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ScienceDirect
Diagnostic Microbiology and Infectious Disease 69 (2011) 410–418
DIAGNOSTIC MICROBIOLOGY AND INFECTIOUS DISEASE
www.elsevier.com/locate/diagmicrobio

A meta-analysis of point-of-care laboratory tests in the diagnosis of novel 2009 swine-lineage pandemic influenza A (H1N1)

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Received 9 July 2010; accepted 17 October 2010

Abstract

This paper reviews 14 published studies describing performance characteristics, including sensitivity and specificity, of commercially available rapid, point-of-care (POC) influenza tests in patients affected by an outbreak of a novel swine-related influenza A (H1N1) that was declared a pandemic in 2009. Although these POC tests were not intended to be specific for this pandemic influenza strain, the nonspecialized skills required and the timeliness of results make these POC tests potentially valuable for clinical and public health use. Pooled sensitivity and specificity for the POC tests studied were 68% and 81%, respectively, but published values were not homogeneous with sensitivities and specificities ranging from 10% to 88% and 51% to 100%, respectively. Pooled positive and negative likelihood ratios were 5.94 and 0.42, respectively. These results support current recommendations for use of rapid POC tests when H1N1 is suspected, recognizing that positive results are more reliable than negative results in determining infection, especially when disease prevalence is high.

Keywords: Influenza A (H1N1); Pandemic; Swine origin; Rapid point-of-care test

1. Introduction

In April 2009, the US Centers for Disease Control and Prevention (CDC) identified a novel influenza A virus in children living in California (Dawood et al., 2009), which also appeared in Mexico (Dominguez-Cherit et al., 2009). While the virus was found to contain genes from triple-reassortant influenza viruses present in North American swine, as well as 2 genes closely related to influenza present in Eurasian swine, these original US patients had no recent history of swine exposure. By June 2009, this new virus had caused thousands of cases and over a hundred deaths in countries around the world, leading the World Health Organization (WHO) to declare a global pandemic (Peiris et al., 2009). WHO designated the new virus as influenza A (H1N1)v, where v indicates variant.

This 2009 pandemic demanded a reevaluation of the approach to diagnostic testing used for detection. Clinical laboratories have more than 20 years experience with commercial point-of-care (POC) rapid antigen assays. Although these POC tests have traditionally demonstrated a lower sensitivity than direct fluorescent antibody (DFA) staining, shell vial culture, or roller tube culture (e.g., Dunn et al. 2003, Zitterkopf et al. 2006), POC tests have the advantages of ease of use, rapid turnaround times of less than 30 min, and addition of significant value to most hospital laboratories that do not have extensive virology facilities. While DFA tests typically require 2 to 4 h, these tests are generally available only to hospital-based physicians and tend to produce many false-negative results (Uyeki 2003). Many of the POC assays have been brought to market through US Food and Drug Administration (FDA) clinical trials and have usually been compared to culture. Although these POC tests have been FDA reviewed, ongoing evaluation is not required despite continual changes in antigenic variation. These POC tests collectively perform better in high influenza prevalence situations. When the

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0732-8893/$ – see front matter
doi:10.1016/j.diagmicrobio.2010.10.009

current pandemic began in April 2009, health care professionals did not know how these POC assays would perform for detecting the new virus. The earliest reports of POC tests (e.g., Faix et al. 2009; Ginocchio et al. 2009) showed suboptimal sensitivity during the influenza A (H1N1)v outbreak, and as of April 2010, there are no commercially available POC kits for the specific detection of this virus.

The relatively recent introduction of antiviral therapy for influenza has been tempered by the finding that effectiveness is generally limited to those in whom therapy is initiated within 48 h of symptom onset (Sintchenko et al., 2002). Accordingly, rapid diagnosis of influenza is particularly important for guiding treatment decisions, in addition to aiding in infection control. The traditional gold standard for identifying influenza viruses has been by viral culture (Cox, Subbarao, 1999), which relies on propagation of the virus and may require days to weeks before a definitive identification can be made. More recently, molecular-based, rapid assays that use reverse transcriptase–polymerase chain reaction (RT-PCR) have been developed. Although these tests have high sensitivity and specificity for strain identification (Pachucki, 2005), RT-PCR methods remain expensive, require a high level of expertise, and are subject to multiple potential technical errors, including failed extractions and problems with PCR inhibition (Bustin, Mueller, 2005). Therefore, RT-PCR tests are currently performed primarily at specified reference laboratories, leading to delays in reporting of results. Rapid antigen POC assays offer an alternative because they may be performed by less-trained personnel at the patient's bedside or in a satellite laboratory, providing results in as little as 10–20 min (Pachucki, 2005; Sintchenko et al., 2002). Unfortunately, the POC seasonal influenza assays published to date have far less sensitivity and specificity than RT-PCR or viral cultures (Rahman et al., 2008).

The goal of this paper is to review available published literature on the 2009 novel swine flu outbreak to assess the potential utility of POC laboratory tests for initiating infection treatment and control for this pathogen. For consistency, this paper will refer to the novel swine flu virus using the WHO designation of *influenza A (H1N1)v* (where *v* means variant) described earlier. One would ideally like to determine the positive predictive value (PPV) and negative predictive value (NPV) associated with the use of these tests alone or in combination with other methods during an epidemic situation, to guide effective protocols for rapid identification during future outbreaks (Altman and Bland 1994). This task is complicated by the fact that studies reporting performance have generally included specimens taken from varying locations (e.g., throat, nasopharynx, nasopharyngeal aspirate), which can result in different viral recoveries and impact the probability of a positive detection. Another limitation of this study is the relatively small number of studies involving POC testing for influenza A (H1N1)v that have been published so far.

2. Materials and methods

Because the novel H1N1 virus first appeared in early 2009, a detailed search of WHO, CDC, and other publications (originally in or translated to English language) was performed for articles published from March 2009 through February 2010. This search included CDC and WHO websites, and the National Institutes of Health PubMed and Google Scholar search engines. Search terms included novel pandemic 2009 influenza A (H1N1) virus and POC testing. Of the 47 articles identified by these searches, only 14 articles that reported at least some measure of POC test performance data (e.g., sensitivity, specificity) for influenza A (H1N1)v were included in our analysis.

2.1. Data analysis

If available, the following data were collected from each study: numbers of true-positive, false-negative, true-negative, and false-positive results of each individual POC influenza test versus the gold standard used for comparison. If the study did not directly provide these raw numbers, we used reported sensitivity, specificity, NPV, PPV, and total sample size to back-calculate to obtain integer numbers. If we were unable to obtain consistent integer numbers from back-calculation, we contacted the corresponding author in an effort to retrieve the missing information.

The overall pooled sensitivity and specificity of POC influenza tests, including their pooled 95% confidence intervals (CIs), were calculated as the weighted average of individual sensitivity and specificity data using Meta-DiSc (Zamora et al 2006). Pooled sensitivities and specificities were also calculated for each commercial POC influenza test if there was more than one study with data available. Pooled positive likelihood ratio and negative likelihood ratio were only calculated for those studies that contained specificity data.

3. Results

A summary of the POC influenza test performance characteristics for influenza A (H1N1)v found in each reviewed paper appears in Table 1. The information provided by these studies varied greatly and not all studies provided comprehensive information. Table 2 shows the pooled results from studies that employed the same assays, with 95% CIs in parentheses. In some cases, there were insufficient data to calculate pooled results for a specific POC test (labeled "NA" in Table 2). However, when all the different POC test reports were combined, sufficient data could be found to derive the broader category of pooled results for the entire set of all POC tests (see "Overall" row in Table 2). Note in Table 1 that only 2 studies did not use real-time RT-PCR (rRT-PCR) as the gold standard (Ginocchio et al. and Fernandez et al.).

In the paragraphs to follow, each published report is briefly discussed to include additional POC test data not

Table 1
Study details of articles that reported sensitivity and/or specificity of POC influenza tests for diagnosis of influenza A (H1N1)v (novel 2009 swine-lineage) on clinical specimens

Citation	Month/ year	Sample size	Population	Specimen type	Gold standard	POC test	Sensitivity	Specificity
Ginocchio et al.	06/2009	1860	ILI patients in New York	Nasopharyngeal swabs/aspirates/washes	DFA	BinaxNow Influenza A&B	31%	99%
		1352			Culture	BinaxNow Influenza A&B	10%	100%
		448			DFA	3M Rapid Detection Flu A+B	71%	98%
		356			Culture	3M Rapid Detection Flu A+B	40%	98%
Faix et al.	06/2009	767	ILI patients in San Diego	Specimen source unspecified	rRT-PCR	QuickVue A+B	51%	99%
Balish et al.	08/2009	45	Confirmed + patients in US	Nasopharyngeal/oropharyngeal swabs	rRT-PCR	BinaxNow Influenza A&B	40%	NA
		43				Directigen EZ Flu A+B	49%	NA
		45				QuickVue A+B	69%	NA
Sabetta et al.	09/2009	63	Outbreaks at 2 schools in Connecticut	Nasopharyngeal washes	rRT-PCR	Remel Xpect Flu A&B	47%	86%
Vasoo et al.	10/2009	60	Confirmed + patients in Chicago	Nasopharyngeal swabs	Luminex xTAG RVP RT-PCR	BinaxNow Influenza A&B	38%	NA[a]
		60				Directigen EZ Flu A+B	47%	NA[a]
		60				QuickVue A+B	53%	NA[a]
Drexler et al.	10/2009	144	Confirmed + patients in Germany	Nasal/throat swabs	rRT-PCR	BinaxNow Influenza A&B	11%	NA
Crum-Cianflone et al.	11/2009	571	ILI patients in San Diego	Nasopharyngeal swabs	rRT-PCR	QuickVue A+B	51%	98%
Echevarria-Zuno et al.	11/2009	11,640	ILI patients in Mexico	Respiratory swabs	rRT-PCR	QuickVue A+B	75%	75%
Blyth et al.	11/2009	20	Confirmed + ICU patients in Australia	Swabs from nose and throat	RT-PCR	QuickVue A+B	25%	NA
Likitnukul et al.	11/2009	841	ILI patients in Bangkok	Nasal swabs	rRT-PCR	QuickVue A+B or SD Bioline Influenza	88%	51%
Fernandez et al.	01/2010	147	ED patients in New York	Nasal or nasopharyngeal swab	DFA or Culture	QuickVue A+B	77%	86%
Garon et al.	01/2010	73	Confirmed + patients in Chicago	Nasopharyngeal swabs?	Some RT-PCR?	BinaxNow Influenza A&B	60%	NA
Nougairede et al.	02/2010	1974	Hospital patients in France	Nasal swabs	rRT-PCR	Directigen EZ Flu A+B	58%	100%
Ortiz de la Tabla et al.	02/2010	995	Suspected cases in Spain	Nasopharyngeal/oropharyngeal swabs	rRT-PCR	ClearView Exact Influenza A&B	19%	100%

NA = not available from the published study.
[a] Vasoo et al. incorrectly reported specificity for POC influenza tests on all confirmed positive specimens.

Table 2
Pooled sensitivity, specificity, positive likelihood ratio, and negative likelihood ratio of the POC influenza test for diagnosis of influenza A (H1N1)v (novel 2009 swine-lineage) on clinical specimens

POC test	Pooled sensitivity	Pooled specificity	Pooled positive likelihood ratio[a]	Pooled negative likelihood ratio[a]
Overall	67.5% (66.2%, 68.9%)	80.7% (80.0%, 81.4%)	5.94 (3.60, 9.78)	0.42 (0.25, 0.72)
Individual test[b]				
BinaxNow Influenza A&B[c]	31.4% (26.3%, 36.7%)	NA	NA	NA
Directigen EZ Flu A+B	52.8% (45.9%, 59.6%)	NA	NA	NA
QuickVue A+B	73.6% (72.1%, 75.0%)	76.6% (75.5%, 77.5%)	7.27 (2.36, 22.35)	0.37 (0.27, 0.51)

[a] Positive and negative likelihood ratios were not available if specificity was not available.
[b] There was only 1 article available for each of ClearView Exact Influenza A&B, 3M Rapid Detection Flu A+B, Remel XpectFlu A&B, and SD Bioline influenza test. Therefore, pooled indicators of these individual POC tests were not calculated. NA indicates there were insufficient data to calculate these quantities.
[c] We were unable to derive consistent values when we attempted to back-calculate the exact true-positive, false-positive, true-negative, and false-negative numbers from sensitivity, specificity, PPV, and NPV provided in the original Table 3 in Ginocchio et al (2009). Because we were unable to obtain from the corresponding author all of the information needed for the pooled analysis, data on BinaxNow Influenza A&B and 3M Rapid Detection Flu A+B from this paper were not included in the pooled analysis.

included in Table 1 and to highlight key differences among studies. Because some studies provided information (such as study design, specimen sources, populations, age groups, or disease prevalence) that may be relevant to the differences in results, this information is mentioned in these study summaries if the study provided it. The following study summaries are listed in the order in which the studies were published. To aid the reader in using these summaries to supplement Table 1, the authors' names appear in boldface font when first mentioned.

In a large cross-comparative study, **Ginocchio et al. (2009)** analyzed the performance of 5 tests for influenza A (H1N1)v, including 2 rapid POC tests (Table 1). A total of 3789 nasopharyngeal specimens were tested, with 2870 tested by BinaxNOW and 919 tested by 3MA+B. Sensitivity, specificity, PPV, and NPV were determined relative to DFA and to viral culture results. The overall prevalence of influenza A (H1N1)v was reported to be 40.8%. When compared with DFA tests, the PPV and NPV for BinaxNOW were 93.8% and 94.1%, respectively, while those for 3MA+B were 72.7% and 98.1%, respectively. When these POC tests were compared with viral culture, the PPV and NPV for BinaxNOW were 100% and 88.9%, respectively, while those for 3MA+B were 73.9% and 96.3%, respectively.

In June 2009, the US Naval Health Research Center (**Faix et al., 2009**) published a brief report on influenza A (H1N1) v detection performance using QuickVue Influenza A+B (Quidel; Quidel Corp., San Diego, CA) relative to RT-PCR in 767 patients tested between April and May 2009. They found that the QuickVue test was positive for 20 of 39 patients who were positive for influenza A (H1N1)v on RT-PCR. Of 3066 PCR specimens processed, 273 were positive for Influenza A (H1N1)v, 18 were positive for seasonal H1N1, and 31 were positive for H3N2. The reported POC test sensitivity for influenza A (H1N1)v (Table 1), seasonal H1N1, and H3N2 were 51% (95% CI = 35–67), 63% (95% CI = 39–82), and 31% (95% CI = 14–57), respectively.

The first US CDC report (**Balish et al., 2009**) of POC testing for influenza A (H1N1)v described findings from 65 clinical respiratory specimens collected between April and May 2009. Specimens were provided by state health laboratories and had previously tested positive for influenza A (H1N1)v, seasonal influenza A (H1N1), or influenza A (H3N2) by RT-PCR. POC tests included Inverness Medical BinaxNOW Influenza A&B (Binax, Inc., Scarborough, ME), the Becton Dickinson Directigen EZ Flu A+B (Becton, Dickinson and Company, Sparks, MD), and the Quidel QuickVue Influenza A+B. Of the 45 specimens that were RT-PCR positive for influenza A (H1N1)v, sensitivities were 40%, 49%, and 69% for BinaxNOW Influenza A&B, Directigen EZ Flu A+B, and QuickVue Influenza A+B, respectively (Table 1). The overall POC test sensitivity was only about 40–69% among all specimens, with higher sensitivity in specimens with high levels of virus and sensitivity decreasing as the specimen virus levels decreased.

The CDC (**Sabetta et al., 2009**) evaluated the performance of the Remel Xpect Flu A&B (Remel Products, Lenexa, KS) POC diagnostic test during 2 school outbreaks of influenza A (H1N1)v in Connecticut. Sixty-three samples, collected from students and some staff (age ranges not provided), were tested and the POC test results were compared with rRT-PCR. Of these samples, 49 were positive for influenza A (H1N1)v by rRT-PCR. Between the 2 schools, there were no reported differences in symptom severity and interval between symptom onset and testing. Of the 14 patients from one school, 79% were positive for influenza A (H1N1)v by rRT-PCR. Of the 49 students and staff from the other school, 78% were positive for influenza A (H1N1)v by rRT-PCR. The PPV and NPV of the POC assay were reported as 92% and 32%, respectively. The authors noted that the median time from symptom onset to

testing was 36 h, but the same percentage of patients was found to be positive in the POC test performance regardless of whether this interval was more than or less than 36 h.

Vasoo et al. (2009) described an evaluation of 3 POC tests (Table 1) using a convenience sample of 84 positive, nonduplicate nasopharyngeal specimens collected from patients presenting with influenza-like illness during May–June 2009. The Luminex xTAG RVP RT-PCR test was used as a standard for evaluating sensitivities of 3 POC tests: BD Directigen EZ Flu A+B (Becton Dickinson), BinaxNOW Influenza A&B (Inverness Medical), and QuickVue Influenza A+B (Quidel). Control specimens included 24 nasopharyngeal swabs positive for other respiratory viruses that were not influenza. The majority of specimens positive for influenza A (H1N1)v were from children and young adults, where the median age was 12.5 years (range 7–58 years). Control patients had a median age of 7 years (range 4 months–66 years). During the study period, the authors determined that the overall prevalence of influenza A (H1N1)v was 17.9% (95% CI = 8.24–27.6%) in all specimens submitted for respiratory virus RT-PCR testing. Based on this prevalence, the PPV was 100% for all 3 POC tests, while the NPVs were 89.6%, 88.2%, and 90.8% for BD Directigen EZ Flu A+B, BinaxNOW Influenza A&B, and QuickVue Influenza A+B, respectively. The authors found no significant correlation of these results with either patient age or duration of symptoms before sample collection. They did find a significant association ($P < 0.01$) between a higher median number of RT-PCR fluorescence intensity units and positive results for all POC tests they studied. The authors noted their study limitations included use of a known convenience sample of positive specimens, the fact that the sample collection technique was not standardized, and that their tested specimens had been refrigerated pending results of RT-PCR.

Drexler et al. (2009) evaluated the BinaxNOW Influenza A&B Rapid Test in nasal and throat swabs taken from 144 patients who had previously tested positive for influenza A (H1N1)v by rRT-PCR. The POC test sensitivity (Table 1) was lower than most of the other studies at only 11.1% (95% CI = 6.7–17.7). The POC-positive samples had a median concentration of 4 570 880 RNA copies/mL of suspension (range 5,370–74,131,020), while the POC-negative samples had a median concentration of 20,089 RNA copies/mL of suspension (range 120–64,565,420). This difference was found to be statistically significant at $P < 0.001$. Drexler et al. compared these results with those from the BinaxNOW test for the 2007–2008 H1N1 seasonal influenza and the 2008–2009 H3N2 seasonal influenza in Germany and found sensitivities to these seasonal flu viruses to be 37.5% and 51.9%, respectively. Similar to their results for the 2009 influenza A (H1N1)v, virus concentration appeared to be the most significant factor for predicting positive POC test results in these earlier influenza seasons. The median age of their cohort was 18, with a range of 1–59 years. It is known that children generally have higher viral shedding than adults, but they found no significant difference in POC-positive/negative results based on age.

In November 2009, the US Naval Medical Center published a study (**Crum-Cianflone et al. 2009**) of an influenza A (H1N1)v outbreak among the US military and their beneficiaries in San Diego. The authors evaluated the sensitivity of rapid influenza testing using QuickVue Influenza A+B (Quidel) compared with rRT-PCR (Table 1). A nasopharyngeal swab sample was obtained for POC testing and a second nasopharyngeal swab was obtained for rRT-PCR testing. Between April 21 and May 8, 2009, a total of 571 patients had both swabs performed. Both RT-PCR and the POC test were negative in 483 of these patients, while both tests were positive for 40 patients. Nine patients with positive POC results had negative RT-PCR results, while 39 patients with negative POC results had positive RT-PCR results. After determining a prevalence of influenza A (H1N1)v as 101 cases per 100,000 persons, the authors found a PPV and NPV of 82% and 93%, respectively. For patients under 18 years of age, the sensitivity of the POC improved to 77.3% (95% CI = 54.2–91.1%), while the specificity remained at 98%. For this age group, the PPV and NPV were 81% and 98%, respectively. For patients 18 years and older, the POC sensitivity fell to 40% (95% CI = 27.8–54.1%), while the specificity remained 98%. For this age group, the PPV and NPV were 82% and 89%, respectively.

Echevarria-Zuno et al. (2009) reported on the testing of outpatients and inpatients in Mexico between April 17 and July 31, 2009. At the end of this time period, 49,196 QuickVue Influenza A+B tests (Quidel) had been performed. Of these POC tests, 9475 (19%) patients were found positive for influenza A (H1N1)v, while 39,721 (81%) were found to be negative. Of the 9475 POC test-positive patients, 4510 patients (48%) also had RT-PCR testing performed and 2430 (54%) of these patients were also influenza A (H1N1)v positive by RT-PCR. Of the 39,721 POC-negative patients, 7130 (18%) patients also had RT-PCR testing and 807 (11%) of them were found to be PCR positive for influenza A (H1N1)v. Table 1 lists the values for sensitivity (95% CI = 73.56–76.58) and specificity (95% CI = 74.32–76.18%) reported by the authors for the QuickVue test.

Blyth et al. (2009) reported poor sensitivity of the QuickVue A+B (Quidel) POC test in 21 patients in an Australian intensive care cohort with severe influenza A (H1N1)v. These patients had acute lung injury requiring mechanical ventilation. Testing was performed on nasopharyngeal swabs and compared with RT-PCR performed on specimens from both the upper and lower respiratory tract. In those patients whose lower respiratory tract specimens were positive for influenza A (H1N1)v by RT-PCR, the POC test was positive in only 5 of 20 patients. Using upper respiratory tract specimens, 17 of the 21 patients with positive for influenza A (H1N1)v by RT-PCR but only 5 of 20 patients were positive by POC testing. The sensitivity found in this study is also shown in Table 1.

Likitnukul et al. (2009) evaluated the sensitivity and specificity of 2 rapid influenza diagnostic tests compared against RT-PCR for the diagnosis of influenza A (H1N1)v during an outbreak in Bangkok, Thailand. They evaluated 871 patients who had a nasal swab specimen tested with both POC and RT-PCR tests between June 11 and July 28, 2009. Of these patients, 477 were tested using the QuickVue Influenza A+B test (Quidel), while 364 patients were testing using the SD Bioline Influenza Antigen test (Standard Diagnostics, Inc., Gyeonggi-do, Korea) as the POC test. However, the authors did not report separate results for each of these 2 POC tests but instead reported combined results for the sensitivity, specificity, accuracy, PPV, or NPV. The median age of patients was 13 years (range 6 months–97 years). The age distribution was as follows: 16.2% were less than 5 years, 19.4% were ages 6–10 years, 37.4% were 11–20 years, and 27% were older than 20 years of age. Of the 3096 nasal swabs tested by either POC test, 1027 were positive for influenza A and 19 were positive for influenza B. For influenza A (H1N1)v, the reported results were sensitivity 87.6% (95% CI = 84.1–90.1%), specificity 50.7% (95% CI = 45.8–55.6%), accuracy 69.5% (95% CI = 66.5–72.7%), PPV 64.9% (95% CI = 60.9–68.8%), and NPV 79.7% (95% CI = 74.3–84.4%).

Fernandez et al. (2010) presented an evaluation of the QuickVue Influenza A+B test (Quidel Corp. San Diego, CA, USA) for detecting influenza A (H1N1)v in nasal or nasopharyngeal swabs taken from emergency department patients at a hospital in Nassau County, near New York City. The authors analyzed 1137 samples collected between April 8 and June 30, 2009. Because RT-PCR test results were unavailable, true positives were defined in this study as those for which viral culture or DFA were positive for influenza A (H1N1)v. The authors note that both culture and DFA are less sensitive than RT-PCR in detecting influenza A (H1N1)v. Of these 1137 samples, only 147 specimens had both the POC and confirmatory tests. Based on these data, the authors found the POC test sensitivity, specificity, PPV and NPV to be 77.4% (95% CI = 63.8–87.7), 85.6% (95% CI = 77–91.9%), 74.6% (95% CI = 61.4–85.3%), and 87.4% (95% CI = 79–93.3%), respectively.

Garon et al. (2010) evaluated the sensitivity of a rapid flu test for influenza A (H1N1)v from April 27 through June 23, 2009, at one hospital in Cook County, IL, USA. During this time period, this hospital processed 16% of Cook County confirmed positive influenza A (H1N1)v cases. The authors reported that they processed or transported 723 nasopharyngeal specimens to the state health laboratory for confirmatory testing for influenza A (H1N1)v. Although PCR testing was mentioned in their paper, it was not clear whether all the confirmatory testing was by this or some other method. Of these 723 specimens, 100 were reported as positive for influenza A (H1N1)v. These 100 patients included 33 hospitalized children and 9 hospitalized adults, but specific age ranges were not provided in the paper. Rapid flu tests were performed on 73 of the 100 specimens. Of these 73 specimens confirmed as influenza A (H1N1)v, 44 were also positive by the POC test that they used. Although Garon et al. (2010) did not specifically mention which POC test they used, they did say it was the one reported to have a 40% sensitivity in the August 7, 2009, *MMWR* article by Balish et al. (2009). According to that article, the POC test would then be the BinaxNow Influenza A+B. We confirmed this was the POC test used via personal correspondence with Garon and listed it as such in Table 1.

Nougairede et al. (2010) evaluated the performance of the Directigen EZ Influenza A+B (Becton, Dickinson) POC test compared with rRT-PCR for the detection of influenza A (H1N1)v. POC tests were performed among 2 laboratories on nasal swab samples taken between June and September 2009 from 1974 patients seen at emergency departments at 2 hospitals and at specific influenza consultations from one hospital, all located in Marseilles, France. For all 1974 patients (adults and children) combined, the mean and median patient age was 25.4 and 21 years, respectively. Of the 1974 samples, 111 tested positive for influenza A (H1N1)v. Among the 596 adults (mean and median ages 42 and 36 years, respectively) seen in emergency departments, 28 tested positive for influenza A (H1N1)v. Among the 682 children seen in emergency departments, 45 tested positive for influenza A (H1N1)v. The authors determined the sensitivity, specificity, PPV, and NPV of this POC test to be 57.7%, 100%, 100%, and 97.5%, respectively. Nougairede et al. also reported sensitivity and specificity of a POC RT-PCR test that takes 2 1/2 h. However, we excluded such rapid RT-PCR tests in this study based on "WHO recommendations on the use of rapid testing for influenza diagnosis" published in 2005 (available at http://www.who.int/csr/disease/avian_influenza/guidelines/rapid_testing/en/index.html).

Ortiz de la Tabla et al. (2010) assessed the ClearView Exact Influenza A&B test (Inverness Medical, Cologne, Germany) in comparison with rRT-PCR testing for detection of influenza A (H1N1)v in a prospective study of 1016 adults and children in Spain (Table 1). Each patient was sampled using 2 foam swabs to collect oropharyngeal and nasopharyngeal specimens that were refrigerated and tested within 4–48 h post collection. In the first 94 patients, additional oropharyngeal and nasopharyngeal specimens were collected for immediate testing by attending physicians at the point of care. The POC test was performed on 995 of the 1016 samples. Most of these patients (75%) were not older than 50 years. This POC test was positive in 55 patients, none of whom proved to be false positives. The study was conducted between July and November 2009 during which influenza A (H1N1)v was the predominant circulating virus and one-third of patients were positive by rRT-PCR. This population-based study used consecutive recruitment of patients with a broad spectrum of disease severity. However, information on viral load and intervals between symptom onset and specimen collection was not available to Ortiz de la Tabla et al. for analysis. Ortiz de la Tabla et al. determined that the

specificity and PPV of the POC test were both 100%. The overall sensitivity and NPV were 19% (95% CI = 14–23) and 75% (95% CI = 72–78%), respectively. The sensitivity was somewhat higher for the youngest (0–14 years, 24%, 95% CI = 13–34%) than for the oldest (over 44 years, 8%, 95% CI = 2–15%). Among age groups, the NPV was lowest for the 15- to 24-year olds (49%, 95% CI = 39–60%) and highest for those older than 44 years (87%, 95% CI = 84–90%). The highest sensitivity (22%; 95% CI = 11–33%) was found among patients admitted to the hospital, while the NPV for these patients was 88% (95% CI = 84–91%). In the 94 patients in whom the POC test was performed immediately at the point of care, the sensitivity was 11% (95% CI = 3–19%). The NPV for these same patients was only 45% (95% CI = 35–56%). The highest NPV was found for 10 patients who presented with pneumonia (93% (95% CI = 88–97%).

4. Discussion

Seven POC tests for influenza A (H1N1)v were identified in the 14 studies included in this review: BinaxNow Influenza A&B, Directigen EZ Flu A+B, QuickView A+B, ClearView Exact Influenza A&B, 3M Rapid Detection A&B, Remel Xpect Flu A&B, and SD Bioline. The highest sensitivity (88%) was reported by Likitnukul et al. (2009), but that study described only combined results for QuickVue A+B and SD Bioline influenza, with insufficient details provided to distinguish individual sensitivities of these 2 tests. Individual POC tests had a range of sensitivities for the influenza A (H1N1)v virus (Table 1). In addition to differences among different POC tests, this range of values may in part be due to different study populations and age ranges, different gold standards, different disease prevalence, and different specimen sources (e.g., Gavin, Thomson 2003). For example, the QuickVue A+B test had reported sensitivities ranging from 25% to 77%. The lowest sensitivity was reported from confirmed influenza A (H1N1)v-positive patients in intensive care units when compared with RT-PCR, while the highest sensitivity was reported from emergency department patients when compared with DFA or culture (Table 1). Among the POC test studies from which there were enough data to determine pooled sensitivity, the QuickVue A+B test had the highest sensitivity (74% in Table 2). While the overall pooled specificity was 81% (Table 2), it ranged from 51% to 100% (Table 1) when mentioned in the reviewed studies. Fernandez et al. (2010) note that POC tests sensitive and specific for H1N1 detection may be important for protecting vulnerable patients, cohorting infected patients in hospital and institutional settings, and for public health surveillance and response. Therefore, updating the sensitivity and specificity of these tests is important. The question for clinicians is whether the level of sensitivity and specificity of available POC tests meets their clinical needs.

By its nature, the influenza virus continues to present a seasonal health threat with pandemic potential. The influenza A (H1N1)v strain that arose in 2009 is the latest example of such a threat. Fortunately, vaccines and antiviral therapy can be effective prevention and treatment if given in a timely fashion. While most confirmatory tests take hours to weeks, rapid POC tests provide results within 30 min and can be administered without the need for highly skilled specialists and sophisticated laboratory facilities. Because these tests vary somewhat in their complexity, WHO recommends personnel training to maintain quality control (see http://www.who.int/csr/disease/avian_influenza/guidelines/rapid_testing/en/index.html). While POC tests may be most often used in settings lacking sufficient laboratory facilities for other tests, these tests may also be useful in hospital settings, such as when there are high patient loads. Based on an extensive literature review, Uyeki (2003) recommended that, regardless of whether the results were positive or negative, POC tests used for outbreaks in institutional settings should be confirmed by viral culture. Sintchenko et al. (2000) recommended POC testing before initiating antiviral therapy, although the accuracy of the clinical assessment was the key variable in their analysis. In Table 2, note that the overall pooled specificity for all the POC tests reviewed here was 81%, so that the corresponding false-positive rate was 19%. If there is a high false-positive rate with POC tests, overuse of antiviral therapy may lead to its limited availability during a pandemic and the potential emergence of resistant organisms. Moscona (2009) discussed the evolution of oseltamivir resistance beginning around 2007 and noted that seasonal H1N1 in the United States became virtually 100% resistant in about 2 years. Obviously, new therapeutic options are needed in addition to greater emphasis on vaccination.

These POC tests have the potential to improve individual outcomes of severely ill patients and to improve population outcomes in the management of an epidemic. However, clinicians, laboratorians, and researchers must clearly understand the severe limitations of the current POC influenza tests for the new 2009 H1N1 pandemic influenza A virus and anticipate the time when new assays are commercially available, such as rapid, easy to use molecular amplification POC assays with subtyping capabilities (Welch and Ginocchio 2010).

It is important to recognize that current POC assays differ with regard to their ability to detect and differentiate between influenza virus types and strains. For example, some kits report only influenza A; other kits have been designed to detect influenza A H3N2, or H1N1 seasonal strains, as well as influenza B. Most identifications of influenza A (H1N1)v virus using these kits were made by process of exclusion, i.e., a positive test for influenza A, but a negative result for either H3N2 or seasonal H1N1. In August 2009, the US CDC published guidelines for using POC tests for influenza A (H1N1)v (http://www.cdc.gov/h1n1flu/guidance/rapid_testing.htm). If a POC test was positive for influenza A, then the CDC recommended treatment with antiviral agents

and consideration of whether additional diagnostic testing to determine the subtype is indicated. If a POC test was negative for both influenza types A and B, then the CDC recommended using clinical symptoms, severity, and comorbid conditions to decide if antiviral therapy was appropriate. The CDC specifically recommended against using a negative POC test result to dictate infection control measures or to send a symptomatic patient back to work or school. Even with a negative POC test, the CDC recommended considering more specific testing by viral culture or RT-PCR, especially if the patient was symptomatic or had comorbid conditions or other risk factors.

The relatively poor performance of POC tests for the 2009 pandemic H1N1 virus appears to affirm the current recommendations by CDC that caution should be used in the interpretation of negative POC results; that a negative result from a POC test does not rule out the 2009 pandemic H1N1 virus (Sabetta et al. 2009). There have been several earlier publications regarding positive results in the management of febrile children (Iyer et al. 2006), helpful triage of infants (Abanses et al. 2006), and febrile infants without signs of focal infection (Benito-Fernandez et al., 2006) in the period before the advent of the 2009 pandemic H1N1 influenza A virus. It appears that collectively, all the published studies recommend that, regardless of age, patients with influenza-like illness who have a negative POC test should have further testing using an RT-PCR assay or culture.

Acknowledgments

This study was supported in part by the US Department of Homeland Security through a grant (N00014-06-0-0991) awarded to the National Center for Study of Preparedness and Critical Event Response (PACER) at Johns Hopkins University. Authors Rothman and Gaydos were also supported in part by the US National Institute of Allergy and Infectious Diseases Mid-Atlantic Regional Center of Excellence for Bio-defense and Emerging Infectious Diseases, Public Health Response Project VI, NIH grant U54-AI057168-06. Any opinions, findings, conclusions or recommendations expressed in this publication are those of the authors and should not be interpreted as representing the official policies, either expressed or implied, of the United States Government or of Johns Hopkins University.

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