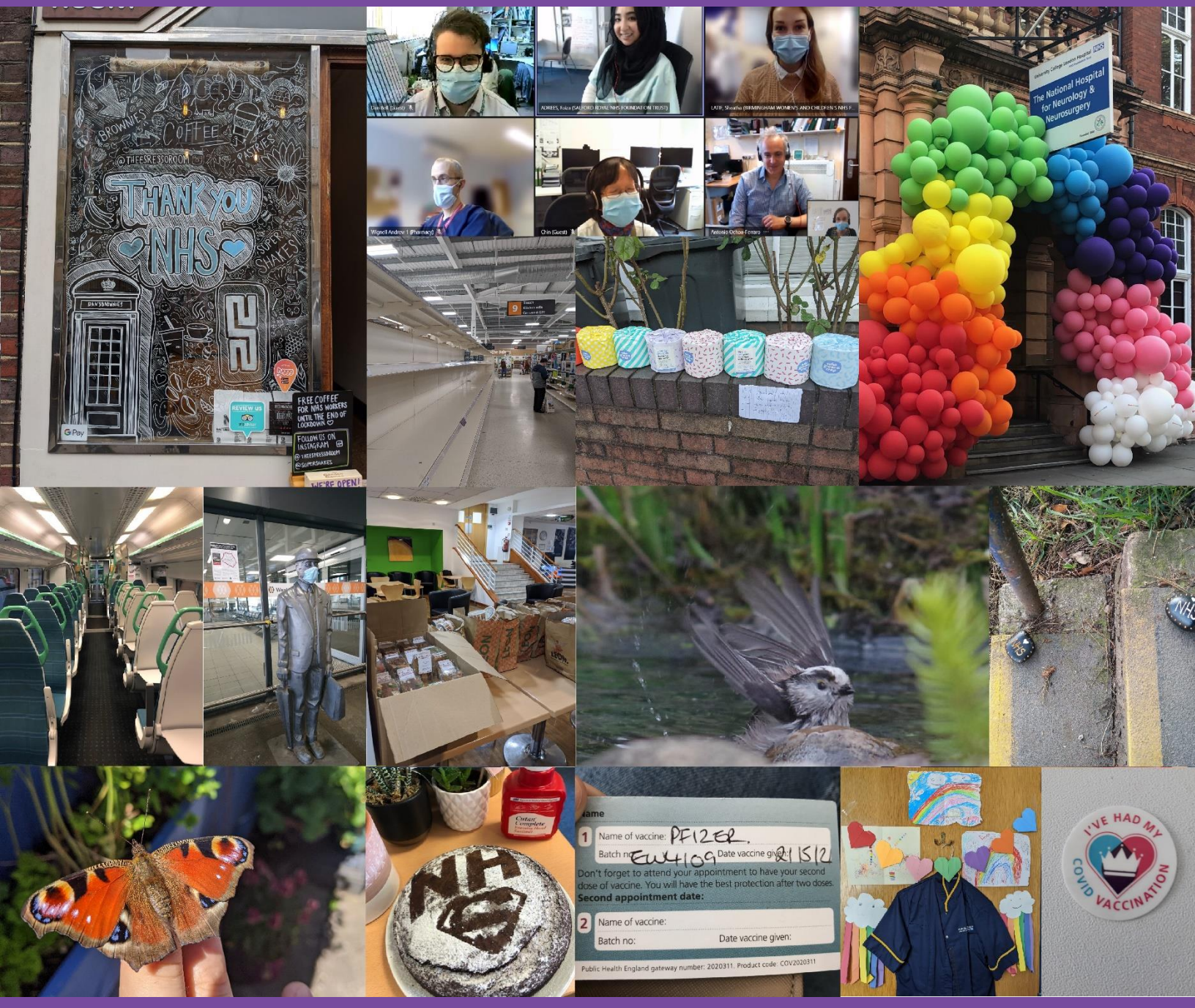
BIMDG Bulletin

British Inherited Metabolic Diseases Group



Summer 2021

Stories from a year with Covid

Bulletin editorial

Over the last year we have all experienced going to work in deserted cities, been separated from family and friends and have had any kind of certainty about the immediate future taken away from us. We have had a stark demonstration of how contingent and constructed the typical day-to-day is, what seemed immutable was in fact very…mutable. Against this backdrop we have seen mass demonstration of resilience, community spirit and the NHS and other public institutions strain but rise to challenge of this pandemic.

Given that articles about Covid (and the word 'unprecedented') have now been produced in similar quantities to Covid vaccines, we partially apologise for adding to this already sizable stockpile. With that said, BIMDG members and the wider metabolic field has worked under extremely stressful, changeable and complicated circumstances, all while putting themselves at personal risk. Under these conditions our community has achieved something to be proud of and deserving of recognition. As such, we have asked BIMDG members to contribute short stories about their last year. Some reflect experiences of redeployment into the national Covid effort, some adapting IMD services to the pandemic and others describing how they have personally been affected by Covid (as all too many healthcare workers unfortunately have been).

We would like to thank BIMDG members for their service over the last year and tentatively look forward to being able to return to something resembling normal over the coming months.

Reflections on an exceptional year
Charlotte Dawson, Consultant in Adult IMD, University Hospitals Birmingham

As the deadline for this article approached and pressure mounted to produce a piece from 'the front line' to complement the other outstanding contributions from our colleagues on this topic, I reflected on why I was finding it so hard to know what to say about my experience of treating patients with COVID. I cannot recall many specifics about the extraordinary year between March 2020 and March 2021, and I think this is what held me back, but on reflection, I do harbour many emotions attached to this year. Understanding what led to these emotions is what reflection is about – it's what makes us caring health professionals and it's why we encourage it from our trainees. I will now try to share some of these thoughts with you.

I didn't think twice when the call came in late February 2020 for ALL consultants to put themselves forward for COVID ward duties unless they or family members had health conditions or other valid reasons not to. However I recall the anxiety I experienced as I my first shift approached. The last time I'd done any general medicine was as a junior registrar level doctor in 2006, and here we were facing a whole new disease that was making people really sick. It was a weekend and I was in charge of 36+ patients with COVID any of whom could deteriorate very rapidly. I was also in charge of a team of junior doctors and souped-up medical students with a range of confusing job titles that hadn't existed fourteen years earlier, all of whom were looking to me as 'the boss'. COVID vaccination was still a pipe dream, though the anxiety I attached to the personal risk of working on the ward was only minor compared with the thought that I may not be able to meet the expectations of my colleagues or that I may inadvertently harm a patient. And

like any of us entering or leaving the hospital environment at that time, I did of course worry about bringing COVID home to share with the family - we neither fully understood its airborne transmission at that time, nor that my work clothes, stripped at the front door, would not have given my family COVID.

Paradoxically, it was the fact that COVID was a 'whole new disease' that made this period manageable, and if not enjoyable, at least somewhat rewarding. Traditional silos that exist in large Trusts with multiple specialties and super-specialties – ours no exception – disappeared overnight, to be replaced by a war-like response effort. Everyone, from the most senior, most experienced downwards was working out of their comfort zone and that made us equals in the eyes of COVID. This sense of togetherness persisted during the second winter wave but perhaps without the undertones of panic that had been there first time around.

I'd done a crash revision course on oxygen prescription in the weeks leading up to that first shift in March 2020, but nothing could have prepared me for the hitherto unprecedented quantities of oxygen we were administering on the medical wards via a range of delivery devices, alongside conscious proning of patients and other techniques previously considered the preserve of a high dependency setting. The real curve-ball though was silent hypoxia – a patient could be sitting out in a chair, apparently comfortable, not visibly short of breath, and suddenly collapse. The only sign may have been a missing oxygen saturation record, which you never ignored. But despite constant vigilance, I lost count of the number of heart-wrenching phone conversations I had with distraught relatives, not of course allowed to visit, who had thought their loved-one was 'doing ok'.

Most patients recovered and left hospital grateful for their care. Ambulances hooted and pots and pans were beaten at 8pm on Thursday evenings, rainbows appeared in front room windows. But all that never sat easy with me in the knowledge that for every few patients who left hospital there was another whose care may not have gone quite so well. And many more with non-COVID conditions whose treatment would have to wait for another time. And I'm still so sorry for all the elderly patients whom we discharged back to their care homes, clinically better but still infectious, who passed it onto their fellow residents who may have succumbed. And I think about the fellow healthcare professionals I treated whose colleagues died of COVID and who will always be wracked with survivors' guilt.

But perhaps what still disturbs me most is my morning walk to work past the house of a former patient, a year older than myself, who had been the first person I escalated to ITU. I was the last person she spoke to before she was sedated and she told me she was sorry to have left it so late to come to hospital but her husband had kept saying it was 'only her asthma'. She didn't blame him, she did have asthma after all, and it had always given her trouble in the winter months. But she died whilst still sedated on ITU and never had the chance to tell this to him herself. I see her relatives coming and going from her house as I pass in the mornings and I think that maybe one day I will identify myself and tell them about this last conversation I'd had with her.

I wouldn't turn the clock back a year for all the COVID jabs in the world. But if another wave hits us I know I'm better prepared now than I was in March 2020.

Vaccinating in the hospital hub

Elaine Murphy (UCLH) & Uma Ramaswami (RFL)

On 8 December 2020, 90 year old Margaret Keenan received her first dose of COVID vaccination. And so began the race to vaccinate the nation. Though of course the story really began as soon as vaccine scientists the world over recognised that a new strain of coronavirus could spread rapidly, with high infectivity and mortality. They promptly redirected their work to sequencing the virus, developing and trialling the vaccine in record time. Vaccine trials of the AZ vaccine started in the UK in April 2020.

RFL and UCLH were named as two of 50 ‘hubs’ chosen to lead the way on the biggest immunisation programme in history. At time of writing more than 38 million people in the UK have received their first dose of vaccination, and 23 million their second.

Royal Free Hospital got up and running quickly and gave their first vaccinations on 8 December 2020. On 13 December, an email from the vaccine co-ordinator asked if there were doctors who could cover the 0800 slot on Monday 14 December and Uma’s journey as a vaccinator started. In December, the vaccine clinic was located in the private wing on the 12th floor of the hospital but by January it had moved to the RFH Atrium (a large auditorium), and the process became very slick from the time of arrival to be vaccinated, having the vaccine, the observation period afterwards and leaving via a separate entrance after the vaccine. 0800-0900 and towards the end of the evening were always the busiest times. Uma and 3 nurses (Ma Cabides, Masoud Kazemi, Niamh Finnegan) from the LSD unit at RFH volunteered as vaccinators.

In the team of 12 clinical staff at the Charles Dent Metabolic Unit – 4 participated in the randomised trial (3 were given the placebo vaccine, but Robin Lachmann lucked out and received active vaccine), and two of the nurses volunteered to work as research nurses.

On Christmas Eve Elaine finished her online training to work as a vaccinator and did her first shift on 30 December in the UCLH vaccination hub, ‘Clinic K’. It was a case then of see one, do one, teach one as all those who hadn’t given an IM injection in years were brought back up to speed (top tip: for best results learn your IM injection technique from a nurse, not a doctor!). In the first few weeks the admin was all a bit laborious, as the consenting process was done on paper. When the team first switched to the online NIVS system that was even more painful as it was excruciatingly slow and prone to crash just as you were about to save the final record. But within a few weeks the backroom IT team got that sorted and now there is a pretty sleek system running seven days a week.

Both hospital hubs were giving the Pfizer vaccination and initially there was some nervousness about vaccination from staff with allergies. At UCLH the team were fortunate to be supported in the hub by the UCH allergy consultant and her CNS – which meant that there were very few staff who couldn’t be vaccinated. In the end we saw only one true allergic reaction (non-anaphylactoid) in the five months the clinic was open. The most common clinical issue was fainting – usually night-staff who had come off shift, and were tired, hungry and dehydrated. We soon learned to send someone out to the queue with drinks and snacks to prevent that. There was never any shortage of food in the hub – local businesses and often other staff members were always dropping food off – not the place to work for anyone trying to lose weight!

Clinic K has just closed and in total has vaccinated 51,284 staff of UCLH and local hospitals, London ambulance staff, social care staff and volunteers, dentists, interpreters, and patients of the hospital who lived locally and were listed as clinically extremely vulnerable. The hospital has also supported the opening of large local community vaccination sites – at the Francis Crick and the Islington Business Centre. A community vaccination bus is also trundling around to local areas – adding some additional jeopardy of trying to hit the deltoid as the bus sways whenever anyone walks onto it!

All of the large vaccination centres throughout the country rely on a team with diverse skills - operations manager, nurse in charge, temperature checkers, volunteer queue managers, administration staff, pharmacists, the allergy team, domestic staff, vaccinators, and nurses monitoring people post-vaccination etc. The photos show Uma surrounded by some of the team at RFH (Maria, Lani and Byrah), and in the second photo, the UCLH ops manager, Sarah, volunteer, Mark, and nurse in charge, Betty, who kept everything running smoothly at UCH.

Uma was also part of the BAME group at RFH and attended and contributed to the discussion regarding vaccine hesitancy and to improve vaccine uptake. She told us that “One morning in early February, I was in clinic and happened to chat with one of the domestic staff about vaccinations and she said she wasn't going to have the vaccination. I listened to her concerns and why she was not going to take up the vaccine and answered as many questions as I could. That afternoon, I went down to the Atrium to start my shift as a vaccinator. I was delighted to see the staff I had had a chat with that morning was down at the Atrium speaking with the admin team to book a date for the vaccine! This was a very rewarding experience and I realised that many staff probably don't access the extensive information provided on Freenet, our hospital communication website on safety of Covid 19 vaccinations. Since then, I have had many one-to-one chats in the canteen and elsewhere, listening to the genuine fears people had about vaccines and it was fulfilling to alleviate some of their fears and seeing some even changing their mind and coming forward to have the vaccine.”

The UCLH hospital clinic closed on May 7 – but the community centres remain open and the vaccination bus continues its day trips.The RFH and Barnet Hospital vaccination sites closed on April 15, having given over 38,000 vaccinations to health care staff and clinically vulnerable patients living locally; the Chase Farm site closed at the end of April. The community vaccination centre based at StoneX Stadium (originally part of the Olympic Stadium) remains open. It is run by Royal Free London and staffed by volunteers from the Royal Free Charity, RFL and healthcare staff across north central London.

For both of us it has been a real pleasure working in the centres – it has felt like such a positive thing to do amidst what has been such a difficult year. Whilst the clinical trial data looked very promising – it has been really fantastic to see that those results have been matched in the real world. It has been an opportunity to meet a lot of people from all parts of the hospital and across the care sector in London, and very moving to meet COVID survivors from ITU and those who have lost family members during the pandemic.

Vaccinating in the community
Gauri Krishna, Clinical Research Fellow, UCLH

GP practices signed up to participate in an enhanced scheme before 7th December 2020 to provide vaccination hubs in the community. I received vaccinator training via my local hospital and GP surgery on 7th January 2021. I was then able to volunteer as a vaccinator in my local community.

My training group consisted of retired GPs and registered healthcare professionals from the NHS. I was first deployed at the GP surgery site to observe a few injections done by the clinical nurse specialist followed by which I had to administer a couple under the watchful eye of my trainer. After the training, I was incorporated into one of the roving teams with a mixed skill set consisting of 2 x vaccinators (1 lead & 1 support), 1 x vaccine manager (nurse leading vaccine reconstitution and cold chain management), 1 x post vaccine observer (paramedic), and 1 x team admin. We were due to starting vaccinating on the 22nd of January at our local care home. Prior to the V-day, we had extensive planning and meetings with the care home staff to ensure good communication and to iron out any problems.

Unlike the hospital setting, a single day of vaccination in the care home required 4 days of planning. This was quite daunting because hospital settings are far more controlled environments, and it is difficult to plan for all the variables in the community. Our team lead had checked the

covid-19 testing results for staff and residents on D1 of planning. He had also reviewed all the medications and allergies. Based on numbers provided by care home staff vaccine provision was done for the roving vaccination. We also had to review care staff vaccination and reserve lists, consent grouping and assurance. There was a separate day of cold chain training by the lead pharmacist, review of our vaccination training, site assurance and sign off.

On the day of vaccination, we reported at 07.30 at the GP surgery and did a debrief with a final check. We arrived at the care home at 08.30. We had a designated area of the care home where we did a final check on residents. We used this same area to reconstitute and deliver vaccines. There was so much preparation and communication that although it seemed like a daunting proposition in the beginning, once we were set up, the vaccination proceeded without any administrative or clinical glitches.

I worked on that day with an excellent lead, care manager, nurse, first aider and admin staff. The whole process which included vaccinating 18 residents and 8 care staff took about 4 hours which included a mandatory tea break where we polished off some custard cream biscuits. At the end, we had a session conclusion which included a debrief with care home and vaccination team, pack-up, and return to the primary care site.

There was a real sense of community and belonging during the process and it was lovely to meet and work with retired health care professionals back in the training. Everyone wanted to beat this pandemic especially as the residents had seen it up, close and personally (there were a couple of unfortunate Covid related deaths in the care home).

The residents were charming and excited to get the vaccination done and we couldn't have asked for a better cohort to vaccinate. From stories about surviving the world war to wanting to see their first great grandchild, there was great enthusiasm for this marvel that was going to save mankind.

Living With Long COVID
Rachel Gould, Lead IMD/NBS Nurse, BWCFT & BIMDG Nurse Co-Chair

On 23rd December 2020 I left work, saying goodbye to friends in the office, putting on my email out of office and headed out excited for Christmas. Christmas Eve I did the shopping for our household and my parents, then we were settled at home for Christmas, just 3 of us observing the rules. On Boxing Day I woke feeling like I had been hit by a bus, unable to lift my head off my pillow, tight chest, banging head, high temperature. Our daughter had gone to bed on Christmas day with a headache and feeling sick, so I did my lateral flow test…..positive…..so as a family we went off to Birmingham Children's Hospital Covid Swabbing site for our PCR test. This was the start of my journey with COVID. Later that evening our results were back, as a family we were all positive!

Our daughter was unwell with temperatures and general aches and flu like symptoms for two days. My husband was poorly with a cough, was febrile and had fatigue for around two weeks and took a few more weeks to get back his fitness to take up his running (he is an ultra-marathon runner). For me, it was more problematic. I had three admissions to hospital throughout January. The first was by ambulance, called by 111 due to my decreased oxygen saturations, tachycardia and breathlessness. On admission I was dehydrated, required high flow oxygen, steroids, antibiotics and luckily was given a cubicle for a few days due to diarrhoea and vomiting. At least I got small amounts of rest that I wouldn't have managed in the open ward. My chest x-ray showed pneumonia as well as the Covid, so I knew I was in for a while and every day hoped that I would continue to fight and not escalate into ITU. My second admission was as a walk in. I was going up for review anyway so I went up to Hospital for my appointment, although my GP had suggested I go back as my oxygen saturations were low again and I was struggling at home. I had a liver ultrasound and was directly admitted, again on oxygen and steroids, antibiotics and further IV

fluids and this time a CT scan to rule out a pulmonary embolism. (PE) The third admission was with centralised chest pain with a further CT scan, again to rule out a PE. During each admission I saw the other side of being a patient, both the amazing side of how hard the staff worked under

the immense pressure the Pandemic added, but also the vulnerability of being a patient who was scared, had no visitors and confined to a cubicle.
I am now left with Long Covid or "Post Covid 19 syndrome" as it is most recently being called. Nothing could have prepared me for this. Those that know me, know that I am my happiest when juggling many things. I am a busy person, both in work and in my social life and have many volunteer activities. Living with Long Covid has halted this and there are no answers as to when things will improve. There are lots of people with Long Covid and many people in the medical world are now trying to find answers for what we are experiencing. The main daily concerns I have are a chronic headache that hasn't left me since Boxing day, that doesn't respond to the traditional headache medicines (I have trailed many), brain fog, lack of concentration and extensive fatigue.

The fatigue is very hard to explain to people that haven't had Long Covid. Simple tasks such as changing a bed takes all the energy for that day and the next where I need to rest and sleep. I have started to learn how to pace throughout the day so I can undertake small tasks without crashing, but walking around a park is still beyond me at the moment. There are other symptoms that come and go including muscle pain, shortness of breath, tachycardia, diarrhoea and vomiting, dizziness and hair loss. Days that I feel well and hoping that I am turning the corner, so far have been followed by days that I can't get out of bed. This is known amongst the Long Covid support group as "Coronacoaster" and why we try so hard to ensure we don't do too much, that means our body will then experience a "crash".

I have listened to many of the webinars and read many of the articles about Long Covid with interest and in the hope I may find something that will help. There has been some speculation as to links with mitochondrial disease; mast cell deactivation and Chronic Fatigue syndrome. Others have speculated that the virus might be hiding in the body like we see in Epstein Barr virus (EBV). (1) Alternatively, that it might be a result of a persistent immune response triggered by the virus that then causes inflammation and damage to other parts of the body (2). Some people have struggled with Long Covid for over a year now and hopefully research will start to find some answers that will help to improve the symptoms, so some normality can be resolved to our lives. The hardest thing is not knowing how long these symptoms will continue. Unravelling the cause of Long Covid will not only help make it easier to diagnose, but will offer hope to people suffering and provide more effective treatment of the long term symptoms.

I hope that day by day I am improving and that I can return to work soon and be back to the job I love and miss and to my role as BIMDG nurse co-chair. Love to you all and I hope you all stay well.

Ref : 1/2. https://royalsociety.org/blog/2021/02/what-do-we-know-about-long-covid/

Covid-19 – Impact on the Newborn Blood Spot Screening Programme Prof. Jim Bonham

The Newborn Blood Spot screening programme in the UK screens all babies for nine serious disorders. Six of these are metabolic conditions: phenylketonuria, medium chain acyl CoA dehydrogenase deficiency, isovaleric acidaemia, glutaric aciduria type 1, maple syrup urine disease and homocystinuria (pyridoxine unresponsive). The remaining three are: sickle cell disease, congenital hypothyroidism and cystic fibrosis.

Three of the IMD's (IVA, MSUD and MCADD) are considered urgent enough to require Saturday morning/Bank Holiday reporting to avoid delays in to treatment. There was therefore heightened

awareness for all our screened disorders, but these in particular, that disruption due to Covid may pose a risk to babies.

The 'First Wave' of Covid cases in the UK began in March of 2020 and showed a peak of cases occurring during April, this resolved to significant extent during May and new infections continued to decline until the first week in August.

Assessment of community transmission during September and October showed a resurgence of the virus and the prevalence of cases doubled in 20 days during October, this 'Second Wave' peaked early in November 2020 and while the number of deaths did not peak until 25th November, the number of cases began to decline, helped by a national lockdown which began on 5th November and ended on 3rd December 2020.

During December 2020 a new variant of Covid-19 with significantly increase transmissibility became more prevalent, particularly in London and the South East, this led to the announcement of a new 'Tier 4' on 19th December 2020. Despite these new arrangements the number of new cases has continued to rise leading to a new national lockdown, announced on Monday 4th January 2021, we are in May 2021 beginning to restore the freedom to travel and meet as the number of cases and deaths decline.

Throughout this time the Newborn Screening Blood Spot Programme has been well preserved and this is a testimony to the hard work of midwives and other health professionals in collecting samples, the laboratory staff who have maintained work flows and turnaround times when analysing and reporting the 15,000 samples received each week and the doctors, nurses and dietitians who have received and treated the 1,000+ babies who are identified each year with a condition suspected as a result of the testing undertaken.

The Blood Spot Programme prepared a report that could potentially be used to guide planning and action in any subsequent periods of increased disruption due to the Pandemic.

In particular we identified those aspects that worked well:

- Staff at all levels demonstrated great commitment and dedication.
- The public maintained confidence in the programme and although some did decline testing due to Covid early in the first wave, the numbers involved were very small, approximately 1:2,000 of those offered testing. These were subsequently re-offered testing as part of the 'restore' strategy.

- Regular weekly communication with the screening laboratories provided both useful insight from a national perspective and reassurance to labs that that they were part of a national programme. It also offered a means of feedback within PHE.
- The Newborn Screening Failsafe System (NBSFS) which tracks newborn screening samples on all babies in the born and resident population from birth was a huge asset in areas where any problems arose – thankfully these were rare, it also provided reassurance.
- National co-ordination and timely production of technical advice to coincide with the first day of the period of social restrictions on 23rd March 2020 helped support labs and midwives to maintain services in a difficult situation.
- Regular virtual meetings within the national blood spot team specifically to help manage the response to COVID-19 were a real asset.
- Regular communication with PHE QA Team, the Screening and Immunisation Teams and NHSE/I provided excellent forums to share data, information and intelligence.
- A provision for logged queries from laboratories and others provided a sense of dialogue and support. Both queries and responses together with the response time were recorded. 39

  queries were logged and a response was provided for more than half of these within 2 hours of their receipt.

And also those areas that could have been improved:

- Robust and rapid routes for communication which empower programme teams to disseminate important messages quickly throughout all aspects of the screening pathway (maternity unis, specialist units where babies are tested, those involved with sample transport, the screening laboratories, NBSFS, the Child Health Information Systems, the clinicians receiving referrals, QA Teams, Commissioners) and log their progress and receipt should be planned well in advance.
- The NBSFS, while a pivotal asset on behalf of born and resident babies does not accommodate “movers in”. This vulnerable group, in terms of their healthcare needs, were potentially left at risk by this omission.
- The transport of samples, despite best efforts, was at times erratic and unpredictable resulting in at least three incidents. Transport of blood spot samples in general, is an area of weakness for the programme and it may be helpful to consider a tracked service with guaranteed 48h delivery.
- Laboratory contingency plans, happily not needed, depend in large part on sending samples to a neighbouring laboratory. In an epidemic it is highly likely that contiguous services may be affected together. We need to review contingency arrangements to reflect this risk and consider how services can be strengthened during an epidemic affecting staff and include these plans, for example greater cross training, within general contingency arrangements.

On this basis we agreed that future planning in the event of further waves should include:

- Assembly of a team and an initial assessment of the situation.
- Use and scheduled scrutiny of NBSFS to identify problems that may arise in the area(s) affected
- The need to consider adaptation to operational practice to preserve services.
- The communication of advice to providers and other stakeholders affected including: midwifery services and laboratories in a timely way.
- Maintenance of a scheduled regular dialogue, perhaps weekly, with laboratories to assess and collate current status with regular feedback.
- A clear and identified route to handle queries and document responses during the active phase of the epidemic.
- Contact with third party providers including Royal Mail, Northgate IT, and providers of equipment, IT systems and reagents.
- Identified routes to report progress and update internal stakeholders within PHE and NHSE including the QA teams and other screening programmes.

- A route to ensure that Screening laboratory contingency plans are collected and stored by the programme.

Conclusions

We have learned a lot during the 20/21 year of Covid. It has re-inforced and made plain, the often trite sounding message that *'our staff are our greatest asset'* but they really were, at every level.

It also emphasised the importance of the processes that happen outside the laboratory including sample transport and the need for rapid, flexible and effective communication across a segmented screening pathway. National architecture such as the Newborn Screening Blood Spot Programme and the Newborn Blood Spot Failsafe Solution were invaluable and the coherence offered by professional organisations such as the UK Newborn Screening Laboratory Network, MetBioNet and BIMDG proved a great resource.

It is a tribute to the individuals and organisations involved that our national newborn screening blood spot programme was maintained during this most difficult of years and that, so far as we are aware, no baby with a serious disorder was missed or had their treatment significantly delayed during this challenging period.

BIMDG Molybdenum Cofactor Deficiency Workshop report. Bernd Schwahn, MFT

The long-planned BIMDG workshop "Molybdenum cofactor deficiency: How to diagnose, when to treat and what to expect" took place as a virtual event on 13th May 2021. The meeting was accredited by the RCPath with 4 CPD points and sponsored with an unconditional educational grant by OriginBiosciences. It was attended by over 80 participants, mostly from the UK but also a good number from overseas. The programme covered biochemical and clinical aspects of sulphite intoxication disorders and in the second half focused on current practice and experience with pharmacological treatment of Molybdenum cofactor deficiency type A in view of the recent licensing of cPMP for the treatment of MoCD-A in the US. All talks were delivered live and participants could contribute with questions and comments in the chatroom.

Prof Guenter Schwarz from Cologne presented an overview of the biochemical disturbance and current pathophysiological concepts of sulphite toxicity in disorders of molybdenum cofactor synthesis and sulphite oxidase deficiency. Besides secondary inhibition of mitochondrial energy metabolism there is an increasing recognition of excitotoxic effects of S-sulphocysteine and of a disturbance of H2S homeostasis contributing to specific manifestations.

Dr Lynette Fairbanks from the Purine Research lab in London presented data on the incidence of MoCD and isolated sulphite oxidase deficiency and of the current biochemical and genetic diagnostic approach in the UK, including practical information on sample requirements, turnaround times for biochemical and genetic testing, reliability of tests and diagnostic pitfalls in the analysis of sulphite, SSC and purines. Participants had a lively discussion in the chatroom of the meeting and after the talk, reflecting variations in practice and availability of tests. There is no reliable and easily available rapid test to diagnose sulphite intoxication and clinicians have to rely on a typical constellation of clinical and biochemical abnormalities.

Prof Ronen Spiegel from Afula presented data of a large international study on the natural history of Molybdenum cofactor deficiency and included recently published data about that of isolated sulphite oxidase deficiency. As with other well-known classical IEMs, the clinical spectrum of sulphite intoxication disorders is widening with identification of milder and atypical manifestations. The clinical sequelae of severe sulphite intoxication are however relatively uniform.

A few genotypes are associated with milder phenotypes and there is no unequivocal correlation between clinical outcomes and biomarker levels.

Dr Albert Misko from Boston presented his studies on brain imaging in sulphite intoxication disorders and delineated spatial and temporal patterns that differ in detail from those seen in HIE and primary disorders of mitochondrial energy metabolism. Phases in the evolution of brain injury can be separated in acute, subacute and chronic. One specific feature of MoCD and ISOD is persistent diffusion restriction in parts of the brain in the subacute and even chronic phase which is not seen in hypoxic brain injury.

Dr Bernd Schwahn from Manchester gave an overview of current supportive, dietetic and pharmacologic treatment options for MoCD-A. He presented the development of protocols for the use of cPMP over the course of the last 12 years and available treatment data. Looking at clinical outcomes of patients from personal experience there was a dichotomy of outcomes depending on whether cPMP treatment could be initiated prior to excitotoxic cell death or not. Outcomes are stable in the long term with sustained biochemical normalisation and no secondary deterioration in treated patients. The increased survival rate of treated patients compared to matched untreated patients (irrespective of their neurological outcome) was used to prove efficacy of cPMP and was instrumental in obtaining a license for cPMP from the FDA.

Prof Francjan van Spronsen from Groningen briefly presented his experience in treating children with MoCD with cPMP and the start and stop criteria for cPMP treatment that are used in the Netherlands. This was followed by a debate with Bernd Schwahn over pre-formulated questions about treatment criteria and ethical and practical aspects of the delivery of cPMP substitution. The debate was meant to both inform and stimulate participants to take part in a subsequent panel discussion. Questions of the audience were addressed and a few participants reported about their diagnostic approach.

The meeting concluded with the expressed intention to create clinical guidelines for the management of MoCD and ISOD and perhaps have another physical meeting in 1 – 2 years. Despite all the shortcomings associated with a virtual meeting, the feedback from 28 participants who sent back the evaluation sheet was very positive. Individual presentations and general aspects of the meeting were scored as good and excellent. A big thank you to all presenters who delivered excellent talks and kept in time despite their enthusiasm, to all participants who took an interest in this niche topic and to the organiser Jacqui Hunter for her expert support!

BIMDG Workshop News

WORKSHOP: Specialized Enzymology Laboratories

There is a plan to arrange a virtual workshop for specialised enzymology laboratories – date to be confirmed (probably July 2021). This will be led by Katie Harvey, Principal Clinical Scientist at Great Ormond Street Hospital. It will be a closed workshop – open only to staff of the enzymology laboratories – but if you think you have been accidently left off the invite list then please do contact Katie directly - *Katie Harvey@gosh.nhs.uk*.

There have been a number of challenges in the last few years that have particularly or uniquely affected specialised laboratories. These include UKAS accreditation, reagent supply, pathology improvement initiatives, advances in genomic medicine (and its impact on diagnostic pathways) and pharma involvement in metabolic testing. More recently COVID has had an impact on specialised laboratories and is likely to have an impact on demands for the future. We are hoping that a workshop will provide a forum for us to discuss these issues and support each other in

dealing with these challenges. It is also hoped we might move towards developing best practice guidelines to provide a framework for shared standards.

A questionnaire has been developed and emailed to potential participants by Katie. Please could each lab try and return the questionnaire no later than 1 June.

WORKSHOP: How to Improve IMD Monitoring with Patient Collected Samples

Friday 8th October 2021 by TEAMs/ZOOM - (Preliminary Programme)

Prior to the COVID pandemic much work was progressing on the use of patient collected samples. The arrival of COVID has intensified the efforts we need to make to monitor patients effectively through alternative methods "at a distance" and thereby reducing the need to physically attend clinical out-patient settings. This BIMDG workshop sets the scene for the challenges we face in order to help assist develop a work-plan to take this important work and opportunity forward.

10-00 Welcome and Introduction – Dr Elaine Murphy, London – Chair of the BIMDG

(To include background of the work already done or in place).

Morning Session - Chair Dr Graham Shortland, Cardiff

10-15 – Getting the Sample – Metabolic Clinical Nurse Specialist/Dietitian

Current practice and education for parents - (20 min talk – 15 min questions/discussion)

10-50 – Blood spot quality and testing issues -Impact upon target treatment ranges.

Professor S Moat, Cardiff (25 min talk – 15 min questions/discussion)

11-30 – Applying the results of Patient Monitored Samples to clinical practice – Strengths and Weaknesses

Dr S Santra, Birmingham (20 min talk – 15 min questions/discussion)

12-05 – Chair summing up.

12-20 – Break

Afternoon Session - Chair – Dr Helena Kemp, Bristol

13-00 – New blood collection devices and laboratory technologies

Dr R Carling, London - (20 min talk, 10 min questions/discussion)

13-30 – 14-30 – Breakout – optional one of three workshops

(What have we learnt from the morning session - 15 mins,

What are the key areas of agreement – 15 mins

Identify the key areas for future work – 15 mins)

1. Patient sample collection

2. Analytical/Laboratory aspects

3. Clinical conditions reviewed (chair - Dr Stephanie Grunewald , GOSH, London)

14-30 to 14-40 - Break

14-40 – All participants

Each Chair to feedback on their discussion.

15-30 – Chair summing up

15-45 – BIMDG Chair Dr Elaine Murphy – next steps

16-00 - Close

BIMDG Conference News

The next BIMDG annual conference will be organised by the Newcastle team in June 2022. The theme is 'Current challenges in IMD' and more details on the precise date and programme will follow soon. We hope to be back to our standard format of an in-person 2 day meeting, with parallel sessions on the first morning, the AGM and a social event.