# Home Self-Collection of Nasal Swabs for Diagnosis of Acute Respiratory Virus Infections in Children With Cystic Fibrosis

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**Background.** Understanding the importance of respiratory viruses in children with cystic fibrosis (CF) has been limited because of challenges using clinic- or hospital-based diagnostic testing. We conducted a pilot study to assess feasibility of home self- (or parent-) collection of nasal swabs (NS).

**Methods.** Cystic fibrosis patients aged 6–18 years with new respiratory illness participated. In clinic, a deep nasal flocked swab was collected by research staff and compared with an anterior foam NS obtained after instillation of saline spray. At home, up to 2 self-collections of paired foam NS (with and without saline) were collected and mailed for real-time polymerase chain reaction (PCR) testing.

**Results.** Paired swabs were collected from 28 patients: 18 sets in clinic (deep nasal vs saline foam NS) and 43 sets at home (saline vs dry foam NS) with 9 (50%) and 35 (81%) virus detections, respectively. Home-collected NS were obtained closer to illness onset, with a mean difference in symptom days of –2.3 between home and clinic collections (95% confidence interval [CI] –3.5, –1.2; $P < .001$). Rhinovirus comprised 73% of virus detections; the difference in mean PCR cycle threshold values for rhinovirus between swabs collected at home versus clinic was –3.8 (95% CI –6.8, –0.9; $P = .014$), indicating significantly higher viral load for home-collected swabs.

**Conclusions.** Home-collected foam NS had a higher positivity rate compared with clinic-collected swabs, likely because collection was closer to illness onset. Home self-collection is feasible and well tolerated for timely respiratory virus diagnosis and provides a novel approach for clinical diagnostics and surveillance of respiratory virus infections among CF patients.

There is a growing body of evidence that respiratory virus infections play an important role in pulmonary morbidity and exacerbations in children with cystic fibrosis (CF) [1–14]. Previous studies using clinic- or hospital-based testing have likely underestimated the true impact of respiratory viruses on CF pulmonary exacerbations due to delays in sample collection relative to onset of symptoms and the lack of sensitive molecular testing methods. Investigations to further elucidate the impact of respiratory virus infections in CF will require timely diagnoses using molecular methods.

Nasal washes or invasive nasopharyngeal swabs collected by medical personnel have historically been considered "gold standard" samples for respiratory virus detection. In children, nasal swabs (NS) have been shown to have reasonable performance for polymerase chain reaction (PCR) detection of most respiratory viruses [15–18]. Community-based studies have used parent- or self-collected swabs for respiratory virus research [19–24]. Although previous studies using self-collection have involved transport medium

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and storage at 4°C, we have recently developed a simple, sensitive, and noninvasive method for self-collection of respiratory samples using foam swabs that does not require transport media or refrigeration [25]. Furthermore, we found that swabs collected with the use of saline spray were superior to swabs collected without the use of saline spray [25]. In the current study, we investigated the feasibility of home self-collection of NS in children with CF experiencing onset of new respiratory illness, with samples mailed to a central laboratory for respiratory virus detection by real-time PCR. Although the main objective was to assess feasibility, we also sought to study whether NS collected at home would compare favorably to swabs collected in clinic for detection of respiratory viruses, and whether foam NS collected with the use of saline spray would perform comparably to swabs collected without saline.

## METHODS

### Human Subjects

The study protocol was approved by the Seattle Children's Institutional Review Board. Children ages 6–18 years with a diagnosis of CF were eligible to enroll if they met the following criteria: (1) attended at least 2 CF clinic visits during the previous 12 months; (2) currently experiencing a new respiratory illness or willing to return for a clinic visit or collect home samples when experiencing a new respiratory illness; (3) willing to perform self-collection of NS (collected by the child or parent); and (4) written informed consent provided. Children were excluded if they had received antiviral medications during the 30 days before enrollment or if they were awaiting or had previously received a lung transplant. The period of study enrollment was February 2009 to January 2010, with up to 15 months of follow-up per patient.

### Sample Collection and Symptom Surveys

If respiratory illness with onset of symptoms in the previous 7 days was present at a clinic visit, subjects were first asked to blow their nose to remove mucus that might inhibit PCR, and paired swabs were obtained as follows: a deep nasal (mid-turbinate) sample was collected by research staff, by first measuring from the opening of one naris to the nasal bridge, and then inserting a standard flexible nasopharyngeal flocked nylon swab (Copan Diagnostics Inc, Murrieta, CA; catalog No. 503CS01) until mild resistance was encountered, approximately one-half to two-thirds the length of the nose. This approach to using nasopharyngeal swabs to collect deep nasal samples was previously found to be well accepted by participants in a study of respiratory viruses in CF patients at our hospital [2]. Next, a polyurethane foam NS (Super Brush, LLC, Chicopee, MA; catalog No. 71-4541) was collected in the opposite naris after instillation of saline nasal spray. Nasal spray was used to closely replicate a standard nasal wash. In brief, 5 sprays of saline from a polyethylene metered bottle (0.1 mL/spray) were instilled into the naris, followed by NS insertion into the anterior naris as far as comfortably possible, and rotation of the swab while exhaling through the nose for 5–7 seconds. During the clinic visit, the research nurse instructed the patient regarding self-collection of foam NS, and either the patient or parent collected the swab while observed and directed by the research nurse, or the swab was collected by the research nurse as an opportunity to demonstrate the proper technique for collection to the patient and parent. Detailed written instructions regarding self-collection were reviewed at the clinic visit and were provided to the family for reference when swab collection at home was indicated (see Supplementary Material). Also provided were kits containing all supplies necessary for collection and mailing of foam NS to be obtained at home at onset of symptoms of a new respiratory illness. Subsequent collections at home consisted of foam NS collected either by the participant or parent with ("saline") and without ("dry") the use of nasal saline spray to evaluate whether the spray was essential to the procedure, as previously described [25]. Dry swabs were collected by inserting a foam swab into the anterior naris as far as comfortably possible, followed by slow rotation of the swab for 5–7 seconds while exhaling through the nose. For home collections, participants were asked to collect the dry swab before the saline swab.

During initial development and optimization of the self-collection procedure, we previously evaluated virus stability over time from foam NS (for influenza A and parainfluenza virus type 3), and we found no difference in viral recovery between room temperature and 4°C, transport medium, and dry tubes, at 1, 2, or 7 days [25]. Thus, for this study each foam swab was placed into an empty dry transport tube (no transport media added) and stored at room temperature. Home-collected NS were mailed to the University of Washington Molecular Virology Laboratory using US Postal Service Pre-paid Priority Mailers with appropriate packaging and labeling for Category B Infectious Substances. Deep NS collected in clinic were placed into lysis buffer and stored at 4°C until laboratory testing.

Study participants received phone or e-mail reminders every 1–2 weeks to collect samples at home at onset of new respiratory illness; home sample collection was allowed during up to 2 illnesses per participant. Each participant (or parent) completed a standardized symptom survey in conjunction with each sample collection. Criteria for a new respiratory illness included (1) presence of at least 1 of the

15 symptoms listed on the standardized symptom survey and (2) symptom duration of a minimum of 24 hours and $\leq 7$ days. Questionnaires related to tolerability of self-collection were also completed. Participants were instructed to mail home swabs and surveys within 1 day of collection.

### Polymerase Chain Reaction Testing

Swabs were processed in the laboratory as soon as possible after receipt. Specimens were tested for qualitative detection by a panel of 8 single or multiplexed real time reverse-transcription (RT)–PCR (for respiratory syncytial virus, influenza virus types A and B, parainfluenza virus types 1–4, human metapneumovirus, human coronaviruses [subtypes OC43, 229E, NL63, and HKU1] and rhinoviruses) and PCR (for adenovirus and bocavirus) using previously described methods [25–31]. Samples were considered positive if the PCR amplification plot crossed the threshold at less than 40 cycles (cycle threshold [$C_T$] <40). All PCR methods were performed according to College of American Pathologist standards, and the laboratory passed proficiency testing in viral diagnostics.

### Statistical Analysis

Data were summarized using counts and proportions and means and standard deviations (SD). Linear regression analyses were used to compare differences in time from collection to laboratory processing, symptom duration, and number of symptoms between swab collections performed at home versus in clinic. A similar method was used to compare differences in RT-PCR $C_T$ values between swabs positive for rhinovirus alone that were collected at the same time and between swabs collected at home versus in clinic. Too few swabs were positive for other virus types to perform statistical analyses. Regression analyses included clustering on participant to account for repeated observations per participant, and 95% confidence interval (CI) estimates were calculated using robust variance estimates. All analyses were performed using STATA version 10.1 (StataCorp, College Station, TX).

## RESULTS

### Sample Collection

A total of 35 children were enrolled, 28 of whom provided paired swab sets collected in clinic or at home during a new respiratory illness. Baseline characteristics were similar between the total study population and those who had samples collected (Table 1). Paired swabs were collected during new respiratory illnesses as follows: 18 sets (deep nasal vs foam NS with saline) collected at clinic visits and 43 sets (foam NS with and without saline) collected at home (7 participants with a single home collection and 18 with 2 home collections). Study samples thus included a total of 61 swab sets collected during new respiratory illnesses, representing a total of 122 swabs available for PCR testing. For the 43 home collections, 27 (63%) swab sets were collected by the parent, 14 (33%) by the participant, and 2 by another adult individual. The mean age of participants who performed self-collection was older than that of participants who had samples collected by someone else (15.7 vs 10.3 years, respectively).

### Respiratory Virus Detections and Symptoms

Viral PCR results are presented for paired swab sets collected in clinic and at home (Table 2). Among the 122 swabs tested, 81 (66.4%) had 1 or more viruses detected, and 41 (33.6%) were negative for all viruses tested. The most prevalent finding was rhinovirus, which was detected in 59 swabs (48.4%). For swabs collected in clinic, overall percent agreement was observed for 13 of 18 pairs (72.2%), including 4 pairs with both swabs positive for the same virus and 9 pairs with both swabs negative. For NS collected at home, overall percent agreement was observed for 39 of 43 pairs (90.7%), including 31 pairs with both swabs

**Table 1.** Baseline Characteristics of the Study Population

| | | All Enrolled (N = 35) n (%) | Samples Collected (N = 28) n (%) |
|---|---|---|---|
| Sex | Male | 16 (45.7) | 12 (42.9) |
| | Female | 19 (54.3) | 16 (57.1) |
| Race/ethnicity | Caucasian (not Hispanic) | 34 (97.1) | 28 (100) |
| | Hispanic | 1 (2.9) | – |
| Genotype | Homozygous dF508 | 23 (65.7) | 18 (64.3) |
| | Heterozygous dF508 | 11 (31.4) | 9 (32.1) |
| | Other | 1 (2.9) | 1 (3.6) |
| Pancreatic status | Sufficient | 3 (8.6) | 3 (10.7) |
| | Insufficient | 32 (91.4) | 25 (89.3) |
| | | Mean (SD) | Mean (SD) |
| Age enrolled (years)[a] | | 11.7 (4.0) | 11.3 (3.8) |
| Sweat chloride (mEq/L)[b] | | 109.4 (19.2) | 112 (19.2) |

Abbreviation: SD, standard deviation.

[a]Age at enrollment ranged from 6.5 to 18.2 years among all enrolled participants and among the 28 participants with samples collected.

[b]Sweat chloride was not required if there were 2 identifiable mutations consistent with cystic fibrosis. Sweat chloride values were available for 25 enrollees, including 20 participants with samples collected.

**Table 2.** Viral Polymerase Chain Reaction Results for Respiratory Swab Pairs Collected in Clinic and At Home

| | Clinic Visits[a] | | Home Collections[b] | | Total |
|---|---|---|---|---|---|
| | Deep nasal flocked swab (n = 18) | Saline foam swab (n = 18) | Dry foam swab (n = 43 ) | Saline foam swab (n = 43) | All swab types (n = 122) |
| No viruses detected | 10 (55.6) | 13 (72.2) | 8 (18.6) | 10 (23.3) | 41 (33.6) |
| Any virus detected | 8 (44.4) | 5 (27.8) | 35 (81.4) | 33 (76.7) | 81 (66.4) |
| Rhinovirus | 6 (33.3) | 4 (22.2) | 25 (58.1) | 24 (55.8) | 59 (48.4) |
| Coronavirus | | | 3 (7.0) | 3 (7.0) | 6 (4.9) |
| Rhinovirus and coronavirus | | | 3 (7.0) | 2 (4.7) | 5 (4.1) |
| Respiratory syncytial virus | | | 2 (4.7) | 2 (4.7) | 4 (3.3) |
| Parainfluenza type 3 | 1 (5.6) | 1 (5.6) | | | 2 (1.6) |
| Parainfluenza type 4 | | | 1 (2.3) | 1 (2.3) | 2 (1.6) |
| Influenza A (2009 H1N1) | 1 (5.6) | | | 1 (2.3) | 2 (1.6) |
| Influenza A (2009 H1N1) and adenovirus | | | 1 (2.3) | | 1 (0.8) |

[a]Among swab pairs collected in clinic, the following paired results were observed: 4 pairs with the same virus detected by deep nasal swab and saline foam swab, 9 pairs with both swabs negative, 4 pairs with deep nasal flocked swab positive (3 rhinovirus, 1 influenza A) and saline foam swab negative, and 1 pair with saline foam swab positive (rhinovirus) and deep nasal swab negative.

[b]Among swab pairs collected at home, the following paired results were observed: 31 pairs with the same virus detected by dry foam swab and saline foam swab, 8 pairs with both swabs negative, 2 pairs with dry foam swab positive (rhinovirus) and saline foam swab negative, and 2 pairs with dry foam swab detecting an additional virus not detected by saline foam swab (influenza A by both swabs and adenovirus by dry swab only; rhinovirus by both swabs and coronavirus by dry swab only).

positive for the same virus and 8 pairs with both swabs negative (2 swab pairs with a virus detected by dry swab alone, and 2 with an additional virus detected by dry swab but not by saline swab, were not counted as exact agreements).

Among the 59 samples positive for rhinovirus alone, the amount of virus did not differ between swab pairs collected at the same time: mean $C_T$ value (95% CI) was 31.0 (27.1, 35.0) and 30.9 (25.2, 36.7) for 6 clinic-collected deep NS and 4 saline NS, respectively, and 28.0 (25.5, 30.5) and 26.3 (25.4, 28.1) for 25 home-collected dry and 24 home-collected saline NS, respectively. The difference in mean PCR $C_T$ values was –3.8 comparing home versus clinic collections (95% CI –6.8, –0.9; $P = .014$), indicating that $C_T$ values were significantly lower on average (ie, more virus present) for swabs collected at home. Comparing only wet self-collected NS, the difference in mean $C_T$ values for 24 home versus 4 clinic collections was –4.6, 95% CI (–8.1, –1.1; $P = .013$), indicating higher viral load on average for swabs collected at home.

The time from collection to laboratory processing averaged 1.1 day (SD = 0.9) for swab sets collected in clinic, 5.4 days (SD = 3.6) for the first home collection, and 6.4 days (SD = 4.0) for the second home collection. There was no association between longer time from collection to laboratory processing and likelihood of negative results by viral PCR.

Symptom surveys were summarized according to timing of sample collection (Table 3). The most common symptoms reported at clinic collections were increased nasal congestion, increased cough, and increased sputum production; increased nasal congestion, sore throat, and increased cough were the most common symptoms reported at home collections. The mean difference in number of symptoms was 1.1 comparing home versus clinic collections (95% CI –0.1, 2.4; $P = .08$), but this result was not statistically significant. The mean difference in days with increased symptoms was –2.3 comparing home versus clinic collections (95% CI –3.5, –1.2; $P < .001$), indicating significantly shorter duration of symptoms at the time of collection for swabs collected at home.

**Feasibility and Safety**

Tolerability surveys were completed by all 28 participants on 59 occasions (16 clinic visits and 43 home collections) and indicated that self-collection of anterior nasal foam swabs was acceptable and not difficult for participants. Questions were answered using a 5-point response scale (strongly agree, agree, neither, disagree, or strongly disagree). Using results from the first tolerability survey completed by each participant, we found that participants regarded that collection of anterior nasal foam swabs was comfortable (71% agree or strongly agree responses, 11% neither agree nor disagree, and 18% disagree responses). Among the 18% (5 subjects) who disagreed that the procedure was comfortable, specific comments included that the swab was "large and uncomfortable" and that self-collection was "hard to do" when not feeling well. Subjects thought that self-collection was simple (96% agree or strongly agree responses) and that instructions were clear and easy to follow. The majority of participants indicated willingness to participate in future studies using the self-collection procedure (85% agree or strongly agree responses). Restricting to responses obtained at the 16 clinic visits, participants indicated that the procedure for collection of anterior nasal foam swabs was preferred over collection of the deep nasal flocked swab (94% agree or strongly agree responses).

Adverse events were minimal. One episode of mild and self-limited epistaxis occurred following a clinic swab

**Table 3.** Symptoms Reported at the Time of Swab Collections

| Symptom | Clinic Visits (18 surveys) n (%) | Home Collection #1 (25 surveys) n (%) | Home Collection #2 (18 surveys) n (%) |
|---|---|---|---|
| Fever | 1 (5.6) | 5 (20.0) | 5 (27.8) |
| Chills/rigors | – | 3 (12.0) | 3 (16.7) |
| Decreased appetite | 1 (5.6) | 4 (16.0) | 4 (22.2) |
| Muscle aches | 3 (16.7) | 2 (8.0) | 3 (16.7) |
| Headache | 1 (5.6) | 7 (28.0) | 10 (55.6) |
| Increased nasal congestion | 17 (94.4) | 24 (96.0) | 17 (94.4) |
| Sore throat | 3 (16.7) | 14 (56.0) | 11 (61.1) |
| Increased cough | 13 (72.2) | 13 (52.0) | 9 (50.0) |
| Increased sputum production | 9 (50.0) | 9 (36.0) | 7 (38.9) |
| Change in sputum appearance | 2 (11.1) | 4 (16.0) | 5 (27.8) |
| Wheezing | 1 (5.6) | 1 (4.0) | 5 (27.8) |
| Shortness of breath | 1 (5.6) | 2 (8.0) | 2 (11.1) |
| Increased chest congestion | 4 (22.2) | 4 (16.0) | 4 (22.2) |
| Chest pain | 2 (11.1) | 0 (0.0) | 0 (0.0) |
| Increased fatigue | 2 (11.1) | 7 (28.0) | 7 (38.9) |
| | Mean (SD) | Mean (SD) | Mean (SD) |
| Total No. of symptoms reported | 3.3 (2.0) | 4.0 (1.8) | 5.1 (2.6) |
| No. of days with new or increased symptoms | 5.3 (2.5) | 2.4 (1.9) | 3.9 (2.9) |

Abbreviation: SD, standard deviation.

collection. In 5 home collections, 3 participants reported cough, 1 reported sneezing, and 1 subject reported "blood smear on sample."

## DISCUSSION

In this pilot study, we demonstrated that self- and parent-collection of foam NS at home and mailing to the laboratory for respiratory virus diagnosis was feasible for patients with CF. This method of home collection was simple, comfortable, and safe, and mailing time did not affect the likelihood of virus detection. Swabs collected at home yielded a higher proportion of positive virus detections compared with swabs collected in clinic (81% vs 47%), likely explained by our finding that home-collected NS were collected significantly closer to the onset of illness. Similarly, rates of virus positivity in the home-collected NS were higher when compared with other recent clinic- or hospital-based studies of respiratory virus surveillance using PCR in CF patients with respiratory symptoms or pulmonary exacerbations, with reported detection rates of 50%–60% [8, 12–14]. Likewise, we found that among PCR-positive swabs for rhinovirus, the amount of virus in swabs collected at home was significantly greater than for swabs collected in clinic.

In this study among children with CF, the self-collection method was feasible using foam swabs collected with saline or dry swabs with comparable rates of viral detection. A recent manuscript showed that self-collected foam NS following the use of nasal saline spray had increased sensitivity over dry swabs for detection of respiratory viruses [25]. These results were in a mostly adult population, whereas the mean age in the current study was 11.7 years. It is likely that children shed high quantities of respiratory virus, and larger studies are needed to evaluate whether the use of saline spray is essential to the self-collection procedure in children.

There are few other studies that have used self-sampling and mailing to study respiratory viral pathogens, although use of self-collected swabs mailed via the postal service in the United Kingdom has been reported to be a feasible method of enhancing community-based syndromic surveillance for influenza [20, 32]. In these studies, viral transport medium was required for shipping, and there were no significant differences in mean times from swabbing to laboratory analysis between positive and negative samples. Our approach allows for samples to be mailed in dry tubes, simplifying the procedure and eliminating the risk of spilling the transport diluent, as previously reported [32].

Because of the small sample size of our study and limited diversity of virus types identified, we are unable to make conclusions regarding the sensitivity of the various swab methods used for collection, especially for viruses other than rhinovirus. The high proportion of swabs positive for rhinovirus may simply reflect the high frequency of rhinoviruses detected in nonmedically attended acute respiratory illness. However, it is important to note that the home-collected swabs did detect a variety of important respiratory viruses, in addition to rhinovirus. Although it is has been documented that children with CF shed respiratory viruses even in the absence of symptoms [2, 8, 14], the increased detection of viruses in home-collected samples in the setting of new respiratory illness suggests that this method is useful to detect incident viral infections.

Because the majority of the virus detections were rhinovirus, and because the more than 100 rhinovirus serotypes

do not amplify with the same efficiency using our RT-PCR assay, quantitative RT-PCR testing was not performed. Using RT-PCR $C_T$ values as a semiquantitative evaluation of viral load for rhinoviruses detected, we found a difference in viral load between swabs collected in clinic versus home. The nearly 3.8 $C_T$ difference between mean $C_T$ values likely represents at least a 10-fold greater viral load in home-collected compared with clinic-collected swabs.

In summary, these results provide a unique method for larger studies of respiratory virus shedding and transmission among children with CF. Studies involving home self-collection of respiratory samples will provide more accurate data on the incidence of respiratory virus infections among children with CF and will help to elucidate the role of viral infections in chronic bacterial colonization and pulmonary function decline in CF lung disease. Because CF patients are generally followed at quarterly clinic visits, home sample collection could provide critical interim data regarding respiratory virus infections that might otherwise go undocumented. Home collection of samples could also prove useful for clinical management of patients with CF, providing more prompt recognition of these infections and potentially decreasing unnecessary or prolonged antibiotic use. Thus, we recommend this approach for future studies of respiratory illness and pulmonary exacerbations in patients with CF.

## Supplementary Data

Supplementary materials are available at the *Journal of the Pediatric Infectious Diseases Society* online (http://jpids.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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