RIDASCREEN® Adenovirus

Article no.: C1001

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1. Intended use

For *in vitro* diagnostic use. RIDASCREEN® Adenovirus is an enzyme immunoassay for qualitative identification of adenoviruses in human stool samples.

2. Summary and explanation of the test

Adenoviruses can be recognized by their typically icosahedral form with spiked structures on the surface. More than 50 different types of the adenovirus are known and can cause infections in the eyes, the respiratory tract, or the intestinal tract. Infections of the intestinal tract. are caused by the types 40 and 41 in particular. Enteritis may also occur as a concomitant symptom of infections due to other types of the virus. Regarding viral diarrhea in children, adenoviruses and astroviruses rank equally as the next most frequent causes after rotaviruses. Adults can also become ill with this kind of infection. Because gastroenteritis caused by an adenovirus cannot be clinically differentiated from infection with a rotavirus or an astrovirus, patients should always be tested for all three pathogens. The monoclonal antibodies used in RIDASCREEN® Adenovirus are reactive to the adenovirus-specific hexon protein, and the range includes both enteral types 40 and 41 as well as most other types of the virus which cause eye infections and infections of the respiratory tract.

3. Test principle

The RIDASCREEN® Adenovirus Test employs monoclonal antibodies in a sandwich-type method. A monoclonal antibody to the hexon antigen of the adenoviruses is coated to the well surface of the microwell plate.

A pipette is used to place a suspension of the stool sample to be examined as well as control specimens into the well of the microwell plate together with biotinylated monoclonal anti-adenovirus antibodies (conjugate 1) for incubation at room temperature (20–25 °C). After a wash step, streptavidin poly-peroxidase conjugate (Conjugate 2) is added and it is incubated again at room temperature (20–25 °C). With the presence of adenoviruses in a stool sample, a sandwich complex will form which consists of immobilized antibodies, the adenovirus antigens, and the antibodies conjugated with the biotin-streptavidin-peroxidase complex. Another wash step removes the unattached streptavidin poly-peroxidase conjugate. After adding the substrate, the attached enzyme changes the colour of the previously colourless solution in the wells of the microwell plate to blue if the test is positive. Addition of a stop reagent changes the color from blue to yellow. The extinction is proportional to the concentration of adenoviruses found in the specimen.

4. Reagents provided

The reagents in the kit are sufficient for 96 determinations.

Plate	96	Microwell plate, 12 microwell strips (which can be divided) in the strip holder; coated with monoclonal anti-adenovirus antibodies
Diluent | 1	100 ml	Sample dilution buffer, protein-buffered NaCl solution; ready to use, blue color
Wash	100 ml	Wash buffer, phosphate buffered NaCl solution (concentrated 10-fold); contains 0.1% thimerosal
Control | +	2 ml	Positive control; inactivated adenovirus culture; ready for use
Control | -	2 ml	Negative control (sample dilution buffer); ready for use
Conjugate | 1	13 ml	Biotin-conjugated monoclonal anti-adenovirus antibodies in stabilized protein solution; ready for use; green color
Conjugate | 2	13 ml	Streptavidin poly-peroxidase conjugate in stabilized protein solution; ready for use; orange colored
Substrate	13 ml	Hydrogen peroxide/TMB; ready for use
Stop	12 ml	Stop reagent; 1 N sulphuric acid; ready for use

5. Reagents and their storage

All reagents must be stored at 2–8 °C and can be used until the expiry date printed on the label. Providing the diluted wash buffer is stored at 2–8 °C, it can be used for a maximum of 4 weeks. Microbial contamination must be prevented. After the expiry date, the quality guarantee is no longer valid.

The aluminum bag must be opened with scissors in such a way that the clip seal is not torn off. Any microwell strips which are not required must be returned to the aluminum bag and immediately stored at 2–8 °C.

The colorless substrate must also be protected from direct light to prevent it from decomposing or turning blue due to auto-oxidation. Once the substrate has turned blue, it must not be used.

6. Additional necessary reagents – and necessary equipment

6.1. Reagents

- Distilled or deionized water

6.2. Equipment

- Test tubes
- Disposable pipettes (Article no.: Z0001)
- Vortex mixer (optional, see 9.3.)
- Micropipette for 50–100 µl and 1 ml volumes

– Measuring cylinder (1,000 ml)
– Timer
– Washing device for microwell plates or multichannel pipettes (300 µl)
– Photometer for microwell plates (450 nm and reference filter 620–650 nm)
– Filter paper (laboratory towels)
– Waste container with a 0.5 % hypochlorite solution

7. Precaution for users

For *in vitro* diagnostic only.

This test must only be carried out by trained laboratory personnel. The guidelines for working in medical laboratories must be followed. Always adhere strictly to the user instructions for this test.
Specimens or reagents must not be pipetted by mouth, and contact with injured skin or mucous membranes must be prevented. Wear personal safety gear (suitable gloves, laboratory coat, safety glasses) when handling the specimens, and wash hands after finishing the test. Do not smoke, eat, or drink in areas where samples are being processed.
For more details, refer to Material Safety Data Sheets (MSDS) at www.r-biopharm.com.

The kit includes a positive control that contains an inactivated adenovirus culture. It must be treated as potentially infectious material and handled in accordance with the national safety regulations, just like the patient samples.

The wash buffer contains 0.1 % thimerosal as preservative. This substance must not be allowed to come into contact with skin or mucous membranes.

Ensure the proper and responsible disposal of all reagents and materials after their use. For disposal, please adhere to national regulations.

8. Specimen collection and storage

Stool samples must be taken as soon as possible within three days after occurrence of the initial symptoms of diarrhea. Until it is used, store the test material at 2–8 °C. If the material cannot be used for a test within three days, we recommend storage at –20 °C or colder. Avoid freezing and thawing the specimen repeatedly. After diluting a stool sample in sample dilution buffer 1:11, it can be stored at 4 °C for use within seven days.
Stool samples and rectal smears should not be collected in transport containers which contain transport media with preservatives, animal sera, metal ions, oxidizing agents, or detergents since these may interfere with the RIDASCREEN® Adenovirus Test.
If rectal smears are used, make sure that the volume of stool material is sufficient (approx. 100 mg) for the test.
Contact tracing should include stool samples taken from contact persons who do not exhibit clinical symptoms, in order to identify asymptomatic carriers.

9. Test procedures

9.1. General information

All reagents and the microwell Plate must be brought to room temperature (20–25 °C) before use. The microwell strips must not be removed from the aluminum bag until they have reached room temperature. The reagents must be thoroughly mixed immediately before use. After use, the microwell strips (placed in sealed bags) and the reagents must be stored again at 2–8 °C. Once used, the microwell strips must not be used again. The reagents and microwell strips must not be used if the packaging is damaged or the vials are leaking.
In order to prevent cross contamination, the samples must be prevented from coming into direct contact with the kit components.
The test must not be carried out in direct sunlight. We recommend covering the microwell plate or placing plastic wrap over it to prevent evaporation losses.

9.2. Preparing the wash buffer

Mix 1 part wash buffer concentrate Wash with 9 parts distilled water. Any crystals present in the concentrate must be dissolved beforehand by warming in a water bath at 37 °C.

9.3 Preparing the samples

Fill a labelled test tube with 1 ml RIDASCREEN® sample dilution buffer Diluent | 1. Use a disposable pipette (article no. Z0001) to aspirate a sample of thin stool (approx. 100 µl) to just above the second marking and add to buffer in the test tube to make a suspension. To make a suspension with a solid stool sample, add an equivalent amount (approx. 50100 mg) with a spatula or disposable inoculation loop.
Homogenize the stool suspension by aspiration into and ejection from a disposable pipette or, alternatively, blend in a Vortex mixer. Let the suspension stand a short period of time (10 minutes) for the coarse stool particles to settle, and this clarified supernatant of the stool suspension can be used directly in the test. If the test procedure is carried out in an automated ELISA system, the supernatant must be particle-free. In that case, it is advisable to centrifuge the sample at 2,500 G for 5 minutes.

Note:

Stool samples diluted in Diluent | 1 can be tested in all RIDASCREEN® ELISAs for which Diluent | 1 is used.

9.4. First incubation

After inserting a sufficient number of wells in the strip holder, add 100 µl of the positive control | +, the negative control | - or the stool sample suspension to the wells. Subsequently add 100 µl of the biotin-conjugated antibody Conjugate | 1 and blend (by tapping lightly on the side of the plate); then incubate for 60 minutes at room temperature (20–25 °C).

9.5. Washing

Careful washing is important in order to achieve the correct results and should therefore proceed strictly according to the instructions. The incubated substance in the wells must be emptied into a waste container for disposal in accordance with local regulations. After this, knock out the plate onto absorbent paper in order to remove the residual moisture. Then wash the plate five times using 300 µl wash buffer each time. Make sure that the wells are emptied completely by knocking them out after each wash on a part of the absorbent paper which is still dry and unused.

If you use a microplate washer or fully automated ELISA, make sure that the machine is correctly adjusted; request settings from the manufacturer, if necessary. Appliances delivered by R-Biopharm are already programmed with validated settings and work protocols. To avoid blocking the wash needles, only particle-free stool suspensions should be dispensed (see Item 9.3., Preparing the samples). Also make sure that all of the liquid is aspirated during each wash step.

9.6. Second incubation

Use a pipette to fill 100 µl streptavidin poly-peroxidase conjugate Conjugate | 2 into the wells, then incubate for 30 minutes at room temperature (20–25 °C).

9.7. Washing

Wash as described in Item 9.5.

9.8. Third incubation

Fill all wells with 100 µl substrate Substrate. Then incubate the plate for 15 minutes in darkness at room temperature (20–25 °C). Subsequently fill all wells with 50 µl stop reagent Stop in order to stop the reaction. After blending cautiously by tapping lightly on the side of the plate, measure the extinction at 450 nm (optional: 450/620 nm). Adjust the zero point in the air, that is without the microwell plate.

Note:
High-positive patient samples may cause black-colored precipitates of the substrate.

10. Quality control – indications of reagent expiry

For quality control purposes, positive and negative controls must be used each time the test is carried out, to ensure that the reagents are stable and that the test is conducted correctly. The test has been carried out correctly if the extinction rate (O.D.) for the negative control is less than 0.2 at 450 nm (less than 0.160 at 450/620 nm) and the measured value for the positive control is greater than 0.8 at 450 nm or at 450/620 nm. A value greater than 0.2 (0.160) for the negative control may indicate that washing was insufficient. Deviation from the required values, just like a turbid or blue coloration of the colorless substrate before it is filled into the wells, may indicate that the reagents have expired.

If the stipulated values are not met, the following points must be checked before repeating the test:

- Expiry date of the reagents used
- Functionality of the equipment being used (e.g. calibration)
- Correct test procedure
- Visual inspection of the kit components for contamination or leaks – a substrate solution which has turned blue must not be used.

If the conditions are still not fulfilled after repeating the test, please consult the manufacturer or your local R-Biopharm distributor.

11. Assessment and interpretation

11.1. Calculating the cut-off

In order to establish the cut-off, 0.15 extinction units are added to the measured extinction for the negative control.

Cut-off = extinction for the negative control + 0.15

11.2. Test results

Assessment of the specimen is positive if the extinction rate is more than 10 % higher than the calculated cut-off value.

Assessment of the specimen is marginal if the extinction rate ranges from 10 % less to 10 % greater than the cut-off value. If the repeat examination with a fresh stool sample again falls within the gray zone, assessment of the sample is negative.

Samples with extinctions more than 10% below the calculated cut-off must be considered negative.

12. Limitations of the method

The RIDASCREEN® Adenovirus Test identifies antigens of the *adenovirus* in stool samples. It is not possible to associate the determined level of extinction to the occurrence or severity of clinical symptoms. The results obtained must always be interpreted in combination with the clinical signs and symptoms.

A positive result does not rule out the presence of other infectious pathogens.

A negative result does not rule out the possibility of *adenovirus* infection. Such a result may be due to intermittent excretion of the virus, or the amount of antigen in the sample may be too small. If the patient history supports a suspicion of adenovirus infection, the examination should be repeated with another stool sample.

A borderline result may be due to non-homogeneous distribution of viruses in the stool sample.

In this case, examination should either be repeated with a second suspension from the same sample or another stool sample should be requested.

13. Performance characteristics

13.1. Test quality

RIDASCREEN® Adenovirus was validated by comparison with three commercially available adenovirus ELISAs. The sample collective that was used consisted of fresh, same-day samples taken at a routine laboratory and of prepared samples that had been frozen in advance at -20 °C for use in the comparison study. One homogeneous baseline suspension was tested by each of the ELISAs in accordance with the manufacturers' instructions. A sample was considered positive or negative, if the results of two out of three reference tests were in agreement. The results of that study are summarized in Table 1.

Table 1: Correlation between RIDASCREEN® Adenovirus ELISA and three other commercial ELISAs

	Competitor ELISA		
RIDASCREEN® Adenovirus	pos	neg	Total
pos	21	0	21
neg	0	115	115
Total	21	115	136

Sensitivity: 100 % Specificity: 100 %

13.2. Cross reactivity

A variety of pathogenic microorganisms from the intestinal tract were examined with the RIDASCREEN® Adenovirus ELISA and showed no cross reactivity.
These studies were conducted with bacterial suspensions shown to have concentrations of 10^6 to 10^9 organisms per ml. Virus culture supernatants and toxins as well as stool samples are listed accordingly. The results of that study are summarized in Table 2.

Table 2: Cross reactivity with pathogenic microorganisms

Organism	**Origin**	**Source**	**[OD 450 nm] mean value**
Acinetobacter Iwoffii	Culture	DSM 2403	0.063
Aeromonas hydrophila anaerogenes	Culture	DSM 30020	0.091
Aeromonas hydrophila hydrophila	Culture	DSM 30016	0.074
Astrovirus cell culture supernatant	Culture	Micromun	0.052
Astrovirus sample	Stool	TU Dresden	0.074
C. difficile	Culture	VPI 1640	0.052

C. perfringens 50 µg/ml	Toxoid	Kit control *C. perfringens* Enterotoxin A	0.057
C. sordellii	Culture	tgcBiomics	0.052
Campylobacter fetus	Culture	DSM 5361	0.060
Campylobacter jejuni	Culture	DSM 4688	0.050
Campylobacter sample	Stool	Routine lab	0.037
Candida albicans	Culture	ATCC 10231	0.079
Citrobacter freundii	Culture	DSM 30039	0.094
Citrobacter spp.	Culture	DSM 30047	0.070
Cryptosporidium parvum	Culture	Waterborne Inc.	0.051
E. coli	Culture	LMU München	0.078
E. coli	Culture	LMU München	0.074
E. coli	Culture	LMU München	0.062
E. coli (O111:H-)	Culture	LMU München	0.079
E. coli (O116:H21)	Culture	LMU München	0.073
E. coli (O157:H-)	Culture	LMU München	0.096
E. coli (O22:H8)	Culture	LMU München	0.095
E. coli (O26:H11)	Culture	LMU München	0.078
E. hermannii	Culture	DSM 4560	0.049
Entamoeba histolytica	Stool	TI Berlin	0.043
Enterobacter cloacae	Culture	DSM 30054	0.071
Enterococcus faecalis	Culture	DSM 2570	0.078
Enterococcus faecium	Culture	DSM 20477	0.090
Giardia lamblia sample	Stool	TI Berlin	0.039
H. pylori sample	Inaktivierted *H. pylori* lysate	Kit control RIDASCREEN FemtoLab H. pylori	0.071
Helicobacter pylori	Culture	DSM 4867	0.051
Lactococcus lactis	Culture	DSM 20481	0.070
Listeria innocua	Culture	DSM 20649	0.060
Morganella morganii	Culture	DSM 6675	0.054
Proteus mirabilis	Culture	DSM 788	0.050
Proteus mirabilis	Culture	DSM 4479	0.052
Proteus vulgaris	Culture	DSM 30119	0.052
Providencia stuartii	Culture	DSM 6676	0.073
Pseudomonas aeruginosa	Culture	DSM 939	0.058
Pseudomonas fluorescens	Culture	DSM 4358	0.058
Pseudomonas fluorescens	Culture	DSM 50124	0.069
Pseudomonas putida	Culture	DSM 291	0.056
Rotavirus cell culture supernatant	Culture	Microbix	0.059
Rotavirus sample	Stool	TU Dresden	0.059
Salmonella agona	Culture	LMU München	0.052
Salmonella choleraesuis	Culture	DSM 4224	0.053

Salmonella enteritidis	Culture	DSM 9898	0.065
Salmonella enteritidis sample	Culture	Routine lab	0.065
Salmonella infantis	Culture	LMU München	0.053
Salmonella ohio	Culture	LMU München	0.053
Salmonella typhimurium	Culture	DSM 554	0.050
Sapovirus	Stool	TU Dresden	0.066
Serratia liquefaciens	Culture	DSM 4487	0.039
Shigatoxin STX1	Toxoid	Toxin Technology	0.054
Shigatoxin STX2	Toxoid	Toxin Technology	0.054
Shigella flexneri	Culture	DSM 4782	0.040
Shigella sonnei	Culture	DSM 5570	0.048
Staphylococcus aureus	Culture	DSM 20372	0.064
Streptococcus agalactiae	Culture	DSM 2134	0.090
Streptococcus dysgalactiae	Culture	DSM 20662	0.074
Streptococcus uberis	Culture	DSM 20569	0.071

13.3. Precision

The reproducibility of the RIDASCREEN® Adenovirus ELISA was tested with six references representing the complete measurement range from weak to high positive.
To determine the intra-assay reproducibility, 40 replicates of these references were assayed. The mean values and the variation coefficients (CV) were determined for three lots.

For the inter-assay reproducibility, references from ten different working days were assayed in duplicates, with two runs per day. The measurements were determined in three lots by three technicians.The inter-lot reproducibility was determined for all three lots. The results of that study are shown in Table 3.

Table 3: Reproducibility and precision of the RIDASCREEN® Adenovirus ELISA

Reference Mean value / CV (%)		Intra-assay			Inter-assay			Inter-lot
		Kit lot 1	Kit lot 2	Kit lot 3	Kit lot 1	Kit lot 2	Kit lot 3	Kit lots 1-3
1	MV	2.236	2.732	3.170	2.363	2.199	2.408	2.323
	CV (%)	5.11%	6.67%	6.08%	15.39%	20.81%	19.91%	18.95%
2	MV	1.359	1.590	1.975	1.411	1.368	1.559	1.446
	CV (%)	5.16%	4.03%	9.64%	14.28%	21.66%	18.81%	19.35%
3	MV	1.244	1.222	1.321	1.096	1.162	1.261	1.173
	CV (%)	8.07%	6.14%	8.16%	13.66%	17.75%	18.93%	18.23%
4	MV	0.813	0.899	1.014	0.794	0.822	0.862	0.826
	CV (%)	7.75%	7.81%	15.22%	16.20%	24.41%	18.37%	20.03%

5	MV	0.597	0.622	0.800	0.570	0.587	0.635	0.597
	CV (%)	7.88%	5.78%	11.73%	16.92%	23.77%	16.84%	19.79%
6	MV	0.368	0.394	0.588	0.407	0.434	0.462	0.434
	CV (%)	8.27%	6.63%	19.65%	24.65%	24.35%	17.00%	22.43%

13.4. Analytical sensitivity

The detection limit of the RIDASCREEN® Adenovirus ELISA was determined with the serial dilution of a stool sample quantified by immunoelectron microscopy (IEM). The measurements were taken in triplicate, based on a virus titer of 1.3 x 10^7 particles/ml. The detection limit was defined as 3.25 x 10^2 virus particles/ml of the stool sample. Results of the titration series are shown in Table 4. Note that the positive OD value in ELISA is caused by intact virus particles, but also by fragments of the virus, which are not counted in the IEM.

Table 4: Determination of the analytical sensitivity of RIDASCREEN® Adenovirus ELISA

IEM	**RIDASCREEN® Adenovirus**	
Virus particles/ml	**Mean value [OD 450]**	**Results**
6.5 x 10^5	1.784	Positive
6.5 x 10^4	3.993	Positive
3.25 x 10^4	4.030	Positive
1.63 x 10^4	4.032	Positive
8.2 x 10^3	4.135	Positive
6.5 x 10^3	4.245	Positive
3.25 x 10^3	3.753	Positive
1.63 x 10^3	2.858	Positive
8.2 x 10^2	1.718	Positive
6.5 x 10^2	1.126	Positive
3.25 x 10^2	0.305	Positive
1.63 x 10^2	0.054	Negative

14. Interfering substances

The following list of substances showed no effects on the test results when they were blended into adenovirus positive and adenovirus negative stool samples in the described concentrations**:** barium sulfate (5% w/w), loperamide (antidiarrheal drug, 5% w/w), Pepto-Bismol (antidiarrheal drug, 5% v/w), mucins (5% w/w), cyclamate (artificial sweetener, 5% v/w), human blood (5% v/w), stearic acid and palmitic acid combination (mixture 1:1, 40% w/w), metronidazole (0.5% solution;5% v/w), diclofenac (0.00263% v/w).

Appendix

Test specific symbols:

Plate	Microwell plate
Diluent | 1	Sample dilution buffer
Wash	Wash buffer
Control | +	Positive control
Control | -	Negative control
Conjugate | 1	Conjugate 1
Conjugate | 2	Conjugate 2
Substrate	Substrate
Stop	Stop reagent

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