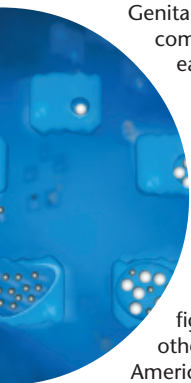




Chlamydia trachomatis: genital infections in Germany



Genital chlamydiosis is one of the most common sexually transmitted diseases (STD) in western industrial nations. The number of STD cases dropped down until the middle of the nineties. This was mainly ascribed to the use of condoms out of fear of an HIV infection. However, there have recently been increased reports in the press of a drastic drop in the use of condoms. At the same time, figures have been published for other western European and north

American countries that indicate a marked rise in sexually transmitted diseases since the mid-nineties.

There is no epidemiological data available for the majority of STD pathogens since these do not have to be reported in Germany. Thus, no statements can be made on the development and incidence of individual pathogens in Germany. Chlamydia trachomatis, however, is probably the most common sexually transmitted pathogen (cf. the Epidemiological Bulletin of the Robert Koch Institute, No. 39 from 24th September, 2004).

The course of a genital chlamydia infection is often without any or with only mild clinical symptoms and is thus frequently overlooked or incorrectly treated. If left untreated, or if treated incorrectly, a primary chlamydiosis leads to a chronic infection with in some cases very serious late sequelae (fallopian pregnancy, infertility, chronic abdominal complaints) and high costs for the health system. Moreover, the pathogen can be transferred to the new-born child during birth and bring on an inclusion conjunctivitis or even a pneumonia in the child.

In the early stage of the infection, the pathogen can be detected by means of amplification methods (PCR) in smears for a diagnosis. In this stage of the infection a direct identification of the pathogen should be given preference over an indirect detection by means of antibodies on account of the

higher sensitivity. But if the infection has already been ascended it is often impossible to detect the pathogen in the smear material.

In this case the identification of antibodies is of further assistance. It is important that specific antibodies against *Chlamydia trachomatis* are identified. *C. trachomatis* is very similar to *Chlamydomydia pneumoniae* in terms of its morphology, culture and antigens, making a laboratory diagnosis more difficult. It is thus important to use species-specific shares of the outer-membrane-protein-complex of *C. trachomatis* for the identification of the antibody.

This is the only way to guarantee a specific identification. Cross-reactions with antibodies against *Chlamydomydia pneumoniae* that often occur in the serum can be largely excluded.

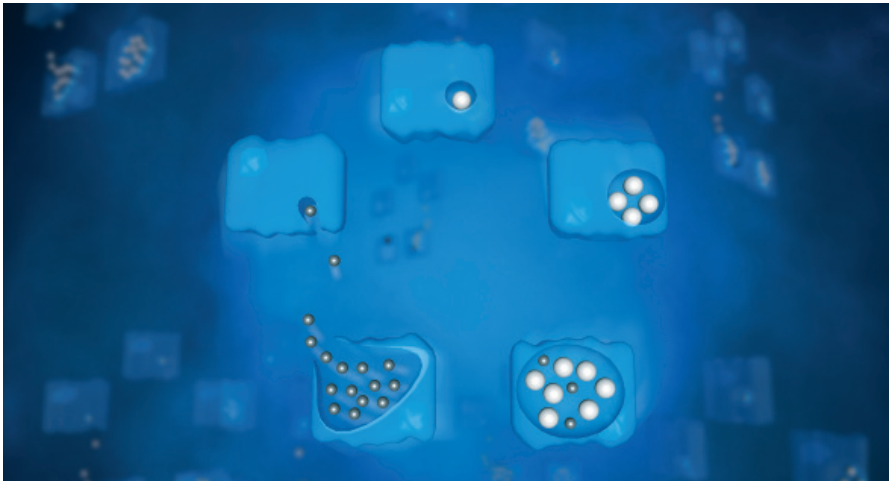
R-Biopharm was one of the first producers of diagnostic agents in Germany to offer a specific test to identify antibodies against *C. pneumoniae*. Since September of this year we have also been able to offer our customers a specific antibody EIA for *C. trachomatis*. The test is identical to that with the *C. pneumoniae* EIA. Since the patient samples are diluted directly in the micro-titration plate in both tests they are ideally suited for automation. The samples do not

have to be diluted before the test is performed.

The *C. trachomatis* EIA is designed as a combination kit. It contains anti-IgG-conjugate to identify IgG-antibodies, an important test for chronic infections. Moreover, it also contains an anti-IgM-conjugate so that IgM can also be determined with the same test kit.

The identification of IgM-antibodies can be important in the diagnosis of a pneumonia in new-born children. In the event of a suspected pneumonia caused by *C. trachomatis* a positive IgM-finding would corroborate this suspicion. IgG is unsuitable here since this could be a maternal antibody. Moreover, the identification of IgM-antibodies can narrow the gap between infection and a positive immunological response with genital infections. A test to detect IgA-antibodies has not been developed. In several recent studies it could be shown that isolated IgA-findings (without IgG) can hardly be expected with a *C. trachomatis* infection.

This is very probably due to the fact that this is a chronic infection. Conversely, no IgA-antibodies could be identified in half the infected persons with a positive IgG-result. A positive IgA result thus provides no additional information when identifying an infection.



Schematic development cycle of chlamydia trachomatis

Nonstop allergy diagnostic

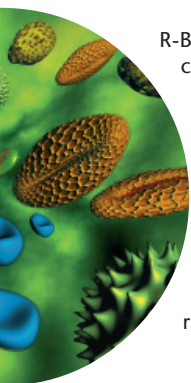
The new **RIDA® maXi-Screen** for the automatic evaluation of the **RIDA® Allergy-Screen**

R-Biopharm can offer not only its classical single allergen test system **RIDASCREEN® Specific IgE** but also the panel system **RIDA® AllergyScreen**. 20 different allergens can be determined and evaluated with the aid of the **RIDA® X-Screen** from only 250 µl of serum with this system. With the current reader each panel has to be

inserted into it, measured and the results have to be printed out.

Laboratories with a high throughput and electronic data transfer can now optimise panel tests in their laboratory routines with the new Random Access Reader **RIDA® maXi-Screen**.

The sample related data requested from the laboratory computer system can be transferred online to the evaluation software and compiled into a work list. The panels are then inserted into the reader at the end of the test according to the work list.



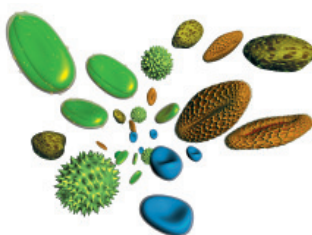
The panels are fed into the reader on a small conveyor belt with a theoretical throughput of around 600 panels per hour.



The measured results are then returned to the laboratory computer system and can be inserted into the findings for the doctor accordingly.

This enables large laboratories to exploit the benefits of the AllergyScreen panel test:

- only 250 µl of serum
- total time for the test only around 2.5 h
- cost-effective
- good conformance with single allergen tests
- bi-directional link to laboratory computer system
- high throughput rate
- 4 different panels:
 - mixed panel (food and inhalational allergens)
 - food panel
 - inhalational panel
 - paediatric panel



Norovirus-induced gastro-enteritis Outbreaks still increasing – world-wide!

Whether in Germany, England, North America or even Japan, the number of notifiable norovirus infections is rising from year to year.

For example, the total number of infections more than doubled in Germany alone, from 7,794 reported cases in 2001 to 17,936 in 2002.

The rise in nosocomial gastro-enteritis occurrences (outbreaks) in particular is very striking. This observation is most likely due to the fact that the majority of individual gastro-enteritis occurrences cannot be detected – not every sufferer runs straight to the doctor!

There is as yet no single, clear method to reliably detect this viral infection.

This is mainly because a comparison of the results of today's rival methods to diagnose a norovirus, polymerase chain reaction (PCR) and ELISA, must be regarded as unsuitable since the two detection methods are aimed at different target structures in the virus.

Whereas PCR tries to recognise and then amplify a nucleic acid sequence on the transcription level through the choice of a suitable primer, the antibodies used in an ELISA are aimed at the target antigens (capsid protein) to be detected on a translation level.

Our almost two years of experience since the launch of the RIDASCREEN® Norwalk-like Virus ELISA in February 2003 has taught

us that any attempt to achieve a 100% concordance between these two methods must be seen as unrealistic. It is more important to produce an extremely sensitive ELISA that at the same time can potentially rule out incorrectly positive results – a very important feature for the diagnosis.

A further acquired and very helpful piece of information to guarantee the comparability of both methods is that the samples to be tested in the PCR and ELISA should come from a previously prepared sample suspension.

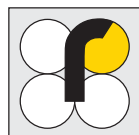
This very simple pre-dilution has proven to be an indispensable precondition, leading to the best correlation between the results of the two methods.

In co-operation with the "Central Public Health Laboratory" in London, Great Britain, we were recently able to demonstrate that the second generation RIDASCREEN® Norwalk-like Virus ELISA can be used as a reliable method to detect an outbreak.

206 samples from 40 outbreaks were examined.

A norovirus-induced gastro-enteritis outbreak was detected when at least two samples from an outbreak displayed a positive result – this applied for both PCR and ELISA. If only one sample from an

r-biopharm



outbreak was positive it was classified as doubtful.

At least two samples were declared positive by means of PCR in 18 out of 40 outbreaks. In four further outbreaks only one sample produced a positive signal in the PCR. No virus could be detected in the samples of the remaining 18 outbreaks.

The correlation with the results generated by the RIDASCREEN® Norwalk-like Virus ELISA are shown in the table below – relative to the outbreaks.

| | | RIDASCREEN® ELISA | | |
|--------|----------|-------------------|----------|----------|
| | | Positive | Negative | Doubtful |
| RT-PCR | Positive | 13 | 1 | 4 |
| | Negative | 1 | 13 | 4 |
| | Doubtful | 0 | 2 | 2 |

If one excludes the doubtful results, that could be traced to only one single sample, the sensitivity and specificity is 92.8 %. Taking the eight doubtful results into account, the sensitivity increases to 95.6 % whereas the specificity drops to 78.3 %. This reduced specificity is due to individual samples that tested positive in the RIDASCREEN® ELISA but could not be confirmed in the RT-PCR.

Furthermore, we were able to detect all genotypes of both genogroups that had

been genotyped beforehand by the Central Public Health Laboratory with our RIDASCREEN® Norwalk-like Virus ELISA.

This simple example demonstrates just how careful one has to be when interpreting data. In addition, the comparability of such studies is complicated by the fact that as yet there are no generally accepted methods of sample storage, RNA isolation and time of testing/length of storage.

Nevertheless, our claim to a reliable diagnostic system and the positive “feedback” from our numerous customers encourages us in our daily efforts at further optimising the quality of our products.

If you require further information or have any questions about the diagnosis of norovirus, our Project Manager Dr. Georgios Kiourkenidis will be pleased to be of assistance. He can be contacted either by phone at +49 (0) 6151/8102-96 or by e-mail (g.kiourkenidis@r-biopharm.de).



Trade Fairs and Conferences

| | |
|-------------------------|----------------------------------------------------------------------------------------------------------------------------------------|
| 30 Jan. - 02 Feb., 2005 | ARAB-LAB, in Dubai, U.A.E. |
| 12 - 15 February, 2005 | ARAB-HEALTH, in Dubai, U.A.E. |
| 09 - 11 March, 2005 | 3rd German Chlamydia Workshop, in Jena |
| 16 - 18 March, 2005 | 13th German MTA Congress, in Berlin |
| End of March, 2005 | LABTECH Exhibition, in Istanbul, Turkey |
| 07 - 09 April, 2005 | 14th Spring Congress of the Professional Society for Doctors for Microbiology & Infection Epidemiology, in Staffelstein (Kloster Banz) |
| 19 - 22 April, 2005 | 6th Ulm Symposium “Hospital Infections”, in Neu Ulm |
| 08 - 11 May, 2005 | 21st Annual Clinical Virology Symposium, in Clearwater, Florida, U.S. |
| 26 - 28 May, 2005 | 13th Annual Meeting of the German Society for Paediatric Infectiology (DGPI), in Düsseldorf |
| 08 - 12 June, 2005 | 8th Congress for Infectious Diseases and Tropical Medicine, in Hamburg |

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