

NATIONAL STANDARD METHOD

MICROBIOLOGICAL INVESTIGATION OF PATIENTS WITH ACUTE LYMPHADENOPATHY AND FEVER

QSOP 44

Issued by Standards Unit, Department for Evaluations, Standards and Training
Centre for Infections



UK Clinical Virology Network

Association of Medical Microbiologists
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AMENDMENT PROCEDURE

Controlled document reference	QSOP 44
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Each National Standard Method has an individual record of amendments. The current amendments are listed on this page. The amendment history is available from standards@hpa.org.uk.

On issue of revised or new pages each controlled document should be updated by the copyholder in the laboratory.

Amendment Number/ Date	Issue no. Discarded	Insert Issue no.	Page	Section(s) involved	Amendment
2/ 11.12.08	1.1	2	1	Front page	CMN and NIMAG logos added
			2	Status page	Taxonomy sentence added
			10	6	Statistics updated
			11	7	LGV section added
			All	All	PDF hyperlinks amended to read document title
			All	All	Department name changed to DEST
			12	8	Relevant National Standard Methods section added
14	References	References reviewed and updated			

MICROBIOLOGICAL INVESTIGATION OF PATIENTS WITH ACUTE LYMPHADENOPATHY AND FEVER

Types of specimen: Serum samples
PCR samples – Urine and throat swab
Genital swabs in syphilis and LGV (others as directed)

INTRODUCTION

This National Standard Method (NSM) aims to explain the microbiological investigation of patients with acute lymphadenopathy and fever.

The following infections will be covered:

- Epstein Barr Virus (EBV)
- Cytomegalovirus (CMV)
- *Toxoplasma gondii* (*T. gondii*)
- Human Immunodeficiency Virus (HIV)
- Rubella
- Syphilis
- Lymphogranuloma venereum (LGV)

This group of agents are major causes of acute lymphadenopathy and fever that are often diagnosed by Virology laboratories. Other agents of significance diagnosed in Bacteriology laboratories are Streptococci (see [BSOP ID 4 - Identification of Streptococcus species, Enterococcus species and morphologically similar organisms](#)), typical and atypical Mycobacteria (see [BSOP 40 - Investigation of specimens for Mycobacterium species](#)), Bartonella (see [BSOPID 1 - Introduction to the preliminary identification of medically important bacteria](#) and [BSOP 37 - Investigation of blood cultures \(for organisms other than Mycobacterium species\)](#)), *Actinomyces* species (see [BSOPID 15 – Identification of Anaerobic Actinomycetes species](#) and [BSOPID 10 – Identification of aerobic Actinomycetes species](#))

The physician also needs to be aware of non-infectious causes of acute lymphadenopathy and fever eg lymphoproliferative and neoplastic disorders.

1 EPSTEIN BARR VIRUS

1.1 EPIDEMIOLOGY

Transmission occurs predominantly before 3 years of age and is largely asymptomatic. In developed countries, primary infection often occurs during adolescence, presenting as Infectious Mononucleosis (IM). By adulthood seroprevalence is 90 to 95%.

1.2 CLINICAL FEATURES

IM can range from a mild to a severe, debilitating illness. Typical features are lymphadenopathy, general malaise, pharyngitis and headache. Atypical lymphocytosis is a characteristic feature of the first two weeks of illness, due to a vast increase in absolute numbers of CD8+ T lymphocytes. More than 20% of white cells may be large "atypical" activated cells, this is virtually pathognomonic. Smaller percentages of white cells may be "atypical" cells during infections other than EBV. Absolute numbers of circulating B-lymphocytes are normal or slightly raised. Lymphadenopathy is largely cervical. Fever occurs in approximately 90% of patients and rash in 5%. Jaundice occurs in 5% of cases, although hepatocellular enzymes are raised in 80 to 90% of cases. Splenomegaly occurs in approximately 50% of cases. Most cases resolve spontaneously over a 2 to 3 week period². Malaise may occur for weeks or months in some patients.

1.3 COMPLICATIONS

Autoimmune haemolytic anaemia occurs in 0.5 to 3.0% of patients with IM, and mild thrombocytopaenia is common. Neurological symptoms occur in less than 1% of cases as an acute, severe, progressive disease although complete recovery is the norm. Stridor and respiratory arrest may be seen in association with massive enlargement of lymphoid tissue in the pharynx. Rarely primary EBV in a person who is immunocompetent may be complicated by fulminant IM associated with haemophagocytosis caused by activation of the monophagocytic system in multiple organs. Infection in boys with X-linked lymphoproliferative syndrome progresses through an IM disease to death in 75% of cases³. Individuals with an immunodeficiency or who are immunocompromised may develop lymphoproliferative disease or lymphoma. EBV is associated with almost 100% of cases of endemic Burkitt's Lymphoma and 12% of sporadic cases.

1.4 LABORATORY DIAGNOSIS⁴

This section should be read in conjunction with [VSOP 26 - Epstein-Barr Virus serology](#).

Heterophile antibodies⁵:

- Appear in the serum early in IM
- The classic test used a doubling dilution titration of serum and sheep red cells (use of horse red cells increases sensitivity). Prior absorption of the serum with guinea-pig kidney emulsion increases specificity, by eliminating agglutination seen in normal serum due to "Forssman antibody". Specificity can be further improved by absorption of reactive samples with ox cell stroma, which specifically removes heterophile antibody seen in IM. Classic tests are usually known as Paul-Bunnell tests
- Commercial IM screening kits (often based on latex particle slide agglutination) developed from these classical techniques are now more widely employed; these are widely known as monospot tests and have been the subject of a 1998 Medical Devices Agency report
- Monospot tests are 84 to 100% sensitive in IM (compared to EBV VCA IgM IF tests). False negatives are seen particularly in cases aged less than 14 years. Specificity for IM is 89 to 100%, but the monospot may remain positive for many months after resolution of symptoms and may be positive in asymptomatic primary EBV infection

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Antibodies to viral capsid antigen (VCA):

- IgG, IgM and IgA are all typically detectable in the serum of patients with IM by the time of onset of symptoms
- IgG has often reached a high titre by presentation, making the demonstration of a rising titre of IgG difficult
- IgA and IgM decline to undetectable levels during convalescence
- IgM detection by Indirect Immunofluorescence (IF) is a highly sensitive test for IM. Complexes of EBV IgG and IgM class rheumatoid factor can cause false positive results. EBV IgG can cause false negatives by competing with EBV IgM. Serum samples should be pre-treated to remove IgG before the IF test. Non-specific anti-cell fluorescence may be seen but should be readily differentiated from specific fluorescence by an experienced observer
- ELISA tests for EBV IgM are less sensitive, but are more widely used
- Weak cross-reactions may cause false positive EBV VCA IgM results, particularly during primary CMV

Antibodies to EBNA-1:

- IgG is not usually detectable until the convalescent period. Its detection excludes recent or current IM. Commercial EBNA-1 IgG ELISAs are available and widely used

EBV DNA tests⁶⁻⁹

- Quantitative PCR assays are used in the monitoring of patients who are immunocompromised and at risk of EBV associated lymphoproliferative disease, where very high levels may be observed. Lower levels are seen in uncomplicated IM. A role for EBV DNA quantitation in the diagnosis and monitoring of IM and its complications has been suggested. Levels are higher in IM than in healthy carriers and higher still in complicated IM.

2 CYTOMEGALOVIRUS

2.1 EPIDEMIOLOGY¹⁰

Infection is widespread and is usually inapparent. In the UK the seroprevalence in adults is around 50%. Seroprevalence ranges from 40 to 100% depending on ethnicity and social class. Congenital infection occurs in approximately 0.5% of all live births. Perinatal transmission can occur at birth or by breastfeeding. Infection can also occur in the early years of childhood, following infection at nurseries or day-care centres, as young children can excrete the virus in respiratory secretions and urine for many months. Sexual transmission to seronegative individuals can occur at the onset of sexual activity. Transmission may also occur through blood products.

2.2 CLINICAL FEATURES

Mononucleosis caused by CMV is difficult to distinguish clinically from that due to EBV infection. Enlargement of lymph nodes and spleen is not striking but may occur. Tonsillitis or pharyngitis is rare. Severe hepatitis or jaundice is unusual although slightly raised hepatocellular enzymes are common. In individuals who are immunocompetent the majority of cases resolve spontaneously.

2.3 COMPLICATIONS

A variety of severe infections can occur in a patient who is immunocompromised, including pneumonitis, retinitis, hepatitis and gastrointestinal disease. If untreated these are associated with severe morbidity or mortality. Severe congenital disease is more likely in cases resulting from maternal primary infection¹¹. Infection of immunocompetent adults may trigger Guillain-Barré syndrome¹⁰.

2.4 LABORATORY DIAGNOSIS

Detection of CMV IgM by commercial ELISA is the most widespread method in use for confirming a diagnosis of primary CMV infection in a person who is immunocompetent with an IM-like syndrome. CMV PCR on blood may be more sensitive but it is not a widely used investigation in this setting. CMV IgG avidity is a well described serological technique for confirming recent infection¹².

3 TOXOPLASMA GONDII

3.1 EPIDEMIOLOGY^{13,14}

Infection occurs as a worldwide zoonosis involving a wide range of mammals, with cats being particularly important vectors of transmission. The incidence varies between countries. In the UK seroprevalence reaches 50% by age 60 with some evidence of regional variation. Infection usually occurs following ingestion of oocysts in raw or under-cooked meats and vegetables contaminated with animal excreta.

3.2 CLINICAL FEATURES

Only 10 to 20% of infections are symptomatic in adults and the clinical presentation is not distinctive¹⁵. When it occurs it is usually cervical lymphadenopathy but any or all lymph nodes may be enlarged. If symptomatic, fever, malaise, myalgia, sore throat, maculopapular rash and hepatosplenomegaly may be present. *T. gondii* is estimated to cause 3 to 7% of clinically significant lymphadenopathy. Infection is usually benign and self-limited. Symptoms, if present, usually resolve within a few months and rarely persist beyond 12 months.

3.3 COMPLICATIONS

Severe disease can occur in patients who are immunocompromised usually following reactivation of latent infection manifesting as encephalitis, pneumonitis or chorioretinitis. Primary infection during pregnancy can result in congenital infection with damage, particularly in the first trimester.

3.4 LABORATORY DIAGNOSIS

Commercial ELISA and latex agglutination systems are available to screen for total *T. gondii* antibodies and *T. gondii* IgM. These are sensitive enough to detect all but the lowest levels of antibody detected on reference tests such as the dye test and ISAGA. Acute toxoplasmosis in individuals who are immunocompetent can, therefore, be effectively excluded by negative screening test results¹⁶. The use of highly sensitive and specific assays for recent infection such as ISAGA, ELISA and IgG avidity is recommended to confirm acute infection, particularly in pregnancy, and will require the involvement of a Reference Unit¹⁷ (See [QSOP 59 - Investigation of Toxoplasma Infection in pregnancy](#) for further information).

4 HUMAN IMMUNODEFICIENCY VIRUS

4.1 EPIDEMIOLOGY¹⁸⁻²⁰

A pandemic is occurring with 33 million people estimated in the UNAIDS 2008 Global Report to be living with HIV/AIDS, including 2.7 million newly infected in 2007. Approximately two-thirds of infected people are in sub-Saharan Africa. By the end of 2005 there were an estimated 63,500 people living with HIV in the UK of whom 20,100 (32%) were unaware of their infection. During 2007, 7,734 persons were newly diagnosed with HIV in the UK. New AIDS diagnoses in infected persons decreased from a peak of 947 cases in 2003 to 645 in

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2007. Worldwide, transmission is predominantly heterosexual. Vertical transmission had infected 998 children in the UK by the end of 2003, but is now largely preventable. Infection through blood transfusion is now very rare and no infections have occurred as a result of blood product treatment since 1985.

4.2 CLINICAL FEATURES²¹

A mononucleosis-like syndrome often occurs during primary infection, approximately 3 to 4 weeks post-exposure. Fever is present in 80 to 90% of cases. Lymphadenopathy occurs in 40 to 70% of cases, often involving several extra-inguinal sites and can on occasions persist for at least 3 months. Rash and pharyngitis both occur in 40 to 70% of cases. Some signs are more a feature of acute HIV than other causes of mononucleosis, including the maculopapular (or morbilliform) rash, diarrhoea, meningoencephalitis and mucocutaneous ulceration. This syndrome can be misdiagnosed and may be under-diagnosed.

4.3 LABORATORY DIAGNOSIS

Tests for HIV antibody first become positive 22 to 27 days after acute infection²¹.

The detection of high titre viral RNA or viral p24 antigen in a patient with a negative test for HIV-1 antibodies establishes the diagnosis of acute HIV-1 infection. Viral RNA testing is the more sensitive assay and detects HIV-1 infection 3 to 5 days earlier than p24 antigen tests and 1 to 3 weeks earlier than antibody assays. Levels of RNA are greater than 50,000 copies/mL in acute HIV infection²¹. Subsequent documentation of seroconversion is essential to confirm HIV infection, though prompt intervention with antiretrovirals may blunt the expected antibody response.

Fourth generation HIV antibody assays that will simultaneously detect HIV-1 p24 antigen are now available and data suggest that they will detect HIV-1 infection 2 to 18 days earlier than third generation assays (for antibody alone)²²⁻²⁵. However, there are reports of two window periods being observed with this assay, presumably because of detection of the antigen peak and then the antibody rise with a period of non-reactivity between²⁶.

5 RUBELLA

5.1 EPIDEMIOLOGY²⁷⁻²⁹

The epidemiology of rubella has changed considerably since the introduction of MMR in 1988 and outbreaks are rare in the UK. Until recently the seroprevalence of antibody in children and adults was 97 to 98%. However in the mid-1990s a fall in vaccine uptake in young children occurred as a result of suggestions of complications to MMR use that have since been refuted, to the extent that rubella epidemics are once more a possibility. People arriving in the UK from less-developed countries, lacking rubella vaccination programmes, may be susceptible and at risk of infection.

5.2 CLINICAL FEATURES

Rubella presents as a mild, febrile illness with a transient erythematous rash and lymphadenopathy affecting the post-auricular, sub-occipital and posterior cervical glands. Arthralgia and arthritis sometimes occur in adults. Children often have few clinical symptoms. In all cases symptoms resolve spontaneously. Clinical diagnosis alone is unreliable.

5.3 COMPLICATIONS

Congenital rubella can follow primary infection in pregnant women. Severe foetal damage can occur if infection occurs in the first 16 weeks of gestation³⁰. Reinfection when it occurs is usually sub-clinical and there is a low but definite risk to the foetus following maternal infection in the first 16 weeks of gestation³¹.

5.4 LABORATORY DIAGNOSIS^{31,32}

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The serological diagnosis of rubella is well established. Commercial EIAs usually make it possible to detect specific IgM within 4 days of onset of rash and for 4 to 8 weeks thereafter. IgM assays can be of high specificity, but the low prevalence of rubella in the UK means that the predictive value of a positive IgM assay alone is now low. It is particularly important in pregnant women to establish the diagnosis with certainty. The collection of multiple blood samples to establish a rising titre of IgG or the presence of low avidity antibody is indicated to confirm a diagnosis of acute rubella. A significant rise in antibody titre can be detected by a quantitative EIA, HAI or LA titration. Seroconversion can be detected by SRH. Although HAI antibodies may develop 1 to 2 days after onset of symptoms antibodies detected by EIA, LA or SRH may be delayed until 7 to 8 days. Rubella specific IgG and IgM antibodies may be detected in saliva using antibody capture immunoassays and results correlate well with serum antibodies³³.

Rubella virus may be detected in clinical samples by isolation in cell culture (vero cells are widely recommended) or by reverse transcription nested PCR in reference laboratories. In rubella acquired postnatally virus excretion is of greatest duration from the pharynx, typically commencing before the onset of clinical symptoms and continuing after the rash has faded but usually ceasing before the lymphadenopathy has settled.

6 SYPHILIS

6.1 EPIDEMIOLOGY^{19,34,35}

The numbers of syphilis cases diagnosed fell sharply during the early to mid 1980s, coinciding with changes in sexual behaviour that were associated with HIV and AIDS awareness campaigns. There has been a substantial increase in numbers of primary, secondary and early latent cases of syphilis diagnosed in the UK. The number of cases rose from 301 in 1997 to 3,702 cases in 2006. Numbers of primary and secondary syphilis diagnosis rose from 162 to 2,766 and those of early latent syphilis rose from 139 to 936 during this period. Until 2000, most syphilis cases in the UK were accounted for by outbreaks in London and the North West of England. Since 2001, outbreaks have developed in the North East, East Midlands, South West, South East Coast, Scotland, Wales and more recently in the West Midlands. Between 2002 and 2006, the greatest increase (847 to 1,873) in cases of infectious syphilis has been in the men who have sex with men (MSM) population, followed by heterosexual men (635 to 1,295) and women (268 to 553).

6.2 CLINICAL FEATURES³⁶

The vast majority of patients with secondary syphilis have a rash and most have lymphadenopathy. All other signs, including fever, chancre still being present, condylomata lata, mucous patches and alopecia are less frequent.

6.3 COMPLICATIONS^{36,37}

Patients with secondary syphilis may suffer hepatitis, meningitis, peripheral neuropathy, perceptible deafness, splenomegaly, periostitis, arthritis or iridocyclitis. None of these is seen in more than 2% of patients.

6.4 LABORATORY DIAGNOSIS³⁷

Diagnosis is most commonly confirmed serologically using a combination of reagin tests such as VDRL and RPR and specific anti-treponemal assays such as TPHA, IgG and IgM by EIA or IF. Combined treponemal IgG and IgM detection EIAs are preferred for screening. False negative reagin tests may occur due to prozone effects. All the specific tests are almost invariably positive in secondary syphilis, delayed serological response is rare - even with HIV co-infection. Serological tests cannot differentiate from other treponemal infections, such as yaws. PCR for *T. pallidum* will be useful in the minority of secondary syphilis cases in which the primary chancre is still observed at diagnosis.

7 LYMPHOGRANULOMA VENEREUM (LGV)

7.1 EPIDEMIOLOGY³⁸

Prior to 2004, lymphogranuloma venereum (LGV) was predominantly a tropical disease, rarely seen in the UK. Following the emergence of this disease in the Netherlands and other parts of Europe an epidemic is now well established in the UK. Similar to the ongoing outbreaks of LGV in Western Europe and America, the epidemic is concentrated in the MSM population. As initially little was known about the transmission and symptoms of this disease, enhanced surveillance was set up in the UK to collect information on demographics, transmission and clinical presentation.

There have been 775 laboratory confirmed cases of LGV in the UK between October 2004 and the end of June 2008. The UK has the largest cohort of LGV cases in Europe. Average number of cases per quarter in 2007 was 47. The group at greatest risk is MSM who are predominately white, often co-infected with HIV (73%) and other STIs (gonorrhoea 18% and syphilis 6%) and present with proctitis. A few heterosexual cases have been detected including a single woman. Despite attempts to raise awareness among MSM and healthcare professionals, the infection has not been controlled.

7.1 CLINICAL FEATURES^{39,40}

Most LGV cases (82%) presented because of symptoms, others presented as contacts (5%), through referral (4%), or were detected during routine examination (5%) and screening for STI or HIV. Proctitis remains the commonest presentation, almost all with systemic symptoms (fever and malaise) also had proctitis. Symptoms include rectal pain, discharge, tenesmus, and other signs of lower gastrointestinal inflammation including constipation and abdominal pain. Genital and inguinal symptoms are rare with only a small minority presenting with inguinal lymphadenopathy. The primary ulcer usually goes unnoticed. The incubation period is extremely variable (range 3-30 days) from time of sexual contact with an infected individual; the primary lesion is transient and often imperceptible, in the form of a painless papule or pustule or shallow erosion. Extra-genital lesions have been reported such as in the oral cavity (tonsil) and extra-genital lymph nodes.

7.2 COMPLICATIONS⁴¹

Left untreated, chronic inflammation may lead to stricture and fistula formation as well as local lymphatic obstruction and lymphoedema. Patients with acute proctitis related to LGV usually respond well to antibiotic therapy. At present the recommended treatment for LGV in the United Kingdom is either oral doxycycline 100 mg twice daily, or oral erythromycin 500 mg four times a day, both regimens given for 3 weeks. Patients with chronic infection including abscess, fistulas, and strictures often require surgical intervention.

7.3 LABORATORY DIAGNOSIS⁴²

The case definition used by the HPA is confirmation of *C. trachomatis* (see [VSOP 37 – Chlamydial Infection – testing by NAATs](#)) and presence of an LGV serovar, L1, L2, or L3, by genotyping. Reference services will test rectal specimens from patients with symptoms of proctitis or urethral specimens from patients with inguinal lymphadenopathy or in contact with LGV that are known to be positive for *C. trachomatis* DNA. Serology for *C. trachomatis* has been used in Europe and can suggest the possibility of LGV, but does not confirm cases because of a lack of specificity, and has not been used in England as part of the case definition.

8 RELEVANT NATIONAL STANDARD METHODS

For additional details on specific areas of diagnosis refer to the relevant NSMs available through the Department for Evaluations, Standards and Training web page (www.hpa-standardmethods.org.uk).

Other documents that may be of relevance to this NSM are:

[BSOP 28 – Investigation of genital tract and associated specimens](#)

[BSOP 37 - Investigation of blood cultures \(for organisms other than Mycobacterium species\)](#)

[BSOP 38 – Investigation of bone marrow](#)

[BSOP 40 - Investigation of specimens for Mycobacterium species](#)

[BSOPID 1 - Introduction to the preliminary identification of medically important bacteria](#)

[BSOPID 4 - Identification of Streptococcus species, Enterococcus species and morphologically similar organisms](#)

[BSOPID 10 – Identification of aerobic *Actinomyces* species](#)

[BSOPID 15 – Identification of anaerobic *Actinomyces* species](#)

[VSOP 26 - Epstein-Barr Virus serology](#)

[QSOP 55 – Investigation of Vesicular rashes](#)

[QSOP 56 – Investigation of red rash](#)

[QSOP 59 - Investigation of Toxoplasma Infection in pregnancy](#)

9 ACKNOWLEDGEMENTS AND CONTACTS

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REFERENCES

1. Department of Health NHS Executive: The Caldicott Committee. Report on the review of patient-identifiable information. London. December 1997.
2. Schooley RT. Epstein-Barr Virus (Infectious Mononucleosis). In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas and Bennett's Principles and Practice of Infectious Diseases. 5th ed. Vol 2. Edinburgh: Churchill Livingstone; 2000. p. 1599-613.
3. Rickinson AB, Kieff E. Epstein-Barr virus. In: Knipe DM, Howley PM, editors. Fields Virology. 4th ed. Vol 2. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 2594-7.
4. Crawford DH. Epstein-Barr virus. In: Zuckerman AJ, Banatvala JE, Pattison JR, editors. Principles and Practice of Clinical Virology. 4th ed. Chichester: John Wiley & Sons Ltd; 2000. p. 117-39.
5. Medical Devices Agency. Fourteen commercial IM screening kits. MDA/98/63. HMSO. Norwich. 1998. p. 5-51
6. van Laar JA, Buysse CM, Vossen AC, Hjalmarsson B, van Den BB, van Lom K, et al. Epstein-Barr viral load assessment in immunocompetent patients with fulminant infectious mononucleosis. Arch Intern Med 2002;162:837-9.
7. Leung E, Shenton BK, Jackson G, Gould FK, Yap C, Talbot D. Use of real-time PCR to measure Epstein-Barr virus genomes in whole blood. J Immunol Methods 2002;270:259-67.
8. Berger C, Day P, Meier G, Zingg W, Bossart W, Nadal D. Dynamics of Epstein-Barr virus DNA levels in serum during EBV-associated disease. J Med Virol 2001;64:505-12.
9. Stevens SJ, Pronk I, Middeldorp JM. Toward standardization of Epstein-Barr virus DNA load monitoring: unfractionated whole blood as preferred clinical specimen. J Clin Microbiol 2001;39:1211-6.
10. Griffiths PD. Cytomegalovirus. In: Zuckerman AJ, Banatvala JE, Pattison JR, Griffiths PD, Schoub BD, editors. Principles and Practice of Clinical Virology. 5th ed. Chichester: John Wiley & Sons Ltd; 2004. p. 85-122.
11. Fowler KB, Stagno S, Pass RF, Britt WJ, Boll TJ, Alford CA. The outcome of congenital cytomegalovirus infection in relation to maternal antibody status. N Engl J Med 1992;326:663-7.
12. Revello MG, Gerna G. Diagnosis and management of human cytomegalovirus infection in the mother, fetus, and newborn infant. Clin Microbiol Rev 2002;15:680-715.
13. Ryan M, Hall SM, Barrett NJ, Balfour AH, Holliman RE, Joynton DH. Toxoplasmosis in England and Wales 1981 to 1992. Commun Dis Rep CDR Rev 1995;5:R13-R21.
14. Ashburn D. History and general epidemiology. In: Ho-Yen DO, Joss AW, editors. Human toxoplasmosis. Oxford: Oxford University Press; 1992. p. 1-25.
15. Remington JS. Toxoplasmosis in the adult. Bull N Y Acad Med 1974;50:211-27.
16. Medical Devices Agency. Biomerieux Vidas Immunoassay System for Chlamydia, Cytomegalovirus and Toxoplasma Assay. MDA/94/57. HMSO. Norwich. 1994. p. 47-76
17. Pinon JM, Dumon H, Chemla C, Franck J, Petersen E, Lebech M, et al. Strategy for diagnosis of congenital toxoplasmosis: evaluation of methods comparing mothers and newborns and standard

MICROBIOLOGICAL INVESTIGATION OF PATIENTS WITH ACUTE LYMPHADENOPATHY AND FEVER

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This NSM should be used in conjunction with the series of NSMs from the Health Protection Agency

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methods for postnatal detection of immunoglobulin G, M, and A antibodies. J Clin Microbiol 2001;39:2267-71.

18. Joint United Nations Programme on HIV/AIDS Global Report. www.unaids.org/en/KnowledgeCentre/HIVData/GlobalReport/2008/2008_Global_report.asp.
19. The UK Collaborative Group for HIV and STI Surveillance. A complex picture - HIV & other Sexually Transmitted Infections in the United Kingdom. HPA, Centre for Infections.
20. New Diagnoses National Overview, Health Protection Agency, 2008. www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1203084373037.
21. Kahn JO, Walker BD. Acute human immunodeficiency virus type 1 infection. N Engl J Med 1998;339:33-9.
22. Ly TD, Laperche S, Courouce AM. Early detection of human immunodeficiency virus infection using third- and fourth-generation screening assays. Eur J Clin Microbiol Infect Dis 2001;20:104-10.
23. Brust S, Duttman H, Feldner J, Gurtler L, Thorstensson R, Simon F. Shortening of the diagnostic window with a new combined HIV p24 antigen and anti-HIV-1/2/O screening test. J Virol Methods 2000;90:153-65.
24. van Binsbergen J, Keur W, Siebelink A, van de GM, Jacobs A, de Rijk D, et al. Strongly enhanced sensitivity of a direct anti-HIV-1/-2 assay in seroconversion by incorporation of HIV p24 ag detection: a new generation vironostika HIV Uni-Form II. J Virol Methods 1998;76:59-71.
25. Gurtler L, Muhlbacher A, Michl U, Hofmann H, Paggi GG, Bossi V, et al. Reduction of the diagnostic window with a new combined p24 antigen and human immunodeficiency virus antibody screening assay. J Virol Methods 1998;75:27-38.
26. Meier T, Knoll E, Henkes M, Enders G, Braun R. Evidence for a diagnostic window in fourth generation assays for HIV. J Clin Virol 2001;23:113-6.
27. Evidence to US Congressional hearing on the subject of autism and MMR from Prof Brent Taylor, Royal Free and University College Medical School. <http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1204100449710?p=1204100449710>.
28. Evidence to US Congressional hearing on the subject of autism and MMR from DR Elizabeth Miller, PHLS, and DR Paddy Farrington, Open University. <http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1204100449710?p=1204100449710>.
29. Conclusions on MMR vaccine safety by the All-Party Parliamentary Group on Primary Care and Public Health. <http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1204100449710?p=1204100449710>.
30. Munro ND, Sheppard S, Smithells RW, Holzel H, Jones G. Temporal relations between maternal rubella and congenital defects. Lancet 1987;2:201-4.
31. Morgan-Capner P, Crowcroft NS. Guidelines on the management of, and exposure to, rash illness in pregnancy (including consideration of relevant antibody screening programmes in pregnancy). Commun Dis Public Health 2002;5:59-71.

MICROBIOLOGICAL INVESTIGATION OF PATIENTS WITH ACUTE LYMPHADENOPATHY AND FEVER

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This NSM should be used in conjunction with the series of NSMs from the Health Protection Agency

www.evaluations-standards.org.uk

Email: standards@hpa.org.uk

32. Best JM, Banatvala JE. Rubella. In: Zuckerman AJ, Banatvala JE, Pattison JR, Griffiths PD, Schoub BD, editors. Principles and Practice of Clinical Virology. 5th ed. Chichester: John Wiley & Sons Ltd; 2004. p. 427-57.
33. Perry KR, Brown DW, Parry JV, Panday S, Pipkin C, Richards A. Detection of measles, mumps, and rubella antibodies in saliva using antibody capture radioimmunoassay. *J Med Virol* 1993;40:235-40.
34. Health Protection Agency. Testing Times - HIV and other Sexually Transmitted Infections in the United Kingdom. http://www.hpa.org.uk/webw/HPAweb&HPAwebStandard/HPAweb_C/1203084355941?p=1158945066450.
35. HIV and Sexually Transmitted Infections Department. All new STI episodes seen at GUM clinics in the UK: 1998 - 2007. Health Protection Agency. http://www.hpa.org.uk/web/HPAweb&HPAwebStandard/HPAweb_C/1195733775264.
36. Mindel A, Tovey SJ, Timmins DJ, Williams P. Primary and secondary syphilis, 20 years' experience. 2. Clinical features. *Genitourin Med* 1989;65:1-3.
37. UK National guidelines on the management of early syphilis. British Association for Sexual Health and HIV. <http://www.bashh.org/ceguidelines.htm>. p. 1-18.
38. Health Protection Agency. Health Protection Report 29th August 2008. Health Protection Agency. <http://www.hpa.org.uk/hpr/news/>.
39. Jebbari H, Alexander S, Ward H, Evans B, Solomou M, Thornton A, et al. Update on lymphogranuloma venereum in the United Kingdom. *Sex Transm Infect* 2007;83:324-6.
40. Ward H, Martin I, Macdonald N, Alexander S, Simms I, Fenton K, et al. Lymphogranuloma venereum in the United Kingdom. *Clin Infect Dis* 2007;44:26-32.
41. Clinical Effectiveness Group. National Guideline for the Management of Lymphogranuloma Venereum (LGV).
42. Health Protection Agency. Enhanced Surveillance - LGV. <http://www.hpa.org.uk/webw/HPAweb&Page&HPAwebAutoListName/Page/1191942171559?p=1191942171559>.

MICROBIOLOGICAL INVESTIGATION OF PATIENTS WITH ACUTE LYMPHADENOPATHY AND FEVER

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