Buckinghamshire Healthcare NHS
NHS Trust

VIROLOGY/SEROLOGY MEDICAL REPORTING

BS-SOP-IV3
Department of Serology and Virology
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Virology Laboratory Repertoire

Test code	Assay	Frequency of testing (working week)	Turnaround time (TAT)
Architect analyser			
HAVT	Hep A total antibody	Daily	1-3 days
HAVM	Hep A IgM	Daily	1-3 days
HBSG	Hep B surface antigen	Daily	1-3 days
HBST	Hep B surface antibody	Daily	1-3 days
HBCM	Hep B core IgM	Daily	1-5 days
HBCT	Hep B core total antibody	Daily	1-3 days
HBVI	Hep B e antigen	Daily	1-5 days
HBVI	Hep B e antibody	Daily	1-5 days
HCVB	Hep C antibody	Daily	1-3 days
	Cytomegalovirus IgG	Daily	1-3 days
	Cytomegalovirus IgM	Daily	1-3 days
EBNA	EBNA antibody	Daily	1-3 days
	Epstein Barr virus VCA IgM	Daily	1-3 days
	Syphilis IgG	Daily	1-3 days
	Toxoplasma IgM	Daily	1-3 days
	Toxoplasma IgG	Daily	1-3 days
HIV	HIV Antigen/Antibody	Daily	1-3 days
Diasorin Liaison XL			
	Cytomegalovirus IgG	Daily	1-5 days
	Cytomegalovirus IgM	Daily	1-5 days
	EBNA antibody	Daily	1-5 days
HBCV	Hep B core total antibody (confirm)	Daily	1-5 days
HBSV	Hep B surface antigen (confirm)	Daily	1-5 days
HCVV	Hep C antibody (confirm)	Daily	1-5 days
HIVV	HIV 1 and 2 antigen and antibody (confirm)	Daily	1-5 days
HSVB	Herpes Simplex virus IgG	Daily	1-5 days

	Borrelia (Lyme) antibody	Daily	1-5 days
	Varicella Zoster IgG	Daily	1-3 days
	Mycoplasma IgM	Daily	1-5 days
	Mycoplasma IgG	Daily	1-5 days
	Rubella IgG	Daily	1-3 days
	Rubella IgM	Daily	1-3 days
PARG	Parvovirus IgG	Daily	1-3 days
PARM	Parvovirus IgM	Daily	1-3 days
	Syphilis IgG (confirm)	Daily	1-3 days
	Measles IgG	Daily	1-5 days
MUMB	Mumps IgG	Daily	1-5 days
DS2			
	Hepatitis E IgM		
	Hepatitis E IgG		
Manual serology			
	HIV Geenius	As required	
	Anti-streptolysin titre	Once a week	
	Streptococcal DNAse B	Once a week	
Antigen detection			
	TPPA	Once a week	
	RPR	Once a week	
	Helicobacter antigen	As required	
	RSV direct antigen detection	As required	1-3 days
Cobas 4800			
	HPV PCR	As required	
	Chlamydia trachomatis	Daily	1-3 days
	Neisseria gonorrhoea PCR	Daily	
Smartcycler			
	HSV PCR	Daily	1-3 days
	VZV PCR	Daily	1-5 days
	LGV PCR	As required	

Contact details:

Dr Nick Wong	Clinical Lead in Serology/Virology	x5327
Dr Ruby Devi	Consultant Microbiologist	x5481
Dr Jean O'Driscoll	Consultant Microbiologist	x5329
Dr Karthiga Sithamparanathan	Consultant Microbiologist	x5593

Test selection and requesting tests in Virology

One of the most important roles of the Clinical microbiologist is to assist the laboratory staff to select tests appropriately according to the clinical situation. The majority of test requesting is straightforward and is dealt with at bench level. Requests which are not clear will be given to the microbiology consultant for test selection. There is a blue box in the serology lab which should be checked at least once daily by the clinical team.

Cards with the following clinical details should show them **directly to medical staff for test selection**:

- Rash in pregnancy
- Anything specifically marked for a doc's attention.
- Requests for immune (pre/post vaccine) status e.g. MMR, rabies
- All send away PCR tests
- Unusual serology requests e.g. Borrelia, Schistosomiasis, Leptospirosis, Dengue fever

Appropriate Specimen Types

	Serum	EDTA	Heparin	Citrate	Notes
HAV Ab Total	√	√	√		
HAV IgM	√	√	√		
HBsAg	√	√	√	√	
Anti-HBs	√	√	√		
Anti-HBc	√	√			
HBeAg	√	√	√	√	
Anti-HBe	√	√	√	√	
HBV DNA	√				
HCV Ab	√	√	√		
HCV PCR/Genotype	√	√			10mls required
HIV Viral Load		√			10mls required
HIV Ab	√	√	√		
CMV IgG	√	√	√	√	
CMV IgM	√	√	√	√	
CMV PCR		√			
Rubella IgG	√	√	√		
Rubella IgM	√	√	√		
Toxoplasma IgG	√	√	√		
Toxoplasma IgM	√	√	√		
HSV IgG	√	√	√	√	
Syphilis Ab	√	√	√	√	
Parvovirus IgG	√	√	√	√	
Parvovirus IgM	√	√	√	√	
EBV EBNA IgG	√	√	√	√	
EBV VCA IgG	√	√	√	√	
EBV VCA IgM	√	√	√	√	
ASOT	√				
DNAse B	√				
VZV IgG	√				
Measles IgG	√				
Mumps IgG	√				
Lyme Ab	√				
VZV IgG	√				
BK virus PCR	√	√			

HSV/VZV (swabs in VTM)
Anti-streptolysin titre
Borrelia (Lyme) antibody
Brucella antibody
Chlamydia trachomatis
Cytomegalovirus IgM
Cytomegalovirus IgG
RSV direct antigen detection
EBNA antibody
Epstein Barr virus VCA IgG
Epstein Barr virus VCA IgM
Adenovirus PCR **(eye swabs, other appropriate sample)**
Gentamicin assay
Hep A total antibody
Hep A IgM
Hep Bsurface antibody
Hep B core total antibody
Hep Be antibody
Hep Be antigen
Hep B surface antigen
HBsAg confirmation
Hep C antibody
HCV genotyping (**EDTA blood)**
HCV PCR (**Serum/EDTA blood)**
HIV antibody
HSV PCR **(genital swabs only)**
Herpes Simplex virus IgG
HIV viral load
Comment (hepatitis)
Legionella urinary antigen
Long term storage
Measles IgG
Mumps IgG
Parvo IgG
Parvo IgM
Respiratory PCR
Rubella IgG
Rubella IgM
Syphilis antibody
Toxoplasma IgM

CMV PCR **(EDTA blood, urine)**
Toxoplasma IgG
Vancomycin assay
HSV/VZV/entero (CSF) PCR
Varicella Zoster IgG
Reference laboratory serology
Sent to reference laboratory for….
Comment line
Additional comment
HIV comment
Comment on reference laboratory result

Test selection according to clinical details

The following are suggested first line tests for common clinical requests:

Clinical details	**Test(s)**
Abnormal LFTs	
Aplastic crisis	
Arthralgia/joint pains	
Atypical pneumonia (serology rarely contributes to patient management)	
Chronic fatigue/TATT	
Encephalitis	
Endocarditis	
Glandular fever	EBNA (EBV IgM if negative) CMV IgM/G Toxoplasma IgM Comment
Guillain Barre/ transverse myelitis	Campylobacter serology EBNA, CMVG (CMVC if detected) Comment
Hepatitis (acute)/ jaundice	1st line: HAV IgM, HBsAg 2nd line: HCV PCR (especially for IVDU), EBNA, CMV, IgM/G, Hepatitis E (gastro request) Comment 3rd line: yellow fever, syphilis, leptospirosis, Q fever
Hepatitis B status – occupational health or vaccinated	HBsAb
Hepatitis B status – no details and not as above	HBsAg
Infectious mononucleosis	EBNA (EBV IgM if negative) CMV IgM/G Toxoplasma IgM/G Comment
Intrauterine death/IUD (maternal sample)	Store with comment
Intrauterine growth retardation/IUGR	Refer to antenatal section
Hydrops fetalis	
Lymphadenopathy	EBNA (EBV IgM if negative) CMVC TOXM ZVCM
Maculopapular rash	PAVM RUBM ZVCM
MMR (acute ?mumps, measles)	Comment
MMR (post routine childhood immunisation)	Comment

Other immune status/ post vaccine requests	Refer to protocols e.g. Haematology
Myalgia	TOXM Comment
Myocarditis	Comment Coxsackie IgM (high threshold for sending – see comment)
Needle stick, donor	HBSG HCV Ab LTS (INID – needle stick donor)
Needle stick, recipient	HBAT LTS (INIR – needle stick recipient)
Pericarditis	Store – use Coxsackie comment Serology is not useful: NEJM 2004: 351: 2195)
Pertussis	If no duration given Duration given >3/52 Pertussis serology (Colindale)
Polyoma/BK/JC	Renal transplant Urine – send to Cytology Blood – comment Other clinical areas Polyoma PCR (Colindale) if appropriate after medical review
Pregnant, contact with chicken pox/zoster	VZV IgG
Pregnant, contact with rash/slapped cheek	PAVM, PAVG RUBM, RUBG
Pregnant, contact with cats etc.	TXG, TOXM
Pregnant, toxo status required	Comment
Pregnant, rash or other symptoms	Refer to protocols
Sore throat	EBNA (EBV IgM if negative) CMV IgM/G Toxo IgM/G ASOT Comment
Streptococcal infection	ASOT
TORCH screen (maternal sample)	Comment
TORCH screen (foetal/infant sample)	Refer to protocols

Reference laboratory user guides are very helpful in deciding whether a test that has been requested is appropriate.

Tests to be done	**Comment**	**Laboratory Sent to**	**Special form if required**
Adenovirus PCR		PHE Bristol	
Amikacin		Southmead Bristol	
Aminoglycoside		Southmead Bristol	
Amoeba	See HTD Parasitology guide	UCLH Parasitology Tottenham	
Amphotericin		PHE Bristol Mycology Unit	
Anti-Fungal (other)		PHE Bristol Mycology Unit	
Aspergillus Ag (see galactomannan)			
Bartonella serology (Cat Scratch fever)		PHE Respiratory & Systemic Laboratory Colindale	1
Beta-D glucan	Max 2 x per week per patient	PHE Bristol Mycology Unit	
BK or JC polyoma virus **(from non-Transplant patients)**	Serology (not quantitative) CSF for ?PML in HIV/immunocompromised	PHE Virus Ref Colindale	
BK polyoma virus **(from Transplant patients)**	Send serum/plasma for quantitation	St Thomas' Hospital	
Blastomycosis		PHE Bristol Mycology Unit	
Borrelia (confirmatory testing)	If screen positive on Liaison	PHE RIPL Porton Down	
B. pseudomallei Antibody		Lab of Health Care Assoc Infection	2
Brucella (confirmatory testing)		Liverpool Microbiology	
Campylobacter Antibody	?GBS	Preston Microbiology	
Chikungunya	Give travel history and duration	RIPL Porton Down	3
Chlamydia (Psitticosis)	Always send convalescent +/- acute sample	PHE Bristol	

Ciprofloxacin		Southmead Bristol	
CMV Avidity		Royal Free Hospital	
CMV quantitative PCR		Micropath	
Colistin		Southmead Bristol	
Coccidioides		PHE Bristol Mycology Unit	
Coxiella	Always send convalescent +/- acute sample	PHE Bristol	
Coxsackie IgM (Enterovirus)		Epsom Collab Centre	
Cysticercosis		UCLH Parasitology, Tottenham	
Cryptococcus antibody		PHE Bristol Mycology Unit	
Dengue	Give travel history and duration	RIPL Porton Down	3
Diphtheria	Post vaccination for microbiology staff	PHE Resp & Systemic Colindale	4
Ehrlichia		PHE Southampton	
Enterovirus Serology (Coxsackie)		Epsom Collab Centre	
Fasciola CFT & Hepatica		UCLH Parasitology, Tottenham	
Filaria		UCLH Parasitology, Tottenham	
Flavi virus	Give travel history and duration	RIPL Porton Down	3
Flu A	Always send convalescent +/- acute sample	Virus Ref unit Colindale	
Fluconazole		PHE Bristol Mycology Unit	
Flucytosine		PHE Bristol Mycology Unit	
Galactomanan	Max 2 x per week per patient	PHE Bristol Mycology Unit	
Hep A confirmation		Birmingham Heartlands Hosp	
Hep B confirmation	E.g. to sort out equivocal ‘e’ markers	PHE Virus Ref unit Colindale	5
Hep B Resistance			Special form
Hep B DNA (quant)		Micropath	5
Hep C Ab confirmation		Micropath	5

Hep C Genotyping			Special form
Hep D		PHE Virus Ref unit Colindale	5
Hep E		Birmingham Heartlands Hosp	
Histoplasma		PHE Bristol Mycology Unit	
HHV-6 & 7		UCHL – Tottenham	
HIV confirmation		PHE Virus Ref unit Colindale	6
HIV PCR (Neonatal diagnosis)		PHE Virus Ref unit Colindale	6
HIV Resistance		Molecular Diagnosis, UCLH Tottenham	
HTLV-1	Routine screen pre-BMT.	PHE Virus Ref unit Colindale	7
Hydatid serology		UCLH Parasitology, Tottenham	
Itraconazole		PHE Bristol Mycology Unit	
Lassa Serology	See VHF guide (PHE)	RIPL Porton Down	3
Leishmaniasis	Tissue samples see notes	UCLH Parasitology, Tottenham	
Leptospira	At least 7 days post-onset of symptoms	Hereford Microbiology	
Malaria IFAT		UCLH Parasitology	
Measles antibody	IgM (IgG done in-house). Salivary kits available from HPT.	Preston Microbiology	
Measles CFT (serum & CSF)	To exclude SSPE	PHE Virus Ref unit Colindale	
Meningococcal studies	including plasma/CSF PCR	Manchester Reference Unit	8
Mycoplasma Antibody	Always send convalescent +/- acute serum sample	PHE Bristol	
Mumps	IgM (IgG done in-house). Salivary kits available from HPT.	Preston Microbiology	
Outbreak D&V	Aim to send 6 samples	PHE Virus Ref unit Colindale	
Parvovirus	To confirm in-house tests eg in	PHE Virus Ref unit Colindale	

	pregnancy. PCR available.		
Pertussis	>3 weeks duratin of cough	PHE Resp & Systemic Colindale	1
Phlebovirus		RIPL Porton Down	3
Pneumococcal PCR	Plasma or CSF	Manchester Ref Unit	
Polio		PHE Virus Ref unit Colindale	
Psitticosis (Chlamydia)	Always send convalescent +/- acute sample	PHE Bristol	
Q Fever	Always send convalescent +/- acute sample	PHE Bristol	
Rabies	See notes. Usually university staff post-immunisation	Veterinary Lab Agency	
Rickettsial		RIPL Porton Down	3
Rift Valley Fever		RIPL Porton Down	3
Ross River Virus	Traval history!	RIPL Porton Down	3
Rota virus	PCR/EM available for selected cases	Virus Ref unit Colindale	
Sandfly Fever		RIPL Porton Down	3
Schistosoma	At least 6 weeks post-exposure	UCLH Parasitology, Tottenham	
Sinbis		RIPL Porton Down	3
Staphylococci Antibody		Lab of Health Care Assoc Infection	2
Streptococci Antibody		Lab of Health Care Assoc Infection	2
Streptomicin		Southmead Bristol	
Strongyloides		UCLH Parasitology, Tottenham	
Syphilis/Treponema (confirmatory testing)		PHE Bristol	
TB Elispot/Quantiferon	Mon-Thurs Only, must be received same day	Oxford Immunology	
Teicoplanin		In house	
Tick borne encephalitis (TBE)	Also post-immunisation	RIPL Porton Down	3
Tobramicin		Southmead Bristol	
Toxocara		UCLH Parasitology, Tottenham	
Trichinella CFT		UCLH Parasitology, Tottenham	
Trypanosoma		UCLH Parasitology, Tottenham	

Toxoplasma	Discuss pregnant cases with Dr Edward Guy, Swansea	PHE Swansea	
VZV (chickenpox)	Eg ?low-titre antibody responses post-vaacine	Royal London Hospital	10
Voriconazole		Manchester Mycology Ref Lab	
Whipples PCR		University of Leeds	
Yellow Fever		RIPL Porton Down	3
Yersinia		Enteric Pathogens, Colindale	9
West Nile Fever	Send serum and CSF	RIPL Porton Down	3

Special Forms Required

Form 1	Atypical Pneumonia Unit Colindale
Form 2	Lab of Health Care Assoc Infection
Form 3	Special Pathogens Porton Down
Form 4	Strep & Diphtheria ref unit
Form 5	Hepatitis Viruses
Form 6	HIV ref test
Form 7	HTLV ref test
Form 8	Meningo ref units
Form 9	Enteric Pathogens – yellow form
Form 10	VZV serology

- Doctors will see ALL positive results and those with ZRCM code

Reporting results

Clinical Interpretation of Architect test ranges

	Not detected	Equivocal	Detected Abnormal result, further tests may be required (includes equivocal range)
HB core Ab	<1.0		≥1.0
HbeAb	>1.1	0.9-1.1	<0.9
HbeAg	<0.9	0.9-1.1	>1.1
Hb core IgM	<0.9	0.9-1.1	>1.1
HBsAg	<1.0		≥1.0
HBsAb	<1.0		≥1.0
HIV Ab	<1.0		≥1.0
Syphilis IgG	<1.0		≥1.0
HCV Ab	<1.0		≥1.0
Toxo IgM	<0.5	0.5-0.6	≥0.6
Toxo IgG	<1.6	1.6-3.0	≥3.0
EBV VCA IgM	<0.5	0.5-1.0	≥1.0
EBNA	<0.5	0.5-1.0	≥1.0
CMV IgM	<0.85		≥1.0
CMV IgG	<6.0		≥6.0
HAVM	<0.8	0.8-1.2	≥1.2
HAVT	<1.0		≥1.0
Rubella IgM	<1.2	≥1.2 -<1.6	≥1.6

Clinical Interpretation of ELISA read-outs –Liason (DiaSorin)

	Not detected	Equivocal	Detected Abnormal result, further tests may be required (includes equivocal range)
HIV Ab	<1		≥1
HBsAg	<0.05		≥0.05
Anti-HBc	≥1.0		<1
HCV Ab	<1.0		≥1.0
Treponemal	<0.9	0.9-1.1	≥1.1
Rubella IgG	<10		≥10
VZV IgG	<50	50-100	>100
HSV ½ IgG	<0.9	0.9-1.1	≥1.1
Measles IgG	<13.5	13.5-16.5	≥16.5
Mumps IgG	<9.0	9-11	≥11
Parvo IgM	<0.9	0.9-1.1	≥1.1
Parvo IgG	<0.9	0.9-1.1	≥1.1
Borrelia IgG	<10	10-15	≥15
Borrelia IgM	<0.9	0.9-1.1	≥1.1
Mycoplasma	<10		≥10

IgG			
Mycoplasma IgM	**<10**		**≥10**
HEV IgM	**<0.9**	**≥0.9-<1.0**	**≥1.0**
HEV IgG	**<0.9**	**≥0.9-<1.0**	**≥1.0**

Occasionally samples will produce a 'low-positive' ELISA reading, and these must be interpreted with caution. All positive HIV and hepatitis C antibody results are sent to the reference laboratory and it should be explained to the clinician that the test result is not diagnostic and requires confirmation. Low positive hepatitis B sAg results should also be sent for confirmation. Hepatitis B results are otherwise confirmed in-house. A second sample is required for confirmation of all BBVs and equivocal results. EBV and CMV serology can be particularly problematic – discuss with consultant.

Comments used for reporting stored samples/samples not usually tested

IUD/miscarriage/TORCH
"Serological tests are not routinely performed in cases of IUD/miscarriage unless there are clinical features suggesting a viral aetiology. If this is the case please contact Virology SpR/consultant. Sample stored."

Chronic Fatigue/TATT
"Serological tests are of low value for investigating chronic fatigue. We are happy to discuss individual cases"

Atypical pneumonia
"Audits show that diagnostic yield for atypical and influenza serology is low, and does not contribute to acute patient management. Sample stored. If Legionella infection is suspected, please send a urine sample for Legionella urinary antigen. We are happy to discuss individual cases."

Insufficient clinical details – sample stored
Sample Stored

Antenatal samples ?toxoplasmosis status
"Antenatal screening for toxoplasmosis is not offered because the harms of screening may outweigh the potential benefit (NICE clinical guidelines 6th October 2003: Antenatal care). Primary prevention measures should be reinforced. Sample stored."

Pertussis serology request with no duration of symptoms
Pertussis serology is only offered by the PHE as part of enhanced surveillance in individuals who have been coughing for more than 3 weeks. Please advise the laboratory of duration of cough. Sample stored.

Reporting PCR/molecular assays

Most PCR based work is reported at bench level and the results are given to the Virology SpR for clinical review and telephone reporting of significant results e.g.

HSV/genital PCR – discuss results in pregnancy with Clinician
CMV PCR – report all positive results to referring clinician
HSV/VZV swab PCR – discuss results that alter patient management
Respiratory PCR – discuss positive results on immunocompromised patients with referring clinician.

HIV antibody, viral load and drug resistance testing requests

New HIV positive patients are screened for HBSG, HCVB, CMV IgG, TXG, VZVG and Syphilis Ab on request.

HIV RNA viral loads are only performed for GUM departments.

Diagnosis of perinatal / mother-child HIV transmission

For children >12 months old, an HIV-Ab test should be performed here, and referred to Colindale if positive.

Virus load testing on infants/children known to be HIV positive (by PCR/virus load) are tested here.

All samples for HIV diagnosis in infants with an HIV positive mother should be referred to Colindale. These samples will occasionally have been positive on an HIV antibody screen in this laboratory, i.e. detecting maternal antibody.

Specimen required
- whole, unseparated, EDTA blood (>1ml),
- plasma is used for p24Ag, HIV RNA and IgA anti-HIV detection
- white cells are used for HIV DNA testing
- maternal sample is required with initial sample to ensure that PCR primers pick up maternal virus

Testing Schedule
- Sample 1: at birth (send maternal EDTA – see above)
- Sample 2: 1 month – in perinatal infection many children will be PCR positive at this stage
- Sample 3: 3 months – most in utero and perinatal infections are diagnosed by this age
- Sample 4: 6 months – HIV infection in a well child is unlikely if this sample is negative
- Sample 5: 12 months – HIV antibody (i.e. maternal) should be reduced or absent
- Sample 6: 18 months – the majority of uninfected infants have lost maternal antibody by this stage
- Optional samples at 2 years or later may be indicated to exclude transmission due to breast feeding etc.,

Diagnostic Criteria:

HIV infected
In 2 specimens, collected on different dates, the detection of two, or more, of:
HIV proviral DNA, HIV viral RNA, HIV p24 Ag (neutralisable), Anti-HIV at >18 months of age

HIV uninfected
In at least 2 specimens, collected at least one month apart, with the former at at least 3 months of age and the latter specimen at 6 months of age or more, the **absence** of reactivity in at least 2 of the following tests:
HIV proviral DNA, HIV viral RNA, HIV p24 Ag (neutralisable), Absence of anti-HIV in a healthy child of > 12 months

Investigation and diagnosis of intrauterine, perinatal and congenital infection

Background

Requests for screening for congenital infections ("TORCH screening") are common, but investigation is not straightforward and requires close liaison with clinicians, microbiology & histopathology. It is not usually possible to confirm or refute congenital infection based on the result of a single neonatal serum sample, although this is the sample most commonly sent. Requests for TORCH screening should be discouraged; the acronym was proposed in the 1970s at which time the range of viruses and other pathogens which could induce intrauterine infections was insufficiently appreciated.

In order to achieve a diagnosis it is important to obtain details (with dates) of maternal illnesses or precise date of exposure during pregnancy without which it is difficult to interpret serological data. A booking serum sample can be very useful to compare with serum samples taken later in the pregnancy or post-delivery to examine for sero-conversion or for specific IgM responses. In the infant, a specific IgM response may not be detected initially; further serum or blood samples may need to be tested. In addition to serological tests for virus-specific IgM antibodies in the infant, attempts to identify the virus itself may be of importance and specimens such as naso-pharyngeal secretions and urine should be examined. If a perinatal infection is suspected, for example herpes simplex or an enterovirus, in addition to the above specimens, attempts should be made to identify virus in the stools, conjunctiva, and if present, vesicular fluid. The presence of CMV in urine collected three weeks or more after delivery may be indicative of post-natally acquired rather than congenitally acquired infection.

Features associated with increased risk

- Features suggestive of early neonatal sepsis
- Multi-organ failure in neonate
- Hypoglycaemia
- Hepatomegaly or splenomegaly
- Organ damage at birth: IUGR/ microcephaly/cerebral calcification/ cardiac/ ocular/ other malformation

Intrauterine death

Intrauterine death is not highly predictive of intrauterine infection
50% of all conceptions miscarry, as do 15% of clinically discerned pregnancies.

Key points:
Toxoplasmosis: primary infection affects 2/1000 pregnancies. IUD due to Toxoplasmosis is mostly associated with early (1st Trimester infection), but 1st trimester accounts for only approximately 1/3 of the infections and the risk even in early infection only 10%, i.e. about 1/10,000 miscarriages may be due to Toxoplasmosis
CMV: primary infection risk is about 2% per pregnancy with transmission to foetus in 40% of these cases. Proportion of loss due to CMV is unclear, but is likely to be a very small proportion of those infected.
Parvovirus B19: risk of foetal loss highest with infection < 20 weeks gestation. Reported rate of foetal loss 3-9%

HSV: no evidence of increased risk
Listeria: a rare cause of late trimester abortion or intrauterine death
Very Rare: syphilis, malaria

Summary: infection is a rare cause of intrauterine death in the UK. The specific infective causes can be diagnosed histologically. Serology is not indicated routinely for investigation of IUD.

Reference:
Infection and Fetal Loss, Regan L. *Infection and Pregnancy*, McLean (ed) (2001).

Target Pathogens

These do not just include "TORCH" agents

Acquired peripartum:
Bacteria - agents of early and late neonatal sepsis: *E. coli*, GBS, *Listeria*
Adenovirus, Enterovirus - agents cause a syndrome similar to the above, with high mortality

Acquired in utero:
Rubella - now very rare

CMV - most infections are asymptomatic, but also IUGR, microcephaly, hepatosplenomegaly

Toxoplasmosis - most infections are asymptomatic, but also IUGR, microcephaly, hepatosplenomegaly, cerebral calcification

Syphilis

Others:
Hepatitis B, C, HIV- these are diagnosed by serial serology and PCR in infancy. See separate SOPs.
Parvovirus - foetal blood (EDTA) for PCR may be helpful, as will IgM/G serology on antenatal and post-natal maternal and foetal samples.

Clinical approach

1. Obtain antenatal screening results (syphilis, rubella, hepatitis B, HIV). Discuss with clinicians, assess symptoms, decide whether to investigate
2. In complex cases, record all decisions and data gathered on the form to be found in the red 'congenital infection file'.
3. Gather maternal antenatal and post-natal samples
4. Gather specimens from the infant as appropriate to the clinical situation:
    - Urine for CMV by PCR
    - Serum for Rubella IgM and Toxoplasma IgM; if there is high clinical suspicion of rubella, repeat at 7 days if negative

- Stool / Throat/respiratory samples (in viral transport medium) for enterovirus and adenovirus.

Rash or exposure to rash in pregnancy

See PHE document
http://www.PHE.org.uk/cdph/issues/CDPHVol5/No1/rash_illness_guidelines.pdf

Principle ultrasound features detectable in cases of congenital infection

Information taken from Infection and Pregnancy Ed MacLean, Regan, Carrington. Use to guide test selection:

Main clinical features		**Congenital infection**
General	Miscarriage	Listeria
		PVB19
		CMV
		Toxoplasmosis
	Non-immune hydrops fetalis	PVB19
		Coxsackie virus
		CMV
		Toxoplasmosis
		Rubella
		Treponema pallidum
	Fetal growth restriction	CMV
		Rubella
		VZV
		Treponema pallidum
Head	Brain tissue calcification	CMV
		Toxoplasmosis
	Hydrocephaly	CMV
		Toxoplasmosis
	Microcephaly	CMV
	Cataract	Rubella
	Choriretinitis	Toxoplasmosis
	Microphthalmia	Rubella
Thorax	Heart defects	Rubella
	Cardiomyopathies	Coxsackie virus B
		Adenovirus
		PVB19
	Isolated pleural effusion	Adenovirus
		PVB19
Abdomen	Hyperechogenicities	CMV
		HSV
		VZV
		PVB19

	Ascites and hepatosplenomegaly	PVB19
		CMV
		Toxoplasmosis
		Treponema pallidum

CMV= cytomegalovirus; PVB19 = parvovirus B19; VZV = varicella-zoster virus

Antenatal screening (routine)

Background:

Routine antenatal screening for Hepatitis B, Syphilis and HIV is offered to all pregnant women in Buckinghamshire ideally at their booking appointment at 8-10 weeks. Rubella is no longer available in our repertoire of tests offered antenatally.

HIV-Ab positives are confirmed by the reference laboratory in Colindale.
Syphilis screening test positives (if new) are confirmed by PHE Colindale, as per usual protocol.

HBsAg positives are confirmed in-house.

Initial sample
The results of reactive samples are copied to the antenatal screening co-ordinator (Alison Wainwright) Screening Co-ordinator (SC), and should be shown to the Microbiology consultant. **The SC will contact the GP/midwife to arrange for a second sample to be sent for confirmation.**

Sometimes the patient is already known to the department, in which case a second sample is not required, but the appropriate paperwork requires completion. In these cases please alert the Role C microbiology consultant.

Confirmatory sample
Second samples received in the laboratory should be processed as requested i.e. for HIV or HBsAg or Syphilis.
Results of confirmatory samples are emailed to the antenatal screening co-ordinator (SC), and should be given to **the role C microbiology consultant** who will write to the GP/O+G team with a management plan.

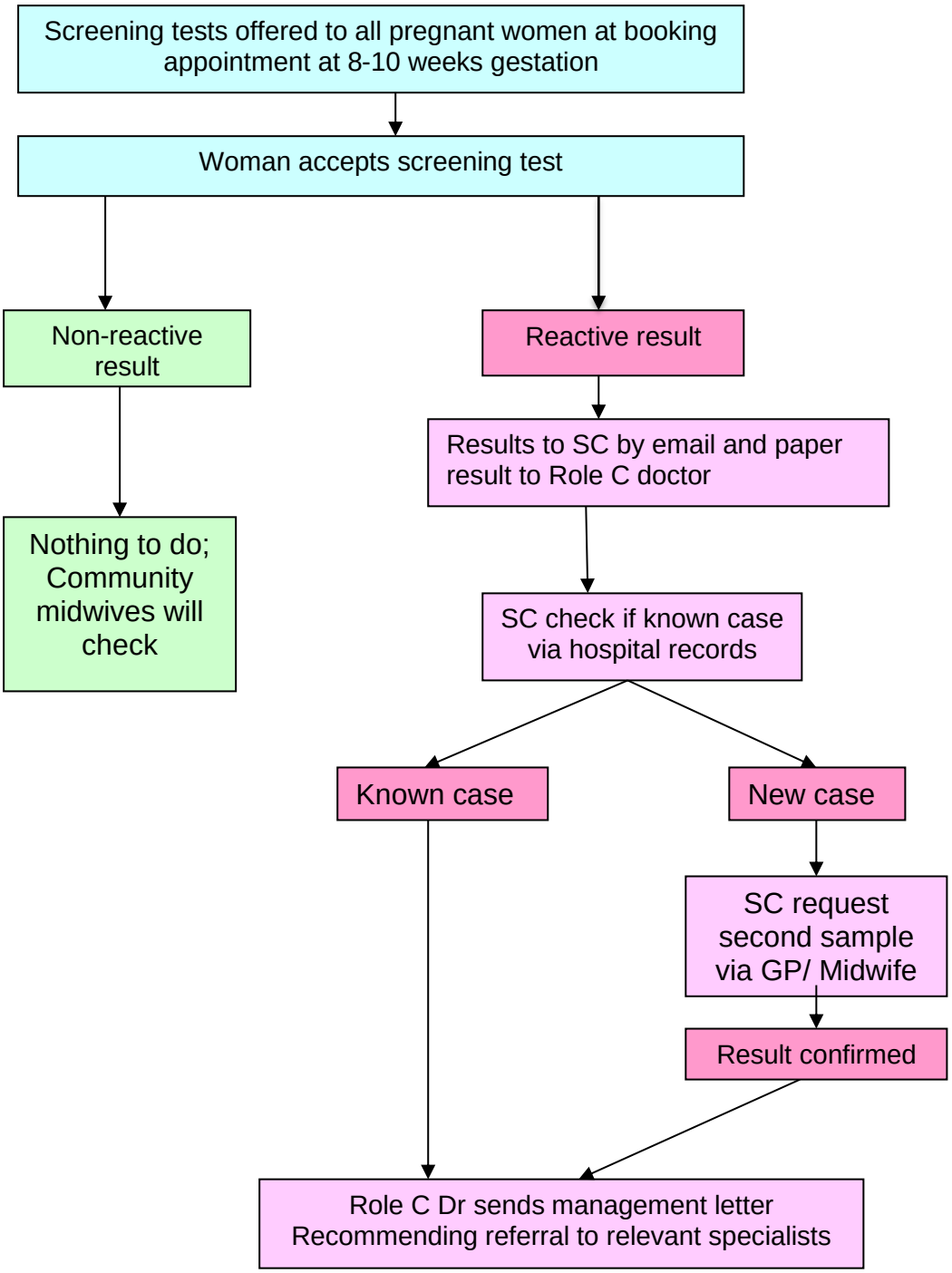
Antenatal screening co-ordinator: Alison Wainwright (Alison.wainwright1@nhs.net) and buc-tr.ScreeningMidwives@nhs.net
Extension 6269

There is no need to phone positive results to the requesting GP as long as the midwives above are aware. However, in circumstances where the patient is not registered with the local antenatal team then a call to the GP may be required.

- For cases with positive **HIV** serology advise referral to Jackie Sherrard (GUM) **and** to Obstetrics.
- **Syphilis** positive patients should be referred urgently to Dr Sherrard (GUM) as treatment should ideally be completed before 20/40 gestation.
- **Hepatitis B** patients can be referred ante-natally or post-natally to the hepatitis clinic (Karen Robinson or Dr James Maggs).

For an eAg positive mother, or a mother with no e markers, a dose of Paediatric HBIG (200IU) is requested from Colindale.

Ante Natal Infectious Diseases Screening Results Pathway



Serology requesting/reporting – specific tests

Anti Streptolysin O Titre [ASOT]

Sero-diagnostic tests for infection by **Group A streptococci** are often needed to establish the diagnosis of the post streptococcal syndromes of rheumatic fever and glomerulonephritis. They have little role in the diagnosis of acute infection.

Interpretation of results

ASOT A four-fold rise in titre between acute and convalescent sera provides the most conclusive evidence of recent Strep. pyogenes infection. Often only a single sample is received making interpretation more difficult. The definition of a significantly raised titre depends on the age range and the type of population surveyed. **The upper limit of normal** is generally accepted as **200 iu/ml** for young adults, but may be higher in children and lower in infants.

Titre (iu/ml)	Report (automatic comments)
<200	Not significant
200-400	Refer to upper limits for age of patient. Report as: 'In upper limit of normal; please send a second sample if still clinically indicated'
>800	Report as: 'Indicative of recent infection with Strep. pyogenes' In the case of rheumatic fever or glomerulonephritis – contact a clinician for further details and a repeat specimen.

Brucella serology

The screening test used in this laboratory is the Rose Bengal plate test. All positive results should be referred for confirmation. Negative results where the clinical suspicion is high should also be referred (diagnosis is more usually made by culture of appropriate specimens).

In acute infection in man, IgM rises first and may be the only immunoglobulin detectable in the early weeks. IgM antibody starts to decay around three months after onset of the illness. IgG antibody levels start to rise during the second week of disease and remain elevated for at least one year in untreated patients. In adequately treated patients IgG brucella antibodies usually disappear or decrease to very low levels by six months after onset. The degree to which IgM antibodies become elevated in relapsing brucellosis is controversial and the status of chronic brucellosis has been questioned.

Hepatitis

A second sample for confirmation is required for all new HIV, hepatitis B and hepatitis C antibody cases
All negative results are reported at bench level.

Hepatitis A

Hepatitis A IgM positive. Check result is a 'good' positive. Contact referring doctor to confirm clinical details, report result with suitable comment and inform Health Protection team or ICT as relevant.

- Specificity of HAV IgM assays is often poor. HAV IgM results should be interpreted in light of results of other assays (eg HAV IgG, EBV VCA IgM), rheumatoid factor (RF), liver function test (LFT), the clinical picture (eg symptoms and onset date), other risk factors (eg contact with case, MSM) and age. False IgM results are more common in older adults, or those from developing countries, as they are more likely to have had hepatitis A in childhood IgM may be reactive after recent vaccination.
- HAV IgM serology may not be reliable in patients who are significantly immunocompromised. Consider referring for HAV PCR
- Report no evidence of recent HAV infection if sample taken ≥5 days after the onset of symptoms. A negative result on a sample taken <5 days after onset of symptoms may not exclude hepatitis A, as it may be too soon for the production of HAV IgM antibodies, so a second blood sample should be requested
- Test for HAV IgG if indicated or when immune status is requested. HAV IgG results can be helpful for interpretation of some negative or suspected falsely reactive HAV IgM results. Testing of a previous or later sample may also be considered.
- Interpret reactive result with caution in the elderly and note also that hepatitis A IgM can be long lived (>200 days)

Send 'Low' or 'non-specific' results via serum, blood or stool samples (if available) to Colindale for confirmation by alternative serological assay or PCR and genotyping for surveillance.

Hepatitis B
Notes

HBsAg is the first marker to appear, followed by HBV DNA, HBeAg and anti-HBc. The diagnosis of acute hepatitis B is made on finding HBsAg and HBcIgM in the context of a patient with clinical and biochemical evidence of an acute hepatitis. By the time of presentation, patients have often already cleared eAg, and in addition HBsAg may only be present transiently, so that in the early stages the only marker of acute infection may be HBcIgM, or subsequent development of anti-HBc and anti-HBs. HBeAg and sAg may clear very rapidly in the context of fulminant hepatitis.

Chronic HBV infection is defined by the persistence of HBsAg for greater than 6 months following acute infection. In chronic infection, a spontaneous remission in disease activity may occur in 10-15% of eAg positive carriers per year with seroconversion to anti-HBe. The seroconversion process may select precore mutants of the virus which are unable to synthesize eAg – such patients have evidence of on-going viral replication.

HBsAg positive.
Check HBsAg has been repeated and confirmed by alternative assay (Liason XL or Architect).
Check full range of markers (cIgM, core total Ab, eAg, eAB)
Discuss with clinicians and request second sample for confirmation (unless hepatitis clinic patient and or patient status known and stated on card)-only perform HBsAg as single confirmatory test.

In addition, if acute:
Repeat in 3 to 6 month to exclude chronic carriage
Report to PHE and/or ICT as relevant
HBsAg is the first marker of infection; if all other markers are negative repeat in 2 weeks.

HBV DNA
Should be checked pre-treatment, 3 monthly during treatment with lamivudine/ adefovir or if HBeAg negative with elevated LFTs (pre-core mutant).

N.B. HBV DNA requests are only accepted from the hepatitis Clinic.

Check **Delta Ab** level if abnormal LFT and HBV DNA negative.

Suggested hepatitis B comments:

a) HBsAg detected: HBsAg detected, suggestive of active (acute or chronic) hepatitis B infection. Please send repeat sample urgently for confirmation.
b) HBsAg not detected: No serological evidence of current hepatitis B infection/carriage
c) HB core antibody (total) detected: Consistent with hepatitis B infection at some time

d) HB core antibody (total) not detected: No serological evidence of past hepatitis B infection

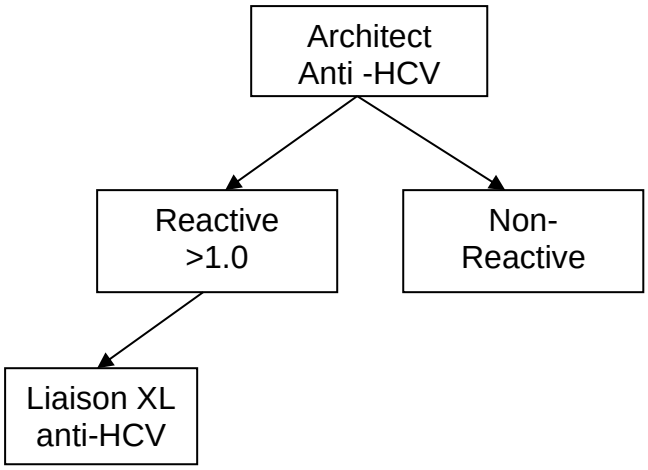
Interpretation of results of serological tests for hepatitis B

HBsAg	Anti-HBc (total)	HBcIgM	HBeAg	Anti-HBe	Anti-HBs	Hep B DNA	Interpretation
-	-	NT	NT	NT	- or NT	NT	No evidence of current or past hepatitis B infection
-	+	NT	NT	NT	+ or -	NT	Consistent with past hepatitis B infection. Hepatitis B may reactivate in patients who are immunocompromised[1]
-	+	+	-	+ or -	- or low +	NT	Suggests relatively recent, resolving infection with hepatitis B. Please send a repeat sample to confirm.
+	-	-	-	-	-	+	Consistent with early acute infection with hepatitis B. Please send a repeat sample urgently to confirm. Household and sexual contacts of people with acute or chronic hepatitis B should be tested and/or immunised as soon as possible to prevent acquisition. Please notify local PHU and refer to hepatology specialist.[2]
+	-	-	-	-	-	- or NT	HBsAg detected. Send further sample in one week, or EDTA blood for HBV DNA, if no history of vaccination[3]
+	-	-	+	-	-	- or NT	Consistent with early acute infection with hepatitis B. Send an immediate repeat to confirm and send another sample in 6 months to determine whether chronic infection has developed or resolution has occurred. Please repeat testing to confirm and notify PHE. Household and sexual contacts of people with acute or chronic hepatitis B should be tested and/or immunised as soon as possible to prevent acquisition. Refer to hepatologist.
+	+	+	+	-	-	- or NT	Consistent with recent infection with hepatitis B. Please send immediate repeat sample to confirm and notify PHE urgently. Send another sample in 3-6 months to check for resolution. Household and sexual contacts of people with acute or chronic hepatitis B should be tested and/or immunised as soon as possible to prevent acquisition. Refer to

							hepatologist.
+	+	-	+ or -	+ or -	- or NT	+ or – or NT	Consistent with current HBV infection-most likely chronic HBV infection. Please review with clinical features and risk factors for acquisition. Please send further sample now and again in 6 months' time to confirm chronic progression. Household and sexual contacts of people with acute or chronic hepatitis B should be tested and/or immunised as soon as possible to prevent acquisition. Refer to hepatologist.
+	+	+	-	+	NT	NT	Please send repeat sample. Resolving acute infection cannot be excluded. A flare in chronic HBV cannot be excluded.

[1] consider confirming anti-HBc result with second sample in case original was false reactive
[2] notify PHE urgently. HBV DNA testing is essential to confirm, request repeat sample to confirm identity of patient and to confirm acute HBV infection by detection of other markers. If patient is pregnant, ensure appropriate treatment of baby or babies.
[3] HBsAg can be detectable about 1 week after vaccination

Hepatitis C



Interpretation and comments:

a) **Architect non-reactive**
HCV antibody not detected.
b) **Architect reactive + Liaison anti HCV reactive**
Initial tests consistent with active HCV infection - Please send repeat serum and EDTA blood for HCV PCR and genotype to confirm HCV infection. If confirmed recommend referral to the viral hepatitis clinic for assessment.
c) **Architect reactive + Liaison anti HCV non-reactive**
Indeterminate result - Please send repeat serum and EDTA samples for further testing. Current sample has been sent to reference laboratory, report to follow.

Newly diagnosed HCV patients, irrespective of community or inpatient provenance, should be notified to Dr James Maggs, Hepatology by email or through his secretary.

HCV- PCR (viral load)

Indications:

- ✓ Immunosuppressed and at risk of HCV
- ✓ Consideration for treatment – 2 negatives are required to conclude that a patient is not viraemic over 3 – 6 months.
- ✓ Monitoring treatment: baseline, 3 and 6 months and end
- ✓ After treatment: 6,12 months

Needle-stick injury from positive or high risk source - 6/52 and 3/12 – (see Needle stick/splash injury protocol)

Processed at present by Micropathology, results can be emailed to Dr James Maggs, Consultant Hepatologist.

Important contact details:
Dr James Maggs jamesmaggs@nhs.net 01494 425267

May 2018
Nick Wong

Hepatitis E

PHE SMI currently awaiting publication.
Ideally, HEV serology should only be performed when the patient's ALT >100. The majority of samples will be sent from hepatology clinic (appropriate to proceed). A small subset may come from neurology where there is a correlation between HEV infection and neurological manifestations, such as Guillain-Barre syndrome, brachial neuritis and an inflammatory polyradiculopathy.
Hepatitis E IgM and IgG are performed in house. HEV PCR can be sent to a reference laboratory N.B. we will only process this if requested by Dr James Maggs or the hepatology team within the Trust.

HIV (to be completed)

Please notify the microbiology consultant if there is a new detected or equivocal HIV result.

Syphilis serology

The screening test used in our laboratory is a **syphilis IgG**. We can then perform both the TPPA and RPR. All positive results are referred automatically at bench level for confirmation to Colindale.

Syphilis tests fall into two main categories:

Non-treponemal tests which rely on a response to host tissue, cardiolipin, provoked by infection with Treponema pallidum
Specific treponemal tests which incorporate treponemal antigens

Confusion surrounds interpretation of the serologic tests for syphilis because:

1. The tests are not specific for T.pallidum and a positive result cannot distinguish between syphilis, yaws or pinta. Clinical manifestations and serologic results of yaws and syphilis may be indistinguishable and the epidemiologic setting is vital in differentiation of these diseases. For this reason a positive result is always referred to non-specifically as 'evidence of a treponematosis'.

2. The results of the non-treponemal and specific treponemal tests vary depending on the stage of the disease, primary, secondary, latent, tertiary or congenital and whether the disease is treated or untreated, past or present. A detailed knowledge of the disease history is necessary for interpretation of results.

3. The non-treponemal tests produce a high proportion of biological false positives.

Non-treponemal tests

Rapid plasma reagin test [RPR]

This test alone is unsuitable for the diagnosis of syphilis because it is non-specific. The presence of anti-cardiolipin antibodies in non-syphilitic conditions [biological false positives] occurs in pregnancy, other infections and auto-immune diseases.

The test is not sensitive; the RPR does not become positive until 1-4 weeks after the appearance of the chancre. However it is rapid and cheap and its main use is in monitoring:-

1. **Response to therapy.** The test becomes negative within one year in almost all cases of successfully treated syphilis.

2. **Reactivation of disease.** The appearance of a rising RPR titre in a previously treated patient may indicate reactivation of disease.

3. **Congenital syphilis.** The RPR shows increasing reactivity during the first few months of life in those infants infected. In contrast, healthy neonates who have acquired maternal antibodies but are not infected show decay in titres.

Specific Treponemal Tests

1. **TPPA** (*T. pallidum* assay)

This test is more specific than the non-treponemal RPR test and is performed in conjunction with the FTA (see later). All TPPA positive results are confirmed by the immunofluorescent test, FTA (fluorescent treponemal antibody) test. The TPPA (unlike the RPR) usually remains positive for life.

2. **FTA** (Fluorescent treponemal antibody test)

This is the most sensitive test for the investigation of syphilis. It is the first test to become positive in primary syphilis and remains positive for life. It is expensive, time consuming and interpretation may be subjective. Its use is restricted to certain groups of patients.

New Patients with Positive Serology

The majority of new patients come via genito-urinary medicine clinics, and no comments or clinical advice are required. For non-GUM positives, contact the Clinician and ask for a repeat specimen to **confirm** the results. Inform them of your interpretation of results and enquire re: ethnic origin, past history of syphilis and treatment with antibiotics, presenting symptoms and possible contacts. Discuss an appropriate treatment plan (e.g. referral to GUM Clinic) once result confirmed.

Interpretation of results
Syphilis IgG should remain positive long-term after infection. However in some individuals with treated disease in the distant past the IgG assay is not 100% sensitive. Syphilis IgM indicates acute/recent disease. In some individuals it can remain positive for several months.

Table (to be completed)

EBV

EBNA IgG is used as a screening test, and if negative, EBV VCA IgM and IgG are performed. EBNA usually appears 3-4 weeks from onset of illness and appears in 95% or more of individuals, but may not be present in the immunocompromised individuals or chronic EBV infections.

N.B. in acute EBV infection, other IgM results can be non-specifically reactive, e.g. CMV, Parvovirus, Rubella.

Comments for EBV reporting:

EBNA IgG	VCA IgM	VCA IgG	Comment
Negative	Negative	Negative	No serological evidence of EBV infection
Positive	NT	NT	Consistent with past EBV infection.
Negative	Positive	Negative	Consistent with but not diagnostic of early acute EBV infection. Repeat to confirm in 4-6 weeks
Negative	Positive	Positive	Consistent with recent acute EBV infection
Negative	Negative	Positive	This profile reflects past infection, but recent infection cannot be excluded. Repeat in 4-6 weeks if recent EBV infection is suspected[1]

[1] consider EBV PCR testing

CMV IgM

N.B. common false positive/cross reactions, especially in acute EBV infection. If possible, obtain earlier samples (especially in pregnancy) to try and demonstrate seroconversion. If strongly reactive and concordant with clinical details, make appropriate comment (usually ‘consistent with acute CMV infection’)

HSV serology

An HSV IgG assay is performed in-house, which gives an indication of ‘status’. It is not useful for acute diagnosis unless seroconversion can be demonstrated. A lesion swab should be sent for PCR in virus transport medium of normal saline. Type specific HSV serology can be performed at Colindale if indicated.

VZV serology

A VZV IgG assay is performed in-house, which gives an indication of ‘status’, and is performed as part of a screen in the immunocompromised. It is not useful for acute diagnosis unless seroconversion can be demonstrated. A lesion swab should be sent for PCR in virus transport medium of normal saline.

VZV PCR

Results are reported at bench level and given to medics for checking and phoning of significant positive results.

Chlamydia serology

Assays done in Bristol:

C. psittaci (EAE strain) titre
C. pneumoniae (TW183 strain) titre
Chlamydia Group/LGV CFT titre

High single titres to *C. psittaci* and *C. pneumoniae* are common, and reflect past exposure/infection in the absence of a significant CFT titre. Titres in excess of 8000 are usually indicative of recent *C. pneumoniae* infection.

Toxoplasmosis

N.B. false positive/cross reactivity possible
Confirm all results in pregnancy with reference laboratory.
If strongly reactive and concordant with clinical details, remove –suppress result, and make appropriate comment (usually 'consistent with acute Toxoplasma infection')

Borrelia

False positive reactions are very common, and the in-house assay should be regarded as a screening assay only. All reactive results are sent to the reference laboratory for confirmation. Discuss with clinician as appropriate.

Pertussis

Send to Colindale (RSIL)

Serology for:
Adults with cough > 21days
Children with cough >14 days

PCR for:
Infants < 6/12

Report results as suggested by reference laboratory.

Leptospirosis

Serology is only useful if > 7 days post-onset of symptoms, not exposure. Send to Micropathology. Blood cultures taken in the acute phase can be sent to Hereford, although our blood culture medium is relatively inhibitory to leptospira, and the diagnostic yield is low.
Report results as suggested by reference laboratory.

Schistosomiasis serology

Serology can be useful > 6 weeks post-exposure. Report results as suggested by reference laboratory.

Guidelines for issuing post-exposure V-ZIG, Hepatitis B Immunoglobulin or Rabies Vaccine and Rabies Immunoglobulin

Refer to The Green Book 2006
http://www.dh.gov.uk/PolicyAndGuidance/HealthAndSocialCareTopics/GreenBook/GreenBookGeneralInformation/GreenBookGeneralArticle/fs/en?CONTENT_ID=4097254&chk=isTfGX

All stores of V-ZIG are held in the first floor of the Pathology Department. Both HBIG and Rabies immunoglobulins are held by pharmacy.

The microbiologist is the single point of access for these products. We are responsible for ensuring appropriate usage. Therefore we may be approached by the CCDC or their deputies, Paediatricians, Physicians, Surgeons, GPs etc.
The prescription of V-ZIG is facilitated by the microbiology consultant covering Role C.
This form is found in a clear pocket outside the 4^{o}C refrigerator on the first floor.

The exposed patient must be assessed for immunisation – explicit guidance on the use of these products is given in the Green book and the Immunoglobulin Handbook (http://www.PHE.org.uk/infections/topics_az/immunoglobulin/pdfs/ig_handbook120704.pdf) – if in doubt, contact the consultant on call.