Public Health England

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VIRUS SPECIAL VACCINE UPDATE

Issue 302, November 2019

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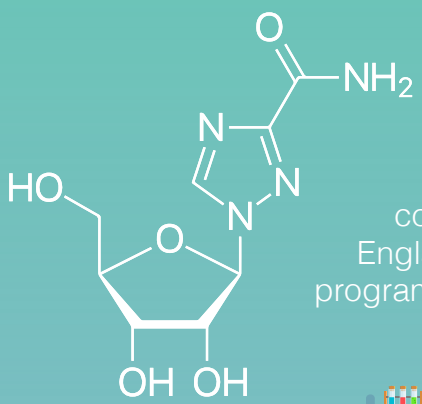
Virus special

Our July edition featured a celebration of the vaccine heroes on the delivery and implementation side of the workforce and we used the October 300 centenary edition to begin our celebration of the roles that the laboratories have in monitoring surveillance and cover as well as identification of bacterial serotypes, cases and outbreaks of infectious disease. Please take a look at the Bug special to find out more see weblink 1.

In this edition we continue our exploration of the roles of the laboratory vaccine heroes which support virus testing, referencing and identifying the strains of sequenced samples. This enables the epidemiologists to determine the correct approach to existing cases, by identifying vulnerable populations and limiting the spread of disease.

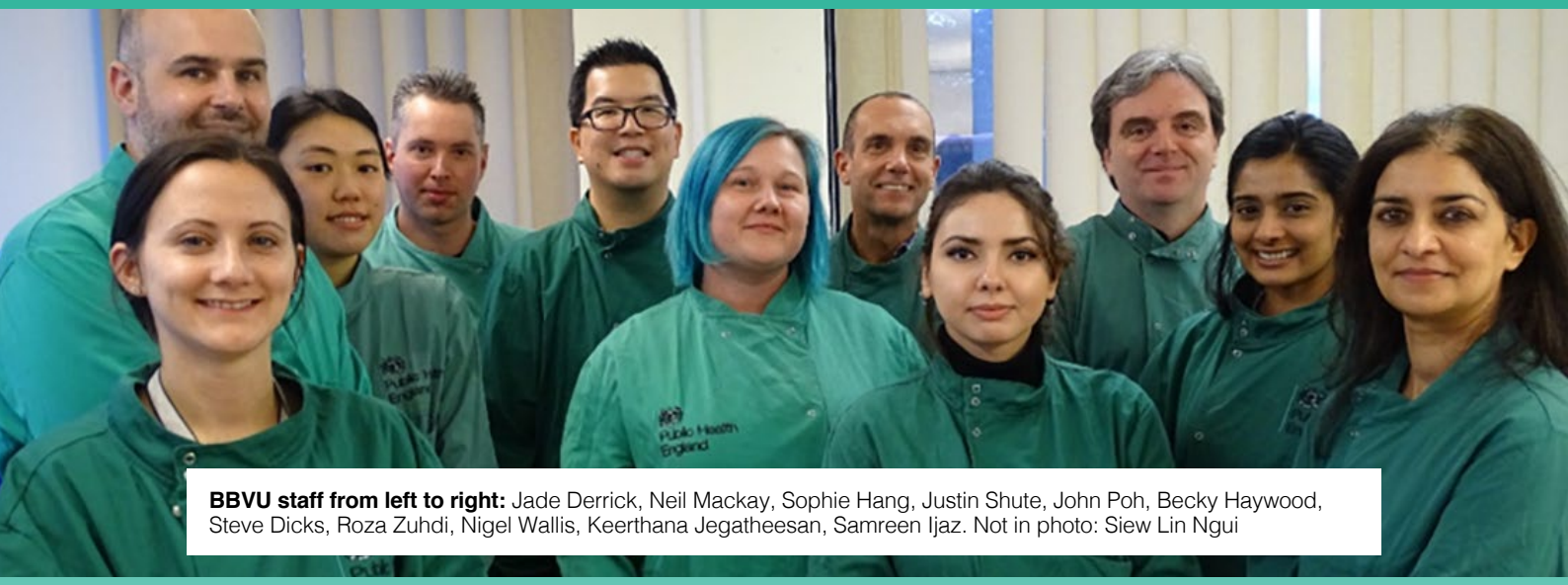


We would like to thank every one of our laboratory #Vaccineheroes for their valuable work and contributions to Public Health England's world class immunisation programme.

CONTENTS

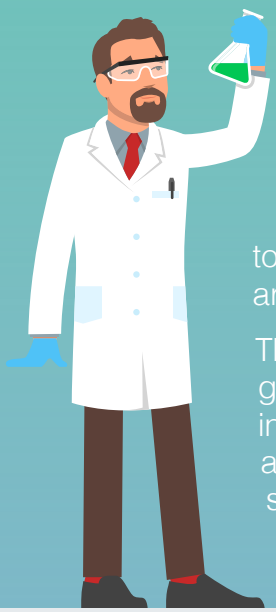
The Blood Borne Virus Unit, Virus Reference Department, NIS Colindale

The Blood Borne Virus Unit (BBVU) is within the Virus Reference Department at PHE, Colindale. The unit has a remit for delivering a specialist clinical service, undertaking national enhanced surveillance programmes and carrying out research and development studies linked to the hepatitis viruses (hepatitis A virus through to hepatitis E virus). There is also a programme of blood safety that is delivered by BBVU. The unit works in close collaboration with colleagues in the Blood Safety, Hepatitis, STI and HIV Division and the Immunisation and Countermeasures Division.



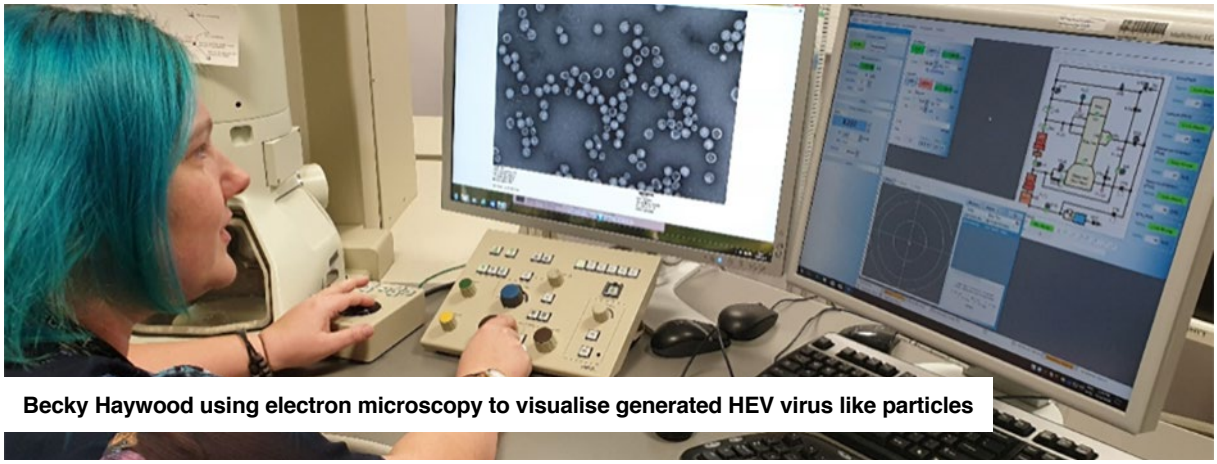
BBVU staff from left to right: Jade Derrick, Neil Mackay, Sophie Hang, Justin Shute, John Poh, Becky Haywood, Steve Dicks, Roza Zuhdi, Nigel Wallis, Keerthana Jegatheesan, Samreen Ijaz. Not in photo: Siew Lin Ngui

The unit undertakes a range of activities supporting immunisation programmes linked to the hepatitis viruses. In order to address data gaps and inform on immunity levels in specific high-risk groups, we have recently completed hepatitis A virus (HAV) seroprevalence investigations both in the general population and in Men who have Sex with Men. The unit also provides laboratory support to guide interventions through immunisation in the event of HAV transmission or outbreak events. This will include molecular typing and phylogenetic analysis to confirm linkage between cases and also the provision of oral fluid testing to identify infections within households and other close contacts.



Whilst the hepatitis E virus (HEV) vaccine is not licensed in the UK, BBVU is working in collaboration with Médecins Sans Frontières (MSF) on the implementation of the vaccine in outbreaks that occur in displaced populations particularly in Africa. We have developed non-venous based tools for measuring antibody response and are also working with local teams around technology transfer for the diagnosis and monitoring of HEV infections.

The prevention of hepatitis B virus (HBV) mother to child transmission is a WHO global hepatitis strategy target to achieve HBV elimination. The BBVU works in close collaboration with our epidemiology colleagues in working towards achieving this target. This work forms a major part of the unit's activities supporting immunisation programmes and is described in more detail below.

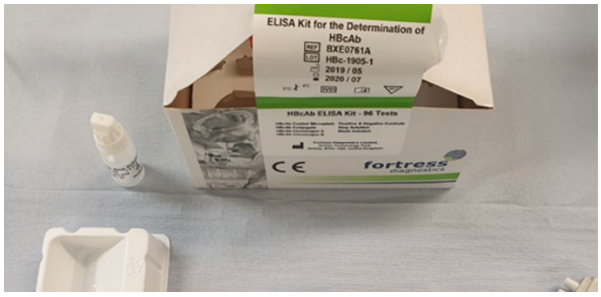


Becky Haywood using electron microscopy to visualise generated HEV virus like particles

BBVU activities supporting the HBV vaccine programme

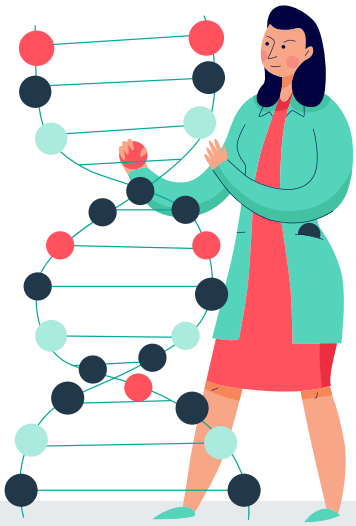
Specialised HBV diagnostics and characterisation

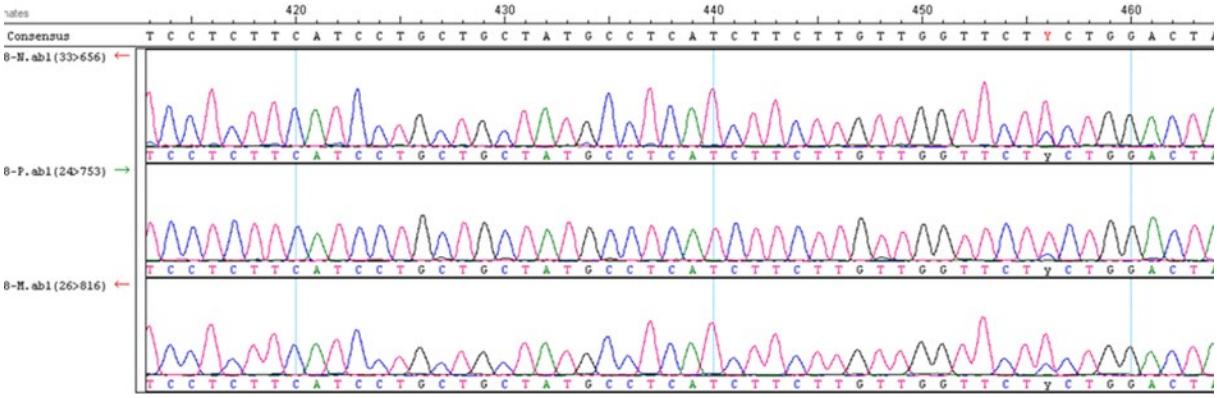
The unit is part of an accredited laboratory and offers a range of molecular and serological methods for the diagnosis and characterisation of HBV infections. As part of the PHE national programme, samples from infants born to known HBV-infected mothers are collected when they are 12 months old and sent to BBVU to investigate for evidence of HBV infection. Over the years the analytes collected from these infants has evolved from venous samples to dried blood spots (DBS). This change has been driven by the need to increase the number of infants who are being tested at 12 months of age and has proved to be very successful. A DBS provides a less invasive method for sample collection and has the advantage that it can be taken in GP services.



Justin Shute processing DBS cards; An example of an ELISA used for the detection of HBV antibodies

The unit has developed methods for detecting the major markers of HBV infection from DBS. Any DBS sample found to be serologically reactive on testing will then have additional molecular analysis undertaken. Sequencing across the virus envelope, specifically the hepatitis B surface antigen (HBsAg), will establish the genotype of the virus but will also determine the presence of amino acid changes that may have allowed the virus to escape the vaccine. The HBsAg is a conformationally dependant and even a single amino acid substitution will lead to an alteration in the antigenicity of this protein resulting in the virus not being recognised by the antibodies generated from HBV immunisation.





An example of a contig of HBV sequences; a mixed base pair is visible at position 456 and may indicate the presence of a wild type and mutant mixed sequence.

Enhanced surveillance in HBV-infected mothers and their infants

In collaboration with our epidemiological colleagues, BBVU delivers a programme of enhanced surveillance which provides an invaluable national platform by which to evaluate the effectiveness of current national strategies aimed at reducing mother to child transmission of HBV. A recent review of possible factors associated with HBV infection in infants who had received HBIG and vaccine in accordance to national recommendations indicated ~40% of infants harboured a virus with amino acid changes associated with vaccine escape. Maternal viral load was also shown to be an important factor in those infants found to be HBV-infected at 12 months of age. The review could not quantify the contribution of genuine vaccine escape versus transmission during pregnancy (in utero) to HBV infections in these infants.

In order to address some of these data gaps and to inform on the better utilisation of interventions available for the management and control of HBV infections, improvements to the current surveillance programme will be launched in April 2020. Maternal HBV markers which define infectivity status will now be monitored at the beginning and at the end of pregnancy and the maternal virus will be sequenced to determine the presence of vaccine escape mutations. In the neonate, additional testing will be undertaken in a DBS collected at birth to investigate for evidence of *in utero* transmission.

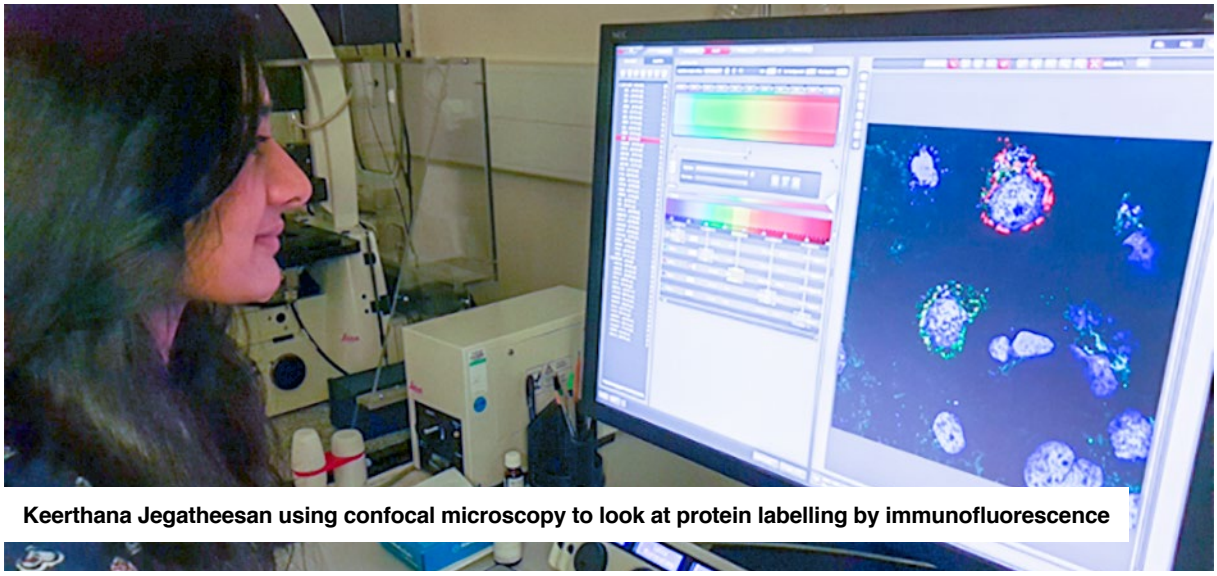
Research and development supporting the HBV vaccine programme

The unit holds a range of skills in the development of novel tools and reagents for investigating the hepatitis viruses. This includes the generation of monoclonal antibodies and expression of recombinant proteins.

Some of these methods have been applied to investigating amino acid changes found in the HBsAg of HBV-infected infants.

Nigel Wallis using tissue culture methods for expressing viral proteins

We have developed a phenotyping method based on epitope mapping using a range of monoclonal antibodies to measure changes in HBsAg antigenicity. This allows us to better understand which amino acid substitutions are clinically significant in allowing the virus to escape vaccine. In addition, recombinant HBsAg proteins based on the virus found in HBV-infected infants have been generated. These are being used to better understand the role specific HBV genotypes/serotypes backbones play in the selection and presentation of altered HBsAg phenotypes.



Keerthana Jegatheesan using confocal microscopy to look at protein labelling by immunofluorescence

The Immunisation and Diagnosis Unit, Virus Reference Department, Colindale

The Immunisation and Diagnosis Unit (IDU) is a small team within the Virus Reference Department, PHE providing specialised testing to support the vaccine preventable disease program, and as such works very closely with colleagues in the Immunisation Department. The Unit is often known as the 'Measles Lab' but has a much wider remit than just measles, with tests for other viruses that cause similar rash like-illness, including rubella, parvovirus B19 and human herpes viruses six and seven. The laboratory also provides testing for varicella zoster virus to support the roll out of the shingles vaccine program, confirmation and genotyping of mumps and rubella, and specialised testing for intrathecal antibodies for the investigation of encephalitis of unknown aetiology. As one of the three WHO Global Specialised Laboratories for Measles and Rubella, the unit also provides technical support and expertise to the global Measles/Rubella (MR) LabNet, and is responsible for the WHO databases collecting genotype information on measles and rubella from all over the world.

The unit tested over 17,000 samples in 2018, of which over 5,000 were for measles.

Members of IDU

Measles and rubella testing

Confirmation of measles, (and mumps or rubella) cases

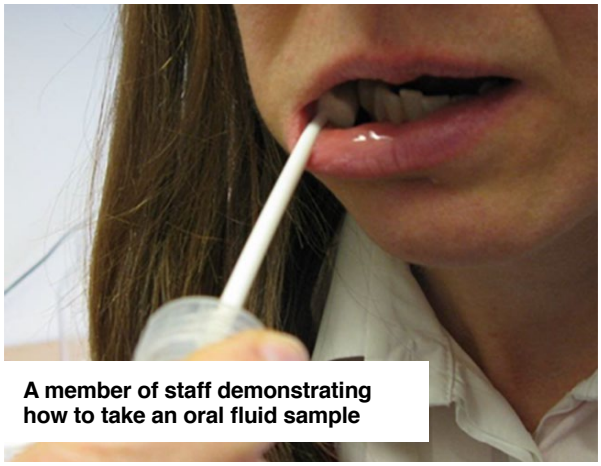
When a case of measles or rubella is suspected, the case is notified to the local Health Protection Team, and an Oral Fluid collection kit is sent out to the patient's address.

The sample is taken by rubbing along the gum line and returned through the post to the Virus Reference Department based at Colindale.

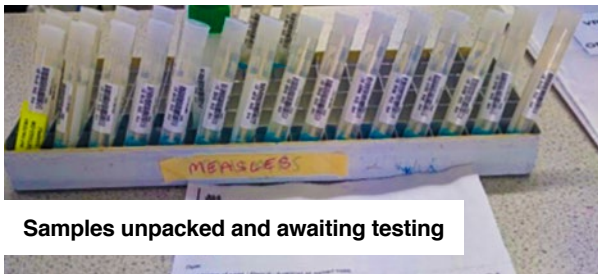
The samples are booked in and the oral fluid extracted for testing by members of the Clinical Specimen Reception (CSR) and Clinical Services Unit (CSU) teams. Initial testing for measles IgM and IgG, and measles RNA is carried out by the CSU, and all positive samples are sent to IDU for confirmation and further testing.

Testing within IDU is co-ordinated through Technical Manager and Senior Technical Lead, who determine which samples need to be tested and time table the testing schedule with the other assays that need to be performed by the unit.

Kit for collecting oral fluid sent to patients home



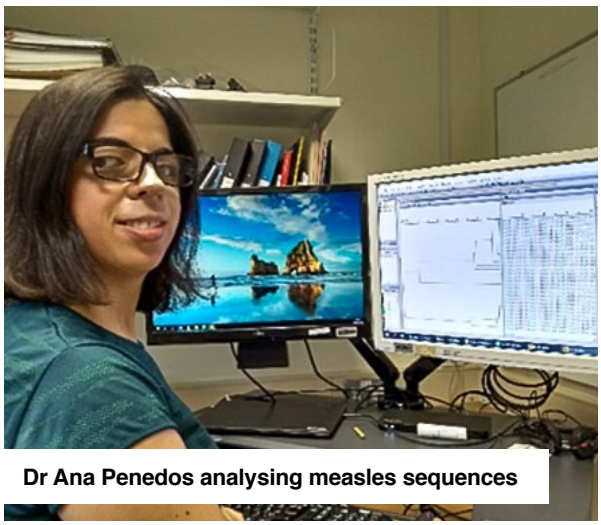
A member of staff demonstrating how to take an oral fluid sample



Samples unpacked and awaiting testing

Technical Manager Mihaela Cirdei and Senior Technical Lead Heather Lawson

Donshiya (Donni) Donpattu setting up a measles amplification for sequencing the measles virus



Dr Ana Penedos analysing measles sequences

Dr Li Jin, Clinical Scientist, reporting results in the laboratory information database

Measles and rubella confirmation and genotyping

Samples that have detectable measles or rubella RNA are confirmed by PCR, and the amplicon then sequenced. The sequences obtained are then analysed to identify circulating genotypes of the virus in question.

The data on the strains of the sequenced samples aids the work of PHE epidemiologists in identifying the correct approach to existing cases, limiting the spread of the disease, and identifying vulnerable populations.

The sequences obtained are reported to the WHO databases that track circulating measles and rubella viruses worldwide: MeaNS and RubeNS (measles and rubella nucleotide surveillance, respectively).

This information is crucial in informing the elimination programme at the local, regional and global levels.

Reporting of results

All results obtained for each sample are input into a central database and technically validated to ensure the accuracy of the tests performed.

Prior to reporting to the physician attending the patient, the overall data for a sample is analysed and clinically validation is carried out to ensure the multiple test results form a coherent picture and are consistent with the reported diagnosis.

Specialised testing

Plaque Reduction Neutralisation Test (PRNT)

Although most serology testing is done by commercial enzyme-linked immunoassays (ELISAs), in some circumstances it is important to check if the patient has developed antibody that will protect against re-infection. This is also the test that is done when new measles vaccines or schedules are being evaluated, or in some patients who may have a poor immune response to infections. The testing is done by incubating the serum sample with measles virus and then seeing whether the measles virus will still grow in tissue culture. This testing is highly specialised and is only done within IDU in the UK.

Laura Craig setting up a measles neutralisation test

Encephalitis testing

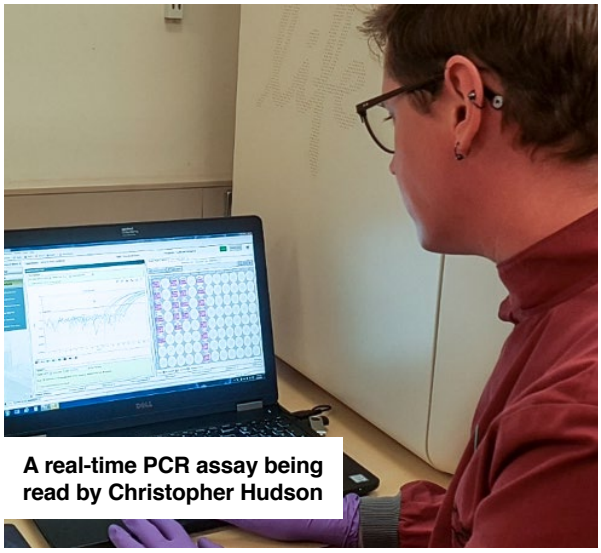
Rarely measles can cause severe neurological complications, including sub-acute sclerosing pan-encephalitis (SSPE), a chronic infection of the brain with measles virus, developing several years after the original infection. The diagnosis is made through looking in the Cerebrospinal fluid (CSF) and serum for evidence of high levels of measles antibody. The test then compares the levels of measles antibody with the levels of albumin also found in the CSF and serum. This testing is another example of the specialised testing that is only performed in IDU.

Stuti Vaghadia setting up and reading albumin results for interpretation of antibody results in the CSF

Hamish Wilson setting up an IgG assay for the detection of chickenpox antibody

Differential diagnosis of rash illness

As part of the measles program it is important not only to confirm measles cases, but also to make sure that other infections that could mimic measles are also identified. The laboratory offers testing for rubella, parvovirus B19, human herpes virus 6 and human herpes virus 7 all of which can cause a rash-illness that could be confused with measles. The testing is by a combination of molecular assays (including real-time PCR assays to detect viral RNA or DNA) and serology where appropriate.



A real-time PCR assay being read by Christopher Hudson

Support for other vaccine preventable disease

Although measles and rubella are the main vaccine-preventable infections that the unit provides testing for, with the introduction of the shingles vaccine into the national immunisation program, the laboratory also provides support in confirmation of shingles/chicken pox, sero-epidemiolgy and molecular testing to distinguish vaccine virus from 'wild-type' virus in patients who have previously been vaccinated against chickenpox or shingles.

Measles Research and Development work

Point of Care Testing

Lenesha Warrener reading a point of care test for measles IgM

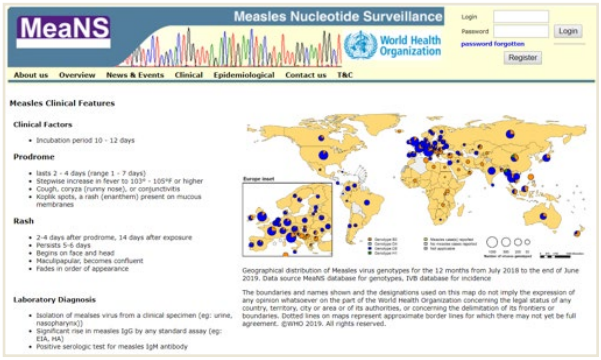
With funding support from the Bill and Melinda Gates Foundation Point of Care Tests (POCT) for the detection of measles IgG or IgM at the place of collection have been developed in the unit. The IgG POCT allows for rapid identification of measles immunity to support global initiatives to improve vaccine uptake, without the need to send the samples to a laboratory, and allowing immediate immunisation of these testing negative. The IgM POCT allows confirmation of recent measles infection without the need for a laboratory. This assay will be particularly advantageous in regions with limited access to laboratories and where patients must travel long distances to be seen by a health practitioner. The measles IgM POCT is currently under evaluation, with studies of its utility in Uganda, India and Malaysia.

Extended sequencing of measles virus

The efforts towards the elimination of measles and rubella have led to a marked reduction in the diversity of circulating viruses. As a result, the region of the genome classically used for genotyping and outbreak characterisation of the disease has become insufficient in providing data for epidemiological studies of transmission chains of the virus. Methods for the sequencing of other parts of the measles genome have been developed and assessed in the unit, and are increasingly being used by other countries in an attempt to track measles infections within and between countries.

WHO work/WER report

As both a WHO regional reference laboratory and a WHO global reference laboratory, the unit actively supports the global measles elimination program with the monitoring of measles sequences globally, and monitoring the decreasing diversity of measles sequences, and developing new methods for identifying measles transmission chains. In addition, personnel within the unit, provide updates both nationally and internationally on the status of measles within the UK, and the challenges of measles elimination globally.

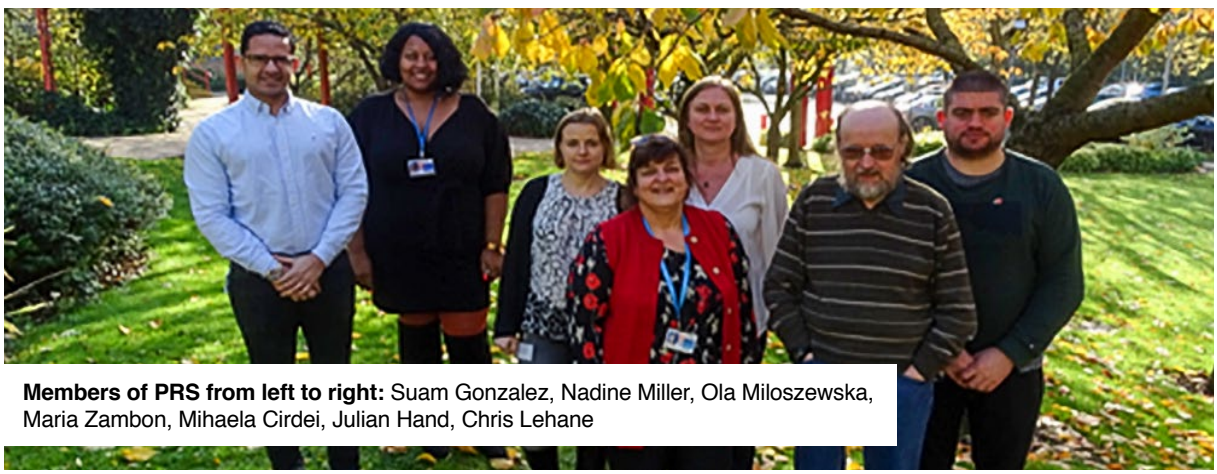


The WHO measles database hosted by PHE and providing global information about measles

Dr Kevin Brown giving a recent presentation on measles and rubella elimination

The Polio Reference Service, Virus Reference Department, Colindale

The Polio Reference laboratory is designated as the UK WHO national laboratory. The activities of the laboratory team include undertaking polio and non-polio virus isolation in tissue culture, surveillance programmes for polio virus detection in clinical and environmental materials and a range of molecular analytical techniques. The team works closely with epidemiology colleagues in the Immunisation department, the National Institute of Biological Standards and Controls (NIBSC) and the WHO EURO office in Copenhagen. Data from the laboratory work is reported back to clinical teams in the NHS and devolved administration and directly to WHO through regular weekly database uploads. If required, the team provide assessment of polio immunity for occupational health and clinical purposes through undertaking virus neutralisation testing.



Members of PRS from left to right: Suam Gonzalez, Nadine Miller, Ola Miloszewska, Maria Zambon, Mihaela Cirdei, Julian Hand, Chris Lehane

As a result of the global initiative to eradicate polio, laboratory work on live polio virus is very strictly regulated. Staff handle virus containing materials in completely closed safety cabinets. This requires manual dexterity.

Member of polios laboratory staff looking at the results of tests on clinical samples using different techniques

Laboratory based surveillance involves detecting viruses through growth of viruses in tissue culture, which is assessed through microscopy or through detection by molecular analysis. Results of laboratory analyses are uploaded to WHO databases.

The Respiratory Virus Unit, Virus Reference Department, NIS Colindale

The Respiratory Virus Unit (RVU) in the Virus Reference Department, NIS Colindale has a team of around 25 staff, including Clinical Scientists, Biomedical Scientists, Healthcare Scientists and students. As well as hosting the UK World Health Organization (WHO) National Influenza Laboratory (Director, Professor Maria Zambon), the unit is a WHO respiratory syncytial virus (RSV) global Reference Laboratory, and a WHO Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) Reference Laboratory.

Figure 1. RVU staff – from left to right; Catherine Thompson, Claudia Rosenow, Joanna Ellis, Maria Zambon, Max Pitcher, Karen Isaacs, Jade Cogdale, Monali Patel, Freja Walters, Mathura Kirupaharan, Joseph Wilmshurst, Christine Carr, Dulcibella Boampong, Suzanna Barrow, Katja Hoschler, Shah Miah, Tiina Talts, Janice Baldevarona, Paola Barbero, Hirushi Rajapakse, Shan Wong. (Not in picture; Omolola Akinbami, Pravesh Dhanilall, Jake Dunning, Sammy Ho, David Jackson, Sarah James, Angie Lackenby, Praveen SebastianPillai, Dipa Vekaria).

RVU undertakes national surveillance of influenza and other respiratory viruses (Scientific Lead, Dr Joanna Ellis). Virological characterisation of influenza viruses is an important component of UK influenza surveillance, and is performed to monitor for changes in currently circulating strains and to compare how similar they are to those included in seasonal influenza vaccines.

Surveillance data is provided to WHO as evidence from the UK to help guide the twice-yearly formulation of the influenza vaccine.

Vaccination remains the principal measure for preventing influenza and reducing the impact of annual epidemics. Current seasonal influenza vaccines are either trivalent, containing two influenza A strains (an A(H3N2) and an A(H1N1)pdm09 virus) and an influenza B strain, or quadrivalent if containing an additional influenza B strain.

PHE virological data is reported weekly, both nationally and internationally, with PHE national surveillance data regarded as Official National Statistics, with some of the highest viewing figures of content on the PHE website. This is reported in the weekly national flu reports, available at: weblink 2

The unit also contributes virological data to assist seasonal influenza vaccine effectiveness (VE) estimates, including assessment of the effectiveness of new vaccination programmes, such as the UK childhood influenza vaccination programme which began in autumn 2013.

Several RSV vaccines are in later stages of development; before their possible licensure and use in the UK, through our participation in a WHO global RSV surveillance pilot, we are establishing the background molecular epidemiology of RSV in England.

Sources of samples

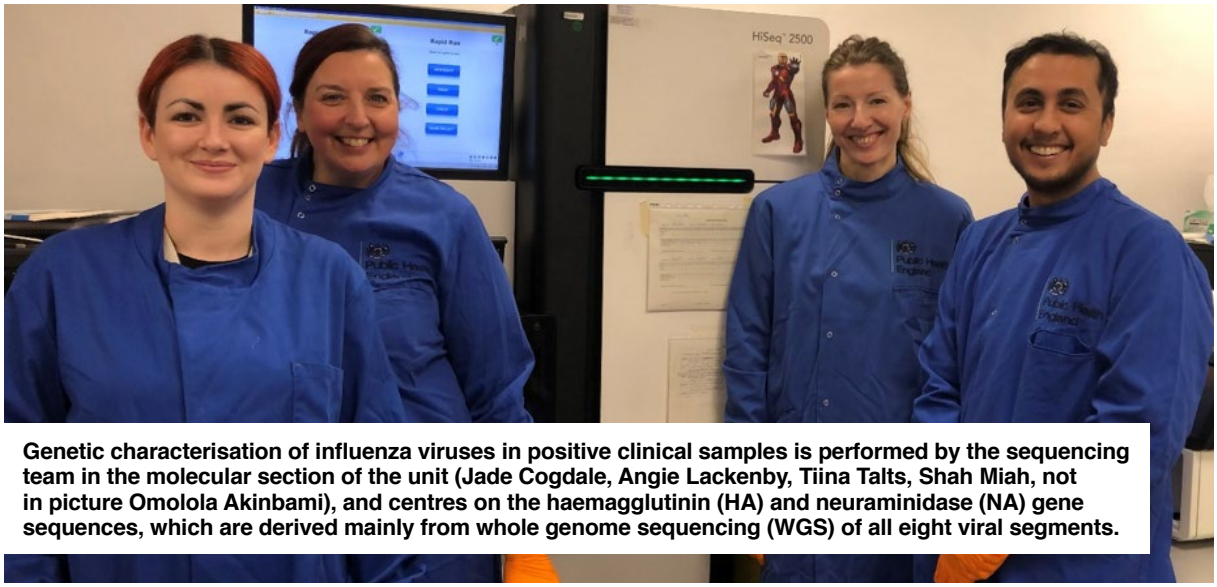
Influenza surveillance in the UK is based on clinical and virological information; clinical activity in England is monitored by the network of GPs co-ordinated by the Royal College of General Practitioners (RCGP). Since the early 1990's, a joint PHE/RCGP swabbing scheme has been undertaken where a subset of these GPs send nose and throat swabs from patients with respiratory infections, to RVU. Once received, the specimens are prepared for testing with multiplex RT-PCR assays for seasonal influenza A(H3), A(H1)pdm09 and influenza B viruses, as well as for RSV A and B and human metapneumoviruses (hMPV A and B).

Hospital laboratories refer influenza positive samples to RVU for further virus characterisation. Generally, hospitals refer all early and late influenza season samples, and a proportion of positive samples during the peak weeks of influenza activity.

Real-time RT-PCR is performed by the PCR team in the molecular section of the unit (Joseph Wilmshurst, Mathura Kirupaharan, Janice Baldevarona, Dulcibella Boampong)

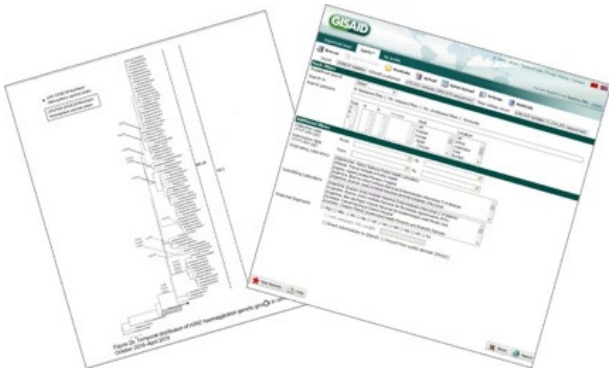
Influenza virus characterisation

Genetic and antigenic virus characterisation and antiviral susceptibility testing of influenza positive samples from all sources, is undertaken centrally at RVU. At the early and late stages of the season, clinical material is selected for performing viral genome sequencing and virus isolation in parallel and, is dependent on viral load and other relevant clinical information. In the peak weeks of the epidemic, a 'sequence first' approach is used, where sequence data is used to select a subset of representative genetic variants circulating, for virus isolation and subsequent antigenic characterisation.



Genetic characterisation of influenza viruses in positive clinical samples is performed by the sequencing team in the molecular section of the unit (Jade Cogdale, Angie Lackenby, Tiina Talts, Shah Miah, not in picture Omolola Akinbami), and centres on the haemagglutinin (HA) and neuraminidase (NA) gene sequences, which are derived mainly from whole genome sequencing (WGS) of all eight viral segments.

Sequence analysis focusses primarily on the HA gene, to monitor for emergence of antigenic drift variants with mutations in the antigenic and receptor binding site regions of the HA.



Viruses once sequenced are reported as belonging to a specific HA genetic group, and the sequences are submitted regularly to the Global Initiative on Sharing All Influenza Data (GISAID) EpiFlu database, an international database for sharing and collaborative use of influenza data.

The timely deposition of genetic data allows for the early identification of emerging genetic variants.

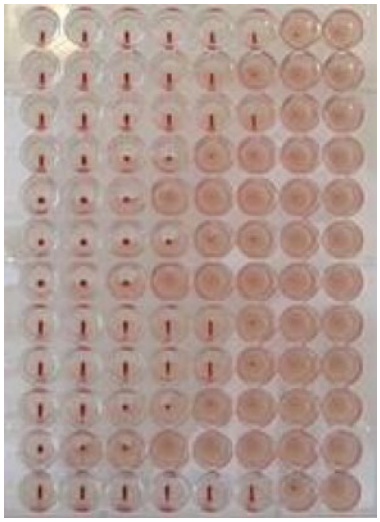
The ability to isolate and propagate influenza virus in cell culture or eggs is an essential tool for the yearly surveillance of circulating virus strains, since influenza virus isolation is required to amplify sufficient virus for antigenic analysis, which is undertaken by the unit's virus culture and antigenic characterisation team.

Staff of the virus culture and antigenic characterisation team (Freja Walters, Karen Isaacs, Paola Barbero, Catherine Thompson, Suzanna Barrow, Hirushi Rajapakse, not in picture Dipa Vekaria – maternity leave)

The haemagglutination inhibition (HI) assay is routinely used to analyse the antigenic relatedness of circulating viruses to vaccine strains. The assay evaluates the ability of specific anti-HA antibodies to inhibit the binding of the virus HA to red blood cells (RBCs). Usually, RBCs in a solution will sink to the bottom of the assay well and form a red pellet. When influenza virus is added to the RBC solution, the virus HA surface protein binds to RBCs, forming a lattice structure (termed hemagglutination).

When antibodies are pre-mixed with influenza virus followed by RBCs, the antibodies will bind to influenza virus antigens that they recognize, covering the virus so that its HA can no longer bind to RBCs, preventing hemagglutination and resulting in haemagglutination inhibition. The degree of inhibition by the antibodies indicates the antigenic similarity of the test virus to the vaccine virus that the antibodies were made against.

However, difficulties in virus isolation, haemagglutination and antigenic typing, in particular of influenza A(H3N2) viruses, due to changes in the properties of these viruses which means that they have lost the ability to agglutinate some species of red blood cells used in haemagglutination and HI tests, has led to the development and increasing use of virus neutralization assays that directly detect antibodies that prevent cell infection, to complement HI analysis, although they have the disadvantage of having a lower sample through-put capacity than HI assays, as they are more labour insensitive and time-consuming.



Example of a haemagglutination inhibition (HI) assay of a test virus, in a 96-well plate

Antiviral susceptibility

Surveillance for antiviral susceptibility is currently performed to rapidly identify the emergence of viruses with reduced susceptibility to the neuraminidase inhibitors (NI), oseltamivir and zanamivir.

A combination of analyses of the NA gene obtained from WGS of clinical material to monitor amino acid substitutions associated with reduced susceptibility to NI's, and cultured virus isolates with sufficient viral neuraminidase enzyme activity analysed by fluorescence-based enzyme inhibition (IC50) assays, is performed in RVU. Rapid subtype specific screening assays using pyrosequencing targeting the more frequently observed mutations affecting NI susceptibility, are used for a minority of clinical samples submitted from hospital sources.

RVU staff performing an influenza NA pyrosequencing assay (Max Pitcher, Claudia Rosenow, Angie Lackenby)

Serology

Population based seroprevalence studies for seasonal influenza are carried out by the serology team to calculate annual infection attack rates. The unit is heavily involved in serological assay developments; the development and validation of serological assays for use with non-standard samples (oral fluids, blood spots) to improve feasibility of vaccine trials and serosurveillance is being undertaken, and methods to distinguish vaccination from natural infection for the same purpose.

RVU serology team (Sammy Ho, Monali Patel, Christine Carr, Katja Hoschler, Shan Wong)

As well as surveillance activities, RVU is involved in the development of diagnostic tests for seasonal and emerging novel respiratory viruses. We also undertake vaccine evaluations, and research activities on respiratory viruses, including with universities in the Respiratory Infections NIHR Health Protection Research Unit.

The quality and integrity of the unit's work, data and systems is overseen by Pravesh Dhanilall (Technical Manager) and Praveen SebastianPillai (Senior Local Information Governance Officer)

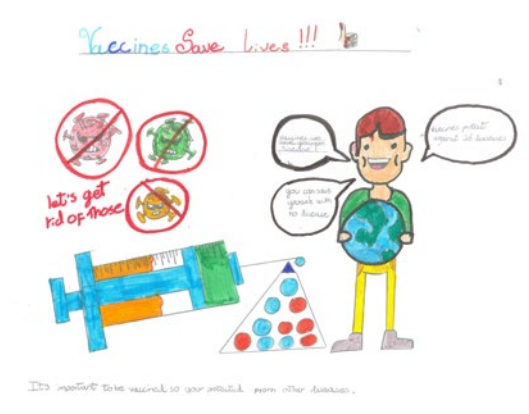
We work closely with colleagues in PHE, including the Immunisation and Countermeasures Service and the Tuberculosis, Acute Respiratory, Gastrointestinal, Emerging / Zoonotic Infections, Travel and Migrant Health Service and the PHE NIS Laboratory network. We have strong links with the Francis Crick Institute and the National Institute of Biological Standards and Controls, and internationally with organisations such as the European Centre for Disease Control, WHO, and other reference laboratories in Europe, providing data, advice and contributing to training courses.

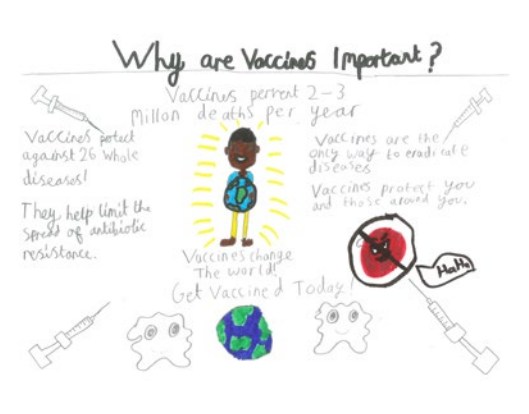
School engagement workshop – exploring 'What do vaccines mean to me?' in a primary school setting

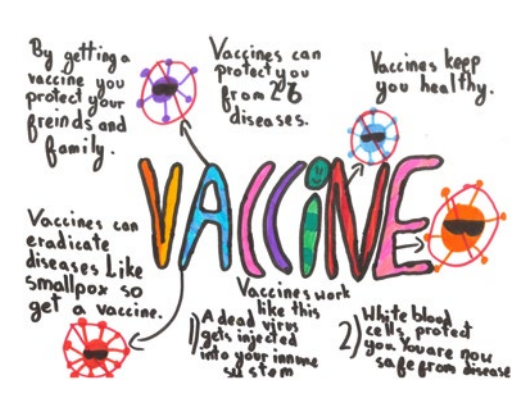
The Health Protection Research Unit (HPRU) in Immunisation – a research collaboration between the London School of Hygiene & Tropical Medicine (LSHTM) and Public Health England (PHE) – conducts research on the English vaccination programme and supports national policy making. Public engagement at the HPRU in Immunisation is a two-way process that helps to inform research, promote research quality and relevance, build trust, and share knowledge and learning.

As part of our engagement activities, HPRU researchers Sadie Bell (Research Fellow, LSHTM) and Pauline Paterson (Assistant Professor, LSHTM) held a workshop on vaccination with Year 5 children at St Clare's Catholic Primary School in Liverpool. The aim of the workshop was for the children to explore what vaccinations mean to them, their families and the wider community. During the session we asked the children to think about what vaccines do and why they are important.

As part of the workshop, the children were invited to design a poster based on the title 'What do vaccines mean to me?' The children worked really hard during the workshop and the posters they designed were all brilliant.







Understandably, the poster judges – HPRU's Joanne Yarwood and Louise Letley from the Immunisation and Countermeasures Division at PHE – had a difficult job in deciding on winners. All children that took part received a small gift as a reward for their great work. In addition, prizes and certificates were awarded to four winners: Aidan, Kai, Kinga and Tiago.

All posters were displayed within the school after the workshop, for the children's families to see and some of the posters are displayed at a Children's NHS Walk in Centre near the school. We will continue to showcase the posters within additional local venues, to share the children's hard work and spark conversation around vaccines within the local community. For us, working with the children emphasised their important role in promoting vaccination discussion in their families and communities.

We would like to thank the teachers and children at St Clare's for welcoming us to hold the workshop at their wonderful school. We would also like to thank the LSHTM Public Engagement Small Grants Scheme for funding this project.

We are very grateful for the help and support we received during this project from members of the HPRU in Immunisation based at Public Health England (Jo Yarwood, Louise Letley, Vanessa Saliba) and LSHTM (Sandra Mounier-Jack), School Improvement Liverpool (Sonia Cross), Leeds City Council (Emma Newton and Gail Evans), Liverpool City Council (Helen Casstles), the Children's NHS Walk In Centre (Joanne Cunningham and Jeanette Warren) and the LSHTM Public Engagement team (Erin Lafferty and Naomi Asantewa-Sechereh).

The Pneumococcal Polysaccharide Vaccine (PPV) coverage report

The Pneumococcal Polysaccharide Vaccine (PPV) coverage report, England, April 2018 to March 2019 has been published online: weblink 5

This report describes vaccine coverage for the fourteenth year of the pneumococcal polysaccharide vaccine (PPV) programme in England, in adults aged 65 and over. It compares vaccine uptake estimates in 2018/19 with the previous years of the programme as well as coverage among those eligible for the programme. New this year are vaccine coverage data for at risk patients aged 2 to 64 years.

Overall, PPV coverage was 69.2% in all patients aged 65 and over, a 0.3% decrease compared with 2017/18. Coverage among those aged 75 and over was unchanged at 82.5%.

Vaccine coverage among groups at risks ranged from 26.7% among patients with liver disease to 76.5% among those with cochlear implants, suggesting that awareness of eligibility for PPV among clinicians varies substantially according to clinical indication.

GPs should continue to encourage patients in risk groups and those aged 65 and above to receive the pneumococcal vaccine.

Note: All individuals become eligible for this one-off vaccination at 65 years of age unless they have received it previously because they are in a clinical risk group.

Changes to the infant pneumococcal conjugate vaccine (PCV) schedule taking place in the New Year (2020)

It was confirmed in April 2019 that England will follow a 1 + 1 PCV schedule, based on the advice of the Joint Committee of Vaccination and Immunisation (JCVI). Public Health England reconvened the PCV project board in May 2019, with NHS England and Improvement and the Department of Health and Social Care, to implement the recommended changes. A decision on which birth cohort this will be implemented for has now been made. All infants born on or after **1 January 2020** will be offered the updated schedule, (referred to as a 1 + 1 PCV schedule). This will be a single dose of PCV13 alongside the routine DTaP/IPV/Hib/HepB and rotavirus immunisations at 12 weeks of age, followed by the PCV13 booster on or after the first birthday. This 1 + 1 schedule will replace the previous schedule of 2 + 1 (at 8 and 16 weeks, and the booster dose given on or after the first birthday).

All infants born before and including 31 December 2019 will remain on the 2 + 1 schedule. The impact to the schedule will come into effect in late February 2020; when babies in the first cohort will no longer require an 8-week PCV dose. The first vaccines to be given on the new 1 + 1 schedule will start in late March 2020 when infants born on or after 1 January 2020 attain 12 weeks of age.

Further details will be published in the December issue of Vaccine Update, with all resources and materials made available in December and January 2020.

Resources

Tetanus Greenbook chapter is now published

This version updates :

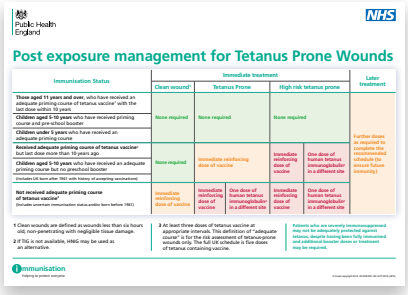
- the epidemiology of tetanus
- the management of tetanus prone wounds
- the dose of immunoglobulin for prevention of tetanus
- the use of immunoglobulins for the treatment of clinical tetanus link. See weblink 3.

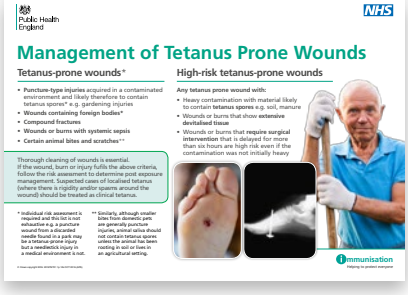
Management of tetanus prone wounds: aide memoires

Management of tetanus prone wounds depends on a risk assessment based on the nature of the wound, patient age and tetanus immunisation status.

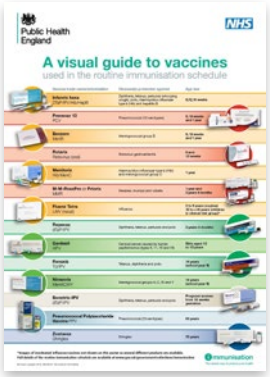
We have produced posters aimed at GP surgeries, A&E and Minor Injuries departments to assist in the identification of tetanus-prone injuries and the risk assessment for their management. These are based on the updated 2019 Tetanus Guidelines for Health Professionals and Tetanus: Green Book chapter.

You can order them using the product code: 2019TET02 and 2019TET01. They can be ordered here: weblink 4





A visual guide to vaccines poster – revised and published



The Visual guide to vaccines poster has been updated to include the extension of the HPV vaccine programme to boys aged 12 to 13 years from September 2019, and now reads boys and girls aged 12 to 13 years. At the same time the image and eligible age for the Fluenz Tetra was updated, and the poster now includes an image of the pre-filled syringe for Pneumococcal Polysaccharide vaccine PPV. We hope this poster continues to be a helpful tool in distinguishing the different vaccines used in the routine immunisation schedule. Download and print your copy today: weblink 6

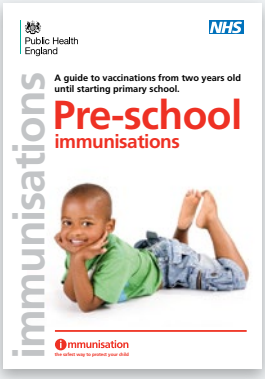
Core leaflet updated – place your orders now

We have now updated the core leaflets to include the immunisation schedule from Autumn 2019. You can order them from: weblink 7

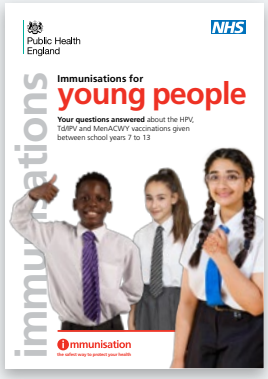
Immunisations for premature babies
Link: weblink 8

Immunisations between 12-13 months– quick guide
Link: weblink 9

Immunisations up to one year of age – main leaflet
Link: weblink 10



Pre-school immunisations for children – three years/ four months of age
Link: weblink 11



Immunisations for young people
Link: weblink 12

Vaccine Supply – centrally supplied

Centrally supplied vaccines can be used for the purposes defined in chapter 3 of the Green Book, and in the 'Vaccines available on ImmForm' helpsheet.

Vaccine supply for the 2019 to 2020 Flu programme

Children's flu vaccine for 2019/20

As in previous years, PHE is centrally supplying the following flu vaccines for children included in this year's flu programme, including those aged from six months to less than 18 years old in clinical risk groups.

Please refer to the ImmForm website for the most up to date information on ordering for both vaccines.

Vaccine	Manufacturer
Fluenz Tetra®	AstraZeneca
Quadrivalent Influenza Vaccine (split virion, inactivated) (QIVe)	Sanofi Pasteur

It remains the responsibility of GPs and other providers to order sufficient flu vaccine directly from manufacturers for older eligible patients of the flu programme in 2019-20.

Please refer to guidance from your respective health departments for arrangements in Scotland, Wales and Northern Ireland.

All influenza vaccines for the 2019/20 season

Information on all influenza vaccines that have been marketed in the UK for the 2019/20 season are available here. Please refer to the flu letter for information on which vaccines are eligible for reimbursement in the 2019/20 season.

Maternal Pertussis programme – upcoming changes to dTaP/IPV vaccine

The maternal pertussis immunisation programme commenced in October 2012, initially using Repevax® vaccine (dTaP/IPV). From July 2014, Boostrix®-IPV (dTaP/IPV) has been supplied.

From mid-January 2020, Repevax® will be available to order through ImmForm for use in the maternal pertussis immunisation programme instead of Boostrix®-IPV. This is a temporary change and it is anticipated that supplies will revert back to Boostrix®-IPV in autumn 2020. This change is necessary as PHE is running down all stock of Repevax® before the introduction of Boostrix-IPV across both the maternal pertussis and the pre-school booster programmes.

There is no other change to the maternal pertussis immunisation programme, further details about this programme can be found in chapter 24 of the Green Book. See weblink 13.

ALL CUSTOMERS – CHRISTMAS AND NEW YEAR DELIVERIES WARNING NOTICE

Due to the Christmas and New Year Bank Holidays, there will not be any deliveries or order processing by Movianto UK on Wednesday 25, Thursday 26 December 2019 or Wednesday 1 January 2020. Order cut-offs will be earlier for some customers with delivery days falling after the bank holidays, to allow sufficient time for order processing. Please see the table below for revised order cut-off and delivery dates.

Customers with a standard delivery day of **Wednesday** should be aware that after **Wednesday 18 December**, the next available delivery day will be **Wednesday 8 January 2020**.

Customers are reminded to be prepared for the break in deliveries and to order accordingly. Please make sure you have sufficient room in your fridge for any additional vaccine you wish to stock over this holiday period. Out of Schedule deliveries cannot be arranged for failure to place orders in good time.

Usual order cut-off day (by 11.55am)	Christmas/New Year period order cut-off dates (by 11.55 am; revisions are in bold)	Delivery date
Friday	Friday 20 December	Tuesday 24 December
	No deliveries Wednesday 25 December 2019	
	No deliveries Thursday 26 December 2019	
Wednesday	**Monday 23 December**	Friday 27 December
Thursday	**Tuesday 24 December**	Monday 30 December
Friday	Friday 27 December	Tuesday 31 December
	No deliveries Wednesday 1 January 2020	
Tuesday	**Monday 30 December**	Thursday 2 January*
Wednesday	**Tuesday 31 December**	Friday 3 January
Thursday	Thursday 2 January	Monday 6 January
Friday	Friday 3 January	Tuesday 7 January
Monday	Monday 6 January	Wednesday 8 January

*Customers in Scotland will receive this delivery on Wednesday 3 January 2020.

Ordering additional Gardasil for the universal HPV immunisation programme

Since 1 September 2019, the human papillomavirus (HPV) vaccine has been offered to boys, in addition to girls, as part of the routine school aged immunisation schedule. Customers can order the additional required volumes of Gardasil through ImmForm alongside vaccine used for the girls' programme.

Update to Bexsero Patient Information Leaflet

Every pack of Bexsero (Meningitis B vaccine; 10 doses) is supplied with a pad of ten Patient Information Leaflets (PILs), as well as there being a single PIL inside each Bexsero pack. Since late-September 2019, an updated version of the PIL pad has been distributed with Bexsero orders. Please dispose of the single PIL from inside the pack, as it will be out-of-date. We will advise further when the PIL supplied in the pack is in line with the PIL pad.

MMR vaccine ordering

There are currently two different vaccines available to order for the MMR programme, MMRvaxPRO® and Priorix®. Orders for Priorix® are capped at **20 packs** per order per week for accounts in England and Wales. Controls are also in place for Scottish customers. This is needed to rebalance central supplies.

The alternative MMR vaccine, MMRvaxPRO®, remains available to order without restriction. If you specifically require additional Priorix® stock, for example because you serve communities that do not accept vaccines that contain porcine gelatine then please contact the ImmForm Helpdesk for assistance at helpdesk@immform.org.uk or 0844 376 0040.

The EU Falsified Medicines Directive (FMD) and Delegated Regulation as applicable to PHE supplied vaccines for the national immunisation programme

Full information on FMD as it applies to centrally supplied vaccines for the National Immunisation Programme can be found in the April 2019 edition of Vaccine update. ImmForm vaccines in FMD-compliant packs (i.e. subject to the requirements of the Delegated Regulation) are being distributed for the majority of centrally-supplied products. The last products to be issued in FMD-compliant packs will go live towards the end of 2019 and into 2020. The exact start dates will be different for different products (the month is indicated in the table below for each product).

We will continue to update this information as forecasts become more accurate so please check for updates via the ImmForm news pages regularly. We would encourage all of our customers to visit the GOV.UK page on FMD and spend some time becoming familiar with the content and links to various other guidance documents on the implementation of the legislation.

Please note that both vaccines supplied by PHE for the 2019 to 2020 children's flu programme will be issued in FMD-compliant packs and will be subject to the requirements of the Delegated Regulation.

Product	Brand name	Month FMD-compliant packs will be issued which require verification and decommissioning
Pneumococcal conjugate vaccine (PCV)	Prevenar13	Live
DTaP/IPV vaccine for pregnant women	Boostrix-IPV	Live
Meningococcal Group ACWY vaccine	Nimenrix	Live
Measles-Mumps-Rubella (MMR) vaccine	MMR VaxPRO	Live
DTaP/IPV/Hib/HepB vaccine	Infanrix Hexa	Live
Tuberculosis vaccine (BCG)	BCG Vaccine AJV	Live
Meningococcal Group B vaccine	Bexsero	Live
Shingles (Herpes zoster) vaccine	Zostavax	Live
Hib/MenC vaccine	Menitorix	Live
Measles-Mumps-Rubella (MMR) vaccine	Priorix	Live
Rotavirus vaccine	Rotarix	Live
Human papillomavirus (HPV) vaccine	Gardasil	Live
DTaP/IPV vaccine for infants	Repevax	December 2019
Td/IPV vaccine	Revaxis	January 2020
Purified protein derivative (Mantoux test)	Tuberculin PPD-2TU	All stock will be in non-FMD packs (as it is unlicensed in UK)

PHE have also issued, and continue to issue, many products in FMD-barcoded packs that were manufactured before the legislation came into force. These packs are not required to be verified and decommissioned, but this can be done optionally.

If you have identified yourself to PHE as being exempt from decommissioning under Article 23 of the Delegated Regulation and this has been agreed, then you will be supplied with decommissioned vaccine.

Please see our guidance for more information on the roles and responsibilities in relation to FMD and the Delegated Regulation, regarding vaccines and other medicines centrally supplied by PHE to the NHS and other customers. This document is accessible via GOV.UK at weblink 14.

Please note that the barcode on Rotarix batch AROLC284AA (exp. 31/05/2021) is non-serialised and therefore cannot be verified or decommissioned.

Vaccine supply – non-centrally supplied

CHOLERA VACCINE

- **VALNEVA:** Dukoral is available
- **DUKORAL:** 2 dose 2 x 3ml vial + 5.6g sachet

HEPATITIS A VACCINE

Adult

- **GSK:** Havrix Adult PFS singles and packs of 10 are available
- **Sanofi Pasteur:** Avaxim is available
- **MSD:** VAQTA Adult is available

Paediatric

- **GSK:** Limited supply of Havrix Paedatric PFS singles is available
- **GSK:** Havrix Paedatric PFS packs of 10 are available
- **MSD:** VAQTA Paediatric is available

HEPATITIS B VACCINE

Adult

- **GSK:** Engerix B PFS singles and packs of 10 are available
- **GSK:** Engerix B vials singles are available
- **GSK:** Engerix B vial packs of 10 are unavailable
- **GSK:** Fendrix is available
- **MSD:** HBVAXPRO 10 µg is unavailable until further notice
- **MSD:** HBVAXPRO 40 µg is unavailable until further notice.

Paediatric

- **GSK:** Engerix B Paediatric singles are available
- **MSD:** HBVAXPRO 5µg are available

COMBINED HEPATITIS A & B VACCINE

- **GSK:** Twinrix Adult singles and packs of 10 are available.
- **GSK:** Twinrix Paediatric is available
- **GSK:** Ambirix is available

COMBINED HEPATITIS A & TYPHOID VACCINE

- **Sanofi Pasteur:** Viatim is available

JAPANESE ENCEPHALITIS VACCINE

- **VALNEVA:** Ixiaro is available

TYPHOID VACCINE

- **Sanofi Pasteur:** Typhim is available
- **PaxVax:** Vivotif is available

RABIES VACCINE

- **GSK:** Limited supply of Rabipur is currently available. Supply issues resulting from manufacturing constraints have now resolved, however, GSK do not expect the situation to fully normalise until late 2019
- **Sanofi Pasteur:** Rabies BP is currently out of stock. An alternative vaccine is available, please contact Sanofi Pasteur directly for more information

PPV (Pneumococcal Polysaccharide Vaccine)

- **MSD:** Limited supplies of Pneumococcal Polysaccharide Vaccine vials are available. (Please see page 12 of Bug Special Vaccine Update, issue 300, October 2019 for further information)
- **MSD:** Supplies of PNEUMOVAX 23 PFS are currently unavailable. Resupply is expected April 2020

PPV (Pneumococcal Polysaccharide Conjugate Vaccine)

- **Pfizer:** Prevenar 13 is available

VARICELLA ZOSTER VACCINE

- **GSK:** VARILRIX is currently available
- **MSD:** VARIVAX is currently available
- **MSD:** Supplies of ZOSTAVAX is currently unavailable. Resupply is expected Q1 2020

DIPHTHERIA, TETANUS AND POLIOMYELITIS (inactivated) VACCINE

- **Sanofi Pasteur:** Revaxis is available

MMR

- **MSD:** Limited supply of MMRvaxPro is currently available
- **GSK:** Limited supply of Priorix is currently available

MENINGITIS ACWY VACCINE

- **GSK:** Supply of Menveo is available
- **Pfizer:** Nimenrix is currently available

YELLOW FEVER

- **Sanofi Pasteur:** Stamaril is available

HUMAN PAPILLOMAVIRUS VACCINE

- **MSD:** Limited supply of GARDASIL is available
- **MSD:** Gardasil 9 is currently available
- **GSK:** Cervarix is currently available

Weblinks

Weblink 1	https://www.gov.uk/government/publications/vaccine-update-issue-300-october-2019-bug-special-edition
Weblink 2	https://www.gov.uk/government/collections/weekly-national-flu-reports
Weblink 3	https://www.gov.uk/government/publications/tetanus-the-green-book-chapter-30
Weblink 4	https://www.healthpublications.gov.uk/Home.html
Weblink 5	https://www.gov.uk/government/publications/pneumococcal-polysaccharide-vaccine-ppv-vaccine-coverage-estimates
Weblink 6	https://www.gov.uk/government/publications/a-visual-guide-to-vaccines-poster
Weblink 7	https://www.healthpublications.gov.uk/Home.html
Weblink 8	https://www.gov.uk/government/publications/a-quick-guide-to-childhood-immunisation-for-the-parents-of-premature-babies
Weblink 9	https://www.gov.uk/government/publications/immunisations-between-12-and-13-months-of-age
Weblink 10	https://www.gov.uk/government/publications/a-guide-to-immunisations-for-babies-up-to-13-months-of-age
Weblink 11	https://www.gov.uk/government/publications/pre-school-vaccinations-a-guide-to-vaccinations-from-2-to-5-years
Weblink 12	https://www.gov.uk/government/publications/immunisations-for-young-people
Weblink 13	https://www.gov.uk/government/publications/pertussis-the-green-book-chapter-24
Weblink 14	https://www.gov.uk/government/publications/fmd-guidance-for-recipients-of-phe-supplied-vaccines