JOURNAL OF CLINICAL MICROBIOLOGY, Sept. 1993, p. 2286–2290
0095-1137/93/092286-05$02.00/0

Vol. 31, No. 9

Comparison of Rapid Diagnostic Techniques for Respiratory Syncytial and Influenza A Virus Respiratory Infections in Young Children

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Received 26 February 1993/Returned for modification 27 April 1993/Accepted 3 June 1993

We performed virus isolation tests for respiratory viruses on combined nasal wash-throat swab specimens collected from infants and children with acute respiratory illnesses presenting to a hospital clinic during a 3-month period of concurrent epidemics of respiratory syncytial virus (RSV) and influenza A virus (Flu A) infections. Virus isolation results were used to assess the utility of commercially available rapid diagnostic kits for these two viruses. The kits employed direct immunofluorescence (IF) of cells (Imagen for RSV and Flu A), indirect IF of cells (Baxter Bartels Microscan), and enzyme immunoassay (EIA) (Becton Dickinson Directigen for RSV and Flu A and Abbott TestPack for RSV). All testing was completed on 81 specimens from 80 subjects. Of the 81 specimens, 53 (65%) yielded a virus: RSV, 28%; Flu A, 25%; rhinovirus, 6%; and enterovirus, cytomegalovirus, herpes simplex virus, and adenovirus, 2 to 4% each. Among the tests, Bartels Microscan and Directigen Flu-A exhibited the highest sensitivities (87 and 75%) and efficiencies (94 and 94%) for RSV and Flu A, respectively. All the tests exhibited high specificity. Thus, optimal detection of RSV and Flu A among infants and children who presented to a hospital clinic required two different detection methods (IF and enzyme immunoassay) and kits from two different companies (Baxter [Bartels Microscan] and Becton Dickinson [Directigen]).

Respiratory syncytial virus (RSV) and influenza A virus (Flu A) are major causes of acute respiratory disease in young children (4, 6, 7, 15). With the availability of effective antiviral agents for these infections, a prompt and specific diagnosis of one of these infections would enable a physician to institute appropriate therapy early in the illness (2, 5, 14, 17). Moreover, an early specific diagnosis would improve decisions regarding the use of antibacterial therapy and hospitalization of sick children.

A number of tests are currently available for the rapid diagnosis of RSV and Flu A infections (9, 10, 12, 13, 16, 18, 19). These tests employ a variety of immunochemical techniques, including direct and indirect immunofluorescence (IF) and enzyme immunoassay (EIA), to detect viral proteins. While there have been recent comparative studies of some of these test kits, no studies have systematically assessed their performance during concurrent epidemics of RSV and Flu A infections (1, 3, 11, 16, 18, 19). The clinical presentations of these infections may be quite similar, preventing a virologic diagnosis from clinical findings alone.

During the winter of 1991 to 1992, Houston, Texas, experienced simultaneous epidemics of RSV and Flu A infections. During this period, we compared several rapid diagnostic tests with virus culture for their abilities to detect these viruses in specimens from a population of young children. The study focused on evaluation in an ambulatory care setting, a feature not present in previous studies.

MATERIALS AND METHODS

Population. Subjects were enrolled from mid-November 1991 to mid-February 1992 through the Ben Taub General Hospital Pediatric Clinic, a clinic which provides primary care to mainly uninsured and underinsured residents of Harris County, Texas. Children were enrolled if they presented with an acute upper or lower respiratory tract illness. Some children were admitted to the hospital from the clinic during the evening; they were enrolled in the study the following day.

A total of 85 children (32 females and 53 males) with 86 episodes of illness were tested for virus. One female was enrolled twice, as she developed a second respiratory illness 2 months after the first. The subjects ranged in age from 1 month to 11 years, with a mean age of 21 months and a median of 7 months. Fifty-one (60%) of the subjects were hospitalized before or after specimens were obtained for tests.

Specimens. Nasal wash and throat swab specimens were obtained in 77 of the episodes, and nasal and throat swab specimens were obtained in the remaining 9. For the former type of specimen, both specimens from each subject were combined in a vial containing concentrated veal infusion broth with bovine albumin and supplemental antibiotics; the final volume was 5 to 6 ml. For the latter type, both specimens were combined in a vial containing 3 ml of veal infusion broth with 0.5% bovine albumin and antibiotics. The specimens were transported on ice to the laboratory, where they were sonicated for 45 to 60 s and separated into two aliquots. One aliquot was used for virus culture, and the other aliquot was centrifuged at 1,600 × *g* for 15 min at 4°C. The supernatant was reserved for EIA evaluations. (It should be noted that one manufacturer counsels against removal of cells from the specimen tested.) The pellet remaining after centrifugation was resuspended in 0.5 to 1.0 ml of veal infusion broth and processed for IF staining according to the manufacturers' directions.

Diagnostic kits. The following rapid diagnostic kits were

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TABLE 1. Viruses isolated from 81 episodes of acute respiratory illness in 80 young children

Age of child (mo)	No. of specimens	No. (%) positive for virus	No. of specimens yielding indicated virus[a]						
			RSV	Flu A	Rhinovirus	Enterovirus	Adenovirus	HSV	CMV
<6	40	27	15	8	4 (2)	0	1	(1)	1
6–24	19	12	4	6	0	2	(1)	0	0
≥24	22	14	4	6	2	0	0	2	(1)
Total	81	53 (65)	23	20	6	2	2	3	2

[a] HSV, herpes simplex virus; CMV, cytomegalovirus. Five specimens yielded two viruses: Flu A and adenovirus, Flu A and HSV, Flu A and CMV, and RSV and rhinovirus (two specimens). Specimens yielding two viruses were included in either the RSV or the Flu A column; parentheses indicate second viruses.

evaluated: Directigen for Flu A and RSV (Becton Dickinson, Cockeysville, Md.), Imagen for Flu A and RSV (Novo Nordisk, Cambridge, United Kingdom), Bartels Microscan for Flu A and RSV (Baxter Healthcare, West Sacramento, Calif.), and Abbott TestPack for RSV (Abbott Laboratories, North Chicago, Ill.). Both the Directigen and TestPack kits employ a solid-phase EIA for detection of viral proteins, while Imagen employs direct IF and Bartels Microscan employs indirect IF of respiratory cells for virus detection.

Following the initial processing, all specimens were evaluated according to the manufacturers' directions (please consult the directions that accompany each kit for details). Some specimens were stored at −20°C for up to 5 days until enough were available to perform EIA testing in batches of five or more. Slides for IF were fixed in acetone and then stored at −20°C so that they could be stained and read in batches. The slides were read independently by two of the investigators (E.D. and L.T.) with a Zeiss halogen-source fluorescence microscope; the investigators had no knowledge of results obtained in virus isolation tests or EIAs. Positive controls, provided by the manufacturers, were included with each series of tests.

Virus cultures. On the day they were obtained, all specimens were tested for virus in four different tissue cultures: human embryonic lung fibroblasts (WI-38), the HEp-2 line of human epidermal carcinoma cells, Madin-Darby canine kidney (MDCK) cells, and the LLC-MK2 line of rhesus monkey kidney cells (Whittaker, Walkersville, Md.). An inoculum of 0.4 ml per tissue culture tube was used. The cultures were then incubated at 33°C on roller drums and examined for cytopathic effects twice weekly for 2 weeks (WI-38 and MDCK) or 3 weeks (HEp-2 and LLC-MK2). Hemadsorption tests with a 0.25% guinea pig erythrocyte suspension were performed on days 4 or 5 and 9 or 10 for all LLC-MK2 and MDCK cultures to screen for Flu A.

Cultures exhibiting hemadsorption or cytopathic effects underwent further tests to identify specific viruses. RSV was identified in indirect IF tests of tissue culture cells, Flu A was identified in type-specific EIA tests, rhinoviruses and enteroviruses were identified by cytopathic effect and acid lability tests, herpes simplex virus and adenovirus were identified by direct IF, and cytomegalovirus was identified by characteristic cytopathic effects and growth only in WI-38 cultures.

Statistical analyses. Frequencies were compared by using the chi-square test or Fisher's exact test for small numbers.

RESULTS

Of the 86 specimens, 81 were evaluated by all virus detection methods. Two specimens lacked cells for IF testing; one of these yielded parainfluenza type 3 virus in cultures. Tissue cultures of three specimens were contaminated with bacteria so that two attempts at testing were unsuccessful; two of these specimens were positive for RSV by all four of the rapid diagnostic tests. Of the 81 completely tested specimens, 53 (65%) yielded a virus by the virus isolation tests and 51 were positive for Flu A or RSV by one or more of the rapid diagnostic tests.

Virus isolation. Table 1 lists the viruses isolated in tissue cultures from the 81 specimens. RSV or Flu A was detected in 81% of the positive cultures during the study period. The two viruses were detected at about the same rate during November and December of 1991, but only RSV was detected during January and February of 1992 (data not shown). Five dual infections were identified, three involving Flu A and two involving RSV (Table 1).

The distribution of isolations, arranged according to the age of the child, is also shown in Table 1. A similar frequency of specimens was positive in each age group, although RSV was somewhat more common among children less than 6 months of age.

Rapid diagnosis. Data regarding the detection of RSV and Flu A by the various diagnostic tests, with results arranged by age of the child, are shown in Table 2. All but two virus isolation-positive specimens were positive by at least one rapid test; two Flu A isolation-positive specimens from children less than 6 months of age were negative by all rapid tests. Nineteen specimens were positive by a rapid test but were negative for that virus by a virus isolation test. For 17

TABLE 2. Detection of RSV and Flu A by various diagnostic tests

Virus and test[a]	No. of specimens positive for virus from children at age (mo)[b]:		
	<6	6–24	>24
RSV			
Virus culture	15	4	4
BB-IF	15 (2)	4	3
I-DF	11 (2)	4	4
A-EIA	11	1	1
BD-EIA	12 (1)	1	4 (2)
Flu A			
Virus culture	8	6	6
BB-IF	6 (2)	3 (1)	3 (1)
I-DF	10 (5)	5 (2)	6 (1)
BD-EIA	5	4	6

[a] Abbreviations: BB-IF, Baxter Bartels Microscan indirect IF; I-DF, Imagen direct fluorescence; A-EIA, Abbott EIA; BD-EIA, Becton Dickinson EIA.

[b] Numbers in parentheses are numbers of specimens testing positive in rapid tests without isolation of the virus.

TABLE 3. Comparison of rapid diagnostic test kits and virus isolation test for detection of RSV and Flu A

Virus and test[a]	% Sensitivity	% Specificity	% Positive predictive value	% Negative predictive value	% Efficiency[b]
RSV					
BB-IF	87	97	91	97	94
I-DF	65	93	79	87	85
A-EIA	57	98	93	85	86
BD-EIA	61	95	82	86	73
Flu A					
BB-IF	40	86	53	82	77
I-DF	65	92	72	89	85
BD-EIA	75	100	100	92	94

[a] Abbreviations: BB-IF, Baxter Bartels Microscan indirect IF; I-DF, Imagen direct fluorescence; A-EIA, Abbott EIA; BD-EIA, Becton Dickinson EIA.
[b] Percentage of specimens for which the rapid diagnostic test and the virus isolation test were in agreement.

of the 19 specimens, only a single rapid test was positive; for two specimens, there were two positive tests. Although the numbers are small, the EIAs were somewhat more sensitive for RSV among children less than 6 months of age ($P = 0.07$ for TestPack).

The performances of the various diagnostic kits as evaluated by comparison with virus culture are shown in Table 3. The sensitivities for RSV varied between 57 and 87%, but the specificities for all tests were over 90%. The Bartels Microscan indirect IF test exhibited the highest sensitivity and efficiency. Moreover, with the Bartels Microscan indirect IF test, the contrast between a positive stain and the background stain appeared more distinct than with the direct test (Imagen). Both IF tests use a murine monoclone as the antigen-binding antibody and Evans blue as the counterstain, but the Imagen test also uses the same monoclonal antibody for detection, while the Bartels Microscan test uses a second polyclonal antibody for this purpose.

Directigen was the most sensitive, specific, and efficient of the three kits for detection of Flu A, despite having a sensitivity of only 75%. The specificity and positive predictive values for this kit were 100% (Table 3). The performances of the two IF tests for Flu A were poorer. Notable in this regard is the poor performance of the Bartels Microscan Flu A test, which contrasts with the good performance of the Bartels Microscan RSV test.

Relation to clinical events. More specimens from children with a lower respiratory illness (LRI) yielded a virus than those from children with an upper respiratory illness (URI) or otitis, but the frequencies were not statistically significant (38 of 53 [72%] yielded a virus among children with an LRI versus 15 of 28 [54%] among those with a URI [$P = 0.10$]). This is attributable to the greater number of RSV isolates from specimens from children less than 6 months of age with an LRI.

When virus isolation tests were evaluated in relation to hospitalization, it was noted that hospitalization was more closely related to age than to the virus detected. Of the 40 infants less than 6 months of age, 30 (75%) were hospitalized compared with 20 of 41 (49%) older children ($P = 0.015$). Similarly, 23 of 27 (85%) infants less than 6 months of age who were virus positive were hospitalized, compared with 10 of 26 (38%) who were virus positive and over 6 months of age ($P < 0.01$). Positive rapid diagnostic test results paralleled virus isolation test results in relation to both the illness pattern and incidence of hospitalization.

DISCUSSION

Four commercially available kits for the rapid antigen detection of RSV and three for the detection of Flu A were compared by using specimens from infants and children with an acute respiratory illness during concurrent outbreaks of both virus infections. This provided an opportunity to compare these tests with virus culture in a situation in which the two infections may be clinically indistinguishable. During the 3-month study period (mid-November to mid-February of 1991 to 1992), these two viruses were isolated from 54% of ill children and accounted for 74% of all viruses detected in cell cultures. This is not surprising, since the sampling period was selected for optimal detection of these two viruses and the age group tested was a population with a high likelihood of developing a respiratory illness, as a result of infection with one of these viruses, that is sufficiently serious to cause a parent to seek health care for a child. Also, as expected, there was a higher frequency of serious illness caused by RSV among children less than 6 months of age, and there was an equal distribution of illness caused by Flu A in the various age groups.

A decision to hospitalize a child (made by physicians uninvolved with the study and without knowledge of virologic results) was most closely related to age; children less than 6 months old were more likely to be hospitalized than those over 6 months of age, regardless of which virus was causing the infection. For each age group, children with an LRI were more likely to be hospitalized than children with a URI. Since RSV infection was a dominant cause of LRI in infants less than 6 months of age, it was the virus infection most often leading to hospitalization. These patterns of occurrence of RSV and Flu A infection among young children have been described elsewhere (4, 6, 7, 15). With relation to rapid diagnosis, it is of interest that positive tests were not more frequent among those hospitalized than among those not hospitalized.

Among the rapid diagnostic kits evaluated for detection of RSV, the Bartels Microscan indirect IF test displayed the best combination of sensitivity, specificity, predictive value, and efficiency when compared with virus culture. Inclusion of the contaminated specimens (two of three indicated the presence of RSV) would improve the sensitivity of the Bartels test to 88% and the sensitivities of the Imagen, Abbott, and Becton Dickinson kits to 68, 60, and 64%, respectively. Similarly, the overall performance of each would also improve. Limiting the analysis to children less

than 6 months of age improved the sensitivity for both EIA kits. It should be noted that the specificity of each kit was greater than 90%.

It is of interest that the kit which used direct fluorescence for detection (Imagen) was less sensitive than the kit which used indirect fluorescence (Bartels Microscan). The greater sensitivity of indirect fluorescence is in keeping with other comparisons of the two techniques (9). However, since the techniques had similar specificities (generally greater for direct fluorescence), the differences in sensitivity could be partly attributable to the labeled antibodies. The direct fluorescence test had a mouse monoclone as a detector antibody, while the indirect test had a polyclonal anti-mouse antibody. The indirect test was easier to interpret because of a greater intensity of staining, a difference referred to earlier (20).

In our hands, the best test overall for detection of Flu A was Directigen Flu-A. Not only was it the most rapid to perform, taking less than 20 min on average, but it also had the greatest sensitivity, specificity, predictive values, and efficiency. Of interest is the fact that the Bartels Microscan indirect fluorescence test exhibited the lowest sensitivity for Flu A and the highest for RSV. Since the RSV- and Flu A-positive specimens were collected, processed, and interpreted by the same persons, the differences are likely attributable to the test. Whether the differences are attributable to differences in the number and pattern of cells infected with RSV versus Flu A or to differences in the reagents provided for the two viruses is uncertain, but the similar, although somewhat low, sensitivities for both viruses with the direct fluorescence test suggests that the lower sensitivity of the indirect test for Flu A is attributable to the reagents provided for the test.

The sensitivities and positive predictive values of all the EIA tests, as determined by comparison with virus isolation, were somewhat lower than most results reported by other groups, who reported sensitivities which were mostly higher (1, 3, 8, 9, 11, 16, 18). One possible explanation for this is that our virus isolation procedure provides greater sensitivity than is provided by procedures used in many of the published studies. This is suggested by the high specificity of each of the test kits in our hands. The lower sensitivity of EIAs could have been due to the protocol used for processing the specimens. The centrifugation step for rapid testing removed much of the cellular material for use in fluorescent tests, leaving predominantly free virus in the supernatant used for the EIAs. This may have decreased the likelihood of a positive reaction. Supporting this concept is a recent report by Ryan-Poirier et al., who noted that the intensity of the Directigen Flu-A reaction did not correspond with the concentration of virus in the fluid phase of a specimen (12). In fact, as few as 20 infected MDCK cells were enough to cause a positive reaction, in comparison with at least 1.63×10^3 PFU of free virus. Ryan-Poirier et al. concluded that inclusion of cells was necessary for optimal sensitivity. This could be true, but it should be emphasized that maximal sensitivity for Flu A was exhibited by the Directigen kit with specimens from which cells had been removed. Perhaps a more vigorous procedure for collection of cells, such as collection by nasal aspiration or nasal scrape, would enhance the likelihood of detection of virus by both IF and EIA. In this regard, 15% of our specimens contained only a few cells (three to six) per slide for the IF tests.

Alternative possibilities for lower sensitivities include the fact that our study was conceived as an outpatient study of infants and children attending a pediatric clinic. Perhaps the quantity of virus was lower in specimens from these children than in specimens from children in the hospital, the site for other studies. This does not seem likely, however, since hospitalization was most closely related to the age of the child and paralleled virus isolation results. It is also possible that our nasal wash procedure reduces sensitivity. It provides a final volume of specimen (5 to 6 ml) that will permit a battery of tissue cultures to be inoculated for virus isolation as well as an aliquot to be retained for future tests. A smaller volume could enhance sensitivity somewhat. More efforts to identify the optimal specimen for the various rapid diagnosis procedures are desirable.

In conclusion, we evaluated several rapid antigen detection kits for RSV and Flu A in a pediatric population during the winter season of 1991 to 1992 in Houston, Texas. Early detection of RSV was best by use of a Bartels Microscan indirect IF kit, and Flu A was best detected by use of the Becton Dickinson Directigen EIA kit, suggesting that the optimal detection of these viruses is dependent more on the particular kit used than the detection method (IF versus EIA). Increased application of these and other rapid diagnostic methods for detecting acute respiratory viral illnesses should aid in decisions regarding the management of sick children.

ACKNOWLEDGMENTS

We thank Orceli Falcao for obtaining some of the patient specimens, Nina Wood and Kirti Patel for performing virus isolation tests, and Darlene Kirk for manuscript preparation. Directigen kits were provided by the Becton Dickinson Company.

This research was supported by Public Health Service contract NO1-AI-15103 from the National Institute of Allergy and Infectious Diseases.

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