SelfCare
Advancing the study & understanding of self-care

ARTICLE

SelfCare 2017;**8**(3):1-11

THE PERFORMANCE OF AN INNOVATIVE SELF-SAMPLING TEST FOR VAGINITIS

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Key words: Vaginal infection, vaginitis, diagnosis, self-test, sensitivity, specificity, ease-of-use.

ABSTRACT

Vaginal infections are a common and recurring problem that affect many. Clinically-based diagnosis is difficult and requires laboratory confirmation. While not as comprehensive as a complete diagnostic workup, a test of vaginal pH offers a quicker check which aids treatment decisions. In women with an infectious cause of vulvovaginal symptoms, an elevated pH is usually associated with either bacterial vaginosis or trichomoniasis, whereas a normal pH is more commonly associated with vulvovaginal candidiasis. Although pH measurement is helpful, it is rarely done.

The VS-SENSE™ swab (Common Sense Ltd, Caesarea, Israel) is a reliable test which can be used by healthcare providers or self-administered. This paper describes a study of the device's accuracy compared with a traditional diagnostic workup. Further, it describes a second study which explored whether subjects were able to follow the instructions for self-administering and reading the test, ease of use and the percentage agreement between self- and clinician-obtained swab diagnoses.

When used according to the instructions VS-SENSE™ showed overall 92% accuracy compared to the diagnostic workup; sensitivity was 91.8% and specificity was 92.9%. We also describe the 25 cases where an illustration provided in the instructions led to uncertainty among the raters, underlining the need for clear instructions for use. In a second study, with improved illustrations, there was 92% agreement between womens' and clinicians' readings of the swab test. The VS-SENSE™ swab is a helpful test in diagnosing vaginal infections.

Impact Statement

Clinical diagnosis of vaginal infection is costly and frequently inaccurate. As a result, inappropriate treatment is often prescribed. A simple vaginal swab test indicating pH value has been found accurate in differentiating between the two most frequent causes of symptoms, bacterial and fungal infections. This distinction is relevant for the choice of treatment in the majority of cases. The swab has been found suitable for self-testing, and therefore facilitates self-care with OTC treatments for vulvovaginal candidiasis.

INTRODUCTION

Vaginitis is common in adult women of all races and uncommon in prepubertal girls; the highest incidence is seen among young, sexually active women. In the USA, bacterial vaginosis (BV) accounts for 40-50% of cases, vulvovaginal candidiasis (VVC) 20-25%, and trichomoniasis, 15-20%[1]. However, in Europe, the prevalence of trichomoniasis is much lower and has been found to vary across demographic groups. For example in the UK, where trichomoniasis is a rare infection, it was detected in only 0.3% of women from a sample of 2559, broadly representative of the sexually active general population. All cases except two were in women of black or mixed ethnicity, or reported recent partners of black or mixed ethnicity[2].

Because the symptoms and signs of vaginal infections can be non-specific, correctly diagnosing infections can be difficult. Furthermore, with the trend toward more frequent self-diagnosis and self-treatment, many affected women may not even present for evaluation.

Although patient history and physical examination provide useful information, a confirmatory diagnosis requires laboratory testing. Unfortunately, not every clinic is equipped with appropriate facilities, and some clinicians may not be proficient at diagnostic microscopy. A test of vaginal pH using pH paper strips can offer a method to narrow the differential diagnosis, but many practitioners avoid this method because of its inconvenience. In the pharmacist setting none of these facilities are likely to be available. These barriers to diagnosis adversely affect clinical practice. Because misdiagnosis and mismanagement of vaginal infections is widespread, current procedures for the diagnosis of vaginitis have been likened to throwing dice[3]. Even trained physicians have been shown to be incorrect in 40-50% of cases[4]. In the pharmacist setting the diagnosis is traditionally based purely on a patient's verbal description of her symptoms.

DIAGNOSTIC WORKUP FOR VAGINAL INFECTIONS

The gold standard of clinical diagnosis of vaginal infections traditionally relies on a combination of patient history, vaginal examination, the amine or 'whiff' test, pH determination, microscopic examination of vaginal secretion and sometimes vaginal cultures for yeast. Although there has been a recent trend toward PCR (polymerase chain reaction) testing for vaginal pathogens, it is unclear where the results from these techniques from molecular biology stand in the current diagnostic algorithm.

Patient reported symptoms and vaginal examination

Patients with vaginal infections mostly report an increase or change in vaginal discharge in terms of quantity, duration, colour, consistency and odour. Irritation, pain or itching may or may not be present. Although helpful, patient-reported symptoms alone are not specific enough to allow a differentiation between BV, trichomoniasis and VVC.

The classic symptoms of BV are an abnormal discharge and odour, usually described as fishy; irritation may also be present. The discharge of a woman with BV is typically thin, homogeneous,

malodorous, and grayish-white in colour[5]. Many women with BV are asymptomatic.

In the case of VVC, pruritus is the most common symptom. Other symptoms may include burning, irritation, and abnormal discharge. Although some women may have a thick white odourless vaginal discharge, many women with VVC notice no change in their discharge.

Similarly to BV, 20-50% of women with trichomoniasis, a sexually transmitted parasitic infection, can be asymptomatic. The discharge can be malodourous, copious, frothy and yellow-green or even bloody (the yellow and green colours are due to the presence of white blood cells). Local pain and irritation are common. Dysuria (20%), pruritus (25%), and postcoital bleeding due to cervicitis are also possible[6].

Traditional pH determination

In premenopausal women, studies on the association between infectious vaginitis and the variable pH level of vaginal secretion show that a pH level in the range of 3.8 – 4.5 is normal and is found in the presence of VVC. A pH level above 4.5 suggests BV or trichomoniasis. Therefore the use of pH paper strips can assist diagnosis. Unfortunately, vaginal pH measurement is not well established in clinical practice and is infrequently taught to residents in training[7]. Barriers to use of pH paper include its relative unavailability, and correct interpretation of gradations of colour change on a reference scale. To do vaginal pH testing, a three-step process must be employed using a small cotton-tipped applicator to first obtain a sample which is transferred to the pH paper strip. The colour change on the pH paper strip is then compared to a reference chart of multiple colours, provided by the manufacturer. In contrast, a device that eliminates these steps and provides an immediate, easily interpreted positive or negative result might encourage and facilitate more widespread pH testing.

Whiff or amine test

This test is performed by placing a drop of 10% KOH on the speculum after the vaginal examination or mixing vaginal fluid with a drop of KOH on a microscope slide. The KOH, by virtue of its alkaline properties, causes the release of volatile amines from the vaginal fluid. The amines are products of anaerobic bacterial metabolism. Discerning the characteristic fishy odour is considered a positive whiff test and suggests BV. The whiff test is positive in up to 70% of patients with BV.

Microscopic evaluation of the vaginal secretion

Microscopic inspection of a saline wet mount can differentiate between BV and *Trichomonas vaginalis* infection. Clue cells (squamous epithelial cells whose borders are obscured by adherent coccobacilli) are highly indicative of BV. The bacterial flora may also be examined microscopically for evidence of changes in the overall bacterial predominance. When candidiasis is present or in the healthy vagina, there is usually a predominance of lactobacilli (large gram-positive rods). The flora of a patient with BV is dominated by coccobacilli, reflecting an increase in the growth of *Gardnerella vaginalis* and other anaerobes. In the presence of trichomoniasis, abundant polymorphonuclear cells (PMNs) may be seen. Motile trichomonads, which are slightly larger than PMNs, are only seen in 60% to 70% of culture-confirmed cases of trichomoniasis. The KOH mount can be useful for

diagnosing candidal vaginitis as branching hyphae of *Candida albicans* can be seen. Microscopy, however, does not always have high diagnostic sensitivity, even in the hands of an experienced operator.

Vaginal cultures

Routine vaginal cultures in patients with BV have no utility. Although *Gardnerella vaginalis* has been demonstrated to grow in most vaginal cultures of women with BV, it has also been cultured in up to 70% of asymptomatic women. The utility of cultures is therefore to exclude other causes, not to confirm BV. Cultures for *T. vaginalis* and yeast are sensitive, but the use of laboratory facilities is resource consuming and associated either with time delay until the start of treatment or, more likely, the prescription of a course of empirical treatment.

For the sake of completeness it must be mentioned that new, albeit expensive, diagnostic tests, are available. These kits include DNA hybridization, PCR assays, immunoassays, and tests based on enzyme activity. For *T. vaginalis* infection, nucleic acid amplification tests such as the APTIMA *T. vaginalis* assay (Hologic Gen-Probe, San Diego, CA) may be more sensitive than culture.

However, in all likelihood the gold standard described above does not actually describe practice in the large majority of cases and never in the pharmacist setting.

Self-diagnosis and self-care

As effective treatments for vaginal yeast infection are available OTC, this is an area where reliable self-diagnosis can play a significant role.

The VS-SENSE™ diagnostic vaginal swab test

Figure 1: VS-SENSE swab; appearance either before use or after use if the pH value is normal

Figure 2: VS-SENSE swab; appearance after use if the pH value is abnormal (raised pH value)

The VS-SENSE™ diagnostic vaginal swab test (Figures 1 and 2) can be used by health care providers or patients themselves. The test facilitates diagnosis of BV and trichomoniasis and the exclusion of yeast infection by identifying changes in the pH of vaginal secretion. The swab is coated with

an innovative proprietary polymer which contains a colorimetric pH indicator, nitrazine yellow. It is comprised of a mixture of a polymer, plasticizer, wetting agent, an ion-balance reagent and an indictor applied on a substrate. When the yellow polymer in the swab touches vaginal fluid with an abnormally high pH level (pH>5.1) there is an immediate colour change to green or blue which is highly suggestive of BV or trichomoniasis. Both of these conditions are associated with a watery vaginal discharge resulting in a lower buffer capacity. Dependent on the exact buffer capacity, <20 mM capacity also leads to the colour change when pH is in the range of 4.3 to 5.2. Combining tests for pH and buffering capacity improves the overall accuracy of VS-SENSE™ relative to standard pH testing. These swabs have been approved as a VS-SENSE™ self-test swab and a VS-SENSE™ professional test swab. Both swabs use the same indicator[8].

Two clinical studies were performed to establish the usefulness of VS-SENSETM in practice. The first study was to test the device against traditional diagnostic procedures. The second study evaluated whether patients were able to follow the instructions for self-administering and reading the test and the correlation between self- and clinician-obtained swabs and the general ease of use.

EVALUATION OF THE VS-SENSE™ DEVICE AGAINST TRADITIONAL DIAGNOSTIC PROCEDURES

The ability of the device to match the gold standard diagnostic procedure was tested in a study from November 2005 to October 2006 in 267 women over the age of 18 with regular menstrual cycles. The subjects all had self-reported vulvovaginal complaints. In conformity with the package instructions for the marketed device, women with blood in their vaginal secretion were excluded as were patients who had had sexual intercourse or applied a vaginal douche within the previous 12 hours. These conditions lead to both false negative and false positive swab readings. Furthermore, those who had used medications for vaginal complaints within the last 3 days and those with signs of pelvic inflammatory disease (PID) were excluded. The subjects were recruited by 3 study centres in the USA. The protocol was approved by the Institutional Review Board at each site and all patients consented to the study.

Using the VS-SENSE™ swab, a study nurse took a specimen of vaginal secretion from the patient and recorded the colour change on a case report form 10 seconds after sampling. The CRF was then sealed in an envelope.

An investigator then did a vaginal speculum examination. Vaginal specimens were obtained for microscopic examination, Gram stain for Nugent score[9] and cultures for yeast and *T. vaginalis*. The principle investigator at each site then determined the clinical diagnosis, without access to the VS-SENSE™ test result performed by the nurse. Candidiasis was diagnosed either by a positive yeast culture or the presence of pseudohyphae or blastospores detected during microscopic examination. BV was diagnosed by Amsel criteria defined as at least 3 positive diagnostic criteria from among the following: a thin homogenous discharge, a positive whiff test and at least 20% clue cells on microscopy[10] or a positive (>7) Nugent's score. Trichomoniasis was diagnosed by a positive culture or evidence of motile trichomonads on saline wet preparation examination[11,12].

The outcome of interest was the extent of agreement between the nurse's interpretation of the VS-SENSE™ test result and the clinician's diagnosis based on the gold standard diagnostic workup. Sensitivity, also known as the true positive rate, measured the percentage of women with a positive pH-relevant diagnoses based on the diagnostic workup, who were also correctly identified as positive by the nurse using the VS-SENSE™ test (colour changed from yellow to blue/green). Specificity, also called the true negative rate, measured the percentage of women with no pH-relevant pathology according to the diagnostic workup who were also correctly identified as negative by the nurse using the VS-SENSE™ test (no colour change, swab remained yellow).

In this study a true positive was defined as the VS-SENSE™ test turning blue or green and the presence of a clinical diagnostic entity associated with an elevated vaginal pH (BV, trichomoniasis, atrophic vaginitis, desquamative inflammatory vaginitis). A false positive was defined as the VS-SENSE™ test turning blue or green in the absence of a clinical diagnostic entity associated with an elevated pH. A false negative was defined as the VS-SENSE™ test remaining yellow in the presence of a clinical diagnostic entity associated with elevated pH. A true negative was the VS-SENSE™ test remaining yellow in the absence of a clinical diagnostic entity associated with elevated pH. Sensitivity, specificity, and 95% exact binomial confidence intervals (CI) were estimated. The study was to be deemed successful if the sensitivity of VS-SENSE™ was above 90% and if the specificity was above 70%. Diagnostic accuracy was also established by summing the number of correct assessments and dividing by the sample size.

The secondary outcome measures were ease of use and reading clarity as judged by the nurse who obtained the reading using the VS-SENSE™. For this purpose 3 questions and five-point response scales were used, see Table 1.

Table 1: Questions regarding comfort of use and reading clarity

Study 1	
Question 1	**Is the comparison to the color code clear**
Question 2	**Is the color change of the indicator tip clear to distinguish?**
Question 3	**Is the VS-SENSE comfortable to use**
The possible responses were: not at all, slightly, somewhat, very, more than very	

Study 2	
Question 1	**Did you understand how to use the swab and where to take the sample from?**
Question 2	**Were the results clear to read?**
Question 3	**Was the product comfortable to use?**
The possible responses were: not at all, slightly, somewhat, very, more than very	

Of the 267 patients, 261 were eligible and consented to take part. Subjects excluded had had sexual intercourse within the last 12 hours (1), menstrual blood in the vagina (2), withdrew consent (2), and missing data (1). The demographical data for the 261 patients are shown in Table 2.

Table 2: Demographic data for 261 subjects included in the trial, Study 1

Age [mean years] 30.8		
Variables	**n**	%
Pregnant		
no	**244**	94
yes	**17**	5.7
Menstruating		
no	**10**	3.9
yes	**250**	95.8
missing	**1**	1
Contraceptive use		
no	**99**	34.6
yes	**161**	65.1
missing	**1**	1
Ethnicity		
Asian	**2**	1
Black	**149**	51.6
White	**106**	46.3
Other	**4**	2

It was found that 90.8% of the women had a history of vaginal infection. The clinician's final diagnosis based on the results of the diagnostic workup were as follows: 103 subjects with BV, 72 with VVC, 11 with trichomoniasis, 5 with a dermatitis, 2 with lichen simplex, 2 with vulvar vestibulitis, and 3 with other causes. No significant differences were found between the centres. The final clinical diagnoses compared with the VS-SENSE™ results for the full analysis set of 261 women results are shown in Table 3. The sensitivity and specificity of the VS-SENSE™ were 82.3% (102 of 124) (95% CI 74.4%-88.5%) and 94.2% (129 of 137) (95% CI 88.82%-97.4%), respectively. The accuracy was 88%.

Table 3: VS-SENSE™ diagnosis made by the nurse compared with the diagnosis made by the investigator based on a diagnostic workup, n=261, Study 1.

	Gold Standard Clinical Diagnosis		
VS-SENSE	**Positive**	**Negative**	**Total**
Positive	102	8	**110**
Negative	22	129	**151**
Total	**124**	**137**	**261**

When reviewing the case report forms after the envelopes were opened, it was found that the nurses had noted that they had been unsure how to interpret the VS-SENSE™ test results in 25 patients (7.0%). According to the protocol, any colour change of uncertain significance should have been considered positive. However, in these 25 cases, swabs with minimal colour change were reported by the nurses as negative. The instructions for use in the study contained illustrations discovered to be misleading as, contrary to the written instructions, they gave the impression that the whole tip had to change colour.

A second analysis excluding the 25 cases where the nurses were unsure how to interpret the result was performed. The result of the analysis is shown in Table 4. The sensitivity and specificity were then 91.8% (95% CI 85.0-96.2) and 92.9% (95% CI 86.9-96.7), respectively. The accuracy was over 90%.

Table 4: VS-SENSE™ diagnosis made by the nurses compared with the diagnosis made by the investigator based on a diagnostic workup (excluding 25 cases where the nurse said they were not sure how to read the result) n= 236, Study 1

	Gold Standard Clinical Diagnosis		
VS-SENSE	**Positive**	**Negative**	**Total**
Positive	101	9	**110**
Negative	9	117	**126**
Total	**110**	**126**	**236**

The secondary outcome measures were the 3 questions concerning ease of use and reading clarity as judged by the nurse who read the VS-SENSE™. These data confirmed that the nurses were unclear about how to interpret the results in some cases. For this reason the 25 cases where the nurses had noted that they were unsure were also excluded from the analysis of the secondary variables. To the question 'Is the comparison to the colour code clear?' 67.8% answered 'very' or 'more than very'. To the question 'Is the colour change of the indicator tip clear to distinguish?' 68.8% responded 'very' or 'more than very'. To the question is the swab comfortable to use 93.8% of nurses rated 'very' or 'more than very'. No adverse events were recorded.

In summary, using the full set of patients the sensitivity result did not reach the expected success rate of 90% but the specificity test met the 70% success rate. In the subpopulation where the nurses did not express doubts about interpreting the result, both sensitivity and specificity of VS-SENSE™ met the success criteria of 90% and 70%. Therefore the final conclusion was that while the diagnostic swab worked satisfactorily, the illustrations accompanying the test instructions needed to be revised.

INVESTIGATION COMPARING PATIENT AND CLINICIAN READING OF THE VS-SENSE™ SWAB

The second study looked at the degree of agreement between volunteers' interpretation of the VS-SENSE™ using the self-test swab and physician interpretations of the VS-SENSE™ using the professional test swab. The 2 tests use the same indicator. The illustrations provided for the second study were updated to show a swab tip with only a partial blue or green stain and the explanation that any partial stain on the yellow indicator tip must be considered a positive result.

The study was conducted in a single centre in Israel. Women with or without symptoms of vaginal infection were given one VS-SENSE™ self-test and 'instructions for use' covering the handling of the test swab and illustrations indicating how to interpret the results. The subject was asked to read the instructions, apply the test and record any colour change to blue or to green 10 seconds after using the test. They recorded their result on a form. The participants also filled out a questionnaire regarding the comfort of using VS-SENSE™ self-test and the clarity of the result. The completed

forms were placed in a sealed envelope with the subject's initials and study number. The subject then had a speculum vaginal examination performed by a physician with no knowledge of the patient's result. The physician used the professional version of the VS-SENSE™ swab to sample vaginal secretion and after 10 seconds again recorded the colour. The principal investigator, based upon his professional experience, then decided whether further examinations, testing, or treatments were required. Any further procedures were done after documenting the result of the swab test, and were for the purpose of providing the best service to the participant. A clinical diagnosis was recorded for all subjects.

The primary outcome measure of this study was the agreement between the volunteer reading and the physician reading. The secondary outcomes were measurements of comfort while using VS-SENSE™ self-test and reading the result. Agreement between volunteer and physician reading was reported as percentage agreement. The ease of use was measured using 3 questions and five-point response scales, see Table 1.

Fifty subjects participated. Their mean age was 31.5 and 76% had been born in Israel. 32 of the 50 had no medical education or training while 4 had some training and for 14 subjects the information is missing. The protocol was approved by the appropriate ethics committee and patients signed a consent form after being informed about the study. For most of the women (66%), the physician did not diagnose any vaginal infection, 8 (16%) women were diagnosed with BV with or without VVC and 3 (6%) with trichomoniasis. The clinical diagnoses are listed in Table 5. The overall agreement between the volunteer's reading and the physician's reading was high with 92% (46/50) agreement between readings as shown in Table 6.

Table 5: Clinical diagnosis, n=50, Study 2

Diagnosis	Frequency	Percent
BV	7	14.0
BV + VVC	1	2.0
VVC	2	4.0
Trichomoniasis	3	6.0
No Infection	33	66.0
Other	4	8.0

Table 6: VS-SENSE™ Patient result compared to physician result, Study 2

	VS-SENSE, Physician reading		
VS-SENSE patient reading	Yellow	Blue/green	Total
Yellow	31	1	32
Blue /green	3	15	18
Total	34	16	50

The secondary outcome measures concerned ease of use. To the question 'did you understand how to use the swab and where to take the sample from?' 98% (49/50) of the women responded that they did. To the question 'were the results clear to read?' 90% (45/50) agreed. Finally, 84% (42/50) felt that the product was comfortable to use. In this study only one volunteer made the

comment that she was unsure how to read the result and made an incorrect diagnosis. No adverse events were reported.

The study showed that with improved illustrations the VS-SENSE™ by self-administered swab is accurate compared to physicians' readings and that the volunteers found the swab easy to use.

DISCUSSION

When used according to the instructions VS-SENSE™ showed over 90% accuracy compared to the diagnostic workup, with a sensitivity of 91.8% and specificity of 92.9% in the subpopulation of women where the swab was correctly interpreted. The necessary exclusion of the data from 25 women in the first study underscored the importance of comprehensive package information. With adequate photographs of swab results, as provided in the second study, there was 92% agreement between patient and clinician readings for all patients.

The information and illustrations provided for patients and healthcare providers in the current package instructions for VS-SENSE™ have been further optimized and undergone parallel translation and readability testing in relevant languages.

Current diagnostic procedures for vaginal infection such as BV and VVC are time consuming and relatively expensive. The result is that practitioners do not always carry out all necessary tests leading, not infrequently, to misdiagnosis, even by the trained physician. The problem of misdiagnosis is compounded by the current state of patient information. Although women have the option to self-diagnose and self-treat, there is little information freely available to aid self-diagnosis. Many women falsely assume that vaginal symptoms are due to VVC. Ferris *et al.* found that only 33.7% OTC fungal self-treatments were appropriate[13]. In that particular study, the majority of women who thought they had VVC actually had BV. Heightened patient awareness that symptoms can also be due to BV or rarely, trichomoniasis, would therefore be welcome. Incorrect diagnosis, regardless by whom, and inappropriate treatment can have serious consequences, particularly when BV is present.

Finally, it must be acknowledged that these are symptoms for which many women feel uncomfortable seeking medical help and where accurate self-diagnosis and successful self-treatment would be welcomed by patients. In the context of rising expenses for publicly funded health systems, accuracy in self-diagnosis and treatment should be encouraged. Furthermore, accompanying information describing symptoms and their appropriate treatments, as now provided with the VS-SENSE™, are a prerequisite for successful self-treatment. As the vaginal swab only leads to the correct action being taken if the result is considered in the context of the patient's symptoms, this is an area where pharmacists are ideally placed to assist patients in their self-care endeavors.

In the presence of symptoms, the VS-SENSE™ diagnostic vaginal swab offers a simple and reliable test that can be used by health care providers or patients themselves and which has relevance for treatment decisions. This test facilitates diagnosis of BV and trichomoniasis and the exclusion of VVC by identifying changes in the pH and buffering capacity of vaginal secretions. It is a simple one-step test that does not require a colour scale for interpretation and provides an immediate reading.

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Acknowledgements: J.D. Sobel was the principle investigator of study 1 and D.G. Ferris was a co-investigator in study 1. Bayer Consumer Care AG thanks Rosemary Bischoff at ClinWrite for drafting and editing this paper.

Declaration: Paul Nyirjesy, MD has ongoing research funded by Curatek Pharmaceuticals. He serves as a consultant for Novadigm. Therapeutics, Viamet Pharmaceuticals, Symbiomix Therapeutics (Lifequal), and Cidara Therapeutics. Hadar Kessary Shoham PhD is employed by Common Sense. Adam Geva MD serves as a consultant to Common Sense.

Funding: Both studies were sponsored by Common Sense, Caesarea, Israel.

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