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Diagnostic Accuracy of Four Commercial Triplex Immunochromatographic Tests for Rapid Detection of Rotavirus, Adenovirus, and Norovirus in Human Stool Samples

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ABSTRACT Noroviruses (NoV), rotaviruses (RVA), and adenoviruses (AdV) are the main viral agents responsible for acute gastroenteritis (AGE) in humans. We aimed to determine the diagnostic accuracy of four commercial immunochromatographic tests (ICTs) intended for the rapid and simultaneous detection of these three pathogens. Diagnostic accuracy of bioNexia Noro/Rota-Adeno (bioMérieux), Immunoquick NoRotAdeno (Biosynex), Rota+Adeno+Noro combo card (CerTest Biotec), and Rida Quick Rota/Adeno/Noro Combi (R-Biopharm) ICTs was assessed retrospectively using a collection of 160 stool specimens (including 43 RVA-, 47 AdV-, and 42 NoV-positive samples) from French patients with AGE and using molecular methods as the reference standard. For RVA, the four ICTs demonstrated similar high sensitivity (93%) and excellent specificity (97.4 to 100%). For AdV, the four ICTs demonstrated similar poor sensitivity (54.3 to 58.7%) but excellent specificity (95.5 to 100%). They performed the best in AdV-F species (sensitivity, 80.8 to 84.6%) and worst in AdV non-F species (sensitivity, 22.2 to 27.8%). For NoV, the Rida Quick Rota/Adeno/Noro combi ICT exhibited high sensitivity (87.5%), but the sensitivity of the three others was poor (42.5 to 47.5%). The four ICTs exhibited high specificity (96.6 to 99.1%). Diagnostic accuracy was genogroup dependent. When we tested genogroup I NoV, the Rida Quick Rota/Adeno/Noro Combi ICT presented high sensitivity (90%), while the three other ICTs presented poor sensitivity (10 to 30%); when we tested genogroup II NoV, sensitivity was similar for the four ICTs (65 to 85%). In conclusion, the four ICTs are suitable first-line tests for the rapid diagnosis of RVA infections. The four ICTs are not suitable for the routine diagnosis of AdV infections but could provide a rapid response in case of positivity, notably in the context of AGE. Only the Rida Quick Rota/Adeno/Noro Combi ICT is suitable for the rapid detection of NoV, while the sensitivity for the detection of genogroup I NoV needs to be improved for the 3 other ICTs before being implemented in the routine diagnosis of NoV.

KEYWORDS sensitivity and specificity, immunochromatography, enteric viruses, gastroenteritis, norovirus, rotavirus, adenovirus

Acute gastroenteritis (AGE), which is most often due to enteric viruses, is a major public health concern that affects hundreds of millions of people worldwide every year. Group A rotaviruses (RVA) are the main agents responsible for severe gastroenteritis in young children; an estimated 215,000 children under 5 years old die from RVA infection every year in the world (1). But these infections can also cause mild to severe diarrhea in adults, and immunocompromised individuals are particularly susceptible (2). Conversely, human noroviruses (NoV), mainly genogroup II, have been recognized as

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the major cause of nonbacterial acute gastroenteritis in adults (second after rotaviruses in children), causing large epidemics in close communities such as nursing homes, hospitals, schools, and restaurants (3). Besides these two viruses, human mastadenovirus, notably F species (types 40 and 41), is still considered an important etiological agent of viral gastroenteritis, especially in children (4).

Numerous commercial immunochromatographic tests (ICTs) have been made available for the detection of NoV alone or for the simultaneous detection of RVA and adenovirus (AdV). Commercial triplex ICTs were only recently introduced for the detection of these three common enteric viruses in human stool samples in one draw. For medical laboratories not equipped to carry out molecular investigations, these relatively inexpensive, easy-to-perform tests provide rapid on-site results. Following the commercialization of these new kits, we evaluated and compared the diagnostic accuracy of four triplex ICTs intended for the simultaneous, differential, qualitative detection of NoV (genogroups I [GI] and II [GII]), RVA, and AdV (all species) in stool samples. The tests were developed by four different companies: bioMérieux, Biosynex, CerTest Biotec, and R-Biopharm. Diagnostic accuracy was retrospectively assessed using real-time PCR or real-time reverse transcription-PCR (RT-PCR) as the reference standard and a wide panel of characterized stool samples from the French National Reference Center for Gastroenteritis Viruses (NRCgev, University Hospital of Dijon Bourgogne, France).

MATERIALS AND METHODS

The four CE-marked ICTs evaluated in this study were the bioNexia Noro/Rota-Adeno (ref. 415089; bioMérieux, Marcy-l'Etoile, France), Immunoquick NoRotAdeno (ref. 1150013; Biosynex, Strasbourg, France), Rota+Adeno+Noro combo card (ref. RA872001V; CerTest Biotec, Zaragoza, Spain), and Rida Quick Rota/Adeno/Noro Combi (ref. N1903, R-Biopharm AG, Darmstadt, Germany). Diagnostic accuracy was assessed on a collection of surplus from raw human fecal samples collected by the NRCgev in France from 2000 to 2018. These samples were from AGE sporadic or outbreak cases and were sent to the NRCgev by local laboratories for the purpose of diagnosing enteric viruses. Stool samples were not treated (e.g., preservative agents) or diluted (e.g., transport medium) before being stored at −40°C. Samples were selected in order to be representative of a variety of the most epidemiologically relevant viral strains. Overall, the collection was made up of 160 specimens and included a total of 42 NoV (21 GI and 21 GII)-, 41 RVA-, and 47 AdV (26 F species, 19 non-F species, and 2 undetermined species)-positive samples and 40 negative samples (i.e., tested negative for the three viruses). A combination of two viruses (AdV plus RVA or NoV plus RVA) was observed in 10 of the 160 specimens from the collection. Patient age ranged from 41 days to 98 years (median, 34.6 years) with a male/female ratio of 0.88. NoV (GI and GII) and RVA were initially screened using in-house real-time RT-PCRs as previously described (5), and AdV were detected using a commercial real-time PCR assay designed to detect all types of human AdV (adenovirus R-gene; bioMérieux, Marcy-l'Etoile, France). Viruses were then further characterized by endpoint PCRs or RT-PCRs associated with sequencing, as previously described (5).

From July to August 2018, the ICTs were performed simultaneously at the NRCgev on thawed raw stool samples. Testing was done according to the manufacturers' instructions. For all the ICTs except Immunoquick NoRotAdeno, a single step of stool sample preparation in a ready-to-use plastic vial containing dilution buffer was needed. For Immunoquick NoRotAdeno, additional steps (adding dilution buffer into a tube and incubation) were needed. Then, the diluted stool samples were added in the sample wells of the test cassettes, and the results were read after 10 min (bioNexia Noro/Rota-Adeno and Rota+Adeno+Noro combo card) or 15 min (Immunoquick NoRotAdeno and Rida Quick Rota/Adeno/Noro Combi) of incubation. The results of the assays were read by two qualified laboratory professionals (plus a third read by another qualified laboratory professional in case of discrepancy) blinded to the results of the enteric viruses screening. The reference standards (RT-PCRs, as mentioned above) were performed again on the same thawed samples on the same day as the ICTs in the following cases: (i) to check for the presence of a virus of interest when all the ICTs yielded a negative result for a sample expected to be positive. If the reference standard was positive, the sample was included in the study, and a false-negative result was assigned to the ICTs. If the reference standard was negative, a potential virus conservation problem was suspected, and the sample was excluded from the study; and (ii) to check the absence of a virus when at least one ICT gave a positive result for a sample expected to be negative for that virus. If the reference standard was negative again, the sample was included in the study, and a false-positive result was assigned to the incriminated ICT. If the reference standard was finally positive, it may have been due to a technical problem during the initial virus screening; thus, the sample was included in the study with an updated viral status taking into account this "discovered" positive result.

For each ICT, the sensitivity, specificity, likelihood ratios (LR), and diagnostic odds ratio (DOR) were calculated with 95% confidence intervals (CIs) using Meta-DiSc software (6). Sensitivity and specificity were pooled similar to a meta-analysis via a Bayesian approach (7). The mean values of quantification cycle (C_q) were assessed for the various strains and compared using a linear regression model with a

bootstrap estimate of variance (8). All statistical analyses were performed using Stata software (9) or R software (10).

RESULTS

Among the 160 specimens obtained from the initial collection, only 3 (1 NoV GI.1, 1 NoV GII.2[P16], and 1 AdV-C) were excluded from the study after a negative result was obtained for the target condition when the reference test was repeated. In addition, the viral status was updated for 2 specimens (one from "no virus" to "RVA positive" and the other from "NoV positive" to "NoV and RVA positive") due to a positive result obtained when the RVA reference standard was repeated. The G and P genotypes of these 2 RVA strains were undetermined. The diagnostic accuracy of ICTs was thus assessed on a total of 157 stool samples, as shown in Table 1. It should be noted that no invalid ICT results (i.e., absence of the control line) were observed during the study.

Rotavirus. The four ICTs exhibited a sensitivity of 93% and a specificity ranging from 97.4% to 100% for the detection of RVA, leading to positive LR (LR+) ranging from 35.3 to 211.7 and negative LR (LR−) ranging from 0.071 to 0.080 (Table 2). The DOR was 493.3 to 2,649.9 (Table 2). The 95% CI overlapped for all of the performance indicators (Table 2).

All the RVA genotypes included in the study were detected by the four ICTs, and only the strains with undetermined G and P genotypes were rarely or not detected (Table 3). Interestingly, these strains displayed the highest C_q values by real-time RT-PCR (from 31.41 to 36.66 for nontypeable strains versus from 8.80 to 26.32 for typeable strains [data not shown]). Because C_q values correlate inversely with the amount of virus in the specimen and are used as a proxy for viral load, the C_q values observed for samples with undetermined G and P genotypes suggested that these samples contained the lowest viral loads among the RVA-positive samples from this study. These low RVA loads may explain why 2 samples had an RVA-negative result with the reference standard during initial screening followed by an RVA-positive result when the assay was repeated.

Adenovirus. The four ICTs demonstrated a sensitivity ranging from 54.3 to 58.7% and a specificity ranging from 95.5% to 100% for the detection of AdV antigens in stool samples (Table 2). LR+ ranged from 13.0 to 131.1, and LR− from 0.417 to 0.459. The DOR went from 30.1 to 314.5 (Table 2). The 95% CI overlapped for all performance indicators (Table 2), and the sensitivity levels for the four ICTs were not significantly different ($P = 0.988$; data not shown).

When considering AdV species F only, sensitivity ranged from 80.8 to 84.6% (versus 22.2 to 27.8% for AdV non-F), LR+ ranged from 18.8 to 186.7 (versus 6.2 to 64.8 for AdV non-F), LR− ranged from 0.161 to 0.205 (versus 0.714 to 0.767 for AdV non-F), and DOR ranged from 116.6 to 1,115.0 (versus 8.2 to 90.9 for AdV non-F) (Table 2).

Among the AdV non-F species included in this study, only AdV-C was detected by the ICTs (Table 3). AdV-B and AdV-D were not detected by the ICTs, but fewer samples were investigated. Finally, the 2 nontypeable AdV strains were not detected by the four ICTs (Table 3).

Analysis of the C_q values obtained by real-time PCR revealed that the mean C_q value for AdV-F (14.39; 95% CI, 11.80 to 16.98; data not shown) was lower than the mean C_q value for AdV non-F (26.18; 95% CI, 22.64 to 29.72; data not shown), suggesting that samples positive for AdV-F had a higher viral load than samples positive for non-F AdV. Moreover, the mean C_q values observed for AdV-F false-negative samples with ICTs were delayed from 14.50 to 15.77 cycles compared to the mean C_q values of AdV-F true-positive samples, suggesting that false-negative samples had lower viral loads than true-positive samples (Table 4). The same trend was observed for AdV non-F samples, where the means of C_q values were 10.58 to 12.08 cycles higher for false-negative samples than for true-positive samples (Table 4).

Norovirus. For the detection of NoV, the Rida Quick Rota/Adeno/Noro Combi assay exhibited a sensitivity of 87.5% and an LR− of 0.126, with a 95% CI that did not overlap the values of the three other ICTs (Table 2). The difference in sensitivity between the

TABLE 1 Sample collection used to assess diagnostic accuracy of immunochromatographic tests

Virus[c]	Strain	No. of samples
Norovirus genogroup I	GI.1	3
	GI.2	1
	GI.2[P2]	3
	GI.4	1
	GI.4[P4]	3
	GI.6[PNA1]	4
	GI.7	1
	GI.7[P7]	3
Total		19
Norovirus genogroup II	GII.2[P16]	3
	GII.4 Sydney[P4 New Orleans]	4
	GII.4 Sydney[P16]	3
	GII.6[P7]	4
	GII.17[P17]	4
Total		18
Total norovirus, genogroups I and II		37
Nonenteric adenovirus	B	2
	C	11
	D	1
Total		14
Enteric adenovirus	F	24
Total adenovirus, all species		38
Group A rotavirus	G1P[8]	7
	G2P[4]	4
	G3P[8]	4
	G4P[8]	5
	G9P[8]	6
	G12P[8]	5
	G-UDP-UD[a,d]	1
Total		32
Adenovirus + group A rotavirus	Adenovirus B + rotavirus G1P[8]	1
	Adenovirus C + rotavirus G2P[4]	3
	Adenovirus F + rotavirus G1P[8]	1
	Adenovirus F + rotavirus G-UDP-UD	1
	Adenovirus UD[d] + rotavirus G2P[4]	1
	Adenovirus UD + rotavirus G3P[8]	1
Total		8
Norovirus + group A rotavirus	Norovirus GI.1 + rotavirus G9P[8]	1
	Norovirus GII.3 + rotavirus g1p[8]	1
	Norovirus GII.4 Sydney[P16] + rotavirus G-UDP-UD[b]	1
Total		3
None	Not applicable	39
Total		157

[a]Viral status updated from "No virus" to "Group A rotavirus positive."
[b]Viral status updated from "norovirus positive" to "norovirus and group A rotavirus positive."
[c]Classification of noroviruses is based on the latest recommendations (28).
[d]UD, undetermined.

Rida Quick Rota/Adeno/Noro Combi assay and the three other ICTs was found to be statistically significant ($P \leq 0.014$; data not shown). For the three other ICTs, sensitivity ranged from 42.5 to 47.5%, and the LR− ranged from 0.534 to 0.595; these results were similar for the three assays (Table 2). The specificity of the four ICTs ranged from 96.6

TABLE 2 Diagnostic accuracy of immunochromatographic tests using RT-PCR as the reference standard

ICT (company)	Total no. of samples tested	No. of samples with expected positives	No. of samples with expected negatives	Viral target	Sensitivity (% [95% CI])	Specificity (% [95% CI])	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)	Diagnostic odds ratio (95% CI)
Rida Quick Rota/Adeno/Noro Combi (R-Biopharm)	157	43	114[a]	Rotavirus A	93.0 (80.9–98.5)	97.4 (92.5–99.5)	35.3 (11.5–108.3)	0.072 (0.024–0.214)	493.3 (95.6–2,544.8)
bioNexia Noro/Rota-Adeno (bioMérieux)	157	43	114[a]	Rotavirus A	93.0 (80.9–98.5)	100 (96.8–100)	211.7 (13.3–3,368.9)	0.080 (0.029–0.218)	2,649.9 (133.9–52,420.1)
Rota+Adeno+Noro combo card (CerTest Biotec)	157	43	114[a]	Rotavirus A	93.0 (80.9–98.5)	98.2 (93.8–99.8)	53.0 (13.4–209.9)	0.071 (0.024–0.212)	746.7 (120.3–4,632.6)
Immunoquick NoRotAdeno (Biosynex)	157	43	114[a]	Rotavirus A	93.0 (80.9–98.5)	100 (96.8–100)	211.7 (13.3–3,368.9)	0.080 (0.029–0.218)	2,649.9 (133.9–52,420.1)
Rida Quick Rota/Adeno/Noro Combi (R-Biopharm)	157	46	111[b]	Adenovirus, all species	54.3 (39.0–69.1)	100 (96.7–100)	121.5 (7.6–1,955.2)	0.459 (0.336–0.627)	264.5 (15.5–4,511.9)
	137	26	111[c]	Adenovirus F	80.8 (60.6–93.4)	100 (96.7–100)	178.4 (11.2–2,852.8)	0.205 (0.097–0.431)	871.7 (46.5–16,352.3)
	129	18	111[d]	Adenovirus non–F	22. 2 (6.4–47.6)	100 (96.7–100)	53.1 (3.0–946.0)	0.767 (0.597–0.985)	69.2(3.5–1,352.4)
bioNexia Noro/Rota-Adeno (bioMérieux)	157	46	111[b]	Adenovirus, all species	54.3 (39.0–69.1)	100 (96.7–100)	121.5 (7.6–1,955.2)	0.459 (0.336–0.627)	264.5 (15.5–4,511.9)
	137	26	111[c]	Adenovirus F	80.8 (60.6–93.4)	100 (96.7–100)	178.4 (11.2–2,852.8)	0.205 (0.097–0.431)	871.7 (46.5–16,352.3)
	129	18	111[d]	Adenovirus non F	22.2 (6.4–47.6)	100(96.7–100)	53.1 (3.0–946.0)	0.767 (0.597–0.985)	69.2 (3.5–1,352.4)
Rota+Adeno+Noro combo card (CerTest Biotec)	157	46	111[b]	Adenovirus, all species	58.7 (43.2–73.0)	100 (96.7–100)	131.1 (8.2–2,104.4)	0.417 (0.297–0.585)	314.5(18.4–5,371.8)
	137	26	111[c]	Adenovirus F	84.6 (65.1–95.6)	100 (96.7–100)	186.7 (11.7–2,981.2)	0.167 (0.072–0.389)	1,115.0 (58.0–21,445.4)
	129	18	111[d]	Adenovirus non-F	27.8 (9.7–53.5)	100 (96.7–100)	64.8 (3.7–1,125.4)	0.714 (0.536–0.951)	90.9 (4.8–1,735.2)
Immunoquick NoRotAdeno (Biosynex)	157	46	111[b]	Adenovirus all species	58.7 (43.2–73.0)	95.5 (89.8–98.5)	13.0 (5.3–31.7)	0.433 (0.306–0.612)	30.1 (10.3–88.0)
	137	26	111[c]	Adenovirus F	84.6 (65.1–95.6)	95.5 (89.8–98.5	18.8 (7.9–44.9)	0.161 (0.065–0.397)	116.6(29.0–469.4)
	129	18	111[d]	Adenovirus non-F	27.8 (9.7–53.5)	95.5 (89.8–98.5)	6.2 (2.0–19.2)	0.756 (0.566–1.010)	8.2 (2.1–32.0)
Rida Quick Rota/Adeno/Noro Combi (R-Biopharm)	157	40	117[e]	Norovirus GI and GII	87.5 (73.2–95.8)	99.1 (95.3–100)	102.4 (14.5–723.2)	0.126 (0.056–0.286)	812 (91.8–7,183.6)
	137	20	117[f]	Norovirus GI	90.0 (68.3–98.8)	99.3 (96.0–100)	123.3 (17.4–873.8)	0.101 (0.027–0.375)	1,224.0 (105.6–14,188.1)
	137	20	117[g]	Norovirus GII	85.0 (62.1–96.8)	99.3 (96.0–100)	116.4 (16.4–827.9)	0.151 (0.053–0.429)	770.7 (75.8–7,831.6)
bioNexia Noro/Rota-Adeno (bioMérieux)	157	40	117[e]	Norovirus GI and GII	47.5 (31.5–63.9)	98.3 (94.0–99.8)	27.8 (6.8–114.1)	0.534 (0.397–0.718)	52 (11.3–240.1)
	137	20	117[f]	Norovirus GI	30.0 (11.9–54.3)	98.3 (94.0–99.8)	17.5 (3.8–80.9)	0.712 (0.534–0.950)	24.6 (4.5–134.0)
	137	20	117[g]	Norovirus GII	65.0 (40.8–84.6)	98.3 (94.0–99.8)	38.0 (9.3–155.9)	0.356 (0.196–0.647)	106.8 (20.0–568.9)
Rota+Adeno+Noro combo card (CerTest Biotec)	157	40	117[e]	Norovirus GI and GII	45.0 (29.3–61.5)	98.3 (94.0–99.8)	26.3 (6.4–108.5)	0.560 (0.422–0.741)	47 (10.2–217.3)
	137	20	117[f]	Norovirus GI	10.0 (1.2–31.7)	98.3 (94.0–99.8)	5.8 (0.9–39.2)	0.916 (0.790–1.062)	6.4 (0.8–48.3)
	137	20	117[g]	Norovirus GII	80.0 (56.3–94.3)	98.3 (94.0–99.8)	46.8 (11.6–188.1)	0.203 (0.085–0.489)	230.0 (38.9–1,358.6)
Immunoquick NoRotAdeno (Biosynex)	157	40	117[e]	Norovirus GI and GII	42.5 (27.0–59.1)	96.6 (91.5–99.1)	12.4 (4.4–34.8)	0.595 (0.455–0.779)	20.9 (6.4–67.8)
	137	20	117[f]	Norovirus GI	15.0 (3.2–37.9)	96.6 (91.5–99.1)	4.4 (1.1–18.1)	0.880 (0.730–1.061)	5.0 (1.0–24.2)
	137	20	117[g]	Norovirus GII	70.0 (45.7–88.1)	96.6 (91.5–99.1)	20.5 (7.5–55.9)	0.311 (0.159–0.607)	65.9 (16.6–262.4)

[a]Includes 38 adenovirus-positive samples, 37 norovirus-positive samples, and 39 negative samples for rotavirus, adenovirus, and norovirus.

[b]Includes 32 rotavirus-positive samples, 37 norovirus-positive samples, 3 rotavirus plus norovirus-positive samples, and 39 negative samples for rotavirus, adenovirus, and norovirus.

[c]Includes 32 rotavirus-positive samples, 37 norovirus-positive samples, 3 rotavirus plus norovirus-positive samples, and 39 negative samples for rotavirus, adenovirus, and norovirus. Positive samples for non-F adenovirus ($n = 18$) and adenovirus with undetermined species ($n = 2$) were excluded from the analysis.

[d]Includes 32 rotavirus-positive samples, 37 norovirus-positive samples, 3 rotavirus plus norovirus-positive samples, and 39 negative samples for rotavirus, adenovirus, and norovirus. Positive samples for adenovirus species F ($n = 26$) and adenovirus with undetermined species ($n = 2$) were excluded from the analysis.

[e]Includes 38 adenovirus-positive samples, 32 rotavirus-positive samples, 8 rotavirus plus adenovirus-positive samples, and 39 negative samples for rotavirus, adenovirus, and norovirus.

[f]Includes 38 adenovirus-positive samples, 32 rotavirus-positive samples, 8 rotavirus plus adenovirus-positive samples, and 39 negative samples for rotavirus, adenovirus, and norovirus. Genogroup II norovirus-positive samples ($n = 20$) were excluded from analysis.

[g]Includes 38 adenovirus-positive samples, 32 rotavirus-positive samples, 8 rotavirus plus adenovirus-positive samples, and 39 negative samples for rotavirus, adenovirus, and norovirus. Genogroup I norovirus-positive samples ($n = 20$) were excluded from analysis.

TABLE 3 Sensitivity of immunochromatographic tests according to virus strain

Virus	Strain	No. of samples	No. (% sensitivity) of positive samples by ICT (company):			
			Rida Quick Rota/Adeno/ Noro Combi (R-Biopharm)	bioNexia Noro/Rota-Adeno (bioMérieux)	Rota+Adeno+Noro Combo Card (CerTest Biotec)	Immunoquick NoRotAdeno (Biosynex)
Group A rotavirus	G1P[8]	10	10 (100)	10 (100)	10 (100)	10 (100)
	G2P[4]	8	8 (100)	8 (100)	8 (100)	7 (87.5)
	G3P[8]	5	5 (100)	5 (100)	5 (100)	5 (100)
	G4P[8]	5	5 (100)	5 (100)	5 (100)	5 (100)
	G9P[8]	7	7 (100)	7 (100)	7 (100)	7 (100)
	G12P[8]	5	5 (100)	5 (100)	5 (100)	5 (100)
	G-UDP-UD[a]	3	0	0	0	1 (33.3)
Total		43	40 (93)	40 (93)	40 (93)	40 (93)
Nonenteric adenovirus	B	3	0	0	0	0
	C	14	4 (28.6)	4 (28.6)	5 (35.7)	5 (35.7)
	D	1	0	0	0	0
Total		18	4 (22.2)	4 (22.2)	5 (27.8)	5 (27.8)
Enteric adenovirus	F	26	21 (80.8)	21 (80.8)	22 (84.6)	22 (84.6)
Untypeable adenovirus	UD[a]	2	0	0	0	0
Total adenovirus, all species		46	25 (54.3)	25 (54.3)	27 (58.7)	27 (58.7)
Norovirus genogroup I	GI.1	4	4 (100)	0	0	0
	GI.2	4	4 (100)	4 (100)	1 (25)	3 (75)
	GI.4	4	3 (75)	0	1 (25)	0
	GI.6[PNA1]	4	4 (100)	1 (25)	0	0
	GI.7	4	3 (75)	1 (25)	0	0
Total		20	18 (90)	6 (30)	2 (10)	3 (15)
Norovirus genogroup II	GII.2[P16]	3	2 (66.7)	1 (33.3)	1 (33.3)	1 (33.3)
	GII.3	1	0	0	0	0
	GII.4 Sydney [P4 New Orleans]	4	4 (100)	3 (75)	4 (100)	3 (75)
	GII.4 Sydney[P16]	4	4 (100)	4 (100)	4 (100)	3 (75)
	GII.6[P7]	4	4 (100)	2 (50)	4 (100)	4 (100)
	GII.17	4	3 (75)	3 (75)	3 (75)	3 (75)
Total		20	17 (85)	13 (65)	16 (80)	14 (70)
Total norovirus genogroups I and II		40	35 (87.5)	19 (47.5)	18 (45)	17 (42.5)

[a]UD, undetermined.

TABLE 4 Quantification cycle values of samples according to the results of immunochromatographic tests (ICTs)[a]

	True-positive samples					False-negative samples					True-positive samples					False-negative samples				
ICT (company)	No.	Min	Max	Mean	Median	No.	Min	Max	Mean	Median	No.	Min	Max	Mean	Median	No.	Min	Max	Mean	Median
Rotavirus A ($n = 43$)																				
Rida Quick Rota/Adeno/Noro Combi (R-Biopharm)	40	8.81	26.32	16.55	15.30	3	31.41	36.66	33.75	33.18										
bioNexia Noro/Rota-Adeno (bioMérieux)	40	8.81	26.32	16.55	15.30	3	31.41	36.66	33.75	33.18										
Rota+Adeno+Noro combo card (CerTest Biotec)	40	8.81	26.32	16.55	15.30	3	31.41	36.66	33.75	33.18										
Immunoquick NoRotAdeno (Biosynex)	40	8.81	33.18	17.01	15.47	3	14.95	36.66	27.67	31.41										
Adenovirus F ($n = 26$)											Adenovirus non-F ($n = 18$)									
Rida Quick Rota/Adeno/Noro Combi (R-Biopharm)	21	6.83	16.67	11.60	10.83	5	19.59	36.31	26.10	24.67	4	15.58	17.65	16.79	16.96	14	19.61	38.25	28.87	31.53
bioNexia Noro/Rota-Adeno (bioMérieux)	21	6.83	16.67	11.60	10.83	5	19.59	36.31	26.10	24.67	4	15.58	17.65	16.79	16.96	14	19.61	38.25	28.87	31.53
Rota+Adeno+Noro combo card (CerTest Biotec)	22	6.83	19.59	11.96	11.30	4	23.79	36.31	27.73	25.42	5	15.58	23.49	18.13	17.61	13	19.61	38.25	29.28	32.40
Immunoquick NoRotAdeno (Biosynex)	22	6.83	19.59	11.96	11.30	4	23.79	36.31	27.73	25.42	5	15.58	25.57	18.54	17.61	13	19.61	38.25	29.12	32.40
Norovirus genogroup I ($n = 20$)											Norovirus genogroup II ($n = 20$)									
Rida Quick Rota/Adeno/Noro Combi (R-Biopharm)	18	15.41	38.43	25.85	24.81	2	28.98	32.15	30.57	30.57	17	12.99	25.26	19.22	18.91	3	22.2	30.84	26.39	26.12
bioNexia Noro/Rota-Adeno (bioMérieux)	6	15.41	29.47	23.40	22.96	14	17.9	38.43	27.57	28.79	13	12.99	25.26	18.78	18.18	7	18.91	30.84	23.11	22.20
Rota+Adeno+Noro combo card (CerTest Biotec)	2	20.37	24.78	22.58	22.58	18	15.41	38.43	26.74	28.79	16	12.99	25.26	19.18	18.81	4	19.86	30.84	24.76	24.16
Immunoquick NoRotAdeno (Biosynex)	3	20.37	29.47	24.35	23.21	17	15.41	38.43	26.67	28.60	14	12.99	25.26	18.70	18.44	6	19.86	30.84	24.03	22.58

[a]Data in the "No." columns represent the number of samples. Data in the "Min" (minimum), "Max" (maximum), "Mean," and "Median" columns represent quantification cycle (C_q) values of samples.

to 99.1%. Finally, the DOR ranged from 20.9 to 812; the DORs of the Rida Quick Rota/Adeno/Noro Combi assay (812) and the Immunoquick NoRotAdeno assay (20.9) were not similar, seeing as the 95% CI did not overlap (Table 2).

When we tested only for NoV GI, the Rida Quick Rota/Adeno/Noro Combi assay presented a sensitivity of 90% (versus 10% to 30% for the other ICTs) and an LR− of 0.101 (versus 0.712 to 0.916). The 95% CI did not overlap (Table 2). The specificity for the four ICTs ranged from 96.6 to 99.3%, LR+ from 4.4 to 123.3, and DOR from 5.0 to 1,224.0. The 95% CI overlapped except for the DOR of the Rida Quick Rota/Adeno/Noro Combi ICT and those of Immunoquick NoRotAdeno and Rota+Adeno+Noro combo card ICTs (Table 2).

When we tested only for NoV GII, sensitivity ranged from 65% to 85%, specificity from 96.6 to 99.3%, LR+ from 20.5 to 116.4, LR− from 0.151 to 0.356, and DOR from 65.9 to 770.7. The 95% CI overlapped for each of the indicators (Table 2).

Among the NoV GI included in the study, only genotype GI.2 was detected by the four ICTs (Table 3). While the other genotypes of NoV GI were well detected by the Rida Quick Rota/Adeno/Noro Combi assay, these genotypes were rarely or not detected by the 3 other ICTs (Table 3). Among NoV GII, only the GII.3 strain was not identified by the four ICTs, whereas the other genotypes were globally well detected (Table 3). The mean C_q value for NoV GII samples (20.30; 95% CI, 18.50 to 22.10; data not shown) was lower than the mean C_q value for NoV GI samples (26.32; 95% CI, 23.74 to 28.90; data not shown), suggesting that NoV GII samples had a higher viral load. Moreover, the means of the C_q values observed for NoV GI false-negative samples were slightly delayed, from 2.32 to 4.72 cycles, compared with the results for NoV GI true-positive samples, suggesting that false-negative samples had lower NoV GI loads than true-positive samples (Table 4). The same trend was observed for NoV GII samples, with the mean C_q values being 4.33 to 7.17 cycles higher for false-negative samples than for true-positive samples (Table 4).

DISCUSSION

ICTs are easy and fast to use, making them an attractive alternative to molecular methods for laboratories that are not adequately equipped. Previously, efforts to diagnose AGE focused on RVA and AdV infections. Healthcare professionals have become increasingly aware that NoV infections are a major health problem, and NoV diagnostic prescriptions have progressively increased to reach the same level as RVA and AdV requests, therefore expanding demand for NoV diagnosis testing in medical biology laboratories. To feed these increased needs, medical diagnostic device manufacturers have developed so-called "triplex" ICTs that are capable of simultaneously detecting AdV, RVA, and NoV.

In the present study, we assessed the diagnostic accuracy of four commercial triplex ICTs using a wide panel of previously collected and characterized stool samples, and RT-PCR techniques were used as the reference standards. To our knowledge, no published studies have evaluated these four triplex ICTs.

With overall sensitivity ranging from 42.5% to 93%, the four tested ICTs were less sensitive than RT-PCR when detecting the three viruses in fecal samples. This was expected, seeing as molecular methods are recognized as being more sensitive than immunological methods for the detection of enteric viruses (11). However, we observed considerable differences in the performances of the assays depending on the virus.

For RVA detection, the four ICTs exhibited high sensitivity and excellent specificity, leading to high LR+, low LR−, and very high DOR. These data indicated a strong association between the result of the ICT and the presence of RVA, and the four assays were found to be highly discriminatory and suitable for the diagnosis of RVA infections. The 95% CI for each performance indicator overlapped, leading to the conclusion that the diagnostic accuracy for the detection of RVA was similar for the four ICTs. Previous evaluations of different RVA ICTs using RT-PCR as the reference standard have also shown high sensitivity (75 to 100%) and specificity (89 to 100%) (12–18). Interestingly, when De Grazia et al. evaluated the Rotavirus + Adenovirus ICT from Certest Biotec,

they found that it had a lower sensitivity and specificity (85% and 93%, respectively) than what we observed with the Rota+Adeno+Noro combo card ICT from the same company (18). De Grazia et al. also reported that the VIKIA Rota-Adeno ICT from bioMérieux had similar sensitivity but lower specificity (94% and 89%, respectively) than the bioNexia Noro/Rota-Adeno ICT (bioMérieux) in the present study. Our previous evaluation of the Vikia Rota-Adeno ICT showed lower sensitivity (77.3%) but the same specificity (100%) (17). Similarly, several previous evaluations of the Rida Quick Rota/Adeno Combi ICT from R-Biopharm showed a range of sensitivity, from 75 to 88.8%, and specificity, from 95% to 100%, while the present study found better sensitivity and similar specificity with the Rida Quick Rota/Adeno/Noro Combi ICT from the same company (12, 14, 17). Again, our previous evaluation of the Immunoquick NoRotAdeno ICT from Biosynex showed lower sensitivity (78.2%) but the same specificity (100%) (17). As of yet, no information about differences in the composition of duplex and triplex ICTs has been released, but these results would suggest that RVA detection has been improved for the triplex assays. Nonetheless, the differences in diagnostic accuracy may also be due to different methodologies, notably in the reference method (real-time or endpoint RT-PCR; in-house or commercial tests) and the sampling strategy (prospective or retrospective study; inclusion or exclusion of samples from patients without symptoms of AGE). Indeed, we highlighted in a previous study that ICT sensitivity was better when only individuals with symptoms of AGE were sampled because their RVA loads were significantly higher than those of asymptomatic individuals (17). Globally, high-titer samples are efficiently identified by ICTs, and false negatives are usually in the low-viral load range, which is in good agreement with clinical relevance. Indeed, it could be argued that finding a rotavirus with a $C_q > 24$ to 27 in a molecular assay is not clinically relevant and should not be interpreted as directly responsible for the symptoms (19, 20).

Concerning the detection of AdV, the four ICTs had a similar diagnostic accuracy, seeing as the 95% CI overlapped for each of the performance indicators. Overall, the four ICTs demonstrated poor sensitivity but excellent specificity, so rather high LR+, high LR−, and rather high DOR were observed. Given that these data suggest a relatively weak association between the result of the ICT and the presence of AdV, negative results are not a good predictor of the absence of an AdV infection. Similar observations of poor sensitivity (6.3 to 36.6%) but good specificity (84 to 100%) have been noted in previous assessments of ICTs (12, 14–16, 21). As for RVA detection, the Rida Quick Rota/Adeno Combi ICT from R-Biopharm tested by Weitzel et al. and Rovida et al. showed lower sensitivity for AdV detection (22% and 28.6%, respectively) than did the Rida Quick Rota/Adeno/Noro Combi ICT, also from R-Biopharm (12, 14). Similarly, the Vikia Rota-Adeno ICT from bioMérieux tested by Çolak et al. showed a sensitivity of 36%, while we found that the sensitivity of the bioNexia Noro/Rota-Adeno ICT was higher (21). Again, these differences could be explained in part by improvements in the manufacturing process and by differences in methodology. The spectrum of AdV genotypes/species in the stool collection may also explain the differences in diagnostic accuracy. When comparing ICT performance for the various species of AdV, all four ICTs performed best for AdV-F. Indeed, the sensitivity, LR+, LR−, and DOR data showed a strong association between the ICT result and the presence of AdV-F, while many false negatives were observed for non-F AdV. It is worrisome because the 4 ICTs are intended for the detection of all AdV species in human stool samples, not only AdV-F. In addition, the C_q values of AdV-F-positive samples were lower than the values of non-F AdV-positive samples, suggesting the former had higher viral loads. Moreover, independently of the AdV species, higher viral loads (i.e., lower C_q values) were observed in true-positive samples than in false-negative samples. Altogether, these observations suggest that an ICT's ability to detect AdV is linked more to the viral load than to the species itself. As for RVA, high-titer samples are efficiently identified by ICTs, while false negatives are usually in the low viral range, which may be in good agreement with clinical relevance. In this study, the viral load difference between non-F- and AdV-F-positive samples could be a reflection of the clinical condition of the patient during

stool sampling. High viral shedding would occur with enteric AdV (mainly AdV-F) and lower viral shedding with nonenteric AdV, the presence of which would be secondary in the infection scheme. Thus, the detection of high-titer AdV-F in an AGE case is highly clinically relevant, whereas the detection of low-titer non-F AdV is not. Although further investigations would be required, the four ICTs may be used as a first-line test for diagnosis of AdV in human stool samples during AGE, all the more so as AdV-F remains the most epidemiologically relevant species (22), but some non-F AdV also associated with AGE symptoms may not be detected with these assays. A positive result by ICTs would allow the rapid diagnosis of AdV infection. Unfortunately, a negative result would require a more sensitive method like PCR in order to accurately diagnose AdV infections.

For NoV, the diagnostic accuracy of the four ICTs was fairly heterogeneous. Indeed, only the Rida Quick Rota/Adeno/Noro Combi ICT exhibited high sensitivity and low LR−, while the three other ICTs presented considerably lower sensitivity and higher LR−. However, all four ICTs had similar high specificity. The DOR for the Rida Quick Rota/Adeno/Noro Combi and Immunoquick NoRotAdeno ICTs were statistically different, seeing as the 95% CIs did not overlap. In previous studies, the evaluation of the Rida Quick Norovirus ICT (ref. N1402, i.e., the latest version) from R-Biopharm showed high sensitivity (72.8 to 100%) and specificity (97 to 100%), similar to those obtained with the Rida Quick Rota/Adeno/Noro Combi ICT in this study (23–25). Previous studies reported lower sensitivity for the Rida Quick Norovirus ICT, but given their date of publication, they were testing the old version of the ICT (reference N1403), whose performance was inferior. Vyas et al. showed 30% sensitivity for the Immunoquick ICT from Biosynex, which is slightly lower than our findings (26). Nonetheless, the stratification of diagnostic accuracy according to the NoV genogroup showed that the differences in performance between ICTs were dependent on their ability to detect GI NoV. Therefore, when considering only GI NoV, the Rida Quick Rota/Adeno/Noro Combi ICT clearly outperformed the three other ICTs, notably in terms of sensitivity and LR−. When considering GII NoV, the four ICTs exhibited rather high sensitivity, rather high LR+, rather low LR−, and rather high DOR. Given that the 95% CIs overlapped for each performance indicator, the diagnostic accuracy of the four ICTs was similar for GII NoV. Altogether, these results suggest that the four ICTs are suitable first-line diagnostic tests for GII NoV infection, while only the Rida Quick Rota/Adeno/Noro Combi ICT is sufficiently accurate for the diagnosis of GI NoV infection. In addition, the viral loads of GII NoV samples were globally higher (i.e., lower C_q values) than those of the GI NoV samples. As observed for AdV, but to a lesser extent, this evaluation also showed that NoV true-positive samples had higher viral loads than NoV false-negative samples, regardless of the genogroup, suggesting that NoV detection was dependent on the viral load. But because the Rida Quick Rota/Adeno/Noro Combi ICT was able to detect GI NoV in samples even with relatively low viral loads, the ability to detect NoV is genogroup dependent as well, as previously described (27). In contrast to AdV and RVA, NoV antigen detection is usually not based on a common antigen, which means that the test must be able to detect many different antigens, which is usually not exhaustive. This may explain why some tests are better than others, or at least appear to be so, and why different evaluations of the same assay can have different results. The higher NoV diagnostic accuracy of the Rida Quick Rota/Adeno/Noro Combi ICT should be put into perspective. Worldwide, GII is the NoV genogroup that infects humans most often, accounting for 72% to 93% of NoV outbreaks in France over the last 5 years (K. Ambert-Balay and J. Kaplon, unpublished data), and the four ICTs evaluated here all performed suitably for the detection of this genogroup. In order to be able to determine the diagnostic accuracy of ICT assays for the detection of both genogroup I and genogroup II NoV, the collection of stool samples used in this study included the same number of GI and GII NoV-positive samples, which is not representative of the genogroup distribution of NoV in the population. Thus, a sample collection that reflected the NoV epidemiology more accurately would have rubbed out the differences observed in the global NoV sensitivity between the four evaluated ICTs.

Nevertheless, as AGE could be caused by any NoV, and in view of the diagnostic performance of NoV ICT assays, it is important to note that molecular testing should be performed for all the samples with a negative result when an ICT was used as first-line diagnostic test. Unfortunately, this might involve molecular testing for a good number of samples.

The present study has two main limitations. First, the relatively low number of samples investigated provides less precise diagnostic accuracy estimates; this is underlined by the wide CI. Second, the selection of an overwhelming majority of well-characterized viral strains by endpoint RT-PCR methods, recognized as slightly less sensitive than real-time RT-PCR, may have led to an overestimation of the sensitivity of the ICTs.

In conclusion, the four evaluated ICTs were found to be suitable for rapid diagnosis of RVA infections in human stool samples. The four ICTs may be useful to provide a rapid response for the presence of AdV in case of a positive result with ICT, notably in AGE patients. However, their low sensitivity, especially for the detection of non-F AdV, makes their utility for routine diagnosis of AdV infections limited, as the testing by molecular methods of all the negative samples by ICTs remains necessary in order to accurately diagnose those infections. Only the Rida Quick Rota/Adeno/Noro Combi ICT was suitable as a first-line test for the rapid diagnosis of NoV. The sensitivity for genogroup I NoV detection of the 3 other ICTs needs to be improved before being implemented in the routine diagnosis of NoV. However, in the event of an ICT-positive result and given their high specificity, these assays allow providing a rapid response for the presence of NoV, which can be useful in some situations.

Regardless of virus, due to their better sensitivity, molecular methods remain the gold standard and should be considered to rule out any suspected ICT false-negative result or when testing samples with potentially low RVA, AdV, or NoV loads.

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