Self-Collected Specimens for Infectious Disease Testing

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Abstract

Self-collected specimens for infectious disease testing are becoming more commonplace. There are multiple published studies demonstrating that self-collected vaginal swabs for detection of sexually transmitted pathogens are as accurate as physician-collected endocervical swabs. Similarly, self-collected penile-meatal swabs are also acceptable for detecting sexually transmitted pathogens; however, unlike self-collected vaginal swabs, penile-meatal swabs are not considered an “on-label” specimen for U.S. FDA-cleared in vitro diagnostic products. Data on the accuracy of self-collected nasal specimens for respiratory tract infections are encouraging, but studies also show that patients do not always follow instructions when mailing samples back to the laboratory. Unfortunately, there are only a few reports of self-collected specimens for detecting enteric pathogens, such as Salmonella, Shigella, or Campylobacter. Microbiologists need to be proactive in making sure that training materials developed for self-collection (such as laminated cards, videos, and other resources) are accurate and easy to understand (which includes being available in multiple languages) and provide clear instructions on how to handle a specimen once it has been collected.

Introduction

Health care delivery systems are changing to try to become more cost-effective. In part, these changes are intended to accommodate the needs of patient populations that are increasingly elderly and less mobile or have limited transportation options to get to a hospital or clinic. As a result, more emphasis is being placed on having patients collect their own specimens for infectious disease testing. Keeping patients with contagious illnesses (like influenza) out of emergency rooms when they can provide a specimen from home for testing also makes good public health sense. However, the idea of patients collecting their own specimens makes many clinical microbiologists nervous. The fear of receiving an “air swab” that gets reported out as negative for sexually transmitted agents or a suboptimal nasal swab from a seriously ill child that is reported as negative for respiratory viruses is a valid concern. Either situation could allow further transmission of infections or result in more serious sequelae. While the literature describing the reliability of self-collected specimens for chlamydia and gonorrhea testing in women is reassuring [1], with very good overall concordance with physician-collected specimens, there are fewer studies of the accuracy of self-collected specimens for respiratory or enteric infections. Several studies on self-collected respiratory specimens raise important concerns, not just about the accuracy of self-collected specimens when tested, but about the ability of patients to package and transport the specimens safely to the laboratory when the specimens are collected at home [2,3]. This article explores several issues for microbiologists to consider when assessing the possibility of patient-collected specimens.
Self-Collection of Specimens for Sexually Transmitted Infections in Women

Multiple studies conducted over the last decade show that a self-collected vaginal swab is as sensitive as a physician-collected endocervical swab for detecting chlamydia and gonorrhoea [4]. Having patients collect their own specimens is also associated with much higher patient satisfaction scores. Lunny et al. [1] performed a meta-analysis of the literature and concluded that self-collected vaginal swabs could be recommended for home-based screening for Neisseria gonorrhoeae and Chlamydia trachomatis. Their study began with consideration of 5,333 reports but finally included just 21 studies (14 for C. trachomatis only, 6 for both C. trachomatis and N. gonorrhoeae, and 1 for N. gonorrhoeae only). The C. trachomatis studies included a total of 12,916 participants, and the N. gonorrhoeae studies included a total of 6,040 participants, resulting in a robust data set. A review of the results from self-collected urine specimens showed reduced sensitivity compared with swab specimens. Self-collected vaginal samples are highly acceptable to women, who prefer such samples to collection of urine or clinician-collected cervical samples [5,6].

Several studies have evaluated the results of self-collected vaginal swabs versus physician-collected swabs for detection of human papilloma viruses (HPV). Quincy and colleagues compared the results from a self-collected brush and a self-collected swab against a physician-collected standard swab and colposcopy [7]. Not surprisingly, the sensitivity of the brush, which has bristles that pick up more mucosal cells than a swab, was about 5% higher than that of the swab. A meta-analysis established comparable performances of self-collected vaginal samples across several investigations [8].

A recent study from Papua New Guinea, which is a region with a high burden of cervical cancer, investigated the utility of self-collected samples from >1,000 women over 30 years of age attending a well-woman clinic [9]. After a brief explanation from a health care worker (HCW) using a flow chart, patients collected a “midcavity” cytobrush sample, after which the gynecologist collected the second sample, using a standard cervical cytobrush during gynecological examination. Among the 104 high-risk HPV (hrHPV)-positive samples, there was >98% overall agreement between the two sample types for HPV types 16 and 18/45 and 93.4% agreement for all hrHPV results combined. Interestingly, among the 47 total discordant results, the self-collected brush sample was more likely to have detected hrHPV types than the physician-collected sample. Eleven of the 15 hrHPV discordant results with type 16 or 18/45 were detected from the self-collected sample only. There were an additional 32 discrepant results with other hrHPV types, among which 28 (87.5%) were positive with the vaginal sample and negative with the cervical sample.

Self-Collection of Specimens for Sexually Transmitted Infections in Men

Self-collected penile-meatal swabs, compared to urine samples, were shown to be highly acceptable and highly accurate for the diagnosis of sexually transmitted infections (STIs) in men by Chai et al. [10]. Two additional studies of the sensitivity of self-collected penile-meatal swabs for detection of STIs from men with symptoms of urethritis were reported by Dize and colleagues [11, 12]. These are important studies, because men often do not seek treatment for STIs, in part because they are concerned about the pain associated with a physician-collected urethral swab. A self-collected “less invasive” penile-meatal swab specimen appears to be more acceptable to men, as determined by both studies and surveys. In the first study, reported in 2013 [11], results from self-collected swabs from 634 men were compared to the results from urine specimens for detection of N. gonorrhoeae, C. trachomatis, and Trichomonas vaginalis. Testing of all specimens was performed using nucleic acid amplification tests. Compared to the urine reference method, the self-collected swabs showed 100% sensitivity for N. gonorrhoeae, 94.2% sensitivity for C. trachomatis, and 80.4% sensitivity for T. vaginalis. However, the self-collected swabs outperformed the urine specimens; the latter showed only 76.7%, 88.9%, and 39.3% sensitivity for the three target pathogens, respectively. In the second study of 203 males [12], Mycoplasma genitalium was added to the list of pathogens and compared to clinician-collected urethral swabs, but urine specimens were not collected. For C. trachomatis, the sensitivity of the self-collected penile-meatal swab compared to the urethral swab was 96.8%; for N. gonorrhoeae, it was 100%; for T. vaginalis, 85.0%; and for M. genitalium, 79.3%. The specificities of the assays ranged from 96.7% (T. vaginalis) to 100% (N. gonorrhoeae). None of the results were statistically different. When asked to rate the collecting of their own specimen, 90% of men rated it as either “very easy” or “easy” to obtain. When shipping is available and pre-arranged, self-sampling can be a major benefit, especially for asymptomatic patients and patients who are reluctant to visit an STI clinic or cannot easily access a health care facility. Despite the benefits, studies have identified a few caveats. The men participating in the latter study were examined at an STI clinic and either were asymptomatic or were a contact of an infected partner and thus may have been more motivated to be tested than other asymptomatic persons in the community. Another caveat to consider is that, while swabs are much easier to transport than urine specimens, which may leak, testing swab specimens poses a technical problem for the laboratory, since this sample type (self-collected swabs from males) is off-label for all of the currently FDA-cleared diagnostic assays for C. trachomatis, N. gonorrhoeae, and T. vaginalis and thus may require a rather extensive validation study before testing can begin.

In 2009, a Dutch study of 1,458 men and 936 women reported 98% correlation between the results of self-collected and physician-collected rectal swabs for detection of C. trachomatis and N. gonorrhoeae both in men who have sex with men (MSM) and in female populations [13]. It is important to note that the major reason for not participating in the study was fear of collecting an inadequate sample (56%). Thus, patients often do have concerns about getting the correct answer when self-collecting their own specimens for testing.

HIV-positive MSM have anal cancer due to HPV infection at rates ranging from 75 to 137 per 100,000 individuals. Thus, screening this population using rectal swab specimens as a way of diagnosing
both anal dysplasia and HPV infection, as well as for monitoring HPV vaccine efficacy, is a critical public health function [14]. However, a Canadian study showed that among self-collected rectal swabs for cytology and HPV testing, only 62.3% of the swab specimens were adequate for anal cytology testing [14]. One caveat is that many of the specimens were not collected in a clinic setting, but in bars and pubs, which may have affected the ability of study participants to collect an adequate sample. However, even when additional explanations of how to collect specimens were provided to patients in the clinic venues, the recovery rate of adequate specimens did not significantly improve. Overall in the study, 33.5% of the rectal swabs did not have detectable β-globin DNA via PCR, which was the marker of cellular adequacy in the study. These specimens had squamous cells only, suggesting that the swab was not inserted beyond the anal canal (i.e., they were not rectal swab specimens). The authors suggested that for ongoing studies, self-collection of specimens should be limited to a clinic setting, where directions for collecting specimens can be better explained.

**Self-Collection of Specimens for Respiratory Tract Infections**

A number of interesting studies that describe self-collected nasal swabs for detection of respiratory tract infections have been published. Several were clinical studies focusing on the diagnostic accuracy of the self-collected specimens versus HCW-collected specimens. Other studies were population-based epidemiologic surveys, where the focus was on establishing disease prevalence in a community, not test accuracy. In the latter studies, there were no HCW-collected specimens for comparison. Instead, attention was focused on the logistics of specimen collection and transportation back to the laboratory for testing. Thus, compliance with packaging and shipping instructions and time to return of specimens were the key study outcome measures.

In one study that focused on the effectiveness of collecting and transporting specimens collected at home, Jackson et al. examined 135 self-collected nasal swabs for respiratory virus detection [3]. Since patients were enrolled in the study over the phone, there were no opportunities for face-to-face training. Specimen collection was based on written instructions provided in the kit and a Web link to a video, which demonstrated how to collect the nasal specimen and package the sample for shipping. The results of the study demonstrated that approximately 13% of patients made one or more shipping errors when returning the samples, while 10.5% excluded one or more of the materials that should have been placed in the return shipping container. Thus, of the 124 kits returned to the laboratory with a clinical specimen, only 78.2% were collected correctly. Nevertheless, the study authors noted that though shipping was not always correct (e.g., some omitted the absorbent padding material), many of the specimens in the “incorrectly shipped” category were still able to be tested successfully for viruses. In terms of timeliness, 83% of the specimens were collected within 48 hours of receiving the kit. Only 37 subjects reported watching the video link on how to collect and ship the specimens appropriately. Even so, those who viewed the video were no more likely to ship the specimens properly than those who did not watch it. The adequacy of the specimens collected could not be ascertained directly, since there was no health care provider-collected specimen taken from the patient. The study authors noted that similar respiratory specimens sent to a reference laboratory in the same region around the same time gave similar results in terms of the pathogens detected. Although modestly reassuring, data from other studies are needed to confirm the accuracy of the procedure.

More to the point, another study conducted by the Mayo Clinic compared the accuracy of the results from a self-collected mid-turbinate swab taken from the patient’s right nostril to the results from an HCW-collected mid-turbinate swab taken from the patient’s left nostril [15]. A mid-turbinate flocked swab was selected because it has a shield on the handle that prevents the patient from inserting the swab too far into the nasal cavity. The Mayo Clinic established goals of decreasing unnecessary utilization of health care services (such as emergency departments) by patients and also sought to minimize the exposure of patients (especially young children, the elderly and immunocompromised patients) to respiratory diseases in crowded emergency departments and clinics during flu season. The study was a critical step in showing that patient-collected swabs that were taken at home would yield accurate results. Emergency department patients >18 years of age who met the Centers for Disease Control and Prevention’s definition of influenza-like illness provided written consent and were enrolled in the study. They were given a flocked swab kit and an instruction card in English. An HCW observed the patients while they collected their specimens but offered no guidance on the process. The patients collected the specimen based solely on the information in the printed guide. Although the data set was small (72 paired specimens), the results showed 94.8% agreement between the results from the two swabs, where the positivity rate for either influenza A or influenza B was 34.7%. In this study, 53.4% of the patients preferred self-collection, while 25.9% had no preference.

Another study allowed HCWs who were ill to self-collect throat and nasal specimens at home, put the swabs into the same transport tube, and mail them to a laboratory for respiratory virus testing. Thus, they did not have to report to the employee health clinic for testing and avoided sharing their illness with others [16]. Interestingly, the self-collected specimens from the HCWs who stayed home yielded a significantly higher positivity rate than the research assistant-collected swabs taken in the hospital (P < 0.0001). However, the HCWs who stayed home may well have been sicker, accounting for the higher positivity rate. Determining the cause of illness in this population has value, especially from a public health perspective, since these positive results would otherwise have gone undetected. Nonetheless, the HCW self-collection may be effective when fully validated.

What are we to learn from these studies on nasal sampling for respiratory viruses? First, although the data are promising, many would still argue that a nasal swab is not the optimal specimen for respiratory viruses, especially influenza viruses, like influenza A H1N1 v2009, which has a predilection for the lower respiratory tract [17]. This makes at least some influenza virus strains in upper airway specimens more difficult to detect and thus less
likely to be detected. Also, conducting epidemiologic studies of viral pathogens in large patient populations is a different paradigm than that of trying to make a diagnosis in a specific patient to determine the optimal management strategy, including whether the patient would benefit from treatment. Missing a diagnosis or two in a large survey does not have the same implications as missing a viral infection in a severely ill child in a hospital setting. What is acceptable for epidemiologic studies in terms of test sensitivity and shipping delays may not be considered adequate for patient management in a rural clinical setting. That said, there are already commercial tests that have FDA clearance for using nasal swabs for detection of respiratory viruses, especially in the outpatient setting. Thus, the challenge becomes how to optimize specimen collection to enhance the value of the test given and where, how, and by whom it is collected.

Moving from the realm of viral to bacterial respiratory pathogens, collecting your own (or your child’s) throat swab for group A streptococcal testing may sound like more of a challenge than collecting a mid-turbinate nasal swab, but published data suggest otherwise. A Mayo Clinic study compared the results from patient- or parent-collected throat swabs to the results from HCW-collected throat swabs when tested for *Streptococcus pyogenes* by a nucleic acid amplification method [18]. Overall, 402 paired specimens were collected; 203 specimens were self-collected by patients ≥12 years of age, and 196 swabs were collected by a parent of a child. The order of collection (patient/parent versus HCW) was randomized to control for bias. The results showed a positivity rate of 33.3% for HCW-collected swabs and 34.3% for self-collected swabs (P = 0.41). The overall concordance of the results was 94%, and the amount of DNA in positive samples was higher in patient-collected swabs. One caveat reported by the authors was that the study was conducted in Rochester, Minnesota, which has a highly educated and motivated population that may not reflect other population centers around the United States. For this situation, at least, the authors concluded that self/parent-collected throat swabs were reliable, saved patients from the inconvenience of travel, reduced exposure to other patients with infectious illnesses, reduced overall health care costs, and allowed patients a more active role in their health care.

**Self-Collection of Specimens for Enteric Infections**

For some enteric pathogens, such as *Shigella*, inoculation into culture medium within 1 hour or less is recommended for optimal recovery of organisms [19]. If that is not possible, the stool specimen can be placed into a transport medium that maintains the viability of most pathogens during transport to the laboratory. Other stool pathogens, including many parasites, can also be preserved in stool placed into suitable preservative/transport media for later laboratory testing. However, in many situations, it may not be practical or feasible for patients to access a caregiver and deliver a fresh stool sample on demand or even to deliver a sample in transport medium to a laboratory during their active disease phase. In the developing world, caregivers may be scarce or a long distance from the patient’s location. Workers in sensitive occupations (such as food handlers) who were previously diagnosed with an enteric infection may require a series of negative stool samples before being allowed to return to work. For all these reasons, the advantages of using a self-collected stool sample for diagnosis are obvious. In fact, self-collection of fecal material to mail to a laboratory for occult blood testing is a standard practice [20]. Thus, self-collected fecal samples (albeit in quantities slightly larger than that required for occult blood testing) for diagnosis of enteric infections makes sense, especially given the ability of nucleic acid amplification systems and broad enteric pathogen panels to utilize preserved samples without the need for culture or direct observation. Thus, the future for self-collected stool specimens for infectious disease diagnostics appears strong.

In one of the few studies available in this field, a pilot study conducted in South Africa in 2014 used a self-collection kit called Bio-Wipes (used like toilet paper) to collect fecal specimens for detection of enteric viruses by a nucleic acid amplification method [21]. No HCW-collected specimen was obtained in parallel to assess the efficacy of the collection process; rather, the goal of the study was simply to determine the feasibility of the collection method. In fact, 82% of the specimens collected, approximately half of which were from patients without diarrhea, had at least one enteric virus detected. Up to four different viruses were detected among diarrheal and non-diarrheal specimens, indicating that the method was a viable option for detecting enteric viruses. Whether the Bio-Wipe method will work as effectively for enteric bacterial pathogens, such as *Salmonella*, *Shigella* or *Campylobacter*, remains to be determined.

**Providing Directions for Specimen Collection**

Most clinics provide laminated instruction cards to patients that describe how to collect a clinical specimen. This is also true for research and epidemiologic studies. However, the quality and clarity of such cards can vary dramatically. In many cases, the clinical microbiologists in the laboratory have not had the opportunity to provide any input to the design of the collection cards or have not even reviewed the final product for accuracy. In some venues, innovative videos are available in specimen collection rooms showing the patient how to collect the sample, or in the case of home testing, collection videos are available online, but these are still uncommon. Examples of videos showing self-collection methods can be found at [https://www.youtube.com/watch?v=vZ95tnbcexs](https://www.youtube.com/watch?v=vZ95tnbcexs) and [https://www.youtube.com/watch?v=UcUx6dbfTQ8](https://www.youtube.com/watch?v=UcUx6dbfTQ8).

In inner city clinics, instructions in multiple languages often are needed. In such cases, a well-constructed video is likely to be more effective than just a laminated card.

**The Value of Sample Adequacy Controls**

Some commercial assays have implemented a sample adequacy control that tests for the presence of human DNA to ensure that specimens, whether collected by a patient or an HCW, are adequate for testing. This gives the laboratory a greater level of confidence that a specimen that gives negative results contains an adequate volume of clinical material for analysis. This is particularly critical for self-collected specimens, where some patients...
may want to hide the fact that they are infected. Bristow et al. [22] noted that the single-copy hydroxymethylbilane synthase gene used in one commercial assay not only served as a specimen adequacy control (SAC), but also served as a good marker of inflammation in urine specimens collected from both men and women for chlamydia and gonorrhea testing. Lower cycle threshold (Cₚ) levels for the SAC in the assay (which suggested more human cellular material detected) were associated with both chlamydia and gonorrhea infections in HIV-infected women compared to the Cₚ values of specimens from women without chlamydia and gonorrhea infections. However, the authors cautioned that the degree to which the Cₚ value of the SAC correlates with actual disease burden or severity is unknown. The presence of an internal inhibition control that is processed with each specimen can also be very helpful when interpreting final test results for STIs by demonstrating the absence of PCR inhibitors in the specimen.

**Summary**

Submitting self-collected specimens for infectious disease testing is becoming more commonplace, especially among younger individuals, who are beginning to assume more responsibility for their own health. Self-collection is desirable from a public health standpoint, as it can reduce exposure of patients to respiratory illnesses in crowded emergency rooms and outpatient settings during influenza season by providing a viable alternative testing and treatment pathway. It also has the potential to reduce health care costs and enhance antimicrobial stewardship by providing specimens and laboratory results that otherwise would not be available to guide therapeutic decisions. However, the relatively small number of studies conducted in this field, a number of which were conducted among highly motivated individuals (like those with STIs) or in well-educated populations, do not prove that self-collection is a panacea. It will require teamwork among physicians, nurses, microbiologists, outpatient clinic directors, and others to make such programs successful. Microbiologists need to be involved in the development of specimen collection protocols that are clear and concise and include shipping and handling instructions to ensure that adequate specimens will be obtained and will yield accurate results. Spending resources on visual teaching tools, laminated cards, and training videos will likely be beneficial investments. Finally, microbiologists need to be prepared to deal with the onslaught of self-collected specimens as more and more CLIA-waived platforms and tests become available.

**Conflicts of Interest**

F.C.T. and E.J.B. are employees of Cepheid; C.A.G. has no conflicts.

**References**


