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Research article

Research and Development of a Device for Nasopharyngeal Swabs for Rapid Testing of the Novel Coronavirus

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Abstract

Objectives: To develop specimen collection equipment for SARS-CoV-2 detection able to collect the specimen from an appropriate position with an adequate quantity and to test the equipment in a laboratory. **Methods:** Research procedures included systematic literature review, expert brainstorming, equipment invention, and laboratory testing of the equipment. Information from literature review and brainstorming was collected and used to design a prototype device. After the preliminary test of the device, the collected information was sent back to the experts for independent review until the final design of the prototype was selected and ready to be constructed. The device was invented by a certified device manufacturer with expertise in device invention under the supervision and inspection of an engineer. A test was conducted in a laboratory by applying the device to a human nose model with the nose, nostril, nasal cavity and sinuses. **Results:** Device prototype A was able to access nasopharynx and extract the whole amount of specimen required. The average collected volume of specimen was 1.71±0.25 mL from 100 replicas of test. **Conclusion:** The output of this study is a prototype device to collect specimens from the nasopharynx for COVID-19 testing. The prototype is also ready to be produced and tested in clinical settings.

Keywords: nasopharyngeal swabs, prototype device; SARS-CoV-2 detection

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บทความวิจัย

การวิจัยและพัฒนาเครื่องมือเก็บตัวอย่างหลังโพรงจมูกสำหรับใช้ตรวจโรคติดเชื้อจากไวรัสโคโรนาอย่างรวดเร็ว

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บทคัดย่อ

วัตถุประสงค์: เพื่อพัฒนาอุปกรณ์เก็บตัวอย่างสำหรับการตรวจ SARS-CoV-2 ที่สามารถเก็บตัวอย่างจากตำแหน่งที่เหมาะสมในปริมาณที่เพียงพอ และเพื่อทดสอบอุปกรณ์ดังกล่าวในห้องปฏิบัติการ **วิธีการ:** ขั้นตอนการวิจัยประกอบด้วยการทบทวนวรรณกรรมอย่างเป็นระบบ การระดมความคิดของผู้เชี่ยวชาญ การประดิษฐ์อุปกรณ์ และการทดสอบอุปกรณ์ในห้องปฏิบัติการ ข้อมูลจากการทบทวนวรรณกรรมและการระดมความคิดถูกรวบรวมและนำไปใช้ในการออกแบบอุปกรณ์ต้นแบบ หลังจากการทดสอบเบื้องต้นของอุปกรณ์แล้ว ข้อมูลที่รวบรวมได้ถูกส่งกลับไปยังผู้เชี่ยวชาญเพื่อตรวจสอบอย่างเป็นอิสระจนสามารถต้นแบบที่พร้อมที่สร้างขึ้น อุปกรณ์ดังกล่าวประดิษฐ์โดยผู้ผลิตอุปกรณ์ที่ผ่านการรับรองซึ่งมีความเชี่ยวชาญด้านการประดิษฐ์อุปกรณ์ภายใต้การดูแลและการตรวจสอบของวิศวกร การทดสอบในห้องปฏิบัติการโดยใช้อุปกรณ์ดังกล่าวทำกับแบบจำลองจมูกของมนุษย์ที่มีจมูก รูจมูก โพรงจมูก และไซนัส **ผลการวิจัย:** อุปกรณ์ต้นแบบ A สามารถเข้าถึงช่องหลังโพรงจมูกและเก็บตัวอย่างที่ต้องการได้ทั้งหมด ปริมาตรที่เก็บรวบรวมโดยเฉลี่ยของตัวอย่างคือ 1.71±0.25 มิลลิลิตรจากการจำลองการทดสอบ 100 รายการ **สรุป:** ผลลัพธ์ของการศึกษานี้เป็นเครื่องต้นแบบสำหรับเก็บตัวอย่างจากช่องหลังโพรงจมูกเพื่อตรวจหาเชื้อโควิด-19 ต้นแบบนี้ยังพร้อมที่จะผลิตและทดสอบในคลินิก

คำสำคัญ: อุปกรณ์เก็บตัวอย่างจากหลังโพรงจมูก อุปกรณ์ต้นแบบ การตรวจหา SARS-CoV-2

Introduction

Covid-19 pandemic has recently seen a rise in infections in Thailand. The existing detection method, a reverse transcription real- time polymerase chain reaction (RT- PCR) technique, cannot respond in a timely manner according to the changing situation (1-3). Therefore, many countries, including Thailand, have adopted rapid virus detection tools, e.g., antigen rapid detection tests (Ag- RDTs). However according to literature review, the devices exhibit several limitations (4).

One major limitation is its low accuracy and reliability. A study by Yamayoshi *et al*. found that the Ag- RDTs were not necessarily reliable. The device cannot always detect the antigens of virus in the specimen (4). Other major limitations include unclear instruction of use and different types of secretion (e.g., saliva or blood), procedures, and positions to collect secretion (e. g., anterior nasal or nasopharynx) as required by each Ag- RDTs brand. Such different instructions and requirement also result in different characteristics of the devices.

Devices recommended for collecting secretion specimens from the anterior nasal spine should be short in length. On the other hand, those for collecting specimens from the nasopharynx should be longer in length in order to reach the specified nasopharynx, which is approximately 7 cm from tip of nose (5). Lui *et al.* suggested that the most appropriate position to collect a specimen for COVID- 19 Ag- RDTs is nasopharynx. The specimen can be collected by inserting cotton swab along the nasal septum parallel to the hard palate. If there is resistance during the procedure, cotton swab should be pulled backward and inserted back at different angles with a more acute angle to nasopharynx. Cotton swab should be left in place for several seconds to absorb the specimen, and then slowly spun as cotton swab is extracted. The procedure is aligned with those of the US Centers for Disease Control and Prevention (US CDC) (6) and the World Health Organization (WHO) (7). Even after following swab procedure, errors in specimen collection could be found. Characteristics of desirable specimen collection included 1) collecting a specimen from an appropriate position, 2) collecting enough quantity of specimen, and 3) not harming any organs or hurting the patients.

Ministry of Public Health in Thailand procured Ag- RDTs for self- testing among public to detect the early stages of infection and for the use by medical personnel in active case finding. The study by Chaimayo *et al*. (8) indicated that the use of Ag-RDTs (Standard™ Q COVID- 19 Ag kit, SD Biosensor®, Republic of Korea) is as effective as the use of RT-PCR (Allplex™ 2019- nCoV Assay (Seegene ®, Korea) in detecting the antigen of severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2). The sensitivity and specificity of AG-RDTS are 98.33% (95% CI, 91.06- 99. 96%) and 98. 73% (95% CI, 97. 06- 99. 59%), respectively. Various studies also support the use of Ag-RDTs (9-12).

Recently, Government Pharmaceutical Organization (GPO) imported Lepu® Ag-RDTs and distributed them to National Health Security Office (NHSO) and to Rajavithi Hospital (13). Lepu® Ag- RDTs recommends collecting the specimen from the nostrils rather than from the nasopharynx, which is the collection position recommended by US- CDC and WHO. Denzler *et al*. (14) compared sensitivity and accuracy of 32 different Ag-RDTs brands in the German market. Samples were taken from the same- pooled nasopharyngeal swab for all 32 AG- RDTS brands. The results indicated that Lepu® Ag-RDTs had the lowest sensitivity compared to the other 31 brands. Even in cases with high concentrations of virus, Lepu® Ag- RDTs was not as sensitive as it should be. The use of Ag-RDTs is not totally useless, but its extreme low sensitivity is a major limitation. However, the Government of Thailand had already purchased this brand of Ag-RDTs. In order to maximize

the effectiveness of its professional or home use, we should focus on accuracy, appropriateness and adequacy of specimen collection procedure.

This study aimed to develop a specimen collection kit. The research questions were: 1) What should the specimen collection equipment for SARS-CoV-2 detection be in order to collect a specimen from an appropriate position with an adequate quantity of specimen? and 2) What is the efficiency of the equipment? The objectives of this study were: 1) to systematically review the literature, then develop a nasopharyngeal sample collection device for SARS-CoV-2 detection, and 2) to test the prototype instrument in the laboratory.

Methods

This study was a mixed-method study consisting of systematic literature review, expert brainstorming, equipment invention, and laboratory testing of the equipment. Details of the methodology are described in the following sections.

Systematic reviews

Data sources

The databases used in literature review were 1) International patent and petty patent databases such as those of Department of Intellectual Property on Thailand, Korea Intellectual Property Rights Information Service, Japan Patent Office, Intellectual Property Office of Singapore, Office of the Controller-General of Patents, Designs and Trademarks, Intel Intellectual Property Australia, German Patent and Trade Mark Office, US Patent & Trademark Office, European Patent Office, State Intellectual Property Office, Patentscope, Espacenet, TotalPatent, Thomson Reuters and Google Patent, 2) International e-databases which include both published and unpublished publications such as PubMed, Cochrane Central Register of Control Trials (CENTRAL), Google Scholar, ScienceDirect, Web of science, CINALH, Open Grey and DART-Europe, and 3) Thai e-databases such as Thai Library Integrated System (ThaiLIS) and Thai Journals Online (ThaiJo).

Searching for Information

Keywords and Medical Subject Headings (MeSH) and Boolean Logic used in searching for information were ((“coronavirus disease starting in 2019”) OR (“COVID-19”)) AND ((“rapid diagnostic method”) OR (“rapid antigen test kit”) OR (“differentiating”) OR (“detection”) OR (“diagnostic”) OR (“diagnostic method”)), ((“severe acute respiratory syndrome”) OR (“SAR-CoV-2”)) AND ((“specificity instrument”) OR (“device”) OR (“nasopharyngeal specimen collection”) OR (“smartphone nasoscope”) OR (“clinical application”) OR (“imaging, nasoendoscopy”) OR (“flexible nasoendoscopy:”) OR (“optical nasoendoscopy”)), ((“coronavirus disease starting in 2019”) OR (“COVID-19”)) AND ((“probe guideline”) OR (“diagnostic guideline”) OR (“clinical practice guideline”) OR (“management”) OR (“recommendation”)), ((“severe acute respiratory syndrome”) OR (“SAR-CoV-2”)) AND (“primary care diagnostic”), ((“coronavirus disease starting in 2019”) OR (“COVID-19”)) AND (“swab method”). Thai keywords with the same meaning as “COVID-19”, “SAR-CoV-2”, “new coronavirus strain”, “rapid diagnostic method”, “rapid antigen test kit” and “rapid antigen test application” were also used.

Information was searched from the beginning of the database establishment until October 1, 2021. Publication in all selected databases was included. Repetitive publications were excluded using computer software. Later, only those relevant publications were selected based on the following criteria: 1) showing good and adequate quantity of specimen for Ag-RDTs and results from Ag-RDTs must be validated with the RT-PCR test results for COVID-19 diagnosis.

Assessment of Research Quality

Two researchers independently assessed the quality of each retrieved publication using the Cochrane guidelines, i.e. the Cochrane Risk of Bias version 2

(ROB-2) (15) for randomized controlled trials (RCTs), the Risk of Bias in the non-randomized studies of interventions (ROBINS-I) for non-RCTs (16), and the Appraisal of Guidelines for Research & Evaluation II (AGREE II) (17) for the studies on quality of Ag-RDTs. If two assessors disagreed, the third researcher evaluated the studies using the same criteria.

For reports on case studies and review articles, bias assessment was conducted according to 4 principles whereby the articles must present: 1) how selection bias was managed: The research must clearly identify the sample inclusion and exclusion criteria and must ascertain that the participant was eligible as an infected SAR-Co-V2 patient and/or has SAR-Co-V2 detection indicators; 2) how the measurement bias was managed: the details on testing procedure and training process for those who conducted the test must be clearly identified; 3) how information bias was managed: An explanation on how the test results were managed must be provided to ensure that the results were correctly reported without any errors; and 4) how the information was managed: The information must be complete, and no incomplete or missing information. How the information was managed must be provided to avoid any misinterpretation of the results.

Any articles with assessment results of "a low risk in all bias aspects" passed the quality assessment standard. The results of the criteria passing articles were collected, summarized and listed in a dummy table for descriptive analysis. The results of interest were the characteristics of the specimen collection device and the details of the specimen collection procedure.

Expert brainstorming

After completing literature review, experts brainstormed to collect additional important information that was still missing but necessary for designing specimen collection device at nasopharynx for COVID-19 detection. Experts consisted of one specialist on rhinology and allergy, two specialists on infectious diseases, one specialist on emergency medicine, one pharmacist with expertise on otolaryngology, two experts specializing in product design and linguistics.

Brainstorming was conducted by using 3 open-ended questions including 1) what do you think are the critical points in specimen collection at nasopharynx for COVID-19 detection that will lead to correct and reliable results? 2) what do you think are the drawbacks or limitations of the currently available devices? and 3) what should be done in order to develop the effective devices? Subsequently, experts could freely express their opinions. The brainstorming session was about one hour long and ended when information saturation or no additional opinions were reached.

In this stage, we controlled any recall bias that may occur during the brainstorming due to the experts' experience or perspective in different processes in device development by asking them to recall their most recent provision of the test or recommendations on the use of Ag-RDTs to patients. Information from brainstorming was prioritized and descriptively analyzed by a Thai language expert. The experts' opinions were confidential and blinded. Subsequently, all of the experts reviewed the results and drew conclusions on the characteristics of the specimen collection device and procedure.

Thai language expert descriptively analyzed the information from systematic review and incorporated with that from brainstorming. The resulting information were clearly and thoroughly examined before submitting to a product designer. The designer considered the possibilities of device prototype in terms of its design and cost. Finally, all information was used to design a device prototype and to collect specimens using the prototype. The collected information was sent back to the experts for independent review until the final design of the prototype was selected and ready to be constructed.

Device invention

The device was made of materials commonly available in the market with Thai industrial standards

that were non-toxic and did not cause any damage to the internal tissues, particularly those in nostrils, nasal cavity and sinuses. The device was invented by a certified device manufacturer with expertise in device invention under the supervision and inspection of an engineer.

Laboratory testing of the equipment

A preliminary test was conducted in a laboratory by applying the device to a human nose model with nose, nostril, nasal cavity and sinuses as illustrated in Figure 1.

Laboratory testing of the device was conducted as follows: An artificial specimen with characteristics similar to the real specimen was formulated under the supervision of an expert in otolaryngology. Dye was added for ease in the assessment process. There were 2 tests including Test 1 with the device placed in the nasopharynx position, and Test 2 with the device placed at the end of the turbinate (Figure 2).

The device prototype was inserted into the model to collect a specimen by placing the prototype in the position designed in each test. The person who collected the specimen was not allowed to see the specimen collection position. During the procedure,

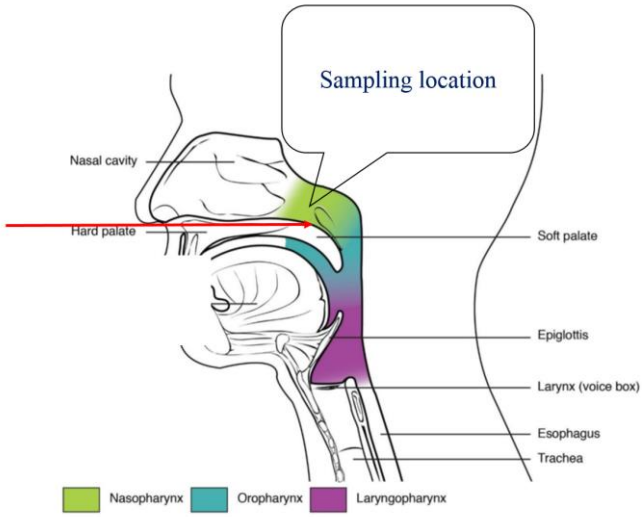


Figure 1. Internal physiology of human nose, nostril, nasal cavity and sinuses.

each test was video recorded. The record was then used in the descriptive analysis to determine the difficulty in conducting each procedure.

Volume of the specimen collected was calculated using the following formula: percentage of capability on collecting a specimen = 100 – [(volume of specimen remaining in the human nose model x 100)/total volume of the specimen]

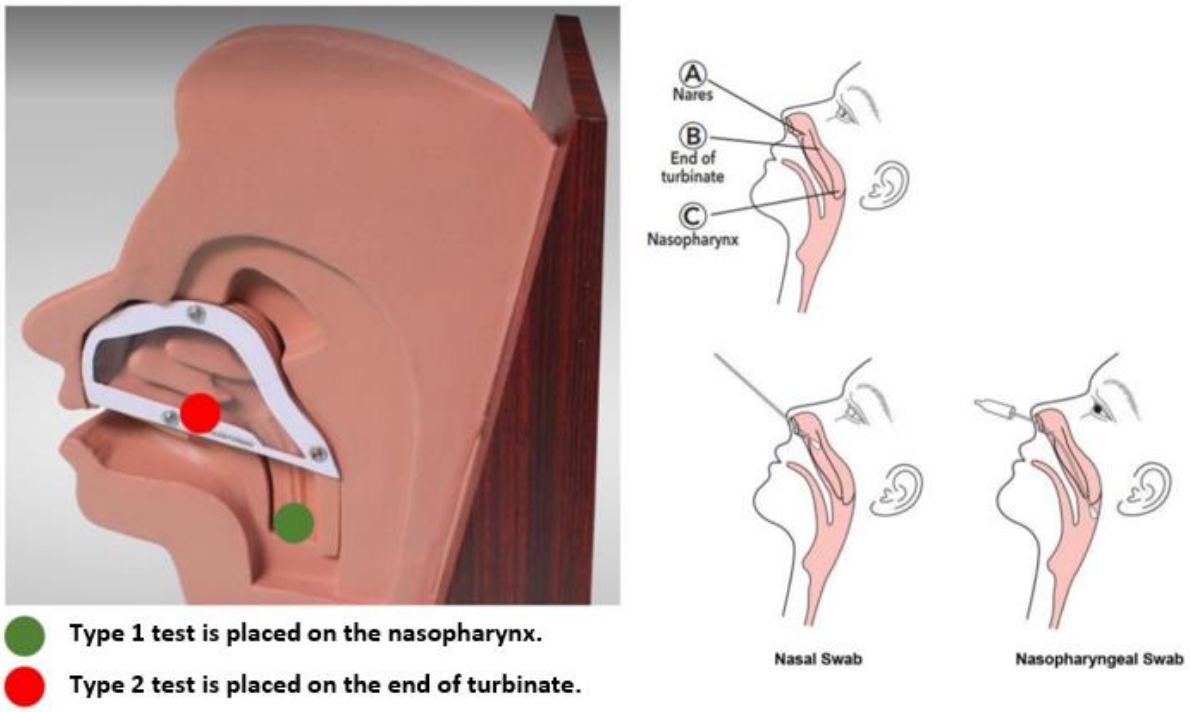


Figure 2. Examples of the testing model design for specimen collection

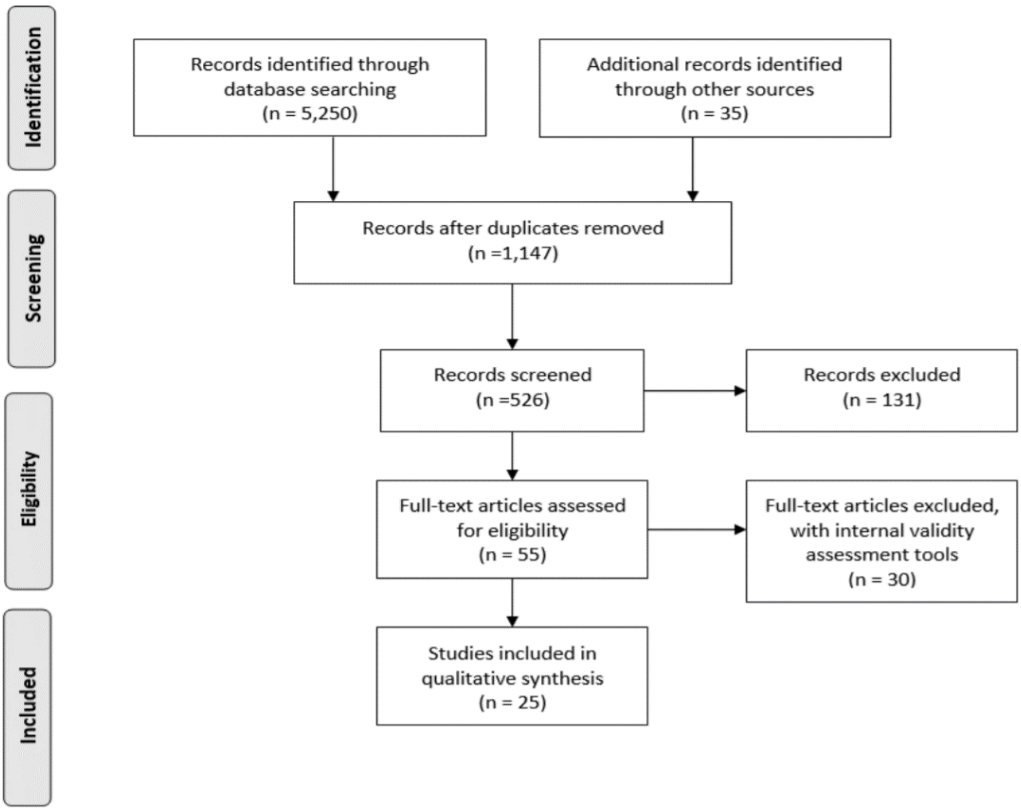


Figure 3. PRISMA flow diagram of this systematic reviews.

Results

Systematic reviews

Twenty-five articles on studies and procedures for nasopharynx swabs for rapid testing of COVID-19 passed the inclusion criteria and were considered to

have a low risk of bias (Figure 3). Content of the articles can be categorized into 3 groups:

1) The device used to collect specimens from nasopharynx in most studies can be divided into 2 types: 1.1 a small cylinder, thin and long with a cotton swab on the end. Materials for the devices varied from wood, silicone, to different types of polymers, and 1.2 a long and small stick with different shapes at the ends to collect the different types of specimen such as liquids, or sticky and thick specimens in adequate quantities.

2) Evidence supported the correct and suitable specimen collection as being the most crucial issue in using an Ag-RDTs for virus detection. There were 2 positions for specimen collection: 2.1 anterior nasal swab and 2.2 nasopharyngeal swab.

3) Specimen collection by nasopharyngeal swab yielded a significantly higher sensitive and more accurate test compared to that by anterior nasal swab. The descriptive results indicated that the specimen collection position and the quantity of specimen collected significantly influenced the quality of the specimen, and sensitivity and accuracy of the test.

As a result, the major characteristic of the device for a nasopharyngeal swab for COVID-19, based on the results from systematic review, was that the device must be able to reach the nasopharynx position and be able to collect an adequate quantity of specimen.

Expert brainstorming

Four aspects in designing the devices could be concluded from brainstorming session. First, the device should reach nasopharynx. As a result, it should be thin, long, small in diameter, and durable. Second, the device should be able to collect at least 0.5-1 mL of specimen. Third, it device should be easy to produce without using any complicated equipment or technology. Lastly, it should be low- cost and economically viable at commercial scale, implying easy access by the public.

Device design

The information from systematic literature review and expert brainstorming was used in designing the device prototype. The aim of the design of device was to be able to reach the most appropriate position with the highest concentration of virus and to be able to take an adequate amount of specimen without causing any pain, in addition to being easy to use and affordable.

Device prototype A was chosen for further testing because it incurred the lowest cost and was deemed to be the most suitable option under current conditions with the need for urgent production and use.

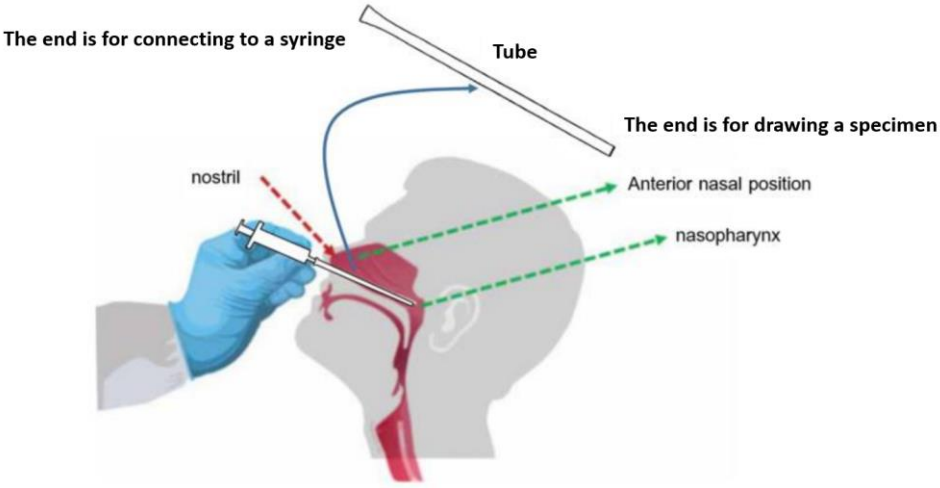
Device invention

The shape of invented prototype is long and cylindrical as depicted in Figure 4. One end of the cylinder is wide enough to connect to a syringe. The other end of the cylinder (tube) is open for specimen collection. The prototype is made of silicone used in medical device molding. The material does not harm human tissues or having any toxic effects when the prototype is inside human body.

According to the design framework, three different designs of the device were obtained. Each design has its pros and cons, as listed in Table 1.

Laboratory testing

Prototype A was able to access nasopharynx and extracted the whole amount of specimen required. The volume of specimen was 1.71±0.25 mL from 100 replicas. The results are presented in Table 2.



A.

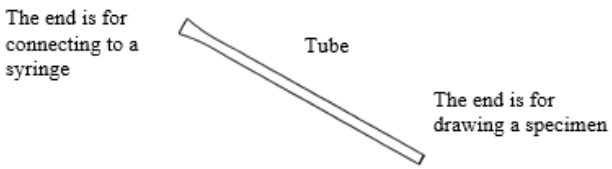
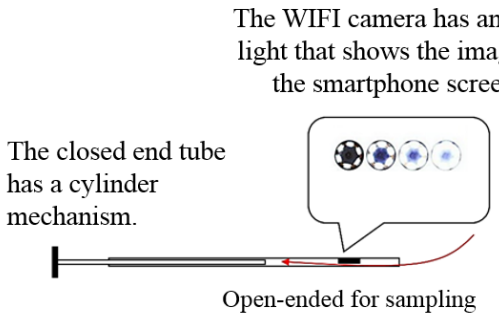
B.

Figure 4. Device prototype in this study

A. Simulation of the use of device prototype.

B. The device obtained from 3-D printing

Table 1. The device prototypes based on the information from systematic reviews and expert brainstorming

device prototype	nasopharynx accessibility	adequate quantity of specimen	level of pain during use	approximate cost per unit (baht)
A .  			might have no pain	3 Baht/10,000 units This cost does not include the cost of mold for manufacturing the device or pre-manufacturing the device for quality test
B. The end tube is connected to the cylinder with a spring mechanism.  	✓ The major advantage of Prototype C is the specimen can be seen while collecting it.	✓ If it has 2 mm in diameter and 7 cm (70 mm) in length, it can . draw a maximum of 2.20 mL of specimen.	might have some pain	12 Baht /unit This cost does not include the cost of mold for manufacturing the device or pre-manufacturing the device for quality test
C.  			might have some pain	1,000 Baht/unit

Remark: The level of pain was assessed from the opinion of physicians. The device designer provided the cost. WIFI stands for wireless fidelity; LED stands for light emitting diode

Table 2. Laboratory testing of prototype A

testing parameters	results
accessibility to nasopharynx position (replica±SD)	100±0.00
capability in extracting specimen* (replica±SD)	100±0.00
volume of specimen extracted (mL±SD)	1.85±0.42
volume of specimen released (mL±SD)	1.71±0.25
percentage of capability in collecting specimen (mL)	100-[(0.15*100)/2]=92.5

Remark The results were based on 100 replications conducted by the same person

* Refers to the capability of extracting the specimen without any trace on any material used in the experiments.

Discussion

During COVID-19 pandemic, Ag-RDTs are the most suitable solution when an RT-PCR cannot be widely accessed (11-14). However, accuracy of Ag-RDTs must be high compared to that of RT-PCR. According to the literature review, two main factors affecting the accuracy of the test were efficiency of the device (sensitivity, precision and relevancy of the test) and appropriate collection of adequate quantity of specimen.

Due to the limitations in Thailand during conducting this study (September-October, 2021), the widely used Ag-RDTs in Thailand was Lepu® (9). The efficiency of Lepu® AG-RDTS was questioned, particularly with the specimen collected from anterior nasal swab. An anterior nasal swab might be more convenient for self-testing. However, the obtained specimen might not contain enough concentration of SAR-Co-V2. Indeed, other chemicals might contaminate. In addition, some studies showed that the anterior nasal position was drier than the nasopharynx position, leading to a smaller quantity of specimen collected (18). Other studies indicated that those suspected with coronavirus infection generally take antihistamines causing a drier anterior nasal cavity (19).

Results from the systematic review showed evidence on several important issues such as nasopharynx swab being a standard practice that should be followed. Each specimen collection device was designed particularly for each brand of Ag-RDTs. The conventional characteristics of the device are small, thin and long enough to collect the specimen from nasopharynx. However, there is limited evidence on the appropriate quantity of specimen that needs to be collected. In addition, after examining the information on each brand of Ag-RDTs, there is no clear information on the minimum quantity of specimen to be collected. The information on each brand is consistent in that as much as specimen should be collected. The swab tip must be left in the specimen collection area for a while before swirling the tip. Our observation is that there are 2 types of swab tip, the cotton swab and the swab tip in the cylindrical tube, concave and of a swirling shape. Once the device tip is maintained or swirled in position, the specimen sticks to the tip. This study suggests a different solution for designing the device. We designed the device based on the suction principle by using the external force from a syringe instead, so a certain volume of the specimen can be adequately collected. Specimen collection without having to leave the device could reduce the specimen collection duration. The most important point is that there is no need to swirl the device, which would reduce the level of pain, discomfort or damage of the tissue in the nostril area.

Expert brainstorming provided interesting opinions and perspectives for designing the prototype e.g., if the specimen can be seen during specimen collection, the device would become more efficient. In addition, risks from the use of device e.g., bleeding, stabbing through the scalp and jabbing nasal tissue, could be reduced. Some experts said that the device, when inserted, had to be precise every time or going to the right area for specimen collection without requiring the users to clearly identify the area. The error ranging from 5% to 10% from the area is acceptable and is considered efficient. However, there were no opinions regarding how this device should be applied, whether the new device should be intended for professional or home use, how to ease the specimen collection and how to safeguard patient safety. These issues should be taken for further consideration in designing the prototype.

With additional concerns on relevant issues such as urgency, possibility for mass production of the device, and unit cost, we found that Prototype A is qualified as the most viable in the current situation. This is due to: 1) Prototype A has an appropriate length, which can access nasopharynx; 2) Prototype A uses the suction principle rather than the absorption principle, thus losing a minimum amount of specimen and has an adequate amount of specimen for the test. Half of its current capability for specimen collection is up to 1.0 mL; and 3) Syringe used for suction is widely available and accessible in many sizes. Users can choose the appropriate size and volume for each task.

This study has important limitations. First, the device was designed for those with normal internal nostril structure only. The device might not be used in an individual with congested, inflamed and swollen nose or nasal polyps because it might cause pain and damage in nose tissues. Secondly, the efficiency test of the device was not conducted in humans due to COVID-19 pandemic. Therefore, we cannot claim that Prototype A will be as efficient in practice. However, we conducted the test on the human nose model (as illustrated in Figure 2). The results from this study can be regarded as a preliminary result for future research in healthy volunteers. Third, 100 replications of the experiment were conducted solely by one researcher a hospital which was under the strict rules and measures during COVID-19 pandemic. Therefore, the study cannot be conducted using a large number of test performers. Reproducibility of the experiment among test performers cannot be confirmed. However, reproducibility of 100 tests within one test performer was indicative in the study.

Future study should be conducted in healthy volunteers and patients by comparing test result from the prototype with those from specimen collection device of Lepu®, other Ag-RDTg brands available in Thailand, and RT-PCR. Thus, a device differing from those recommended by the application might yield the results that cannot be certified or legally binding.

Conclusion

The output of this study is a prototype device to collect specimens from the nasopharynx for rapid COVID-19 testing. The prototype is also ready to be produced and tested in clinical settings.

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