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The Broad Street Pump

Post vaccine genomic evolution of serogroup 19 invasive pneumococcal isolates in NSW

Rebecca J. Rockett,[1]#, Shahin Oftadeh[1,2], Nathan L. Bachmann[3], Fanrong Kong[2], Gwendolyn L. Gilbert[1,4], Vitali Sintchenko[1,2,4]

[1]Centre for Infectious Diseases and Microbiology - Public Health, Westmead Hospital, Westmead, NSW, Australia. [2]NSW Pneumococcal Reference Laboratory, Institute of Clinical Pathology and Medical Research - Pathology West, Westmead Hospital, Westmead, NSW, Australia. [3]Centenary Institute, The University of Sydney, Sydney, NSW, Australia. [4]Marie Bashir Institute for Infectious Diseases and Biosecurity, The University of Sydney, Sydney, NSW, Australia

Streptococcus pneumoniae is a highly recombinant Gram positive bacterium which is both a commensal and pathogen of the respiratory tract.[1] Invasive pneumococcal disease (IPD) occurs when virulent strains enter the blood stream and cause a range of syndromes, most importantly pneumonia, meningitis and sepsis. The burden of IPD remains greatest in children under 5 years of age and the elderly and is associated with high morbidity and mortality. A relatively small number of the >90 serotypes are commonly associated with IPD and the polysaccharide capsule is considered the most important pneumococcal virulence factor.[2]

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Seven of the most common IPD-associated serotypes were used as antigens in a polysaccharide-protein conjugate vaccine (PCV-7) that has been publically funded for all infants in Australia, since 2005. The incidence of IPD dramatically declined in countries where PCV-7 was widely used, due to individual protective and herd immunity. [3–5] In Australia, rates of IPD in children less than 5 years of age declined by 96% between 2004 and 2008.[6,7] However, the success of PCV-7 was tempered by the increased numbers and proportions of non-vaccine serotypes causing IPD. In Australia a 196% increase in non-vaccine serotypes was observed between 2004 and 2008, notably with a four-fold increase in the prevalence of serotype 19A.[6] This concerning increase in serotype 19A IPD was noted throughout the world, and was associated with high-level antibiotic resistance in many countries, [8–10] but less so in Australia, where most 19A IPD isolates were of intermediate susceptibility [11]. To address this increase in IPD caused by serotype 19A pneumococci this antigen was included in the 13-valent polysaccharide-protein conjugate vaccine (PCV-13). In Australia PCV-13 replaced PCV-7 vaccine in 2011, however three years after PCV-13 introduction 32.5% of IPD in children >5 years of age is still caused by Serogroup 19 pneumococcus.

In countries with routine conjugate vaccination, IPD is now predominately attributed to non-vaccine serotypes, which fill the ecological niche vacated after vaccine serotypes are removed. Furthermore, evidence of 'capsular switch' recombination has been reported.[12] This occurs when highly successful, and often multi-drug resistant (MDR) pneumococcal clones recombine to replace their vaccine capsular, with non-vaccine capsular, types.[12–15] These serotype switch variants emerged rapidly after the introduction of PCV-7, and caused concern for the long-term efficacy of pneumococcal vaccines. Genomic 'hotspots' of recombination have been described on either side of the capsular biosynthesis (*cps*) locus, which is flanked by the penicillin binding protein genes, *pbp*1a and *pbp*2x. [16] Therefore recombination within these hotspots enables pneumococci to escape both vaccine and antibiotic pressure. Recently whole genome sequencing (WGS) has been applied to examine pneumococcal recombination due to antibiotic and vaccine pressures.[17] WGS provides high-resolution molecular typing of isolates and offers important insights into recombination and variability within the genome than traditional multi-locus sequence typing (MLST) or multi-locus variable number of tandem repeats analysis (MLVA) approaches. The high-resolution monitoring of pneumococcal evolution enabled by WGS becomes essential for informing design of future pneumococcal vaccines and reducing the incidence of IPD. The aim of this study was to apply WGS for genome-wide analysis of the evolution of serogroup 19 (serotypes 19F and 19A) IPD isolates from children under 5 years of age in New South Wales (NSW), Australia, in the year before (2004), and three years after (2008) routine PCV-7 vaccination was introduced.

Materials and Methods

All serogroup 19 IPD isolates from children under 5 years of age, referred by public and private pathology providers to the NSW Pneumococcal Reference Laboratory (PRL) in 2004, and 2008 (n= 101) were included in the study.

Serotyping was performed by Neufeld's Quelling test, using pool, type and factor specific antisera (Statens serum Institut, Copenhagen, Denmark). Extraction was performed using the Blood and Tissue Mini Kit (Qiagen, Australia). DNA libraries were prepared using the Nextera XT Library Preparation Kit. Multiplexed libraries were sequenced using paired-end 150bp chemistry on the NextSeq 500 (Illumina, Australia).

Sequencing reads were trimmed, based on a minimum quality read score of 20. Trimmed reads were *de novo* assembled using SPAdes and annotated using Prokka.[18,19] Extended whole genome sequence typing (ST) was conducted *in silico* using the SeqSphere+ software (Ridom, Germany). Core allelic profile (1241 genes) was used to cluster isolates using Bayesian Analysis of Population Structure (BAPS) software. [21]

Results

Table 2. Serogroup 19 isolates from children < 5 years of age, in NSW, 2004, 2008.

	Serogroup 19/total (%)		P value
Year	2004	2008	
Total IPD isolates from children <5 yrs (all serotypes)	245	99	
Total serogroup 19	41 (16.7)	60 (60.6)	p=0.0001*
Serotype 19F	33 (13.5)	4 (4.0)	p=0.0001*
Serotype 19A	8 (3.2)	56 (56.6)	

* Statistically significant increase in number and proportion of serotype 19A in 2008

Figure 1. Minimum spanning tree of 101 serogroup 19 IPD isolates based on the allelic profile of 1241 genes.

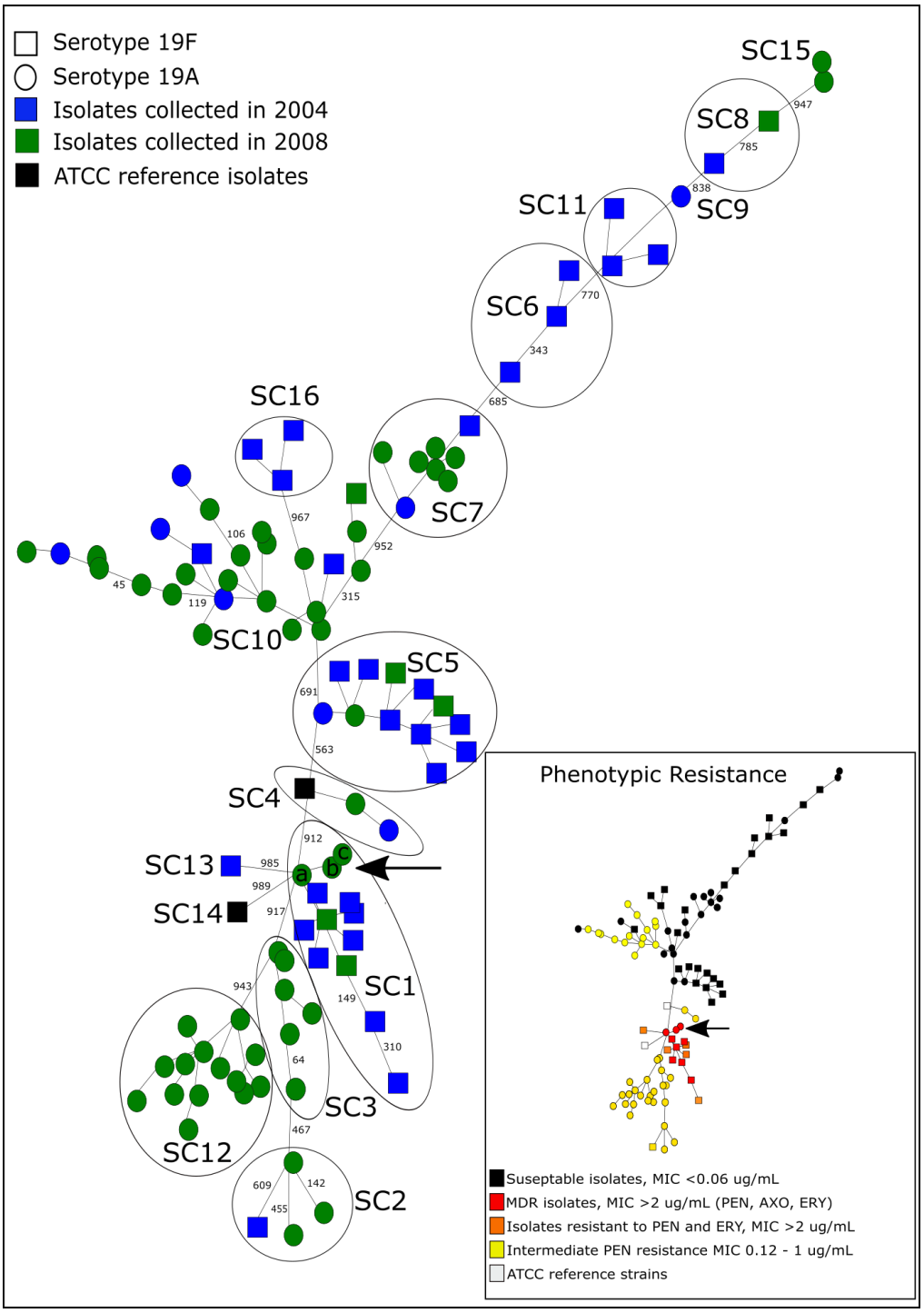

Figure 1. Minimum spanning phylogeny of the 1241-gene core genome (cg) sequence types are represented above. Serogroup is denoted by the shape of isolate node (squares represent 19F serotype and circles represent 19A isolates). The colour of the node depicts the year the isolate was collected, blue nodes represent isolates collected in 2004 and green nodes isolates from 2008. The minimum spanning phylogeny is separated into fifteen sequence clusters (SCs). Arrows indicate the three isolates shown in Figure 3, in which high level homology in genes flanking *cps* clusters suggested capsular switching (19F to 19A) by recombination between (labelled a, b and c).

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Discussion

The findings of our genome-wide analysis of IPD-associated strains from Australia demonstrated that the emergence of non-vaccine serotypes, especially 19A with corresponding decrease in susceptibility to penicillin can be explained by the expansion of core genome clusters SC3, SC10 and SC12.

Vaccine coverage in our cohort of children with IPD in 2008 was high. Most cases of IPD in this group were due to nonvaccine serotypes, but four of the five serotype 19F 2008 isolates were collected from fully vaccinated children, with no reported comorbidities. Vaccine escape due to variation in the *cps* loci has been reported in IPD due to serotype 6 and 35, [15,22,23] but the *cps* loci from all 19F 2008 isolates from immunized children had >99% homology with the *cps* phylogenic clade of 2004 isolates. The cases are likely to be due to a relatively poor serological response to the 19F component of conjugate vaccines.

The significant increase in the prevalence of intermediate penicillin resistance among serotype 19A, in Australia, [11] can be largely attributed to the emergence of SC3/ST2345 and SC12/ST63; both clusters consisted, exclusively, of 19A isolates and were not represented among serogroup 19 isolates collected in 2004. ST63 has been more commonly associated with serotypes 15A and 14, but has been described in small numbers of serotypes 19A and 19F isolates (http://pubmlst.org). Ardanuy *et al* reported ST63 among serotype 8 (an uncommon cause of childhood IPD) associated with capsular switching events where the *cps* donor, serotype 8/ST53, recombined with a serotype 15A/ST63 strain to form serotype 8/ST63 [24]. This recombination included mutated *pbp* genes conferring intermediate penicillin resistance, which was also found in all ST63 isolates sequenced in our study. Pneumococcal recombination hotspots, that include all six *pbp* genes, have been recently reported [16,25], suggesting the potential for penicillin intermediate clones, like ST63, to acquire high level resistance through recombination, in addition to its propensity for capsular switching. It is possible that the emergence of 19A/ST63 in NSW, was another capsular switch recombination, possibly from a serotype 14 clone, which has recently been shown to have the highest recombination rates of all encapsulated pneumococci.[16] ST63 has been widely reported, usually in serotype 15A, as an increasingly frequent cause of IPD in post PCV-7, PCV-10 and PCV-13 studies, in other countries. [26–28]

In contrast to ST63, only four ST2345 isolates have been deposited, previously, in the pubMLST database, all of which were serotype 19. Its emergence may represent serotype expansion of an uncommon pre-existing clone, after the introduction of PCV-7. Phylogenetically, both ST63/SC12 and ST2345/SC3 are closely related to the MDR ST320/SC1 (see Figure 1) but have intermediate penicillin resistance.

Studies throughout the world have reported an increase in prevalence of MDR ST320 (SC1 in our study).[8,29–31], due to a capsular switch from 19F to 19A, which probably occurred independently of vaccine use, but which then allowed clonal expansion of this previously unrecognized clone, after removal of highly successful clones of vaccine serotypes. [14,25,32]. MDR ST320/SC1 was present in Australia before and its prevalence did not increase after the introduction of PCV-7. Unexpectedly, three 'capsular switch' 19A/ST320 variants were detected among our 2008 isolates. Several other countries, including Germany and Norway, have also reported relatively low prevalence of ST320, raising the possibility that this could be related to the level of antibiotic usage.[9,33] This is supported by genomic data showing mutations in *pbp* genes that confer resistance flux with antibiotic consumption.[16] and the fact that Germany and Norway are considered to have a relatively low antibiotic usage.[34] In contrast, Australia is considered to have a high antibiotic prescription rate, higher than other European countries that reported expansion of the 19A/ST320 clone, such as France. [35,36] Interestingly, the German study traced the majority of ST320 IPD cases to children who had recently immigrated to Germany.[9] Whereas the three children with 19A/ST320 in this study had no recent travel history.

In conclusion, gradual replacement of vaccine serotype 19F with serotype 19A with corresponding decrease in susceptibility to penicillin has been driven by the serotype expansion of successful IPD clones represented by core genome clusters SC3, SC10 and SC12. These clones are more likely to have reduced susceptibility to penicillin exemplified by the emergence of SC3/ST2345 and SC12/ST63. The recent emergence of 19A/ST63 in Australia could be a result of a capsular switch recombination, although we have no direct evidence of this among these isolates. Whole genome sequencing improves our understanding of changes in pneumococci associated with IPD, characterized by high levels of genomic plasticity, in the face of selective pressures.

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Translational Research Grant Update

The translational research grant, ***"Translating pathogen genomics into improved public health outcomes: Prospective evaluation of the effectiveness of genome sequencing-guided investigation of outbreaks"*** led by Associate Professor Vitali Sintchenko and Professor Jon Iredell is well underway. The project aims to use whole genome sequencing of pathogens for rapid identification, tracking and assessment of antibiotic resistance of tuberculosis and control of salmonellosis and listeriosis.

Project updates include:

- Sequencing of all isolates of *Mycobacterium tuberculosis*, *Listeria monocytogenes*, and *Salmonella* Typhimurium began in October 2016.
- Content and format for TB sequencing cluster report has been agreed upon and reporting is expected to commence soon.
- The first *Salmonella* cluster report was produced in February. Since then, four more reports have been received, and results correlated with epidemiological information. A comparison of sequencing-based clusters and traditional typing methods (MLVA) is underway.

Update on Translation Research Grant

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Partnership Projects

Project title	Principal investigator	Leading institution	Network partners
NSW VanA VRE: emergence of new threat	A/Prof Sebastian van Hal	RPAH	Network of nine NSW public hospitals
Diversity of viral quasispecies and HIV-1 drug resistance	Dr Shailendra Sawleshwalkar	Western Sydney Sexual Health	RPAH and Western Sydney LHD
MRSA acquisition and transmission in the Intensive Care and Burns Unit	Dr Genevieve McKew	Concord Hospital	Sydney LHD, Sydney South West Pathology Service
Pathogenesis of Enterovirus 71	Prof W Rawlinson	Prince of Wales Hospital and SEALS	Sydney Children's Hospital, Randwick, UNSW
Sources of Salmonella Wangata in north east NSW	Dr Julie Collins	Hunter New England Population Health	PHU and USyd Vet Sciences, ANU
Respiratory virome in lung transplant patients	Dr Alicia Mitchell	Woolcock Institute	Woolcock Institute, St Vincent's Hospital, UTS
Human norovirus diversity in NSW	Prof Peter White	UNSW	POWH and UNSW

Translational Research Grant Team

Name: Daneeta Hennessy

Position: Epidemiologist

Email: DHENN@doh.health.nsw.gov.au

Daneeta Hennessy is an epidemiologist with CIDM-PH and the Communicable Diseases Branch of Health Protection NSW. She is working on the NSW Health Translational Research Grant project examining the effect of using whole genome sequencing in surveillance and outbreak investigation on public health outcomes for salmonellosis, listeriosis and tuberculosis.

Daneeta has 12 years' experience working as a medical scientist in diagnostic and reference microbiology laboratories in Melbourne and London. She developed an interest in epidemiology and public health microbiology while working on a team investigating outbreaks of antimicrobial-resistant bacteria in hospitals, and went on to obtain a Master of Public Health from the University of Melbourne.

In 2014, she joined the NSW Health Biostatistics Training Program, undertaking placements at the Ministry of Health, the Kolling Institute for Medical Research, and Cancer Institute NSW. She is due to complete a Master of Biostatistics in July.

Translational Research Grant Team

Name: Dr Chayanika Biswas, BSc (Hons), MSc, PhD

Position: Postdoctoral Research Fellow

Email: Chayanika.Biswas@health.nsw.gov.au

Chayanika Biswas is a microbiologist with a Masters in Microbiology and Microbial technology. She was awarded her PhD in 2014, from The Faculty of Medicine, The University of Sydney. She is particularly interested in mechanisms of antimicrobial drug resistance and control of infectious diseases using modern biosurveillance technologies. She has publications in peer-reviewed international microbiology journals. She is a member of the American Society of Microbiology (ASM) and Australian Institute of Medical Scientists (AIIMs).

During her PhD, Chayanika studied multi-drug resistance in fungi and development of novel antifungal drugs against emerging fungal pathogens. Her first postdoctoral project involved identifying important biomarkers of tuberculosis (TB) transmission within Australia using whole genome sequencing (WGS) technology. She identified mutations in virulence-associated gene families in *Mycobacterium tuberculosis* that may facilitate higher TB transmission.

In collaboration with A/Prof S. Chen and A/Prof V. Sintchenko, she also completed a pilot project for rapid detection of antifungal drug resistance in *Candida glabrata* using WGS. In addition, she has participated in national and international drug trials of new antifungal agents for *in vitro* evaluation of antifungal susceptibilities against pathogenic fungi.

Chayanika is currently a research fellow at CIDM-Public Health WGS laboratory headed by A/Prof Vitali Sintchenko. She has recently started her second postdoc under the translational research grant establishing the utility of WGS in management of endemic cases and community outbreaks caused by *Salmonella*, *Listeria monocytogenes* and *Mycobacterium tuberculosis*.

Anup Patel is a Medical Scientist with the Centre for Infectious Diseases and Public Health. He graduated from the University of Central Lancashire (UK) and started his trainee programme in Diagnostic Microbiology in 2003 at North Manchester General Infirmary also in the UK, after which he gained state registration with the Health and Care Professions Council (HCPC) in 2006. He then moved to the Royal Oldham Hospital (UK) gaining further laboratory experience in areas such as TB and Serology.

In 2007 he moved to Australia and then worked at the Royal North Shore Hospital (Sydney) during the same year. He then moved to the Canberra Hospital in 2008.

In 2012 he gave the opening presentation at the Australian Institute of Medical Scientists (AIMS) Advancing Medical Science Together Conference in Canberra on “Laboratory Automation” and in the same year he was the author of a published article in a peer review journal on *Anaerobiospirillum succiniciproducens* bacteraemia.

In 2012 Anup again re-joined the Royal North Shore Hospital gaining experience in Molecular Diagnostics and undertaking research on “Molecular platforms for detection of Group B Streptococcus compared to traditional culture based methodology”. He also had the opportunity to present a poster upon this research at the Australia Society of Microbiology (ASM) National Conference.

More recently in 2017 Anup joined A/Prof Vitali Sintchenko’s group undertaking Whole Genome Sequencing work of *Salmonella* Typhimurium and *Mycobacterium tuberculosis* on the NSW Health Translational Research Grant with the Centre for Infectious Diseases and Public Health (CIDM-PH) based at Westmead Hospital.

Anup has over 13 years experience in laboratory Diagnostic Microbiology and during this time his main areas of interest have included laboratory automation, lean six sigma and molecular diagnostics.

Name: Anup Patel

Position: Technical Officer

Email: Anup.Patel@health.nsw.gov.au

Sydney Summer School in Pathogen Genomics

The Sydney Summer School in Pathogen Genomics was hosted by the Centre for Infectious Diseases and Microbiology – Public Health (CIDM-PH), and Marie Bashir Institute (MBI), with the support from the University of Sydney Strategic Education Grant. The Summer School was held at the Charles Perkins Centre, University of Sydney from 20-24 February 2017. Participants representing NSW, ACT, Victoria, Queensland, Tasmania, New Zealand and Singapore were among the 99% of satisfied attendees.

The program included a mix of inspiring keynotes, informatics reviews and master classes, practical hands-on demonstrations and a laboratory visit to the Genome Sequencing Facility at the Centre for Infectious Diseases and Microbiology, ICPMR, Westmead.

Topics included:

- *What can the analysis of microbial genomes tell translational researchers clinicians? How to select sequencing and bioinformatics solutions for specific research questions? Genome-wide association studies and patient outcomes*
- *Integration of genomic, clinical and epidemiological data: global and local perspectives and solutions*
- *Integrated data models, data analytics for knowledge discovery and data visualisation*
- *Effective and ethical data sharing and translation of genomics into precision medicine and public health*
- *Modelling and evaluation of genomics-guided interventions in hospital and community settings; genomics knowledge networks.*

*Course dinner at Sancta Sophia College with guest lecture by **Professor Lyn Gilbert AO**, speaking on **'Ethics of pathogen genomics'**.*

Hands-on exercises were organised to illustrate the power of genomics, functional genomics and metagenomics in answering important questions on the assessment of evolution, virulence, transmissibility and drug resistance as well as on detection of outbreaks and deciphering of transmission pathways.

Staff Profile

Name: Dr Alicia Arnott

Position: Research Fellow in Pathogen Genomics, Centre for Research Excellence in Emerging Infectious Diseases (CREID)

Email: alicia.arnott@sydney.edu.au

Dr Alicia Arnott earned her PhD in Virology from Monash University in 2009. Alicia then completed post-doctoral training in Cambodia at the Institut Pasteur, working on emerging respiratory viruses and at the Walter and Eliza Hall Institute working on the population genetics of *Plasmodium vivax* malaria. In February 2015, Alicia undertook the two-year Master of Applied Epidemiology (MAE), Australia's Field Epidemiology Training Program (FETP) with the Australian National University. For the duration of the MAE program, she was placed with the Communicable Disease Epidemiology and Surveillance Unit at the Victorian Department of Health and the Victorian Infectious Diseases Reference Laboratory (VIDRL). Upon completion of the program in October 2016, she commenced working as a Research Fellow in Pathogen Genomics within the Centre for Research Excellence in Emerging Infectious Diseases (CREID) at Westmead.

Save the date…

20 October 2017 : Advances in Microbial Genomics, Westmead Education & Conference Centre

17 November 2017: MBI Colloquium, University of Sydney

24 November 2017: CIDM-PH Colloquium, Westmead Education & Conference Centre

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CIDM-PH

Centre for Infectious Diseases and Microbiology - Public Health
Mailing Address: PO Box 533
Wentworthville NSW 2145
Phone: (612) 9845 9870
Website: www.wslhd.health.nsw.gov.au/CIDM-PH
Email: WSLHD-CIDM-PH@health.nsw.gov.au

Contact: Ms Lou Orszulak

MBI

Marie Bashir Institute for Infectious Diseases & Biosecurity
Mailing Address: Level 4, Westmead Millennium Institute for Medical Research
176 Hawkesbury Road, Westmead NSW 2145
Phone: (612) 8627 3402
Website: www.sydney.edu.au/mbi/
Email: mbi@sydney.edu.au

Contact: Ms Christine Aitken

Congratulations to MBI's Professor Lyn Gilbert AO
Australia Day Honours 2017

Professor Lyn Gilbert has been awarded an Officer in the Order of Australia (AO) for distinguished service to medical research, particularly the study of infectious disease prevention and control, to tertiary education as an academic, and to public health policy.

Professor Gilbert said *"it's a real surprise to me and a great honour. I've always just done what I thought I was supposed to be doing and if people thought I was going beyond, then that's great".*

Professor Gilbert has over 25 years of outstanding service at the Centre for Infectious Diseases Laboratory Services ICPMR, Westmead Hospital, Westmead Local Health District, MBI and the University of Sydney, interspersed with major roles in most of the communicable diseases & microbiology advisory committees at local, state and national levels.

Professor Lyn Gilbert AO

Congratulations to MBI's Professor Ben Marais winner of the
2017 Gust av Nossal Medal for Global Health

Professor Ben Marais

Professor Ben Marais has been awarded the prestigious 2017 Gustav Nossal Medal for Global Health by the Council of the Australian Academy of Science.

The Gustav Nossal Medal recognises research of the highest standing in the field of Global Health Research. It honours the contributions made to the fields of cellular immunology, antibody formation and tolerance and vaccine research science by Sir Gustav Victor Joseph Nossal, AC CBE FAA FRS FTSE. Funds for the medal were donated by Sir Marc Feldman AC FAA FRS.

Tuberculosis (TB) is the biggest infectious disease killer on the planet, but the fact that young children suffer high rates of disease and death is rarely appreciated. In addition, the emergence and spread of multidrug-resistant (MDR)-TB threatens the very fabric of global TB control efforts. His research helped to measure and characterise the TB disease burden suffered by children, highlighting the absence of care in places where this is needed most. His work has been acknowledged by the WHO and UNICEF, with renewed commitments to find pragmatic solutions to prevent and treat TB in children. He also raised awareness that MDR-TB is actively transmitted within communities, which puts children at risk and require urgent containment strategies. He wrote the first "survival guide" for paediatricians caring for children with MDR-TB, and contributed to global and regional initiatives to limit its spread.