Chlamydia trachomatis

A new genetic variant of *Chlamydia trachomatis*

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A thrilling story in Sweden, with global impact

A new variant of *Chlamydia trachomatis* was discovered in Sweden in 2006. This variant contains a mutant sequence that cannot be detected with either the Abbott m2000 (Abbott Diagnostics, Chicago, IL, USA) or Cobas Amplicor/TaqMan48 (Roche Diagnostics, Basel, Switzerland) systems.[1] The first description reported that the new variant constituted 13% of all detected chlamydia infections (from mid-September to October 2006) in the county of Halland (south west of Sweden). It soon became apparent that the proportion was higher and that the new variant had spread widely in Sweden.[2–4] We now know that in the counties that have used the Abbott or Roche test systems during the past year or so the new variant accounts for 20% to 65% of all detected chlamydia cases. In local areas, as many as 78% of all cases have been found to have the mutation (Britta Loré, personal communication).

How great is the national impact of this emerging variant of *C trachomatis*? As in many other countries chlamydia rates have increased in Sweden during the past 10 years. However, for 2006 the national figures showed a reversal of this trend.[5] The 2% decrease in reported cases was because of the inability of some diagnostic systems to detect the new variant. Counties using the Abbott or Roche test systems reported fewer chlamydia cases in 2006 compared to 2005, while counties using methods that detected the strain, mainly the BectonDickinson ProbeTec, reported an increase. In a preliminary analysis, if we assume that 30% of all chlamydia cases are caused by the new variant in counties using the Abbott or Roche systems in recent years, about 8000 chlamydia cases have escaped detection. Instead of the reported decrease, the number of reported chlamydia cases would have increased by 20%, continuing the rising trend.

The spread of the new variant differs between counties, but the reasons for this remain unexplained. There are, however, most probably many sexual networks where cases have escaped diagnosis and thus treatment and mandatory contact tracing. These areas are in almost the same situation as before chlamydia was recognised as a pathogen. The number of additional cases of salpingitis, ectopic pregnancies, and infertility will never be known, but failure to detect the new chlamydia variant during this period has certainly resulted in episodes of complicated infection in many parts of the country.

An obvious question is—when did the mutation take place? It may actually have occurred several years ago, but the data suggest that it has not spread widely until recently. The increasing trend in reported cases in counties using the Abbott or Roche systems was broken during 2005. This could be interpreted as the emergence of the new variant. Ongoing high-resolution genotying of such chlamydia strains by multilocus sequence analysis[6] will provide further knowledge about the clonal nature of the new variant and its emergence. In addition, almost no cases of the new strain have been found outside Sweden. In Malmö, the regional capital of southern Sweden 25% of all detected chlamydia cases contain the mutation, but on the other side of the bridge in Copenhagen, Denmark not a single case was seen until March 2007 after examination of well over 2000 samples since October 2006 (Jörgen Skov Jensen, personal communication). This is remarkable considering the massive daily migration for work and pleasure between the two countries. A few cases have been detected in Norway[7] (Amir Moghaddam, personal communication in May), but in more distant countries such as the Netherlands and Ireland not a single case of the new variant has been found.[8 9] See summary in table 1.

What can we learn from the emergence of this new variant of chlamydia? This thrilling story provides several lessons. Firstly, how to design a diagnostic test. The new variant is a striking example of diagnostics driven evolution that must be considered when new methods are designed. Since routine diagnostics for chlamydia uses high volume testing based on nucleic acid detection, it is important that the targets used are not only conserved genetic elements but also essential for the organism. In the case of the new variant three major commercial companies use the cryptic plasmid as their target (Abbott, Roche, and Becton Dickinson). However, the Becton Dickinson ProbeTec system is not affected by the mutation. The rationale is that there are 5–10 copies of this plasmid per cell, which increases the sensitivity compared to using a single copy gene in the chromosome. However, since genes on the plasmid are not essential for survival, a mutation can take place without major impact for the bacteria, but obviously with dramatic consequences for diagnostics. Plasmid free strains of *C trachomatis* were actually reported in the early 1990s,[10 11] but this finding had no major effect on the design of detection methods. Use of dual target regions in the same test could avoid such a detection failure and such a system is already available (artus C trachomatis Plus PCR, Qiagen, Hilden, Germany). Another point to consider is the importance of using several test systems at a national level. If a single test system dominates a market too much, the appearance of a mutant will be more difficult to observe and the lack of alternative detection systems will make laboratory diagnostics even more vulnerable.

Secondly, surveillance is important. The discovery of the new *C trachomatis* variant started when Dr Ripa in Halmstad observed a decrease of 25% in chlamydia rates in his county that were not seen in the national rates. The national mandatory reporting system therefore stimulated the microbiological investigation that led to the discovery of the new variant. Thirdly, we should ask how the authorities should deal with outbreaks of emerging diseases or failing detection systems. In Sweden, the new variant was first reported in October 2006, when the proportion of mutants was estimated to be 13%. The Swedish Institute for Infectious Disease Control recommended that, in counties using Abbott or Roche tests, samples with suspected chlamydia infection should be sent to a laboratory using a method capable of detecting the mutant strain. When the proportion of new variant chlamydia was reported to be 39% in another county, each county was urged to handle the situation according to local conditions. In contrast, only four days after the first case of the new variant was found in Denmark on 30 March 2007, the National Board of Health requested that laboratories should either change method or send samples to other laboratories. The slow Swedish response could be the result of a strongly decentralised healthcare system, where the local authorities are supposed to act, although that is not always the case. On the other hand, the Danish response to a single case could be seen to be an over-reaction in a country that reports 25 000 chlamydia cases a year.

Table 1 Investigations of the new variant of *Chlamydia trachomatis* outside Sweden*

Country	No of examined samples	No of positive tests	Test systems used	Test system used for confirmation variant cases	No of new variant	Reference
Norway	409	49	(1) Roche Taqman 48 CT (2) In house dual target plasmid/ ompA gene PCR		2†	7
Ireland	8797 750	780	(1) Becton Dickinson ProbeTec (2) Roche Taqman 48 CT	In-house mutant specific plasmid PCR on 30 discrepant samples	0	9
Netherlands	687	63 75	(1) Becton Dickinson ProbeTec (2) Roche CT Amplicor	In-house mutant specific plasmid PCR on 13 discrepant cases	0	8
Denmark	>2600	ca 10%	(1) In-house plasmid PCR (2) 16S RNA PCR	In-house mutant specific plasmid PCR on discrepant cases	0	Jörgen Skov Jensen, personal communication
	150	100	(1) Becton Dickinson ProbeTec (2) In-house plasmid PCR	Mutant specific plasmid PCR on discrepant cases, as in ref 2	1	

*Time period for collection of samples differs, but all investigations are based on collection periods within the time range October 2006 to April 2007. The new variant has been reported from Finland in ESSTI Newsletter N.4, 2007 (http://essti.org/docs/ESSTI_Newsletter_issue_4.pdf), check up of this information with ESSTI showed it to be incorrect. Thus no confirmed cases of the new variant have been detected by May 2007 in Finland.
†More cases were found later (Amir Moghaddam, personal communication).

The emergence of this new variant of chlamydia has already taught us several things. Adequate detection methods are now in place. The European Surveillance for STI (ESSTI) network and the European Centre for Disease Prevention and Control (ECDC), which is based in Stockholm, have launched a survey to examine the response of member states[12] and to date (May) 11 countries have performed investigations to find the new variant. We should also soon have some local data that can be used to investigate the spread of the mutant strain and shed light on the efficiency of contact tracing. By developing agreed standards for responding to outbreaks such as this we should also make sure that we can continue to learn.

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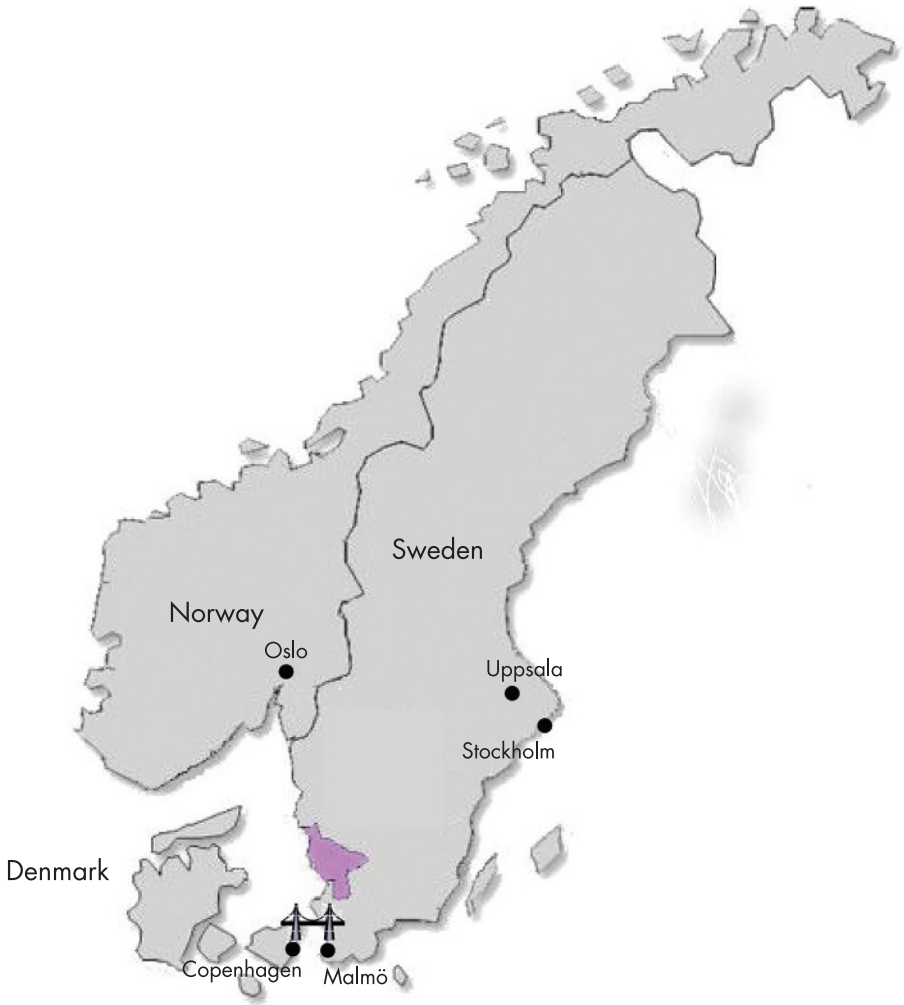

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Anders Nilsson produced the figure.

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