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Free Scientific Paper 1

Title **Diabetes mellitus is not a driver of poor Tuberculosis treatment outcomes in a UK cohort**

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Abstract

Introduction
The effect of diabetes mellitus (DM) on active tuberculosis (TB) treatment outcomes currently remains unclear.

Methods
Retrospective observational cohort study of all notified TB cases from Northwick Park Hospital over a five-year period. World Health Organization criteria were used to define TB treatment outcomes.

Results
TB was microbiologically confirmed in 64.3% of cases (539/838). The prevalence of DM at TB treatment initiation was 15% (126/838). Most DM patients (83.3%, 105/126) were on hypoglycaemic treatment and well-controlled (median glycated haemoglobin HbA1c 53.5mmol/mol). DM patients were older and more likely to be of Asian ethnicity. They had a higher pre-treatment weight but were less likely to gain weight during treatment. Time from presentation to treatment initiation was longer (median 87.5 vs 63 days, $p < 0.001$), while they were significantly more comorbid (median Charlson Comorbidity Index 3 vs 0, $p < 0.001$). Overall, favorable treatment outcomes were recorded for 89.5% of patients (87.7% vs 89.8% for DM and non-DM patients respectively, $p = 0.52$). In multivariable analysis, neither DM (odds ratio 0.49, 95% confidence intervals 0.23 – 1.04, $p = 0.06$), nor poorly-controlled DM (odds ratio 0.93, 95% confidence intervals 0.12 – 7.29, $p = 0.95$) were associated with unfavorable TB treatment outcomes. Independent predictors of unfavorable outcome included age, lung cavitation, chronic neurological disease, and the presence of a malignant neoplasm.

Discussion
In a well-resourced setting, with predominantly well-controlled diabetes patients on treatment, DM was not an independent predictor of unfavorable TB treatment outcomes.

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Free Scientific Paper 2

Title **COVID-19 vaccine hesitancy among a UK cohort of patients living with HIV**

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Abstract

Introduction
There is evidence that people living with HIV (PLWH) have a higher risk of death and hospitalisation from COVID-19, particularly those with low CD4 counts or detectable viraemia. There have been calls to prioritise vaccination for PLWH globally, with early access to vaccination available in the UK.

Methods
We performed a retrospective review of 200 sequential patients booked into HIV clinic within Sheffield Teaching Hospitals between November 2021 and January 2022 collecting HIV treatment and vaccination uptake (VU) data.

Results
In this cohort of PLWH, triple VU by age closely matched national vaccination rates (89% in the 60-64 age group vs 84% nationally and 42% vs 43% in the 30-39 age group). Within the cohort there was no significant difference in VU between ethnic groups (white 89%, black 90%, asian 100% (p=0.57)). There was a significant difference in VU in those with detectable viraemia, with 42% having received $\geq$3 vaccinations, compared with 69% in the undetectable group (p=0.016). There was a similar difference for those with known treatment adherence issues (50% vs 70% (p=0.002)).

Discussion
To our knowledge, this is the first study looking at COVID-19 vaccine uptake amongst PLWH within the UK. We identified patients most at risk of severe outcomes from COVID-19, are the least likely to be fully vaccinated. The same methods used to engage patients with anti-retroviral treatment is likely to be of benefit in increasing VU. Understanding the reasons for both poor adherence and poor VU would enable improved healthcare engagement with this population.

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Free Scientific Paper 3

Title **Pathway to a controlled human infection model for *Leishmania major***

Authors Vivak Parkash[1,2], Helen Ashwin[1], Georgina Jones[3], Jovana Sadlova[4], Barbora Vojtkova[4], Charles Jaffe[5], Petr Volf[4], Alison Layton[1], Paul Kaye[1], Charles Lacey[1]

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Abstract

Introduction
We describe the development of a controlled human infection model (CHIM), using natural sand fly challenge, for selection of candidate vaccines for the neglected tropical disease leishmaniasis.

Methods
A public involvement (PI) exercise determined acceptability of a sand fly biting study on humans. Study design, potential adverse events, and endpoints were reviewed. Subsequently a pathogen-free sand fly biting study on human volunteers evaluated biting frequency and adverse effects. 12 healthy participants (mean age 40.2 ± 11.8 years) were recruited to 2 study arms (1:1) using either *Phlebotomus papatasi or P. duboscqi*, two vectors of *Leishmania major* (a candidate species for CHIM). Exposure using five female sand flies in a biting chamber took place over 30 minutes. Biting was confirmed by participant-reported sensation, investigator observation and microscopic examination of sand flies.

Results
The PI activity suggested sand fly biting on humans and use of an excision biopsy as treatment were acceptable as part of a CHIM. This fed into study design of a pathogen-free sand fly biting study. All participants sustained at least one successful sand fly bite with no serious adverse events recorded. Self-reported pain on a visual analogue score reached a maximum of 2/10 during the study. Corresponding assessment of sand flies confirmed that for each participant at least 1/5 sand flies had successfully taken a blood meal (mean 3.67±1.03 bites/participant).

Conclusions
These results confirm efficacy, safety and acceptability of a protocol for achieving successful sand fly bites on the pathway to a *Leishmania*-infected sand fly CHIM.

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Free Scientific Paper 4

Title **Synergy testing between Ceftazidime-Avibactam and Aztreonam: an evaluation of six laboratory methods**

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Abstract

Introduction
Some antimicrobial combinations display synergy, which may be beneficial when treating multi-resistant bacterial infections. There is no gold standard for synergy testing of Aztreonam (ATM) and Ceftazidime-Avibactam (CZA) for metallo-beta-lactamase (MBL) producing Enterobacterales. The aim of this study was to evaluate the most appropriate method for use in a busy diagnostic laboratory.

Methods
Six methods were evaluated as follows; (1) CZA and ATM discs placed 15mm apart; (2) CZA and ATM discs 18mm apart; (3) Simultaneous E-tests; (4) Sequential E-tests; (5) Perpendicular E-tests; (6) ATM E-test and CZA Disc.
25/94 carbapenemase-producing organisms from Cambridge University Hospitals met the inclusion criteria for synergy testing. The 25 isolates comprised of 12 Escherichia coli, 9 Klebsiella pneumoniae, 3 Citrobacter freundii and 1 Enterobacter cloacae. MBL enzymes included NDM-1 (n = 22) and IMP-1 (n = 3).

Results
In total 150 synergy tests were performed. Synergy was observed in 76/150 (51%) tests. A performance score considering cost, time, ease of set-up, ease of interpretation and heavily weighted for consistency of results and number of isolates showing synergy, was devised and Method 1 (CZA and ATM discs at15mm separation) performed the best.

Discussion
Further evaluation against a gold standard would be ideal. The ATM and CZA discs placed at 15mm apart performed best in detecting synergy against MBL-producing Enterobacterales. This method will be implemented in our diagnostic laboratory with the aim to generate a result in an actionable turn-around time for an additional therapeutic option against these difficult to treat organisms.

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Free Scientific Paper 5

Title **Outcomes of Tuberculosis contact tracing and predictors of success: a 10-year retrospective cohort analysis**

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Abstract

Background
The Covid-19 pandemic risks disruption to diagnosis and treatment of Tuberculosis (TB) globally, jeopardising the 2035 eradication target. Between 1990-2010 40.9% of contacts did not complete Tuberculosis (TB) contact screening in Birmingham, UK. Understanding screening outcome success is urgently needed to guide future resource allocation.

Aim
To evaluate changes made to TB screening since 2010. To identify predictors of contact screening non-completion, and of screening outcomes.

Methods
A retrospective cohort analysis of all index and contact patients in Birmingham between 2011-2020, with separation of Covid-19 data, and stratification of contacts by Pulmonary TB (PTB) or Extra-Pulmonary TB (EPTB) index infection. Univariate and multiple logistic regression models were used to identify predictors of screening completion and clinical outcome.

Results
3,255 index cases and 27,820 contacts were identified. Screening non-completion has improved from 40.9% of contacts to 25% since 2010. Contacts were less likely to complete screening if they were >65 years ($P=0.001$) had no BCG ($P<0.001$), were male ($P<0.001$ PTB, $P=0.02$ EPTB), had had TB themselves ($P<0.001$ PTB, $P=0.025$ EPTB), were a close contact ($P<0.001$), or were from the Indian subcontinent (PTB only, $P=0.019$). Contacts were significantly more likely to require treatment for TB if they were born outside the UK ($P<0.001$), were <65 years ($P<0.001$ PTB, $P=0.01$ EPTB), if they were male, close contacts, or of Black ethnicity (all $P=0.001$, PTB only).

Conclusions
Changes to contact screening since 2010 have substantially improved screening completion rates. Significant predictors of screening non-completion exist, which warrant further investigation and targeted screening support.

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Free Scientific Paper 6

Title **"My milkshake... it's better than yours!" - an outbreak of bacterial gastrointestinal illness fuelled by a social media craze.**

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Abstract

Introduction
We highlight a regional outbreak of Campylobacter from raw dairy milk (RDM) milkshakes, focusing on initial detection, then outbreak-control measures by the Health Protection Team (HPT).

Methods
In April 2021, HPT convened a multi-agency Outbreak-Control Team (OCT) after initial notifications of food-poisoning from Primary/Emergency Care sectors in Northumberland. Active case-finding was pursued via:

- case interviews
- outbreak awareness-alerts to GPs/Urgent/Emergency Care
- surveillance systems (based on case-definition / geography / exposures)
- online questionnaire to recent food-poisoning cases.

Multi-agency partnerships with Environmental Health / Food Standards Agency ensured a swift response.

Results
43 cases were identified in the outbreak (27 laboratory-confirmed Campylobacter, plus 16 strongly suspected based on clinical symptoms), aged 3-65 years, who had all visited a specific Northumberland dairy farm in the weeks preceding. Symptoms were typical: abdominal pain +/- (bloody) diarrhea +/- fevers +/- myalgia. 11 cases (all children) required emergency admission to hospital. The common exposure was they had all consumed RDM novelty milkshakes from a specific farm.

We present Epidemiological results (Epicurves of exposure dates, symptom-onset, which supported outbreak investigations and hypothesis development) and Microbiological results (whole genome sequencing (WGS) which matched Campylobacter isolates from the farm's milk storage tank to faecal samples obtained from multiple cases).

We present graphic representation of Outbreak Control measures.

Discussion
Clinicians should be encouraged to notify suspected cases if there is potential for an outbreak (i.e. not awaiting confirmation). Clinicians must aim to send diagnostic samples as WGS of pathogens is crucial to support outbreak investigations. Many cases consumed the contaminated milkshakes after they were popularised via social-media.

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Free Scientific Paper 7

Title **The Join Well Study: Chronic *Strongyloides stercoralis* infection in Fijian migrants to the United Kingdom serving in the Armed Forces**

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Abstract

Background
Strongyloides stercoralis infects over 300 million people globally. Infection is often asymptomatic, but fatal hyperinfection syndrome can occur in the immunocompromised.
There are few data on strongyloidiasis in Fiji. Following several cases of incidental serological diagnosis in Fijian-born UK Armed Forces personnel, a prospective cohort study was undertaken to investigate the prevalence of infection.

Methods
Fijian-born UK military personnel provided written informed consent for collection of baseline demographic data and screening tests: FBC for eosinophilia; serum for *S. stercoralis* IgG ELISA; stool for FEA concentration and microscopy, charcoal culture, and multiplex protozoa/helminth PCR. Subjects with any positive test result were offered follow up for assessment and treatment.

Results
167 participants were recruited between September 2021 and March 2022. Median age was 37 (IQR 27.5-43.5) years and median time in the UK 15 years (IQR 4-19). Eosinophilia (>0.5 x 109) was present in 53/152 (34.9%). Serology was positive in 67/162 (41.4%). Both these tests were positive in 38/152 (25%). *S.stercoralis* was detected in stool by at least one method in 9/71 (12.7%). Overall, 18.1%-31.9% of participants were estimated as having probable chronic strongyloidiasis.

Discussion
Using robust methodology, this study has shown an unexpectedly high prevalence of chronic strongyloidiasis in Fijian migrants, most of whom were asymptomatic. The possibility of strongyloidiasis should be considered in migrants with established or planned immunosuppression. The findings have led to an active response by the Defence Medical Services, including distribution of a Patient Safety Notice and institution of a Strongyloides Working Group.

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Free Scientific Paper 8

Title **Determining a potential alternative empirical antibiotic regimen for the treatment of neonatal sepsis in low- and middle-income settings using pre-clinical *in vitro* techniques**

Authors Christopher Darlow[1,2], Nicola Farrington[1], Laura McEntee[1], Adam Johnson[1], Jennifer Unsworth[1], Ana Jimenez-Valverde[1], Bhavana Jagota[1], Fernando Docobo-Perez[3], Ruwanthi Kolamunnage-Dona[1], Renata de Costa[4], Sally Ellis[4], François Franceschi[4], Mike Sharland[5], Michael Neely[6], Laura Piddock[4], Shampa Das[1], William Hope[1]

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Abstract

Introduction
Neonatal sepsis kills ~680,000 infants annually, predominantly in low and middle-income countries. The WHO currently recommends ampicillin and gentamicin in combination for the empiric treatment of neonatal sepsis. However, emerging epidemiological evidence demonstrate that this regimen is increasingly compromised by antimicrobial resistance. An alternative regimen that is affordable, efficacious and safe for use in neonates is needed. The hollow-fibre infection model (HFIM) is an *in vitro* model that allows replication of human-like antibiotic time-concentration profiles and examination of their effect on bacterial inoculua.

Methods
MICs of candidate antibiotics were determined for a panel of representative bacteria using the broth microdilution method. Selected antimicrobial candidates were examined in combination in dose-ranged HFIM experiments against a single CTX-M-14-producing *E. coli* strain to characterise each combination's pharmacodynamic interaction. Further HFIM experiments tested the efficacy of neonatal-like regimens of each candidate antibiotic combination against a variety of Gram-negative strains.

Results
The three pairwise combinations of fosfomycin, flomoxef and amikacin had a predicted spectrum of activity of >90% for the tested bacterial panel. All three combinations were synergistic in HFIM experiments, with respect to bacterial killing and prevention of emergence of resistance to fosfomycin and/or amikacin. All combinations demonstrated efficacy in HFIM experiments at killing bacterial strains to sterility where monotherapy with either constituent agent could not.

Discussion
All possible combinations of fosfomycin, flomoxef and amikacin are synergistic and demonstrate extended spectrum of activity. All three combinations are therefore going to be tested in a planned international multi-centre neonatal sepsis clinical trial.

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Free Scientific Paper 9

Title **Exhaled SARS-CoV-2 viral load kinetics measured by facemask sampling and its association with household transmission – a longitudinal cohort study**

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Abstract

Background
Few studies have examined the pattern of exhaled SARS-CoV-2 viral load (VL) over the course of acute infection. Using facemask sampling (FMS), we report the natural history of viral RNA emission from community-managed SARS-CoV-2 infections and their relation to household transmission.

Methods
Between December 2020 and February 2021, participants recruited within 24 hours of a positive polymerase chain reaction (PCR) on upper respiratory tract sampling (URTS) (day 0) gave FMS (for 1 hour) and URTS (self-taken) on 7 occasions up to day 21. Samples were analysed by RT-qPCR; exposed masked were processed by analysis of sampling matrix strips within the mask and symptom diaries recorded. Participants who transmitted to their households were assessed through reporting of URTS PCR analyses on household contacts.

Results
Analysis of 203 FMS and 190 URTS from 34 participants revealed similar overall patterns of VL change, peaking in the first five days following sampling; most individuals tested negative by day 10. URTS results were poor predictors of contemporary FMS result and symptom scores. Of 28 participants who had household contacts, 12 (43%) reported positive transmission. In contrast to URTS, negative FMS was associated with households negative for transmission on days 1 and 3 while frequency of transmission showed a biological gradient trend with peak FMS VL (negative VL, 0% household transmission, 1-1000 copies/strip: 20%, 1001 – 10,000 copies/strip: 50%, >10,000 copies/strip: 75%, p=0.07).

Conclusions
Exhaled viral load measured by FMS is highest in early infection and is an important route of SARS-CoV-2 transmission.

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Free Scientific Paper 10

Title **Lessons Learned from COVID Outbreaks in Prisons in the North East of England, 2020**

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Abstract

Introduction
The UK criminal justice system faced unprecedented challenges during the COVID-19 pandemic, with vulnerable prison residents at risk of infection and outbreaks causing considerable pressures. We assess the impact of COVID-19 outbreaks in North East England's prisons during 2020, to inform future outbreak control.

Methods
Descriptive epidemiology was performed using standardised data collected on all regional prisons (n=7) during 2020. Cases were defined as staff or residents positive for SARS-CoV-2 by PCR. Qualitative data from written questionnaires and semi-structured interviews of Outbreak Control Team (OCT) members and OCT minutes were coded by themes.

Results
Fourteen outbreaks from seven prisons occurred in 2020 (median size: 44 cases, IQR:16.5-188; median duration: 94 days, IQR:64-102 days), with 1862 cases reported (59.6% residents (median attack rate 2.9%, IQR 0.5-14.8%) and 40.4% staff (median attack rate 6.3%, IQR 2.9-21.5%)). Data from 34 questionnaires (45.9% response rate), 12 semi-structured interviews and 107 OCT minutes were analysed. Ongoing transmission was influenced by movement within the system, lack of social distancing and symptom concealment. Prison type and layout influenced the success of control measures. The impact on wellbeing of regime restrictions was a substantial challenge, although reductions in violence and self-harm were reported. Prison staff felt well supported during outbreaks and strong cross-sector relationships were key to the success of OCTs.

Conclusions
The prison environment, resident characteristics and pressures within the wider system presented unique challenges for controlling transmission. Learning identified from these outbreaks can be used to minimise the impact of future outbreaks in prisons.

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Free Scientific Paper 11

Title **Is confirmatory testing with penicillin gradient test strips necessary for cases of streptococcal infective endocarditis in the age of automated susceptibility testing (AST)?**

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Abstract

Introduction
Streptococcus spp. are important pathogens in infective endocarditis (IE). The requirement for synergistic gentamicin in treatment guidelines (European, US) is partly determined by the penicillin minimum inhibitory concentration (MIC), categorising isolates as susceptible (≤0.125µg/mL or ≤0.12µg/mL) or relatively/fully resistant (0.25-2µg/mL or >0.12µg/mL).
Although automated antimicrobial susceptibility platforms (e.g. BD Phoenix M50™ system) are widely used and generate MIC-level information, many centres use gradient test strips (e.g. E-testsTM) for confirmation. We audited concordance between testing modalities, and assessed how discordance would have affected IE guideline interpretation.

Methods
We compared penicillin MICs from the BD Phoenix (AST) with confirmatory E-Test MICs for streptococci identified (using MALDI-ToF) in blood cultures in a single centre in Oxfordshire, UK, Jan 2017-Jun 2020. We examined how differences in MICs would have affected treatment according to ESC (European) and IDSA (US) guidelines for the management of native valve IE.
Results: 1273 Streptococcus spp. isolates cultured from blood were analysed. Of these, 47 (3.7%) had both penicillin E-test and AST performed. 23/47 (49%) of MICs were fully concordant; of 24 discordant MICs 18/24 (75%) differed by 1 dilution, and 6/24 (25%) by 3 dilutions. E-testing changed treatment in 2 (ESC) and 8 (IDSA) patients respectively, but only for cases with MICs within ≤2 dilutions of the guideline breakpoints.

Conclusion
MICs from AST (BD Phoenix) and E-tests correlate well for streptococcal isolates that are highly susceptible or intermediate Our data suggest confirmatory E-testing appears necessary only if MICs are within ≤2 dilutions of the guideline breakpoints.