Journal of Clinical Microbiology, March 2010, p. 852-856, Vol. 48, No. 3
0095-1137/10/$12.00+0 doi:10.1128/JCM.01897-09

Comparison of Polyurethane Foam to Nylon Flocked Swabs for Collection of Secretions from the Anterior Nares in Performance of a Rapid Influenza Virus Antigen Test in a Pediatric Emergency Department ▽

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Received 24 September 2009/ Returned for modification 30 October 2009/ Accepted 26 December 2009

ABSTRACT

Rapid antigen testing of upper respiratory secretions collected with various swab types is often utilized for laboratory diagnoses of influenza virus infection. There are limited data on the effects of swab composition on test performance. This study compared the performance of the Quidel QuickVue Influenza A+B test on secretions from the anterior nares when a polyurethane foam swab was used for collection to that when a nylon flocked swab was used for collection. One hundred subjects who presented to a pediatric emergency department with symptoms suggestive of an influenza virus infection were recruited for the study. Foam and flocked swabs of the anterior nares were obtained from separate nares of each subject before a posterior nasopharyngeal swab was collected and placed into viral transport medium. The QuickVue test was performed directly on each swab type, and the results were compared to the results of reverse transcription-PCR (RT-PCR), direct fluorescent antibody (DFA) test, and viral culture performed on the transport medium. RT-PCR alone and DFA combined with culture were utilized as separate gold standards. There were 56 cases of influenza detected by RT-PCR; the QuickVue test was positive for 40 foam and 30 flocked swabs, for sensitivities of 71% and 54%, respectively (P = 0.01). Similarly, there were 49 influenza cases detected by DFA and/or culture; the QuickVue test was positive for 38 foam and 30 flocked swabs, for sensitivities of 78% and

61%, respectively (P = 0.13). This study suggests that polyurethane foam swabs perform better than nylon flocked swabs for the collection of secretions from anterior nares in the Quidel QuickVue Influenza A+B test.

INTRODUCTION

Influenza is a seasonal respiratory illness that imposes various degrees of morbidity and mortality. The greatest disease burden falls on the oldest and the youngest individuals. During peak influenza season, rates of infection of healthy school-aged children may range from 10 to 40% (**4**). Children infected with influenza are at an increased risk of hospitalization, with a higher number of hospitalizations for younger children or children with chronic disease (**18**, **19**).

The characteristic signs of influenza—fever, cough, headache, fatigue, myalgia, congestion, rhinorrhea, and/or sore throat—result in a large number of hospital emergency department (ED) and outpatient visits (**22**). The accurate and timely diagnosis of influenza can help to control the spread of influenza through contact and droplet precautions. This is particularly important for children and immunocompromised individuals, who are known to shed the virus for longer periods of time (**4**). Rapid diagnosis also aids clinical management by differentiating influenza from other viral illnesses and allows the option of timely antiviral therapy for maximum effectiveness (**20**, **25**). Previous research has also shown that a diagnosis of influenza not only decreases antibiotic use but also decreases testing and the length of stay in the ED (**1**, **6**, **7**).

Rapid antigen testing for influenza is widely available and frequently utilized. Because of previously reported data indicating that such rapid tests are significantly less sensitive than viral culture and other methods for laboratory diagnosis, such rapid tests are best used as stand-alone tests when applied to the diagnosis of influenza in mildly ill outpatients without underlying disease (**23**-**26**). Posterior nasopharyngeal (NP) swab collections have been shown to be superior to swabs of the anterior nares (AN) for sample collection in such antigen tests (**3**); however, NP swab samples are uncomfortable and more difficult to collect. Swabs of anterior nares are better tolerated and easier and quicker to collect, and some influenza rapid antigen tests are FDA cleared for this specimen type (**16**, **17**, **21**). In addition, the amount of infectious virus and virus-infected cells is reported to be greater in children, and thus, rapid antigen tests for influenza virus and other viruses generally perform better for children.

There have been several recently published studies that demonstrate the ability of flocked, nylon fiber swabs to collect significantly more respiratory epithelial cells from the posterior nasopharynx than swab types of other compositions (**11**). This may be a potential advantage for any laboratory test that utilizes such specimen types for the detection of intracellular or cell-associated pathogens such as respiratory viruses. Moreover, nylon flocked swabs have been reported to collect and hold a greater volume of fluid than similarly sized polyester fiber or

polyurethane foam swabs and to more readily release the collected fluid into a testing matrix. However, it is unknown whether these features of flocked swabs offer an advantage over other swab types for the collection of material from the AN for the detection of influenza virus antigen. We hypothesized that nylon flocked swabs, because of the features described above, would perform better than traditional swabs in collecting respiratory secretions from the AN for the subsequent detection of influenza virus antigen. In this study, we tested this hypothesis by examining the relative performance of nylon flocked swabs compared to the performance of polyurethane foam swabs for the collection of AN specimens in the Quidel QuickVue A+B antigen test for the diagnosis of influenza virus infection in our pediatric ED population. The performance of the antigen test for the diagnosis of influenza was based on two gold standards: (i) reverse transcription-PCR (RT-PCR) alone and (ii) a combination of viral culture and direct fluorescent antibody (DFA) detection performed on a posterior NP swab placed into viral transport medium.

MATERIALS AND METHODS

Approval for the study was obtained from the Nationwide Children's Hospital Institutional Review Board. Written consent was obtained from the legal guardian, and written assent was obtained from any child 9 years of age or older. We recruited patients younger than 18 years old who presented to the ED with symptoms of influenza meeting enrollment criteria. These criteria included a fever of >100.4°F in the ED and/or a reported fever of >100.4°F in the last 48 h at home in conjunction with two or more of the following symptoms: chills/sweats, cough, dyspnea, fatigue, headache, myalgia, nasal congestion, rhinorrhea, and/or sore throat. Exclusion criteria included the administration of any antiviral agents in the previous 7 days. Candidates with qualifying symptoms had study procedures performed irrespective of physician order for a rapid influenza test. For the uniformity of the collection technique, specimens were collected by two prespecified research personnel: a nurse (E.S.) and a physician (K.A.S.). If the treating physician did not order a rapid influenza test, the test was still collected by the research nurse or physician, but the results were utilized only for study purposes and not for management. Subjects were enrolled during two separate influenza seasons: either from January 2007 through March 2007 or from January 2008 through February 2008. Fifty subjects were enrolled for each of the study periods.

The study was designed as a prospective cohort study with a head-to-head comparison of two types of swab devices used for AN collections. One swab device was a traditional polyurethane foam-tipped swab (catalog number 20171; manufactured by Puritan Medical Products, Guilford, ME, for Quidel Corporation, San Diego, CA) in a dry, hard-plastic transport tube. Quidel established the performance characteristics of the rapid influenza test using polyurethane swabs, and these are recommended for collection of secretions from AN. The Quidel test kit is packaged with polyurethane swabs in paper wrappers; the same swab type in a dry, hard-plastic tube suitable for transport and as used in this study is available as a separate item. The other swab

device was a flocked, nylon fiber-tipped swab (catalog number 552C; Copan Diagnostics, Murrieta, CA) in a dry plastic transport tube. Quidel makes no claims regarding the performance of nylon swabs in the rapid influenza test; thus, testing with these swabs is considered off-label use.

When the respiratory specimens were collected, the AN swabs were obtained first, with one swab placed into each naris. The swab was inserted just inside the opening of one naris, rotated for several seconds, removed, and placed directly into the swab collection sheath. The swabs were placed directly into separate transport tubes rather than into viral transport medium. Following the collection of the two AN specimens, a single posterior NP swab was then collected by using a Dacron polyester minitipped aluminum shaft swab (catalog number 25-800D; Puritan Medical). The Dacron swab was inserted into one naris and extended past the turbinates until resistance was met at the level of the posterior nasopharynx. The swab was rotated for several seconds and then removed with further rotation. The swab tip was then cut off and immediately placed into 2 ml of M4 viral transport medium (catalog number 12520; Remel, Lenexa, KS). The AN swabs in the transport tubes and the NP swab in a vial of M4 medium were immediately transported to the clinical virology laboratory to arrive within 30 min for testing.

The Quidel QuickVue Influenza A+B test (catalog number 20183) is an FDA-cleared test for the detection and differentiation of nucleoprotein antigens of the influenza A or B virus. It was performed directly on the AN swab samples according to instructions provided on the package insert. Testing requires 10 to 15 min to complete, with no more than 5 min of hands-on time.

For DFA testing, up to 1.0 ml of the remaining M4 sample was washed with 10 ml of phosphate-buffered saline (PBS) in a 15-ml sterile centrifuge tube and centrifuged, and the cells were resuspended in 1.5 ml of PBS. Double-well cytospin slides were prepared by using 200 μl of the cell suspension per well, fixed with acetone, and stained. One well was stained with SimulFluor respiratory screening reagent (catalog number 3296; Millipore/Chemicon, Temecula, CA), and the other well was stained with Flu A/B direct FA reagent (catalog number 3121; Millipore/Chemicon) according to the manufacturer's recommendations.

For the viral culture, 0.2 ml of the posterior NP swab specimen in M4 medium was inoculated into each of two R-Mix vials (catalog number 96-0102; Diagnostic Hybrids, Athena, OH) and incubated at 36°C according to the manufacturer's recommendations. One vial was stained approximately 42 h later with the SimulFluor respiratory screening reagent, and if positive, the companion vial was stained with SimulFluor Flu A/B direct FA reagent to differentiate between the two influenza virus types.

For RT-PCR, total nucleic acids were extracted from 0.2 ml of the NP swab specimen in M4 medium by use of an easyMag extractor (bioMerieux Inc., Durham, NC) and eluted into 55 μl. RT-PCR was performed by a method developed and validated in our laboratory and utilized the Prodesse (Waukesha, WI) Pro Flu-1 analyte-specific reagent (ASR) (catalog number HSM58). This reagent is no longer available and has been replaced by the Prodesse ProFlu Plus FDA-cleared assay (detection kit catalog number H44VK00 and control kit catalog number H44VK55). The laboratory-developed RT-PCR method was shown to be 100% sensitive for the detection of influenza A and B virus RNAs in clinical specimens that were positive by culture, DFA, or both. The RT-PCR method was also subsequently shown to be equivalent to RT-PCR using the ProFlu Plus FDA-cleared assay (our unpublished data). Amplification was performed by use of a 7500 sequence detection system (Applied Biosystems, Foster City, CA) using 5 μl eluate and 20 μl mastermix for a total reaction volume of 25 μl and the following amplification profile: 30 min at 42°C (1 cycle), 5 min at 95°C (1 cycle), and a cycle program consisting of 5 s at 95°C and 60 s at 55°C (40 cycles). Results of each run were determined by comparison of amplification curves with the positive- and negative-control curves and the cycle threshold.

Paired samples were analyzed with a marginal model for repeated binary outcomes (SAS PROC GENMOD) so that correlations between diagnoses of the same subject were taken into account. We used two separate gold standards against which the performances of rapid antigen testing of AN swabs were compared: the result of RT-PCR alone with a posterior NP swab sample (**26**, **28**, **31**) and the result of DFA and/or culture. A positive result by either DFA or culture was indicative of a patient with an influenza virus infection. Statistical significance was set at an α value of <0.05.

RESULTS

During the two study periods (2007 and 2008), a total of 100 subjects were enrolled, with 200 AN swabs and 100 NP swabs collected. When utilizing RT-PCR performed on secretions from the posterior NP as a gold standard, there were 56 confirmed cases of influenza: 37 cases of influenza A virus infection and 19 cases of influenza B virus infection. Forty of the 56 RT-PCR-confirmed cases of influenza were detected with the QuickVue test performed on secretions from the AN collected with polyurethane swabs, 30 cases of influenza A virus infection and 10 cases of influenza B virus infection, for an overall sensitivity of 71% (confidence interval [CI], 58 to 83%). In comparison, 30 of the 56 RT-PCR-confirmed cases of influenza were detected by the QuickVue test performed on secretions from the AN collected with flocked nylon swabs, 22 cases of influenza A virus infection and 8 cases of influenza B virus infection, resulting in an overall sensitivity of 54% (CI, 40 to 67%). The specificity was 98% for both swab types. Negative predictive values were 73% for foam swabs and 62% for flocked swabs. Positive predictive values were 98% for foam swabs and 97% for flocked swabs (Table **1**). When gauging overall accuracy, the odds of making a correct diagnosis was 0.55 times lower with the flocked swab than with the foam swab ($P = 0.01$).

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TABLE 1. Performance of the QuickVue Influenza A+B test compared to that of RT-PCR for specimens from the anterior nares collected with foam swabs versus flocked swabs[a]

Data analysis by influenza virus type showed that 30 of 37 cases of influenza A virus infection were detected by the QuickVue test performed on foam swabs (sensitivity, 81%), whereas only 22 of the 37 cases of influenza A virus infection confirmed by RT-PCR were detected by the QuickVue test performed on flocked swabs (sensitivity, 59%). Similarly, 10 of the 19 RT-PCR-confirmed cases of influenza B virus infection were detected when the QuickVue test was performed on foam swabs (sensitivity, 53%), whereas only 8 of 19 RT-PCR-confirmed cases of influenza B virus infection were detected by the QuickVue test performed on flocked swabs (sensitivity, 42%).

When DFA and culture were performed on secretions from the posterior NP and this was used as the gold standard, there were 49 cases of influenza: 34 cases of influenza A virus infection and 15 cases of influenza B virus infection. Thirty-eight of the 49 cases of influenza were detected with the QuickVue test performed on AN foam swabs, 29 cases of influenza A virus infection and 9 cases of influenza B virus infection, for an overall sensitivity of 78% (CI, 63 to 88%). In comparison, 30 of the 49 cases of influenza based on DFA and culture results were detected by the QuickVue test performed on flocked AN swabs, 22 cases of influenza A virus infection and 8 cases of influenza B virus infection, resulting in an overall sensitivity of 61% (CI, 46 to 75%). Overall, the specificities of the QuickVue test based on DFA and/or culture were 93% for testing with foam swabs and 98% for testing with flocked swabs. Negative predictive values were 81% for foam swabs and 72% for flocked swabs. Positive predictive values were 93% for foam swabs and 97% for flocked swabs (Table **2**). There was a trend toward a lower accuracy—odds of correct diagnosis—when flocked swabs were used, but this trend did not reach statistical significance ($P = 0.13$).

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TABLE 2. Performance of the QuickVue Influenza A+B test compared to those of DFA and culture of specimens from the anterior nares collected with foam swabs versus flocked swabs[a]

Data analysis by influenza virus type showed that 29 of the 34 cases of influenza A virus infection based on DFA and/or culture were detected when the QuickVue test was performed on foam swabs (sensitivity, 85%), whereas only 22 of the 34 cases of influenza A virus infection were detected by the QuickVue test performed on flocked swabs (sensitivity, 65%). Similarly, 9 of the 15 cases of influenza B virus infection based on DFA and/or culture results were positive with the QuickVue test performed on foam swabs (sensitivity, 60%), while only 8 of the 15 cases of influenza B virus infection were detected by the QuickVue test on flocked swabs (sensitivity, 53%).

DISCUSSION

Rapid antigen detection for influenza virus infection continues to have multiple clinical applications. Previous studies have shown not only that a positive laboratory test for influenza establishes a diagnosis but also that children diagnosed with influenza A virus infection have a lower prevalence of bacteremia, urinary tract infection, pneumonia, or serious bacterial infection (**27**). While carefully considering the possibility of false-positive testing, rapid antigen testing of young febrile infants during influenza season may also assist with medical decision making. Definitive diagnosis also leads to decreased testing, decreased antibiotic use, and shorter stays in the emergency department, all of which help to decrease medical costs (**1**, **6**, **7**).

This study compared the detection of influenza virus from secretions from the AN in a rapid antigen test when specimens were collected with polyurethane foam swabs to detection when specimens were collected with flocked nylon swabs. Utilizing RT-PCR positivity of NP specimens as a gold standard, we found a better performance with foam swabs than with flocked swabs. A similar trend was noted when DFA and/or culture positivity was used as our gold standard; however, this trend did not reach significance. These differences were robust when data were further analyzed by type of influenza but again failed to reach significance due to smaller sample sizes per influenza type. Rapid antigen testing is known to have a lower sensitivity for influenza B virus than for influenza A virus, and this trend was also present in our study regardless of the swab type and gold standard used (**3**, **30**).

These results are somewhat similar to the performance data for the Quidel test on AN swabs versus culture, as reported by two studies noted in the package insert of the product. For the two studies, the test sensitivities were reported to be 94% and 72% for influenza type A virus and 70% and 73% for influenza B virus. This compares to the sensitivities of 85% for influenza A virus and 60% for influenza B virus using foam swabs in our study. Only data from one study cited in the package insert were stratified by age group, and very few subjects <18 years old were enrolled. Thus, it is difficult to make comparisons between our data and data provided in the package insert. The relatively low Quidel test sensitivity for the detection of influenza B virus compared to the sensitivities of viral culture and RT-PCR as shown in this study was reported previously by others (**3**, **30**). The more recent use of RT-PCR as a gold standard for comparison to the Quidel test and other antigen detection methods suggests that traditional tests for influenza have greater limitations in terms of sensitivity than previously appreciated.

We hypothesized that flocked swabs would yield a greater test sensitivity in a rapid influenza antigen test because of a larger surface area, a higher absorbency, and an ability to release captured material (**10**). Consequently, the higher test sensitivity with foam swabs of secretions from the AN was contrary to our expectation. These results also differ from those from recent studies that evaluated the utility of flocked swabs for the detection of respiratory viruses from secretions from the AN by tests other than the rapid antigen test. Walsh et al. demonstrated a better performance of flocked swabs in RT-PCR tests when respiratory viruses were evaluated, including influenza virus isolated from nasal secretions of children (**29**). Abu-Diab et al. reported

100% sensitivity and specificity for the detection of influenza A virus from secretions from AN collected by flocked swabs and tested by DFA (**2**). Our study differs from those studies in that we analyzed the performance of a rapid antigen test for influenza on specimens from the AN.

An ideal laboratory test for diagnosing influenza virus infection in the ED would combine ease of collection and tolerability with accuracy and timeliness for decision making. Based on these criteria, RT-PCR, DFA, and culture, often performed with secretions from the posterior NP, are not ideal for use in the ED because test complexity requires that these assays be performed in the main laboratory, and the turnaround time is often extended. In contrast, rapid antigen testing performed at the point of care or in the main laboratory on specimens obtained from the AN is a more timely option for clinicians and more comfortable for patients. An enhanced diagnostic yield may be possible if swab types that capture a higher load of virus-infected cells are utilized. Unfortunately, despite theoretical advantages based on swab composition and prior studies that demonstrated improved performance when secretions from the AN were tested with RT-PCR, DFA, and culture, our study shows that flocked swabs do not perform better than polyurethane foam swabs for Quidel QuickVue rapid influenza antigen testing of secretions obtained from the AN of children.

The reasons for our present results are unclear. One of the differences between previous studies and ours is that in our study, swabs were placed into dry transport tubes rather than into viral transport medium, and antigen tests were done directly on the transported swabs. The package insert for the Quidel test states that swabs may be stored refrigerated or at room temperature in a clean, dry, closed container for up to 8 h prior to testing. However, this alone does not adequately explain the observed differences because this factor affected both swab types equally. It is possible that secretions were lost from the flocked swabs during transport in the dry tubes, although we saw no evidence of this. Future studies are needed to explain these differences.

One limitation of this study is the modest number of subjects. However, a paired sample design and the number of influenza cases balanced many confounders and resulted in a well-powered study for the detection of performance differences between the two swab types. It should also be pointed out that the prevalence of influenza was very high during the times when subjects were enrolled in this study (49% and 56% based on culture and RT-PCR, respectively). Thus, predictive value data should be viewed in the context of such high prevalences (**15**).

In summary, these data support the use of polyurethane foam swabs over flocked nylon swabs for the collection of specimens from the AN of children for the Quidel QuickVue A+B rapid influenza antigen test. Physicians should remain aware of the probable lower sensitivity of influenza virus rapid antigen tests with AN swabs than with of posterior NP samples, either NP swabs, washes, or aspirates, and also than with more sensitive diagnostic tests like RT-PCR, culture, and DFA (**9**). Such antigen testing is probably best relegated to managing only mildly ill outpatients without underlying risk factors, while more sensitive testing methods are recommended for more seriously ill inpatients at risk for severe complications of influenza. Our findings and recommendations should be considered in light of emerging influenza A virus subtypes, including 2009 H1N1 influenza virus, and the previously reported performance data for the detection of these agents by rapid tests (**8**, **12**, **14**). Furthermore, physicians should be aware of the inability of such rapid tests to distinguish among influenza A virus subtypes in light of known differential activities of antiviral agents against various subtypes (**5**, **13**).

ACKNOWLEDGMENTS

We thank the technologists in the Viral Diagnostic Laboratory, Nationwide Children's Hospital, for their assistance in performing the study.

This work was partially supported by Quidel Corporation, San Diego, CA, and Puritan Medical Company, Guilford, ME.

FOOTNOTES

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▽Published ahead of print on 6 January 2006.

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Journal of Clinical Microbiology, March 2010, p. 852-856, Vol. 48, No. 3
0095-1137/10/$12.00+0 doi:10.1128/JCM.01897-09