# Low Sensitivity of BinaxNOW RSV in Infants

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SUPPLEMENT ARTICLE

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***Background.*** Respiratory syncytial virus (RSV) is a major cause of hospitalization in infants. Early detection of RSV can optimize clinical management and minimize use of antibiotics. BinaxNOW RSV (BN) is a rapid antigen detection test that is widely used. We aimed to validate the sensitivity of BN in hospitalized and nonhospitalized infants against the gold standard of molecular diagnosis.

***Methods.*** We evaluated the performance of BN in infants with acute respiratory tract infections with different degrees of disease severity. Diagnostic accuracy of BN test results were compared with molecular diagnosis as reference standard.

***Results.*** One hundred sixty-two respiratory samples from 148 children from October 2017 to February 2019 were studied. Sixty-six (40.7%) samples tested positive for RSV (30 hospitalizations, 31 medically attended episodes not requiring hospitalization, and 5 nonmedically attended episodes). Five of these samples tested positive with BN, leading to an overall sensitivity of BN of 7.6% (95% confidence interval [CI], 3.3%–16.5%) and a specificity of 100% (95% CI, 96.2%–100%). Sensitivity was low in all subgroups.

***Conclusions.*** We found a low sensitivity of BN for point-of-care detection of RSV infection. BinaxNOW RSV should be used and interpreted with caution.

**Keywords.** antigen detection; birth cohort; diagnosis; point-of-care test; respiratory syncytial virus.

Respiratory syncytial virus (RSV) is the most common pathogen identified in young children with acute lower respiratory tract infections [1]. Respiratory syncytial virus is a major cause of hospital admissions with an estimated hospitalization rate of 19 per 1000 children under the age of 1 year worldwide [2–4].

Reliable rapid diagnostic tests are needed to improve patient management regarding unnecessary use of antibiotics [5, 6] and to enable cohorting of hospitalized children in the RSV season. An evolving role for rapid tests is as a companion diagnostic for the development of novel RSV antivirals and evaluation of efficacy of new RSV vaccines, for which it will be important to have both a reliable and rapid RSV test.

The current gold standard for RSV diagnosis is laboratory-based reverse-transcriptase polymerase chain reaction (RT-PCR). This technique is highly sensitive and specific, but it is time-consuming, relies on trained laboratory staff, and typically has a long lag time to provide results to clinical teams (24–48 hours), negating its clinical value. Although in recent years point-of-care tests (POCTs) utilizing molecular methods have been developed, they remain expensive and consequently are not widely adopted in clinical practice. A range of alternative POCTs are available and used in clinical practice that are fast, easy to use by nonlaboratory personnel, and often less expensive compared with routine RT-PCR. The turnaround time of most POCTs is less than 1 hour. Respiratory syncytial virus rapid antigen detection tests (RADTs) are POCTs with high specificity, but a wide range in sensitivity, partially depending on viral load [7, 8]. Two recent meta-analyses showed a pooled sensitivity of 81% (95% confidence interval [CI], 78%–84%) [9] and 75.9% (95% CI, 73.1%–78.5%) for RSV RADTs in general in children compared with RT-PCR [10]. There is large heterogeneity in these studies, which are often sponsored by the tests' manufacturer. In addition, many studies are performed retrospectively and in hospitalized children, whereas diagnostics are not evaluated at point of care (POC). As a result, sensitivity of individual studies vary considerably from 41.2% [11] to 83% [12].

The aim of the current study was to evaluate for the first time the performance of the RADT BinaxNOW RSV ([BN] Alere Inc., Waltham, MA) [13] to diagnose RSV infection in infants with acute respiratory tract infection (ARTI) in different clinical settings in a large international prospective clinical study.

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## METHODS

### Study Population

The study population consisted of infants (<1 year old) with an ARTI who were participating in the REspiratory Syncytial virus Consortium in EUrope (RESCEU) [14] birth cohort study or the case-control study during 2 RSV seasons between 1 October 2017 and 28 February 2019. The RESCEU is a European Union-funded consortium study aiming to define RSV burden of disease in Europe. The current study was performed in the Netherlands, Spain and the United Kingdom. The birth cohort study consists of healthy infants prospective followed up from birth. In their first year of life, during the RSV season(s), a RSV test was performed each time they experienced any symptoms of an ARTI. Infants were tested by a trained member of the study team at home or at the clinic and could be tested during more than 1 separate episode. The case-control study is a cross-sectional study performed in infants admitted to hospital, attending emergency departments (ED) or general practitioners (GPs) with symptoms of ARTI. Details of the study design and procedures can be found at clinicaltrials.gov (NCT03627572, NCT03756766). Informed consent was obtained from the parents of all study participants. All children with ARTI were eligible for RSV POC testing. For practical reasons, not all children could be tested with both the BN and the reference test. For this analysis, we included only samples on which both BN and a molecular reference test were performed (Figure 1).

Data on age, sex, comorbidities, duration of symptoms of ARTI, and level of medical care needed (hospitalized, medically attended [MA] ARTI, and non-MA ARTI) were obtained by completing questionnaires and case report forms. We defined 3 levels of medical care: (1) infants with ARTI who were hospitalized (including a subgroup of infants who were admitted to the pediatric intensive care unit [PICU]); (2) infants with MA ARTI, defined as infants who were seen at the ED or GP but were not admitted to the hospital; and (3) infants with non-MA ARTIs who did not see any doctor during the entire ARTI episode. In addition, the ReSViNET score was used to determine disease severity (Supplementary Table 1) [15].

### Study Procedures

A nasal flocked swab (FLOQSwab; Copan Diagnostics) was collected by a trained member of the study team and directly stored in one of the following viral transport media: MicroTest M4RT (3 mL; Remel) or UTM (3 mL; Copan Diagnostics). A maximum of 400 µL of the viral transport medium was used for POC testing. Samples were transported at room temperature. The BN test was performed within 4 hours. The remaining sample was stored in aliquots at −80°C or discarded if RSV was negative (infant case-control study). The molecular reference test was either Xpert Xpress Flu/RSV assay (Cepheid, Sunnyvale, CA) [16] or Alere i RSV assay (Alere Inc., Waltham, MA) [17] depending on availability of the tests at participating sites. The staff had hands-on training on how to sample patients and how to use the available POC tests before the start of the studies.

All tests were performed according to the manufacturer's instruction. In short, for the BN assay, 100 µL of the viral transport medium mixed with the swab was aspirated with the included transfer pipette. The BN card was opened, and the entire content of the filled pipette was slowly expelled onto the sample pad of the device. A timer was set at 15 minutes to avoid inaccurate test results. After these 15 minutes, test results were read immediately from the BN test card, by visual inspection (Supplementary Text).

### Statistical Analysis

A positive molecular test for RSV was defined as the reference outcome. The BN results were compared with the reference test to measure diagnostic accuracy. Dichotomous variables were compared using $\chi^2$ or Fisher's exact test as appropriate. $P < .05$ were considered statistically significant. Univariate logistic regression analysis was used to determine whether false-negative BN tests results were associated with age, duration of symptoms, or ReSViNET score. Statistical analyses were conducted using IBM SPSS Statistics for Windows, version 25.0 (IBM Corp., Armonk, NY).

## RESULTS

In total, 162 nasal swabs from 148 infants with symptoms of ARTI were tested with BN and the reference test. One hundred thirty-four infants were tested once and 14 infants were tested twice during 2 separate ARTI episodes. Of the 162 samples, 36 (22.2%) were from hospitalized infants, 83 (51.2%) from infants who had an MA ARTI, 41 (25.3%) from infants who had a non-MA ARTI, and 2 samples were from infants with missing data about level of care. Baseline characteristics are summarized in Table 1. Median age at moment of ARTI was 84 days (interquartile range, 39–178 days). Ninety-eight (78.4%) of the swabs were taken within 5 days after the start of symptoms. Four infants had comorbidities, including the following: prematurity, cardiomyopathy, and congenital bronchomalacia.

There were 66 RSV infections detected in 162 nasal swabs (40.7%), 5 (7.6%) of which tested positive by BN (Figure 1). All BN-positive samples also tested positive by the reference test. One infant had 2 RSV-positive episodes (1 episode of which was BN positive). Test characteristics of BN are shown in Table 2. Sensitivity was not significantly related to age, duration of symptoms, disease severity, or level of care required (Table 3). Sensitivity was higher in the subgroup of infants admitted to a PICU compared with other infants (22.2% versus 5.3%), although this difference was not statistically significant ($P = .134$). Univariate logistic regression analysis confirmed low sensitivity of BN in all subgroups.

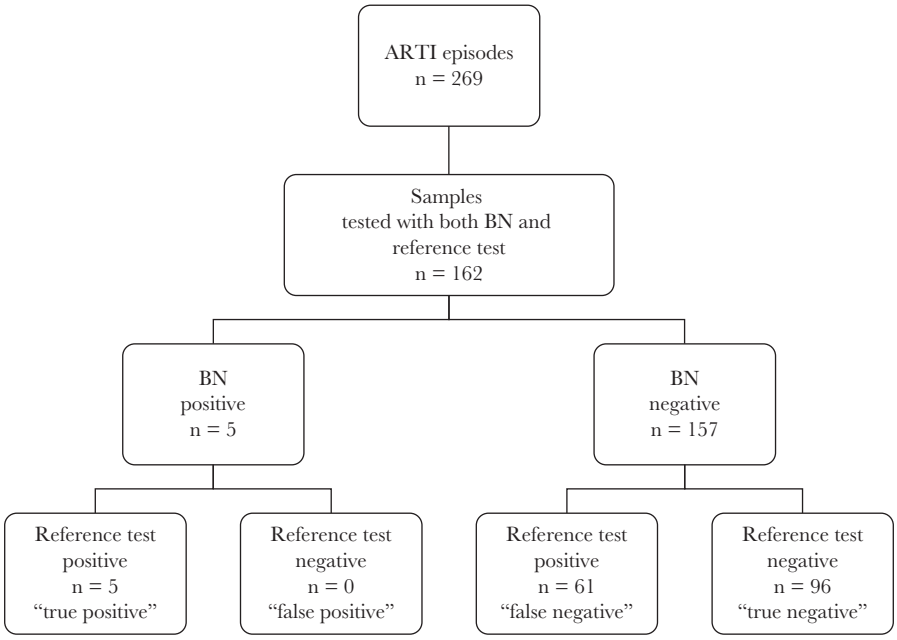


**Figure 1.** Study flow chart showing eligible acute respiratory tract infection (ARTI) episodes and test results of samples that were tested by BinaxNOW RSV (BN) and the reference test. n, number of ARTI episodes.

#### Test Procedure

Because sensitivity of BN was lower than previously published, we carefully analyzed our procedures. Uniform standard operating procedures regarding sample collection and POC testing with BN was written and distributed to all participating centers before the start of the study. In the course of the study, BN test procedure was thoroughly evaluated, including a careful analysis by employees from the manufacturer (Supplementary Text). No technical explanation was found for the low sensitivity of BN.

## DISCUSSION

In this study, we have shown that the overall sensitivity of BN was only 7.6% (95% CI, 3.3%–16.5%) in infants with ARTIs of varying clinical severity (hospitalized, MA ARTI, and non-MA ARTI). Highest sensitivity was seen in infants admitted to the PICU, although this was still only 22%. The sensitivity of BN in the current study is remarkably lower than previously reported. Two recent meta-analyses showed a pooled sensitivity of BN of 81% (95% CI, 74%–87%) [9] and 72.2% (95% CI, 65.2%–79.1%) [10], respectively. Individual studies showed a sensitivity varying from 41.2% to 83% in children when compared with RT-PCR [7, 11, 12, 18–21]. Characteristics of these studies are shown in Table 4. The sample size of the studies varied between 66 and 720 participants with various age limitations. The 4 larger studies were all performed in children under the age of 3 years with nasopharyngeal aspirate (NPA) or nasal wash (NW) and showed a sensitivity of 63%–83% compared with RT-PCR. The 3 other studies were smaller and mainly used nasopharyngeal swab (NPS) as sampling method. The sensitivity of these studies varied between 41% and 80% compared with RT-PCR. The sample size of our study was 162, which is comparable but still smaller than the 4 larger studies. The low sensitivity in our study compared with the other studies is striking and necessitated a thorough analysis of the differences with the other studies and other possible explanations for the low sensitivity observed in our study. One of the differences between our study and the other studies is that we also included infants with non-MA ARTI, whereas other studies evaluated the performance of BN mainly in hospitalized children.

We reflected on possible explanations for the low sensitivity observed in our study. We considered that reduced disease severity could be linked to lower viral loads in infants recruited [22] and subsequently a lower sensitivity. However, even in the group of infants with severe disease who were admitted to hospital, sensitivity was less than 10%. Other factors that might influence sensitivity are age and duration of symptoms because both are probably related to viral load. False-negative results are more often seen with an increasing age [20] or longer duration of symptoms [7, 20, 21, 23]. However, all children in our study were younger than 1 year of age, and the majority (78.4%) were tested within 5 days after the start of symptoms, thus this could not explain the low sensitivity.

We also considered sampling methods as a cause of the low sensitivity in our study. Compared with the other published studies, we used nasal flocked swabs in 3 mL UTM or M4RT instead of NPS in 1 or 1.5 mL viral transport medium or NW/

**Table 1. Characteristics of Infants at Moment of ARTI Episode**

| Reference Test[a] | | RSV Positive | | RSV Negative |
|---|---|---|---|---|
| | Total ARTI Episodes n = 162 | BinaxNOW Positive (TP) n = 5 | BinaxNOW Negative (FN) n = 61 | BinaxNOW Negative (TN) n = 96 |
| Age at moment of ARTI episode, days (median [IQR]) | 84 [39–178] | 42 [33–203] | 99 [49–197] | 67 [34–161] |
| Sex, male (n, %)[b] | 94 (58.0%) | 4 (80.0%) | 33 (54.1%) | 57 (59.4%) |
| Comorbidity (n, %)[c] | 4 (2.5%) | 1 (20.0%) | 3 (4.9%) | 0 (0%) |
| Duration of symptoms[d] days (median [IQR]) | 3 [2–5] | 4 [2–5] | 3 [2–4] | 3 [2–6] |
| Level of Care Needed (n, %)[e] | | | | |
| Non-MA ARTI | 41 (25.3%) | 0 (0.0%) | 5 (8.2%) | 36 (37.5%) |
| MA ARTI | 83 (51.2%) | 3 (60.0%) | 28 (45.9%) | 52 (54.2%) |
| Hospitalized | 36 (22.2%) | 2 (40.0%) | 28 (45.9%) | 6 (6.3%) |
| PICU | 11 (30.6%) | 2 (100%) | 7 (25.0%) | 2 (33.3%) |
| Country (n, %) | | | | |
| Netherlands | 118 (72.8%) | 3 (60.0%) | 53 (86.9%) | 62 (64.6%) |
| United Kingdom | 14 (8.6%) | 0 (0.0%) | 0 (0.0%) | 14 (14.9%) |
| Spain | 30 (18.5%) | 2 (40.0%) | 8 (13.1%) | 20 (20.8%) |
| ReSViNET score[f] (median [IQR]) | 3 [1–6] | 6 [5–16] | 5 [3–9] | 1 [1–3] |
| Reference Test (n, %) | | | | |
| Alere i RSV | 120 (74.1%) | 5 (100.0%) | 32 (52.5%) | 83 (86.5%) |
| Xpert Xpress | 42 (25.9%) | 0 (0.0%) | 29 (47.5%) | 13 (13.5%) |
| Flu/RSV | | | | |

Abbreviations: ARTI, acute respiratory tract infection; FN, false negative; IQR, interquartile range; MA ARTI, medically attended ARTI; n, number of ARTI episodes; PICU, pediatric intensive care unit; RSV, respiratory syncytial virus; TN, true negative; TP, true positive.

NOTE: Categorical data are expressed as frequency (%), and continuous data are expressed as median [IQR]. Percentages may not equal 100, because of rounding and missing values. *P* values were not determined because of the low number of positive test results with BinaxNOW RSV.

[a]Alere i RSV or Xpert Xpress Flu/RSV were used as reference test.

[b]Including 10 males that were tested twice.

[c]None of the infants with comorbidity were tested twice.

[d]Data available for 125 episodes.

[e]Data available for 160 episodes.

[f]Data available for 99 episodes.

NPA. We have previously shown that nasal aspirates are associated with higher sensitivity than nonflocked swabs to detect RSV by PCR [24]. Other studies have shown that sensitivity was comparable between NW or NPA and NPS with flocked swabs for detection of viruses by PCR [25, 26]. In addition, Blaschke et al [27] showed that midturbinate (nasal) flocked swabs are comparable to NPS for quantitative detection of RSV in infants, showing similar viral loads. Although no studies have previously compared the performance of rapid antigen testing in nasal swabs compared with aspirates or washes, we do not think that sampling methods fully explain the low sensitivity of BN. Temporal evolution of the binding site of the RSV fusion protein may have changed over time with loss of binding to the BN antibody, ultimately resulting in decreased sensitivity. We have limited information on viral sequences in our patient population. Because most of the known antigenic sites of the RSV fusion protein are generally well conserved, we believe this explanation for the low sensitivity of BN is unlikely [28]. Taken together, we have not found a methodological or biological explanation for the low sensitivity of BN in our study compared with previous reports.

A strength of our study is that it is part of a large prospective clinical study with a well defined study population performed in different centers across Europe. Our study is based

**Table 2. Primary Analysis of BinaxNOW RSV Performance[a]**

| | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| Primary analysis (n = 162) | 7.6 (5/66) | 100 (96/96) | 100 (5/5) | 61.1 (96/157) |
| 95% CI | 3.3–16.5 | 96.2–100.0 | 56.6–100.0 | 54.3–68.4 |

Abbreviations: CI, confidence interval; n, number of acute respiratory tract infection episodes; NPV, negative predictive value; PPV, positive predictive value.

[a]Data are percentages (proportions) of BinaxNOW RSV test results compared with the reference test.

**Table 3. BinaxNOW RSV Performance by Different Variables**

| Variable | Sensitivity (%) | Specificity (%) | PPV (%) | NPV (%) |
|---|---|---|---|---|
| Level of Care Needed[a] | | | | |
| Non-MA ARTI (n = 41) | 0 (0/5) | 100 (36/36) | NA (0/0) | 87.8 (36/41) |
| MA ARTI (n = 83) | 9.7 (3/31) | 100 (52/52) | 100 (3/3) | 65.0 (52/80) |
| Hospitalized (n = 36) | 6.7 (2/30) | 100 (6/6) | 100 (2/2) | 17.6 (6/34) |
| PICU (n = 11) | 22.2 (2/9) | 100 (2/2) | 100 (2/2) | 22.2 (2/9) |
| *P* value | .726 | NA | NA | <.005 |
| Age | | | | |
| ≤60 days (n = 68) | 12.5 (3/24) | 100 (44/44) | 100 (3/3) | 67.7 (44/65) |
| >60 days (n = 93) | 4.8 (2/42) | 100 (51/51) | 100 (2/2) | 56.0 (51/91) |
| *P* value | .345 | NA | NA | .183 |
| Duration of Symptoms Before Testing[b] | | | | |
| ≤5 days (n = 98) | 9.8 (5/51) | 100 (47/47) | 100 (5/5) | 50.5 (47/93) |
| >5 days (n = 26) | 0 (0/8) | 100 (18/18) | NA (0/0) | 69.2 (18/26) |
| *P* value | >.999 | NA | NA | .119 |
| ReSViNET score[c] | | | | |
| ≤3 (n = 53) | 0 (0/17) | 100 (36/36) | NA (0/0) | 67.9 (36/53) |
| >3 (n = 46) | 12.8 (5/39) | 100 (7/7) | 100 (5/5) | 17.1 (7/41) |
| *P* value | .309 | NA | NA | <.005 |

Abbreviations: ARTI, acute respiratory tract infection; MA ARTI, medically attended-ARTI; n, number of ARTI episodes; NA, not applicable; NPV, negative predictive value; PICU, pediatric intensive care unit; PPV, positive predictive value; RSV, respiratory syncytial virus.

NOTE: Data are percentages (proportions) of BinaxNOW RSV performance test results compared with the reference test. ReSViNET score was used to evaluate disease severity (Supplementary Figure 1).

[a]Data available for 160 episodes.

[b]Data available for 125 episodes.

[c]Data available for 99 episodes.

on clinical endpoints rather than virological, ensuring a low risk of bias. Another strength is that we evaluated the performance in different clinical settings with a wide range of disease severity. This enabled us to evaluate test performance not only in a hospital setting but also in primary care and EDs. Because the availability of POCTs is increasing, these tests might also be introduced into outpatient settings. Our study added valuable information about the sensitivity in different clinical settings, which is important to know before implementing POCTs in these settings. Finally, we evaluated the test procedure of BN thoroughly during the study period to avoid any bias due to incorrect handling of the tests (see Supplemental Text). We also

**Table 4. Overview of Characteristics of Published Studies About the Performance of BN Compared With Molecular Tests in Children**

| Study | Age | Type of ARTI | Reference Test | Type of Sample | POC Setting | n= | Sensitivity (95% CI) | Specificity (95% CI) |
|---|---|---|---|---|---|---|---|---|
| Present study | <1 year (median 84 days) | Hospitalized, (non)-MA ARTI | Alere i, Xpert Xpress | NS (flocked swabs in 3 mL UTM/M4RT) | Yes | 162 | 7.6% (3.3–16.5) | 100% (96.2–100) |
| Bruning et al [18] | <16 years | Hospitalized (PICU), respiratory illness | RT-PCR | NPS, NPW | No | 66 | 80% (64.3–95.7) | 100% (NA) |
| Jung et al [19] | <2 years | Hospitalized, ALRI | RT-PCR | NPS in 1.5 mL VTM (in-house) | No | 91 | 71.4% (61.4–79.7) | NA |
| Khanom et al [11] | <5 years | Hospitalized, ARTI | RT-PCR | NPS in 1 mL VTM (in-house) | Yes | 159 | 41.2% (27.9–55.8) | 100% (95.7–100) |
| Miernyk et al [7] | <3 years (mean 9.3 months) | Hospitalized, LRTI | RT-PCR | NPW | No | 311 | 72% (61–74) | 97% (94–99) |
| Mills et al [12] | <2 years (mean 7 months) | ED, respiratory symptoms | RT-PCR | NPA, NPW | Yes | 579 | 83% (79–87) | 83% (78–87) |
| Papenburg et al [20] | <3 years (median 5.7 months) | Hospitalized, ARTI | RT-PCR | NPA | No | 720 | 80% (76–83.5) | 96.9% (94–98.6) |
| Pfeil et al [21] | <3 years (mean 7.9 months) | Hospitalized, ARTI | RT-PCR | NW | Yes | 242 | 63% (61–76) | 100% (NA) |

Abbreviations: ALRI, acute lower respiratory tract infection; ARTI, acute respiratory tract infection; BN, BinaxNow RSV; CI, confidence interval; ED, emergency department; LRTI, lower respiratory tract infection; MA ARTI, medically attended ARTI; NA, not applicable; NPA, nasopharyngeal aspirate; NPS, nasopharyngeal swab; NS, nasal swab; NPW, nasopharyngeal wash; NW, nasal wash; PICU, pediatric intensive care unit; POC, point of care; RT-PCR, reverse-transcription polymerase chain reaction; VTM, viral transport media.

worked closely with the manufacturer of BN to ensure we used the correct procedure.

There are several limitations to our study. First, we did not compare viral loads between true-positive and false-negative test results. Alere i and Xpert Xpress are qualitative tests. The RADT sensitivity depends on viral load [7, 8], whereas viral load is positively associated with disease severity [22]. In our study, sensitivity in the infants who were admitted to the PICU was higher, but this was still only 22% and not statistically significant higher compared with other clinical settings. Second, in our study, we used the Alere i RSV and Xpert Xpress Flu/RSV as reference standards, whereas RT-PCR has been used as the gold standard in some other studies [7, 11, 12, 18–20]. These new molecular assays are reported to have a sensitivity (93%–100%) and specificity (96%–100%) comparable with RT-PCR [29–34]. Third, we have not subtyped RSV. Respiratory syncytial virus genotype-B infection has been associated previously with false-negative results of RADT [20]. Fourth, we used nasal swabs and not NPS. Viral loads could be lower in this anterior nasal region and thus affect sensitivity. However, midturbinate flocked swabs have shown to be comparable for quantitative detection of RSV in infants [27]. Last, we have not analyzed why BN performed suboptimally. It is possible that both transport media used in this study, although recommended by the manufacturer, had some form of inhibitory effect on the test.

## CONCLUSIONS

In conclusion, we have performed the first international prospective population-based study to define the sensitivity of a RADT for RSV infection. We showed that BN has low sensitivity in infants with ARTI in different clinical settings when collected with a nasal flocked swab in UTM or M4RT transport medium. Even in infants with the most severe disease, sensitivity was only 22%. Our study indicates that BN should be used and interpreted with caution. More studies are needed to determine variation in sensitivity with different sampling methods. Physicians should consider using more sensitive molecular assays for RSV POC testing.

### Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

### Notes

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***Potential conflicts of interest.*** L. J. B. has regular interaction with pharmaceutical and other industrial partners. He has not received personal fees or other personal benefits; he is also the founding chairman of the ReSViNET Foundation. M. D. S., on behalf of the University of Oxford, has acted or acts as a Chief/Principal Investigator on research studies funded or sponsored by vaccine manufacturers including GlaxoSmithKline, Janssen, MCM, Novavax, MedImmune, and Pfizer. He receives no personal financial benefit from this work. A. J. P. is Chair of UK DHSC's JCVI and the European Medicines Agency scientific advisory group, on vaccines, and is a member of the WHO's Strategic Advisory Group of Experts (SAGE). A. J. P. is an NIHR Senior Investigator. F. M.-T. received honoraria from GSK, Pfizer, Sanofi Pasteur, MSD, and Janssen for taking part in advisory boards, expert meetings, and for acting as speaker in congresses outside the scope of the submitted work. F. M.-T. has also acted as principal investigator in randomized controlled trials of the above-mentioned companies as well as Seqirus, Ablynx, Regeneron, Abbott, Novavax, and MedImmune, with any honoraria being paid to his institution. S. C. provides consultancy (including trial development and data monitoring) for which the University of Edinburgh receives payment from Janssen, Ablynx (Sanofi), Pulmocide, and ReViral. 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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