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IMAGEN Respiratory Syncytial Virus (RSV)

REF K610211-2.....50 Tests **EN**

A direct immunofluorescence test for the detection of Respiratory Syncytial Virus (RSV).

1. INTENDED USE

The IMAGEN™ Respiratory Syncytial Virus (RSV) test is a qualitative immunofluorescence test for the direct detection of RSV in clinical specimens.

2. SUMMARY

RSV is an enveloped, spherical, RNA virus of the family paramyxoviridae and is classified in the genus Pneumovirus. This genus has four members: human RSV, bovine RSV, pneumonia virus of mice and turkey rhinotracheitis virus[1,2].

RSV is the major cause of lower respiratory tract disease in infants and young children causing seasonal epidemics of respiratory illness each year[3,4]. RSV is spread by virus-laden droplets of respiratory secretions from infected individuals.

Infection may manifest as a variety of symptoms, ranging from rhinitis to pneumonia, which are influenced by factors such as the age, sex and socio-economic background of infected individuals[5]. Approximately 50% of infants infected during the first year of life may develop lower respiratory tract illness involving bronchitis, bronchiolitis, bronchopneumonia and croup which may require hospitalisation[6].

Infants with underlying complications such as congenital heart disease, bronchopulmonary dysplasia and congenital or other immunodeficiencies may be susceptible to severe, sometimes life threatening, infection with RSV[7,8]. Recurrent less severe infections occur in all age groups, occasionally resulting in pneumonia in children and the elderly[9,10]. Co-infections of RSV with other micro-organisms may result in increased severity of respiratory disease[9,11,12]. Outbreaks in geriatric wards have been associated with considerable morbidity and occasional mortality. Nosocomial transmission of RSV occurs in paediatric wards and nursery units resulting in prolonged hospitalisation and treatment of infected children[13,14,15,16,17,18].

The laboratory diagnosis of RSV plays an important role in patient management and assists in the control of outbreaks[15,16,17,19].

Methods commonly employed for laboratory diagnosis of RSV infection include direct detection of virus or viral proteins in clinical samples such as nasopharyngeal aspirates and isolation of viable virus in cell culture monolayers inoculated with respiratory secretions[20,21].

Isolation of RSV from clinical specimens can be accomplished in continuous cell lines such as HeLa and Hep2 cells in which a characteristic cytopathic effect (CPE), formation of syncytia, may develop. Successful diagnosis by virus isolation is time consuming and may require from 5 to 20 days for characteristic CPE to develop. Isolation of RSV is complicated by the lability of the virus and the insensitivity of some cell cultures[22]. Cell culture techniques are costly, laborious and inappropriate for the rapid diagnosis of RSV infections.

A direct immunofluorescence test utilising specific monoclonal antibodies offers a rapid, sensitive and specific method for direct detection of RSV in clinical samples such as nasopharyngeal aspirates.

IMAGEN RSV is a direct immunofluorescence test for the rapid detection and identification of RSV in human clinical specimens. The test utilises three monoclonal antibodies in order to detect specific structural proteins expressed in all strains of human Respiratory Syncytial Virus.

3. PRINCIPLE OF THE TEST

The IMAGEN RSV test contains monoclonal antibodies conjugated to fluorescein isothiocyanate (FITC). The conjugated antibodies bind specifically to viral antigens present in all strains of human RSV. The Reagent is used in a one-step direct immunofluorescence technique.

Specimens are incubated with the Reagent containing FITC conjugated antibodies for 15 minutes, then excess Reagent is washed off with phosphate buffered saline (PBS). The stained area is mounted and viewed microscopically using epi-fluorescent illumination. If RSV antigen is present, characteristic bright granular apple-green fluorescence is seen within infected cells, which contrasts with the red background staining of uninfected cells.

Acknowledgement

The monoclonal antibodies used in this test were produced in The Institute for Research on Animal Diseases, Compton, Berkshire, United Kingdom.

4. DEFINITIONS

The following symbols have been used throughout the product information.

REF	Product code and catalogue number
	Consult the Instructions for Use
Σ N	Contains sufficient for <N> tests
	Manufactured by
IVD	*In vitro* diagnostic medical device
	Use by
LOT	Batch Code
	Storage temperature limitations

5. REAGENTS PROVIDED

Σ 50 - Each kit contains sufficient materials for 50 direct specimens or cell culture preparations. - The shelf life of the kit is as indicated on the outer box label.

5.1. IMAGEN RSV REAGENT

Instructions for Use .

POSITIVE CONTROL SLIDE 2 x 1 well Positive Control Slide containing acetone fixed human epithelial cells (Hep2) infected with RSV.

One bottle of each of the following:

MOUNTING FLUID 3mL of Mounting Fluid. The Mounting Fluid contains a photobleaching inhibitor in a glycerol solution (pH 10.0).

REAGENT 1.4mL of IMAGEN RSV Reagent. The Reagent consists of a mixture of purified murine monoclonal antibodies specific to RSV and conjugated to FITC. The monoclonal antibodies are directed against the Fusion protein and Nucleoprotein of RSV.

5.2. PREPARATION, STORAGE AND RE USE OF KIT COMPONENTS

In order to ensure optimal kit performance it is important that unused kit components are stored according to the following instructions:

5.3. POSITIVE CONTROL SLIDES - POSITIVE CONTROL SLIDE

The slides are provided individually in sealed foil pouches with nitrogen. Store unused slides at 2-8°C. The slide should be left for 5 minutes at room temperature (15-30°C) before opening.

Stain the slide immediately after opening.

5.4. MOUNTING FLUID - MOUNTING FLUID

Ready to use. Store unused Mounting Fluid at 2-8°C. The Mounting Fluid should be left at room temperature (15-30°C) for 5 minutes before use.

5.5. REAGENT - REAGENT

Ready to use. Store unused Reagent in the dark at 2-8°C. Reagent should be left at room temperature (15-30°C) for 5 minutes before use.

6. ADDITIONAL REAGENTS

6.1. REAGENTS

Fresh acetone (for fixation).

Phosphated buffered saline (PBS) pH 7.5 for washing stained specimens and for specimen preparation.

6.2. ACCESSORIES

The following products are intended for use in conjunction with IMAGEN RSV. Contact your local distributor for further information.

Teflon coated glass microscope slides with single 6mm diameter well (100 slides per box) available from your local distributor, (Code No. S611430-6).

IMAGEN RSV Positive Control Slide (Code No. S610830-2).

7. EQUIPMENT

The following equipment is required:

Precision pipette and disposable tips to deliver 25µL

Wash bath

Coverslips suitable to cover 6mm diameter well

Non-fluorescing immersion oil

Epifluorescence microscope with filter system for FITC (maximum excitation wavelength 490nm, mean emission wavelength 520nm) and x200-x400 magnification

Incubator at 37°C

Low speed centrifuge

Mucus extractor (nasopharyngeal specimens only)

8. PRECAUTIONS

IVD - For *in vitro* diagnostic use. Anyone performing an assay with this product must be trained in its use and must be experienced in laboratory procedures.

8.1. SAFETY PRECAUTIONS

8.1.1 The IMAGEN RSV Reagent contains 15mmol/L sodium azide, which is a poison. Sodium azide may react with copper and lead plumbing systems to form explosive metal azides. Always dispose of materials containing azide by flushing with large quantities of water.

8.1.2 RSV on the positive control slide has been shown to be non-infectious in cell culture, however, the slide should be handled and disposed of as though potentially infectious.

8.1.3 Evans blue dye is present in the Reagent. This may be carcinogenic and contact with the skin should be avoided.

8.1.4 Care should be taken when using the mounting fluid as it may cause skin irritation. Skin should be flushed with water if contact occurs.

8.1.5 Do not eat, drink, smoke, store or prepare foods or apply cosmetics within the designated work area.

8.1.6 Do not pipette materials by mouth.

8.1.7 Wear disposable gloves while handling clinical specimens and infected cells and always wash hands after working with infectious materials.

8.1.8 Dispose of all clinical samples in accordance with local legislation.

8.1.9 Safety data sheet available for professional user on request.

8.2. TECHNICAL PRECAUTIONS

8.2.1 Components must not be used after the expiry date printed on the labels. Do not mix different batch lots of reagents.

8.2.2 The reagents are provided at fixed working concentrations. Test performance will be adversely affected if the reagents are modified or stored under conditions other than those detailed in Section 5.

8.2.3 Prepare fresh phosphate buffered saline (PBS) as required on the day of use.

8.2.4 Avoid microbial contamination of reagents.

8.2.5 The reagents must not be frozen.

9. COLLECTION AND PREPARATION OF SPECIMENS[22]

The collection and preparation of specimens is of fundamental importance in the diagnosis of RSV by direct immunofluorescence and cell culture methods. Specimens must be collected from the site of infection during peak time of viral shredding and be prepared in such a way as to preserve intact cells which are free from adherent mucus.

The recommended respiratory sample is nasopharyngeal aspirate which, when correctly collected, should provide large numbers of respiratory epithelial cells.

9.1. NASOPHYARYNGEAL ASPIRATES/SECRETIONS

Collection

Collect secretions from the nasopharyngeal region into a mucus extractor through a size 8 feeding tube. The mucus extractor and tubing should be sent to the laboratory as soon as possible for processing. Cell separation techniques are necessary for direct immunofluorescence staining.

Specimen or supernatant material from cell separation techniques may be used for virus culture inoculation.

Cell Separation

If necessary add 2mL phosphate buffered saline (PBS) to the specimen prior to centrifugation to reduce the viscosity and dilute the mucus. Centrifuge the mucus extractor at room temperature (15-30°C) for 10 minutes at 380g. Remove the supernatant which can be used for cell culture. Suspend the cell deposit in 2mL PBS and gently pipette the cells up and down with a wide bore pipette, or vortex gently, until the mucus is broken up and cellular material released. Avoid vigorous pipetting/vortexing to prevent damage to the cells. When a smooth suspension has been obtained add further PBS as required, pipetting or vortexing after addition of the extra volume to wash the cells further. Remove and discard any visible flecks of mucus remaining at this point. Excess mucus must be removed as it will prevent adequate penetration of the Reagent and may result in non specific fluorescence.

If all secretions remain in the feeding tube and none reach the mucus extractor, wash all secretions out of the tube into PBS. This is best achieved by inserting a pasteur pipette into the end of the tube which was attached to the mucus extractor. Suck up the appropriate fluid into the tube and expel it repeatedly until the secretions adhering to the wall of the tube have been dislodged. Pipette the suspension up and down until the mucus has been adequately broken up.

Preparation of Slides

After completing the cell separation process, centrifuge the resultant cell suspension at room temperature (15 30°C) for 10 minutes at 380g and discard the supernatant. Resuspend the cell deposit in sufficient PBS to dilute any remaining mucus while at the same time maintaining a high cell density. Place 25µL of the resuspended cell deposit into the well area on the slide. Allow the specimen to air dry thoroughly at room temperature (15 30°C) and fix in fresh acetone at room temperature (15 30°C) for 10 minutes. If the specimen is not stained immediately store at 4°C overnight or freeze at -20°C for longer storage periods.

10. TEST PROCEDURE

PLEASE REFER TO SECTION 8.2 TECHNICAL PRECAUTIONS BEFORE PERFORMING TEST PROCEDURE.

10.1. ADDITION OF REAGENT

Add 25µL of IMAGEN RSV Reagent to the fixed cell preparation on the slide (see Section 9) or to a Positive Control Slide. Ensure that the Reagent covers the entire well area.

10.2. FIRST INCUBATION

Incubate the slides with Reagent in a moist chamber for 15 minutes at 37°C. Do not allow the Reagent to dry on the specimen, as this will cause the appearance of non specific staining.

10.3. WASHING THE SLIDE

Wash off excess Reagent with phosphate buffered saline (PBS) then gently wash the slide in an agitating bath containing PBS for 5 minutes. Drain off PBS and allow the slide to air dry at room temperature (15-30°C).

10.4. ADDITION OF MOUNTING FLUID

Add one drop of IMAGEN RSV Mounting Fluid to the centre of each well and place a coverslip over the Mounting Fluid and specimen ensuring that no air bubbles are trapped.

10.5. READING THE SLIDE

Examine the entire well containing the stained specimen using an epifluorescence microscope. Fluorescence (see Section 11) should be visible at x200 x500 magnification.

(For best results specimens should be read immediately after staining, but specimens may be stored at 2 8°C in the dark for up to 72 hours).

11. INTERPRETATION OF TEST RESULTS

11.1. CONTROLS

11.1.1 Positive Control Slides

When stained and viewed (see Section 10) the Control Slide should show cells with apple-green fluorescent intracellular cytoplasmic granules contrasting against a red background of counterstained specimen. These cells are slightly larger than respiratory epithelial cells but show similar cytoplasmic fluorescence when infected with RSV. Positive Control Slides should be used to check that the staining procedure has been satisfactorily performed.

11.1.2 Negative Control

If a Negative Control is required, uninfected intact cells of the type used for the culture and isolation of RSV are recommended. The cells should be prepared, fixed and stained (see Section 10).

11.2. CLINICAL SPECIMENS

11.2.1 Appearance of RSV Infected cells

Apple green fluorescent intracellular cytoplasmic granules are seen in respiratory epithelial cells infected with RSV.

In later stages of infection, RSV antigen may be restricted to isolated areas in the cytoplasm appearing as small ill defined granules singly or in clusters.

Uninfected cells stain red with the evans blue counterstain.

11.2.2 Interpretation

A positive diagnosis is made when one or more cells show typical fluorescence in the fixed, stained specimen.

A negative diagnosis is made when fixed stained specimens do not exhibit fluorescence after staining with the Reagent.

For directly stained nasopharyngeal aspirate specimens at least 20 uninfected respiratory epithelial cells must be visible within the slide well before a negative result is reported (see Section 11.2.3 if insufficient cells are present).

11.2.3 Insufficient cells

If insufficient cells are present in the slide well preparation, the remainder of the clincial specimen should be centrifuged at 380g for 10 minutes at room temperature (15 30°C). Resuspend the cells in a smaller volume of PBS before redistribution (25µL) on the slide. Alternatively, a repeat specimen should be requested.

12. PERFORMANCE LIMITATIONS

12.1. The FITC Reagent may non specifically stain *Staphylococcus aureus* strains containing large amounts of protein A. This is due to non immune interaction of protein A with the Fc region of the monoclonal antibody, an observation reported for other monoclonal and polyclonal based fluorescent assays[23]. However, this staining does not give the typical intracellular fluorescence pattern seen in cells infected with RSV (see Section 11.2.1) and should be interpreted as non specific staining.

12.2. Use only the Mounting Fluid provided.

12.3. The visual appearance of the fluorescence image obtained may vary due to the type of microscope and light source used.

12.4. It is recommended that 25µL of Reagent is used to cover a 6mm well area. A reduction in this volume may lead to difficulties in covering the specimen area and may reduce sensitivity.

12.5. All reagents are provided at fixed working concentrations. Test performance may be affected if the reagents are modified in any way or not stored under the recommended conditions as outlined in Section 5.

12.6. Failure to detect RSV may be a result of factors such as collection of specimen at an inappropriate time of the disease, improper sampling and/or handling of specimen, failure of cell culture etc. A negative result does not exclude the possibility of RSV infection.

12.7. The presence of RSV in nasopharyngeal secretions does not necessarily exclude the possibility of concomitant infection with other pathogens[9,12]. Test results should be interpreted in conjunction with information available from epidemiological studies, clinical diagnosis of the patient and other diagnostic procedures.

12.8. Test results should be interpreted in conjunction with information available from epidemiological studies, clinical assessment of the patient and other diagnostic procedures.

13. EXPECTED VALUES

The detection rate for RSV is influenced by the time of specimen collection and the handling, storage and transportation of specimens. It is also dependent on age, general health, geographical location and socio-economic status of the population tested. Respiratory syncytial viruses are prevalent throughout the world and are associated with significant seasonal respiratory tract infections in temperate and tropical regions. In temperate climates annual outbreaks of RSV infection occur predominantly during winter months.

Lower respiratory tract infections are generally higher during these periods and RSV accounts for 20% of respiratory tract infections. Therefore, during seasonal outbreaks, a significant number of nasopharyngeal aspirates can be expected to be positive for RSV. RSV infections occur in all age groups but the symptoms are most severe in infants. 50% of all infants experience RSV infection during the first year of life. RSV has been implicated in outbreaks of respiratory tract infection in hospitals, particularly paediatric wards and in geriatric institutions where it has been associated with increased morbidity and mortality.

14. SPECIFIC PERFORMANCE CHARACTERISTICS

14.1. CLINICAL TRIALS

The IMAGEN RSV test was evaluated in two clinical trial centres on nasopharyngeal secretions from hospitalised infants showing symptoms of respiratory infection.

Trial centre 1 tested 305 specimens collected during the 1982 - 83 and the 1983 - 84 winter epidemics by IMAGEN RSV test and the centre's standard RSV diagnostic test (virus isolation in HeLa cell culture monolayers and indirect bovine polyclonal immunofluorescence). A result was considered positive if either indirect bovine polyclonal fluorescence or cell culture culture was positive. In 8 specimens, in which indirect fluorescence gave non-specific binding, a diagnosis was made solely on the cell culture result.

Trial centre 2 tested 200 specimens collected during the 1983-84 winter epidemic and 50 known positive specimens collected during epidemics occuring in the previous 5 years by IMAGEN RSV test and indirect polyclonal immunofluorescence. Culture for virus isolation was also inoculated at the time of specimen collection on all specimens but culture was discontinued on specimens subsequently found positive by immunofluorescence.

Specimens negative by immunofluorescence for RSV and those from patients where infection with a second virus in addition to RSV was considered possible were also cultured. A result was considered positive if either the indirect immunofluorescence or cell culture was positive. 8 specimens showed antigen deterioration with slide storage (as measured by a change in the indirect immunofluorescence result after storage and observation of poor fluorescence with both reagents).

The IMAGEN RSV test diagnosed RSV infection in known positive specimens collected over 5 consecutive epidemics, indicating that the monoclonal antibodies used are directed against stable

RSV antigens.Therefore, the diagnostic capacity of the Reagent is unlikely to be affected by the minor antigenic changes known to occur[2,24].

The results of the two trials are shown in Table 14.1. Of the 547 specimens tested, the IMAGEN RSV test correlated with the standard RSV diagnostic test in 525 cases (a correlation of 96%). The overall sensitivity and specificity of the IMAGEN RSV test was 93% and 98% respectively, assuming that the standard methods were 100% specific and sensitive.

The predictive values for positive and negative tests were 98% and 94% respectively.

Sensitivity, specificity and predictive values were calculated as described previously[25].

Table 14.1 Comparison of test results by the IMAGEN RSV test and the standard RSV Diagnostic test used at two trial centres

	TEST RESULT			
Standard test	**Neg**	**Pos**	**Pos**	**Neg**
IMAGEN RSV test	**Neg**	**Pos**	**Neg**	**Pos**
Trial Centre 1	220	74	6	5
Trial Centre 2	64	167	11	0
TOTAL No. of Specimens	284	241	17	5

14.2. CROSS REACTIVITY

The IMAGEN RSV test was performed against preparations of other viruses and micro-organisms likely to be present in respiratory secretions. All organisms tested (Table 14.2) were negative with the IMAGEN RSV test Reagent.

Table 14.2 Organisms tested in the IMAGEN RSV test and found to be non reactive

Adenovirus 1-4, 7, 21	*Neisseria gonorrhoeae*
Branhamella catarrhalis	*Neisseria lactamica*
Chlamydia trachomatis	*Neisseria meningitidis*
Coxsackie Virus types A9, B1, B3	*Neisseria perflava*
Cytomegalovirus	
Parainfluenza virus types 1, 2 and 3	
Echovirus types 3, 6, 9	*Picornavirus*
Herpes Simplex virus types 1 and 2	*Polio virus types 1 and 2*
Influenza virus types A and B	*Rhinovirus*
Mycoplasma pneumoniae	*Streptococcus pneumoniae*
Neisseria cinerea	*Varicella zoster virus*

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