



Accredited to ISO 15189:2012

# Rare and Imported Pathogens Laboratory (RIPL)

Specimen referral guidelines and service user manual

PHE Microbiology Services Porton Version 25, April 2021, QPulse SPATH039

# About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing and reduce health inequalities. We do this through world-leading science, research, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. We are an executive agency of the Department of Health and Social Care, and a distinct delivery organisation with operational autonomy. We provide government, local government, the NHS, Parliament, industry and the public with evidence-based professional, scientific and delivery expertise and support.

Public Health England Wellington House

133-155 Waterloo Road London SE1 8UG

Tel: 020 7654 8000 www.gov.uk/phe Twitter: @PHE\_uk

Facebook: www.facebook.com/PublicHealthEngland

Prepared by: Rare and Imported Pathogens Laboratory

For queries relating to this document, please contact: ripl@phe.gov.uk

This document is available in other formats on request. Please call 01980 612100 or email ripl@phe.gov.uk



### © Crown copyright 2021

You may re-use this information (excluding logos) free of charge in any format or medium, under the terms of the Open Government Licence v3.0. To view this licence, visit OGL. Where we have identified any third-party copyright information you will need to obtain permission from the copyright holders concerned.

Published April 2021
PHE publications
gateway number: GOV-7916

PHE supports the UN Sustainable Development Goals





# Contents

General information	5
RIPL history Population served Contact details and where to find RIPL Laboratory opening times Use of the laboratory	5 5 5 8 9
Diagnosing a rare or imported pathogen Map of regions Typical incubation periods Risks of viral haemorrhagic fevers in different countries Requesting procedure (routine, urgent and out of hours) Requesting additional tests Completing the request form Specimens from patients who might have Viral Haemorrhagic Fever Specimen labelling Types of specimens and specimen collection methods Consent Submitting tissue samples from deceased people Packaging and transporting specimens Courier and postal deliveries Specimen limitations potentially affecting assay results Specimen rejection criteria Results and reports Biological reference values Clinical decision making, treatment of infection and medical advice Specimen referrals Cost of testing Available assays and turnaround times (TAT) UK Imported Fever Service Services to the public Education services Protection of personal information Terms and conditions RIPL complaints procedure Accreditation Appendix 1: Lyme Disease	9 10 11 12 13 13 16 16 17 18 18 19 20 20 20 21 21 21 22 22 23 29 29 29 29 30 31 31 31
Tests offered Sample type Prices Contact details Appendix 2: Leptospirosis	32 32 33 33 34
Testing for Leptospirosis Tests offered Sample type	34 34 35

Prices	35
Contact details	36
Appendix 3: Zika virus	37
Testing for Zika virus	37
Tests offered	37
Sample type	37
Prices	38
Contact details	38

# General information

# **RIPL** history

The Rare and Imported Pathogens Laboratory (RIPL) is now incorporated into the functions of Public Health England (PHE), which was established on 1 April 2013. Previously, RIPL operated within the Health Protection Agency's (HPA) Microbiology Services Porton and was known until November 2011 as the Special Pathogens Reference Unit (SPRU). From 2005 to 2009, SPRU operated as part of the Novel and Dangerous Pathogens Department at the HPA Centre for Emergency Preparedness and Response (CEPR), then later as part of the Medical Affairs Department. RIPL now operates as part of the National Infection Service.

RIPL provides a clinical diagnostic service for rare or imported pathogens such as pathogenic arboviruses, haemorrhagic fever viruses and a number of Hazard Group 3 bacterial pathogens including rickettsiae, *Coxiella burnetii* and *Bacillus anthracis*.

RIPL is the frontline laboratory providing diagnostics for the Imported Fever Service following its inception in June 2012.

RIPL also provides an environmental detection service for investigation and identification of anthrax.

The Lyme disease testing service was transferred from HPA Southampton to RIPL on 1 June 2012. See Appendix 1 for details.

The Leptospira diagnostic service was transferred from Hereford to PHE laboratories at Porton on 1 April 2015.

# Population served

RIPL provides specialist expertise and advice to PHE, the NHS, government departments, the commercial sector, and to clinical, veterinary and environmental services throughout the UK, Europe and elsewhere in the world.

RIPL is the core component of the WHO Collaborating Centre for Virus Reference and Research (Special Pathogens) at Porton Down.

#### Contact details and where to find RIPL

Address: Rare and Imported Pathogens Laboratory (RIPL)

Public Health England, Porton Down, Salisbury, Wiltshire SP4 0JG

**United Kingdom** 

DX address DX 6930400 Salisbury92/SP

Telephone 09:00 to 17:00 hours, weekdays: +44 (0) 1980 612348

Out-of-hours (Porton reception): +44 (0) 1980 612100

UK Imported Fever Service telephone line 0844 77 88 990

Fax +44 (0) 1980 612695

E-mail ripl@phe.gov.uk (checked on weekdays only)

Web https://www.gov.uk/phe

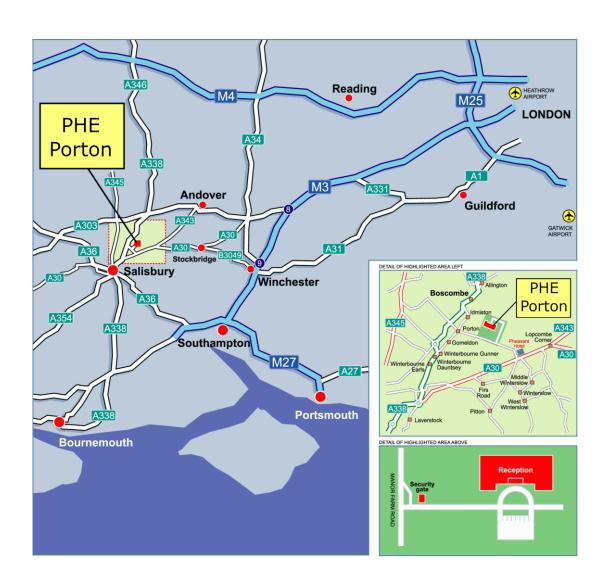
https://www.gov.uk/government/collections/rare-and-imported-

pathogens-laboratory-ripl

Sat Nav users: Specify "Manor Farm Road, Porton Down" rather than the address

postcode SP4 0JG, and approach via Winterslow Road to avoid being directed to the wrong entrance. Actual co-ordinates for the

entrance to the site are: 51°07'46.7"N, 1°42'21.3"W



#### Research

The laboratory and associated research groups included in the WHO Collaborating Centre undertake a wide range of research activities. This extends from investigation of clinical isolates from specific cases and outbreaks by isolation, phenotypic and genotypic characterisation through to assessment and development of new diagnostic tests and platforms for use within the conventional and field laboratory. Research also includes development and assessment of interventions in models of infection. We also welcome participation in prospective and retrospective clinical studies, serosurveillance and disease prevalence studies as well as therapeutic studies for a number of potential pathogens with partners worldwide.

#### SARS CoV-2 PCR

In response to the COVID-19 pandemic, RIPL has developed capability for SARS CoV-2 PCR diagnostic testing and this is included in our current UKAS scope. Please contact the laboratory at portonswabtesting@phe.gov.uk if interaction with this service is required or desirable. Testing utilises the COBAS 8800/6800 platforms and full details of acceptable sample types, turnaround times and reporting strategy will be provided on request.

### Personnel and contact details

Name	Designation	Email
Dr Tim Brooks	Consultant Microbiologist & Clinical Services Director	tim.brooks@phe.gov.uk
Dr Tommy Rampling	Consultant Medical Microbiologist/Virolo gist	tommy.rampling@phe.gov.uk
Dr Matthew	Consultant	matthew.dryden@phe.gov.uk
Dryden	Microbiologist	(Mondays and Tuesdays only)
Dr Jane Osborne	Clinical Scientist	jane.osborne@phe.gov.uk
Dr Abbie Bown	Clinical Scientist	abbie.bown@phe.gov.uk
Mr Barry Gibney	RIPL Laboratory Manager	barry.gibney@phe.gov.uk
Mrs Jodie Owen	SARS CoV-2 PCR Laboratory Manager	jodie.owen@phe.gov.uk
Dr Richard Vipond	General Project Manager	richard.vipond@phe.gov.uk

To contact staff please use main RIPL telephone number 01980 612348.

# Laboratory opening times

Normal working hours: 09:00 to 17:00, Monday to Friday.

Note that, in order to arrange urgent testing outside these normal working hours, it will be necessary to discuss the clinical case with the RIPL on-call medical consultant.

# Use of the laboratory

# Diagnosing a rare or imported pathogen

The presentation of most imported diseases is very similar, and it can be difficult to distinguish between them clinically. Co-infections with more than one agent are also relatively common. For this reason, we provide panels of tests based upon the patient's symptoms and travel history that include the commonest differential diagnoses (see Map of regions, page 10). The charge for this is more than for a single assay, but significantly less than 2 separate tests. Unless you have a specific reason for testing for a single agent, or are very familiar with current disease prevalence, we suggest that you provide as many clinical and travel details as possible and allow us to select the appropriate panel of tests. An appropriate geographical test panel will be run on all samples unless the appropriate opt out option is ticked on the request form.

Panels include both serology and PCR as required, with PCR tests being offered as well as serological tests for acute cases. PCR tests are not normally performed for long-term conditions except Q fever, as they are highly unlikely to be positive and diagnosis relies on serology.

Arboviruses and rickettsiae are causes of febrile illness in travellers returning to the UK from many areas. Less frequently, illness caused by viral haemorrhagic fevers may have to be considered. Although not common, leptospirosis, Q fever, anthrax, plague and other bacterial infections, derived either from within the UK or abroad, may also be considered as part of the differential diagnosis.

Common conditions such as malaria or enteric fever (typhoid) must not be forgotten and should be tested for, alongside more exotic diseases, as prompt treatment may be life-saving. Please note that testing for malaria and enteric fever is NOT provided by RIPL and must be arranged separately through local laboratories or specialised reference centres.

Additional tests may be available other than those listed, for special cases. If appropriate, please telephone to discuss (01980 612348 during working hours).

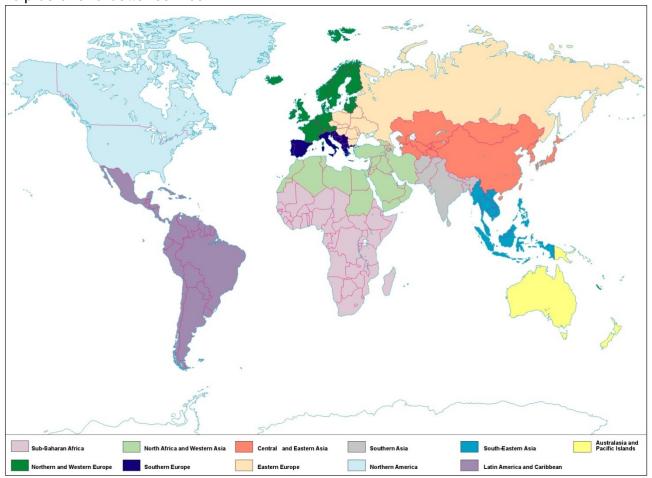
For Lyme disease testing, please see Appendix 1: Lyme Disease

For Leptospirosis testing, please see Appendix 2: Leptospirosis

For Zika virus testing, please see Appendix 3: Zika virus

# Map of regions

Routine tests are run in geographic and symptomatic panels. Additional tests are added if the clinical details justify them or by discussion with the referring physicians. The map below shows the main geographic groupings we use; the incidence of diseases is not constant across any given region, and we welcome additional information that could help us offer a better service.



Map produced by PC Graphics (UK) Limited

The map shows that the main geographic groupings are:

- Sub-Saharan Africa
- North Africa and Western Asia
- Central and Eastern Asia
- Southern Asia
- South-Eastern Asia
- Australasia and Pacific Islands
- Northern and Western Europe
- Southern Europe
- Eastern Europe
- Northern America
- Latin America and Caribbean

Note that the tests included in each of the basic geographical panels may change over time but the table on pages 23 to 27 lists available assays. Please see notes below on viral haemorrhagic fevers (page 11) for additional information.

# Typical incubation periods

Short <10 days	Medium 10-21 days	Long >21 days
Arboviruses	Malaria	Viral hepatitis
Enteric bacteria	Enteric fever (typhoid)	Malaria
Haemorrhagic fevers	Scrub typhus	Tuberculosis
Typhus & spotted fevers	Brucellosis	HIV
Plague	Leptospirosis	Filariasis

# Risks of viral haemorrhagic fevers in different countries

	Countries where human outbreaks have occurred	Countries with evidence of endemicity, through sporadic cases or seroprevalence studies	Countries/areas with a theoretical risk based on geography but no reports of cases
Ebola and/or Marburg	Angola, Congo, DRC, Gabon, Guinea, Kenya, Liberia, Mali, Nigeria, Sierra Leone, South Sudan, Sudan, Uganda.	Ivory Coast, Zimbabwe,	Other Central and West African countries.
CCHF	Afghanistan, Albania, Bulgaria, China, Iraq, Iran, Kazakhstan, Kosovo, Mauritania, Pakistan, Russia, South Africa, Tajikistan, Turkey, UAE, Uganda, Uzbekistan.	Benin, Burkina Faso, DRC, Egypt, France, Georgia, Greece, Hungary, India, Kenya, Oman, Portugal, Spain (Avila region) Tanzania.	Africa, Balkans, Caucasus, Central Asia, Eastern Europe, Middle East.

Lassa	Benin, Guinea, Liberia, Nigeria, Sierra Leone, Togo.	Burkina Faso, Ghana, Ivory Coast, Mali.	Cameroon, Central African Republic, other West African countries.
Lujo		Zambia	

Note: The following viruses also have the potential to cause haemorrhagic features: hantaviruses, chikungunya virus, rift valley fever virus, dengue viruses and yellow fever virus.

Refer to the UK Advisory Committee on Dangerous Pathogens (ACDP) Guidelines: 'Management of Hazard Group 4 viral haemorrhagic fevers and similar human infectious diseases of high consequence' and the associated ACDP viral haemorrhagic fevers risk assessment algorithm.

# Requesting procedure (routine, urgent and out of hours)

#### All samples/routine

Use the request form downloaded from the PHE RIPL website (see page 13).

#### Urgent during working day

Please telephone the UK Imported Fever Service number 0844 7788990 or, if this is inappropriate (that is not an imported fever case), please telephone 01980 612348 with all the clinical details so that the approximate arrival time of the specimen can be discussed.

#### Out-of-hours testing

Out-of-hours testing is based on discussions with the RIPL on-call medical consultant available via the UK Imported Fever Service number 0844 7788990 or, if this is inappropriate (that is not an imported fever case), via PHE Porton Reception on 01980 612100.

# Requesting additional tests

Please telephone 01980 612348 during working hours to request additional tests and provide any additional information available. We will normally store samples for a limited time after initial testing, as shown in the table below.

### Sample type and time limit for requesting extra tests

Non-blood samples	
CSF	6 months
Other Fluids	6 months
Swabs	7 days
Dry tissue (skin, nail etc)	28 days
Respiratory tract samples	28 days
Post-mortem samples (Page 18)	3 months
Wet tissue samples (ante-mortem)	6 months
Blood samples	
Whole blood samples	Spun on receipt. Plasma fraction kept for 6 months
Plasma	6 months
Serum	6 months
Medico-legal samples (plasma or sera)	30 years

# Completing the request form

The Rare and Imported Pathogens request form (labelled P1) is available to download from the PHE RIPL website.

It is important to include a mobile number or a direct telephone number for the referring microbiology or virology team on the request form so that any significant result can be communicated promptly by the RIPL team.

Requests submitted must include the following patient demographics.

Rare and Imported Pathogens Laboratory: Specimen referral guidelines and service user manual

PATIENT/SOURCE INFORMATION					
☐ Human ☐ Animal* ☐ Other*	*Please specify				
☐ Inpatient ☐ Outpatient ☐ GP Patient ☐ Other*	*Please specify				
NHS number	Gender male female				
Surname	Date of birth   D   M   M   Y   Y   Y   Age				
	Patient's postcode				
Forename	Patient's HPT				
Hospital number	☐ ITU or Other ward/clinic				
Hospital name (if different from sender's name)	Pregnant Yes No Unknown				
Have previous samples been sent to RIPL Yes No	RIPL Lab ref. no P1 _ CO				
n general, it is difficult to clinically diagnose imported viral and rickettsial infections without laboratory-generated evidence. It is important that travel history and clinical details are given to let the RIPL team decide on the correct set of tests for the region of travel. As discussed above (Page 9), unless you have a specific reason for testing for a single agent, or are very familiar with current disease prevalence, we suggest that you provide as many clinical details as possible and allow us to select the appropriate panel of tests.					
TESTS REQUESTED					
RIPL will select the most appropriate panel of tests based on information provided below (i.e. travel and clinical details and suspected diagnosis).  To opt out of this approach, tick the box and state test(s) required.	Limit testing to the test(s) specified here ONLY				

The request form should include the following clinical and epidemiological information.

CLINICAL/EPIDEMIOLOGIC	CAL INFORMATION	NC		
Foreign Travel within previous 2	1days? Yes No		Arthralgia	Other clinical details
Purpose of travel			Encephalitis	
Date of travel (from UK)	M   M   Y   Y		Endocarditis	
Date returned (to UK)		Ш	Eschar	
Date returned (to UK)	M M Y Y		Fever	
Onset date	M M Y Y		Haemorrhage	
Countries/areas visited	Urban area		Leucopenia	
	Rural area		LFTs raised	
	Open country	,	Lymphocytosis	
	Forests		Meningitis	
☐ Mosquito bite ☐ Tick bite ☐	Other insect bite*		Myalgia	
Livestock exposure	Other exposure*		Neutrophilia	Any unusual activities?
*Please specify			Rash	
Travel Vaccination History			Respiratory symptoms	Suspected Diagnosis?
			Retro-orbital pain	
Relevant Occupational History			Sore throat	Autotophilip i va
Reference Occupational History			Thrombocytopenia	Antimicrobials given?

Information on antibiotic treatment should accompany requests for rickettsial and bacterial studies.

There are separate request forms for Borrelia (Lyme disease) testing and for Leptospirosis testing. Please see **Error! Reference source not found.** and Appendix 2: Leptospirosis.

Note, however, that Leptospirosis testing will always be performed routinely on returning travellers where travel and clinical details compatible with this diagnosis are provided. Therefore, for returning travellers, it is not necessary to submit a Leptospirosis request form in addition to the standard RIPL request form (P1).

Please note that the completed request form constitutes a contract between the service user and RIPL and therefore acts as a de facto service agreement to perform diagnostic testing as outlined in this manual.

# Specimens from patients who might have Viral Haemorrhagic Fever

Samples for which the clinical and travel details on the request form could suggest VHF (for example fever on return from Nigeria) will only be processed if the information provided is adequate for the RIPL team to determine whether or not testing for VHF is appropriate. To avoid delays in processing of such samples whilst RIPL contacts the relevant clinical team for more information, we strongly advise that all such cases should be discussed with a local microbiologist, virologist or Infectious Disease physician. Thereafter, either the local Infection doctor should call the Imported Fever Service on 0844 7788990 to discuss the case before sending the sample(s), or further information should be added to the request form showing that the possibility of a VHF has been considered and is highly unlikely (for example fever on return from Nigeria, Lagos only).

#### Detailed VHF sample testing advice

# Specimen labelling

Use printed labels wherever possible. The specimen must be labelled with the same patient details as on the request form. Please ensure the full patient name and date of birth are legible. This is the minimum patient identification information required for sample processing. Please note that unlabelled specimens will not be processed as the identity of the individual from which they have been taken cannot be guaranteed.

# Types of specimens and specimen collection methods

#### Serum

1 tube of serum for serology tests; ideally 1 mL

If this volume of sample is not available RIPL may be unable to perform all tests within a geographical panel.

Note that for VHF testing, a primary tube of clotted blood should be submitted rather than a separated serum aliquot.

#### EDTA plasma

1 tube of EDTA plasma for PCR assays; ideally 1 mL

Samples may not be suitable for testing if blood is lysed.

Note that for VHF testing, a tube of whole (unseparated) EDTA blood should be submitted; plasma will be separated on receipt.

#### Tissue samples

Tissue samples received for PCR testing should be received un-homogenised and frozen. Samples received at room temperature may give rise to unreliable results, particularly for RNA viruses. Please note that fixed samples are more difficult to process by nucleic acid extraction procedures and may give false negative or inhibitory results. Given the extended time required to process fixed samples, turnaround times may be longer than those quoted in this manual.

#### Urine

Urine sent in a sterile, universal container without preservatives such as boric acid may be useful for testing when certain diagnoses are suspected, for example Leptospira and WNV. Ideally, a minimum of 1 mL of urine should be sent for testing.

#### **CSF**

CSF samples must be sent with a paired serum. Ideally, a minimum of 250uL should be sent for testing (600uL for Lyme neuroborreliosis investigation).

#### Viral swabs

Swabs for viral diagnosis should be transported in viral transport media (VTM). Please check that swabs are appropriate for viral not bacterial diagnosis. Charcoal swabs are not appropriate for molecular diagnosis. Any charcoal swabs received for PCR will be discarded.

#### Vesicle fluids

For poxvirus investigations contact the laboratory on 01980 612348 for advice. Vesicle fluid or a swab in VTM are preferred.

Sample types, such as heparinised blood or urine with preservatives, that are inappropriate for RIPL tests will not be processed.

Taking the samples: Specimens should be taken by experienced professionals using appropriate personal protective equipment and in accordance with local procedures and risk assessments. When obtaining bloods the use of a vacuum blood sampling system is strongly advised as this reduces the risk of sharps injuries.

#### Consent

We assume that the diagnostic samples received in RIPL are arriving with implicit consent for all assays relevant to the best interest of the patient. RIPL does not require separate consent documentation to be sent. This does, however, depend on the sample being sent by a recognised service user. Samples received directly from patients cannot be processed without consent from an appropriate medical professional.

Usually, highly experienced RIPL staff will determine the appropriate Geographic Panel based testing according to written or discussed clinical details given. However, we do undertake single pathogen based diagnostic tests when specifically requested (for example dengue virus IgG and IgM), but it is our evidenced experience that this may reduce the likelihood of obtaining a diagnostic answer.

Requests for further testing on samples received by RIPL can be made within the specified storage times for samples (see page 13).

In all instances, RIPL may perform additional assays to confirm or clarify earlier assay results.

# Submitting tissue samples from deceased people

# Compliance with the Human Tissue Act

Obtaining consent to remove, store and use human tissues for a scheduled purpose is one of the underlying principles of the Human Tissue Act 2004. RIPL receives postmortem samples from coroners' post-mortems or from NHS establishments across the UK and, therefore, we are performing the examination under the authority of the coroner. Unless consent has been obtained or the coroner has requested that samples are retained for further testing, samples are disposed of or returned to the sending laboratory within 3 months of the testing being performed.

During this period, samples are stored under appropriate conditions for the sample type and in adherence with the Caldicott Report and legislation laid down by the Data Protection Act 2018.

# Packaging and transporting specimens

#### General recommendation

A triple packaging system is recommended by the World Health Organization; this should be used for all infectious substances and comprises 3 layers.

# **Primary receptacle**

A primary watertight, leak-proof receptacle containing the specimen. The receptacle is packaged with enough absorbent material to absorb all fluid in case of breakage.

#### Secondary packaging

A second durable, watertight, leak-proof packaging to enclose and protect the primary receptacle(s). Several cushioned primary receptacles may be placed in one secondary packaging, but sufficient additional absorbent material shall be used to absorb all fluid in case of breakage.

#### **Outer packaging**

Secondary packagings are placed in outer shipping packagings with suitable cushioning material. Outer packagings protect their contents from outside influences, such as physical damage, while in transit. The smallest overall external dimension shall be 10 x 10cm.

# Category A

An infectious substance which is transported in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Infectious substances meeting these criteria which cause disease in humans or both in humans and animals shall be assigned to United Nations number UN 2814 and packed according to Packing Instructions P620 for transport by road or rail. Samples known or reasonably expected to contain viral haemorrhagic fever viruses fall into Category A.

Further information on packaging requirements necessary for Category A substances, and examples of these, can be found in the WHO Guidance on regulations for the Transport of Infectious Substances.

#### Category B

An infectious substance that does not meet the criteria for inclusion in Category A. Infectious substances in Category B shall be assigned to UN 3373 and must be packed to Packing Instructions P650. The vast majority of samples sent to RIPL will be Category B infectious substances.

# Courier and postal deliveries

Recommended couriers for transporting urgent Category A samples are:

PDP: 01784 420 466DGI: 0208 814 0404

Topspeed: 01565 631840 or 0800 856 2464

It is the responsibility of the sender to ensure that arrangements are in place in their contracts with courier companies so that transport arrangements do not fall foul of current UK law, or delay the transport of urgent samples to RIPL.

#### Detailed guidance on VHF testing

# Specimen limitations potentially affecting assay results

Factors that can affect assay performance are:

- acquired factors (passively acquired antibody, immune response to vaccination, immunosuppression)
- biological factors (lipaemic, haemolysed, high bilirubin content for example liver ITU patients)
- collection factors (use of correct blood collection tubes)

# Specimen rejection criteria

Samples may be rejected if:

- there is insufficient patient identifiable information on either the sample or accompanying paperwork – some specimens are difficult to repeat (CSF, biopsies etc) and these are discussed by the RIPL clinical team with the referring medical team and, in exceptional circumstances, these may be processed
- the sample type is inappropriate for the investigation requested (for example urine requesting serology, charcoal swabs for PCR etc)
- the sample has leaked in transit with little or no residual fluid in the original container
- multiple liquid samples have leaked in transit within a larger container leading to potential cross-contamination of samples
- the sample container is inappropriate for safe processing (for example broken glass, syringe needles etc)

Note that RIPL does not routinely return samples back to the original referring laboratory. Under exceptional circumstances, for example if a sample is unrepeatable, returning a rejected sample may be possible, but we strongly recommend that sending laboratories always retain aliquots of all samples submitted other than those from suspected VHF cases.

# Results and reports

#### Reports

Printed results are no longer routinely sent unless the referring laboratory is not registered to E-lab. E-lab details

Missing reports and archived reports can be posted if requested.

#### Telephoned results

All on-call (urgent) results and routine significant results are telephoned out to the referring laboratories or clinical teams as relevant.

# Biological reference values

Unlike Clinical Biochemistry, biological reference values do not usually apply to pathogen based diagnostics.

#### In general:

- IgG positive suggests exposure to an associated antigen at some time. IgM positive suggests recent exposure to an associated antigen
- indeterminate IgG or IgM implies that we are unable to clarify the presence of these serological markers
- an RNA or DNA positive result is diagnostic for that specific pathogen
- inhibitory RNA or DNA result implies that we are unable to assess the presence of the target nucleic acid because of inhibitors present in the sample

# Clinical decision making, treatment of infection and medical advice

Clinical interpretation, decision making, diagnostic, treatment and infection control advice is provided using evidence-based laboratory algorithms and standardised interpretative comments. These have evolved over time with input from published literature, UK and international guidelines and input from leading UK-based and international microbiologists, virologists, infectious diseases physicians, veterinarians, histopathologists and epidemiologists. By the very nature of the work performed in the laboratory, quite often the clinical decision making is complex, and comments are intended to communicate effectively with microbiologists, virologists and infectious disease physicians within UK.

# Specimen referrals

Rarely, samples may be sent to other UK or international laboratories to clarify a result. However, RIPL does not routinely refer samples to other laboratories or return samples back to the original referring laboratory.

# Cost of testing

Please note: Listed prices are for 1 April 2021 to 31 March 2022 and are adjusted annually.

#### NHS hospital laboratories

The differential diagnosis for travellers returning to the UK with acute fever, or for an undiagnosed rare infection, typically requires a panel of tests to be carried out to arrive at either a positive diagnosis or to exclude potential infections in a timely manner compatible with responsive patient care. In general, it is difficult to clinically diagnose imported viral and rickettsial infections without laboratory-generated evidence.

From 1 April 2021 to 31 March 2022, the cost for running an initial panel of serological and molecular tests is £171.89. All these prices are subject to inflationary fluctuations.

Laboratories requesting specific individual tests only will be charged per test from:

Immunofluorescence £96.72
 Serology £101.57
 Real-time PCR £110.53

Lyme disease See Appendix 1Leptospirosis See Appendix 2

Exceptions to this are tests for *Coxiella* serology (£91.37 for ELISA screen, £171.89 for those requiring immunofluorescence or PCR in addition) and *Rickettsia* spp immunofluorescence (£103.40).

Borrelia tests are not covered by the screen charge and are charged separately.

Leptospira tests may be charged differently depending on mode of submission (see Appendix 2)

A disposal/handling fee will be made for specimens that are not tested (see below).

#### Private hospital laboratories

The cost for running a panel of serological and molecular tests based on the clinical history and epidemiology provided will be £257.84

Laboratories requesting specific individual tests only will be charged as follows per test from:

Immunofluorescence £145.07
 Serology £152.36
 Real-time PCR £165.79

Lyme disease See Appendix 1Leptospirosis See Appendix 2

Exceptions to this are tests for Coxiella serology and, *Rickettsia* spp. immunofluorescence, for which separate charges apply.

Borrelia tests are not covered by the screen charge and are charged separately.

Leptospira tests may be charged differently depending on mode of submission (see Appendix 2)

A disposal/handling fee will be made for specimens that are not tested (see below).

Non-UK international hospital laboratories: Pricing similar to private hospital laboratories as above.

Please note that rejected or inappropriate specimens due to inappropriate packaging, incorrect referrals etc incur a disposal/handling fee (£18.66 NHS, £27.99 for other customers).

# Available assays and turnaround times (TAT)

The assays used in RIPL are:

- IgG and IgM Enzyme Immunoassays
- IgG and IgM Indirect Immunofluorecent assays
- RNA and DNA block-based PCRs
- RNA and DNA real-time PCRS
- RNA and DNA sequencing
- Pathogen culture

Assays obtained from commercial manufacturers are performed according to the manufacturer's instructions. Assays developed within RIPL are developed according to in-vitro diagnostic assay development guidelines. Quality of examination procedures are ensured by having appropriate assay controls relevant to each pathogen. In addition, RIPL participates in multiple national and international External Quality Assurance schemes.

The standard turnaround times (TAT) in the following table indicate the time taken from receipt of the sample at RIPL to the test result being reported, and are given in working days (that is excluding weekends and public holidays). Any significant results (for example PCR positive) are telephoned. In the case of retrospective testing, TAT is

measured from the time of the addition of the test code. TATs for non-standard sample types may exceed those stated in this manual.

On-call testing is focused on viral haemorrhagic fevers (VHFs), but other assays may be performed for exclusion purposes at the discretion of the RIPL consultant. On-call turnaround is generally between 7-12 hours depending on the panel of tests being performed. VHF samples arriving within routine working hours are processed on the day of receipt. All VHF test results are telephoned once available.

All assays are performed and technically validated either by, or under direct supervision of, HCPC registered biomedical scientists who have been deemed competent to undertake these investigations. Results are medically authorised by appropriately trained and registered clinicians.

Investigation and method	Plasma	Serum	Non-blood samples	Standard TAT
Anaplasma phagocytophilum IgG by immunofluorescence (IF)		•		10 working days
Anaplasma phagocytophilum DNA by RT-PCR	•	•		Developmental Assay
Bacillus anthracis (anthrax) DNA by real- time PCR (RT-PCR)	•	Note that serology is not useful for acute diagnosis	Tissue biopsy <sup>§</sup> , post-mortem tissue <sup>§</sup> , culture, eschar <sup>§</sup> , lesion washings <sup>§</sup> , suspect colonies <sup>§</sup>	3 working days
Borrelia burgdorferi C6 ELISA		•		5 working days
Borrelia burgdorferi IgG/IgM Immunoblot		•	CSF§	7 working days
Pan Borrelia RT-PCR°	•		Joint fluid <sup>§</sup> , tissue biopsy <sup>§</sup> , CSF <sup>§</sup>	7 working days
Brucella spp. RT-PCR*	•		Suspect colonies§	Developmental Assay
Burkholderia mallei RT- PCR*	•		Tissue biopsy <sup>§</sup> , pus/discharge <sup>§</sup> Suspect colonies <sup>§</sup>	Developmental Assay

Investigation and method	Plasma	Serum	Non-blood samples	Standard TAT
Burkholderia pseudomallei (melioidosis) RT-PCR*	•		Tissue <sup>§</sup> , pus/discharge <sup>§</sup> Suspect colonies <sup>§</sup>	Developmental Assay
Chikungunya IgG and IgM ELISA	•	~		4 working days
Chikungunya RT-PCR	~	~		3 working days
Coxiella burnetii  (Q-fever) Serology (ELISA screen for IgG and IgM. Positives titrated to end point by IF)	•	•		10 working days
Coxiella burnettii RT- PCR	•	•	Tissue⁵, heart valve⁵	7 working days
Crimean-Congo haemorrhagic fever (CCHF) virus RT-PCR	•	•	Urine§	Contact Fever service in advance. Result phoned directly to referring clinician.
Dengue IgG and IgM by ELISA		~		4 working days
Dengue virus RT-PCR	~	~		3 working days
Ebola group viruses RT-PCR	•	•	Urine <sup>§</sup> Semen <sup>§</sup>	Contact Fever service in advance. Result phoned directly to referring clinician.
Western, Eastern & Venezuelan equine encephalitis viruses RT-PCR*	•	•	CSF§	Developmental assay
Venezuelan equine encephalitis viruses IgG by IF*		~	CSF§	Developmental Assay

Investigation and method	Plasma	Serum	Non-blood samples	Standard TAT
Francisella tularensis spp. IgG and IgM by ELISA	•	•		5 working days
Francisella tularensis spp. RT-PCR	•	•	Tissue <sup>§</sup> , wound swab <sup>§</sup> , suspect colonies <sup>§</sup>	3 working days
Hendra virus / Nipah virus RT-PCR*	•	~	CSF§	Developmental Assay
Hantaviruses IgG by IF	~	~		4 working days
Hantaviruses RT-PCR*	•		Urine§	Developmental Assay
Japanese encephalitis virus IgG by IF	•	•	CSF§ (accompanied by serum)	5 working days
Japanese encephalitis virus RT-PCR	•	•	CSF <sup>§</sup> (accompanied by serum)	3 working days
Lassa virus PCR	•	•	Urine <sup>§</sup> , throat swab <sup>§</sup>	Contact Fever service in advance. Result phoned directly to referring clinician.
Leptospira spp. IgM by ELISA		•		4 working days
Leptospira spp. RT- PCR	•	•	Urine CSF§	3 working days
Marburg virus RT-PCR	•	•		Contact Fever service in advance. Result phoned directly to referring clinician.
Murray Valley encephalitis virus IgG by IF*	~	~	CSF§ (accompanied by serum)	Developmental Assay

Investigation and method	Plasma	Serum	Non-blood samples	Standard TAT
Orientia tsutsugamushi (scrub typhus) IgG and IgM by ELISA°		•		5 working days
Orientia tsutsugamushi RT-PCR	•	•	Eschar biopsy§ / CSF§	3 working days
Orthopoxviruses RT- PCR*			Vesicle fluid <sup>§</sup> / crusts / swab <sup>§</sup>	3 working days for routine otherwise Contact Fever service in advance. Result phoned directly to referring clinician.
Parapoxviruses RT- PCR*			Vesicle fluid <sup>§</sup> / crusts / swab <sup>§</sup>	3 working days for routine otherwise Contact Fever service in advance. Result phoned directly to referring clinician.
Rickettsia (spotted fever and epidemic typhus groups) IgG and IgM by IF		•		5 working days
Rickettsia RT-PCR	•	~	Eschar biopsy <sup>§</sup> / CSF <sup>§</sup> / swab <sup>§</sup>	3 working days
Rift Valley fever virus IgG by IF*	•	~	CSF§	Developmental Assay
Rift Valley fever virus RT-PCR*	•	~	CSF§, Urine§	Developmental Assay
Ross River virus IgG by IF*	•	~		Developmental Assay
Sandfly fever viruses (incl. Toscana virus) IgG by IF	•	•	CSF <sup>§</sup> (accompanied by serum)	4 working days
Sindbis virus IgG by IF°	~	~		5 working days

Investigation and method	Plasma	Serum	Non-blood samples	Standard TAT
Tick-borne encephalitis group viruses IgG by IF	•	•	CSF§ (accompanied by serum)	5 working days
Tick-borne encephalitis RT-PCR	•	•	CSF§ (accompanied by serum)	3 working days
West Nile virus IgM and IgG by ELISA	•	•	CSF <sup>§</sup> (accompanied by serum)	5 working days
West Nile virus RT- PCR	•		CSF§ (accompanied by serum), urine§	3 working days
Yellow fever virus IgG by IF	•	~	CSF§ (accompanied by serum)	4 working days
Yellow fever RT-PCR	•		CSF§ (accompanied by serum), tissue§	3 working days
Yersinia pestis				Developmental
(plague) RT-PCR*				Assay
Zika virus IgG and IgM by ELISA	•	~		5 working days
Zika virus RT-PCR	~	~	Urine, semen	3 working days
SARS CoV-2 PCR			Viral swab (contact portonswabtesting @phe.gov.uk for details)	Contact portonswabtesting@phe.gov.uk for details

<sup>\*</sup> indicates developmental assays which are not included in the laboratory's UKAS scope. These are assay for which there has been limited technical validation data and which may not be performed routinely/regularly. Despite this, every effort is made to provide testing for these assays within a clinically relevant timeframe. Please contact the laboratory to discuss individual cases.

<sup>°</sup> indicates assays which are fully validated but do not currently form part of the laboratory's UKAS scope.

<sup>§</sup> indicates secondary sample type(s) for which the assay is not fully validated. Turnaround times for these samples may be longer than those indicated for validated sample types.

For additional tests please discuss with the clinical team on 01980 612348.

# **UK Imported Fever Service**

Urgent clinical advice on management and diagnosis of imported diseases can be obtained through the UK Imported Fever Service telephone line 0844 7788990. The Imported Fever Service is a partnership between RIPL, the Tropical and Infectious Diseases Unit, Royal Liverpool Hospital and the Hospital for Tropical Diseases, London. The service details are available through local consultant microbiologists, virologists and infectious disease physicians who should be contacted in the first instance.

# Services to the public

RIPL serves the UK public by providing reference service to medical and public health teams across UK and the world.

RIPL does not offer diagnostic services or health advisory service or email-based communication directly to members of the public or patients. We discourage patients and relatives from contacting us directly.

All our communications are with a registered medical practitioner or accredited laboratory personnel. RIPL does not run a clinic or a hospital ward.

Results can only be issued to the requesting physician or medical unit and will not be given to patients directly. We reserve the right to check the authenticity of callers in order to protect the privacy of patients' personal data.

#### **Education services**

RIPL can provide occasional support for educational activities for groups or individuals. School and professional groups are invited to write to us with their requirements. Professional scientists and medical staff may visit for familiarisation with our work or for research attachments subject to approval from RIPL staff, their own management and if relevant, national authorities. Such visits require prior approval by the management regarding date, duration and content and are subject to the availability of RIPL staff to provide suitable input.

# Protection of personal information

RIPL staff are trained to treat all personal details in the strictest confidence, in compliance with the Data Protection Act 1998 and NHS Caldicott Guidelines. Surveillance reports about individual patients are shared only with the healthcare professionals caring for that patient and those who are investigating the source of an infection or outbreak. Competency is regularly reassessed through mandatory training exercises provided through Civil Service Learning.

#### Results over the telephone

RIPL staff will only give results to an appropriate Healthcare Professional.

Results will not be given to a patient, patient relative or associate under any circumstances.

When preliminary results are provided over the telephone, the enquirer will be made aware that "unvalidated results" could be subject to change when the final results become available.

#### Faxed reports

Manual transmission of reports by facsimile: the criteria for the transmission of a report by facsimile must meet the same criteria as a telephone report as defined above with the following additions:

The security of data transmitted by fax must be as protected as is reasonably possible. It is expected that the receiving fax machine is in a secure position (safe haven). This must be established by telephone conversation with the intended recipient or by a fax transmission from them. Transmission to an unknown destination could have serious consequences and will not be considered.

# **Emailing patient information**

Emails generally cannot be relied on to guarantee security of patients' data because they can be intercepted by a third party en route. NHSmail is an exception, allowing staff working in different NHS trusts to exchange confidential emails via nhs.net accounts.

#### Public health

Where appropriate, information is shared with relevant Health Protection Unit teams in order to determine the cause and extent of an outbreak in a community (institution, family group or the wider community) or to see whether an observed cluster of cases is related and constitutes an outbreak.

Any further pathogen culturing or sequencing of pathogens for public health benefit are performed in such a way that patient identity is not compromised.

#### Terms and conditions

RIPL services are provided in accordance with PHE terms and conditions of business the current version of which can be found on the PHE website.

# RIPL complaints procedure

A complaint may be defined as any contact by a customer, in writing, by telephone or direct communication, where a customer is dissatisfied with the service provided.

Complaints can be made in writing to: Rare and Imported Pathogens Laboratory (RIPL), Public Health England, Porton Down, Salisbury, Wiltshire, SP4 OJG, United Kingdom

Complaints can be made by telephone to 01980 612348 or email to ripl@phe.gov.uk

All complaints are taken seriously, even if it is suspected that the problems may be caused by factors other than a fault with the service concerned. All complaints are investigated.

If local resolution of the complaint is not satisfactory or unsuccessful, the complainant has the right to request an independent review of the complaint. For details of the escalation process, please refer to the PHE Complaints Procedure, details of which are available through the PHE website.

#### Accreditation

RIPL is accredited by the United Kingdom Accreditation Service (UKAS) to ISO 15189:2012 for the test repertoire stated on the Schedule of Accreditation.

# Appendix 1: Lyme Disease

#### Tests offered

Antibody testing on serum is the primary test for Lyme disease. RIPL uses a two-tier testing methodology. The screening test is a sensitive, commercial, CE marked VIsE and pepC10-based ELISA (combined IgG and IgM). Positive results are confirmed by a more specific immunoblot (separate IgG and IgM line blots).

Laboratory confirmation of neuroborreliosis is based on demonstrating intrathecal synthesis of borrelia-specific antibodies. RIPL has developed a CSF serology service using the ViraChip assay. This service is not currently included in the UKAS scope for the department. Serological testing of CSF samples requires simultaneous testing of a contemporary serum in order for the CSF results to be interpretable. It also requires measurement of albumin, IgM and IgG levels in both the CSF and the serum.

In addition to serology, PCR is also available and may be useful in testing joint fluid, biopsy tissue and CSF. PCR is not usually performed on blood but please contact us to discuss if this test may be required.

We also have capacity to perform further testing for diseases that share some common features with Lyme. Medical personnel are invited to contact us to discuss the most suitable tests we can offer for their patient.

# Sample type

Please send serum (500 µl minimum volume) for routine Lyme testing.

If CSF serology testing is required, please submit at least 600  $\mu$ l CSF as well as at least 500  $\mu$ l of serum taken on the same day. If albumin, IgM and IgG levels on the CSF and serum are available, these should be provided on the request form. If the values are not provided by the referring laboratory, RIPL will arrange for these to be measured at University Hospital Southampton Immunology Department.

For PCR, the following sample types are accepted:

Joint fluid, tissue, CSF and EDTA plasma (after discussion with RIPL microbiologist). A minimum volume of 150 µl will be required (or 0.1g of tissue).

Please refer samples with as much clinical data as possible including clinical presentation, date of symptom onset, history of tick bite, and UK location or country of exposure. Please also provide the results of any Lyme screening tests you or other laboratories have performed. A request form is available on the PHE website Lyme page: Lyme disease test request form – Publications – GOV.UK

#### **Prices**

Listed prices are for 1 April 2021 to 31 March 2022 and are adjusted annually.

	NHS	Commercial
Lyme EIA	£29.44	£60.60
Lyme immunoblot (IgG+IgM) and EIA	£112.00	£167.99
Albumin, IgM and IgG on serum and CSF	£29.24	£44.16
Lyme PCR	£47.74	£102.43
Anaplasma IFA	£9672	£145.07

Please note: An out-of-hours testing service is not provided.

#### Contact details

In case of queries, medical professionals should contact +44 (0)1980 612348 (09:00 – 17:00 Monday to Friday) or email lyme.RIPL@phe.gov.uk.

There is no clinic at PHE Porton and we are unable to see patients or give telephone medical advice directly to members of the public. Please note that we may verify the authenticity of callers before giving results to ensure that we meet the requirements of patient confidentiality and good medical practice.

Further information about Lyme disease

# Appendix 2: Leptospirosis

# **Testing for Leptospirosis**

The Leptospira Reference service was transferred from Hereford to PHE laboratories at Porton and Colindale on 1 April 2015. RIPL provides the frontline diagnostic service for Leptospira, with confirmatory testing performed at PHE laboratories in Colindale.

#### Tests offered

A full diagnostic service is provided 5 days a week (Monday to Friday) and in addition the PCR service is be available at weekends, if deemed urgent by discussion (9 am - 5 pm). Clinical advice is available 24 hours, 7 days a week and should be accessed through RIPL or the Imported Fever Service where clinically appropriate (01980 612348 weekdays or 0844 77 88 990 weekends).

For patients in whom UK-acquired leptospirosis is suspected, requests for Leptospiraspecific testing (both primary and follow-up samples) should be submitted to RIPL at Porton Down using the Leptospirosis request form.

Note, that Leptospirosis testing will always be performed routinely on returning travellers where travel and clinical details compatible with this diagnosis are provided. Therefore, for returning travellers, it is not necessary to submit a Leptospirosis request form in addition to the standard RIPL request form (P1).

Positive samples may be referred from PHE Porton to BRD Colindale after primary positive PCR testing or testing positive in IgM ELISA. Samples should not be sent to the BRD unit directly.

Serology is the primary investigation for Leptospirosis diagnosis. The primary serological test performed will be an IgM ELISA.

PCR has shown improved detection on samples taken within 7 days of onset and will be performed on all samples collected within this period. Validation of the PCR for urine samples is under development as evidence suggests that urine may be PCR positive early in infection and for a longer period than in serum or plasma. Urine samples for PCR should be sent with a corresponding serum sample. Molecular typing is under development.

An environmental water testing service is not offered.

# Sample type

# Serology

1 mL preferred serum, plasma or clotted blood.

#### **PCR**

Serum, EDTA blood, plasma.

Urine, CSF, bronchoalveolar lavage and tissue may be tested if supplied with corresponding blood sample.

Post-mortem tissue specimens

Not fixed.

#### Cerebral spinal fluid (CSF)

150 μl (Minimum volume)

Please refer samples with as much clinical data as possible including clinical presentation, date of symptom onset, UK location or country of exposure, occupation.

Leptospirosis request form

#### **Prices**

Leptospirosis diagnosis frequently requires multiple samples. The service costs a flat fee of £106.27 (NHS) or £159.42 (Commercial) per patient for leptospirosis testing.

This charge includes:

- clinical advice
- any leptospira-specific diagnostic testing (multiple tests) that clinical information suggests is appropriate
- convalescent sample testing, which is essential for confirmation of diagnosis
- testing of multiple sample types, and follow-up samples

If clinically appropriate, testing for hantavirus may also be undertaken at RIPL, in which case the combined cost for leptospirosis and hantavirus testing per patient will be £135.71 (NHS), £203.57 (Commercial).

Samples tested for leptospirosis as part of the initial panel of serological and molecular tests on a returning traveller will incur the standard RIPL panel charge.

Listed prices are for 1 April 2021 to 31 March 2022 and are adjusted annually.

#### Contact details

In case of queries, medical professionals should contact +44 (0)1980 612348 (09:00 to 17:00 Monday to Friday) or email RIPL@phe.gov.uk (checked on weekdays only).

There is no clinic at PHE Porton and we are unable to see patients or give telephone medical advice directly to members of the public. Please note that we may verify the authenticity of callers before giving results to ensure that we meet the requirements of patient confidentiality and good medical practice.

Further information on Leptospirosis infections can be found at:

- Leptospirosis
- Introduction to Leptospirosis

# Appendix 3: Zika virus

# Testing for Zika virus

At this time, access to NHS testing for Zika virus is available only through RIPL.

#### Tests offered

The diagnostic service, which is based on validated real-time PCR and serology assays, is provided 5 days a week (09:00 to 17:00, Monday to Friday). Clinical advice specifically relating to Zika virus infection is also available within these hours, but potential service users should read the on-line guidance – Zika virus: sample testing advice – in the first instance.

PCR detection of Zika virus RNA is the mainstay of diagnostic testing at RIPL. However, Zika virus RNA is only detectable in blood for a few days after symptoms begin, whereas Zika antibodies often appear within a week of symptom onset. Following evaluation of a commercial assay, RIPL routinely uses ELISAs for Zika virus IgM and IgG for diagnosis of the infection in patients with recent symptoms.

Note that negative Zika IgM and IgG results for a blood sample taken within 2 weeks of symptom onset cannot be taken to exclude acute infection.

A testing service for asymptomatic pregnant women who have travelled to countries with active Zika virus transmission is not currently offered. These pregnant women should be managed according to the published guidance.

RIPL does not provide a Zika screening service (NHS or private) for returning holiday-makers who neither have nor have had symptoms suggestive of Zika virus infection, but who would like to be tested for family planning reasons. They should be advised to follow PHE guidance on contraception after travel to countries at risk for Zika virus transmission.

Appropriate samples for Zika virus testing must be submitted with an adequately completed request form – see Zika virus: sample testing advice. Inappropriate or unnecessary samples (for example EDTA plasma sent in addition to serum, or urine samples taken >21 days after symptom onset) and those submitted with inadequate clinical information will be stored without testing. Note that a sample handling and storage fee is charged in such cases.

# Sample type

Specific guidance on who to test for Zika virus infection and which samples to collect is available.

#### Serology

The preferred sample for serological testing is serum (0.6 mL minimum volume).

#### **PCR**

Zika virus PCR will be performed on any serum sample taken within 7 days of onset of symptoms suggestive of Zika virus infection, and on any urine sample taken within 21 days of onset of symptoms suggestive of Zika virus infection.

Other sample types for PCR testing - saliva (that is mouth swabs), semen, amniotic fluid and tissue such as placenta or umbilical cord – should only be submitted *after* individual case discussion with RIPL.

#### **Prices**

The charges to NHS hospital laboratories for Zika virus serology alone or for Zika virus real-time PCR alone are:

serology £101.57real-time PCR £110.53

Where both Zika virus serology and PCR are performed, with or without additional tests for other flavivirus infections, this will incur the standard RIPL panel charge as indicated on page 21.

The corresponding charges to private hospital laboratories are as indicated on page 21. Listed prices are for 1 April 2021 to 31 March 2022 and are adjusted annually.

#### Contact details

In case of queries, health care professionals should contact +44 (0)1980 612348 (09:00 to 17:00 Monday to Friday) or email RIPL@phe.gov.uk (checked on weekdays only).

There is no clinic at PHE Porton and we are unable to see patients or give telephone medical advice directly to members of the public. Please note that we may verify the authenticity of callers before giving results to ensure that we meet the requirements of patient confidentiality and good medical practice.

Further information on Zika virus testing can be found at:

Zika virus: sample testing advice – GOV.UK