (Swine Influenza), MERS (Middle East respiratory syndrome), and SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). Experts believe the ease of international travel has made non-endemic countries more vulnerable to the spread of infectious diseases. Rapid testing of RTIs is essential to the management of patients experiencing respiratory symptoms as it drives decision points such as treatment and disposition. In this paper, I will explore the efficacy of self-collected (SC) specimens for RTI testing and its potential role in our biodefense countermeasures for communicable diseases such as SARS-CoV-2. For this paper, the term COVID-19 will be used to refer to both the virus (SARS-CoV-2) and the disease state (COVID-19).

On March 11, 2020, just over two months after the first confirmed case in China, the World Health Organization (WHO) declared the COVID-19 outbreak a global pandemic. The rapid spread and severity of the disease coupled with inactivity by many nations were cited by the WHO as a major cause for concern [22, 23]. The COVID-19 outbreak has highlighted numerous weak links in our biodefense preparedness, allowing the virus to reach pandemic proportions within a short period. Delays in our testing responses have been cited as a major contributor to our failure to contain the disease [1, 2] and continues to be an Achilles heel in our defensive

measures. Disease testing is a precursor to other crucial bio-defensive actions such as contact tracing and containment [24].

As of August 23, 2020, there are approximately 23.1 million (803,000 deaths) confirmed COVID-19 cases globally, 5.6 million (176,000 deaths) of which are in the United States. This number continues to rise and is likely underreported given the limitations and barriers to confirmatory testing. There are also concerns regarding incomplete data on COVID-19 cases because, in most situations, only symptomatic or severely ill individuals are being tested [23]. According to recent updates from the Centers for Disease Control and Prevention (CDC), nasopharyngeal swabbing is the gold standard collection method for COVID-19 [25]. This process can be somewhat invasive and traumatizing for patients as it requires probing of the posterior nasopharynx with a stiff swab applicator for approximately 20 seconds per nostril. In some cases, this procedure has been known to result in pain, injury, and retention of the swab applicator requiring surgical removal. Because of the invasive nature of the procedure, patients often refuse testing or hesitate during the collection process resulting in inadequate specimen procurement, particularly in the pediatric population. It is also felt the nasopharyngeal swab technique has the potential for high rates of collection error, even when done by professionals, prompting the CDC to publish procedure aids to improve compliance [25].

In general, available testing modalities for COVID-19 such as real-time reverse transcription quantitative-polymerase (RT-qPCR) and antigen testing have shown acceptable sensitivity and specificity for the virus. However, this process is still hampered by inconsistent specimen collection. Poor specimen collection has raised concerns for high false-negative rates, prompting clinicians to consider alternative and costly confirmatory diagnostics such as radiographic imaging [26]. Misdiagnosis of COVID-19 could lead to the reintroduction of infected individuals back into the general population as seen in transmission cases in long-term care facilities [27]. There have been numerous proposed solutions to mitigate the risk of false-

negative outcomes including mass testing, home testing, and serial testing. However, our reliance on the conventional nasopharyngeal swab method is prohibitive to a large-scale testing scenario. Despite widespread usage, nasopharyngeal swabs have been consistently insensitive when detecting for COVID-19 and can be unreliable in serial testing [28-32]. The invasive nature of the nasopharyngeal swab procedure impedes compliance and, ultimately our ability to implement a reliable home or mass testing option [33]. The collection of specimens by using nasopharyngeal swabbing also presents a considerable cross-infection risk to healthcare workers due to their proximity to the patient and the swab's propensity to induce sneezing, coughing, or gagging [34, 35].

Nevertheless, RTI testing is critical to our ability to manage the spread of communicable diseases. As observed with the global COVID-19 response, South Korea was quick to implement mass testing which has been cited as the key action needed for the South Korean government to contain the spread of COVID-19 [36, 37]. Unfortunately, other nations' mass testing initiatives have been hampered by supply and personnel shortages [23, 38], but more importantly, ease of community access to test sites has proven difficult [35]. A potential solution to this problem is to offer patients an alternative such as a self-collection method. In a community-based survey study by Hall et al., as high as 87.7% of participants reported willingness to collect their own specimens [1]. Self-collection diagnostic research has proven promising in the area of SC specimens for sexually transmitted infections (STI). Self-vaginal swabs have been shown to have similar diagnostic reliability to professionally collected (PC) specimens and higher patient satisfaction [5]. By implementing a self-collection process for RTIs such as COVID-19, we can alleviate pressure points on our resource chains while improving community access to testing [39]. In general, it is also felt self-collection diagnostics has the potential for economic savings [4], which is a particularly important variable for future pandemic planning.

With that being said, self-collection research for RTIs has yielded inconsistent results. Some studies show SC nasopharyngeal swabs have poorer diagnostic reliability when compared to a PC specimen [40], while other studies suggest a non-inferior comparison [41]. The nasopharyngeal swab method often requires formal training and is susceptible to collection errors [4]. As previously mentioned, the nasopharyngeal swab method is an invasive and painful procedure, potentially making it less conducive to a patient-self-collection model. Some studies have attempted to evaluate alternative techniques of collecting specimens such as the nasal or the oropharyngeal swab methods, both of which are felt to be better tolerated by patients while producing similar outcomes as the nasopharyngeal swab method [4, 23]. The nasal swab is significantly less invasive when compared to the nasopharyngeal swab as it only involves swabbing between the nasal vestibule to the mid-turbinate. Furthermore, the CDC has endorsed the SC nasal swab as an acceptable specimen for PCR testing [25].

The objective of this paper is to perform a review of the literature evaluating the efficacy of SC specimens for RTI diagnostics. A meta-analysis of SC specimens for influenza diagnostics was published by Seaman et al. in 2019, and it was a thorough review of articles published between 2009 to 2017. Given our current landscape, I felt it was prudent to continue the work started by Seaman et al. and explore the potential of a self-collection model for COVID-19 testing.

Methods

In this review, I will evaluate the current literature on SC specimens for RTI diagnostics starting from 2017 to September 1, 2020. Although this paper is not meant to function as a full systematic review or meta-analysis of the literature, PRISMA 2009 guidelines [42] were used to provide structure to the review process.

Search Parameters:

I conducted a literature search of the PubMed/Medline, Scopus, and Embase databases using the following search terms/parameters:

influenza OR *virus* OR *COVID-19* OR *SARS-CoV-2*

AND

self-OR *collected* OR *test* OR *swab*

Eligibility Criteria:

All article titles were reviewed to determine topic relevance to my review objectives. A keyword search was performed on all returned article titles using the following words: respiratory, tract, infections, influenza, COVID-19, SARS-CoV-2, self, patient, home, collected, and collection. Articles with one or more of these words in their title progressed to a secondary screening where the abstracts were reviewed for topic relevance. Only full articles published between the years 2017 to 2020 were considered. Abstracts only and poster presentations were excluded from consideration.

Results

My literature search yielded a total of 81 articles (Scopus: 27, PubMed: 19, Embase: 35) published between 2017 to 2020. After reviewing titles and abstracts, it was determined that 61 of these articles did not apply to the topic of RTI self-collection and were excluded from consideration. After accounting for duplicate results, there was a total of 12 reviewable articles. Two additional articles were removed after determining that they were protocol proposals and did not include any diagnostic or comparative data. These articles are referenced within this paper but were not included in the review synthesis. Of the articles included in this review, 1 was a meta-analysis article on the topic of interest, 2 studied the acceptance of self-collection by patients, and 7 articles evaluated the diagnostic fidelity of SC specimens either as a sole variable or in comparison with PC specimens. See Figure 4.

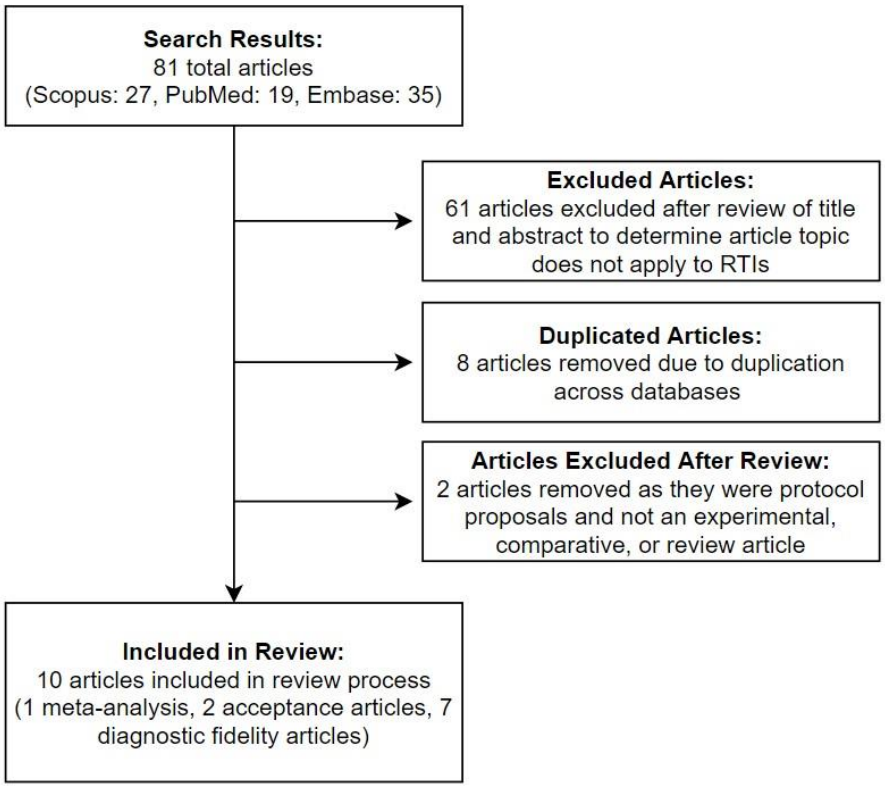

Figure 4. PRISMA flowchart of review process.

With the implementation of any self-collection initiative, approval from the general population is as important as the accuracy of the test itself. Research by teams Hall et al. and Valentine-Graves et al. was able to provide some insight on patient's perception of various self-collection methods for respiratory pathogens. According to data from Hall et al., a total of 1,435 participants were surveyed with the majority (87.7%) rating in favor (agree or strongly agree) of a SC saliva specimen and an 83.1% acceptance rate for SC throat specimens. A similar study was conducted by Valentine-Graves et al., where 148 participants were surveyed regarding their perception of three mail-in self-collection methods (saliva, oropharyngeal swab, and dried blood spot card), with 84% of participants reporting high acceptance of all three methods. Similar acceptance was seen in another study of adults and children, with both cohorts respectively reporting 99% and 96% acceptance of a self-collection model [43]. Valentine-Graves et al. also asked study participants to rate their confidence level regarding the integrity of their collected

specimen, with 87% reporting “confident” or “very confident” [2]. Data from these studies provide a better understanding of the patient’s willingness to not only SC for respiratory pathogens but also their acceptance of a distance testing model.

Critics of the self-collection model have cited collection errors by the patient as a potential barrier to a successful implementation. These concerns are well-founded and deserve further evaluation, particularly in scenarios where a mail-in or ad hoc model is used. As reported in one study, approximately 23.5% of mail-in specimens had one or more errors related to packaging and shipping [5]. In the same study, only 37 of 124 (29.8%) participants reported reviewing the instructional material prior to proceeding with the self-collection procedure. In a qualitative survey study assessing patient’s perception of a self-collection model, the majority of dissatisfied comments pertained to unclear collection instructions or overly complicated collection kits [2]. It is important to note that, despite the collection errors, the authors suggested there was minimal effect on the testability of the submitted specimens. Nevertheless, these studies demonstrate the potential for patient errors that could translate to lower compliance rates or errors in the downstream diagnostic results.

In the meta-analysis conducted by Seaman et al., 13 articles on SC respiratory pathogens were reviewed to evaluate the diagnostic fidelity of SC specimens. When compared to a PC nasal swabs, SC nasal swabs had a pooled diagnostic sensitivity of 87% (95% CI: 80%, 92%) and a specificity of 99% (CI: 98%, 100%). Seaman et al. also reported high acceptance of SC nasal swabs by patients [4].

In my literature review, an additional seven articles published between 2017-2020 were identified, evaluating the diagnostic fidelity of SC specimens. In a study conducted by Fisher et al., SC nasal and throat swabs by individuals with RTI symptoms showed a sensitivity of 96% (95% CI: 88-99%) and 76% (95% CI: 65-85), respectively. This data is consistent with findings from a three-arm (SC nasal swab vs PC nasal swab and PC oropharyngeal swab) study evaluating

SC nasal swab for COVID-19 testing, which saw a sensitivity of 100% (95% CI: 72-100%) and specificity of 95% (95% CI: 74%-100%) [41].

In a comparative study conducted by Goyal, et al., the acceptance rate and diagnostic fidelity of SC versus PC specimens were evaluated. Two cohorts were enrolled, with the first including elderly participants from the community, and the second enrolled participants from a geriatric clinic. The community group was asked to provide a SC nasal swab specimen at the onset of their RTIs symptoms, whereas the other cohort was enrolled at time of presentation to their geriatric clinic for RTI symptoms. The clinic-based group was asked to provide a SC nasal swab along with a PC collected nasal and nasopharyngeal swabs. All subjects were asked to rate their acceptance of the SC and PC methods. Of the 235 participants, 99% reported the self-collection method was acceptable and easy to perform. In the community cohort, 92% of the SC specimens tested positive for ribonuclease P (RNase P), indicating it was an adequate specimen, while 99% of the clinic-based specimens were positive for RNase P. The sensitivity of SC nasal swabs, when compared to PC nasal swabs was 88% (95% CI: 40-100%) while SC nasal swabs versus PC nasopharyngeal swabs had a sensitivity of 78% (95% CI: 40-97%) [44]. In this study, SC nasal swabs had an acceptable sensitivity when compared to PC specimens, consistent with data from the Seaman et al. meta-analysis and other studies in my review. With that being said, nasopharyngeal swabs have consistently been shown to have a slightly higher sensitivity for respiratory pathogens when compared to nasal swabs, although the difference is not statistically significant. As seen in a literature review published in the African Journal of Primary Health Care & Family Medicine, the diagnostic fidelity of respiratory specimens collected via a nasal swab versus a nasopharyngeal swab was found to have no significant statistical difference. The sensitivity of nasal swabs and nasopharyngeal swabs was 89% and 94% respectively [35]. A similar outcome was observed in another study comparing SC nasal swabs with nasal washing, although the sensitivity was slightly better with nasal swab specimens. The author also reviewed

a study comparing SC nasal swabs to PC nasal swabs and found no significant difference between the two collection methods [35].

The two remaining comparative studies in my review evaluated for diagnostic fidelity of SC specimens but implemented descriptive and Cohen's Kappa statistics to report their findings. Haussig et al. enrolled participants into a longitudinal study looking at SC respiratory specimens collected at the onset of symptoms. Participants were asked to self-collect nasal swab specimens and mail them in for testing. Of the 225 swabs received, 151 participants reported symptoms consistent with a RTI and had an overall 71% positive rate for one or more respiratory pathogens. In contrast with the asymptomatic cohorts (58) who only had a 14% positive rate for respiratory pathogens [43]. In the Wehrhahn, et al. article, the diagnostic fidelity of SC specimens for COVID-19 testing was compared to PC specimens. Using Cohen's Kappa statistics, the authors evaluated for the degree of agreement between the different collection methods and found SC specimens had a high agreement ($k = 0.890$) with PC specimens [39]. In another study comparing SC to PC specimens, there was also high agreement (94.8%) between the two collection methods when testing for influenza [5].

To quantify specimen quality, cyclic threshold (CT) values were collected in some of the reviewed studies. The CT value is reported as a numeric value and is the threshold in which the fluorescent signal used in PCR testing is detectable among the background signals within the test specimen. CT value parameters may differ depending on the test assay and equipment used, but in general, lower CT values (≤ 29) equate to higher concentrations of nucleic acid in the test specimen. CT values from one study showed consistent readings for SC specimens and PC specimens [39]. Another study showed the median CT values for SC nasal swabs (25.9) being consistently lower than throat swabs (32.5) when data was aggregated from eight different viral tests, suggesting nasal swabs may contain a higher viral yield [45]. This data is particularly

important as we continue to assess for the optimal collection site and method for respiratory pathogens.

Discussion

The diagnostic accuracy of SC respiratory specimens has received a lot of attention within the past decade of research, but the recent global pandemic has made it more important than ever to reevaluate self-collection as a viable alternative testing model. As previously mentioned, a meta-analysis of recent literature on self-collection diagnostics for influenza had been conducted by Seaman et al. In their review, Seaman et al. were able to present strong quantitative data in support of SC specimens as a viable alternative to PC specimens for RTI diagnostics. As their article was published months before the first case of COVID-19, I felt a continuum of their work would be valuable.

The COVID-19 pandemic has become a world-changing event and has highlighted a grave need to reevaluate our biodefense countermeasures, particularly our testing protocols. Delays in our testing initiatives have allowed the disease to rapidly spread across borders, infecting millions, and resulting in global economic hardship [46]. The call for social distancing and self-quarantine only foreshadowed the worse to come as cities across our nation were forced to shut down, putting millions out of work. Despite our best efforts to contain the disease, our infection and death rates continue to rise. Many health facilities are forced to operate at critical mass despite personnel and supply shortages. Now armed with the clarity of hindsight, many believe disease testing was the fatal kink on our armor that could have been prevented [1, 2]. I believe self-collection is a logical shift in our testing paradigm.

As demonstrated in my literature review, patients are very accepting of the self-collection concept [1, 2, 4, 43] and have shown they can collect reliable specimens [39, 45]. The diagnostic sensitivity and specificity for SC specimens have been largely consistent with PC specimens

when testing for RTIs [4, 35, 41, 44, 45], with similar results observed for COVID-19 testing [39, 41].

By adopting a self-collection model, I anticipate significantly higher testing rates, providing us with the comprehensive intel needed for policy development and planning [23, 38]. Patients who were previously unable or unwilling to access conventional testing facilities now have an alternative testing option. Additionally, the benefits of a self-collection model include potential economic savings as it reduces our reliance on costly PPE and the personnel needed to staff testing facilities. It also minimizes the risk of cross-infection to our healthcare workers, helping to mitigate further deterioration of our workforce. It is estimated a self-collection model is five times more cost-efficient when compared to a PC model [4].

Thus far, the data appears to support the use of SC specimens as a legitimate alternative to PC specimens for RTI diagnostics, including COVID-19. All things considered, I must address the limitations in my review findings and potential barriers to the successful implementation of a self-collection model. Studies that evaluated the efficacy of a true distance testing model either required the patients to mail their specimens in for testing or utilized a courier service to collect the specimens. This approach has inherited problems as observed in one of the studies where almost a quarter of the participants committed an error when shipping their specimens in for testing [5]. Even when instructional media is provided, many patients admitted to not utilizing the aid material [5], while others felt the instructions were overly complicated [2, 44]. Reliance on a courier service to collect specimens may not be a cost-effective means of gathering specimens, particularly if an ad hoc approach is implemented requiring a nonsystematic pickup schedule. We should also acknowledge the smaller sample sizes in most of the articles reviewed in this paper resulting in the generally wider confidence intervals, limiting the generalizability of the data.

It is important to note this literature review was not conducted with the same stringent parameters commonly seen with a dedicated systematic review or meta-analysis. There is

potential for missed literature during my database search as my search yielded a small collection of articles. Most of the studies in my review were pilots or feasibility studies with small sample sizes. Each study implemented varied collection methods, specimen sites, and window of symptom onset – all critical factors in determining specimen quality and diagnostic outcomes [44]. I also observed a fair distribution of studies across multiple nations with differing cultural preferences and resource systems. It may be sensible to consider these variables when trying to generalize these findings.

Conclusion

As we continue to explore potential alternative testing models to combat the COVID-19 pandemic, evidence demonstrates SC specimens are a practical alternative. As demonstrated by the literature data, SC specimens for RTI diagnostics have equivalent sensitivity and specificity when compared to a PC specimen. Although, the wide confidence intervals in these studies indicate more research is needed. Patients are accepting of the self-collection concept and have shown they can reliably produce high-quality specimens. However, continued research is essential as we navigate the current pandemic, but more importantly, as we plan for the next one.

CHAPTER 3: Manuscript 2

Pandemic Driven Innovation: Development of an Alternative Respiratory Pathogen Self-Collection Device

Introduction

Each year the United States (US) experience billions in lost revenue and healthcare expenditure as the result of respiratory tract infections (RTI) such as influenza [47]. Although vaccines for the influenza virus have generally been shown to provide strong immunity against the disease, annual infection rates continue to remain high. During the 2018-2019 US influenza season, there were approximately 35 million cases of influenza infections resulting in 21 million healthcare visits, 766,000 hospital admissions, and 52,000 deaths [48]. Despite being highly contagious, the influenza virus has a relatively low reproductive number (R_0) when compared to other RTI's such as the SARS-CoV-2 virus, 1.46 to 5.7, respectively [49, 50]. The R_0 is an estimation of how many people will contract the disease from a single infected individual during their contagious period – the higher the R_0, the faster the rate of transmission. Our widespread vaccination practices for influenza is likely the primary contributor to its lower R_0, but as with the case for the SARS-CoV-2 virus, there are hundreds of respiratory viruses of which a vaccine does not exist. The SARS-CoV-2 virus is currently at the center of a global health and economic crisis. In the absence of a vaccine or developed immunity, having the means to quickly test for an infectious pathogen is critical to our ability to manage the spread of a communicable disease. Research has also shown early diagnosis of RTI reduces unnecessary treatments and healthcare expenditures [51].

The SARS-CoV-2 virus is responsible for the illness known as COVID-19. It is but one of the many novel respiratory viruses discovered within the past 10 years, but more concerning is the projected rate of new infectious pathogens emerging at a pace of one per year [21]. Novel infectious pathogens are particularly problematic due to our unfamiliarity with their pathogenicity

resulting in delays in our response efforts. Within four months of the first recorded COVID-19 case, the outbreak was officially declared a global pandemic by the World Health Organization (WHO). The unprecedented pace and severity in which the virus was able to spread across the globe has demonstrated how underprepared we were to combat a virus as pathogenic and virulent as SARS-CoV-2. As of September 29, 2020, there are approximately 33 million global cases of COVID-19, with 1 million deaths. This outbreak has been compared to other calamitous events such as the 1918 Spanish Flu outbreak and the 1957 influenza pandemic.

As with any black swan event, it is important we learn from our missteps as we plan for the future. When surveying our global response to COVID-19, there appears a central theme to our success and failure in navigating the outbreak – and this theme is *disease testing*. As observed in Asia, the South Korean government was able to contain the spread of COVID-19 by rapidly implementing a mass testing program, allowing them to detect early cases and deploy containment strategies such as contact tracing [36, 52]. In contrast, the US's implementation of a testing initiative continues to be hampered by shortages in testing supplies [23, 37]. This shortage spurred an innovative drive from the academic and corporate communities to develop alternative testing modalities such as the oropharyngeal saliva swab and the serum antigen test. Despite the influx of interest to develop new testing methods, the nasopharyngeal swab is still considered by the CDC as the specimen collection gold standard for COVID-19 [25], which received an emergency use authorization (EUA) approval by the US Food and Drug Administration (FDA) for PCR testing.

Nasopharyngeal specimens were found to have the most reliable diagnostic sensitivity for influenza [4], however, data on nasopharyngeal swab sensitivity for the SARS-CoV-2 virus is inconsistent [29-32]. Nevertheless, the nasopharyngeal cavity is the ideal collection site for SARS-CoV-2 based on early data suggesting a higher viral concentration in this area [29]. A small study from China observed higher diagnostic reliability for COVID-19 when the specimens

were collected from the nasopharyngeal cavity as compared to the oropharynx. The authors also noticed an improvement in diagnostic reliability when employing a mucus inducing technique prior to a nasopharyngeal swab collection [53]. Participants in this study were asked to inhale 10 ml of nebulized 3% hypertonic saline at a flow rate of 6 L of oxygen for 20 minutes or until sputum was produced.

The traditional nasopharyngeal swab collection method utilizes a stiff nasal swab applicator to probe the posterior nasopharynx cavity for approximately 20 seconds per nostril [25]. This procedure is somewhat invasive and can be traumatizing for some patients. Furthermore, this collection method has been known to result in pain, injury, and retention of the swab applicator, potentially requiring surgical extraction. Due to the invasive nature of the procedure, patients often refuse testing or withdraw during the collection process resulting in suboptimal specimen procurement.

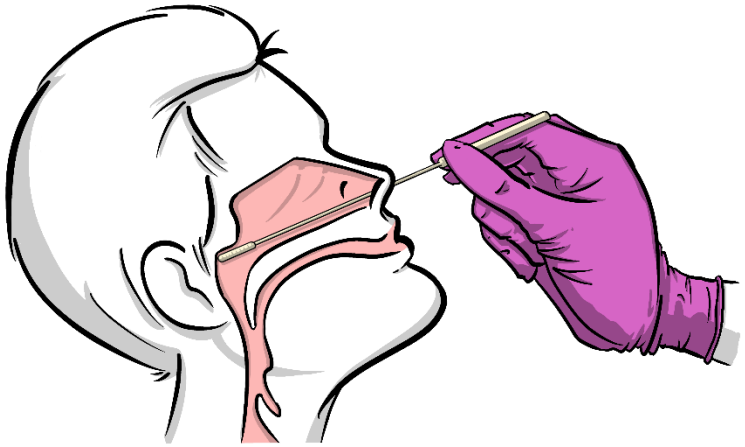

Figure 5. CDC recommended nasopharyngeal swab technique for COVID-19 testing.

The collection of specimens by nasopharyngeal swabbing is a resource-intensive procedure as healthcare workers are expected to don personal protective equipment (PPE) to administer the procedure, often needing new PPE for subsequent patients. The procedure also presents a considerable cross-infection risk to healthcare workers due to their proximity to the

patient and the swab's propensity to induce sneezing or coughing [34]. Studies have reliably shown patients are more accepting of alternative collection methods when compared to the nasopharyngeal swab method [4]. This has led researchers to evaluate alternative collection methods such as the mid-turbinate or oral swab methods, both of which are slightly less sensitive for respiratory pathogens [44]. Diagnostic testing for COVID-19 continues to be a weak link in our countermeasures and is in dire need of improvement.

In response to the observed deficiencies in our current testing procedures and infrastructure, I proposed an alternative specimen collection device for RTI diagnostics. My primary aim was to develop a respiratory pathogen collection device designed for self-administration by the patient. User comfort and ease of use were core design requirements for my proposed device. This paper will establish a narrative around the development cycle of a novel respiratory pathogen self-collection device. I will outline my development cycle and discuss how established product development principles such as design controls influenced my process. Design controls is a development principle adopted by the FDA to facilitate the development of medical equipment for medical device manufacturers [7].

To provide a groundwork for my project aims, I offer the following *problem statements (PS)*:

PS1) The nasopharyngeal swab method is invasive and traumatizing for patients.
PS2) The nasopharyngeal swab method places healthcare workers at risk for cross-infection.
PS3) The nasopharyngeal swab method is not conducive to a self-collection or mass testing model because of its low patient acceptance.

Methods

Design Process

Using the FDA's Design Control Guidance for Medical Device Manufacturers as a foundation, I formulated a systematic approach to solving the identified problems. As illustrated

in Figure 6, the development cycle for a medical device follows a waterfall path involving cyclic review, verification, and validation processes at each iterative phase of development.

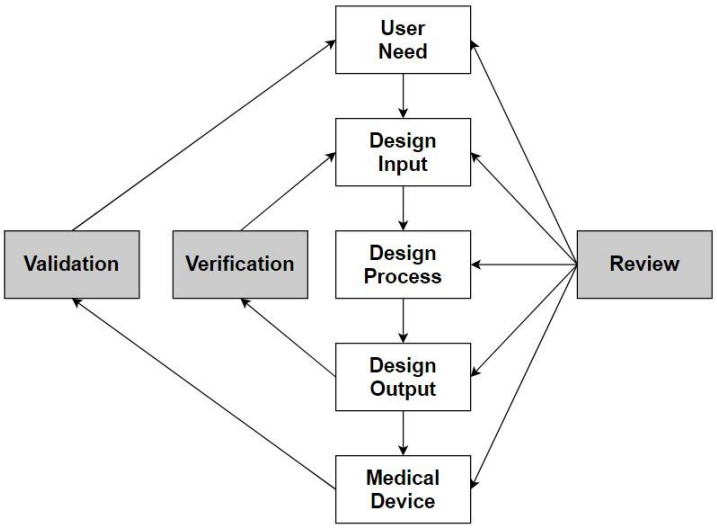

Figure 6. Design Controls.

This process is the design control cycle and can be applied to the development of any device. It is common for device development projects to involve multiple design control cycles. Design controls are specific engineering or design parameters established to meet a predetermined core deliverable of the device [7]. For example, a core deliverable for a toothbrush is to debride the dentition and mucosal surfaces of contaminates without injuring the user. To satisfy this core deliverable, soft bristles were incorporated into the design of a toothbrush. To further elaborate on this example, another design output for the toothbrush defined by a core deliverable was the inclusion of a handle to facilitate the user's brushing motion during use. As with any device on the market, toothbrushes encompass a wide range of designs, with these variations resulting from the predetermined core deliverables that are unique to each design team.

An initial step of developing a medical device is to identify validated user needs or pain points in a particular process. In this case, as an emergency medicine clinician, I was able to identify a *user need* through personal experiences with our testing procedures and infrastructure.

But more importantly, I *validated* the user need by reviewing the literature. Patients' low acceptance of the nasopharyngeal swab collection method is well documented in the literature [4] with patients reporting procedural discomfort as their rationale for disliking the method [44]. Even when allowed to self-swab, patients still preferred alternative collection methods such as nasal or oral swabs [1, 2]. Despite this, the nasopharyngeal cavity is still considered the ideal collection site for respiratory pathogens [29].

In the *design input* phase, I proposed removing the nasal swab from the nasopharyngeal collection method to minimize the invasiveness of the procedure and replacing it with a fluid debridement mechanism. I believe this proposed change would address my first and third problem statements (PS1 and PS3). I postulate by replacing the nasal swab with a fluid debridement mechanism, the procedure would be less invasive, resulting in higher patient acceptance. Sinus irrigation is a common home procedure performed by patients to debride their sinus cavities via the nasopharyngeal route. This procedure is well tolerated by most patients and is classified by the FDA as a Class I product, meaning there is minimal risk to patients who use it. I further minimized potential risk by only utilizing 5 ml of saline in the study device as compared to the 240 ml used in most sinus irrigation devices.

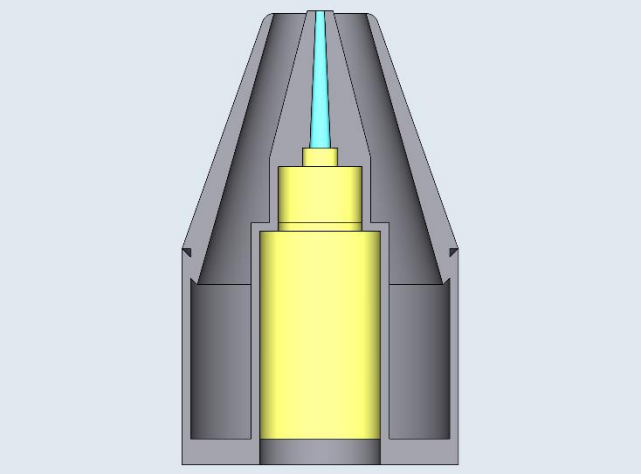

Figure 7. Sliced view of the study device. Design outputs as dictated by the design control cycles included a 2mm to 1mm taper of the ejection bore to generate adequate PSI and an approximate 40-degree inclusive angle for the cone tip to facilitate fit and seal against most adult noses.

Fluid debridement is also a common technique used to remove foreign contaminants from traumatic wounds and has demonstrated improved success when using the appropriate combination of irrigation pressure and volume [54, 55]. The literature suggests the optimal

wound irrigation pressure to sufficiently overcome the pathogen adhesion threshold is 5-15 PSI (pounds per square inch) [56-59]. Multiple design control cycles were dedicated to ensuring the study device was capable of achieving this PSI range. I also incorporated safeguards to prevent the study device from exceeding 20 PSI under normal use, which could lead to potential tissue injury. By studying the fluid mechanics employed in most wound irrigation devices (*design process*), I was successful in developing a functional concept for fluid debridement of the nasopharyngeal cavity (*design output*). Much of my design process involved iterative modifications to the ejection tip (blue in Figure 7) to ensure proper irrigation pressure is generated while not sacrificing fluid volume and flow. These modifications included elongation of the ejection tip and tapering of its inner bore diameter from a 2mm inlet to a 1mm outlet.

My primary goal is to use the fluid irrigation mechanism to debride the nasopharyngeal cavity of epithelial cells as commensurate to the nasopharyngeal swab technique. It is important to reiterate, as part of the user need identification and design input processes, a list of core device deliverables should be developed to guide one's design and verification process. For example, it was established early in the conceptualization phase that the proposed device must irrigate with sufficient pressure to debride the posterior nasopharynx of epithelial cells while ensuring the pressure does not result in pain or injury. Each design output was verified against the pre-established core deliverables (*verification*) before new design parameters were incorporated into the *medical device.* At each iterative design stage, the medical device was subjected to a *validation* check to ensure the addition or subtraction of a design parameter did not affect the original aim(s) of the device. Figure 8 demonstrates this design control cycle as applicable to the development of the device's irrigation mechanism.

The cycle outlined in Figure 8 is only a fragment of the overall development process as multiple design control cycles were constructed before the first prototype was fabricated. As stated, each pre-established core deliverables had at least one design control cycle to validate the

design output before incorporating it into the medical device. Other core deliverables for my proposed device included: 1) the device must achieve universal fit for all adult noses, 2) the device must seal against the user's nasal ala, 3) the device must have universal fit on a standard 5ml syringe, 4) the device must facilitate passive collection of specimens, 5) the device must collect a minimum of 3 (of 5) ml of irrigation fluid, 6) the device must be compact and self-contained, and 7) the specimen chamber must be leakproof.

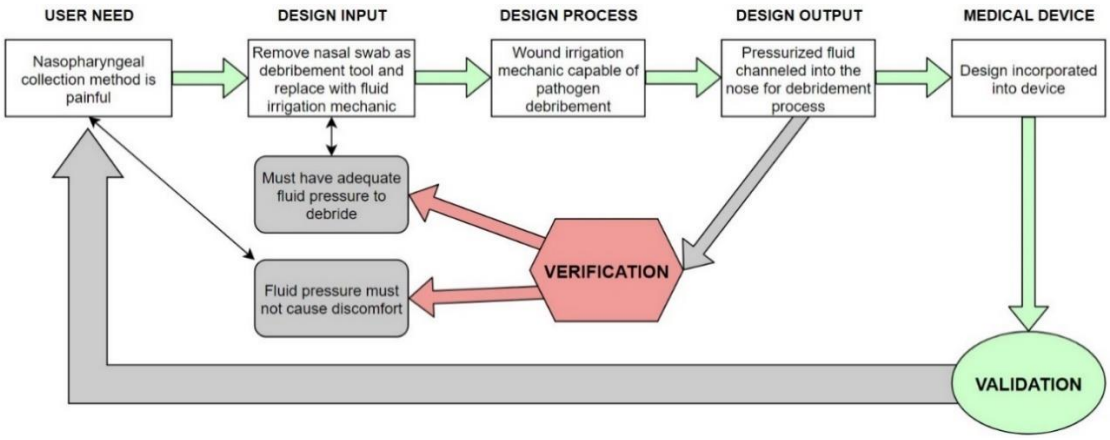

Figure 8. Design control cycle for the fluid irrigation concept.

Design Tools

The majority of my device design process was conducted on an Apple iPad Pro 12.9 (2018 variant). Procreate is an illustration app available on the Apple Appstore and served as my sketching platform for the conceptualization of early design concepts. I used Shapr3D to model my designs in a three-dimensional space and output the models in industry-standard 3D formats (OBJ, STEP, STL). The ability to visualize my designs in 3D allowed me to freely manipulate the model and conduct simulation tests before the fabrication process. I collaborated with a medical device development firm (APOMed Consultants) in San Jose, California, on this project and Shapr3D facilitated the sharing of my models for rapid iterations. APOMed's primary input involved ensuring my design parameters could be translated to an injection molding process for large scale fabrication if warranted. The ability to share and store my designs in 3D formats

allowed me to maintain a detailed design log as each 3D file retained large amounts of metadata specific to each iterative design control cycle.

Fabrication Tools

Our emergency department is equipped with three fused deposition modeling (FDM) 3D printers, two of which (Ultimaker S3, Creality Ender 3) were used for the fabrication of my prototypes after each design cycle. I used the free slicer software, Ultimaker Cura 4.6, to convert my Shapr3D models to a printable format. All prototypes were printed in either Ultimaker or Hatchbox brand polylactic acid (PLA) filament, which are biodegradable vegetable-based polymer-blends composed primarily of cornstarch. Water-soluble polyvinyl alcohol (PVA) natural filament was used on the Ultimaker S3 to print the structural supports for the prototypes. PLA filament was selected because it is durable, non-toxic, and safe for human use. The Creality Ender 3 was used primarily for rapid prototyping while the Ultimaker S3 was used for batch printing once a design has been finalized.

The 3D Printer Parameters

<u>Creality Ender 3</u>:

Layer height/line width: 0.2 mm

Infill: 20%

Support: Yes

Adhesion: Brim

Extruder temp: 200℃

Extruder temp (initial layer): 210℃

Print bed temp: 50℃

Print bed temp (initial layer) 65℃

<u>Ultimaker S3</u>:

Layer height/line width: 0.1 mm

Infill: 20%

Support: Yes

Adhesion: Brim

Extruder temp: 215℃

Extruder temp (initial layer): 215℃

Print bed temp: 60℃

Print bed temp (initial layer) 60℃

Prototype Testing

Fit and compatibility of the 3D printed prototypes were tested using standard medical grade 5ml BD Plastipak syringes. The Luer lock mechanic is a universal design across all medical syringes. The irrigation solution was normal 0.9% saline. Irrigation pressure measured as PSI (pressure per square inch) was checked on every prototype. To test for irrigation pressure, I developed a pressure measuring tool using a Weiss Instruments brand analog pressure gauge that was attached to the prototype via a medical-grade silicone tube. I used the medical air delivery system equipped in most emergency departments and the Anest Iwata compressed air conversion factors [60] to develop a PSI control for the pressure measuring tool. Each fabricated prototype was subjected to a quality control process including 1) print quality and integrity, 2) fit of the individual components, and 3) pressure testing.

Once the design was finalized, I produced 15 devices to be used solely for PSI testing. A 5ml syringe filled with saline was attached to each device and a single user was asked to dispel the saline from the device while it was attached to the PSI test gauge. The user was asked to compress the syringe plunger with standard compression force as if they were flushing an intravenous line. This process was repeated on the same device, but this time, the user was asked to use maximum compression force when dispelling the saline from the syringe. The order of

standard compression and maximum compression was alternated between each subsequent device until all 15 had been tested. I averaged the two PSI measurements taken from each test device, then took an overall average of the means of all 15 test devices.

Figure 9. PSI test gauge.

Preliminary Testing Process

Preliminary testing involved allowing five members of the development team (testers) to use the device and provide feedback on design, comfort, and ease of use. The feedback was provided to me on a one-on-one session in an open conversation format. To validate my core deliverable of being able to debride the nasopharyngeal cavity for epithelial cells, the study device was self-administered by five testers. Each tester was provided the following instructions on proper usage of the device prior to self-administration:

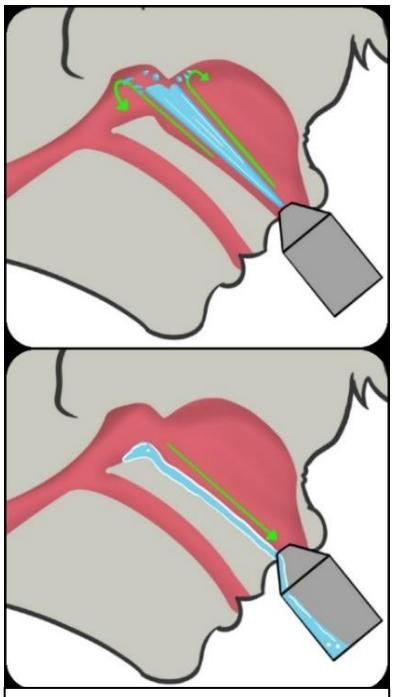

Figure 10. Irrigation of the nasopharyngeal cavity with the study device.

1) Insert the tip of the device into your nose allowing the upward pressure to seal the device against your nasal rim.

2) Flex your neck forward at about 10-15 degrees to prevent drainage into your throat or opposite nostril.

3) Angle the device so it is pointing to your ear.

4) Take a deep breath and hold your breath prior to injecting the saline into your nose.

5) Apply a firm and steady compression pressure on the syringe plunger as your irrigate your

nose.

6) Once the irrigation process is completed, keep the device pressed against your nose for 5 seconds to allow for drainage. You can breathe normally during this time.

A total of 5 ml of saline was used to irrigate their nasopharyngeal cavity. All samples collected from the testers were evaluated for the presence of epithelial cells via a manual microscope examination at 40x objective magnification without staining.

Results

A total of 9 prototype variants were fabricated during the development process, each with slight alterations in its design parameters as dictated by the design control cycle. Of the 9 prototypes, only three (indicated by the black arrows in Figure 11) were made available for review by the testers to provide feedback. A total of 15 test devices based on the 9th design was printed for quality control testing. Only the final (9th) design was used on the five testers to collect nasopharyngeal wash samples.

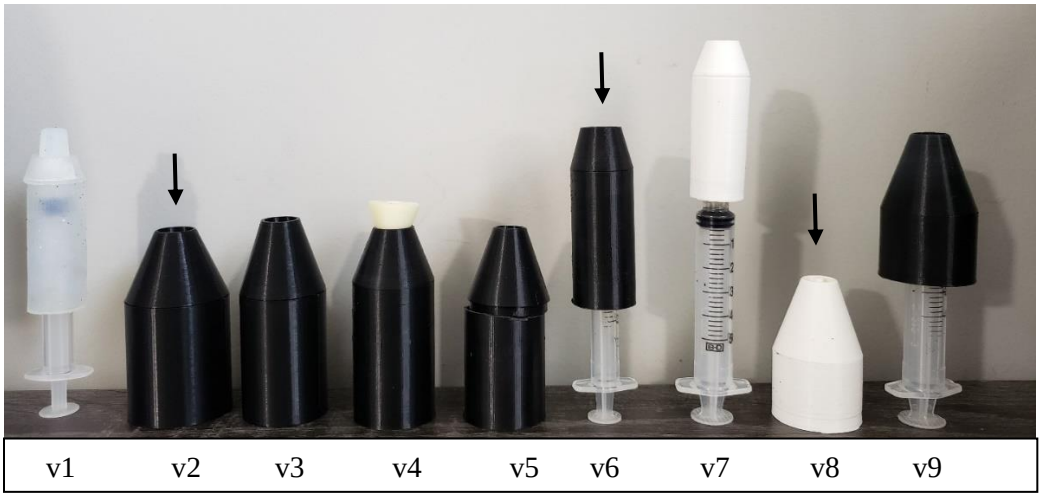

Figure 11. *Project WWash* prototype fabrication timeline.

Four design control cycles were conducted to ensure adequate irrigation pressure, these changes took place between prototypes v1 to v2, v2 to v3, v3 to v4, and v4 to v5. There were eight design control cycles addressing device size and specimen chamber capacity, these changes spanned the entire product timeline. Three design control cycles were conducted to develop the mechanics of attaching the device to a syringe, these changes involved prototypes v1 to v6, v6 to v7, and v7 to v8. The only change between v8 and v9 involved the reduction of the specimen chamber size.

DEVICE	TEST1 PSI	TEST2 PSI	DEVICE MEAN	
1	9	20	14.5	
2	20	8	14	
3	10	20	15	
4	20	9	14.5	
5	9	20	14.5	
6	20	9	14.5	
7	10	22	16	
8	25	8	18	
9	8	18	13	
10	22	9	15.5	
11	9	25	17	
12	20	10	15	
13	8	22	15	
14	25	9	17	
15	9	20	14.5	
			OVERALL MEAN	15.2

Table 1. Pressure test of 15 prototypes based on v9 design.

Pressure testing was conducted on 15 devices with two output readings per device. The overall pressure average for all 15 devices was 15.2 PSI. The results of the pressure test are outlined in Table 1.

Three of the five (60%) collected samples were positive for the presence of epithelial cells during the microscopic examination. The presence of epithelial cells is a confirmatory finding to suggest the study device can achieve adequate fluid flow and pressure to displace skin cells. The presence of skin cells is considered an acceptable precursor for pathogens [61].

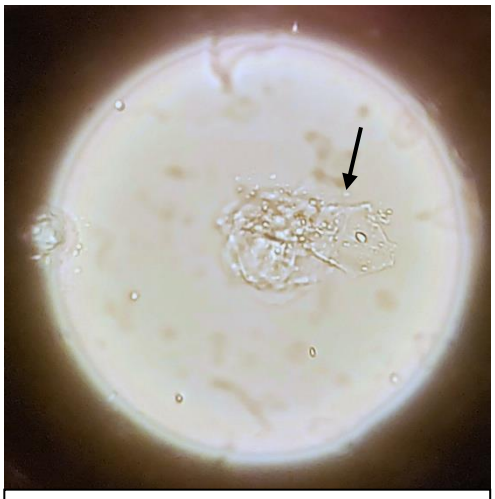

Figure 12. Epithelial cell captured in nasopharyngeal irrigation solution at 40x objective magnification.

From a qualitative standpoint, none of the five testers reported any discomfort with the use of the study device, all reported the device was easy to use and understand. Three of the five

testers have had a nasopharyngeal swab administered in the past and all reported the study device was more comfortable to use. The most common feedback was regarding the fit of the device when inserted into the nose. Three of the testers felt they could not achieve a proper seal against their nasal rim, with each attributing their smaller nostril openings as a possible rationale for the poor fit. One of the testers experienced drainage of the saline to the opposite nostril and into their throat. It is felt this tester's positioning when using the device is the likely cause for this occurrence as they were standing upright as opposed to flexing their neck forward as originally instructed.

Discussion

The primary purpose of this paper is to outline my development process as I attempted to develop an alternative respiratory pathogen collection device. I consider this phase of the project as the alpha testing phase, with all evaluations and testing occurring within a closed lab and with members of the development team. I also saw this as an opportunity to outline my development process as part of an improvement process for our young fabrication lab.

Overall, my project was successful in clearly defining a user need and addressing the need through a systematic approach. I used literature data to guide my design process and through the implementation of the FDA's Design Control Guidance for Medical Device Manufacturers, I was able to validate all design parameters at both the micro and macro levels. The concept of design controls provided an ideal check and balance process when manipulating multiple design outputs, each with potential downstream effects on other design parameters. For example, there were instances where a design output was either added or subtracted from the medical device to satisfy a particular core deliverable only to nullify another core deliverable. These discrepancies were often discovered during the validation process. When this occurred, depending on the importance of the new design output, it often resulted in a separate design control cycle to resolve the issue. This occurrence was common when design outputs were made to change the size of the

device for compactness, which frequently resulted in multiple alterations of other critical design parameters. This error was most evident when the diameter of the device was decreased to make it more compact, nullifying the passive drainage mechanic of the device.

At the conclusion of this project, I was successful in developing a potential alternative respiratory pathogen collection device that does not require the use of a nasal swab applicator, which the literature suggested is generally not preferred by patients. The study device was positively received by the testers, none of whom reported experiencing discomfort when using the device. I was also successful in debriding the nasopharyngeal cavity for epithelial cells with a 60% (3/5) positive rate. The units that were unable to capture epithelial cells were subjected to a repeat quality control process to determine potential causes for the negative findings. Despite passing all quality control parameters, I was unable to ascertain the exact cause for the negative findings. Possible explanations could be related to user error, examiner error, variations in the tester's nasal anatomy, or mucosal lining.

Though my preliminary findings were supportive of my concept, the sample size was small, limiting my ability to make any generalized and statistical claims. I also acknowledge potential bias or examiner errors in my evaluation process. For instance, there is potential for examiner error when interpreting an analog PSI gauge. Also, the PSI testing process only involved one user for all 15 devices. A similar claim could be made for the manual microscopic evaluation for epithelial cells, particularly when there are automated and more accurate measurements for specimen quality such as assessing for the presence of RNase P – a gene fragment that is only present in human cells and is commonly used as a quantitative measurement for the presence of epithelial cells [44].

In addition to comparable specimen collection, the study device's self-contained design minimizes the need to handle infectious bodily fluids. Via implementation of the study device, I anticipate potential paradigm shifts in RTI collection and testing procedures such as 1)

minimizing the invasive nature of the specimen collection procedure and promoting testing compliance, 2) enhancing the availability of self-collection for mass testing via a home/distance testing model, and 3) minimizing the risk of cross-infection for healthcare workers.

The outcome of my project is encouraging as I strive to develop an alternative collection device that is accepted by patients and possess equal diagnostic fidelity to the nasopharyngeal swab. I am planning a follow-up pilot study to objectively validate my data on a larger sample size while collaborating with a pathologist to provide the objective analysis of the specimens. I feel the development process outlined in this paper establishes a strong foundation for other medical device development efforts, particularly those with an academic root and lacking industry experience.

Conclusion

With this project, I developed an alternative respiratory pathogen collection device while using the task to formulate a medical device design template that could be used on future projects. My process was heavily influenced by guidelines established by the FDA for medical device manufacturers. I was successful in adopting this process and applying it to an academic setting. Given the success of my feasibility project, I intend to continue the development of my device with plans for future pilot and prospective studies.

CHAPTER 4: Manuscript 3

A Pilot Evaluation of an Alternative Respiratory Pathogen Self-Collection Device

Introduction

Diagnostic testing for the SARS-CoV-2 virus continues to be a limiting factor in our ability to accurately project case numbers and contain the disease known as COVID-19. After the first confirmed case of COVID-19 in China, the virus quickly became the center of a global pandemic resulting in economic and social shutdowns. Its foothold in the United States (US) has been most severe. As of October 1st, the US leads the world with the highest number of confirmed COVID-19 infections and deaths [3]. Many experts believe it was our delay in establishing an effective testing model that prevented the US from deploying critical countermeasures such as contact tracing and containment [36, 52]. According to the Centers for Disease Control and Prevention (CDC), the US is projected to experience a substantial increase in death rates (4.78-11%) before the end of October 2020 [62]. As we enter the influenza season, it is more important than ever to have reliable alternative testing modalities to bolster our current infrastructure.

In recent months there has been an influx of interest from the academic and corporate communities in developing alternative testing methods for COVID-19. Research in this area is making significant strides in advancing our understanding of testing for the SARS-CoV-2 virus. The US Food and Drug Administration (FDA) recently approved emergency use authorization (EUA) for saliva polymerase chain reaction (PCR) testing in COVID-19 cases [63], adding to our testing arsenal. Despite this, the nasopharyngeal swab collection method is still the diagnostic gold standard for COVID-19 [25], with data suggesting a higher viral concentration in this area [29]. However, the literature also suggests lower

Figure 13. Study device attached to a 5 ml syringe.

patient acceptance of the nasopharyngeal swab collection method [4] with procedural discomfort attributing to the low acceptance rate [44]. This procedure is somewhat invasive and traumatizing for patients as it requires deep probing of the posterior nasopharynx with a stiff swab applicator. The nasopharyngeal swab procedure has been known to cause pain, but more significant injuries have been reported. For example, in a recent case study published by Medscape, there was a recorded incident where a cerebrospinal fluid (CSF) leak was linked to a nasopharyngeal swab injury [64]. To compound the issue, there is also a considerable cross-infection risk to healthcare workers administering the nasopharyngeal swab as patients tend to cough or sneeze during the procedure.

In exploring a potential alternative nasopharyngeal specimen collection method, I developed the concept of nasopharyngeal debridement using fluid irrigation. This alternative respiratory pathogen self-collection device was designed to be self-administered by the user to irrigate their nasopharyngeal cavity with saline. As a self-contained device, the irrigation solution is immediately recaptured into the device, minimizing the need to handle infectious bodily fluids. By the nature of a self-administered and self-contained device, there is considerably less cross-infection risk for healthcare workers. I propose the premise in which the nasopharyngeal cavity is irrigated with a specific irrigation pressure to debride for pathogens as proportionate to the nasopharyngeal swab method.

I also postulate the replacement of the traditional nasal swab with a fluid debridement mechanism will make the procedure less invasive, resulting in higher patient acceptance. Using data from the wound care literature, I established the optimal irrigation pressure to be 5-15 PSI (pounds per square inch), which is sufficient to overcome the pathogen adhesion threshold [56-58]. I adopted the FDA's Design Control Guidance for Medical Device Manufacturers as a guiding principle for my development process and was successful in manufacturing working prototypes of my concept. A small feasibility study was conducted in our lab, where the study

device was used by five members of the development team (testers), followed by microscopic examination of the recollected specimens to determine for the presence of epithelial cells. The presence of epithelial cells is often used as a measurement for specimen adequacy and is accepted as a precursor for pathogens [61].

Although the preliminary data from my feasibility study was supportive of my hypothesis, I acknowledge the potential limitations in my study design such as 1) my test participants were members of the development team, possibly leading to bias feedback, and 2) there is potential for examiner's error or bias in the manual microscopic evaluation of the specimens. This study is a follow-up pilot evaluation of the study device to further expand on my feasibility study. In this study, I enrolled volunteer participants from a pool of emergency medicine staff, including physicians, nurses, care technicians, and medical scribes. The objective evaluation of all collected specimens was conducted in a Clinical Laboratory Improvement Amendments (CLIA) approved lab and by a third-party pathologist. Using PCR testing, I evaluated the specimens for the presence of RNase P, which is a genetic fragment only found in human cells. RNase P is well supported in the literature as an objective measurement of specimen adequacy [56].

Methods

Study Approval

My study protocol was reviewed and approved by our organization's Institutional Review Board (IRB). Since my study was conducted during a global pandemic and involved an investigational device, my study proposal was also reviewed by our organization's COVID-19 Research Steering Committee, Investigation Device Review Committee, and The Human Subjects Research Safety Review Committee, all of whom approved the proposal.

Participant Enrollment

Study participants were enrolled from a convenient sampling of emergency department staff during their shift. Study inclusion criteria included: 1) age 19 years or older, and 2) current staff member of the emergency department. Participants were approached during their shift to inquire about interest in participating in the study. The consenting process included: 1) a brief overview of the study protocol as outlined in the IRB protocol, 2) a brief demonstration of the study device, 3) all participants were allowed to review the consent form at their leisure, and 4) adequate time was provided for a question and answer session. All enrolled participants signed the IRB approved consent form.

Study Device Fabrication

All study devices were fabricated on an Ultimaker S3 brand fused deposition modeling (FDM) 3D printer. The free slicer software, Ultimaker Cura 4.6, was used to convert my Shapr 3D models to a printable format. The study devices were printed in Ultimaker brand polylactic acid (PLA) material with support structures printed in water dissolvable polyvinyl alcohol (PVA) natural material. PLA material was selected because it is a biodegradable vegetable-based polymer-blend composed primarily of cornstarch, but more importantly, it is durable, non-toxic, and safe for human use. I used the following printer settings in manufacturing the study devices.

<u>Ultimaker S3 Print Settings:</u>

Layer height/line width: 0.1 mm

Infill: 20%

Support: Yes

Adhesion: Brim

Extruder temp: 215℃

Extruder temp (initial layer): 215℃

Print bed temp: 60℃

Print bed temp (initial layer) 60℃

I printed 20 study devices, all of which were subjected to a quality control process including 1) print quality and integrity, 2) fit of the individual components, and 3) pressure testing. The study devices were submerged in a container of tap water for 2 days to remove the PVA print supports. Pressure testing was conducted by attaching the study devices to a PSI gauge (Figure 14) with measurements taken each time the study personnel injected the saline into the PSI gauge. Each study device received three pressure tests with the mean outcome recorded as the final pressure measurement for the respective device. The first 15 study devices tested passed all quality control parameters and were used on the enrolled participants. I used the medical air delivery system equipped in most emergency departments and the Anest Iwata compressed air conversion factors [60] to develop a PSI control for the pressure measuring tool. To account for potential variations in pressure within our air delivery system, two rooms on opposite ends of our emergency department was used to test for PSI control.

Figure 14. PSI test gauge

All study devices were sanitized using PDI P13872 sanitation wipes, allowed to air dry, then sealed inside a specimen bag along with a prefilled 5 ml syringe and a 15 ml centrifuged tube. The study devices were prepped and sanitized one week prior to use to allow for adequate curing and dry times.

Specimen Collection Process

To ensure consistency in the specimen collection process, all irrigation procedures were administered by the study personnel. All participants received the following verbal instructions before the procedure was initiated:

1) The device's tip will be inserted into your nose with firm upward pressure to maintain a seal against your nasal rim.
2) Flex your neck forward 10-15 degrees to prevent drainage into your throat or opposite nostril.
3) The device will be angled toward your ear on the same side.
4) On the count of three, take a deep breath and hold. (The irrigation process was initiated after the participant has held their breath).
5) Once the irrigation process is completed, the device will be held against your nose for five seconds to allow for drainage. Continue breathing normally during this time.

After the irrigation process was completed, the recollected specimens were transferred from the study device into a capped 15 ml centrifuged tube for transport. At the end of the collection process, there were impromptu feedback conversations with each participant. The study personnel did not initiate these conversations but did make note of each participant's feedback.

Specimen Evaluation Process

The enrollment process took approximately 2.5 hours, after which, all collected specimens were transported to a CLIA approved laboratory. The specimens were evaluated using the Applied Biosystems QuantStudioDx RT-PCR test and the NECoV19 assay test. The NECoV19 assay is an EUA approved real-time reverse transcription polymerase chain reaction (rRT-PCR) assay developed specifically to detect for the SARS-CoV-2 E and N genes within the viral RNA. The human RNase P gene expression is detected as an internal control in human RNA. The RNase P internal control serves to confirm specimen cellularity, adequate extraction of nucleic acids, and intact amplification.

For this pilot study, only the presence of RNase P was evaluated to inform specimen adequacy of the recollected nasopharyngeal irrigation solution. Total nucleic acid was extracted from the study device specimens using the MagMAX Viral/Pathogen Nucleic Acid Isolation kit

(Applied Biosystems) on the KingFisher Flex (ThermoFisher Scientific) automated extraction instrument. The extracted RNA, if present, is reverse transcribed to form cDNA, which is then amplified by PCR using primers and probes specific to the RNase P gene target. The probe is tagged with FAM (fluorescein) dye, which fluoresces when the probes hybridizes to target DNA sequence. The fluorescence in each well is measured at the completion of each PCR cycle using the Applied Biosystems QuantStudioDx RT-PCR instrument. The presence or absence of RNase P in the sample is determined by evaluating the cycle threshold (CT) value. The CT value is the intersection between an amplification curve and a threshold line. It is a relative measure of the concentration of the gene target (e.g., RNase P) in the PCR reaction. The CT value is reported as a numeric value and is the threshold in which the PCR fluorescent signal is detectable among the background signals within the test specimen. CT value parameters may differ depending on the test assay and equipment used, but in general, lower CT values ($\leq$ 29) equate to higher concentrations of nucleic acid in the test specimen.

All 15 specimens underwent three separate RT-PCR tests. To establish an external control and account for potential inherent variables that may inhibit PCR testing, the first batch of specimens was spiked with an Escherichia coli (E. coli) bacteriophage. A RT-PCR test was then conducted on this batch to detect for the MS2 gene that is unique to the E. coli bacteriophage. The second and third batches were not spiked with the E. coli bacteriophage, both batches underwent RT-PCR testing to detect for the RNase P gene target. The Applied Biosystems QuantStudioDx RT-PCR Master Mix test and the NECoV19 assay were used on the second and third batches, respectively. The NECoV19 test assay was developed in-house at the Nebraska Medicine Clinical Laboratory and has received EUA approval for COVID-19 PCR testing.

Statistical Analysis

I consulted with a statistician and pathologist regarding my study design. For a single cohort non-comparison pilot study, it was determined fifteen specimens would provide sufficient

power to detect for an intervention effect. The decision to only enroll 15 participants was also based on principles observed from the lean manufacturing principles in which batch manufacturing can facilitate the rapid validation of a particular design parameter to guide the development process. Data from this pilot study are reported using descriptive statistics.

Results

A total of 15 participants were enrolled in the study. On average, the study device recollected approximately 3.1 ml of the saline used during the irrigation process. There were two instances where approximately 5 ml was recollected with two other instances where approximately 2 ml was recollected. All 15 participants felt the study device irrigation procedure was faster than the nasopharyngeal swab, with none experiencing any discomfort from the irrigation mechanism. Only one participant experienced some discomfort related to the study device poking them in the nasal septum during insertion. Four participants have had a nasopharyngeal swab performed on them in the past, with all reporting the study device was more comfortable to use.

Three separate RT-PCR tests were performed on each study specimen. In the first (control) batch, all 15 specimens tested positive for the MS2 gene indicating there were no inhibitors to PCR testing in the specimens. The Applied Biosystems TaqPath RT-qPCR and the NECoV19 assay tests were conducted on the second and third batches, respectively. All specimens in the second and third batches tested positive for RNase P with respective mean CT values of 29.5 and 30.7. Both tests had the same distribution of specimens with strong amplification (26.67%), adequate amplification (73.33%), and weak or negative amplification (0%). The amplification plots for the TaqPath and NECoV19 tests are illustrated in Figures 15

and 16, each test had a CT threshold of 0.200. The CT values for each test are outlined in Table 2.

Sample Name	Target Name	Reporter	CT
EDWW1	MS2	CY5	28.441
EDWW2	MS2	CY5	29.254
EDWW3	MS2	CY5	28.548
EDWW4	MS2	CY5	26.143
EDWW5	MS2	CY5	27.519
EDWW6	MS2	CY5	28.133
EDWW7	MS2	CY5	27.821
EDWW8	MS2	CY5	26.341
EDWW9	MS2	CY5	29.905
EDWW10	MS2	CY5	29.75
EDWW11	MS2	CY5	27.514
EDWW12	MS2	CY5	29.575
EDWW13	MS2	CY5	28.92
EDWW14	MS2	CY5	28.185
EDWW15	MS2	CY5	29.273

Sample Name	Target Name	Reporter	CT
EDWW1	RNase P	FAM	30.041
EDWW2	RNase P	FAM	30.891
EDWW3	RNase P	FAM	30.548
EDWW4	RNase P	FAM	29.947
EDWW5	RNase P	FAM	30.102
EDWW6	RNase P	FAM	29.95
EDWW7	RNase P	FAM	26.394
EDWW8	RNase P	FAM	25.443
EDWW9	RNase P	FAM	29.003
EDWW10	RNase P	FAM	26.794
EDWW11	RNase P	FAM	34.153
EDWW12	RNase P	FAM	30.214
EDWW13	RNase P	FAM	28.048
EDWW14	RNase P	FAM	29.664
EDWW15	RNase P	FAM	30.684

Sample Name	Target Name	Reporter	CT
EDWW1	RNase P	FAM	30.872
EDWW2	RNase P	FAM	30.927
EDWW3	RNase P	FAM	34.466
EDWW4	RNase P	FAM	30.791
EDWW5	RNase P	FAM	31.022
EDWW6	RNase P	FAM	30.364
EDWW7	RNase P	FAM	27.341
EDWW8	RNase P	FAM	26.019
EDWW9	RNase P	FAM	29.134
EDWW10	RNase P	FAM	27.011
EDWW11	RNase P	FAM	37.886
EDWW12	RNase P	FAM	32.049
EDWW13	RNase P	FAM	27.999
EDWW14	RNase P	FAM	30.008
EDWW15	RNase P	FAM	34.4

Table 2. Results of Control (tan), TaqPath (blue), and NECoV19 (green) tests.

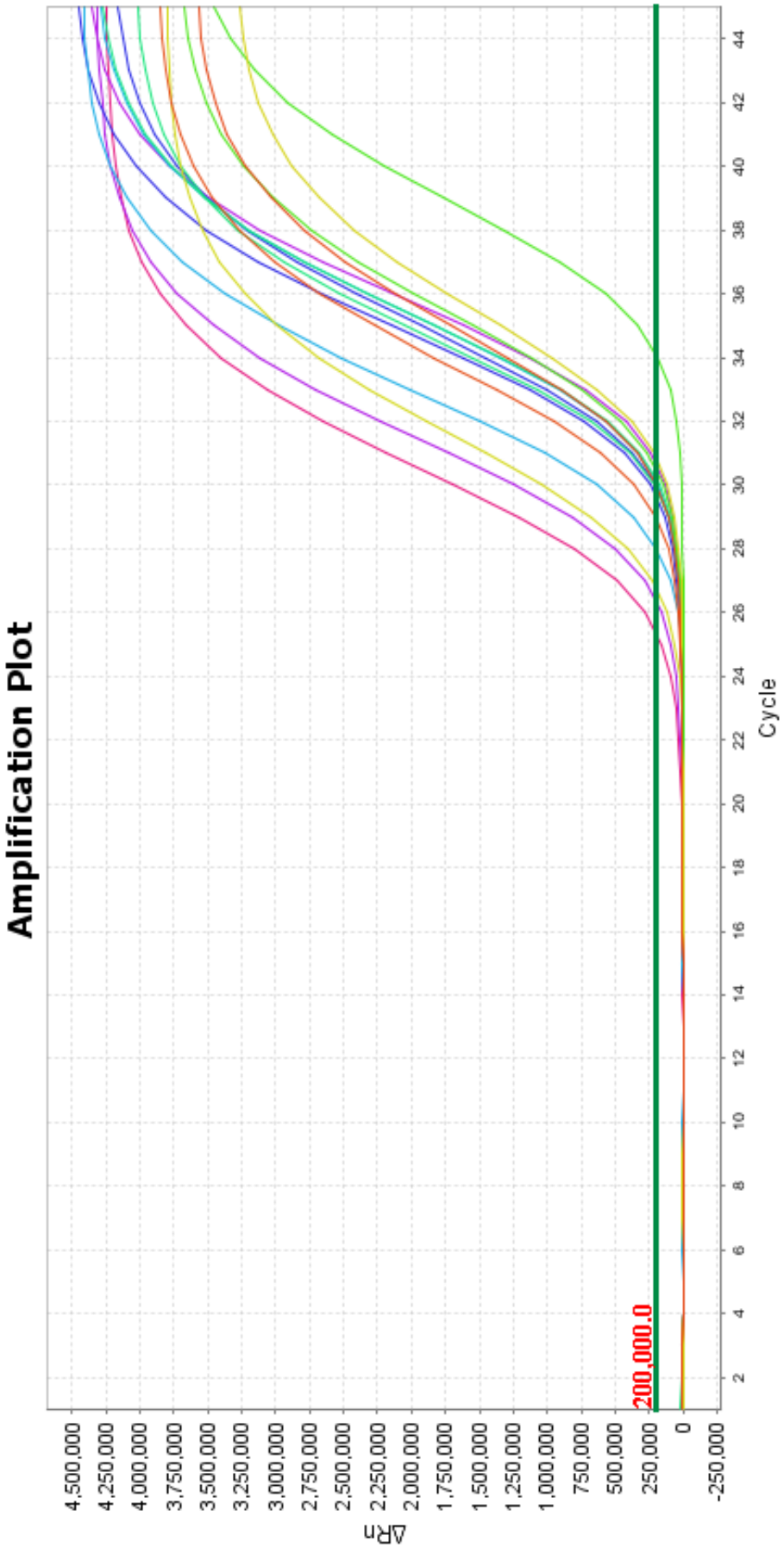

Figure 15. Amplification plot for TaqPath test.

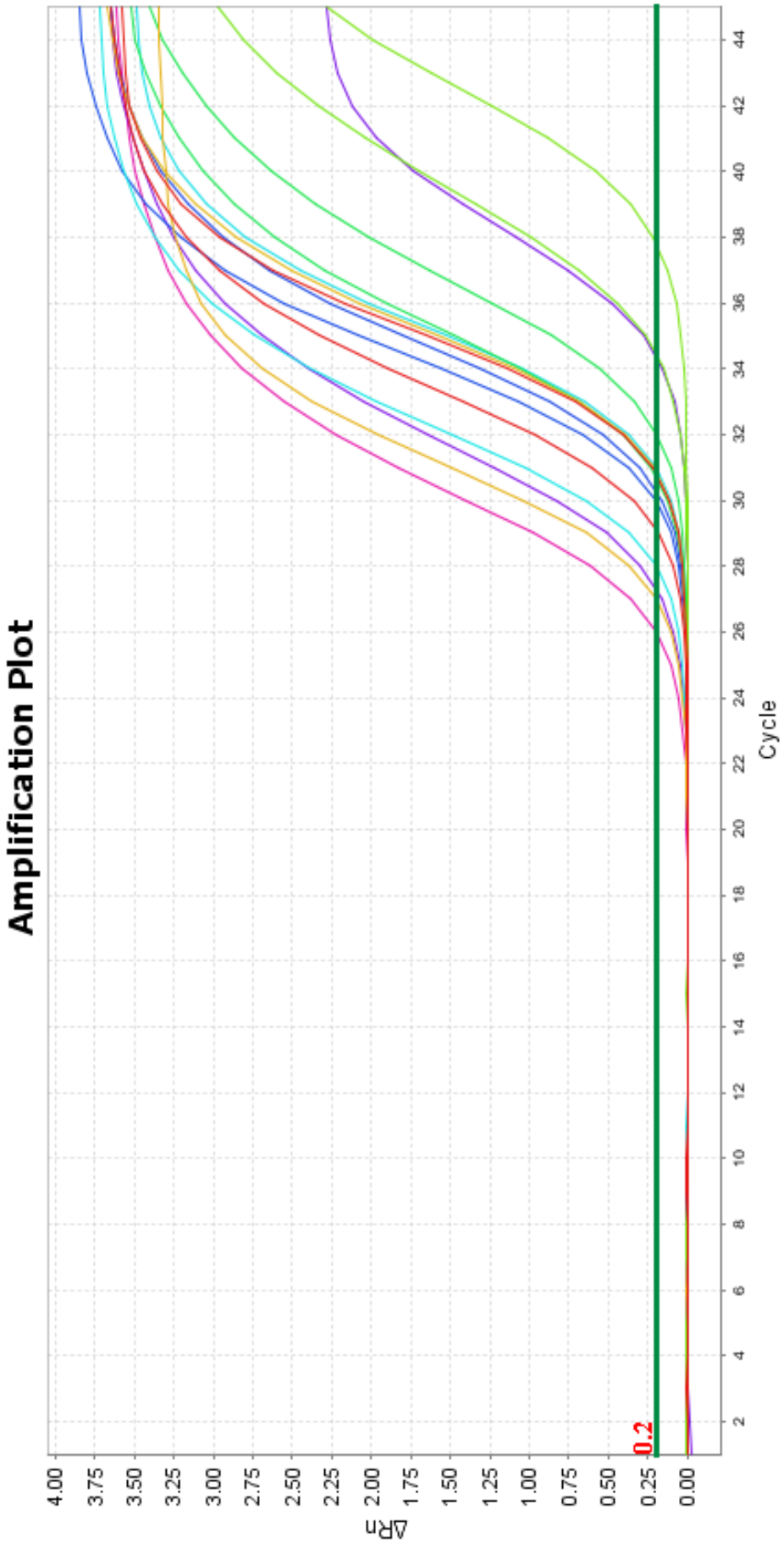

Figure 16. Amplification plot for NECoV19 test.

Figure 17. CT values from each batch. Values above the red line indicates weak or negative gene amplification, values between the red and black lines indicates adequate gene amplification, and values below the black line indicates strong gene amplification.

Discussion

The nasopharyngeal cavity has consistently demonstrated a higher viral concentration for the SARS-CoV-2 virus and is endorsed by the CDC as the gold standard collection site for COVID-19 testing [25, 29]. A small study in China demonstrated the potential for improved diagnostic sensitivity for COVID-19 when the nasopharyngeal cavity was premoistened before swabbing for the SARS-CoV-2 virus [53]. When considering most laboratories are equipped with PCR testing instruments calibrated for nasopharyngeal samples, I felt it was wise to explore alternative collection methods for nasopharyngeal specimens. Drawing from my experience as an emergency medicine clinician, I applied the principles of wound irrigation to develop my study device. Through my literature review, I was able to determine the optimal irrigation pressure to debride tissue surfaces for pathogens is approximately 5-15 PSI. Using this knowledge, I successfully developed an alternative respiratory pathogen collection device that does not require mechanical debridement of the nasopharyngeal cavity with a stiff swab applicator.

Data from my feasibility study was supportive of my concept but I am fully aware of the limitations of my study design. This was the basis for my follow-up pilot study where a larger sample size was enrolled, but more importantly, I employed an objective measurement for specimen quality by testing for the presence of the RNase P gene target. RNase P is a well-studied genetic fragment that is only found in human cells and is widely accepted as a good indicator of specimen adequacy [44]. Along with the presence of RNase P, which was detected in 100% of the specimens, I also utilized the CT value as an additional objective measure for specimen adequacy. Lower CT values are indicative of higher specimen quality. The study specimens demonstrated a consistently low CT value, with 73.33% indicating adequate amplification and 26.67% indicating strong amplification of the target gene. This data suggests the study device was successful in debriding the nasopharyngeal cavity for epithelial cells but

more importantly, the specimens were consistently high in quality as indicated by the low CT values.

Further research is needed to continue my evaluation of this alternative collection method. I acknowledge the potential for a false positive outcome in the data as the presence of bacterial deoxyribonucleic acid (DNA) could, in theory, trigger a positive RNase P finding. Nevertheless, the presence of bacteria in the specimens is a confirmatory indicator that the study device was successful in overcoming the pathogen adhesion threshold. This means debridement for the SARS-CoV-2 virus is also possible. It was important to have an objective evaluation of the study device as it is essential in demonstrating efficacy in my novel concept. The data from this pilot study has validated the engineering parameters for the study device as I was successful in capturing epithelial cells in 100% of the sample population. Given the study device is intended to fulfill a gap in RTI diagnostic testing, it would be sensible to evaluate the diagnostic fidelity of the study device when compared to the gold standard collection method in RTI cases – the nasopharyngeal swab. A prospective study comparing diagnostic outcomes for viral PCR testing is the logical next step.

As a result of the study, I have identified multiple design limitations in my study device. In its current iteration, the device will only fit on a 5 ml BD brand syringe, which would limit the potential for wider adoption. Given my goal is to see this technology used in mass and distance testing scenarios, it would be practical to redesign the device to improve compatibility with any standard syringe. I also noticed multiple instances where the device was not able to form a consistent seal against the user's nasal rim due to their smaller nostril openings. I believe this improper fit is likely the cause for one study participant to experience some mild discomfort when using the device. The improper fit could also lead to potential user errors, low compliance rates, or contamination risk. I anticipate the need for interchangeable irrigation cones to ensure proper fit not just for adults but also for the inevitable pediatric version. Most laboratories process

their specimens in centrifuge tubes and having to transfer the specimen from my device to a centrifuge tube is an unnecessary cross-infection risk. I have already begun design work to address all identified limitations of the device.

Conclusion

I have established the importance of early diagnostic testing and its role in our countermeasures for communicable diseases such as COVID-19. Innovation to bolster our testing infrastructure is more important now than ever. Using the principles of fluid debridement, I was successful in developing an alternative nasopharyngeal respiratory pathogen collection device. Data from this pilot study demonstrated the study device was successful in producing high-quality specimens for PCR testing. Feedback from the study participants was also in favor of my concept.

CHAPTER 5: Discussion and Conclusion:

This dissertation work was successful in adopting elements from three different design principles and applying them to an academically driven innovation project. By adopting the principle of design control for medical device development as established by the FDA, I was able to formulate a project timeline with obtainable development milestones. Design control also allowed for a systematic evaluation of the project's progress through the review, verification, and validation processes. But more importantly, design control facilitated the process of maintaining a design log that is vital to obtaining regulatory approval for a medical device. The most important first step of a project is to identify a problem or pain point that needs improvement. But more importantly, the problem must be validated. Problem validation can be achieved through numerous methods such as consumer testimonies, observation, or literature data. The process of problem validation allows the project team members to define the problem while developing empathy for the affected population. Empathy building is a critical component of the design thinking principle because the data synthesized during this process drives many of the project's design decisions. As a final validation process, HFE principles were adopted to help prevent potential use errors that could lead to injuries to the patient.

As an emergency medicine clinician, I was able to observe the inefficiencies of our testing procedures for RTIs. I have also heard patient testimonies regarding their dissatisfaction with the process. Furthermore, a literature review was performed with data suggesting patients are not accepting of our current respiratory pathogen collection procedures. There is also a larger problem of patients not being able to access testing resources through the traditional channels, further supporting the need for a distance self-collection model. As demonstrated by the literature data presented in this dissertation, these shortcomings continue to hamper our ability to contain the COVID-19 outbreak.

The current gold standard for respiratory pathogen collection is the nasopharyngeal swab method, which has been shown to have a low patient acceptance rate. It could be argued that a poorly received collection method is a hindrance to a mass or ad-hoc testing model as compliance rates would likely be poor. As the COVID-19 pandemic has demonstrated, there is a dire need for innovation in our testing infrastructure for highly communicable diseases. Nations that were able to quickly pivot their testing approach experienced tangible decreases in their infection rates while the US continues the lead the world with new cases.

In this dissertation work, I proposed a simple alternative to our current specimen collection method. I adopted the fluid dynamic principles used in the wound care literature and developed a novel device designed to irrigate the nasopharyngeal cavity with a specific fluid pressure to debride for potential pathogens. Data from my preliminary studies demonstrated the device's ability to debride for epithelial cells from the nasopharyngeal cavity. This data was crucial in validating my proposed concept and the engineering parameters incorporated into the device. In my follow-up pilot trial, I evaluated 15 specimens collected by the study device using PCR testing, all of which were positive for the RNase P gene target. The presence of RNase P is an objective confirmation for specimen cellularity. The 15 specimens also had consistently low CT values indicating high specimen quality for PCR testing. None of the study participants experienced any discomfort from the device's irrigation mechanism, with all reporting the procedure was more efficient than the nasopharyngeal swab.

I believe the broader impact of my dissertation work is two-fold. First, the development template used in my prototyping process is based on the Design Controls principle established by the FDA for medical device manufacturers. This template was designed for a corporate setting, but I was successful in translating it to an academic setting. It is essential that we continue to cultivate innovative ideas as we prepare for the next inevitable pandemic. By having an established process to systematically validated one's proposed concept, there is a level of

assurance in the quality of our rapid development cycles. Second, I have demonstrated the feasibility and validity of debriding the nasopharyngeal cavity by means of fluid irrigation to procure potential pathogens. With that being said, participant feedback suggests a much higher acceptance of my concept when compared to the nasopharyngeal swab method. I strongly believe further research is needed to continue exploring this concept and its ultimate place in our testing infrastructure. A self-administered device designed specifically to ensure simplicity in its use while being comfortable has the potential for a stronger buy-in from patients.

With this being a pilot evaluation of my proposed device, I recognize there are limitations in my procedures and outcomes. An FDM 3D printer was used to fabricate the study devices, and though this approach was suitable for a pilot study, it is not ideal for mass production. 3D printing is known to have relatively low internal reliability between each printed device. 3D printing filament can also be expensive, making it impractical for a mass-production model. Once cured, PLA material should not be subjected to traditional sanitation procedures such as autoclaving or UV disinfection as there are concerns these processes may compromise the integrity of the material, making it unsafe for human use. With these limitations in mind, I specifically collaborated with APOMed Consultants to ensure my design parameters were translatable to an injection molding manufacturing process.

Although the data from my pilot study was supportive of my concept, the small sample size limits my ability to make any generalizable or statistical claims. When designing a new collection or diagnostic method, it is more logical to conduct a comparative study with the current gold standard. Although my plan is to follow-up this dissertation work with a prospective trial to evaluate the diagnostic fidelity of specimens collected by my device when compared with a nasopharyngeal specimen, I felt it was prudent to assess the concept in a pilot study.

In conclusion, this dissertation work was successful in establishing a foundational framework for future research as I continue to evaluate the concept of fluid debridement to collect

respiratory pathogens. Data from my pilot study is encouraging as I was able to demonstrate the study device's ability to consistently deliver high-quality specimens along with strong user acceptance.

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